Number of positive nodes – Current relevance in determining prognosis of oral cavity cancer after the recent AJCC staging update

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ABSTRACT

Introduction: Lymph node involvement and the number of positive nodes is a significant prognosticator in oral cavity cancers and current staging system does not incorporate it as an integral part.
Material and methods: This was a retrospective study of oral cavity cancer patients who were operated during the time period of 2009–2017. The data was collected and analysed to assess the impact of increase in the number of positive nodes on survival and its comparison of survival statistics to current AJCC staging.
Results: A total of 1431 patients were included in this study and 32.5% of these patients had a node positive disease. Nodal positivity was a significant prognosticator on multivariate analysis. Number of positive nodes was modelled with restricted cubic spline function and it showed progressive worsening of survival functions with increase in number. On Kaplan Meier analysis there was a better separation of curves when number of positive nodes was used and Akaike information criterion (AIC) showed that it was a better prognosticator than existing AJCC staging.
Conclusion: Number of positive nodes is a significant prognosticator of prognosis and hence should be considered in the AJCC staging system.

Introduction

Oral cancer constitutes a major health burden in India and the recent rise in incidence has been documented by the National cancer registry programme [1]. Several clinical and pathological factors affect the prognosis in oral cancer and identifying them will help in the development of better and improved treatment protocols. TNM staging since its inception in 1959 has been incorporating various prognostic factors in staging system. Recently the updated AJCC 8th edition of head and neck staging system included extra-nodal extension (ENE) and depth of invasion (DOI) in staging classification [2]. Lymph nodal involvement is a well-established prognostic factor in head and neck cancer [3] and the latest edition of AJCC 8th staging includes lymph nodal site (ipsilateral and contralateral), size, presence of ENE in the nodal staging category [4]. However, only greater than one lymph node has been included as a criterion for upstaging and no consideration for increasing number of positive lymph nodes as a part of staging classification has been made. Ho et al. in their study have observed an

inverse relation of number of positive lymph nodes with survival and have proposed a newer staging classification with inclusion of number of positive lymph node [5]. Similarly, the prognostic importance of number of positive lymph nodes has been observed by few other authors in their studies [6–8]. The aim of our study is to study the association of number of positive nodes on recurrence in oral cancer and compare this with the AJCC 8th edition nodal staging model.

Methods

Retrospective analysis was conducted at a tertiary care centre in northern India. All adult patients (≥ 18 years) of oral cancer registered at the centre were considered for analysis and only those who underwent upfront surgical resection with neck dissection as primary treatment were considered for analysis. Patients with non-squamous histology, < 2-year follow up, and who did not complete treatment were excluded from the analysis. A total of 1431 patients were included in the study cohort and data of these patients was extracted from

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electronic medical records. Adjuvant therapy was given as per institutional protocol, all patients with LVI, PNI and T3-T4 and Node positivity received radiation alone and patients with ENE (extra nodal extension) positive and margin positivity received concurrent radiation with chemotherapy. All patients were initially staged as per AJCC 7th edition staging system and later they were reviewed and restaged as per the latest 8th edition. Patients were stratified with respect to number of positive lymph nodes as 0, 1, 2, ≥3 positive nodes as per the findings of our study.

Statistical analysis

Descriptive summaries were presented in mean and standard deviation for continuous variables and frequencies with percentages for categorical variables. Primary outcome was disease free survival, which was calculated from the date of diagnosis till first recurrence or censored at last follow up. Number of positive lymph nodes were cross tabulated with disease free survival and the results were graphically represented. As the number of positive lymph nodes have a non-linear relationship with disease free survival (DFS) status, they were modelled using a restricted cubic spline function with five knots. Estimated associations were illustrated with smoothened restricted cubic spline plot of number of metastatic lymph nodes on X axis and log adjusted hazards ratio on Y-axis. Survival analysis was performed using Kaplan Meier method and comparison between two groups was done by Log rank test. Hazards ratio for covariates on DFS and OS was calculated by Cox proportional hazards model and univariate and multivariate analysis was represented in tabular format. Akaike information criterion (AIC) was calculated for restricted cubic spline model of number of positive nodes and AJCC 8th nodal staging Cox proportional hazards model. Statistical analysis was done using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium), IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp and Regression Modelling Strategies R package (RMS) (Version 5.1–2). P-value of < 0.05 was considered significant.

