

Investigating the Relationship between Tumor Depth and Lymphatic Spread in Oral Squamous Cell Carcinoma

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Abstract

Background: The presence of cervical lymph node metastasis (LNM) plays a pivotal role in determining prognosis and is essential for enhancing survival rates among patients with oral squamous cell carcinoma (OSCC). This study aimed to explore the relationship between the depth of tumor invasion and the likelihood of cervical LNM in patients with OSCC. **Material and Methods:** A total of 100 cases of OSCC, clinically diagnosed and histopathologically confirmed, were gathered from the Bharat Cancer and Research Institute in Saroli, Surat. The primary focus of the study was the depth of invasion (DOI), while additional factors examined included age, sex, tumor location, and tumor size. Two histological parameters, namely the degree of differentiation and perineural invasion, were also evaluated to determine their relationship with cervical LNM. The latest American Joint Committee on Cancer system was utilized for microscopic measurement of tumor depth. **Results:** Approximately, 31% of patients with clinical negative and pathological positive lymph nodes exhibited a tumor depth of ≥ 10 mm, a result that holds statistical significance. Statistical significance was observed with a $P \leq 0.05$. The prevalence of perineural invasion was observed in approximately 34% of clinical and pathological positive lymph nodes; however, this association did not reach statistical significance ($P > 0.05$). A notable correlation was identified between the degree of differentiation and the occurrence of cervical LNM. **Conclusion:** The DOI of OSCC (DOI) emerges as a significant prognostic indicator for the early identification of this malignancy.

Keywords: Cervical lymph node metastasis, Oral squamous cell carcinoma, Perineural invasion, Tumor depth.

INTRODUCTION

Oral cancer predominantly consists of oral squamous cell carcinoma (OSCC), accounting for 95% of cases affecting the oral mucosa. The cancer in question ranks as the sixth most prevalent type, representing between 0.6% and 5% of all cancer cases in Europe, the United States, and Australia. In stark contrast, it accounts for as much as 45% of cancer cases in India.^[1,2] The tumor-node-metastasis (TNM) classification has long served as a standardized and objective framework for assessing cancer patients on a global scale. Numerous studies indicate that a range of factors beyond size, node involvement, and metastasis can significantly impact a patient's prognosis.^[3,4]

Even with improvements in imaging technologies aimed at identifying lymph node involvement, hidden metastases remain undetected in 20–50% of patients who are classified as lymph node-negative. Patients in this category typically manifest a clinically noticeable cervical metastasis, often occurring within a 2-year timeframe.^[5] Lymph node metastasis

(LNM) is a crucial factor in the assessment of cancer patients, significantly influencing disease staging, clinical management, and prognostic outcomes. Recent advancements in medical technologies and research centered on LNM have facilitated more effective detection and treatment of this condition.^[6,7]

The presence of cervical LNM plays a pivotal role in determining prognosis and is essential for enhancing survival rates among patients with OSCC.^[8] In the early stages of OSCC, the presence of occult LNM has been documented to carry a risk as high as 40%.^[9] The depth of invasion (DOI)

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currently plays a crucial role as a prognostic factor in the identification of occult LNM. The integration of this element into the American Joint Committee on Cancer (AJCC) (eighth edition) manual underscores its importance in classification and staging.^[10]

The evaluation of tumor depth can be conducted using the methodology outlined in the latest AJCC (8th edition) manual. The DOI was assessed by measuring from the basement membrane of the adjacent normal mucosa to the deepest point of tumor invasion, utilizing an optical micrometer or a transparent ruler placed over the slide. The histological characteristics of OSCC exhibit significant variability and are often subject to diverse interpretations by pathologists. This variability arises from the heterogeneity present not only among different tumors but also within individual tumors and across adjacent, yet biologically distinct, oral anatomical sites. We utilize Broder's grading system, known for its simplicity and ease of use, as one of the parameters in our study.^[11] The presence of perineural invasion has garnered attention in recent studies, emphasizing the associated risks of cervical LNM and the potential for local recurrence of the primary tumor.^[12]

This study aimed to explore the relationship between the depth of tumor invasion and the likelihood of cervical LNM in patients with OSCC.

