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ORIGINAL ARTICLE

Immunohistochemical Pattern and Histopathological Association of Vascular Endothelial Growth Factor in Oral Squamous Cell Carcinoma

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ABSTRACT

Background: *Oral squamous cell carcinoma constitutes the majority of oral malignancies, with a particularly high burden in South Asia. Because VEGF-mediated angiogenesis may influence tumor growth, invasion, and progression, its immunohistochemical expression may provide additional information beyond conventional histopathological grading.* ***Aim of the study:*** *This study aimed to evaluate the immunohistochemical pattern of VEGF expression in oral squamous cell carcinoma and determine its association with histopathological grade.* ***Methods & Materials:*** *This cross-sectional observational study included 50 histopathologically confirmed OSCC cases at Rajshahi Medical College from September 2018 to August 2020. Tumors were graded histologically and evaluated immunohistochemically for VEGF expression using staining intensity and the percentage of positive tumor cells. VEGF expression was classified as negative, weakly positive, positive, or strongly positive. Data were analyzed using SPSS version 23, and $p<0.05$ was considered statistically significant.* ***Results:*** *The mean age of the patients was 52.96 ± 11.19 years, 56.0% were female, and 60.0% had Grade I tumors. VEGF positivity was observed in 86.0% of cases, including 38.0% with strong expression, while 69.8% of VEGF-positive tumors showed both cytoplasmic and membranous staining. VEGF staining intensity was significantly associated with histopathological grade ($p=0.037$), with maximal staining most frequent in Grade III tumors (50.0%). However, VEGF-positive cell percentage, combined VEGF score, and overall positivity were not significantly associated with grade.* ***Conclusion:*** *VEGF was frequently expressed in oral squamous cell carcinoma, and its staining intensity increased significantly with poorer histopathological differentiation. These findings suggest that VEGF staining intensity may serve as a useful adjunct marker of tumor aggressiveness in OSCC.*

Keywords: *Oral squamous cell carcinoma; Vascular endothelial growth factor; Immunohistochemistry; Histopathological grade; Angiogenesis*

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INTRODUCTION

Globally, oral squamous cell carcinoma (OSCC) represents approximately 90% of malignant tumors arising in the oral cavity and remains a substantial cause of cancer-related morbidity and mortality. In 2020, an estimated 377,000 new cases of lip and oral cavity cancer occurred worldwide, with the greatest burden concentrated in Asia [1]. Between 1990 and 2019, the global age-standardized incidence rate of oral cancer increased from 4.28 to 4.52 per 100,000 population, while South Asia recorded the highest age-standardized incidence, mortality, and disability-adjusted life-year rates in 2019 [2]. Despite improvements in diagnosis, surgery, radiotherapy, systemic therapy, and supportive care, survival remains unsatisfactory, particularly when disease is diagnosed at an advanced stage [1,3]. In South and South-Central Asia, the burden of OSCC is amplified by widespread exposure to tobacco smoking, smokeless tobacco, areca nut, betel quid, poor oral hygiene, and other socio-behavioral risk factors [4,5]. Within this region, cancers frequently involve the buccal mucosa because carcinogenic substances are often retained against the oral mucosa during chewing [5]. Although researchers have also investigated human papillomavirus, evidence on its independent contribution to OSCC in South-Central Asian populations remains inconsistent [4]. Because Bangladesh belongs to this high-risk geographical region, evaluation of locally relevant tumor characteristics and biological markers is particularly important for understanding disease behavior and improving risk stratification. Clinically, OSCC may produce pain, ulceration, difficulty in mastication and swallowing, impaired speech, disfigurement, and deterioration of quality of life [1,3]. Histopathological assessment remains fundamental for confirming the diagnosis and characterizing tumor differentiation. Although histological grade indicates cellular differentiation, substantial biological heterogeneity may occur among tumors with similar morphology [6]. In a large series of 2,535 patients, poorly differentiated OSCC showed more aggressive clinicopathological behavior and poorer survival than well- or moderately differentiated tumors [6].

