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Research Protocol

Oncology Section

Incidence of Skip Metastasis and Its Correlation with Depth of Invasion in Oral Squamous Cell Carcinoma: A Cross-sectional Study Protocol

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ABSTRACT

Introduction: Oral Squamous Cell Carcinoma (OSCC) is the most common malignancy of the head and neck region, with a global mortality of approximately 177,000 deaths reported in 2018. Despite advances in diagnostic techniques and therapeutic modalities, the five-year survival rate remains around 50%. Cervical Lymph Node (LN) metastasis is a critical prognostic factor, even in early-stage OSCC. Although OSCC generally follows a predictable pattern of LN spread, a phenomenon known as skip metastasis—wherein tumour cells bypass adjacent lymph nodes and involve non sequential nodes—has been observed, particularly in carcinomas of the tongue. This atypical metastatic behaviour complicates treatment strategies and underscores the need for further investigation. The 8th edition of the Tumour Node Metastasis (TNM) staging system emphasises parameters such as extranodal extension and Depth of Invasion (DOI), which may correlate with metastatic patterns.

Need of the study: This study aims to investigate the association between DOI and skip metastasis in OSCC to enhance the understanding of lymphatic spread patterns. By clarifying this relationship, the study seeks to support more accurate risk stratification, refine surgical management—particularly neck dissection strategies—and ultimately contribute to improved prognostication and personalised treatment planning for patients with OSCC.

Materials and Methods: This is a cross-sectional study over a period of 12 months, from July 2025 to June 2026 will be conducted in the Department of Oral Pathology and Microbiology, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Higher Education and Research (DMIHER), a tertiary care hospital in Sawangi Meghe, Wardha, Maharashtra, India. A total of 80 Haematoxylin and Eosin (H&E)-stained OSCC slides will be analysed for lymph node involvement, both qualitatively and quantitatively, under low and high magnification (400×). The depth of invasion will be measured from the deepest point of tumour infiltration into the connective tissue using a Leica DMLB2 research microscope. Blinded evaluations will be performed independently by two histopathologists, including the primary investigator and a co-researcher.

Keywords: Cervical lymph node metastasis, Carcinoma, Lymphatic spread, Neck dissection

INTRODUCTION

The OSCC is the most prevalent malignancy affecting the head and neck region [1]. In 2018, it was responsible for approximately 177,000 deaths worldwide [2]. Despite advancements in diagnostic methods and treatment approaches over the past two decades, the overall five-year survival rate for head and neck cancers has remained stagnant at approximately 50% [3]. OSCC frequently metastasises to cervical lymph nodes, even during its early stages. The presence of lymph node metastasis is a critical prognostic factor influencing patient survival.

Metastasis, a defining characteristic of cancer, allows tumour cells to spread from the primary site to distant organs, often via lymphatic pathways [4]. Patients with metastatic disease, or those who develop metastases after primary tumour treatment, typically have a poor prognosis [5]. According to Lambert AW et al., metastasis is responsible for nearly 90% of cancer-related deaths [6]. Tumour cells invade the systemic circulation through blood or lymphatic vessels, facilitating their spread to distant organs. Consequently, the status of regional lymph nodes serves as a key indicator of survival in malignancies [7].

Recent research has provided insights into the complex mechanisms by which malignant tumours invade the lymphatic system and metastasise to regional lymph nodes [8]. OSCC usually follows a predictable pattern of spread to adjacent lymph nodes. Advances in radiation therapy targeting high-risk nodal areas and modifications in radical neck dissection have contributed to reduced treatment-related morbidity [9].

A phenomenon known as skip metastasis occurs when cancer cells bypass expected lymphatic drainage pathways and spread to non-adjacent lymph nodes. Byers RM et al., first described this phenomenon, reporting a 15.8% incidence of skip metastasis in OSCC and recommending routine neck dissection up to level IV [10]. This atypical pattern of metastasis challenges conventional treatment approaches and warrants further investigation. Skip metastasis remains a subject of debate, particularly in oral cavity tumours, notably those of the tongue. Instead of following a sequential metastatic route, tumour cells may deviate from expected lymphatic drainage patterns. Studies suggest that this phenomenon is not exclusive to head and neck malignancies but also occurs in various other cancer types [11].