Results

Mean age at presentation was 49 ± 12.4 (22–93), with male: female ratio being 5.2:1. Tobacco usage was present in 71% of patients and 27% patients had history of smoking. Lymph-nodal positivity was seen in 32.5% of patients out of which 44% patients had ENE. Demographic profile has been represented in Table 1. Number of positive nodes were modelled with restricted cubic spline function and graphically represented in Fig. 1. Based on the graphic representation 0, 1, 2, > 2 were taken as cut-off points for number of positive nodes (Fig. 1). On univariate Cox regression analysis for disease free survival (DFS), lymphovascular invasion (LVI), perineural invasion (PNI), AJCC T and N Stage, margin status and number of positive nodes were all statistically significant. Multivariate analysis included all factors without linear correlation and it showed that PNI, AJCC T stage and number of positive nodes were statistically significant predictors of DFS (Tables 2 and 3). Univariate regression was used to assess the impact of number of positive lymph nodes in only node positive and ECE positive patients and 1, 2 and > 2 positive lymph nodes significantly affects DFS in both groups (Table 3). Univariate and multivariate analysis was done for factors affecting the overall survival and is represented in Table 4 with new T staging, no. of positive nodes and PNI having significant associations with overall survival. Five-year DFS for N0, N1, N2 and N3 as per AJCC 8th staging was 80.2%, 66.5%, 64.1% and 49.8% respectively and 5-year DFS for number of positive lymph nodes category 0, 1, 2 and > 2 was 80.2%, 68.5%, 58.8% and 49.6% respectively (Fig. 2 and Fig. 3). Five-year DFS for no. of positive nodes (1, 2 and > 2) in all ECE positive patients was (Fig. 4)71.6%, 60.9% and 43.8% (p = 0.005). AIC for restricted cubic spline model of number of positive lymph nodes and AJCC 8th nodal staging was 5016 and 5022 respectively.

Table 1
Demographic profile of the patients in the study.

Age (mean)	49 ± 12.4 (22–93)
Gender (M: F)	5.2:1
Smoking	27%
Tobacco	71%
Node positive	32.5%
Number of positive nodes	Median 2 (1–33)
Number of nodes	26(11–60)
Number of positive nodes	
0	(965) 67.4%
1	(211) 14.7%
2	(114) 8%
> 2	(141) 9.9%
Nodal staging	
N0	(965) 67.4%
N1	(159) 11.1%
N2	(157) 11%
N3	(150) 10.5%
Perineural invasion	21.2%
Lympho-vascular invasion	35.3%
Adjuvant therapy	NO – 32.1%
	RT – 51.7%
	CT/RT – 16.1%
Extracapsular extension	14.4%
Follow up (median)	41 months (40.1–41.9)