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Consequently, attention has increasingly focused on molecular and immunohistochemical biomarkers that may complement conventional histopathological assessment [7,8]. At the molecular level, angiogenesis is essential for sustained tumor growth, invasion, and metastatic dissemination. Among the principal regulators of angiogenesis, vascular endothelial growth factor (VEGF), promotes endothelial-cell proliferation, vascular permeability, and formation of new blood vessels. In OSCC, VEGF and its receptors may contribute to tumor progression through both paracrine and autocrine signaling mechanisms [9]. Recent experimental evidence has further demonstrated that angiogenic signaling can enhance vascular formation and lymphatic metastatic potential in OSCC [10]. Immunohistochemical investigations have reported associations between increased VEGF expression and recurrence, metastasis, or more aggressive tumor characteristics [11]. However, findings concerning its relationship with histopathological differentiation remain inconsistent. While some studies have reported higher VEGF expression with greater tumor aggressiveness, others have not demonstrated a significant association between VEGF expression and histological grade [11,12]. Despite expanding interest in molecular biomarkers, no single immunohistochemical marker has yet replaced conventional clinicopathological assessment for OSCC prognostication [7,8]. Variations in antibody selection, scoring systems, staining cut-offs, sample size, tumor composition, and population characteristics may partly explain the conflicting findings reported for VEGF. Moreover, evidence from Bangladesh on the immunohistochemical pattern of VEGF and its relationship with histopathological grade remains limited. Therefore, evaluating VEGF staining characteristics in locally diagnosed OSCC may provide useful information on tumor biology and contribute to the regional evidence base. Accordingly, this study aimed to evaluate the immunohistochemical pattern of VEGF expression in oral squamous cell carcinoma and determine its association with histopathological grade.

METHODS & MATERIALS

This cross-sectional observational study was conducted in the Department of Pathology, Rajshahi Medical College (RMC), Rajshahi, Bangladesh, from September 2018 to August 2020. Data collection was carried out from December 2018 to May 2020. A total of 50 patients with histopathologically confirmed oral invasive squamous cell carcinoma (OSCC) were included through consecutive sampling. Patients who had received preoperative chemotherapy or radiotherapy, those with benign oral lesions, and cases with inadequate or poorly preserved biopsy specimens were excluded. Written informed consent was obtained from all participants, and ethical approval was obtained from the Ethical Review Committee of RMC. For each participant, relevant demographic and clinicopathological information, including age, sex, socioeconomic status, tobacco-use history, oral hygiene, and tumor site, was recorded using a predesigned case record form. Following routine tissue processing, formalin-fixed paraffin-embedded tissue blocks were sectioned and stained with hematoxylin and eosin for histopathological diagnosis and grading. Based on morphological features, tumors were classified as Grade I (well differentiated), Grade II (moderately differentiated), or Grade III (poorly differentiated) OSCC. For immunohistochemical evaluation, representative paraffin-embedded tumor sections of approximately 4–5 µm thickness were prepared. Following deparaffinization and rehydration, endogenous peroxidase activity was blocked, and antigen retrieval was performed using citrate buffer at 95–99°C. Sections were then incubated with a rabbit polyclonal anti-VEGF primary antibody (1:100), followed by a peroxidase-labeled visualization system. Immunoreactivity was visualized using 3,3′-diaminobenzidine, and the sections were counterstained with hematoxylin. A known VEGF-positive colon adenocarcinoma was used as the positive control, while omission of the primary antibody served as the negative control. VEGF expression was assessed according to staining intensity and the percentage of immunopositive tumor cells. Intensity was scored from 0 to 3, and distribution from 0 to 3, based on the proportion of positive cells. The two scores were added to classify VEGF expression as negative, weakly positive, positive, or strongly positive. For statistical analysis, data were entered into Microsoft Excel and analyzed using SPSS version 23. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequency and percentage. Associations were assessed using the Chi-square or Fisher's exact test as appropriate, with $p<0.05$ considered statistically significant.

RESULTS

In *Table I*, the mean patient age was 52.96 ± 11.19 years. Regarding sex, 56.0% were female, while 44.0% were male. Concerning socioeconomic status, 68.0% belonged to the lower socioeconomic group, and 82.0% had poor oral hygiene.

Table I: Baseline characteristics of the study participants (*n*=50)

Variable	Category	n (%)
Age (years)	Mean ± SD	52.96 ± 11.19
Sex	Male	22 (44.0)
	Female	28 (56.0)
Socioeconomic status	Lower	34 (68.0)
	Middle	16 (32.0)
Oral hygiene	Good	9 (18.0)
	Poor	41 (82.0)

The buccal mucosa was the most common tumor site (46.0%), followed by the tongue (10.0%), while other sites together accounted for 44.0%. Regarding histopathological grade, Grade I tumors were most frequent, 60.0%, followed by Grade II, 28.0%, and Grade III, 12.0% (*Table II*).

