Original Article

From Adhesion to Invasion: Role of E-cadherin and Vimentin in Oral Squamous Cell Carcinoma Progression

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DOI
10.21276/apalm.3794

Article History
Received: 25-12-2025
Revised: 28-01-2026
Accepted: 08-02-2026
Published: 02-03-2026

How to cite this article
Samin F, Chauhan R, Awasthi S, et al. From Adhesion to Invasion: Role of E-cadherin and Vimentin in Oral Squamous Cell Carcinoma Progression. Ann Pathol Lab Med. 2026;13(3):A135-A140.

Abstract

Background: Oral squamous cell carcinoma (OSCC) is a leading cause of cancer mortality and morbidity in India. It is an aggressive malignancy with potential for local invasiveness and metastasis. This study was conducted to study the expression of *E-cadherin* and *vimentin* in different histological grades of OSCC and to correlate their expression patterns with lymph node metastasis.

Materials and Methods: 28 biopsy cases diagnosed as primary OSCC over 3 years were obtained from department's histopathology archives. Immunohistochemical staining for *vimentin* and *E-cadherin* was done, and their expression was compared in different histological grades of OSCC and correlated with lymph node metastases. As control, six benign lesions of oral mucosa were used. Independent t-test and Chi-square test were used to correlate expression of *E-cadherin* and *vimentin* in different histological grades of OSCC as well as with nodal status positivity. p value < 0.05 was considered significant.

Results: Benign lesions did not express *vimentin*, but they exhibited strong positivity for *E-cadherin*. *Vimentin* expression increased with increasing OSCC grades, but the difference was not significant statistically. However, *E-cadherin* expression dramatically declined with increasing grades of OSCC (p value 0.005). There was a significant difference in expression of *Vimentin* and *E-cadherin* in OSCC cases with and without nodal metastasis.

Conclusion: Regional metastasis and poor histological differentiation in OSCC might be related to downregulation of *E-cadherin* expression, along with aberrant *vimentin* expression. Thus, *vimentin* and *E-cadherin* can be helpful prognostic indicators in oral squamous cell carcinoma.

Keywords: immunohistochemistry; squamous cell carcinoma; cell adhesion molecules

Introduction

Oral squamous cell carcinoma (OSCC) is one of the most commonly occurring malignancies of neck and head region, contributing to a significant global cancer burden. Every year, approximately 900,000 new cases are reported, with over 400,000 deaths worldwide.[1] The incidence is particularly high in the Indian subcontinent, where habits like tobacco use, betel nut chewing, and alcohol consumption are major risk factors.[2] Despite advancements in treatment, OSCC remains a challenge due to its aggressive behaviour and high propensity for local invasion and lymph node metastasis, which significantly worsens prognosis.

A crucial factor in OSCC progression is epithelial to mesenchymal transition (EMT), a process by which tumor cells develop mesenchymal traits and lose epithelial traits like cell adhesion and polarity, leading to increased motility and invasion. Among

the key markers regulating EMT, *E-cadherin* and *vimentin* have significant function. *E-cadherin*, a calcium-dependent cell adhesion protein, maintains epithelial integrity, and its loss is associated with tumor invasiveness. On the other hand, *vimentin*, a mesenchymal intermediate filament protein, is responsible for tumor progression and metastasis, aiding in cell migration and invasion.[3, 4]

Several immunohistochemical (IHC) studies have shown that a cadherin switch, where *E-cadherin* expression is lost, and *vimentin* is upregulated, is linked to poor tumor differentiation in advanced stage, as well as lymph node metastasis in OSCC. Recent research highlights that low *E-cadherin* expression in invasive front of tumors correlates with adverse prognosis, while high *vimentin* expression has been related to aggressive tumor behavior. Further studies analyzing different OSCC histological grades and cases with and without lymph node metastasis reinforce the potential of these markers as prognostic indicators.[5]

Considering the growing evidence supporting the role of EMT markers in OSCC progression, the present study aims to evaluate the immunohistochemical expression of *E-cadherin* and *vimentin* in different grades of OSCC and correlate their expression patterns with lymph node metastasis. Understanding these molecular changes can help in better prognostic stratification and potentially guide therapeutic decisions, ultimately improving patient outcomes.

Material and Methods

This retrospective study was approved by the Institutional Ethics Committee (IEC no. IRB/132/2025). Here 28 primary OSCC cases collected over a 3-year duration were studied. Formalin-fixed and paraffin-embedded tissue blocks were extracted from the departmental histopathology archives. Clinical details and lymph node status were documented from patient files. Cases showing radiological or cytological evidence of nodal metastasis were considered as node-positive. Six benign oral mucosal lesions were used as controls. Sections of 4 µm were stained with H&E and graded as well-, moderately-, or poorly-differentiated OSCC on microscopy. IHC was performed for *Vimentin* and *E-cadherin* using DAKO antibodies.

