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Diagnostic and Prognostic Significance of E-cadherin and β-catenin in Oral Squamous Cell Carcinoma with or without Lymphnode Metastasis

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ABSTRACT

Background: *To study the role of cell adhesion molecules like E-cadherin and β-catenin expression in oral cancers in predicting tumor invasion and metastasis. The intercellular adhesions loss in epithelial malignancy is an important component of the acquisition of invasive and malignant properties.* ***Material and Methods:*** *All biopsies/ specimens were fixed in 10% neutral buffered formalin solution. Diagnosis was made on histopathology by using hematoxylin and eosin stains and further typing was done. Immunohistochemistry has been applied to see the expression of E-cadherin and β-catenin in different grades of oral squamous cell carcinoma.* ***Results:*** *In this study, the assessment of E-cadherin and β-catenin immunohistochemical stained slides were examined for pattern of staining (membranous, cytoplasmic or nuclear), proportion and intensity of staining of the tumor cells. The total score ranges between 0-12. Immunoreactivity was divided into three groups on the basis of final score: a total score of 0 is considered as negative immunoreactivity score, 1-4 score as low immunoreactivity score and >4 as high immunoreactivity score.* ***Conclusion:*** *In the present study, it was found that the reduced expression E-cadherin and β-catenin is an indicator of a poor prognosis in oral squamous cell carcinoma.*

Keywords: Oral cancers, Squamous cell carcinoma, E-cadherin, β-catenin, Histopathology, Immunohistochemisry

INTRODUCTION

Squamous cell carcinoma of the oral cavity is the sixth most common malignancy in the world and first in males in Indian subcontinent. It is one of the major cause of cancer morbidity and mortality [1]. More than 90% of all oral cancers are Squamous Cell Carcinomas (SCC) and this type of cancer comprises about 95% of all oral cancers in India [2]. Oral cancer has a serious health issue to the nations undergoing economic transition [3].

Oral Squamous Cell Carcinomas (OSCCs) are cancers developing from potentially malignant lesions or normal epithelium linings. Potentially malignant disorders such as oral submucus fibrosis, erythroplakia, leukoplakia, and lichen planus are the precursor of oral cancers [4]. Locations include the tongue, buccal mucosa, labial mucosa, floor of the mouth, gingiva, lips, angle of mouth, hard palate and soft palate [5]. Tobacco consumption has been the predominant factor causing oral cancer. The long-term use of tobacco in various forms like gutka, zarda, kharra, khaini, mawa, cigarettes, bidi, hookah, etc. is the leading cause of tumour

development in the oral cavity in both young as well as the adult people in India [6]. However, high-risk Human Papilloma Virus (HPV) infection and low intake of fresh fruits and vegetables are also seen in the aetiopathogenesis of oral malignancy [7].

In normal epithelial structures, the cell-cell junctions play a key role in the maintenance, integrity and morphology of the epithelium [8]. It is found that the E-cadherin/ β-catenin complex of adhesion molecules play a crucial role in this processes [9]. Alterations in the E-Cadherin/β-Catenin complex have been suggested in the oncogenesis of carcinomas arising from various anatomic sites and have been correlated with adverse clinico-pathological parameters [10]. The intercellular adhesions loss in epithelial malignancy is an important component of the acquisition of invasive and malignant properties.

Hence, it is important to study the role of cell adhesion molecules like E-cadherin and β-catenin expression in oral cancers in predicting tumour invasion and metastasis. In this study, we analysed the diagnostic and prognostic significance of E-cadherin and β-catenin in oral squamous cell carcinoma with or without lymph node metastasis.

MATERIALS AND METHODS

This study was conducted after obtaining clearance from the institutional ethical committee. The inclusion criteria were all consecutive cases histopathologically diagnosed with oral squamous cell carcinoma. Exclusion criteria were based on patients who had history of previous surgery or received neoadjuvant cancer therapy to aerodigestive tract. The present study was carried out on a total of 180 cases of histopathologically proven oral squamous cell carcinoma received in the Department of Pathology, JNMCH, AMU, Aligarh. Detailed medical history, clinical examination and other relevant investigations were obtained from the Medical Records Department at our hospital and also retrieved from the pathology reports and recorded on a proforma.

Histopathological tissues were fixed in 10% formalin, grossed and processed according to the standard procedure followed in the department. 3 microns to 4 microns thickness paraffin blocks section were made with the help of microtome and stained by Hematoxylin and Eosin. Subsequently, Immuno-histochemistry for E-cadherin and β-catenin was performed on paraffin embedded tissue sections using the kits, thermo scientific E-cadherin and thermo scientific β-catenin respectively. The antibody provided is pre-diluted and ready to use, their visualization being obtained with DAB (3,3'-Diaminobenzidine), Dako.