Discussion

Lymph node involvement in oral cancer is a proven prognostic factor and has been incorporated in TNM staging since its inception. Number of positive lymph nodes has been included in TNM staging of oral cancers where > 1 positive node is staged as N2, however no further stratification as per increasing number of nodes has been included in staging [4]. Number of positive lymph nodes forms a part of TNM staging for many malignancies like breast cancer, testicular cancer, gastric cancer and colorectal cancers [9], however in head and neck cancers there is scarcity of data for prognostic significance of number of positive lymph nodes. Aim of this present study is to study the association of number of positive lymph nodes in oral cancer patients on disease free survival. AJCC nodal staging for oral cancer constitutes a very heterogenous group of patients, especially N2 and N3 category where multiple lymph nodes irrespective of number have been included in same category and this heterogeneity has been observed in various studies [8,10,11]. Incorporation of ECE in nodal staging by AJCC 8th edition update is a major change and has helped to better stratify this heterogenous group [2], however number of positive lymph nodes was not considered in this update of staging system. Number of positive lymph nodes has been observed as an important prognostic factor by various authors [12,13]. Sinha et al. have observed number of positive lymph nodes as a poor prognostic factor in p16 positive oropharyngeal squamous cell cancer [6]. Similar results were observed in hypopharyngeal and laryngeal cancers in a study by Ho et al. [7]. Shibuya et al. in their study observed significantly worse prognosis for ≥10 positive lymph nodes as compared to < 10 in oral cavity cancer patients [10]. Another study by Liao et al observed a significant increase in distant metastasis rate on multivariate regression analysis in patients with ≥5 positive lymph nodes [14]. In the present study number of positive lymph nodes has been observed to significantly affect the DFS on multivariate regression analysis. Smoothened restricted cubic spline plots in the study also suggest that increasing number of positive lymph nodes is associated with increased chances of recurrences (Fig. 1). Since presence of ENE significantly affects the survival and adjuvant treatment decisions, its inclusion in nodal staging has made this system comprehensive. Thus, the impact of number of positive lymph nodes on prognosis in addition to ENE is still not known. Secondly, landmark randomised control trials for adjuvant therapy in oral cancer did not show any advantage of intensifying therapy based on number of positive lymph nodes [15,16]. However, there were many
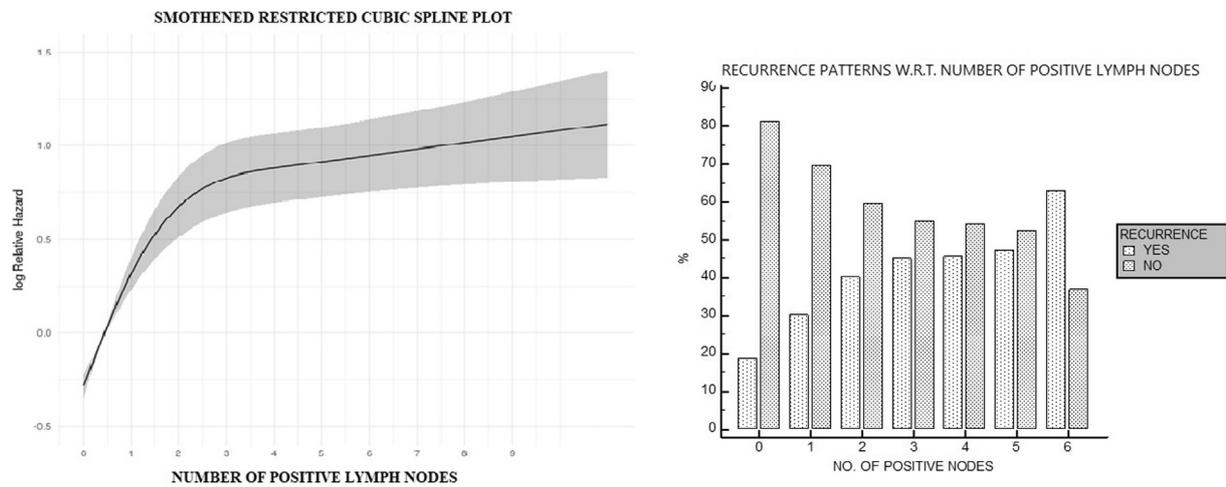
Fig. 1. Recurrence patterns based on number of nodes.

Table 2
Cox-regression analysis for disease free survival.

Prognostic Factor	Univariate analysis			Multi-variable analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Gender						
Male	1					
Female	0.98	0.74–1.30	0.921			
Tobacco						
No	1					
Yes	1.24	0.98–1.57	0.075			
LVI						
No	1			1		
Yes	2.06	1.65–2.57	< 0.001	1.08	0.81–1.43	0.592
PNI						
No	1			1		
Yes	1.68	1.36–2.07	< 0.001	1.28	1.02–1.61	0.031
AJCC T stage						
T1	1			1		
T2	2.15	1.48–3.12	< 0.001	1.71	1.16–2.49	0.006
T3	2.68	1.82–3.94	< 0.001	1.74	1.16–2.61	0.008
T4	2.51	1.64–3.81	< 0.001	1.71	1.10–2.63	0.017
ECE						
Negative	1					
Positive	1.3	0.97–1.74	0.078			
Positive nodes						
0	1			1		
1	1.74	1.31–2.31	< 0.001	1.46	1.06–2.02	0.021
2	2.48	1.79–3.43	< 0.001	2.01	1.39–2.90	< 0.001
> 2	3.35	2.53–4.42	< 0.001	2.57	1.84–3.60	< 0.001
Margin						
Adequate	1			1		
Close	1.32	1.06–1.64	0.011	1.13	0.91–1.41	0.279

Table 3
Cox regression analysis for disease free survival.

