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A Prognostic Model to Predict Nodal Metastasis in Oral Squamous Cell Carcinoma Patients

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Original Article

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ABSTRACT

Background: The incidence of oral squamous cell carcinoma (OSCC) is increasing globally and is a leading cause of death accounted for 8.8 million deaths. It is one of the most common cancers in the Indian male population. The survival rates have not improved significantly despite the advances in technology and treatment protocols. Difficulty in precise decision making on the necessity of surgery is a major problem when managing oral squamous cell carcinomas (OSCCs) with a clinically negative neck. Therefore, the use of clinical and histopathological parameters in combination would be important to improve patient management. This study is designed is an attempt to predict nodal metastasis by histopathological parameters.

Aim and Objective

- The main objective is to develop a model that predicts the presence of nodal metastasis in patients with OSCC.

Material Methods

- 100 Patients faced neck dissections with buccal mucosa, vestibule, or complex & tongue squamous cell carcinoma were selected from patients' recorded between 2018 and 2020 were retrospectively studied, from archives of the Department of Oral Pathology and Microbiology, Rural dental college, loni.
- Demographic data including age, gender, and clinical information such as the size of the tumor (T), primary site, and pathological factors such as (Pattern of invasion (POI), depth of invasion (DOI), and lymph node metastasis) were recorded.

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Results and Conclusion: Results showed statistically significant associations between the status of nodal metastasis and each of the following four histopathological parameters individually: the size of the tumor (T), site, a pattern of invasion (POI), and Depth of invasion (DOI). This model showed that the probability of nodal metastasis is higher among tongue carcinoma with increasing POI, with increasing T, and with larger depths while other characteristics remained unchanged. The proposed model provides a way of using combinations of histopathological parameters to identify patients with higher risks of nodal metastasis for surgical management.

Keywords: Oral Squamous, Cell Carcinoma, Nodal Metastasis, Pattern of Invasion, Depth of Invasion.

Introduction

There are Diverse malignant tumors of various cellular lineages originate in the oral cavity. Among all these, squamous cell carcinoma (SCC) constitutes a significant proportion, comprising 90-95% of head and neck cancers.[1] Oral squamous cell carcinoma (OSCC) is of significant public health problem in India, and it accounts for approximately 30% of all cancers in the country.[2] Severe alcoholism, use of tobacco like cigarettes, smokeless tobacco, betel nut chewing, and human papillomavirus (HPV) are the most common risk factors for oral cancer.[3] The incidence of oral squamous cell carcinoma (OSCC) is increasing globally and is a leading cause of death accounted for 8.8 million deaths in 2015. It is one of the most common cancers in the indian male population. And it causes substantial chances of mortality and morbidity.[4]

Despite enormous advancements in the field of diagnostics and therapeutics, the overall survival rate in most countries ranges between 45% and 50% and has not shown significant improvement during the past few decades.[1]

The prognosis of OSCC depends on multiple factors. But among them, the Tumor stage and lymph node (LN) status are the 2 most important factors that determine the treatment plan and outcome. Lymph node metastasis is best determined by histological examination of the resected Lymph nodes. Clinical examination and radiological investigations show a sensitivity of 60% to 70% to detect nodal metastasis.[5]

The presence of lymph node metastasis diminishes locoregional control rates and is the most important factor for prognosis in head and neck cancer. Accurate clinical staging of the neck and the appropriate choice of neck dissection type is crucial in treatment planning. Radical or modified radical neck dissections that include levels I–V are widely used treatments for patients with clinically positive lymph nodes (N+). However, selective neck dissections are increasingly being used to treat select N+ patients in order to avoid the functional and cosmetic morbidities associated with comprehensive neck dissections.[6]

This metastatic spread is mostly done through lymphatic to the cervical lymph nodes of the same side of the face. Further, extracapsular extension in some patients is followed by a poor prognosis, including increased risk of regional recurrence, distant metastasis, and reduced survival rate.[7]

