

The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is a neoplasm that originates from the epithelial mucosa of oral cavity. More than 90% of carcinomas of the oral cavity are Squamous Cell Carcinoma (SCC). Tobacco, alcohol and HPV are considered to be the primary risk factors. The most common intra-oral site for head and neck cancers is the tongue.

Neck nodal metastasis has been established as the predictor of survival for oral cavity tumors. Neck dissection is mandatory if the risk of nodal metastasis is >15-20%. Tumor Thickness (TT) and Depth of Invasion (DOI) represent the most important prognostication in terms of loco-regional control and survival.

It also helps to assess Disease-Specific Survival (DSS).

Aims and Objectives: The aim of the study was to assess the risk of neck nodal metastasis in relation to DOI, and to find out its diagnostic and prognostic implications in different intra-oral lesions.

Materials and methods: We have studied 140 patients with suspected intra-oral SCC having lesions in mucosal lip, buccal mucosa, floor of the mouth, hard palate and anterior 2/3rd of tongue. Ocular micrometer was used to measure depth of invasion

Results: Among 140 patients, 80.0% of the cases were moderately differentiated squamous cell carcinoma. The optimal cut-off value of DOI in discriminating lymph node metastasis from non-lymph node metastasis was found to be 9.1 mm. Lymph node metastasis was found more often in patients with DOI $\geq$ 5mm.

Conclusion: The depth of invasion is the strongest histological predictor of metastatic tumour growth, according to the recent AJCC pT classification.

KEYWORDS: Depth of invasion, Lymph node metastasis, Oral carcinoma, squamous cell carcinoma, pT, TNM classification

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INTRODUCTION

Oral cancer is one of the top three cancers in Indian subcontinent, where it represents a serious public health concern¹. Oral squamous cell carcinoma (OSCC), which develops in the oral mucosa, is a common type of head and neck malignancy.^{2,3,4} According to data collected by the Global Cancer Observatory (GCO), there were 377,713 cases

of OSCC worldwide in 2020, with the majority occurring in Asia.⁵ OSCC affects more males than females, with middle-aged to elderly men being the most susceptible. OSCC routinely evaluated in Hematoxylin & Eosin (H&E) stained sections to assess the tumor grade, surgical margin status, depth of invasion (DOI), lympho-vascular invasion (LVI), perineural invasion (PNI), host response, and mitotic

The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

activity⁶. Depth of invasion (DOI) measures the extent of carcinoma invasiveness independent of exophytic component. It is measured in millimeters from the closest normal basement membrane to the tumor's deepest point. The "horizon" of basement membrane of squamous mucosa is first located. From this horizon to the deepest point of tumor invasion, or DOI, a perpendicular "plumb line" is constructed. The DOI is recorded in millimeters. Printing rulers on acetate sheets and overlaying them on glass slides makes measuring in millimeters simple.⁷⁻⁸ A cancer with squamous differentiation that originates from the mucosal epithelium is known as oral squamous cell carcinoma (OSCC). Roughly 25% of head and neck cancers, which are primarily squamous cell carcinomas (SCC), start in the oral cavity, with the oral tongue being the most often afflicted subsite.⁹ The predictive significance of DOI has significantly influenced treatment strategy in recent times. It was described as the separation between the tumor invasive front and the level of the epithelial basement membrane (BM). Tumor thickness (TT), which is the entire thickness of the tumor and includes both the exophytic region above the BM and the invasive depth, is different from DOI¹⁰. The invasive front tumor cells were shown to differ greatly from the core and superficial tumor cells. The invasive front of the tumor often indicates the aggressiveness of OSCC. Moreover, the depth of infiltration could potentially represent the development of the tumor. It was also shown that the invasive front of esophageal tumors was predictive of metastasis and prognosis¹¹. The prognosis of oral cavity squamous cell carcinoma is highly correlated with the degree of invasion of the tumor (OSCC)¹². In the underdeveloped world, oral SCC is the most prevalent and typically affects older persons. Concerns have been raised over the persistent rise in younger patients, especially women without established risk factors, and HPV-related infections in the oropharynx¹³. One significant risk factor for mouth cancer is tobacco use. Low-reactive free radicals found in cigarette smoke interact with redox-active metals in saliva. Saliva may as a result loses its antioxidant property and it is converted into a strong pro-oxidant environment¹⁴. So dysplastic changes start and progresses to carcinoma in situ and ultimately in invasive carcinoma.¹⁴

Following the release of the AJCC Staging Manual's most recent version, emphasis was placed on the distinctions between DOI and TT, as well as the significance of understanding their exact meanings. While TT is measured in millimetres from the highest point of the tumor surface to the deepest point of the tumour, DOI is measured in millimetres from the neighbouring normal basement membrane to the deepest point of the tumour^{8, 15-19}.

