Original Article

Ratio of Metastatic Lymph Nodes: A Significant Prognostic Factor in Patients with Oral Squamous Cell Carcinoma

Anshuman Kumar[1], Birsubhra Roy[2,✉], Hema Malini Aiyer[3], Garima Rawat[4]

[1]Department of Surgical Oncology, Clinical Lead- Academic Services, Dharamshila Narayana Superspeciality Hospital, New Delhi
[2]DJ College of Dental Sciences and Research, Modinagar, Ghaziabad, Uttar Pradesh
[3]Department of Pathology, Dharamshila Narayana Superspeciality Hospital, New Delhi
[4]Department of Pathology, Dharamshila Narayana Superspeciality Hospital, New Delhi

Abstract

Background: One of the significant prognostic factors for survival in squamous cell carcinoma of the oral cavity is the presence or absence of cervical metastasis. Thus, management of cervical lymph nodes becomes a vital component of the overall treatment strategy for patients with cancers of the head and neck. The aim of this study was to investigate the prognostic value of the ratio of metastatic lymph nodes in patients with oral squamous cell carcinoma.

Methods: A retrospective analysis of 225 biopsy-proven oral squamous cell carcinoma (OSCC) patients with T1-T4a status of the primary tumor was done. All cases had a history of surgical excision of the primary lesion and neck dissection with a follow-up period of two years. Primary tumor sites include viz buccal mucosa, tongue, alveolus, gingivo-buccal sulcus and retromolar trigone. Patients with loco-regionally advanced disease and a history of any previous surgery or radio-therapeutic treatment of the head and neck were excluded from the study. Locoregional recurrence, disease-free survival, and the associations between clinicopathological features and recurrence were analysed using univariate and multivariate analysis. p-value ≤ 0.001 was found to be significant. Survival curves were plotted using the Kaplan-Meier method for 5-year disease-free survival.

Results: The patients with positive lymph nodes were divided into high- or low-risk groups using the best nodal parameter cut-off values (0.06). Our univariate analysis showed a significant correlation between locoregional recurrence and type of neck dissection, pN classification, staging, extranodal extension, perineural invasion, and ratio of metastatic lymph nodes (RML). However, on multivariate analysis, RML showed an independent prognostic predictor (p= 0.04) for locoregional recurrence.

Conclusion: The findings of our study suggest that RML is a strong independent predictor of prognosis in patients with oral squamous cell carcinoma.

Keywords

Oral cancer; lymph node metastases; neck dissection; locoregional recurrence; Ratio of metastatic lymph node.

Corresponding Author

Dr. Birsubhra Roy
M.D.S. Oral & Maxillofacial Surgery
Assistant Professor, DJ College of Dental Sciences and Research
Modinagar, Ghaziabad, Uttar Pradesh
Email id-drbirsubhraroy@gmail.com

Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common malignancy worldwide.[1] With an estimated 2,63,900 new cases and 1,28,000 deaths per year, OSCC is a significant source of morbidity.[2] OSCC is the most common malignant tumor in the Asian subcontinent, accounting for about one-third of all malignancies. In India, it accounts for approximately 30-40% of all cancers.[3] The high incidence of oral cancer and oral potentially malignant disorders in India has been linked with the habit of betel nut and tobacco chewing, which is a major cause of mortality.[4]

Despite significant diagnostic and therapeutic advances, the prognosis

How to cite:
Kumar A, Roy B, Aiyer HM, et al. Ratio of Metastatic Lymph Nodes: A Significant Prognostic Factor in Patients with Oral Squamous Cell Carcinoma. Future Health 2023; 1(1):55-61.
Submitted: 22 May 2023
Accepted: 1 September 2023

of patients with OSCC has not improved in the past three decades[1], and survival rates remain below 50%.[5] Therefore, it is crucial to improve treatment outcomes by finding reliable prognostic factors and identifying head and neck cancer patients who are at high risk of locoregional recurrence.[6]

