ORIGINAL ARTICLE OPEN ACCESS

Association Between Depth of Invasion and Tumor Stages in Oral Squamous Cell Carcinoma

Shanzay Rehman[*1], Saima Butt[1], Sana Fatima[1], Zofeen Hashim[1], Fizza Abidi[1], Faraz Baig[2]*
[1]Oral Pathology Department, [2]Pathology Department, Ziauddin University, Karachi, Pakistan.

ABSTRACT

Background: Depth of Invasion (DOI) in Oral Squamous Cell Carcinoma (OSCC) is an important factor of nodal metastasis and also aids with diagnosis, treatment planning, and prognostic assessments. The study's objective was to find the association between DOI and Tumor Stages in OSCC patients.

Methods: This is a cross-sectional study. 150 histologically verified biopsies of OSCC patients were retrieved from Ziauddin Hospital's Department of Histopathology from March 2023 to 2024. The sampling technique was consecutive. Specimens were preserved in formalin, embedded in paraffin, and stained with Hematoxylin and Eosin. Oral cancer was graded according to WHO requirements and the American Joint Committee on Cancer (AJCC) classification (TNM classification) for staging. Digital microscopic imaging determined the (DOI), as defined by the AJCC eighth edition. Statistical analysis was conducted using IBM SPSS version 24. DOI, PNI, and LVI were compared with Tumor Grade, Tumor Size, Nodal Stage, and Tumor Stage by using Chi-square/Fisher's exact test. P-value < 0.05 is considered statistically significant.

Results: Buccal mucosa (59.3%) and tongue (18.0%) were the most common sites. The majority of tumors were moderately differentiated (96.7%), with over half having a DOI >10mm (50.7%) and T4 tumor size being most prevalent (39.3%). DOI is statistically significantly associated with tumor grade (p-value = 0.011) while not significantly associated with tumor size, nodal stage, and tumor stage (p=value > 0.05).

Conclusion: Our study highlights the insignificant association between DOI and tumor size, nodal stage, or overall tumor stage, but emphasizes its importance in assessing and staging OSCCC, distinguishing superficial and deeply invasive tumors, and improving patient outcomes.

Keywords: Depth of Invasion, Staging, Oral Cancer, Pakistan

Corresponding Author:
Dr. Shanzay Rehman
Oral Pathology Department,
Ziauddin University,
Karachi, Pakistan.
Email: shanzay.15052@zu.edu.pk
Doi: https://doi.org/10.36283/ziun-pjmd13-4/013

How to cite: Rehman S, Butt S, Fatima S, Hashim Z, Abidi F, Baig F Association between Depth of Invasion and Tumor Stages in Oral Squamous Cell Carcinoma. Pak J Med Dent. 2024;13(4): 100-107. Doi: https://doi.org/10.36283/ziun-pjmd13-4/013

Received: Thu, May 23, 2024 **Accepted:** Mon, Sep 16, 2024 **Published:** Thu,Oct 24 ,2024

INTRODUCTION

Globally the prevalence of Oral Cavity Cancers is 350,000 cases, with a ratio of 2.1:1 in males and females respectively[1]. About 500,000 new instances of "head and neck squamous cell carcinoma (HNSCC)" are detected each year, with a rise in "oral squamous cell carcinoma (OSCC)"[2]. The annual global mortality rate among OSCC patients is 145,000 where alcohol and tobacco usage stand out as the primary risk factors. This is heightened in Southern Asian countries due to the widespread use of chewing tobacco, which is frequently coupled with betel quid use[2]. In Pakistan, OSCC is reported to be the most prevalent cancer in males[3]. Despite advancements in diagnosis and treatment of OSCC prognosis continues to be unfavorable, with a low five-year survival rate[4].

Oral cancers are highly aggressive due to their ability to spread to nearby lymph nodes, leading to a poorer prognosis[5]. Metastasis of Lymph nodes is an important predictor in the outcome of "(OSCC)" and is linked to tumor relapse and lower survival rates. The most significant factor in predicting occult metastases is the depth of tumor invasion[6].

