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Improving accuracy in nodal staging of oral cancer: Proposal of a new system

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ABSTRACT

Background: Despite introduction of extranodal extension (ENE) into the AJCC 8th edition of oral cancer staging, previous criticisms persist, such as limited discrimination between sub-stages and doubtful prognostic value of contralateral nodal disease. The purpose of this study was to compare our novel nodal staging system, based on the number of positive nodes and ENE, to the AJCC staging system in surgically treated patients.
Methods: Retrospective analysis of 4710 patients with oral squamous cell carcinoma (OSCC) treated with surgery ±adjuvant therapy in 8 institutions in Australia, North America and Asia. With overall survival (OS) and disease specific survival (DSS) as endpoint, the prognostic performance of AJCC 8th and 7th editions were compared using hazard consistency, hazard discrimination, likelihood difference and balance.
Results: Our new nodal staging system (PN) a progressive and linear increase in hazard ratio (HR) from pN0 to pN3, with good separation of Kaplan Meier curves. Using the predetermined criteria for evaluation of a staging system, our proposed staging model outperformed AJCC 8th and 7th editions in prediction of OS and DSS.
Conclusion: PN was the lymph node staging system that provided the most accurate prediction of OS and DSS for patients in our cohort of OSCC. Additionally, it can be easily adopted, addresses the shortcomings of the existing systems and should be considered for future editions of the TNM staging system.

1. Background

Lymph node involvement arguably remains the most important prognostic determinant in oral squamous cell carcinoma (OSCC) [1]. The 8th edition of American Joint Committee Cancer and Union for International Cancer Control (AJCC/UICC 8) introduced extranodal extension (ENE) to improve the accuracy of the nodal staging. Although this represents an improvement over the 7th edition (AJCC 7), several criticisms remain unaddressed, such as the doubtful prognostic value of bilateral nodal disease and poor discrimination between sub-categories within N2 [2]. A multi-institutional study also demonstrated that the pathological N3a category in AJCC/UICC 8 carries no prognostic

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significance and is therefore likely redundant [5].

Recent studies have shown that number of positive lymph nodes is a valuable prognostic determinant in OSCC [3] and may perform better than AJCC/UICC 8 [4]. Given that the number of positive lymph nodes and ENE have consistently been shown to be important predictors of survival, our aim was to use these parameters to derive a nodal staging system with improved predictive value and reduced heterogeneity, while addressing previous criticisms of the TNM staging system.

There is still a lack of consensus in OSCC staging on whether the size of an involved lymph node or the size of the tumour deposit within the involved lymph node is more prognostically relevant. Deriving a nodal staging system based on number of positive lymph nodes would be more consistent with other cancer types as head and neck squamous cell carcinoma (HNSCC) remains the only tumour for which nodal dimensions are considered a staging determinant [6]. We hypothesize that number of positive lymph nodes better reflects the tumour burden and may address the issues of poor discrimination within the N2 category, and the limited prognostic value of bilateral nodal disease [7]. To test the hypothesis, we proposed an alternative nodal staging system based on the number of nodal deposits and ENE. In this study we evaluate this alternative nodal staging system and compare its performance with AJCC 7 and AJCC/UICC 8.

2. Materials and methods

2.1. Study population

The cohort for this study was derived from a multi-institutional collaboration of patients treated in cancer centres in Australia (Chris O'Brien Lifehouse Hospital Sydney, Westmead Public Hospital Sydney, Prince of Wales Hospital Sydney and Royal Brisbane and Women's Hospital Brisbane), North America (Princess Margaret Cancer Centre Toronto) and Asia (National Cancer Center Singapore, Amrita Institute of Medical Sciences Kochi India and Mazumdar Shaw Medical Center Bangalore India). In total, there were 4710 patients with OSCC who were treated with curative intent surgery with or without adjuvant therapy between 1989 and 2016. Detailed information on patient demographics, clinical and pathological parameters, treatment, and follow-up were obtained. Institutional ethics committee approval was received before the study was commenced (RPA X16-0464).