The American Joint Committee on Cancer (AJCC) or the Union for International Cancer Control (UICC) staging system for OSCC is based on primary tumor classification (T), on quantification of nodal metastases (N) according to size, number, and distribution, and on the presence of distant metastases (M).[7] However, pathologic lymph node status and current nodal classification may not necessarily predict prognosis.8 Apart from tumor node metastasis (TNM) staging, recent studies have shown the importance of other lymph-associated factors such as the exact number of positive nodes, total number of harvested nodes in the neck dissection, lymph node ratio, and the presence of extra nodal extension (ENE) as they can be the determinants of prognosis in OSCC.[9,10]

Local spread of the tumor occurs mostly through the lymphatic vasculature to the lymph nodes of the neck.[11] For this reason, the primary assessment of lymph nodes is imperative for staging and treatment planning. The lymph node ratio (LNR) or ratio of metastatic lymph nodes (RML) and lymph node yield (LNY) have been successfully validated as a strong predictor of survival with potential prognostic implications in oral cancer.[11,12] LNY is defined as the number of lymph nodes retrieved after neck dissection, whereas RML or LNR is defined as the ratio of pathologically positive lymph nodes to the total number of retrieved lymph nodes after neck dissection. However, accurate estimation of RML depends on the LNY, which has been shown to vary depending on anatomical, surgical, and pathological factors.[12-14] It is likely that a higher RML means that more potential, occult, pathological tissue has been removed, and for this reason, this should be a favorable prognostic factor. On the other hand, a lower RML may signify that few lymph nodes are positive out of the total removed, and thus, higher the survival rate. Furthermore, multiple studies indicated that the LNR is superior to the conventional nodal staging system and should be considered in daily clinical routine.[2,10,12] The main objective of this study was to determine the prognostic value of RML in patients with OSCC and to ascertain the association of locoregional recurrence with sex, type of neck dissection, stages, grading, LNY, ENE, and perineural invasion.

Materials and methods

In this retrospective study, clinicopathological data were collected from tertiary care hospital records of patients who underwent management for biopsy-proven OSCC between January 2017 and December 2018. The inclusion criteria were patients with a confirmed diagnosis of OSCC with T1-T4a status of the primary tumor and N0-N2b status of the lymph nodes. All cases had a history of surgical excision of the primary lesion and neck dissection with a minimum follow-up period of two years. Primary tumor sites included buccal mucosa, tongue, alveolus, gingivo-buccal sulcus and retromolar trigone. Patients with loco-regionally advanced disease not suitable for surgical resection, history of any previous surgery or radiotherapeutic treatment of the head and neck, patients not available for follow-up, cases with T4b tumors and N2c and N3 status of neck nodes were excluded.

The procedures were followed in accordance with the ethical standards of the committee on human experimentation of the tertiary care centre and in accord with the Helsinki Declaration of 1975, revised in 1983.

The parameters collected included age, sex, type of dissection, pathological node staging(pN), UICC stage, grading, extra nodal extension (ENE), perineural invasion (PNI), lymph node yield and RML. Surgical resection of primary tumor i.e. wide local excision depending upon tumor extension along with $\geq$ 1cm clear margins, was done in all patients. Patients who were clinically classified as cN0 received selective neck dissection (level I-III/IV), and those with clinically positive cervical lymph node status (cN1) were treated with a modified radical neck dissection of levels I-V with or without preserving sternocleidomastoid muscles or internal jugular vein depending upon radiological imaging. Depending on the type of resection i.e., soft tissue or soft tissue with hard tissue reconstruction was done. The adjunct procedures like radiotherapy or/and chemotherapy were given on a case-to-case basis. The histopathological staging was done according to the American Joint Committee on Cancer (AJCC), TNM classification system 8th edition. The resected specimen was sent for intraoperative margin assessment to confirm $\geq$ 1 cm negative margin status. Depending upon the final histopathological staging and other factors (RML, PNI, ENE, and Grading), adjuvant treatment was decided. Patients were then kept on regular follow-up visits for periods of two years for clinical evaluation of recurrence or local and regional metastasis.