Aims and Objectives

The aim of this study was to evaluate the clinicopathological features of oral squamous cell carcinoma with special reference to depth of invasion. Another objective was to see the risk of neck nodal metastasis and its correlation with the value

of DOI, and to find out the diagnostic and prognostic implications of depth of invasion in different intra-oral lesions.

MATERIALS AND METHODS

The Study was conducted in the department of Pathology in association with the department of Otorhinolaryngology in a super specialty and Tertiary Care Hospital. The study was carried out from December 2022 to June 2024 over a period of 18 months. The patients attending the ENT OPD with oral lesions with suspected intra-oral squamous cell carcinoma were assessed. Their age, sex, clinical history and clinical examination findings and other relevant investigation reports were written in the evaluation form. Informed consent was taken from each of them. The incisional biopsy specimens or post-operative excisional biopsy specimens of oral lesions were sent to the Pathology department with duly filled evaluation form. During surgery wide local excision of tongue and oral cavity was performed by the Department of Otorhinolaryngology and the specimen sent to the Department of Pathology in 10% formalin.

The specimens were sent along with the outpatient department ticket (in case of small biopsy) for the confirmation of the diagnosis. After final surgery the evaluation form with intra-operative details and histopathology requisition form containing relevant clinical history that included patient's contact details, age, sex, presentation of oral lesions and provisional diagnosis were sent to the Pathology department along with the specimen. After receiving the specimen it was fixed properly. Then grossing was done. Multiple sections were taken for proper assessment of DOI.

After routine processing paraffin blocks were made. The sections were stained with Hematoxylin and Eosin(H&E). The histopathological examination was done and assessed by two Pathologists independently for arriving at final diagnosis and the measurement of DOI.

Depth of Invasion(DOI) was measured using the ocular micrometer attached with the microscope. It is measured in millimeters from the closest normal basement membrane to the tumor's deepest point. From the horizon of the basement membrane to the deepest point of tumor invasion, or DOI, a perpendicular "plumb line" is constructed. The DOI is recorded in millimeters. Printing rulers on acetate sheets and overlaying them on glass slides are needed for its measurement. Our sample size was 140. It was calculated by Open Epi software, version 3.01

The study variables/parameters were Clinical parameters and pathological parameters.

The clinical parameters were Demographic details of patients – age, sex, Family history of any oral lesion or other systemic disease(s), Duration of the lesion(s), Site of lesion(s), Status of habit of smoking, Status of consumption of alcohol, Status of habit of betel-nut chewing, and Tumor laterality.

The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

The Pathological parameters were, Gross morphology, Tumor diameter, Tumor stage, Status of resection margins, Site of invasion, Histological type of tumor, Depth of invasion

Statistical analysis

Data collected was analyzed by appropriate statistical tests using statistical software along with graph pad prism. The Data was presented as Mean (+) (-) Standard Deviation (SD) or as median and inter-quartile range for normally distributed data. A p-value <0.05 was considered, indicative of statistically significant.

RESULTS AND ANALYSIS

140 patients with primary OSCC were evaluated for DOI over a period of 18 months from December 2022 to June 2024. The Cut off value of depth of invasion in discriminating lymph node metastasis from non-lymph node metastasis was found to be 9.1 mm (Fig.1)

The area under the ROC curve of depth of invasion in detecting lymph node metastasis was 0.69 (p<0.0001). (Table 1)