Literature reports "DOI (Depth of Invasion)", as an elective neck surgery guide in patients of OSCC began in the 1980s. Following research, it was recommended for DOI to be integrated into staging for oral cancers[7]. The major benefits of a cancer staging system is to help predict prognosis and plan appropriate treatment. Any change in staging therefore must be based on solid evidence as it has a direct impact on patient care. The "AJCC TNM's 8th edition" made an important change to the T category of oral cavity tumors, incorporating "(DOI)" into the staging[8].

DOI was chosen over tumor thickness (TT), based on DOI's ability to forecast tumor aggressiveness accurately[9]. It has demonstrated independent prognostic significance for concealed cervical metastases, cancer recurrence, and disease-specific survival (DSS). It has also become a common criterion for identifying the necessity for "elective neck dissection (END)" in early stage OSCC patients (T1/T2)[10].

DOI in "OSCC" has emerged as an important prognostic indicator, determining outcomes such as local recurrence, lymph node metastases, and overall survival. However, reliable implementation and interpretation of DOI in clinical practice remains difficult. Our study aims to explore the relationship between tumor depth and clinicopathological parameters in OSCC patients aiming to improve prognostic models and inform personalized treatment strategies.

METHODOLOGY

This is a Cross Sectional study. 150 histologically verified biopsies of OSCC patients of all stages were retrieved from Histopathology Department, Ziauddin Hospital from March 2023 to March 2024, along with their records. The sampling technique used was consecutive. Patients of OSCC including both genders were included in the study while those who had undergone any type of cancer treatment and malignancies other than OSCC were excluded. Demographics included; patient's age, gender, tumor site and dimensions, such as size of tumor and DOI. Specimens were kept in formalin (10%), embedded in paraffin and stained by Hematoxylin and Eosin (H&E). Using Broader's method, grading of the oral cancer was done which adhered to the World Health Organization's (WHO) requirements. The AJCC classification (TNM classification) was used for staging.

DOI was determined using digital microscopic imaging. It was defined as the mass present underneath the basement membrane of cancers, or the theoretical reconstruction of basement membrane in presence of exophytic lesions, according to "American Joint Committee on Cancer (AJCC)" eighth edition, TNM classification. Statistical analysis was performed by using SPSS version 24. Descriptive statistics, including frequencies and percentages, were utilized to summarize demographic and clinicopathological characteristics. Chi-square / Fisher's exact test was applied to assess the association of DOI, perineural invasion (PNI), and lymph vascular invasion (LVI) with tumor grade, tumor size, nodal stage and tumor stage with a significance level set at 0.05.

RESULTS

The study included 150 participants diagnosed with OSCC with predominance of male participants found in the age group 30-50 years and above 50 years (Fig 1).