2.2. Deriving the novel nodal staging model

The novel nodal staging model was based on two well-established parameters-the number of lymph nodes involved pathologically by the tumour and the presence of ENE. In this model, pN1 represents pathological involvement of a single lymph node with no evidence of ENE, pN2 represents pathological involvement of a single node with ENE or pathological involvement of >1 node with no ENE and pN3 was pathological involvement of >1 node with ENE (Table 1). pN2 sub-categories were combined and category pN3a was omitted, reverting to a single pN3 category. When compared with the AJCC/UICC 8, pN1 and pN3 are identical, while pN2 is a simplified category that encompasses patients with similar survival outcomes.

Table 1
Proposed nodal staging.

N-category	
N0	No pathological involvement
N1	Pathological involvement of a single node without extranodal extension
N2	Pathological involvement of a single lymph node with extranodal extension OR multiple lymph nodes without extranodal extension
N3	Pathological involvement of multiple lymph nodes, ny with extranodal extension

2.3. Statistical analysis

Statistical analysis was performed using R version 4.0.2 [8] and SPSS version 20 (IBM, New York, NY). Survival curves were generated using the Kaplan Meier (KM) method and comparisons were made using the Cox proportional hazards model. The outcomes analyzed were overall survival (OS), calculated from the date of surgery to date of death or last follow-up, and disease specific survival (DSS), calculated from date of surgery to date of death due to oral cancer or last follow-up. The prognostic performance of the AJCC 7 and 8 were evaluated using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Harrell's concordance index (*C*-Index), as well as criteria previously postulated by Xu et al. [9] – hazard consistency, hazard discrimination, likelihood difference and balance. The AIC and BIC take into account how well a model fits the data with penalties for model complexity, where a lower number indicates a better model. The *C*-index provides a measure of model discrimination, with a value of 1 indicating perfect prediction and 0.5 equivalent to the toss of a coin. Xu et al. [9] proposed additional criteria to assess a model for their prognostic ability and stability of the model. These additional criteria included [1] hazard consistency [2], hazard discrimination [3], likelihood difference and [4] balance.

The following three criteria, introduced by Xu et al. [9], are based on the concept of the *likelihood*, which is, in general, the probability of having observed the data set at hand, under the assumption that a particular assumed statistical model is correct. These criteria use likelihoods from multivariate Cox proportional hazards regression models [10] and appear in logarithmic form as, for example, $\log(\mathscr{L}_1)$, where model 1 is the assumed model. The following Cox models for overall survival and disease specific survival, with the following as predictor variables, are used in the criteria:

- Model 1. Each of the 16 pT and pN subgroups
- Model 2. Grouping according to the staging model under consideration
- Model 3: Grouping according to the staging model under consideration, where the grouping levels are treated as a continuous variable
- Model 4: No additional predictor variables

Models for overall survival are also adjusted for the demographic and clinical variables age, country, radiotherapy, DOI and diameter; and models for disease specific survival for age, radiotherapy, DOI and diameter. N_G is the number of groups in the staging model.

Hazard consistency - addresses the issue of the homogeneity of the patients within each subgroup for all stage groups. It calculates a weighted average of the survival difference between each stage grouping for a given model and the subgroups that make up that grouping, where the weights were based on the amount of person time contributed by the subgroups. Zero indicates the perfect model.

$$\mathrm{HC} = \frac{-2 \times (\log(\mathscr{L}_2) - \log(\mathscr{L}_1))}{16 - N_G}$$

Hazard discrimination – addresses the question of the heterogeneity of patients between each adjacent stage group. It was measured by evaluating how evenly the group survival curves are spaced and how large a survival rate difference they span over the entire observation period. A lower number reflects the better the model in addressing the differences between the group.

$$\mathrm{HD} = \frac{-2 \times (\log(\mathscr{L}_3) - \log(\mathscr{L}_2))}{N_G - 2}$$

Likelihood difference - compares the performance of the model with and without the proposed staging system. A higher value indicates a better model.

$$LD = \frac{-2 \times (\log(\mathscr{L}_4) - \log(\mathscr{L}_2))}{N_G - 1}$$

Balance - is quantified by computing the sum of the absolute differences between the observed proportions of cases in each group compared with the expected if an equal number of patients were in each. In this model, a lower number indicates a better fit.

$$M_4 = \frac{1}{N_G} \sum_{G=1}^{N_G} \frac{|c_G - C/N_G|}{C/N_G}$$

(c_G is the number of patients in staging group G, and C is the total number of patients.)