The management of clinically negative neck nodes (N0) poses a significant challenge for surgeons, as there are no reliable parameters to predict occult metastasis. In order to identify patients who are likely to have nodal metastases, several parameters like tumor differentiation, perineural invasion, lymph vascular invasion, pattern of invasion (POI) and depth of invasion (DOI) have been previously studied. Although most

authors substantially agree that DOI is an important parameter for nodal metastasis and survival, the results vary in the literature and there is no cut-off point to prompt neck dissection.[8, 9]

Models based on multiple variables that predict outcome in terms of lymph node metastasis seem to be more accurate than prediction based on single variables.[10] Hence, the prediction of metastasis will enable the surgeon to select the best mode of treatment to improve the prognosis. We, therefore, aimed to evaluate the association between DOI, POI, and occurrence of metastasis of Oral squamous cell carcinoma.

Aims and Objectives

1. To evaluate the associations between these clinical parameters and the presence of nodal metastases,
2. Develop a simple model for predicting nodal metastasis.
3. To identify combinations of clinical parameters that can be used as a screening tool for nodal metastasis that can be used for oral squamous cell carcinoma (OSCC) patients.

Material and Methods

This is a retrospective type of Descriptive cross-sectional study, a review of 100 patient records, and preserved biopsy slides performed in Rural Dental College, Loni (Maharashtra). The study was carried out within a duration of 2 years. In the Department of Oral Pathology & Microbiology, Rural Dental College, Loni. Ethical clearance for the study was obtained from the Institutional Ethical Review Committee.

- All patients who underwent surgery for Oral Squamous cell carcinoma (OSCC) with neck dissection between 2018-2020 were studied.
- The cases were selected from archives of the Department of Oral Pathology and Microbiology.
- Demographic data including age, gender, and clinical information such as the size of the tumor (T), primary site, and pathological factors such as (Pattern of invasion (POI), depth of invasion (DOI), and lymph node metastasis) were recorded.
- The full width of the tumor in a single section is not possible in a certain section, which prevented the accurate depth of measurement of the depth of tumor. we recorded the DOI of these sections and used in the analysis as a lower end for the actual tumor depth.
- Patients were categorized as the age above >40and below <40 years for the purpose of analysis. Depth was categorized into five groups; four 1mm groups and one group containing 5mm or more depths. The Association between each variable and the presence of nodal metastasized was assessed using the chi-square test.

Arrangement of Tumor Cells at the Invasive Front was Graded as Shown in (Figure: 1-4)

1. Large cohesive tumor islands (POI-I)
2. Small islands (POI-II)
3. Thin islands (POI-III)
4. Individual tumor cells (POI-IV)

International Journal of Drug Research and Dental Science
Volume 2 Issue 3 (Page: 77-86), 2020 ISSN: 2582-0826

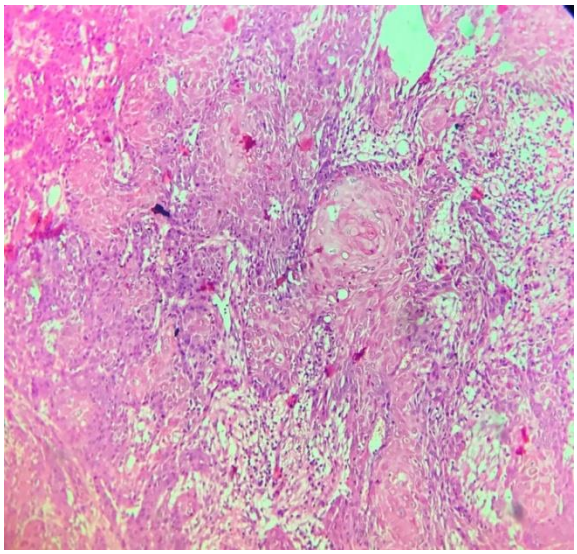

Figure: 1 Large Cohesive Tumor Islands (POI-I)