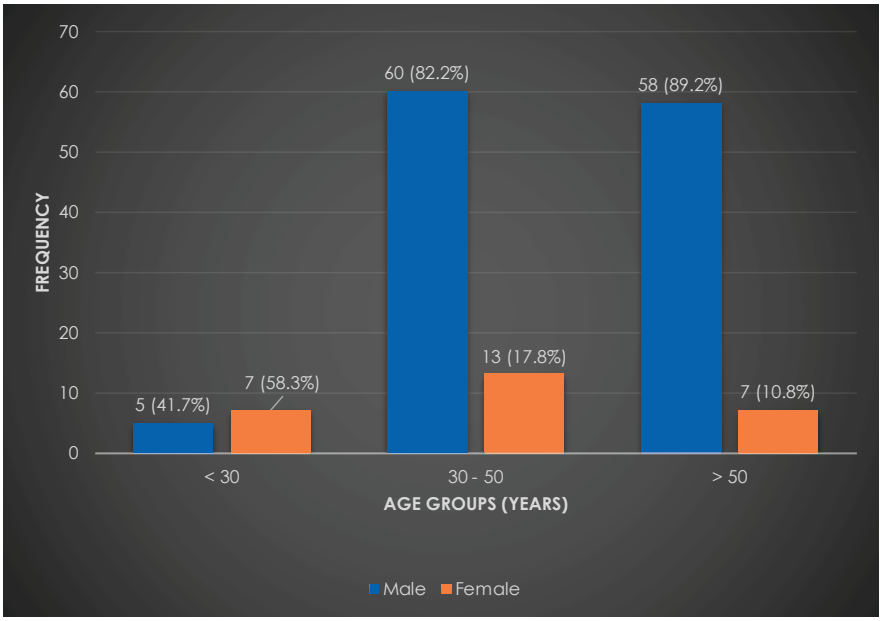

Figure 1: Patient's Demographics

Regarding the clinical and pathological characteristics of OSCC (Table 1), the buccal mucosa was the most common anatomical location (59.3%), followed by the tongue (18.0%). Majority of tumors were moderately differentiated (96.7%), with a considerable proportion exhibiting a depth of invasion (DOI) >10mm (50.7%). Advanced-stage tumors (T4) were predominant, comprising 39.3% of cases. Muscle involvement was observed in 76% of samples while perineural invasion (PNI) was present in 60.0% of cases, and lymph vascular invasion (LVI) in 16%, indicating aggressive disease features. Additionally, bone involvement was observed in 38% of the cases.

Table 1: Clinical and Pathological Characteristics of Tumor

Characteristics	**N (%)**
Anatomical Location:	
Buccal mucosa	89 (59.3)
Gingiva	15 (10.0)
Hard palate	13 (8.7)
Lip	6 (4.0)
Tongue	27 (18.0)
Grades Of Tumor:	
Well Differentiated	2 (1.3)
Moderately Differentiated	145 (96.7)
Poorly Differentiated	3 (2.0)
DOI:	
<5mm	18 (12.0)
5-10mm	56 (37.3)
>10mm	76 (50.7)

 DOI: https://doi.org/10.36283/PJMD13-4/013

Tumor Size:	
T1	7 (4.7)
T2	46 (30.7)
T3	38 (25.3)
T4	59 (39.3)
Nodal Stage:	
No	68 (45.3)
N1	47 (31.3)
N2a	15 (10)
N2b	7 (4.7)
N3	13 (8.7)
Perineural Invasion:	
Absent	60 (40.0)
Present	90 (60.0)
Lymphovascular Invasion:	
Absent	126 (84)
Present	24 (16)
Muscle Involvement:	
No	36 (24.0)
Yes	114 (76.0)
Bone Involvement	
No	93 (62.0)
Yes	57 (38.0)

Figure 2 represents the highest number of cases in stage 4 (48.7%) followed by 50 (33.3%), 20 (13.3%), and 7 (4.7%) in stage-3, stage-2, and stage-1 respectively.

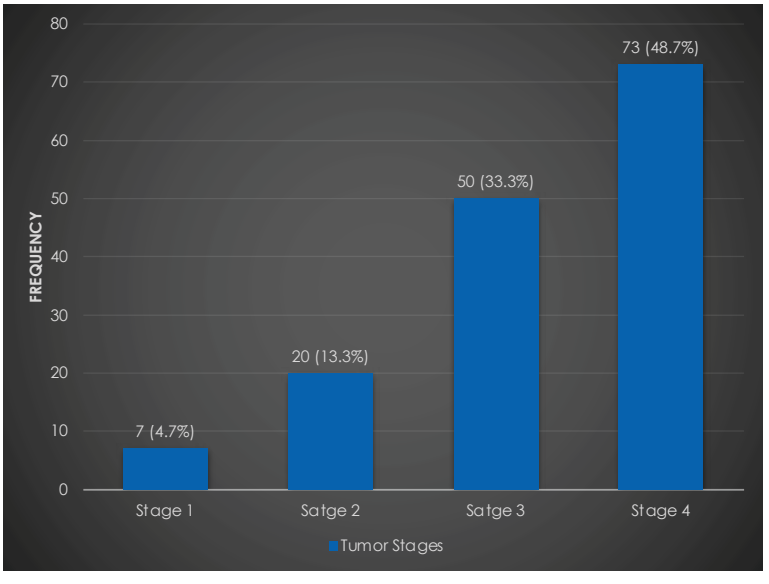

Figure 2: Frequency Distribution of Tumor Stages

H and E staining of OSCC samples across different grades is shown in Figure 3.