3. Results

3.1. Patient, disease and treatment characteristics

A total of 4587 patients were included in the analysis, after excluding 113 patients with incomplete data. The median age was 59.3 (range 18–97) years with a median follow up of 2.9 (range 0.1–27) years. The distribution of subjects according to AJCC7 *N*-category were 2985 N0 (65.1 %), 601 N1 (13.1 %), 897 N2 (19.6 %) and 104 N3 (2.3 %). The distribution of subjects according to AJCC8 *N*-category was 2985 N0 (65.16 %), 470 N1 (10.2 %), 531 N2 (11.6 %) and 601 N3 (13.1 %). The distribution according to the proposed *N*-category was 2985 N0 (65.16 %), 484 N1 (10.6 %), 563 N2 (12.3 %) and 555 N3 (12.1 %). ENE was present in 16.4 % (n = 752) of patients. Adjuvant radiotherapy and chemoradiotherapy was administered in 1897 (40.3 %) and 570 (12.1 %) patients respectively. Clinical and demographic data is shown in Table 2.

3.2. Nodal category prediction of overall survival

The performance of AJCC 7 and AJCC/UICC 8 in predicting OS by N category is shown in Tables 3a and 3b. AJCC 7 demonstrated a progressive increase in hazard ratio (HR) from pN1 to pN2c categories; however, pN3 had a lower HR (2.1) compared to pN2b and pN2c (HR 2.76 and 3.61, respectively) as shown in Fig. 1a. Using AJCC/UICC 8, the pN2 subcategories (pN2a, pN2b and pN2c) had overlapping survival estimates as shown in Fig. 1b. In addition, pN3a lacked precision (wide confidence intervals) due to the small same size (n = 6, HR 2.55, 95 % CI 0.953–6.81, p = 0.062). Due to the unreliability of pN3a and the lack of prognostic discrimination between pN2 subcategories in spite of having such a large study population, we re-assessed AJCC/UICC 8 by combining pN2a-c and pN3a-b into single categories. The simplified AJCC/UICC 8 system provided a progressive and linear increase of HR from pN0 to pN3 (Table 3a) and good separation of the KM survival curves (Fig. 1c). The newly proposed staging system also demonstrated a progressive linear increase in HR from pN0 to pN3 but with greater separation of KM curves between pN2 and pN3, compared to the simplified AJCC/UICC 8 (Fig. 1d).

Table 2
Baseline clinical and pathological data.

Variable	No.	%
Age, y		
<60	2437	51.7
>60	2273	48.3
Sex		
Male	3047	64.7
Female	1663	35.3
AJCC 7th edition pathological T-stage		
T1	1899	40.3
T2	1587	33.7
T3	470	10
T4	754	16
Extranodal extension	799	26.7
AJCC 7th edition pathological N-stage		
N0	1597	33.9
N1	153	3.2
N2	2854	60.6
N3	106	2.3
AJCC 7th edition TNM stage		
I	1653	35.1
II	850	18
III	597	12.7
IV	1610	34.2
AJCC 8th edition TNM stage		
I	1045	23.4
II	959	21.5
III	731	16.4
IV	1728	38.7
Adjuvant treatment		
Radiotherapy	1897	40.3
Chemoradiotherapy	570	12.1

Table 3a
Predictors of overall survival in different nodal staging systems on multivariate analysis by Cox proportional hazards regression model.