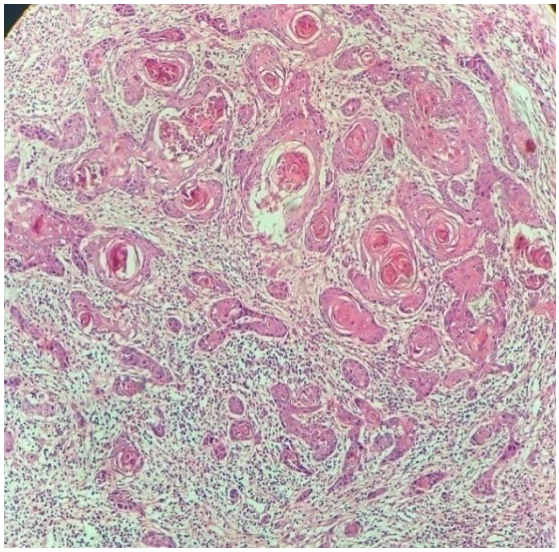

Figure: 2 Small Islands (POI-II)

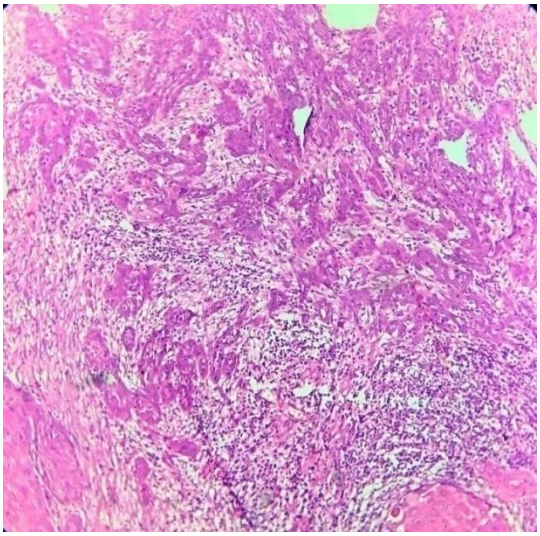

Figure: 3 Thin strands (POI-III)

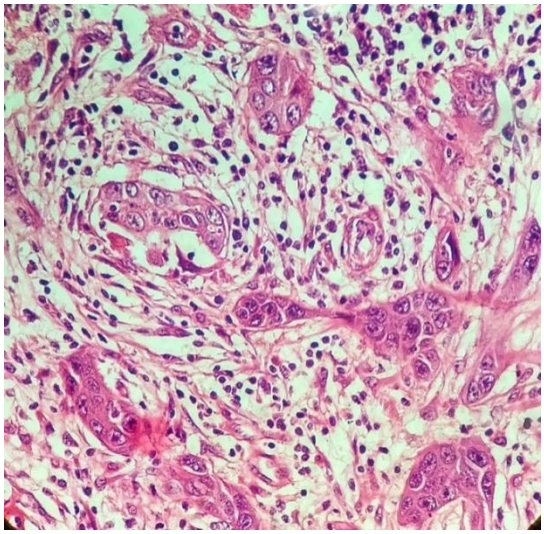

Figure: 4 Individual tumor cells (POI-IV)

- Depth of invasion (DOI) was obtained from histological sections following the standard method of measuring the distance from the deepest point of infiltration to the basal layer of the overlying epithelium.