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Table II: Tumor site and histopathological grade of OSCC (*n*=50)

Variable	Category	n (%)
Tumor site	Buccal mucosa	23 (46.0)
	Tongue	5 (10.0)
	Other sites	22 (44.0)
Histopathological grade	Grade I	30 (60.0)
	Grade II	14 (28.0)
	Grade III	6 (12.0)

Table III shows overall VEGF positivity in 86.0% of cases, with 38.0% showing strong positivity, 26.0% positive expression, and 22.0% weak positivity. Among VEGF-positive tumors, 69.8% showed both cytoplasmic and membranous staining. Regarding staining intensity, 32.0% showed moderate staining and 30.0% showed maximal staining.

Table III: Immunohistochemical characteristics of VEGF expression

VEGF parameter	Category	n (%)
Overall expression (n=50)	Negative	7 (14.0)
	Weakly positive	11 (22.0)
	Positive	13 (26.0)
	Strongly positive	19 (38.0)
Staining pattern (n=43)	Cytoplasmic only	7 (16.2)
	Membranous only	6 (14.0)
	Both	30 (69.8)
Staining intensity (n=50)	No staining	7 (14.0)
	Slight	12 (24.0)
	Moderate	16 (32.0)
	Maximal	15 (30.0)

Regarding *Table IV*, 40.0% of tumors showed VEGF expression in 1 to <25% of tumor cells, representing the largest group. Expression in 25–50% of cells were observed in 28.0%, while 18.0% had >50% positive cells; 14.0% showed no VEGF-positive cells.

Table IV: Distribution of VEGF-positive tumor cells (*n*=50)

Positive tumor cells	n (%)
0%	7 (14.0)
1–<25%	20 (40.0)
25–50%	14 (28.0)
>50%	9 (18.0)

In *Table V*, maximal VEGF staining was most frequent in Grade III tumors (50.0%), while moderate staining predominated in Grade II tumors (64.3%). Slight staining was more frequent in Grade I tumors (36.7%). A statistically significant association was found between VEGF staining intensity and histopathological grade (p=0.037).

Table V: Association between VEGF staining intensity and histopathological grade

Grade	No staining	Slight	Moderate	Maximal	p value
Grade I	5 (16.7)	11 (36.7)	6 (20.0)	8 (26.7)	0.037
Grade II	1 (7.1)	0	9 (64.3)	4 (28.6)	
Grade III	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	

No statistically significant association was found between histopathological grade and the percentage of VEGF-positive cells (p=0.473), the combined VEGF expression score (p=0.536), or overall VEGF positivity (p=0.684). Thus, only VEGF staining intensity showed a significant relationship with histopathological grade (*Table VI*).

Table VI: Association of VEGF expression with histopathological grade

VEGF parameter	p value
Percentage of VEGF-positive cells vs. histological grade	0.473
Combined VEGF expression score vs. histological grade	0.536
Overall VEGF positivity vs. histological grade	0.684