Stage	5-year overall survival	Hazard ratio	95 % CI		p-value
AJCC 7th edition staging					
pN0	76 %	Referent			
pN1	65 %	1.49	1.298	1.72	<0.001
pN2a	56 %	1.90	1.241	2.90	<0.001
pN2b	43 %	2.76	2.432	3.12	0.003
pN2c	34 %	3.61	2.932	4.44	<0.001
pN3	43 %	2.08	1.463	2.95	<0.001
AJCC/UICC 8th edition staging					
pN0	76 %	Referent			
pN1	65 %	1.37	1.180	1.61	0.002
pN2a	57 %	1.67	1.454	2.39	<0.001
pN2b	48 %	1.86	1.760	2.51	<0.001
pN2c	43 %	2.10	1.761	3.44	<0.001
pN3a	36 %	2.55	0.953	6.81	0.062
pN3b	38 %	3.39	2.988	3.86	<0.001
AJCC/UICC 8th edition simplified staging					
pN0	73 %	Referent			
pN1	64 %	1.38	1.18	1.61	<0.001
pN2	49 %	2.08	1.80	2.40	<0.001
pN3	38 %	3.36	2.94	3.84	<0.001
Proposed staging model					
pN0	76 %	Referent			
pN1	65 %	1.39	1.380	2.13	<0.001
pN2	50 %	2.15	2.502	3.59	<0.001
pN3	37 %	3.49	4.230	5.91	<0.001

Table 3b
Parameters to assess impact of nodal staging systems on overall survival.

Staging evaluation parameter	AJCC 7th edition	AJCC/ UICC 8th edition	Simplified AJCC/UICC 8th edition	Proposed staging system
Hazard consistency	10.830	8.190	6.390	6.300
Hazard discrimination	3.910	1.000	10.280	1.110
Likelihood difference	63.150	58.380	115.780	116.150
Balance	0.810	0.860	0.550	0.550
C-index	0.670	0.675	0.676	0.676
AIC	22,759	22,727	22,724	22,723
BIC	22,813	22,786	22,767	22,765

Key: Underlined value indicates best performance.

3.3. Overall survival model performance

The performances of the various models assessed according to hazard consistency, hazard discrimination, likelihood difference, balance, *C*-index, AIC and BIC are summarized in Table 3b. The newly proposed