International Journal of Drug Research and Dental Science
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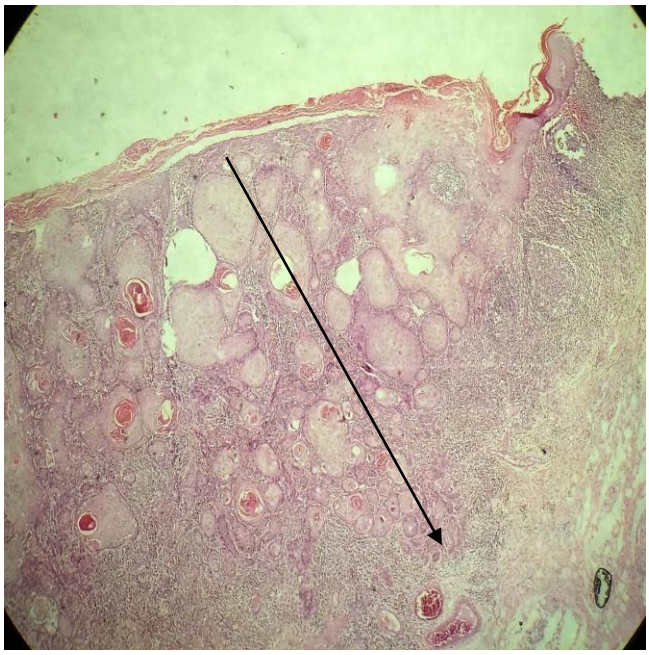

Figure: 5

- The depth was taken from an imaginary line at the basement membrane of the healthy oral mucosa to the deepest point of tumor invasion as shown in figure 5.

➢ **The Patients were Selected after Applying the Following Inclusion and Exclusion Criteria's:**

Inclusion Criteria

1. All patients who underwent surgery for OSCC with neck dissection between 2016 and 2019 were retrospectively studied.
2. Demographic data including age, gender, and clinical information such as the size of the tumour (T), primary site, and pathological factors (POI, lymph node metastasis) will be recorded.

Exclusion Criteria

1. Patients of oral squamous cell carcinoma having psychological disorders.
2. Patients of oral squamous cell carcinoma undergoing any major surgery involving carotid and coronary interventions.
3. Patients with recurrent tumors or extensive tumors involving multiple intraoral sites were excluded.

Risk: No risk to a human while performing the study.

Statistical-Analysis

The parameters which will show significant association with nodal metastasis were analyzed by descriptive statistics as mean, SD, and percentage/proportion, etc. Association was done by applying the Chi-square test at 5% (p, 0.05) and 1% (p, 0.01) level of significance. Statistical analysis software namely SYTAT version 12 (By Crane's Software, Bangalore) was used to analyze data.

International Journal of Drug Research and Dental Science
Volume 2 Issue 3 (Page: 77-86), 2020 ISSN: 2582-0826

Clinical Parameters	Nodal Metastasis Absent n= 66	Nodal Metastasis Present n= 34	p-value
AGE (years)			
40 or Below	23(34.85%)	11(32.35%)	Value of χ^2 = 0.0017, p=0.9674, not significant
41 or above	43(65.15%)	23(67.65%)	
Sex			
Female	21(31.81%)	10(29.41%)	Value of χ^2 = 0.0097, p=0.9402, not significant
Male	45(68.19%)	24(70.59%)	
Primary site of cancer			
Buccal muosa	22(33.33%)	10(29.42%)	Value of χ^2 = 9.0678, p=0.0119, significant
Tongue	18(27.27%)	12(35.29%)	
Retromolar area	9(13.64%)	5(14.70%)	
Vestibule	17(25.76%)	7(20.59%)	
Size of Tumor (T)			
T1	11(16.67%)	4(11.76%)	Value of χ^2 = 12.987, p=0.0094, significant
T2	29(43.94%)	7(20.59%)	
T3	12(18.18%)	10(29.41%)	
T4	14(21.21%)	13(38.24%)	
Pattern of invasion(POI)			
I	6(9.09%)	3(8.82%)	Value of χ^2 = 12.024, p=0.0090, significant
II	9(13.64%)	6(23.53%)	
III	29(43.94%)	10 (23.53%)	
IV	22(33.33%)	15(29.42%)	
Depth of invasion(DOI)			
Less than < 4mm	21(31.82%)	13(38.23%)	Value of χ^2 = 6.347 p=0.0321, significant
Above > 4mm	45(68.18%)	21(61.777%)	

Table1. Univariate Relationships between Clinical Parameters and Presence of Nodal Metastasis