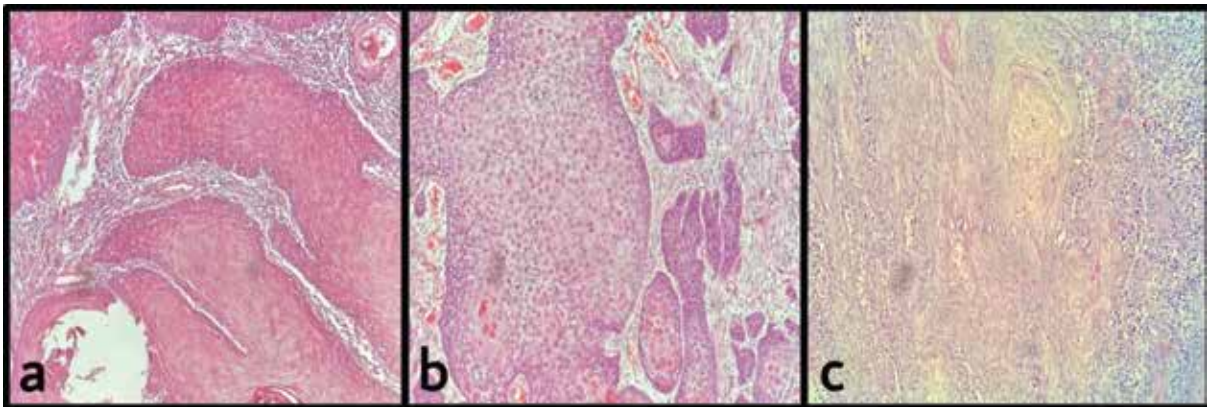

Figure 3: Histopathological images of different grades of OSCC; Well differentiated, (a: H&E), moderately differentiated (b: H&E) and poorly differentiated (c: H&E)

Table 1: Association of DOI, PNI, and LVI across Tumor Grade, Tumor Size, Nodal Stage and Tumor Stage

	DOI (mm)			P-value	PNI		P-value	LVI		P-value
	< 5 N (%)	5 – 10 N (%)	> 10 N (%)		Absent N (%)	Present N (%)		Absent N (%)	Present N (%)	
Tumor Grade										
G1	2 (100)	0 (0)	0 (0)	**0.011£**	2 (100)	0 (0)	0.142£	2 (100)	0 (0)	0.587£
G2	15 (10.3)	55 (37.9)	75 (51.7)		56 (38.6)	89 (61.4)		122 (84.1)	23 (15.9)	
G3	1 (33.3)	1 (33.3)	1 (33.3)		2 (66.7)	1 (33.3)		2 (66.7)	1 (33.3)	
Tumor Size										
T 1	1 (14.3)	1 (14.3)	5 (71.4)	0.242£	6 (85.7)	1 (14.3)	0.056£	7 (100)	0 (0)	**0.018***
T 2	7 (15.2)	18 (39.1)	21 (45.7)		19 (41.3)	27 (58.7)		44 (95.7)	2 (4.3)	
T 3	1 (2.6)	18 (47.4)	19 (50)		16 (42.1)	22 (57.9)		31 (81.6)	7 (18.4)	
T 4	9 (15.3)	19 (32.2)	31 (52.5)		19 (32.2)	40 (67.8)		44 (74.6)	15 (25.4)	
Nodal Stage										
N0	7 (10.3)	23 (33.8)	38 (55.9)	0.242£	37 (54.4)	31 (45.6)	**0.013***	63 (92.6)	5 (7.4)	**0.001£**
N1	6 (12.8)	21(44.7)	20 (42.6)		15 (31.9)	32 (68.1)		40 (85.1)	7 (14.9)	
N2a	0 (0)	4 (26.7)	11 (73.3)		5 (33.3)	10 (66.7)		13 (86.7)	2 (13.3)	
N2b	2 (28.6)	3 (42.9)	2 (28.6)		1 (14.3)	6 (85.7)		3 (42.9)	4 (57.1)	
N3	3 (23.1)	5 (38.5)	5 (38.5)		2 (15.4)	11 (84.6)		7 (53.8)	6 (46.2)	
Tumor Stage										
Stage 1	1 (14.3)	1 (14.3)	5 (71.4)	0.199£	6 (85.7)	1 (14.3)	**0.023£**	7 (100)	0 (0)	0.055£
Stage 2	4 (20)	7 (35)	9 (45)		11 (55)	9 (45)		19 (95)	1 (5)	
Stage 3	3 (6)	25 (50)	22 (44)		19 (38)	31 (62)		45 (90)	5 (10)	
Stage 4	10 (13.7)	23 (31.5)	40 (54.8)		24 (32.9)	49 (67.1)		55 (75.3)	18 (24.7)	