MATERIALS AND METHODS

The human ethics committee at Bharat Cancer and Research Institute in Saroli, Surat, has granted approval for the study protocol. A total of 100 cases of OSCC, clinically diagnosed and histopathologically confirmed, were gathered from the Bharat Cancer and Research Institute in Saroli, Surat, during the period from 2016 to 2019. Each patient provided written consent. All specimens were subjected to standard procedures for fixation, processing, and staining using H and E stains.

Inclusion criteria

(1) All samples from neck dissections. (2) Cases with no history of prior treatment are included.

Exclusion criteria

Patients with a history of proven or suspected metastasis are excluded.

The evaluation of lymph nodes before surgery was conducted through a physical examination. Individuals with confirmed or suspected distant metastasis were not included in our study.

All relevant information was extracted from hospital charts and histopathological reports and documented in our case sheet. Pathological reports and slides from all primary tumors were forwarded to a pathologist who was unaware of the patient's clinical history. This step was taken to reconfirm the initial diagnosis of squamous cell carcinoma and to assess various histopathologic parameters, including tumor depth, degree of differentiation, and perineural invasion.

The primary focus of the study was the DOI, while additional factors examined included age, sex, tumor location, and tumor size. Furthermore, two histological parameters were evaluated: The degree of differentiation and perineural invasion, all in relation to their potential association with cervical LNM.

The latest AJCC system was employed to microscopically measure tumor depth. The degree of differentiation was assessed using Broder's grading system, which categorizes tumor cell differentiation and keratinization into four classifications: Well-differentiated OSCC, moderately differentiated OSCC, poorly differentiated OSCC, and anaplastic OSCC. The slides underwent an assessment to determine whether perineural invasion was present or absent.

Statistical analysis

The collected data were organized and input into a spreadsheet application (Microsoft Excel 2019) before being transferred to the data editor interface of Statistical Packages for the Social Sciences (SPSS) version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were characterized using means and standard deviations or medians and interquartile ranges, depending on their distribution patterns. Qualitative variables were reported in terms of counts and percentages. The relationships between qualitative variables were examined through the Chi-square test. The confidence level for all tests was established at 95%, while the level of significance was determined to be 5%.

RESULTS

The relationship between age and cervical LNM in patients with OSCC is detailed in Table 1. The highest number of lymph nodes was noted in individuals aged 41–50 years, although this association did not reach statistical significance ($P > 0.05$).

Table 2 outlines the relationship between gender and the presence of clinical and cervical LNM in patients with OSCC. A total of 155 patients were identified as male, while 45 patients were identified as female. Approximately 39% of male patients presented with clinical and pathological positive nodes. The statistical analysis revealed no significant association between gender and cervical LNM, with a $P > 0.05$.

Table 3 presents the relationship between tumor depth and cervical LNM in patients with OSCC. Approximately 31% of patients with clinical negative and pathological positive lymph nodes exhibited a tumor depth of ≥ 10 mm, a finding that reached statistical significance. Statistical significance was observed with a $P \leq 0.05$.

Table 4 outlines the relationship between perineural invasion and the presence of cervical LNM. The highest incidence of perineural invasion was noted in approximately 34% of clinical and pathological positive lymph nodes; however, this association did not reach statistical significance ($P > 0.05$).

Table 5 outlines the relationship between the degree of differentiation and the occurrence of cervical LNM. A notable

Table 1: Association of age and cervical lymph node metastasis

Age (years)	CP				Total	P-value
	Clinical and patho positive	Clinical positive and patho negative	Clinical negative and patho positive	Clinical and patho negative		
30–40	9 (34.61)	9 (34.61)	7 (26.92)	1 (3.84)	26 (26)	0.20
41–50	8 (23.52)	11 (32.35)	8 (23.52)	7 (20.58)	34 (34)	
51–60	5 (20.83)	5 (20.83)	8 (33.33)	6 (25)	24 (24)	
61–70	3 (21.42)	5 (35.71)	4 (28.57)	2 (14.28)	14 (14)	
71–80	0	0	1 (50)	1 (50)	2 (2)	
Total	25 (25)	30 (30)	28 (28)	17 (17)	100	