Prognostic Factor	Univariate analysis		
	HR	95%CI	p-value
AJCC 8TH Edition N stage			
N0	1	1	
N1	1.86	1.36–2.54	< 0.001
N2	2.11	1.56–2.85	< 0.001
N3	3.25	2.47–4.28	< 0.001
Number of positive nodes			
Node negative	1		
1	1.74	1.31–2.31	< 0.001
2	2.48	1.79–3.43	< 0.001
> 2	3.35	2.53–4.42	< 0.001
Number of positive nodes in all lymph node positive patients			
1	1		
2	1.41	0.96–2.06	0.075
> 2	1.91	1.35–2.68	< 0.001
Number of positive nodes in ECE positive group			
1	1		
2	1.42	1.36–3.61	0.297
> 2	2.33	1.31–4.15	0.004

shortcomings for this observation, firstly the trial included all head and neck cancers and cancers of oral cavity were just 1/4th of the cohort and secondly that it was an unplanned subset analysis. The question of importance of number of positive lymph nodes has been addressed recently by Ho et al. in their study where they stress upon the prognostic significance of number of positive lymph nodes as a continuous variable and have also proposed a new staging system for oral cancers incorporating only ENE and the number of positive lymph nodes. The proposed nodal staging is represented as N0, N1 (1 Lymph node (LN) ENE-)), N2 (2LN+/1 LN + and ENE +), N3a (3–7 LN), N3b (> 7LN) and this model in their study does better than the current AJCC 8th edition TNM nodal staging model [5]. Similarly, Ebrahimi et al. in their

study on oral cancer have categorised number of positive nodes as ≤ 2, 3–4 and ≥ 5 and have proposed a new staging incorporating these three categories as N2a, N2b and N2c which as per their study is prognostically better than original nodal staging [8]. Roberts et al. in their study including 12,437 patients of head and neck cancers suggested that number of positive lymph nodes model (0, 1, 2–4 and ≥ 5 lymph nodes) was superior to AJCC 7th edition N staging model [17]. Current AJCC nodal staging system includes site and size of lymph nodes for categorisation however many authors suggest that modelling with respect to number of positive lymph nodes and ENE performs better than multivariable nodal staging [5,8]. Contralateral node involvement is considered an aggressive disease and staged higher in the current staging, however these concepts of predictable patterns of stepwise lymph node drainage are 40 years old and recent lymphoscintigraphy studies have demonstrated unpredictable lymphatic drainage patterns are common and do not portend an aggressive behaviour [18,19]. The second criteria in nodal staging is size of the lymph node, the general consensus was that with increasing size of lymph node the chances of ENE increase and now since ENE is incorporated in new staging system the importance of size of lymph node remains to be known. In the present study we confirm the prognostic significance of number of positive nodes and observed that in all ENE positive patients also 1, 2

Table 4
Cox-regression analysis for Overall Survival.

Prognostic Factor	Univariate analysis			Multi-variable analysis		
	HR	95%CI	p-value	HR	95%CI	p-value
Gender						
Male	1					
Female	0.81	0.54–1.22	0.325			
Tobacco						
No	1					
Yes	1.21	0.87–1.68	0.246			
LVI						
No	1			1		
Yes	1.98	1.45–2.70	< 0.001	0.81	0.55–1.18	0.276
PNI						
No	1			1		
Yes	1.96	1.47–2.62	< 0.001	1.41	1.02–1.92	0.034
AJCC T stage						
T1	1			1		
T2	4.06	2.03–8.10	< 0.001	1.97	1.23–2.98	0.001
T3	6.23	3.11–12.5	< 0.001	2.53	1.53–4.20	< 0.001
T4	4.71	2.24–9.89	< 0.001	3.60	2.34–5.53	< 0.001
Positive nodes						
0	1			1		
1	2.21	1.51-3.23	< 0.001	3.22	1.60–6.47	0.001
2	2.80	1.76-4.45	< 0.001	3.88	1.89–7.97	< 0.001
> 2	4.28	2.94-6.22	< 0.001	3.21	1.51–6.84	0.002
Margin						
Adequate	1					
Close	1.33	0.99–1.79	0.062			