Immunohistochemistry controls and evaluation

Known positive control tissues were used for *E-cadherin* and *vimentin*. Negative controls were prepared by omitting the primary antibody. Stromal fibroblasts and endothelial cells served as internal positive controls for *vimentin*. Immunohistochemical scoring was performed independently by two pathologists who were blinded to the histological grade and lymph node status of the cases.

Immunostaining was scored using the Immunoreactive Score (IRS):[6] IRS = "Intensity Score (IS) $\times$ Proportion Score (PS), IS- 0: negative, 1: weak, 2: moderate, 3: strong. PS- 0=negative, 1:$<$10%, 2:10-50%, 3:50-80%, 4:$>$80%. Total score: 0 to 12. Final scores: 0 = negative, 1–4 = low, 5–12 = high immunoreactivity.

Localization of immunostaining

E-cadherin expression was evaluated as membranous staining in tumor cells. *Vimentin* expression was assessed as cytoplasmic positivity in tumor cells.

For statistical analysis, Independent t-test and Chi-square test were used to correlate expression of *E-cadherin* and *vimentin* in different histological grades of OSCC as well as with nodal status positivity. p value < 0.05 was considered as significant.

Results

The benign control group consisted of 6 cases, which included 3 cases of Squamous cell papilloma, 2 of Papillary hyperplasia and 1 of Frictional keratosis. A total of 28 biopsy cases diagnosed as primary OSCC were studied. Mean age of the patients was 54.7 years, with a male predilection (n=26, 93%).

Site and Histological Distribution

Among 28 OSCC cases, tongue (39%) was the most common site followed by the buccal mucosa (36%).

Histologically, cases were classified as: Well-differentiated (WDSCC): 67.8% (n=19), Moderately differentiated (MDSCC): 28.6% (n=8), Poorly differentiated (PDSCC): 3.6% (n=1) .

Comparison with Controls and Tumor Grades

All benign controls showed high *E-cadherin* (100%) with high immunoreactivity (IRS 5-12) and negative *vimentin* expression (100%, IRS 0) [Table 1], [Figure1]. Oral Squamous cell carcinoma

Table 1: Expression of *E-cadherin* and *vimentin* immunoreactivity in benign oral mucosa and various grade of OSCC.

	E-Cadherin				P-value	Vimentin			P-value
	(n=28)	Negative	Low (1-4)	High (5-12)		Negative	Low (1-4)	High (5-12)	
Control									
Benign	6	0	0	6	0.005	6	0	0	
OSCC									
WDSCC	19	0	12	7		1	9	9	0.79
MDSCC	8	1	5	2		0	3	5	
PDSCC	1	1	0	0		0	0	1	

Well differentiated squamous cell carcinoma
Moderately differentiated squamous cell carcinoma
Poorly differentiated squamous cell carcinoma

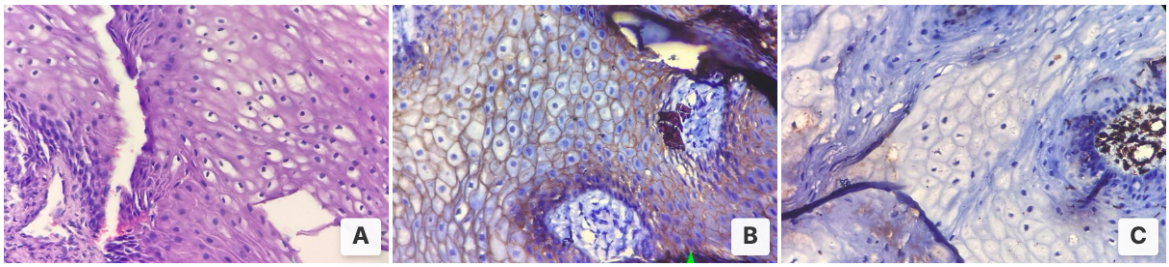

Figure 1: *E-cadherin* and *vimentin* expression in benign oral mucosa. A: H & E section, B: *E-cadherin* (IRS high), C: *Vimentin* (IRS negative).