Statistical analysis was performed using univariate and multivariate analysis to analyse the associations between clinic-pathological features and recurrence. The dependent variable was the presence of recurrence, and the independent variable was the clinicopathological parameters i.e., pathological staging, UICC stage, ENE, PNI, lymph node yield and RML. In multivariate analysis, the Cox proportional hazard model was used to estimate the impact of

significant patient and tumor-related factors from univariate analysis on locoregional recurrence. p-value $\leq$ 0.001 was considered to be statistically significant. 5-year disease-free survival (DFS) was calculated using the Kaplan–Meier method, and the log-rank test assessed the difference in survival rate.

Results

Hospital databases of 231 patients were retrospectively reviewed. Six of these patients were excluded because of previous primary surgery and radiotherapy history. 225 patients aged 30 to 80 years with a mean age of 50 years (Male, n=190, Female, n=35) were collected. All patients underwent primary surgery and neck dissection. 165 patients (73.3%) were also treated with adjuvant radiotherapy(RT) (with or without chemotherapy). A negative resection margin (>1 cm) was achieved in all patients. The staging was dominated by patients with a stage IV tumor (41.7%), followed by stage III (25.3%), stage II (19.5%), and stage I (13.3%). Primary tumor (pT) in patients was confirmed histopathologically after surgery, where 29.3% of patients revealed T2 tumors. The conventional pathological staging of the lymphatic metastasis (pN) was done in 225 patients where the majority of patients showed N0 (63.1%) status and N3b in nearly 12.9% of patients. Specifically, the percentage of ENE was positive in 39 (17.3%) and negative in 186 (82.6%) patients.

In this cohort, patients with more nodal yield and positive lymph nodes were found to be associated with poor outcomes. The patients with positive lymph nodes were divided into high- or low-risk groups using the best nodal parameter cut-off values(0.06). Of the 83 patients with positive lymph nodes, 47 had RML $\leq$0.06, and 36 had RML $\geq$0.06. The results of our univariate analysis revealed RML (p=0.02), a significant prognostic indicator for locoregional recurrence and 5-year DFS. We also found a significant correlation between locoregional recurrence and pN classification (p=<0.001), pathological staging (p=<0.001), grading (p=0.004), ENE(p=<0.001), PNI (p=<0.001), and RML (p=0.02). Therefore, patients with high RML underwent more adjuvant RT or concurrent chemoradiotherapy (CCRT) than those with low RML. (Table 1)

To further investigate whether RML predicts the prognosis of patients, a multivariate analysis was constructed where RML was shown as an independent risk factor for locoregional recurrence (p=0.04). Thus, RML $\leq$0.06 was associated with better locoregional control and DFS. Interestingly, histopathological grading was also found to be a significant predictor for DFS and locoregional control in multivariate analysis. However, other variables, including conventional N classification, were not determined as an independent risk factor for locoregional recurrence(Table 2).

DFS for N0 and N+ neck was 90.1% and 56.6%, respectively. Out of 36 patients with N+ presented with recurrence, 15 had RML $\leq$0.06, and 21 had RML $\geq$ 0.06. The five-year DFS curves were plotted, and the risk of locoregional recurrence was higher for patients with RML $\geq$0.06. (Figures 1 and 2).

Discussion

Locoregional recurrence is an important factor for morbidity in 15-50% of patients with Head and Neck squamous cell carcinoma (HNSCC).[15] The standard of care for patients with recurrent OSCC is more complex and includes combined treatment modalities such as salvage therapy, radiotherapy, chemotherapy, and CCRT.[15] Various factors predispose to locoregional recurrence and affect the prognosis. The absence or presence of cervical lymph node metastases is the solitary prognostic factor in OSCC. Thus, the management of the neck is obligatory if metastases to the cervical lymph nodes are clinically visible. Our statistical analysis found that cervical lymph node metastasis was significantly associated with locoregional recurrence (p = <0.001) for patients with OSCC.