£Fisher Exact Test
*Chi-square Test

Table 2 represents the association of DOI, PNI and LVI with tumor grade, tumor size, nodal stage, and tumor stage. DOI was found statistically significant with tumor grade (p-value = 0.011) while insignificantly associated with tumor size, nodal stage and tumor stage (p-value > 0.05). PNI is statistically significantly associated with nodal stage (p-value = 0.013) and tumor stage (p-value = 0.023). LVI is significantly associated with tumor size (p-value = 0.018) and nodal stage (p-value = 0.001).

DISCUSSION

OSCC has high global prevalence predominantly affects males, notably in Pakistan, where it ranks as the most prevalent cancer according to Globocan 2024[3, 24]. Staging plays a pivotal role in the management of cancer patients, guiding treatment decisions and prognostic assessments. DOI, which was incorporated in the sixth edition of cancer staging manual enhances data precision. DOI's inclusion influences the T category, underscoring the importance of distinguishing between superficial and deeply invasive tumors[11].

Higher DOI has been associated to an increased risk of lymph node metastasis, poor survival and reoccurrence in early-stage OSCC[11-13]. It is a strong predictor of tongue cancer and a crucial component of preoperative staging[14].Our findings offer insight on the relationship between tumor stage, DOI, and other clinicopathological features in patients with OSCC.

Our results demonstrated no correlation between DOI and Tumor Size, Nodal Stage or Overall Tumor Stage, which contrasts with other research indicating that DOI improves patient risk categorization and prognostic accuracy[15, 16]. Wunchel et. al in 2020 emphasized the use of DOI evaluation in early-stage OSCC[17].

We found no significant variance in the DOI between tumor stages contrasting with other studies[11, 12]. However a positive correlation was seen between DOI and variables such as tumor site, perineural invasion, and lymphovascular invasion. Conversely, a weakly negative correlation was identified with patient age consistent with the findings reported by Abidi. et al. in 2020, where no association was seen with patient's age. These findings highlight the significance of tumor stage in predicting DOI and justify the inclusion of DOI in TNM staging for OSCC. Furthermore, moderate to positive link between DOI and tumor stage was observed, which is consistent with other researches indicating that DOI assessment improves patient risk categorization and prognosis accuracy[15, 16]. A positive correlation was seen between DOI and variables such as tumor site, perineural invasion, and lymph vascular invasion Conversely, a weakly negative correlation was identified with patient age, consistent with the findings reported by Abidi et al. in 2020 where no association was seen with age20.Our results also align with findings reported by Maheer et al. in 2020, where DOI was significantly associated with Lymph vascular invasion cross different DOI categories[18]. Sheikh et al., however, reported that younger patients with "OSCC" tend to have increased DOI[21].

Perineural invasion in OSCC is found to be more common with deeper tumor depth similar to our study[13]. DOI was also reported to be distinct from TT as it represents the invasive behavior of the tumor[19, 22, and 23]. Understanding the impact of clinicopathological variables on DOI can assist clinicians in tailoring treatment approaches and predicting outcomes[17, 25].

Our study has certain limitations, such as small sample size and variability in DOI measurement; also, a lack of longitudinal data and a narrow scope of factors may restrict the depth of analysis and applicability of the results. Despite these limitations, this study offers a detailed analysis of Depth of Invasion with several clinicopathological parameters, providing useful insights into OSCC progression and treatment planning. To corroborate these findings, more studies with bigger, more diverse populations are required.

CONCLUSION

The study highlights the importance of Depth of Invasion (DOI) in OSCC diagnosis, but found no correlation with tumor size, nodal stage, or overall tumor stage. DOI is useful for assessing tumor aggressiveness and differentiation but does not predict tumor size, lymphatic spread, or overall staging. Further research is needed to understand DOI's effect on OSCC management.

ACKNOWLEDGEMENTS

We want to acknowledge the staff at the Histopathology lab for their contribution.