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DISCUSSION

In the present study, oral squamous cell carcinoma occurred at a mean age of 52.96 ± 11.19 years, with a slight female predominance (56.0%). Buccal mucosa was the most frequent tumor site, 46.0%, while Grade I, well-differentiated OSCC constituted 60.0% of cases. Similar demographic heterogeneity has been reported across South Asian populations, where variations in tobacco, smokeless tobacco, betel-quid exposure, socioeconomic status, and referral patterns influence the age, sex, and anatomical distribution of OSCC. Importantly, Rivera et al.'s systematic review emphasized that conventional clinicopathological characteristics alone provide incomplete prognostic information, supporting the incorporation of molecular biomarkers into OSCC assessment [13]. Regarding VEGF expression, 86.0% of tumors were VEGF-positive, including 38.0% strongly positive, 26.0% positive, and 22.0% weakly positive. This high frequency is comparable to the study by Patil et al., in which all 49 OSCC specimens demonstrated VEGF immunopositivity, although VEGF expression did not differ significantly between well- and moderately differentiated tumors [12]. Similarly, Sales et al. demonstrated VEGFA overexpression in OSCC, with VEGFA transcript levels 1.7-fold higher than normal mucosa; expression was particularly increased in T3–T4 tumors, metastatic lymph nodes, and stage III–IV disease [14]. Concerning cellular localization, 69.8% of VEGF-positive tumors showed both cytoplasmic and membranous staining, whereas 16.2% showed cytoplasmic staining alone and 14.0% membranous staining alone. Such heterogeneous localization probably reflects the complex autocrine and paracrine functions of the VEGF pathway. Consistent with this concept, Aga et al. demonstrated VEGF localization in tumor-cell membranes and cytoplasm in OSCC [15]. Furthermore, Shigetomi et al. showed that activation of the VEGF-C/Flt-4 axis promoted OSCC-cell proliferation and migration, while tumor-cell Flt-4 expression independently predicted neck metastasis (p=0.046) [16]. Regarding staining intensity, moderate and maximal VEGF staining occurred in 32.0% and 30.0%, respectively. More importantly, VEGF staining intensity was significantly associated with histopathological grade (p=0.037). Maximal staining increased from 26.7% in Grade I to 28.6% in Grade II and 50.0% in Grade III tumors. This finding agrees closely with Peterle et al., who found that positive cytoplasmic VEGFA expression was significantly associated with poorer differentiation (p=0.035) [17]. Likewise, the Sri Lankan study by Edirisinghe et al. found progressively higher VEGF-related measurements with worsening tumor differentiation; poorly differentiated OSCC showed a mean serum VEGF concentration of 1262.0 ± 354.7 pg/mL, and VEGFR-2 optical density increased from 0.48 ± 0.12 in well-differentiated to 0.68 ± 0.17 in poorly differentiated tumors [18]. Further support for an association between angiogenic activity and aggressive disease comes from de Aquino et al., who found that VEGFR-3 expression was associated with histological grade (p<0.005), metastasis (p=0.009), and mortality (p=0.008) [19]. Similarly, Nakao et al. reported significant relationships between VEGF-A/VEGF-C-related signaling and invasive behavior, with high NPRA expression associated with markedly poorer 5-year disease-specific survival (39.7% versus 97.0%) [20]. Yamagata et al. also demonstrated increased VEGF-mediated lymphangiogenesis, detecting VEGF-C in 74.2% of tumors containing CD163-positive tumor-associated macrophages, with macrophage density correlating with nodal metastasis [21]. However, the present study found no significant association between histological grade and the percentage of VEGF-positive cells (p=0.473), combined VEGF score (p=0.536), or overall VEGF positivity (p=0.684). Such findings indicate that staining intensity may capture biological activity better than simple positivity. Patil et al. [12] reported comparable discrepancies, and differences among studies may arise from antibody selection, staining protocols, scoring thresholds, tumor heterogeneity, sample size, and inclusion of different anatomical subsites. Supporting this complexity, Kawasaki et al. showed that VEGF/HIF-related expression varies with mTOR signaling and invasive characteristics rather than differentiation alone [22]. More recent evidence strengthens VEGF's biological relevance beyond tissue staining. In 187 OSCC patients, Batelja-Vuletic et al. found significant differences in VEGF and other biomarkers between metastatic and non-metastatic disease, with VEGF significantly associated with TNM stage [23]. Moreover, Cai et al. demonstrated significant VEGF overexpression in both OSCC tissue and saliva compared with controls, supporting its potential as a non-invasive biomarker [24]. More recently, Xu and Lou reported significantly elevated serum VEGF in 160 OSCC patients compared with 51 controls (p<0.001), further linking circulating angiogenic markers to clinicopathological behavior [25]. Clinically, the significant increase in VEGF staining intensity with poorer histological differentiation suggests that VEGF immunohistochemistry may complement conventional grading when assessing tumor aggressiveness. Supporting the broader role of angiogenesis, recent CD105-based studies have demonstrated significantly higher microvascular density in OSCC and across histological grades [26]. Therefore, VEGF should not be considered a standalone prognostic marker; integrating it with histopathological grade, nodal status, invasion parameters, and additional angiogenic markers may improve risk stratification and help identify patients who could benefit from closer surveillance or future anti-angiogenic therapeutic strategies.

LIMITATIONS

The study was limited by its relatively small sample size and single-center design, which may restrict generalizability. The study did not evaluate clinical outcomes or survival data, and it assessed VEGF expression only by immunohistochemistry, without molecular confirmation such as RT-PCR. Self-reported information on tobacco exposure may also have been subject to recall bias.

CONCLUSION

The study demonstrated that VEGF expression was common in oral squamous cell carcinoma, with 86.0% of tumors showing immunopositivity and 38.0% showing strong expression. VEGF staining intensity increased with worsening histopathological grade and was significantly associated with tumor differentiation (p=0.037). However, overall VEGF positivity, percentage of positive cells, and combined VEGF score were not significantly associated with grade. These findings suggest that VEGF staining intensity may have potential value as an adjunct marker of tumor aggressiveness in OSCC.

RECOMMENDATIONS

Given these findings, VEGF immunohistochemical assessment may be considered an adjunct to histopathological grading in oral squamous cell carcinoma. Further multicenter studies with larger sample sizes and survival follow-up are recommended to clarify the prognostic value of VEGF expression and its potential role in targeted therapy.

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CONFLICT OF INTEREST
None declared

ETHICAL APPROVAL
The study was approved by the Institutional Ethics Committee.

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