Numerous studies show that conventional N staging, PNI, ENE, grading, and resection margin status were crucial predictors for poor prognosis.[12,16-19,23] Usually, a traditional N classification is associated with a higher risk of locoregional failure, worsening the prognostic outcome.[9,12] In this study, we found that 19% of patients with pN0 showed locoregional recurrence, whereas 30% of patients with pN+ experienced locoregional recurrence. However, the results of our univariate analysis show traditional N staging to be a significant prognostic indicator (p= <0.001), which is similar to the study by Safi et al[10], Lee et al.,[20] and Patel et al.[12] who found a significant correlation between locoregional recurrence and classification. However, multivariate analysis did not prove N classification to be a significant predictor for prognosis. Various literature has demonstrated the shortcomings of conventional N staging in predicting locoregional recurrence.[2,10,12,21]

Lymph node status is primarily based on sampling of lymph nodes and secondarily on examination by a pathologist. The RML has been described as a significant predictor of good disease-free outcomes in patients with OSCC. This ratio weighs three factors that can potentially influence nodal staging viz; tumor factors (number of positive lymph nodes), surgical factors (number of lymph nodes dissected during neck dissection and sampling factors (completeness of the pathological analysis, including those related to surgeon and pathologist).[2] In recent years, multiple studies have exhibited the influence of RML as a risk factor in locoregional recurrence in oral cancer. The

Table 1. Univariate Analysis of loco-regional recurrence factors

VARIABLES	NO. OF PATIENTS, n(%)	RECURENCE(n)	p-VALUE
SEX			0.21
MALE	190(85%)	45	
FEMALE	35(15%)	05	
NECK DISSECTION			
SOHND (I-III/IV)	12 (5.3%)	01	0.01*
MRND (I-V)	180 (80.0%)	34	
RND	03 (1.3%)	02	
B/L	30 (13.3%)	13	
p- N			
N0	142 (63.1%)	14	
N1	22 (9.7%)	7	<0.001*
N2	30 (13.3%)	10	
N3	31 (13.7%)	19	
STAGE			
I	30 (13.3%)	1	
II	44 (19.5%)	5	<0.001*
III	57 (25.3%)	13	
IVA	60 (26.6%)	11	
IVB	34 (15.1%)	20	
GRADING			
G1	104 (45.2%)	14	0.004
G2	109 (48.5%)	30	
G2	12 (5.3%)	6	
EXTRA-NODAL EXTENSION (ENE)			
-VE	186 (82.6%)	00	<0.001*
+VE	39 (17.3%)	22	
PERINEURAL INVASION			
NO	191 (84.8%)	00	<0.001*
YES	34 (15.1%)	12	
LYMPH NODE YIELD (LNY)			
0-20	14	03	0.434
21-40	129	24	
41-60	62	18	
61-Above	20	05	
RATIO OF METASTATIC LYMPH NODES FOR N+ NECK			
<0.06	47	15	0.02*
>0.06	36	21	

Table 2. Multivariate analysis of significant parameters

Variables	Hazard ratio	P value	95% Confidence interval
1. Lymph node density (RML) (<0.06 VS >0.06)	1.72	0.04*	0.65-6.99
2. Grading (G1/G2 vs G3)	3.27	0.09*	0.82-13.33
3. ECE (Negative vs Positive)	1.89	0.19	0.49-11.39
4. Stage (I+II+III+IV)	2.16	0.44	0.31-15.08