CONFLICT OF INTEREST

None to declare

ETHICAL APPROVAL

Approval was taken from Ziauddin University, reference number (6341222SROM)

FUNDING

None to declare

AUTHOR'S CONTRIBUTIONS

All authors equally contributed to the manuscript.

REFERENCES

1. Aaboubout Y, van der Toom QM, de Ridder MA, De Herdt MJ, van der Steen B, van Lanschot CG, Barroso EM, Nunes Soares MR, Ten Hove I, Mast H, Smits RW. Is the depth of invasion a marker for elective neck dissection in early oral squamous cell carcinoma?. Frontiers in Oncology. 2021 Mar 12;11:628320. https://doi.org/10.3389/-fonc.2021.628320

2. Wunschel M, Neumeier M, Utpatel K, Reichert TE, Ettl T, Spanier G. Staging more important than grading? Evaluation of malignancy grading, depth of invasion, and resection margins in oral squamous cell carcinoma. Clinical oral investigations. 2021 Mar;25:1169-82. https://-doi.org/10.1007/s00784-020-03421-2

3. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://g-co.iarc.who.int/today, accessed [2-5-2024]. https://-doi.org/10.1002/ijc.33588

4. Ferreira AK, de Carvalho SH, Granville-Garcia AF, de Santana Sarmento DJ, Agripino GG, de Abreu MH, de Melo MC, de França Caldas Jr A, Godoy GP.