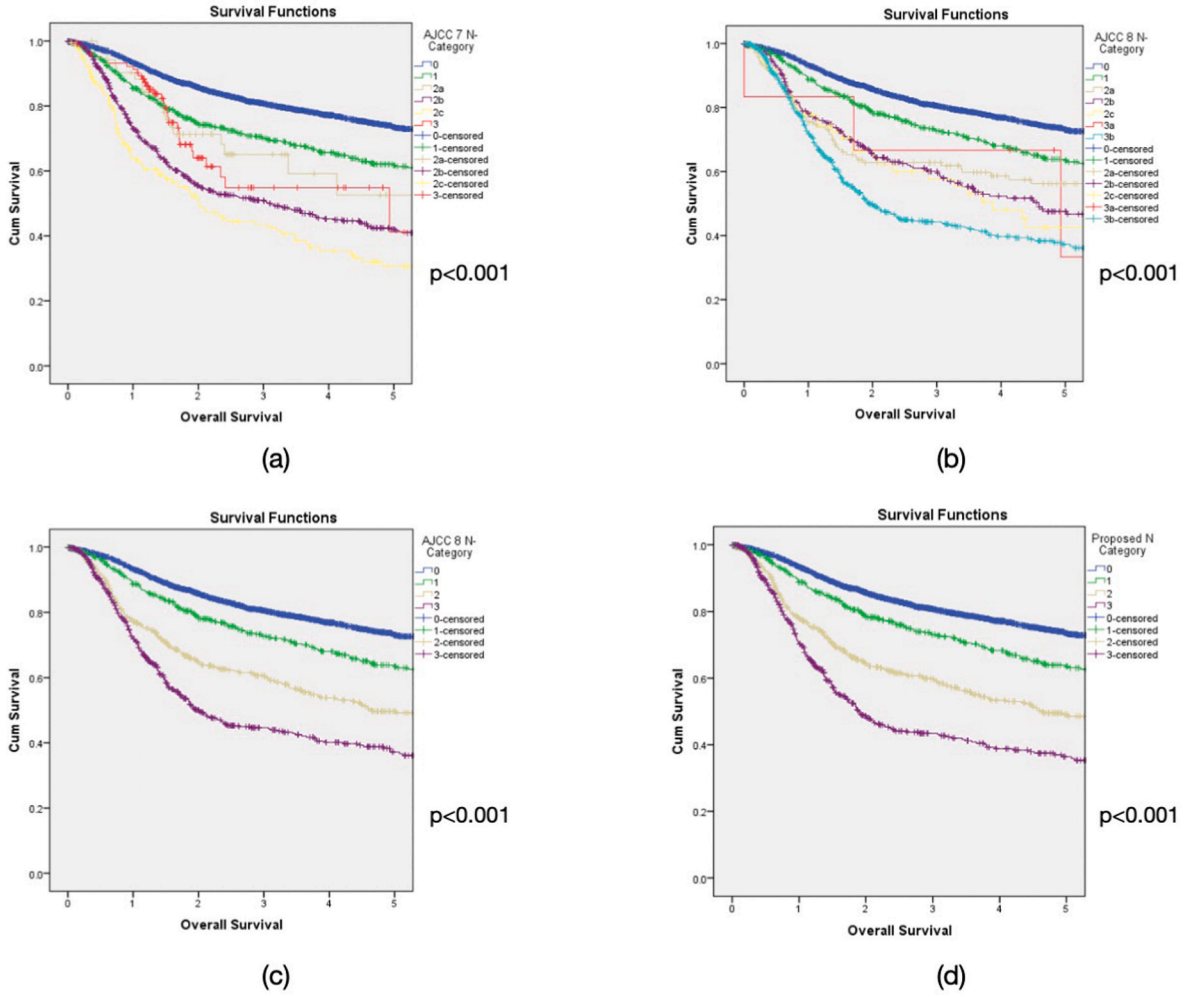

Fig. 1. Kaplan-Meier plots of overall survival based on (a) AJCC 7th edition (b) AJCC 8th edition (c) AJCC 8th edition simplified version and (d) our proposed nodal category.

model had superior hazard consistency (6.30), as compared to AJCC 7, AJCC/UICC 8, and simplified AJCC/UICC 8 (10.83, 8.19, and 6.39, respectively) and good hazard discrimination (1.11 vs 3.91, 1.00 and 1.28 respectively) suggesting better homogeneity within pN categories and favorable discrimination between categories (note, AJCC/UICC 8 performed best in this regard). The balance distribution was the same for both the proposed model and the simplified AJCC/UICC 8 (0.55) compared to AJCC 7 (0.81) and AJCC/UICC 8 (0.88). This indicates that the proposed model and simplified AJCC/UICC 8 perform better than the other models in distributing an equal number of similar cases into each of the categories. In terms of model performance, the proposed model was superior in terms of likelihood-difference, AIC, and BIC, and performed identical to the simplified AJCC/UICC 8 in terms of *C*-index.

3.4. Nodal category prediction of disease specific survival

The performance of AJCC 7 and AJCC/UICC 8 in predicting DSS by N category is shown in Tables 4a and 4b. AJCC 7 demonstrated a progressive increase in HR from pN1 to pN2c categories; however, pN3 had a lower HR (2.08) compared to pN2b and pN2c (HR 2.76 and 3.60, respectively) as shown in Fig. 1a. Using AJCC/UICC 8, the pN2 subcategories (pN2a, pN2b and pN2c) had overlapping survival estimates as shown in Fig. 2b. In addition, pN3a lacked precision (wide confidence intervals) due to the small same size (n = 6, HR 2.55, 95 % CI 1.29–12.5, p = 0.016). The simplified AJCC/UICC 8 (derived by combining pN2a-c and pN3a-b into single categories), as with OS, provided a progressive

Table 4a
Predictors of disease specific survival in different nodal staging systems on multivariate analysis by Cox proportional hazards regression model.