Additionally, the 8th edition of the TNM staging system for OSCC, introduced in 2017, incorporates two important parameters—extranodal extension of lymph nodes and DOI—in defining the T stage [12]. Increasing emphasis in oral and maxillofacial pathology suggests that integrating clinical staging with histological grading enhances prognostic accuracy and facilitates personalised treatment planning [1]. However, limited research has explored the association between skip metastasis and DOI. Therefore, the present study aimed to investigate this correlation in cases of OSCC.

REVIEW OF LITERATURE

Lee DJ et al., conducted a study on Tonsillar Squamous Cell Carcinoma (TSCC) to identify risk factors for LN metastasis, which remain largely unknown, particularly with respect to histological prediction [13]. The study evaluated clinicopathological variables, including tumour stage, invasion patterns, and histological characteristics, in 53 patients who underwent surgical resection with neck dissection. The findings revealed that ipsilateral LN metastasis was associated with muscle and lymphatic invasion, whereas contralateral metastasis correlated with higher T stages and soft palate invasion. Skip lesions, base of tongue invasion, and advanced T stage were associated with poorer overall survival and Disease-free Survival (DFS). Therefore, skip lesions and advanced T stage are important prognostic variables in TSCC and should be included in pathology reports.

Woolgar JA analysed 439 cases of oral and oropharyngeal cancer and reported lymph node metastasis in 47% of patients [14]. Skip metastasis was identified in 10% of cases and was observed at all tumour sites except the retromolar region. The extent of nodal involvement was highest in oropharyngeal tumours, followed by cancers of the lateral tongue, ventral tongue, and floor of the mouth.

According to De Zinis LO et al., approximately 15% of patients with OSCC and lymph node involvement exhibited metastasis at level IV [15]. Among these cases, 28% of level IV nodal metastases represented skip metastases.

Kowalski LP and Sanabria A defined skip metastases as metastatic deposits that bypass the expected lymphatic drainage pathway of a tumour [16]. In oral cavity malignancies, lymphatic spread typically follows a sequential pattern, initially involving levels I and II before progressing to levels III to V. However, the reported incidence of skip metastasis at level IV ranges from 3% to 8%.

Giresh A et al., conducted a prospective observational study analysing 100 biopsy-proven OSCC cases undergoing surgical treatment with neck dissection to determine the prevalence of skip metastasis [17]. Data regarding DOI, perineural invasion, lymphovascular invasion, and nodal metastasis characteristics were collected from histopathology reports. The study population included 73 males and 27 females, with a mean age of 49.5 years. The most common tumour subsites were the buccal mucosa (40%), tongue (37%), and lower alveolus (14%). Cervical LN metastasis was observed in 36% of cases, predominantly at levels I, II, and III. Skip metastasis was identified in four cases (4%), involving levels IIb, III, and V, primarily in advanced tongue squamous cell carcinoma with a DOI greater than 5 mm. No skip metastasis was observed at level IV. These findings suggest that although skip metastases are uncommon, they occur predominantly in tongue carcinomas, and selective neck dissection may be appropriate to minimise surgical morbidity.

Yüce I et al., investigated the relationship between DOI and level IV cervical LN metastasis in clinically N0 tongue carcinoma [18]. The study concluded that tumours with a DOI greater than 8 mm and a size exceeding 2.5 cm were more likely to demonstrate level IV metastasis, particularly in poorly differentiated tumours. Notably, no isolated level IV metastasis was observed, and such involvement was absent in well-differentiated tumours. These findings suggest that DOI may serve as a useful parameter in determining the necessity for level IV neck dissection, thereby potentially reducing surgical complications.