For the assessment of E-cadherin and β-catenin, immunohistochemically stained slides were examined for pattern of staining (membranous, cytoplasmic or nuclear), proportion and intensity of staining of the tumour cells. E-cadherin cells labelled by the antibody were identified by strong, distinct, continuous dark brown membranous staining of epithelial cells. β-catenin cells labelled by the antibody were identified by strong dark brown membranous and cytoplasmic staining of epithelial cells. Normal buccal mucosa was taken as positive control and tonsil lymphoid cells were taken as negative control.

- Grading of E-cadherin and β-catenin on the basis of pattern/location of staining: 1- Membranous staining, 2-Both membranous and cytoplasmic staining, 3-Cytoplasmic staining, 4-Nuclear staining, 5-Absence of staining.
- Grading of E-cadherin and β-catenin on the basis of intensity of immunostaining**:** 0 absence of staining, 1+ weak staining, 2 + moderate staining, 3+ strong staining.
- Grading of E-cadherin and β-catenin on the basis of proportion of cells with membranous staining: 0 if <20% of cells were positive, 1 if 21% to 40% of cells were positive, 2 if 41% to 60% were positive, 3 if 61% to 80% cells were positive, 4 if >80% cells were positive.

The immunoreactivity of E-cadherin and β-catenin was assessed semi-quantitatively by calculating Immunoreactivity Score (IRS) based on the proportion of stained tumour cells and intensity of staining. The total score ranges between 0-12. Immunoreactivity was divided into three groups on the basis of final score: a total score of 0 is considered as negative immunoreactivity score, 1-4 score as low immunoreactivity score and >4 as high immunoreactivity score.

Statistical Analysis

In the present study, all the qualitative variables were analysed by using Pearson Chi Square test and Fisher's exact test. All the quantitative variables were analysed by using Kruskal Wallis one way Anova test. A p-value of <0.05 was considered statistically significant.

RESULTS

Clinicopathological Characteristic

All 180 cases were classified into different grades i.e., well, moderately and poorly differentiated oral squamous cell carcinoma on the basis of histopathological diagnosis. Out of 180 cases, 87 (48.3%) were of well differentiated (Figure 1a), 82 (45.6%) of moderately differentiated (Figure 1b) and 11 (6.1%) of poorly differentiated squamous cell carcinoma (Figure 1c). WDSCC constituted the maximum number of cases (48.3%) followed by MDSCC (45.6%) (Table 1).

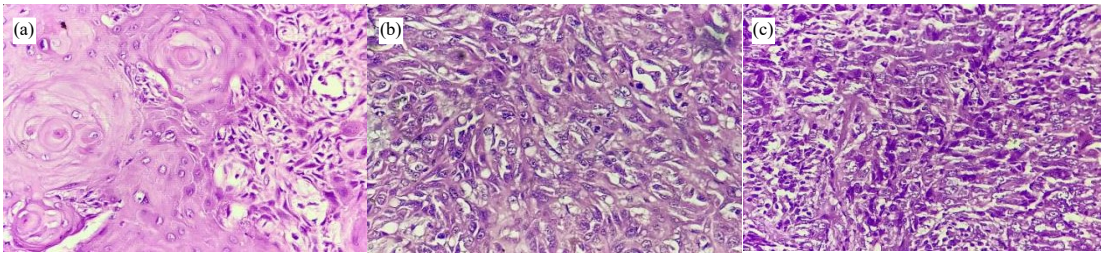

Figure 1(a) WDSCC: Shows pleomorphic, hyperchromatic cells and keratin pearls (H&EX 400); (b) MDSCC: Shows pleomorphic, hyperchromatic cells with irregular nuclear membrane and individual cell keratinization with few mitotic figures. (H&E X 400); (c) PDSCC: Shows discohesive malignant cells, highly pleomorphic, hyperchromatic cells with irregular nuclear membranes (H&E X 400)

Table 1 Hierarchically branching papillary structures

Degree of differentiation	No. of cases (%)
WDSCC	87 (48.3%)
MDSCC	82 (45.6%)
PDSCC	11 (6.1%)
Total	180 (100%)

WDSCC-Well Differentiated Squamous Cell Carcinoma; MDSCC- Moderately Differentiated Squamous Cell Carcinoma; PDSCC-Poorly Differentiated Squamous Cell Carcinoma.

The peak age incidence in all grades of squamous cell carcinoma was found in the 4th and 5th decade with mean age of 47.49 years ± 12.89 years. Out of 180 cases, 161 cases (89.4%) were males and 19 cases (10.6%) were females with male to female ratio of 8.5:1. The most commonly involved site was tongue 85 cases (47.2%) followed by buccal mucosa 68 cases (37.8%). Lip and gingiva was involved in 1 case (0.6%) each. The most common presenting feature was growth in 99 cases (55%), followed by ulceration in 34 cases (18.9%). Some cases also presented with white/red patch and bleeding.