Stage	5-year disease specific survival	Hazard ratio	95 % CI		p-value
AJCC 7th edition staging					
pN0	84 %	Referent			
pN1	76 %	1.49	1.66	2.43	<0.001
pN2a	63 %	1.89	1.57	4.42	<0.001
pN2b	57 %	2.76	3.30	4.57	<0.001
pN2c	43 %	3.60	3.83	6.44	<0.001
pN3	43 %	2.08	2.15	4.59	<0.001
AJCC/UICC 8th edition staging					
pN0	84 %	Referent			
pN1	76 %	1.37	1.45	2.26	<0.001
pN2a	67 %	1.67	2.12	4.09	<0.001
pN2b	66 %	1.86	2.27	3.63	<0.001
pN2c	56 %	2.10	2.23	5.27	<0.001
pN3a	34 %	2.55	1.29	12.5	0.016
pN3b	48 %	3.39	4.32	6.00	<0.001
AJCC/UICC 8th edition simplified staging					
pN0	85 %	Referent			
pN1	75 %	1.807	1.45	2.26	<0.001
pN2	64 %	2.979	2.46	3.60	<0.001
pN3	48 %	5.045	4.26	5.97	<0.001
Proposed staging model					
pN0	84 %	Referent			
pN1	76 %	1.71	1.38	2.13	<0.001
pN2	68 %	2.99	2.50	3.59	<0.001
pN3	48 %	5.00	4.23	5.91	<0.001

Table 4b
Parameters to assess impact of nodal staging systems on disease specific survival.

Staging evaluation parameter	AJCC 7th edition	AJCC/ UICC 8th edition	Simplified AJCC/UICC 8th edition	Proposed staging system
Hazard consistency	9.570	8.840	6.810	6.460
Hazard discrimination	14.650	3.250	18.740	0.100
Likelihood difference	60.940	53.470	106.250	107.640
Balance	0.760	0.800	0.370	0.340
C-index	0.689	0.692	0.692	0.693
AIC	12,400	12,386	12,382	12,378
BIC	12,447	12,437	12,419	12,415

Key: Underlined value indicates best performance.

and linear increase of HR from pN0 to pN3 (Table 4a) and good separation of the KM survival curves (Fig. 2c). The newly proposed staging system also demonstrated a progressive linear increase in HR from pN0 to pN3 but with greater separation of KM curves between pN2 and pN3, compared to the simplified AJCC/UICC 8 (Fig. 2d).

3.5. Assessment of the models with disease specific survival

The assessments with hazard consistency, hazard discrimination, likelihood difference, balance, *C*-index, AIC and BIC were applied to each of the models with DSS as the outcome measures. The proposed model consistently outperformed the AJCC 7, AJCC/UICC 8 and simplified AJCC/UICC 8 in hazard consistency (6.30 vs 10.830, 8.190, 6.390 respectively). Hazard discrimination was better in the proposed model than AJCC 7 and simplified AJCC/UICC 8 (1.110 vs 3.910 and 10.280 respectively), but AJCC/UICC 8 was slightly superior (1.000). Likelihood difference was better in the proposed model vs AJCC 7, AJCC/UICC 8 and simplified AJCC/UICC 8 (116.150 vs 63.150, 53.380 and 115.780 respectively). Balance of distribution in the proposed model was the same as the simplified AJCC/UICC 8, but better than the AJCC 7 and AJCC/UICC 8 (0.550 vs 0.810 and 0.860 respectively).

With *C*-index, the proposed model performed equally well comparing to the AJCC/UICC 8 edition, and marginally better than the AJCC 7 edition and AJCC/UICC 8 (0.676, 0.675 and 0.670 respectively). Assessment with AIC and BIC indicated that the proposed model was better and simpler model compared to the AJCC 7, AJCC/UICC 8 and simplified AJCC 8 (AIC – 22,723 vs 22,759 vs 22,727 vs 22,724 respectively and BIC – 22,765 vs 22,813 vs 22,786 vs 22,767). These results suggested that the proposed model based on number of positive lymph nodes and ENE performed better than the existing models based on size of nodes and ENE.