International Journal of Drug Research and Dental Science
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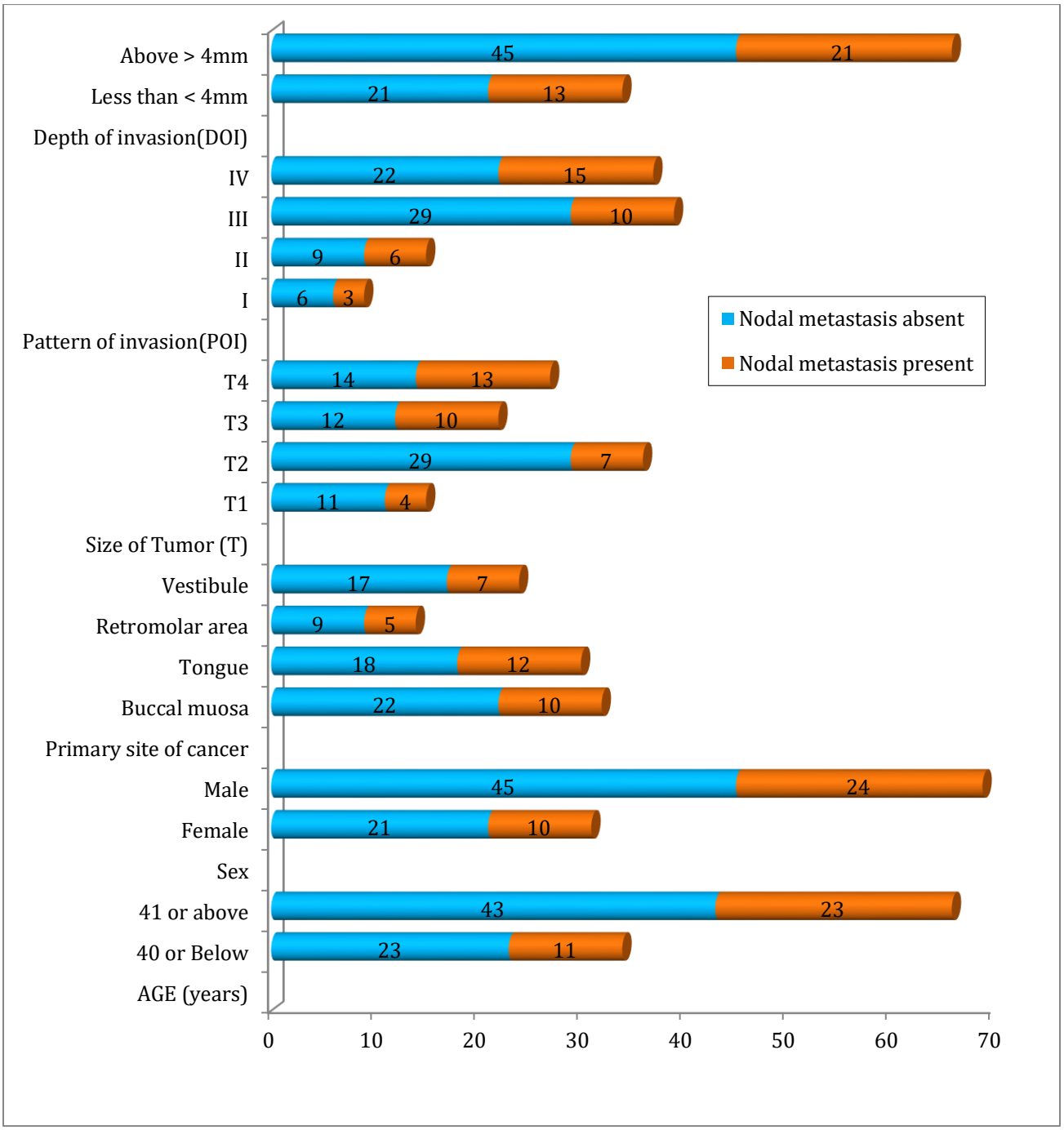