Most of the cases had association with more than one risk factors. The most common association was found with tobacco/betel quid chewing in 111 cases (61.7 %), followed by smoking in 76 cases (42.2%). Out of 180 cases of oral squamous cell carcinoma, 52/180 (28.89%) cases were found to have positive lymph node metastasis. On comparing with different grades of squamous cell carcinoma, 14/87 (16.09%) cases of WDSCC, 32/82 (39.02%) cases of MDSCC and 6/11 (54.55%) cases of PDSCC were found to have positive lymph node metastasis which was statistically significant ($p<0.01$). Thereby indicating that decrease in the differentiation shows increased chances of metastastic dissemination (Table 2).

Table 2 Status of lymphnode metastasis in different grades of OSCC

Lymphnode	Grade of OSCC						Total		p-value
	WDSCC		MDSCC		PDSCC				
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)	
Positive	14	16.09	32	39	6	54.55	52	28.89	P<0.01
Negative	73	83.91	50	60.98	5	45.45	128	71.11	
Total	87	100	82	100	11	100	180	100	

Table 3 Correlation between clinicopathologiocal variables and lymphnode status

	OSCC with Lymph node metastasis (n=52)	OSCC without Lymph node metastasis (n=128)	p-value
Age			
≤ 50	32	85	0.385
>50	20	43	
Sex			
Male	43	118	0.061
Female	9	10	
Site			
Tongue	29	56	0.269
Buccal mucosa	18	50	
Floor of mouth	2	1	
Retromolar Trigone	2	5	
Soft Palate	1	1	
Hard Palate	0	1	
Angle of mouth	0	0	
Gingiva	0	1	
Lip	0	11	
Grading of OSCC			
WDSCC	14	73	0.00068
MDSCC	32	50	
PDSCC	6	5	

In patients without lymph node metastases, 85 were in age groups of ≤ 50 years and 43 cases were >50 years of age. Whereas patients with lymph node metastases, 32 were in the age group of ≤ 50 years and 20 were >50 years of age. In the present study, there were no statistically significant association between OSCC with and without lymphnode metastases and clinical variables like age, sex and site. However, there is significant association between OSCC with and without lymphnode metastases and histological differentiation (p<0.01) (Table 3).

Immunohistochemical Study

71 cases were subjected to immunostaining by E-cadherin and β-catenin for comparison and statistical analysis. 35 cases of well differentiated squamous cell carcinoma, 25 cases of moderately differentiated squamous cell carcinoma and 11 cases of poorly differentiated squamous cell carcinoma were subjected to E-cadherin and β-catenin immunostaining. Immunostaining by E-cadherin and β-catenin showed different immunoreactivity score in all grades of OSCC.

E-cadherin immunoreactivity score decreased as the tumour grade increased from well to poorly differentiated carcinoma. E-cadherin immunohistochemistry showed high immunoreactivity in 91.43% cases, and low

immunoreactivity in only 8.57% cases. In poorly differentiated carcinoma 72.73% cases showed low immunoreactivity and 27.27 % cases were totally negative for E-cadherin staining. Thereby stating the loss of E-cadherin with de-differentiation or lower grade of tumour morphology (Table 4).

Table 4 E-cadherin expression in different grades of OSCC

Grade of OSCC	E-Cadherin Immunoreactivity Score								p-value
	Negative (0)		Low (1-4)		High (5-12)		Total		
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)	
Well	0	0	3	8.57	32	91.43	35	100	p<0.001
Moderately	2	8	19	76	4	16	25	100	
Poorly	3	27.27	8	72.73	0	0	11	100	
Total	5	7.04	30	42.25	36	50.7	71	100	
p-values: a:b <0.001; a:c <0.001; b:c >0.05									

A statistical significant difference in E-cadherin expression was noted on comparing well differentiated carcinoma with moderately differentiated carcinoma, p-value<0.001; and well differentiated carcinoma with poorly differentiated carcinoma, p-value<0.001. However, no statistical significance (p-value>0.05) was found in E-cadherin expression amongst moderately differentiated carcinoma and poorly differentiated carcinoma.