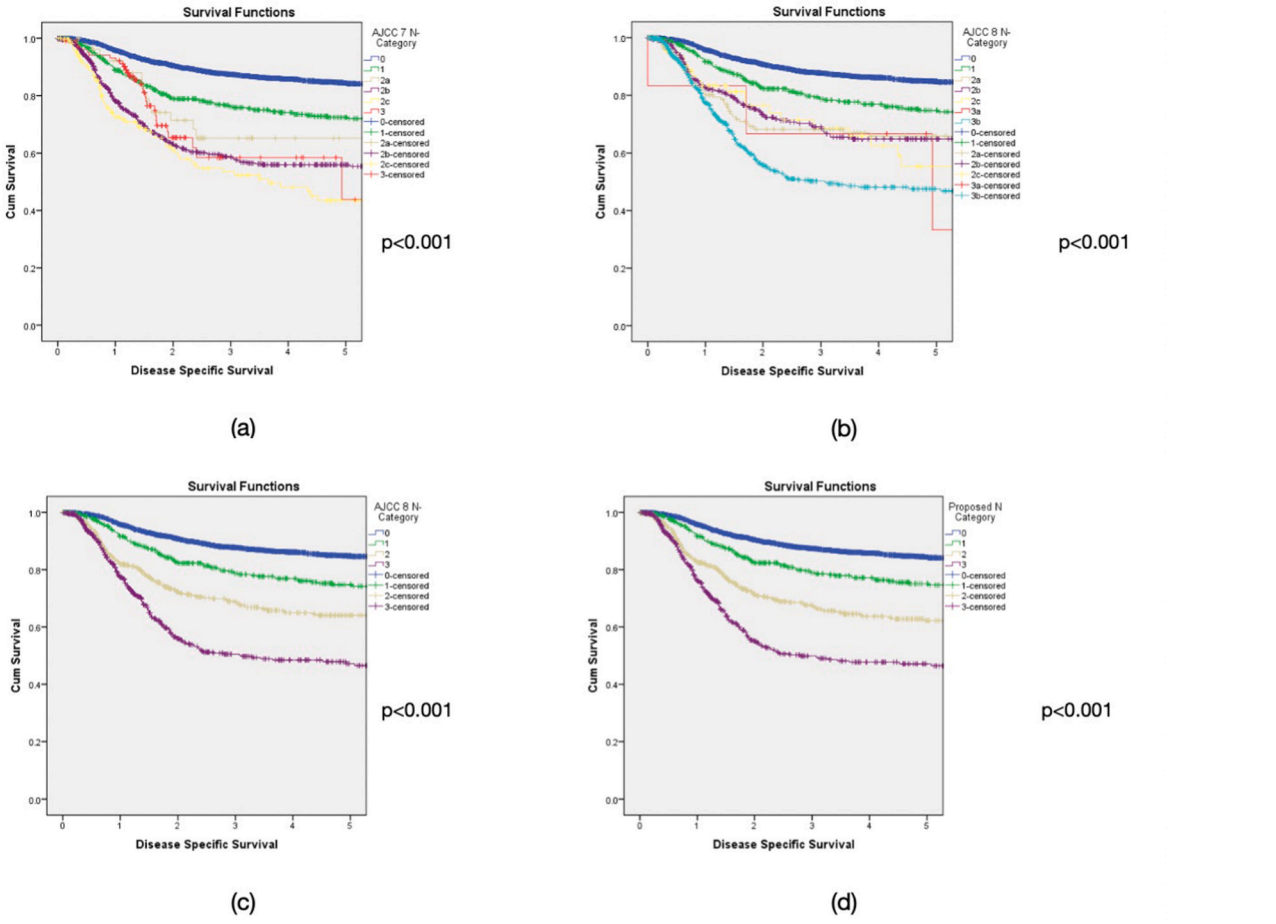

Fig. 2. Kaplan-Meier plots of disease specific survival based on (a) AJCC 7th edition (b) AJCC 8th edition (c) AJCC 8th edition simplified version and (d) our proposed nodal category.