and > 2 positive lymph nodes had progressively worse survival with the finding being statistically significant with HR of 1.42 and 2.33 respectively (Table 3 and Fig. 4). Secondly in the present study it is also observed that there is better separation of Kaplan Meier curves when number of positive lymph nodes categories (0, 1, 2 and > 2) are used as opposed to AJCC 8th nodal staging (Fig. 3). Lastly, restricted cubic spline model of number of positive nodes had a lesser AIC as compared to conventional nodal staging conferring number of positive nodes to be a better model for prediction of recurrences. Similar to the results by Ho et al, we suggest that number of positive nodes to be an important prognosticator and increasing number of positive lymph nodes should form the basis of nodal staging as it is simpler and more effective way of categorisation as compared to the current multivariable nodal staging which is based on primitive concepts. However, the cut-offs points for number of positive lymph nodes in the present study did not seem to corroborate with other studies especially when ≥5 lymph nodes were
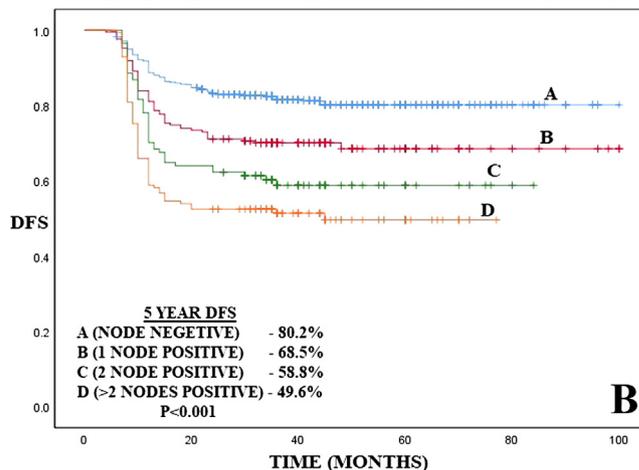
Fig. 3. Kaplan Meier curve showing disease free survival with respect to number of positive nodes.
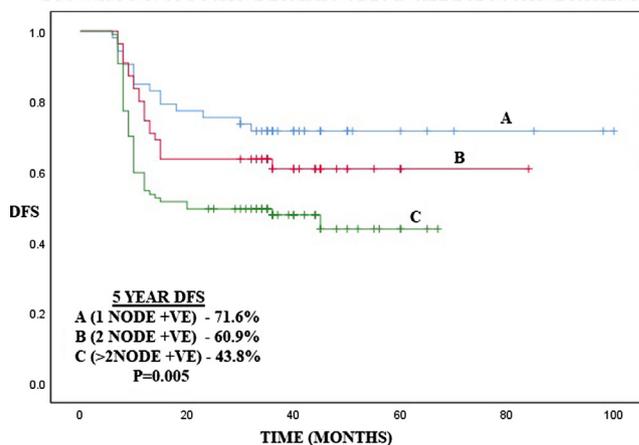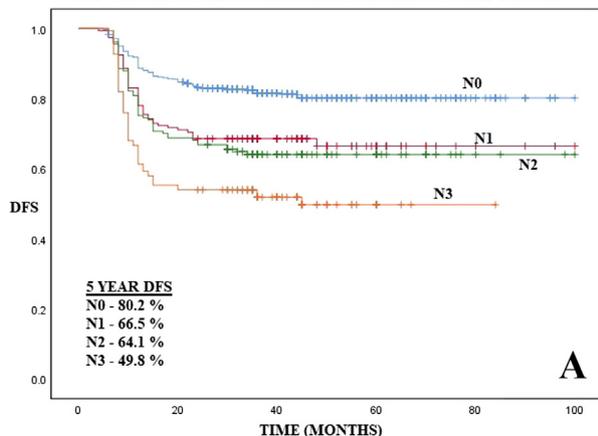
Fig. 4. Kaplan Meier curve showing disease free survival with respect to positive nodes with extracapsular extension.

considered as the number of patients in this group were less in comparison with other similar studies [5,17]. Second point to consider before we jump the gun is intensification of adjuvant therapy according to number of positive lymph nodes. There are no prospective trials addressing this issue in particular in oral cavity cancers. Lastly as this is
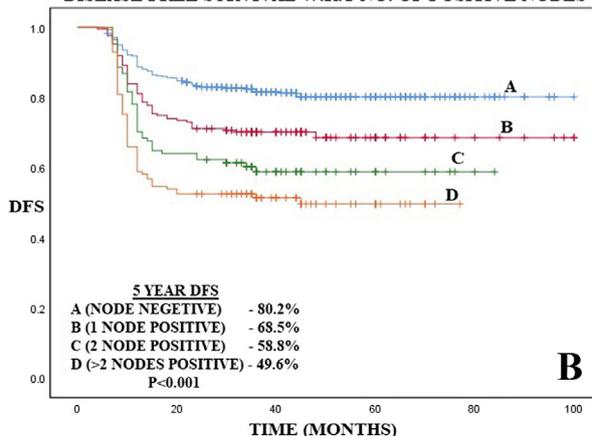
Fig. 2. Kaplan Meier curve showing disease free survival as per AJCC eighth edition nodal staging.

a single institution retrospective study generalising the observations of the study would be difficult and would need external validation. The strength of the study is the scarcity of data regarding number of positive lymph nodes and its effect on survival, long term follow-up data and good overall numbers for a single institution study.