Yang X et al., conducted a retrospective study involving 544 patients with early-stage Oral Tongue Squamous Cell Carcinoma (OTSCC) to evaluate factors associated with Occult lymph Node Metastasis (ONM) and skip metastasis, as well as their impact on DFS [19]. Tumour thickness of 6.4 mm or greater on Magnetic Resonance Imaging (MRI) was significantly associated with ONM and demonstrated predictive accuracy comparable to histological DOI. Skip metastasis was infrequent (1.3%) and did not significantly affect DFS. In contrast, ONM was associated with reduced DFS and higher recurrence rates within the first two years. Tumour thickness may therefore serve as a valuable preoperative indicator for ONM. Neck dissection of levels I–III appears adequate, with close follow-up recommended for patients with ONM.

- Hence, the aim of the present study protocol is to assess and correlate skip metastasis with DOI in OSCC.

Primary objective

to determine the correlation between skip metastasis and DOI in OSCC.

Secondary objectives:

to evaluate the incidence of skip metastasis in OSCC and to assess the DOI in OSCC cases.

MATERIALS AND METHODS

This cross-sectional study will be conducted in the Department of Oral Pathology and Microbiology, Sharad Pawar Dental College and Hospital, Datta Meghe Institute of Higher Education and Research (DMIHER), Sawangi Meghe, Wardha, Maharashtra, India. The study is planned over a period of 12 months, from July 2025 to June 2026, encompassing patient recruitment, surgical specimen evaluation, histopathological assessment, data analysis, and report preparation. Ethical approval has been obtained from the Institutional Ethics Committee of Datta Meghe Institute of Higher Education and Research (IEC Approval Ref. No. DMIHER(DU)/IEC/2024/256).

A total of 80 cases meeting the inclusion criteria will be selected. All diagnosed cases of OSCC undergoing neck dissection will be included.

Inclusion criteria: Surgically treated OSCC cases with confirmed clinical and histopathological diagnosis.

Exclusion criteria:

- Patients with recurrent OSCC
- Prior surgical intervention beyond biopsy
- History of oral cancer
- Presence of distant metastases
- Preoperative chemotherapy or radiotherapy.

Sample size calculation: Using the single-proportion formula and considering the prevalence of OSCC in the Department of Oral Pathology and Microbiology (70.7%), the sample size was calculated as follows:

$n \geq Z^2(1-\alpha/2)*p*(1-p)/d^2$

Where:

- $Z^2(1-\alpha/2)=1.96$ (95% confidence interval)
- p=70.7% (0.707)
- d=10% (0.10)

$n= (1.96^2 \times 0.707 \times (1-0.707))/0.10^2=80$ cases

Study Procedure

Patient records will be reviewed to obtain demographic details (age and gender), tumour site, clinical presentation, habits (tobacco and alcohol use), and lymph node involvement.

Evaluation of skip metastasis: A total of 80 Haematoxylin and Eosin (H&E)–stained OSCC slides will be analysed. LN involvement will be assessed both quantitatively and qualitatively under low and high magnification (400×) using an Leica DMLB2 research microscope. Blinded evaluations will be performed independently by two histopathologists, namely the primary researcher and the co-researcher.

Interobserver agreement between the two histopathologists will be assessed using Cohen's kappa statistic, which measures the degree

of agreement beyond chance. A kappa value close to 1 indicates strong agreement, whereas a value near 0 indicates little or no agreement. In cases of disagreement, the slides will be reviewed jointly by both pathologists, and a final diagnosis will be reached through mutual consensus.

Evaluation of Depth of Invasion (DOI): The DOI will be measured from the basement membrane or, if the basement membrane is absent, from an estimated line reconstructed based on the adjacent normal epithelium. Measurements will be taken from the deepest point of tumour infiltration into the connective tissue using a Leica DMLB2 research microscope equipped with Leica Q-Win standard software (Switzerland).