Survival and prognostic factors in patients with oral squamous cell carcinoma. Medicina Oral, Patología Oral y Cirugía Bucal. 2021 May;26(3):e387. 10.4317/medoral.24242
5. Baig MS, Bhutto RA, Muhammad S, Siddiqui MI. Epidemiology of oral cancer in Southern Punjab, Pakistan. Pak J Med Heal Sci. 2015 Oct 1;9:1269-71.
6. Bur AM, Holcomb A, Goodwin S, Woodroof J, Karadaghy O, Shnayder Y, Kakarala K, Brant J, Shew M. Machine learning to predict occult nodal metastasis in early oral squamous cell carcinoma. Oral oncology. 2019 May 1;92:20-5. https://doi.org/10.1016/j.oraloncology.2019.03.011
7. Caldeira PC, Soto AM, de Aguiar MC, Martins CC. Tumor depth of invasion and prognosis of early-stage oral squamous cell carcinoma: A meta-analysis. Oral diseases. 2020 Oct;26(7):1357-65. https://doi.org/10.1111/odi.13194
8. D'Cruz AK, Dhar H, Vaish R, Hawaldar R, Gupta S, Pantvaidya G, Chaukar D, Chaturvedi P, Pai P, Deshmukh A, Kane S. Depth of invasion in early oral cancers-is it an independent prognostic factor?. European Journal of Surgical Oncology. 2021 Aug 1;47(8):1940-6. https://doi.org/10.1016/j.ejso.2021.03.243
9. Lee YJ, Kwon TG, Kim JW, Lee ST, Hong SH, Choi SY. Evaluation of depth of invasion and tumor thickness as a prognostic factor for early-stage oral squamous cell carcinoma: A retrospective study. Diagnostics. 2021 Dec 23;12(1):20. https://doi.org/10.3390/diagnostics12010020
10. Larson AR, Kemmer J, Formeister E, El-Sayed I, Ha P, George J, Ryan W, Chan E, Heaton C. Beyond depth of invasion: adverse pathologic tumor features in early oral tongue squamous cell carcinoma. The Laryngoscope. 2020 Jul;130(7):1715-20. https://doi.org/10.1002/lary.28241
11. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, Loomis AM, Shah JP. Head and neck cancers—major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA: a cancer journal for clinicians. 2017 Mar;67(2):122-37. https://doi.org/10.3322/caac.21389
12. Ebrahimi A, Gil Z, Amit M, Yen TC, Liao CT, Chaturedi P, Agarwal JP, Kowalski LP, Kreppel M, Cernea CR, Brandao J. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA Otolaryngology–Head & Neck Surgery. 2014 Dec 1;140(12):1138-48. doi:10.1001/jamaoto.2014.1548
13. Rasheed FS, Abdullah BH. Perineural Invasion in Oral Squamous Cell Carcinoma in Relation to Tumor Depth. Journal of Baghdad College of Dentistry. 2019 Jun 15;31(2):1-6. https://www.iasj.net/iasj/download/b52d6164cb63682d
14. Li M, Yuan Z, Tang Z. The accuracy of magnetic resonance imaging to measure the depth of invasion in oral tongue cancer: a systematic review and meta-analysis. International Journal of Oral and Maxillofacial Surgery. 2022 Apr 1;51(4):431-40. https://doi.org/10.1016/j.ijom.2021.07.010
15. Amit M, Tam S, Takahashi H, Choi KY, Zafereo M, Bell D, Weber RS. Prognostic performance of the American Joint Committee on Cancer 8th edition of the TNM staging system in patients with early oral tongue cancer. Head & Neck. 2019 May;41(5):1270-6. https://doi.org/10.1002/hed.25553
16. Lee NC, Eskander A, Park HS, Mehra S, Burtness BA, Husain Z. Pathologic staging changes in oral cavity squamous cell carcinoma: Stage migration and implications for adjuvant treatment. Cancer. 2019 Sep 1;125(17):2975-83. https://doi.org/10.1002/cncr.32161
17. Wunschel M, Neumeier M, Utpatel K, Reichert TE, Ettl T, Spanier G. Staging more important than grading? Evaluation of malignancy grading, depth of invasion, and resection margins in oral squamous cell carcinoma. Clinical oral investigations. 2021 Mar;25:1169-82. https://doi.org/10.1007/s00784-020-03421-2
18. Masood MM, Farquhar DR, Vanleer JP, Patel SN, Hackman TG. Depth of invasion on pathological outcomes in clinical low-stage oral tongue cancer patients. Oral Diseases. 2018 Oct;24(7):1198-203. https://doi.org/10.1111/odi.12887
19. Piazza C, Bresciani L, Giannini L. Depth of invasion for prognostic stratification in oral cavity cancer: do we need further validation?. Annals of translational medicine. 2019 Jul;7(Suppl 3). doi: 10.21037/atm.2019.04.19
20. Abidi F, Fatima S, Zaidi A, Butt S, Saeed S, Batool H. Depth of Invasion as Tumor Indicator in Cervical Lymph Node Metastasis in OSCC. DOI: 10.9734/JPRI/2022/v34i27A35993
21. Shaikh SA, Abbas SA, Ayub B, ul Haq ME, Qureshi TA, Khalil A. Association of age with the depth of invasion and extracapsular spread in patients with oral squamous cell carcinoma: A retrospective study. J Clin Images Med Case Rep. 2022;3(1):1590. www.doi.org/10.52768/2766-7820/1590
22. Liu B, Amaratunga R, Veness M, Wong E, Abdul- azak M, Smith M, Coleman H, Gebski V, Sundaresan P. Tumor depth of invasion vs tumor thickness in determining risk of nodal disease in early oral tongue squamous cell carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2018 Nov 1;102(3):e331-2. https://www.redjournal.org/action/showPdf?pii=S0360-3016%2818%2932474-X
23. Harada H, Tomioka H, Hirai H, Kuroshima T, Oikawa Y, Nojima H, Sakamoto J, Kurabayashi T, Kayamori K, Ikeda T. MRI before biopsy correlates with depth of invasion corrected for shrinkage rate of the histopathological specimen in tongue carcinoma. Scientific reports. 2021 Oct 25;11(1):20992. https://doi.org/10.1038/s41598-021-00398-0
24. Qureshi MA, Syed SA, Sharafat S. Lip and oral

cavity cancers (C00-C06) from a mega city of Pakistan: Ten-year data from the Dow Cancer Registry. Journal of Taibah University Medical Sciences. 2021 Aug 1;16(4):624-7. https://doi.org/10.1016/j.jtumed.2021.02.001
25. Tandon S, Ahlawat P, Pasricha S, Purohit S, Simson DK, Dobriyal K, Umesh P, Mishra M, Kumar L, Karimi AM, Gairola M. Depth of invasion as an independent predictor of survival in patients of stage III squamous cell carcinoma of the oral tongue. The Laryngoscope. 2022 Aug;132(8):1594-9. https://doi.org/10.1002/lary.29990