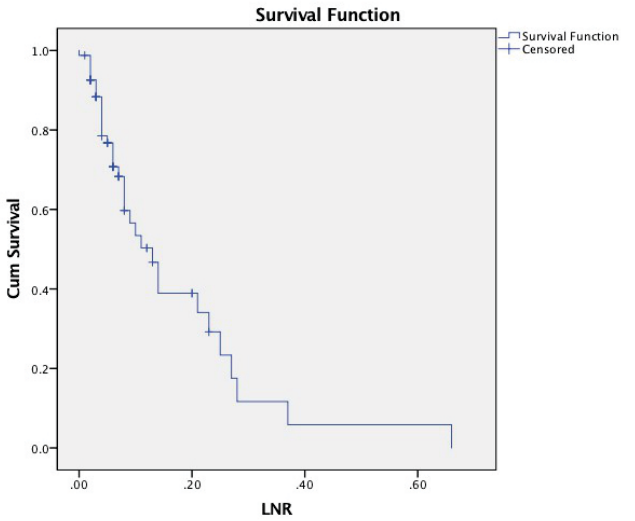

Figure 1. Disease-free survival rates calculated using Kaplan Meier method in patients with RML/LNR ≤0.06 (n=15)

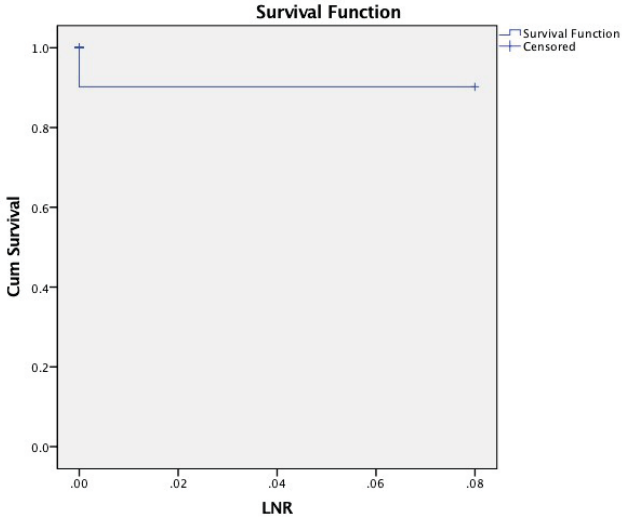

Figure 2. Disease-free survival rates calculated using Kaplan Meier method in patients with RML/LNR ≥0.06 (n=21)

results of our univariate(p=0.02) and multivariate analysis (p=0.04) also show that RML is superior to conventional N staging in predicting disease-free survival and locoregional recurrence.

Furthermore, the patients with positive necks were divided into two subgroups with a cut-off value of 0.06, in accordance with the study by Shah and Gill2, who used a cut-off value of 0.06 (RML threshold,6%). We found that patients with RML > 0.06 have a higher risk of locoregional recurrence (0.02). The Kaplan-Meier analysis revealed that patients with RML > 0.06 have poor disease-free survival, which revealed that patients with RML < 0.06 are associated with recurrence-free survival.

Potential errors in the resection or evaluation of lymph nodes are one of the major drawbacks due to its dependence on surgical technique and sampling by pathologists.[13] However, to eliminate such errors, this study did not include patients with an RML score of zero; selective neck dissection with low nodal yield and high RML, as it cannot assess the extent of the disease, ultimately leading to poor prognosis. Shrime et al[22] have demonstrated that high RML is correlated with inadequate surgical resection and thus requires adjuvant treatments. In this study, LNY has clearly shown a significant correlation with locoregional recurrence as patients with smaller nodal yield have poor prognosis compared to patients with more nodal yield. For example, a patient with 2 positive lymph nodes among 20 lymph nodes examined has a better prognosis than a patient with 2 positive lymph nodes out of 6 excised lymph nodes, leading to higher RML. Similar to our article, Ebrahimi et al[9] found that the prognostic significance of RML may be baffled by a limited number of resected lymph nodes or nodal yield. Thus, they suggested proper surgical technique, thorough pathological analysis, and tumor factors to reduce the incidence of loco-regional recurrence. Interpretation of the anatomical groups and proper labelling of the specimen by the surgeon can improve the accuracy of neck dissection and the precise analyses and processing by a pathologist rendering a good prognosis.