Both H&E-stained and Immunohistochemically (IHC) stained sections, cut at a thickness of 4 µm, will be analysed to ensure accurate depth measurement. DOI will be categorised according to the American Joint Committee on Cancer (AJCC) 8th edition staging guidelines [12] as follows:

- DOI ≤5 mm - T1 category
- DOI >5 mm and ≤10 mm - T2 category
- DOI >10 mm - T3 category

This categorisation will be utilised to analyse the correlation between DOI and the presence and pattern of LN metastasis, including skip metastasis.

Primary outcome: The biological behaviour of OSCC plays a pivotal role in disease progression and prognosis. Evaluating the correlation between skip metastasis and DOI is essential for understanding recurrence patterns and overall survival. Although LN metastasis is recognised as an important prognostic indicator, its role is considered passive rather than active in tumour progression. Existing prospective and retrospective clinical studies have not conclusively established regional nodal metastasis as an independent determinant of prognosis.

The present study aims to determine the incidence of skip metastasis in OSCC and to assess the statistical correlation between DOI and the occurrence of skip metastasis. Additionally, the study seeks to evaluate the impact of skip metastasis on DFS and overall prognosis.

Secondary outcomes: The study will examine the association between skip metastasis and various histopathological parameters, including perineural invasion, lymphovascular invasion, and tumour differentiation. It will also evaluate the distribution of skip metastasis across different subsites of the oral cavity. Furthermore, the influence of skip metastasis on decisions regarding postoperative adjuvant therapy will be assessed. Lastly, the role of imaging modalities in the preoperative prediction of skip metastasis will be analysed.

STATISTICAL ANALYSIS

Data will be entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS) software (version XX; specify the exact version, e.g., SPSS version 25.0). Descriptive statistics, including mean, standard deviation, frequency, and percentage, will be used to summarise patient demographics, tumour characteristics, DOI, and LN involvement.

- The incidence of skip metastasis will be expressed as a percentage of the total OSCC cases.
- The Chi-square test or Fisher's exact test will be applied to evaluate the association between skip metastasis and DOI.
- Cohen's kappa statistic will be used to assess interobserver agreement between the two histopathologists.
- A p-value <0.05 will be considered statistically significant.

If required, logistic regression analysis will be performed to determine whether DOI is an independent predictor of skip metastasis.

REFERENCES

[1] Dikshit R, Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, et al. Million death study collaborators. Cancer mortality in India: A nationally representative survey. Lancet. 2012;379(9828):1807-16. Doi: 10.1016/S0140-6736(12)60358-4. Epub 2012 Mar 28. Erratum in: Lancet. 2012 May 12;379(9828):1790. PMID: 22460346.

[2] Wild CP, Weiderpass E, Stewart BW, editors. World Cancer Report: Cancer research for cancer prevention. Lyon (FR): International Agency for Research on Cancer; 2020. PMID: 39432694.

[3] Li Y, Bai S, Carroll W, Dayan D, Dort JC, Heller K, et al, Brandwein-Gensler M. Validation of the risk model: High-risk classification and tumor pattern of invasion predict outcome for patients with low-stage oral cavity squamous cell carcinoma. Head Neck Pathol. 2013;7(3):211-23. Doi: 10.1007/s12105-012-0412-1. Epub 2012 Dec 19. PMID: 23250819; PMCID: PMC3738758.

[4] Alkureishi LWT, Ross GL, Stoeckli SJ. Sentinel Node Biopsy in Oral Cancer. In: Myers J. (ed). Oral Cancer Metastasis. New York, NY; Springer; 2009. Available from: https://doi.org/10.1007/978-1-4419-0775-2_3.

[5] Khanna C, Hunter K. Modeling metastasis in vivo. Carcinogenesis. 2005;26(3):513-23. Doi: 10.1093/carcin/bgh261. Epub 2004 Sep 9. PMID: 15358632.