Out of 19 cases of WDSCC, 63.1% showed low *E-cadherin*, while 47.4% had high *vimentin* expression. Out of 8 cases

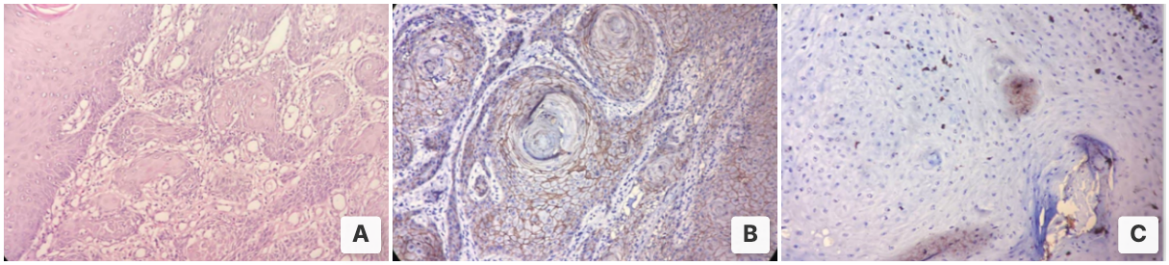

Figure 2: *E-cadherin* and *vimentin* expression in well-differentiated oral squamous cell carcinoma without lymph node metastasis. A: H & E section, B: *E-cadherin* (IRS high), C: *Vimentin* (IRS low).

of MDSCC, 62.5% cases showed low *E-cadherin* and 62.5% showed high *vimentin* expression. The single PDSCC case exhibited negative *E-cadherin* and high *vimentin* expression (p = 0.79).

A statistically significant association was observed between *E-cadherin* expression and tumor grade (p=0.005), while *vimentin* expression showed no significant association. Although *vimentin* expression showed an increasing trend with higher tumor grades, the association was not statistically significant (p = 0.79), possibly due to the limited number of poorly differentiated cases.

Nodal Metastasis

Positive nodal status was seen in 60.7% cases (n=17). Negative nodal status was noted in 39.3% cases (n=11).

E-cadherin and *Vimentin* Expression: Correlation with Nodal Metastasis

Low *E-cadherin* expression (IRS ≤4) was observed in 70.6% of node-positive cases vs 63.7% of node-negative cases. High *vimentin* expression (IRS 5–12) was significantly more frequent in node-positive cases (70.6%) than in node-negative cases (27.3%).These differences were statistically significant for both *E-cadherin* and *vimentin* (p value 0.034 and 0.005 respectively). [Table 2],[Figure 3,4].

Table 2: Comparison of expression of *E-cadherin* and *vimentin* immunoreactivity in OSCC cases with and without nodal metastasis.

	E-Cadherin			P-value	Vimentin		P-value
	(n=28)	≤4	5-12		≤4	5-12	
Nodal metastasis (-)	11	7	4	0.034	8	3	0.005
Nodal metastasis (+)	17	12	5		5	12	

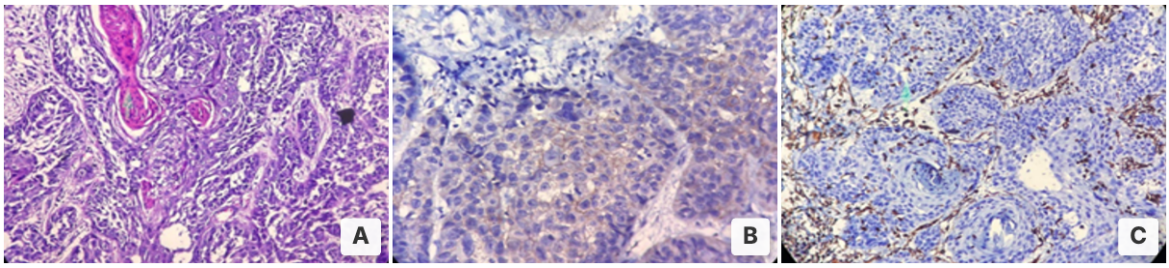

Figure 3: *E-cadherin* and *vimentin* expression in well-differentiated oral squamous cell carcinoma with lymph node metastasis. A: H & E section, B: *E-cadherin* (IRS low), C: *Vimentin* (IRS high).

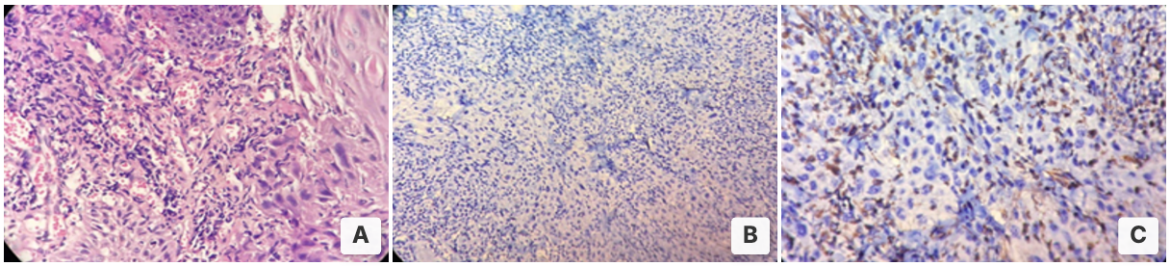

Figure 4: *E-cadherin* and *vimentin* expression in moderately differentiated oral squamous cell carcinoma with lymph node metastasis, A: H & E section, B: *E-cadherin* (IRS negative), C: *Vimentin* (IRS high).