Test applied Chi-square test, Level of significance $P \leq 0.05$ **Table 2: Association of Gender and cervical lymph node metastasis**

Gender	Lymph node metastasis				Total	P-value
	Clinical and patho positive	Clinical positive and patho negative	Clinical negative and patho positive	Clinical and patho negative		
Male	20 (25.97)	23 (29.87)	18 (23.37)	16 (20.77)	77 (77)	0.19
Female	5 (21.73)	7 (30.43)	10 (43.47)	1 (4.3)	23 (22.5)	
Total	25 (25)	30 (30)	28 (28)	17 (17)	100 (100)	

Test applied Chi-square test, Level of significance $P \leq 0.05$ **Table 3: Association of tumor depth and cervical lymph node metastasis**

Tumor depth	Lymph node metastasis				Total	P-value
	Clinical and patho positive	Clinical positive and patho negative	Clinical negative and patho positive	Clinical and patho negative		
<5 mm	1 (14.28)	3 (42.85)	1 (14.28)	2 (28.57)	7 (7)	0.02*
≤5–<10 mm	2 (13.33)	6 (40)	2 (13.33)	5 (33.33)	15 (14)	
≥10 mm	22 (28.20)	21 (26.92)	25 (32.05)	10 (12.82)	78 (78)	
Total	25 (24)	30 (30)	28 (28)	17 (17)	100 (100)	

Test applied Chi-square test, Level of significance $P \leq 0.05$ **Table 4: Association of perineural invasion and cervical lymph node metastasis**

Invasion	Lymph node metastasis				Total	P-value
	Clinical and patho positive	Clinical positive and patho negative	Clinical negative and patho positive	Clinical and patho negative		
Present	8 (34.78)	6 (26.08)	7 (30.43)	2 (8.69)	23 (23)	0.26
Absent	17 (22.07)	24 (31.16)	21 (27.27)	15 (19.48)	77 (77)	
Total	25 (25)	30 (30)	28 (28)	17 (17)	100 (100)	

Test applied Chi-square test, Level of significance $P \leq 0.05$

correlation was identified between the degree of differentiation and the occurrence of cervical LNM. Statistical significance was observed with a $P < 0.05$.

DISCUSSION

A comprehensive approach to managing oral cancer focuses on addressing both the primary lesion and the neck involvement. Lesions classified as T1-T2 generally present a risk of regional metastasis ranging from 10% to 30%, whereas T3-T4 lesions exhibit a markedly elevated risk. Typically, the approach to managing the neck, particularly through elective neck

dissection (END), is advised when there is a risk of cervical lymph node involvement exceeding 15%.^[13-16]

Since the late 1800s, radical neck dissections have been performed with the aim of preventing cancer recurrences, even though these procedures have been associated with significant post-operative complications, including shoulder dislocation. During the more targeted neck dissections of the 1980s, the lymph nodes responsible for draining the tumor's original location were surgically excised. Shoulder dysfunction can still arise occasionally, even with conservative treatment approaches.^[17] Several factors play a crucial role

Table 5: Association of the degree of differentiation and cervical lymph node metastasis

Degree_diff	Lymph node metastasis				Total	P-value
	Clinical and patho positive	Clinical positive and patho negative	Clinical negative and patho positive	Clinical and patho negative		
Well	20 (25.31)	25 (31.64)	22 (27.84)	12 (15.18)	79 (79)	0.05*
Moderate	4 (21.05)	4 (21.05)	6 (31.57)	5 (26.31)	19 (19)	
Poor	1 (50)	1 (50)	0	0	2 (2)	
Total	25 (25)	30 (30)	28 (28)	17 (17)	100 (100)	

Test applied Chi-Square test, Level of significance $P \leq 0.05$

in determining the rate of cervical metastasis and survival outcomes for patients with oral cavity cancer. These include the size and location of the primary tumor, the T-stage, the grade, the DOI, biological tumor markers, perineural invasion, and patient compliance.^[18] Historically, the size of the tumor and its location were considered critical factors in predicting outcomes, leading to the creation of various prognostic models aimed at assessing the extent of metastatic spread. Recently, the significance of DOI has been recognized as a crucial prognostic factor for the early detection of OSCC.