[6] Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. Cell. 2017;168(4):670-691.

[7] Kapoor C, Vaidya S, Wadhwan V, Malik S. Lymph node metastasis: A bearing on prognosis in squamous cell carcinoma. Indian J Cancer. 2015;52(3):417-24. Doi: 10.4103/0019-509X.176750. PMID: 26905157.

[8] Nathanson SD. Insights into the mechanisms of lymph node metastasis. Cancer. 2003;98(2):413-23. Doi: 10.1002/cncr.11464. PMID: 12872364.

[9] Capote A, Escorial V, Muñoz-Guerra MF, Rodríguez-Campo FJ, Gamallo C, Naval L. Elective neck dissection in early-stage oral squamous cell carcinoma--does it influence recurrence and survival? Head Neck. 2007;29(1):03-11. Doi: 10.1002/hed.20482. PMID: 17103411.

[10] Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck. 1997;19(1):14-19. Doi: 10.1002/(sici)1097-0347(199701)19:1<14::aid-hed3>3.0.co;2-y. PMID: 9030939.

[11] Ferlito A, Shaha AR, Rinaldo A, Pellitteri PK, Mondin V, Byers RM. "Skip metastases" from head and neck cancers. Acta Otolaryngol. 2002;122(7):788-91. PMID: 12484658.

[12] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99. Doi: 10.3322/caac.21388. PMID: 28094848.

[13] Lee DJ, Kwon MJ, Nam ES, Kwon JH, Kim JH, Rho YS, et al. Histopathologic predictors of lymph node metastasis and prognosis in tonsillar squamous cell carcinoma. Korean J Pathol. 2013;47(3):203-10. Doi: 10.4132/KoreanJPathol.2013.47.3.203. Epub 2013 Jun 25. PMID: 23837012; PMCID: PMC3701815.

[14] Woolgar JA. The topography of cervical lymph node metastases revisited: The histological findings in 526 sides of neck dissection from 439 previously untreated patients. Int J Oral Maxillofac Surg. 2007;36(3):219-25. Doi: 10.1016/j.ijom.2006.10.014. Epub 2007 Jan 18. PMID: 17239562.

[15] De Zinis LO, Bolzoni A, Piazza C, Nicolai P. Prevalence and localization of nodal metastases in squamous cell carcinoma of the oral cavity: Role and extension of neck dissection. Eur Arch Otorhinolaryngol. 2006;263(12):1131-35. Doi: 10.1007/s00405-006-0128-5. Epub 2006 Sep 27. PMID: 17004089.

[16] Kowalski LP, Sanabria A. Elective neck dissection in oral carcinoma: A critical review of the evidence. Acta Otorhinolaryngol Ital. 2007;27(3):113-17. PMID: 17883186; PMCID: PMC2640044.

[17] Giresh A, Parida PK, Chappity P, Adhya AK, Nayak A, Pradhan P, et al. Prevalence of skip metastases to cervical lymph-nodes in oral cavity cancer in eastern india-an observational study. Indian J Otolaryngol Head Neck Surg. 2022;74(Suppl 3):6374-83. Doi: 10.1007/s12070-021-03048-z. Epub 2022 Apr 25. PMID: 36742498; PMCID: PMC9895623.

[18] Yüce I, Oflaz Çapar A, Çetinaslan V, Deniz K, Vural A, Çağlı S, et al. The depth of invasion and level iv cervical node metastasis in patients with clinically n0 tongue cancer. Head Neck Pathol. 2024;18(1):41. Doi: 10.1007/s12105-024-01647-0. PMID: 38727801; PMCID: PMC11087439.

[19] Yang X, Xiang W, Sun Y, Li W, Ji X, Gao S, et al. Risk factors and impact of occult and skip metastasis in early-stage oral tongue squamous cell carcinoma. Clin Oral Investig. 2024;28(9):510. Doi: 10.1007/s00784-024-05897-8. PMID: 39218959.

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