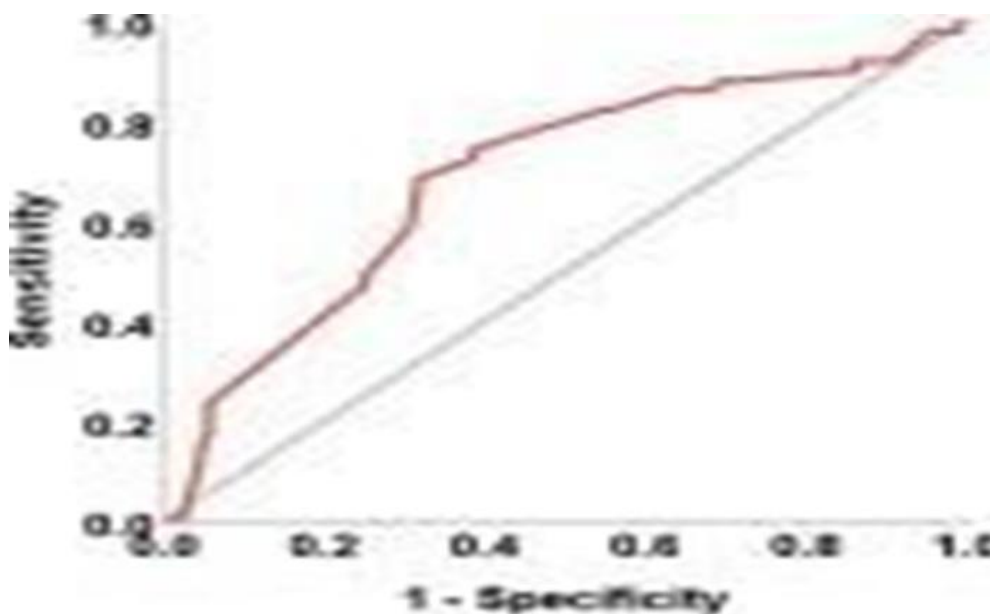


Fig.1 ROC (Receiver Operating Curve) and Area Under Curve (AUC) of ROC

Fig. 1 The area under the ROC curve of depth of invasion in detecting lymph node metastasis was 0.69 (p<0.0001). The optimal cut-off value of depth of invasion in discriminating lymph node metastasis from non-lymph node metastasis was found to be 9.1 mm using Youden's statistic.

Table 1.: Area under curve (AUC) of depth of invasion in detecting lymph node metastasis was to find the cut off of depth of invasion for lymph node metastasis.

Area Under the Curve				
Test Result Variable(s): Depth of Invasion				
Area	Std. Error	p-value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.690	0.047	<0.0001 S	0.597	0.783

S-Statistically significant

Table 2 Efficacy of level of DOI

Comparison	Number	%
TP	66	47.1%
TN	36	25.7%
FP	22	15.7%
FN	16	11.4%
Total	140	100.0%

The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

TP-True Positive, TN-True Negative, FN- False Negative, FP- False Positive

The diagnostic accuracy was 72.6%. The sensitivity was 80.49% and specificity was 62.07%. Positive predictive value was 75.00% and negative predictive value was 69.23%.

(Table 2). The comparison between age and lymph node metastasis was statistically significant . The comparison between Tumor diameter and lymph node metastasis and also between depth of invasion and lymph node metastasis were statistically significant (Table 3)

Table 3. Comparison between parameters with lymph node metastasis and without lymph node metastasis

Parameters	Group	Mean	S.D.	t-value	p-value
Age (years)	With LN metastasis	57.67	13.71	2.470	0.015 S
	Without LN metastasis	51.88	12.62		
Tumour diameter (mm)	With LN metastasis	3.55	1.67	4.842	<0.0001 S
	Without LN metastasis	2.31	0.95		
Depth of Invasion (mm)	With LN metastasis	9.22	5.30	3.133	0.002 S
	Without LN metastasis	6.32	5.19		

The diameter of the tumor 3.55 mm with SD 1.67 was associated with lymphnode metastasis. Tumor diameter 2.31mm with SD 0.95 was devoid of metastasis. These were statistically significant. The lymphnode metastasis took place when DOI measured 9.22mm. No metastatic deposit in lymph node was seen if the DOI was 6.32 mm. Nodal metastasis and its association with depth of invasion was also statistically significant.

Various clinicopathological parameters like Pathological Staging pT1 to pT4 with or without lymph node metastasis , infiltrative tumor or ulcerated tumor with or without lymph node metastasis, Lymphovascular invasion with or without metastasis were statistically significant.

Various types of tumors showing ulcerproliferative growth of lateral border of tongue (Fig.2,A), Ulcerative growth of buccal mucosa and lip (Fig.2 ,B,D) growth in ventral surface

of tongue (Fig.2 , C) were seen. In the oral cavity the tongue was the commonest site for squamous cell carcinoma in our present study. We saw that the squamous cell carcinoma occurred predominantly on the lateral border of tongue followed by buccal mucosa. It is more frequent in males and in the middle aged people.