Discussion

The current study aimed to evaluate *E-cadherin* and *vimentin* expression in OSCC, along with its correlation with tumor differentiation and metastasis to lymph nodes. Our findings suggest significant association of *E-cadherin* down-regulation and *vimentin* upregulation with loss of histological differentiation and nodal metastasis in OSCC cases.

E-cadherin has a pivotal role in maintaining epithelial cell adhesion; its loss attributes to the process of epithelial to mesenchymal transition (EMT),[7] which provides a tumor its property to invade and metastasize. In our study, *E-cadherin* expression was observed to be significantly reduced in poorly differentiated OSCC as compared to well-differentiated tumors, aligning with earlier research by Liu *et al.* (2017) and Akhtar *et al.* (2016), which exhibited decreased *E-cadherin* expression with increasing tumor grade as well.[3, 8] The results reinforce the notion that *E-cadherin*-mediated adhesion loss contributes in OSCC progression and dissemination. Recent studies, including those by Kar *et al.* (2021) and Puneeta *et al.* (2022),[9, 10] further emphasize *E-cadherin*'s role in OSCC progression, highlighting its potential as a prognostic biomarker.

Clinically, altered expression of EMT markers like *E-cadherin* and *vimentin* can help in identifying oral squamous cell carcinoma cases with aggressive behavior. Reduced *E-cadherin* expression, especially when associated with increased *vimentin* expression, indicates higher invasive and metastatic potential. Evaluation of these markers may help in risk stratification and in identifying patients who need closer follow-up, early neck assessment, or more aggressive treatment. Thus, *E-cadherin* and *vimentin* can be used as adjunct prognostic markers along with routine clinicopathological parameters.

On the other hand, *vimentin*, a mesenchymal marker, was found to be highly expressed in high histological grades of OSCC cases and ultimately associated with tumor invasion and metastasis. This observation supports the notion that OSCC cells undergo EMT, acquiring a mesenchymal phenotype that enhances their migratory and invasive properties. Our findings are in line with Kumar *et al.* (2021) and Balasundaram *et al.* (2014), who also reported elevated *vimentin* levels in metastatic OSCC cases.[6, 7] Additional recent research by Liu *et al.* (2010) and Fernández *et al.* (2017) confirmed the predictive value of *vimentin* in metastatic OSCC, reinforcing its clinical significance.[11, 12].

The lack of a statistically significant association between *vimentin* expression and histological grade may be attributed to the limited sample size and the uneven distribution of tumor grades, particularly the low number of poorly differentiated cases. However, the significant association of *vimentin* expression with lymph node metastasis suggests that its role may be more closely related to tumor invasiveness and metastatic behavior rather than differentiation alone.

The comparative analysis with previous studies highlights some discrepancies, particularly in *E-cadherin* expression. While Kumar *et al.* (2021) reported a higher *E-cadherin* expression in OSCC, we observed a significant decrease in its expression, particularly in high-grade tumors.[7] These variations could be attributed to differences in sample size, immunohistochemical techniques, and tumor heterogeneity. More recent studies, including that of Kar *et al.* (2021),[9] suggest that *E-cadherin* expression patterns may also be influenced by tumor micro-environment factors and the presence of inflammatory mediators.

Furthermore, while comparing node negative cases with the cases having nodal metastasis, we discovered significant reduction in *E-cadherin* expression along with a concomitant increase in *vimentin* levels in metastatic cases. This suggests that EMT-associated molecular alterations could serve as potential biomarkers for predicting aggressiveness and metastatic capacity. Puneeta *et al.* (2022) in their research also support this notion, demonstrating a strong correlation between *E-cadherin* down-regulation, *vimentin* upregulation, and OSCC progression.[10]

Research limitations of present study include a comparatively smaller sample size and need of functional assays to validate the mechanistic role of *E-cadherin* and *vimentin* in OSCC progression. Further research with larger cohorts along with molecular validation techniques are warranted for confirming these results.

Conclusion

Within the limitations of this study, reduced *E-cadherin* expression and increased *vimentin* expression were found to be associated with aggressive tumor behavior and lymph node metastasis in oral squamous cell carcinoma. These findings support the role of epithelial–mesenchymal transition in OSCC progression. However, larger studies are required to validate the prognostic utility of these markers before routine clinical application.

Abbreviations: OSCC: Oral squamous cell carcinoma; EMT: Epithelial to mesenchymal transition; IHC: Immunohistochemical; IRS: Immunoreactive Score; IS: Intensity Score; PS: Proportion Score; WDSCC: Well-differentiated squamous cell carcinoma; MDSCC: Moderately differentiated squamous cell carcinoma; PDSCC: Poorly differentiated squamous cell carcinoma.

Acknowledgements: None.

Funding: Nil.

Competing Interests: None.

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