Conclusion

Number of positive lymph nodes is one of the most important prognostic factor in oral cavity cancer and increase in number of positive lymph nodes has increasingly worse DFS even in patients with ENE. This model does better than the AJCC 8th nodal staging model and in future incorporation of number of positive lymph nodes in the staging system should be considered. We also suggest intensification of adjuvant chemotherapy to be considered for patients with higher number of positive lymph nodes, however further prospective studies would be required to back this suggestion.

Conflicts of interest

The authors declare that there are no known conflicts of interest.

References

[1] Katoch VM. Three-Year Report of Population Based cancer Registries 2012–2014. Bengaluru, India: National Centre for Disease Informatics and Research-National Cancer Registry Programme; 2016.

[2] Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(2):122–37.

[3] Marur S, Forastiere AA. Head and neck squamous cell carcinoma: update on epidemiology, diagnosis, and treatment. Mayo Clin Proc 2016;91(3):386–96.

[4] Amin MB, Edge S, Greene F, editors. AJCC Cancer Staging Manual. 8th ed.Springer International Publishing; 2017.

[5] Ho AS, Kim S, Tighiouart M, et al. Metastatic lymph node burden and survival in oral cavity cancer. J Clin Oncol. 2017;35:3601–9.

[6] Sinha P, Kallogjeri D, Gay H, et al. High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. Oral Oncol 2015;51:514–20.

[7] Ho AS, Kim S, Tighiouart M, et al. Association of quantitative metastatic lymph node burden with survival in hypopharyngeal and laryngeal cancer. JAMA Oncol 2017(November).

[8] Ebrahimi A, Gil Z, Amit M, et al. The prognosis of N2b and N2c lymph node disease in oral squamous cell carcinoma is determined by the number of metastatic lymph nodes rather than laterality: Evidence to support a revision of the American Joint Committee on Cancer staging system. Cancer 2014;120:1968–74.

[9] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(6):1471–4.

[10] Shibuya Y, Hasegawa T, Akashi M, Shigeta T, Minamikawa T, Komori T. Oral squamous cell carcinoma with multiple neck metastases–cases with more than ten pathologically positive lymph nodes in the unilateral side. J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2013;71(4):793–7.

[11] Liao C-T, Lee L-Y, Huang S-F, et al. Outcome analysis of patients with oral cavity cancer and extracapsular spread in neck lymph nodes. Int J Radiat Oncol Biol Phys 2011;81(4):930–7.

[12] Cerezo L, Millan I, Torre A, Aragon G, Otero J. Prognostic factors for survival and tumor control in cervical lymph node metastases from head and neck cancer: A multivariate study of 492 cases. Cancer 2010;69:1224–34.

[13] Mamelle G, Pampurik J, Luboinski B, Lancar R, Lusinchi A, Bosq J. Lymph node prognostic factors in head and neck squamous cell carcinomas. Am J Surg 1994;168(5):494–8.

[14] Liao C-T, Wang H-M, Chang JT-C, et al. Analysis of risk factors for distant metastases in squamous cell carcinoma of the oral cavity. Cancer 2007;110(7):1501–8.

[15] Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350(19):1945–52.

[16] Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350(19):1937–44.

[17] Roberts TJ, Colevas AD, Hara W, Holsinger FC, Oakley-Girvan I, Divi V. Number of positive nodes is superior to the lymph node ratio and American Joint Committee on Cancer N staging for the prognosis of surgically treated head and neck squamous cell carcinomas. Cancer 2016;122:1388–97.

[18] Chandler JR, Guillamondegui OM, Sisson GA, Strong EW, Baker HW. Clinical staging of cancer of the head and neck: A new "new" system. Am J Surg 1976;132(4):525–8.

[19] Spiro RH, Alfonso AE, Farr HW, Strong EW. Cervical node metastasis from epidermoid carcinoma of the oral cavity and oropharynx: A critical assessment of current staging. Am J Surg 1974;128(4):562–7.