The specimens of glossectomy with wide local excision were sent to the Pathology department for histopathology and for evaluation of DOI (Fig.3 A-D). Most of the specimens showed moderately differentiated squamous cell carcinoma (Fig.4 , A- D). The mean ($\pm$ S.D.) depth of invasion of tumor of the patients was 7.33 ± 5.39 mm with range 0.6 –30.0 mm. Adverse histopathological tumour characteristics (such as infiltrative growth, lympho-vascular invasion and perineural invasion) were all associated with DOI ≥ 5 mm (all $p < 0.001$)

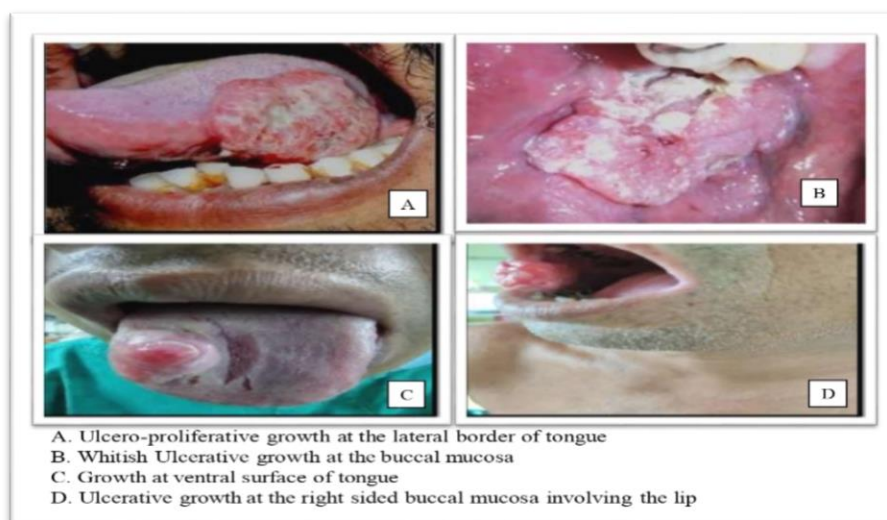


Fig.2 Clinical Photograph



Fig 3: Gross Specimen of Glossectomy

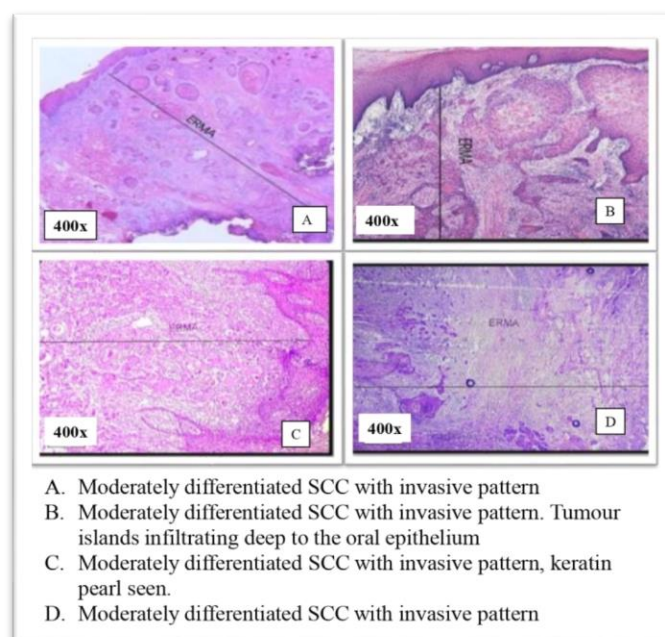


Fig.4 Photomicrograph of SCC (H&E)

DISCUSSION

The tongue is the commonest subsite for oral squamous cell carcinoma in our study.

In the present study we have observed that, Lateral border of tongue (25.2%) was the most common site. It was followed by Buccal mucosa (22.3%). **You-Jung Lee et al.** also found in their study that tongue was the most common site of oral squamous cell carcinoma²⁰⁻²¹. Tongue as a subsite of oral cavity is having higher risk factors of cervical nodal metastasis as compared to other subsites, because it is rich in lymphatics. The floor of the mouth is also another common site for OSCC and there is also abundance of lymphatics in the floor of mouth.²⁰⁻²¹

On the contrary, **Wei-Chin Chang et al.** found that buccal mucosa was the most common site of oral squamous cell carcinoma.²² In our study it was the second commonest site of OSCC.