Univariate analysis shows other pathological markers, including, ENE and PNI to be significant in reference to locoregional control. However, the results of our multivariate analysis do not prove pathological markers (ENE and PNI) to be independent significant indicators for prognosis. It was also found that locoregional recurrence is closely associated with ENE status (p= <0.001) which is similar to other researchers who found that the presence of ENE with metastatic lymph nodes is associated with recurrent disease and requires adjuvant treatment protocols.[23,24] PNI has shown to be a valuable marker for predicting recurrence and disease-free survival (DFS) 25 similar to the results of our statistical analysis (p= <0.001).

The current edition of WHO classification head and neck tumors[26] differentiates grading systems as low, moderate, and high according to the Broders system of tumor grades. Moreover, they stated that histopathological grading is not independently associated with locoregional recurrence, which is supported by many studies indicating the shortcomings of the prognostic significance of the grading system.[27,28] Although the present study revealed grading to be significant independently in association with the recurrence of primary tumor (p=0.09). Further studies on the importance of grading in the prognosis of patients with relapse are suggested as it requires more validations to be potentially effective.

The limitations of the present study are the potential inconsistency in neck dissection and processing of pathological specimens that affect the outcome. Therefore, we believe that potential errors can be retrieved by the quality of surgical technique by meticulous dissection of lymph nodes during neck dissection. The current study was also limited by its retrospective design and moderate sample size. Indeed, it lacked the statistical power to include other prognostic factors and their association with locoregional recurrence in multivariate analysis. However, the indication of adjuvant treatment in patients with high LNR should be taken into consideration for further research.

Conclusion

RML has proven to be an independent risk factor for the prognosis of patients with N+ disease, and high RML≥ 0.06 was associated with poor prognosis. In patients with N0 neck, the effectiveness of RML needs more literature evidence for further validation. To assess the prognostic behavior of RML as a reflection of tumor behavior, the potential errors affecting RML (dissection and examination of lymph nodes) should be minimized by standardized surgical and pathological protocols. However, the author further suggests that there is a need for well-planned multi-center prospective studies with long follow-up of OSCC cases and their biological behavior in relation to RML.