Relationships between Clinical Parameters and Presence of Nodal Metastasis

Results: By applying the Chi-square test there is a significant association found between the primary site of cancer, Pattern of invasion (POI), and Size of Tumor (T), depth of invasion (DOI), and presence of nodal metastasis ($p<0.001$). Majorities were males above 40years of age, 55% cases had cancer of the

tongue, the majority of cases were (POI) Type III & IV, and 45% were in T2 and almost equal numbers in T3&T4. More than half (57%) have more than (>4mm) Depth of invasion. All these associations were statistically significant. However such associations were not found to be significant with regard to age or gender.
Our descriptive and univariate analyses showed a significant association between DOI and nodal metastasis; however, in contrast to what was observed with POI and T, a dose-response relationship was not observed in this association. One possible reason for this could be the censored DOI measurements.

Discussion: The prognosis of oral cavity cancers depends on multiple clinical and pathological parameters. A significant percentage of patients with early stages of OSCC has a Poor prognosis despite the small size of the tumor.[11,12,13] Hence, the TNM staging system used in clinical practice does not provide information on the biological characteristics and aggressive clinical behavior of oral SCC. Lymph node metastasis is considered as an independent poor prognostic factor for OSCC. Histological examination of the excised cervical Lymph Nodes is the gold standard to detect the presence of Lymph Node Metastasis. In fact, Radiological investigations such as computed tomography scans are routinely been used to determine Lymph Node metastasis, but with variable sensitivity.[14] At present, it is generally accepted that elective neck dissection is indicated for patients presenting with OSCC with a clinically N0 if the reported risk of occult metastases exceeds 15% - 20%.[15]

Shah et al 1990 carried out a study revealed that even in the clinically node-negative neck, nodal metastases were present in levels I-IV in up to 40% of neck dissections. PET/CT and CT and/or MRI imaging are being commonly used in developed countries to diagnose distant nodal metastasis in patients presenting with OSCC. But is controversial and it is not practical in most developing countries due to the lack of modern facilities.

So far it is evident that the most significant determinant of overall survival in patients with OSCC is the cervical lymph node metastasis that is associated with a 50% decrease in survival rate.[16,17] Due to the fact that the detection of micrometastases and metastases of the clinically negative neck is difficult, many cancer researchers were persuaded to develop predictive models to predict metastasis, recurrences, and survival. Our study specifically designed to develop a model to predict the likelihood of nodal metastasis by using clinical and histopathological parameters rather than depending on the existing literature.

Our data showed a higher proportion of nodal metastasis in increased tumor size cases and tongue cancer patients. The greatest diameter of the tumor surface shows a significant association with nodal metastasis. The tongue is characterized by a rich supply of lymphatic vessels and neurovascular bundles hence having increased nodal metastasis in patients with tongue cancers.[18,19]. Dissanayaka et al 2012 found a significant association between the pattern of invasion (POI) of the tumor and metastasis of the tumor to regional lymph nodes. The results of the current study show tumors invading with POI 3 and 4 show a higher tendency to metastasize compared to tumors with POI 1 and 2 hence a significant association, the pattern of invasion with cervical nodal metastasis.[20] Breslow et al measured the Depth of invasion (DOI) vertically, starting from the surface of the tumor or from the base of the ulcer to the deepest point of invasion. Our univariate analyses showed a significant association between DOI and nodal metastasis.[21,22,23] DOI alone may not predict nodal metastasis with high accuracy. We hypothesized that the use of these parameters together may increase the accuracy of predicting nodal metastasis. Therefore, we used these four parameters to develop a multivariate logistic model which predicts the possible presence of nodal metastasis more accurately.

Conclusion: In our study 66% of the patients did not have neck metastasis yet undergone elective neck dissections, this model showed that the probability of nodal metastasis is higher among tongue/buccal mucosa cancers with increasing POI, with increasing size of the tumor (T), and with larger depths while other characteristics remained unchanged. The proposed model provides a way of using combinations of histopathological parameters to identify patients with higher risks of nodal metastasis for surgical management.

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