Endoscopic evaluation can serve both diagnostic and therapeutic purposes, offering crucial pathological insights regarding the condition of neck nodes. This information is instrumental in assessing the necessity for additional adjuvant therapies. In addition, it eliminates any clinically undetectable metastases. However, a considerable proportion of patients who undergo END may show no signs of regional lymph node metastases, potentially exposing them to the risks associated with neck dissection. The status of cervical lymph nodes stands out as the most crucial prognostic indicator for patients diagnosed with head and neck carcinoma. Consequently, the prediction of nodal metastasis emerges as a significant concern, making the identification of reliable parameters to assess the risk of cervical lymph node involvement highly valuable.^[14,16]

A recent study examined the significance of invasion depth in determining the prognosis of OSCC. Their analysis also focused on its role in carcinoma. Histological parameters, including DOI, have been suggested as potential prognostic factors in carcinoma. The detection of invasion, particularly in the underlying tissue, effectively rules out DOI. Following a histological examination, the patient's treatment plan may be adjusted. Incorporating DOI measurement into routine histological examination is essential.^[9]

The current study revealed that approximately 31% of patients with clinical negative and pathological positive lymph nodes exhibited a tumor depth of ≥ 10 mm, a finding that was statistically significant. Statistical significance was observed with a $P \leq 0.05$. Individuals with a depth of < 9 mm demonstrated significantly better outcomes compared to those with a depth exceeding 9 mm ($P < 0.05$).

Hoşal *et al.* found that patients with a tumor depth of < 9 mm had significantly better outcomes compared to those with a depth > 9 mm ($P < 0.05$).^[19] Consequently, it is essential

to consider tumor depth when determining the appropriate neck treatment. Hoşal *et al.* suggested that elective node dissection should be reserved for patients with a tumor depth exceeding 9 mm. This approach aims to enhance cure rates while minimizing surgical morbidity in individuals who are unlikely to experience neck metastasis.^[19] In a similar vein, Ambrosch *et al.* observed a significant correlation between tumor depth and nodal disease; however, they did not identify any such relationship with pathologic tumor size or histologic grade.^[20] The study revealed that a depth of 2 mm serves as a significant threshold for assessing the risk of LNM. Yuen *et al.* found that among the various tumor parameters and predictive models assessed, tumor thickness emerged as the sole factor with a statistically significant predictive value for subclinical node metastasis, local recurrence, and survival outcomes.^[21]

In our study, we also considered the histologic differentiation of the tumor as a key parameter. Our findings indicate that well-differentiated tumors show a notable correlation with the lowest occurrence of neck metastasis, whereas poorly differentiated tumors are linked to a significantly higher prevalence. This finding aligns with the results of several other foundational studies on oral cavity squamous cell carcinoma. A study conducted by Chen *et al.* examined 94 patients diagnosed with tongue cancer. The findings revealed that individuals with poorly and moderately differentiated tumors exhibited a greater incidence of neck node involvement compared to those with well-differentiated tumors.^[22] The research conducted by Fukano *et al.* revealed no notable correlation between the level of tumor differentiation and the statuses of pN0 and pN+.^[23]

The presence of LNM, blood vessel involvement, perineural invasion, and tumor grading are critical factors influencing the prognosis for patients with OSCC. The clinical relevance and value of histopathological parameters are established through the clinical TNM classification. Nonetheless, inconsistencies remain. Notable instances of early oral cancer diagnosis, particularly those involving smaller tumor sizes, are associated with poorer prognoses. This clearly suggests that the aggressiveness of tumors and their biological environment are not influenced by TNM staging.^[24-26]

The primary limitation of this study lies in its retrospective design and the fact that it was conducted at a single center. Future research should focus on conducting a multicentric prospective study utilizing standard protocols to establish a

correlation between the DOI and the radiological features alongside the histopathological characteristics of tumors.

CONCLUSION

The degree of differentiation and the DOI showed a significant correlation with the presence of neck node metastasis. Consequently, DOI emerges as a significant prognostic indicator for the early identification of OSCC. We suggest conducting a prospective multi-center study to explore the relationship between radiological modalities and the histopathological assessment of the DOI.

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