Moderately differentiated OSCC cases (80.0%) were significantly higher than well differentiated (19.3%) and poorly differentiated (0.7%) cases. This result is in accordance with the findings of **Cornelia G.F. van Lanschot et al.**²³ Here they had found that 60.0% of cases were moderately differentiated, and 16.9% cases were well differentiated. On the other hand, **Faisal M et al.** found that

The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

54.75% cases were under the category of well differentiated cases.²⁴

The mean ($\pm$ S.D.) DOI of tumor of the patients was 7.33 ± 5.39 mm with range 0.6–30.0 mm and the median depth of invasion of tumor was 6.0 mm. In 73 patients out of 140 patients, DOI was between 5–10 mm resulting into 52.5% of the cases the depth of invasion was between 5–10 mm which was significantly higher than other depth of invasions. Adverse histopathological tumour characteristics (such as infiltrative growth, lympho-vascular invasion and perineural invasion) were all associated with $\text{DOI} \geq 5$ mm ($p < 0.001$). Our results are found to be similar to the findings of **Faisal M et al.** who had shown in their study that in 46.93% of the cases the depth of invasion was between 5–10 mm.²⁴ Lymph node metastasis was found in 36.4% of the cases. However, in 63.6% of the cases lymph node metastasis was not found. The risk of occult lymph node metastasis rises with the increasing DOI, particularly when it is more than 10 mm. ROC-analysis was performed to determine the optimal DOI cut-off value for predicting Lymph Node Metastasis (LNM) per mm DOI, based on positive predictive value $> 20\%$. The area under the ROC curve of depth of invasion in detecting lymph node metastasis was 0.69 (95% CI. $p < 0.0001$). The optimal cut-off value of depth of invasion in discriminating lymph node metastasis from non-lymph node metastasis was found to be 9.1 mm using Youden Method. A cut-off value of 9.1 mm showed a positive predictive value of 75.00% (95% CI: 17.8%–31.6%), with 80.49% sensitivity and 62.07% specificity, for prediction of LNM. Thus, the diagnostic accuracy, sensitivity, specificity, positive predictive value and negative predictive value of depth of invasion > 9.1 mm in detecting lymph node metastasis were 72.86%, 80.49%, 62.07%, 75.00% and 69.23% respectively.

Cornelia G.F. van Lanschot et al.²³ in their study had performed a ROC-analysis to determine the optimal DOI cut-off value for predicting LNM per mm DOI, based on positive predictive value $> 20\%$. A cut-off value of 4.0 mm showed a positive predictive value of 24.2% (95% CI: 17.8%–31.6%), with 95.1% sensitivity and 52.9% specificity, for prediction of LNM.

Lymph node metastasis was found more often in patients with $\text{DOI} \geq 5$ mm ($p = 0.002$) which was statistically significant. In our study, the mean value of DOI in the patients with lymph nodal metastasis was 9.22 mm. In our study, 36% patients with lympho-vascular invasion presented with lymph node metastasis and 15% patients without lympho-vascular invasion presented with lymph node metastasis. The p-value found to be < 0.0001 which was statistically significant. **Faisal M et al.** in their study found 32.74% 36% patients with lympho-vascular invasion presented with lymph node metastasis and 54.55% patients without lympho-vascular invasion presented with lymph node metastasis.¹⁷

In this study we found that 32% patients with perineural invasion presented with lymph node metastasis and 19%

patients without perineural invasion presented with lymph node metastasis, (p -value = 0.52).

Faisal M et al. in their study found that 30.07% patients with perineural invasion presented with lymph node metastasis and 50% patients without perineural invasion presented with lymph node metastasis.¹⁷ DOI and lymph node metastasis are interrelated. DOI also increases with tumor size. The cut off value of DOI varies from 1.5 mm to 10 mm. Neck dissection is suggested when DOI is more than 4 mm²⁴.

CONCLUSION

Radiological investigations [ultrasonography (USG), magnetic resonance imaging (MRI), computed tomography (CT) scan] play an important role in nodal metastasis detection hence should be considered in OSCC specially in tongue and buccal mucosa in clinically N0 cases.

The Depth of Invasion (DOI) is an important prognostic factor for Oral Squamous Cell Carcinoma. It is measured in millimeters. The measurement is taken from the basement membrane to the deepest point of invasion. There is a correlation between measurement of DOI and lymph node metastasis and recurrence and overall survival. The DOI has been incorporated in the TNM staging system. Value of DOI also determine the requirement of neck dissection in OSCC cases. So the prognosis of OSCC depends not only on LVI, PNI, Margin status but also on DOI.

A cut-off value of 9.1 mm showed a positive predictive value of 75.00%, with 80.49% sensitivity and 62.07% specificity, for prediction of Lymph Node Metastasis (LNM). The mean value of DOI in the patients with lymph nodal metastasis was more than the DOI in the Patients without lymph nodal metastasis. Lymph node metastasis was found more often in patients with $\text{DOI} \geq 5$ mm.

CONFLICT OF INTEREST STATEMENT

None.

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The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

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The role of Depth of Invasion as a prognostic factor in Oral Squamous Cell Carcinoma

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