Financial Support

None

Conflict of Interest

None

References

1. Jemal A, R Siegel, E Ward, Y Hao, J Xu and MJ Thun. Cancer statistics. CA Cancer J Clin. 2009;59(4):225-249.
2. Gil Z, Carlson DL, Boyle JO, et al.Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer.2009;115(24):5700–5710.
3. Kadam CY, Katkam RV, Suryakar AN, Kumber KM, Kadam DP. Biochemical markers in oral cancer. Biomedical Research. 2011;22(1): 76-80.
4. Sankaranarayanan R.Oral cancer in India: An epidemiologic and clinical review.Oral Surg Oral Med Oral Pathol. 1990;69(3):325-330.
5. Vormittag L, Thurnher D, Geleff S, et al.Co-expression of Bmi-1 and podoplanin predicts overall survival in patients with squamous cell carcinoma of the head and neck treated with radio(chemo)therapy. Int J Radiat Oncol Biol Phys 2009;73(3):913-918.
6. Chien-Chih Chen, Jin-Ching Lin, Kuan-Wen Chen. Lymph node ratio as a prognostic factor in head and neck cancer patient. Radiat Oncol.2015;10:181.
7. Patel SG, Shah JP.TNM staging of cancers of the head and neck: striving for uniformity among diversity. CA Cancer J Clin. 2005;55(4):242–258, quiz 261-2, 264.
8. Shingaki S, Takada M, Sasai K,et al. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. Am J Surg. 2003;185(3):278–84.
9. Ebrahimi A, Zhang WJ, Gao K, Clark JR. Nodal yield and survival in oral squamous cancer: Defining the standard of care. Cancer. 2011;117(13) :2917-25.
10. Safi A.F, Grandoch A, Nickenig HJ, Zoller JE, Kreppel M. Importance of lymph node ratio for locoregional recurrence of squamous cell carcinoma of the buccal mucosa.Head Neck. 2017;39(12):2488-2493.
11. Locca O,Farcomeni A, Armando De V, et al.Prognostic significance of lymph node yield and lymph node ratio in patients affected by squamous cell carcinoma of the oral cavity and oropharynx: Study protocol for a prospective, multicenter, observational study.Contem Clin Trials Commun. 2009;14:100324.
12. Patel SG, Amit M, Yen TC, et al. Lymph node density in oral cavity cancer: Results of the International Consortium for Outcomes Research. Br J Cancer. 2013;109(98):2087-95.
13. Marres CC, Ridder M, Hegger I, et al. The influence of nodal yield in neck dissections on lymph node ratio in head and neck cancer. Oral Oncol. 2014;50(1):59-64.
14. Friedman M, Lim JW, Dickey W, et al. Quantification of lymph nodes in selective neck dissection. Laryngoscope.1999;109(3):368-70.
15. Jer-Hwa Chang, Chia-Che Wu, Kevin Sheng-Po Y, Alexander T.H. Wu, Szu-Yuan Wu.Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors and treatment outcomes. Oncotarget 2017;8(33):55600-12.
16. 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):494–498.
17. Pentenero M, Gandolfo S, Carrozzo. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. Head Neck. 2005;27(12): 1080–1091.
18. Diaz EM Jr, Holsinger FC, Zuniga ER, Roberts DB, Sorensen DM. Squamous cell carcinoma of the buccal mucosa: one institution's experience with 119 previously untreated patients. Head Neck. 2003;25(4): 267–273.
19. Larsen SR, Johansen J, Srensen A, Krogdahl A. The prognostic significance of histological features in oral squamous cell carcinoma. J Oral Pathol Med.2009; 38(8):657-62.
20. Lee C. C, Y. S. Lin, B. H. Kang, et al.Incorporation of log odds of positive lymph nodes into the AJCC TNM

classification improves prediction of survival in oral cancer. Clin Otolaryngol. 2017;42(2):425-432.

21. Kim SY, Nam SY, Choi SH, Cho KJ, Roh JL.Prognostic value of lymph node density in node-positive patients with oral squamous cell carcinoma. Ann Surg Oncol. 2011; 18(8):2310-17.
22. Shrime M. G, Bachar G, Lea J, et al.Nodal ratio as an independent predictor of survival in squamous cell carcinoma of the oral cavity. Head Neck. 2009; 31(11):1482-88.
23. Kwon M, Roh J, Lee J, et al.Extranodal extension and thickness of metastatic lymph node as a significant prognostic marker of recurrence and survival in head and neck squamous cell carcinoma.J CranioMaxillofac Surg. 2015;43(6):769-778.
24. Bernier J, Cooper J, Pajak T, et al.Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck.2005; 27(10):843-50.
25. Shaw R, Brown J, Woolgar A, Lowe D, Rogers S, Vaughan E.The influence of the pattern of mandibular invasion on recurrence and survival in oral squamous cell carcinoma. Head Neck. 2004;26(10):861-69.
26. El- NaggarAK, Chan J, Grandis J, Takata T, Slootweg P. The Fourth editionof the head and neck World Health Organization blue book: editors' perspectives.Human Pathol.2017; 66:10–12.
27. Almangush A, Bello IO, Harri Keski–Santti H, et al. Depth of invasion, tumor budding, and worst pattern of invasion: Prognostic indicators in early-stage oral tongue cancer. Head Neck. 2014;36(6):811-8.
28. Dik EA, Ipenburg NA, Kessler PA, van Es RJJ, Willems SM. The value of histological grading of biopsy and resection specimens in early stage oral squamous cell carcinomas. J Craniomaxillofac Surg. 2018; 46(6): 1001-6