4. Discussion

The incorporation of ENE into the AJCC/UICC 8th edition staging system represented an acknowledgement of the impact that this key adverse pathological feature has on survival. The incorporation of ENE in AJCC/UICC 8 (which is based on node size, number and laterality), improved the performance its predecessor (AJCC 7), as assessed with hazard consistency, hazard discrimination, likelihood difference, balance, *C*-index, AIC and BIC. However, we note that the new system has its own deficiency, including poor discrimination of the pN2 category and a non-predictive pN3a category and with very small number of patients within that category.

The AJCC nodal staging system has undergone little change over the last four and a half decades [15]. It was founded on concepts that were valid at the time, such as predictable lymph node drainage patterns, importance of the size of the node with tumour deposit(s) and prognostic value of contralateral nodal disease [16]. Number of positive lymph nodes is a well-known prognostic determinant that has been applied across multiple cancers and is believed to be an accurate reflection of the tumour burden [11–14].

In this study, we created a staging system utilizing one vs two or more lymph nodes as the differentiation factor, as well as ENE. Using this very simple model, it allows an accurate conversion of the existing AJCC-7 nodal category. For example, cases with AJCC-7 pN1 and pN2a with no ENE will remain the new pN1, whilst those with ENE will be upstaged to pN2. Patients with pN2b (more than 1 node) and pN2c (presence of contralateral node) without ENE will remain as the new pN2, whilst those with ENE will be upstaged to the new pN3. Using predefined criteria as described in the literatures [2,9], we evaluated the staging system with number of nodal deposits and ENE, it out-performed the existing nodal staging system in almost all measures and performed similar or better to the simplified AJCC/UICC 8 model.

The current model allows conversion from previous editions of the AJCC staging system. This is important as it allows data from historical databases and previous published datasets to be recoded and analyzed without the requirement for any additional information, other than ENE. We acknowledge that the current model of dividing the pN category in 4 categories (pN0, pN1, pN2, pN3) might be too simplistic and lacks details. Other models, such as those proposed by Ho et al. utilized more complex categorization, utilizing cutoffs at 1 node, 2 nodes, 3–7 nodes and>=8 nodes and ENE and those utilizing lymph node ratio should be explored and allows for subdivision of the categories for better prognostic groups [7]. Incorporating these additional data will, however, pose problematic for historical datasets that do not capture those additional data, hence limiting the ability to recode datasets that uses previous versions of AJCC *N*-staging for further analysis. The extent of ENE also poses a similar challenge. Although it has been shown that a cut-off of 1.7 mm of ENE predicted disease specific survival [17], it is unclear if this can be reliably demonstrated in larger populations. It also remains to be seen if inter-observer variation can impact these findings.

This current dataset consists of a large heterogeneous group of patients of OSCC from 8 multi-national cancer centres. Whilst the result will need to be validated against another large dataset from other institutions, the data support the argument that we should start moving towards a nodal staging system with number of nodal deposits as the basis instead of size of involved lymph nodes [4,7]. This proposed system supports the philosophy that a staging system should be simple, homogenous within the group, have good separation and discrimination between the groups, and predictive of the prognosis [9]. Literature to date supports the concept that the number of positive lymph nodes reflects the tumour burden, hence, it could be used as a surrogate marker for contralateral nodal deposit [2], allowing us to simplify the AJCC nodal staging system.

5. Conclusion

This study supports the concept of utilizing number of nodal deposits as the basis of the pN category. The existing staging systems perform poorly due to their over-complexity and could be improved by combining subcategories into a simplified AJCC/UICC 8 model. The proposed nodal staging system represents an alternative approach, combining the nodal burden with ENE; in the cohort studied, it was the superior model.

Author contributions

a. Study concept: NS, THL, JRC
b. Study design: THL, NS, GH, JRC
c. Data collection: ALL
d. Quality control of data and algorithms: ALL
e. Statistical analysis: GH, THL, JRC
f. Manuscript preparation: NS, THL
g. Manuscript editing: ALL
h. Manuscript review: ALL.

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Declaration of competing interest

There are no conflicts of interest for any of the authors.

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