Table 5 E-cadherin staining pattern/location in different grades of OSCC

Staining Location	Grade of OSCC								p-value
	WDSCC		MDSCC		PDSCC		Total		
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)	
Membranous	25	71.43	8	32	0	0	33	46.48	p<0.001
Both Membranous and Cytoplasmic	9	25.71	14	56	3	27.27	26	36.62	
Cytoplasmic	1	2.86	2	8	2	18.18	5	7.04	
Absent	0	0	1	4	6	54.55	7	9.86	
Total	35	100	25	100	11	100	71	100	

Table 5 depicts, 32 (91.43%) cases of well differentiated carcinoma showed membranous staining of E-cadherin (Figure 2a), as compared to 4 (16%) cases of moderately differentiated and none of the poorly differentiated carcinoma. Both membranous and cytoplasmic staining was seen in 3 (8.57%) cases of well differentiated carcinoma, 13 (52%) cases of moderately differentiated carcinoma (Figure 2b), and 5 (45.45%) cases of poorly differentiated carcinoma. 6 (24%) case of moderately differentiated and 3 (27.27%) cases of poorly differentiated carcinoma had cytoplasmic staining (Figure 2c). While 3 (27.27%) cases of poorly differentiated carcinoma and 2 (8%) cases of moderately differentiated carcinoma showed absent staining. However, no nuclear staining was seen. So we concluded that E-cadherin expression changed from membranous to cytoplasmic to complete absent staining pattern as tumour grade increased from well to poorly differentiated oral squamous cell carcinoma. Chi square test showed a p-value of <0.001, which was statistically significant.

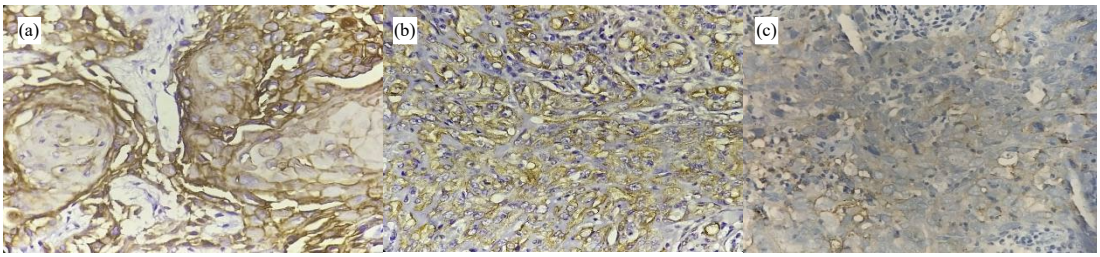

Figure 2 (a) WDSCC: Shows nests of tumour cells with membranous positivity of E-cadherin (3+) (IHC E-cadherin X 400); (b) MDSCC: Shows both membranous and cytoplasmic positivity of E-cadherin (2+). (IHC E-cadherin X 400); (c) PDSCC: Shows cytoplasmic staining (1+) (IHC E-cadherin X 400)

β-catenin immunoreactivity score decreased as the tumour grade increased from well to poorly differentiated carcinoma. β-catenin immunoreactivity was high in 77.14% cases of well differentiated carcinoma and low in 22.86% cases. None of the case showed negative immunostaining. While in poorly differentiated carcinoma, 81.82% cases showed low immunoreactivity and 9.09% cases each showed high and negative immunostaining. Thereby stating the fact that as the tumour progresses to a lower grade, there is loss of β-catenin expression (Table 6).

Table 6 β-catenin expression in different grades of OSCC

Grade of OSCC	β-catenin Immunoreactivity Score								p-value
	Negative (0)		Low (1-4)		High (5-12)		Total		
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)	
Well	0	0	8	22.86	27	77.14	35	100	p<0.001
Moderately	3	12	14	56	8	32	25	100	
Poorly	1	9.09	9	81.82	1	9.09	11	100	
Total	4	5.63	31	43.66	36	50.7	71	100	
p-values: a:b <0.01; a:c <0.001; b:c >0.05									

A statistical significant difference in β-catenin expression was noted on comparing well differentiated carcinoma with moderately differentiated carcinoma, p-value<0.01; and well differentiated carcinoma with poorly differentiated carcinoma, p-value<0.001. However, no statistical significance (p-value>0.05) was found in β-catenin expression amongst moderately differentiated carcinoma and poorly differentiated carcinoma.

Table 7 β-catenin staining pattern/location in different grades of OSCC

Staining Location	Grade of OSCC								p-value
	WDSCC		MDSCC		PDSCC		Total		
	Cases	(%)	Cases	(%)	Cases	(%)	Cases	(%)	
Membranous	28	80	13	52	0	0	41	57.75	p<0.001
Both Membranous and Cytoplasmic	7	20	10	40	2	18.18	19	26.76	
Cytoplasmic	0	0	1	4	2	18.18	3	4.23	
Absent	0	0	1	4	7	63.64	8	11.27	
Total	35	100	25	100	11	100	71	100	

Table 7 depicts, 27 (77.14%) cases of well differentiated carcinoma (Figure 3a) showed membranous staining of β-catenin as compared to 8 (32%) cases of moderately differentiated and 1 (9.09%) case of poorly differentiated carcinoma. Both membranous and cytoplasmic staining was seen in 8 (22.86%) cases of well differentiated carcinoma, 11 (44%) cases of moderately differentiated carcinoma (Figure 3b) and 3 (27.27%) cases of poorly

differentiated carcinoma. 3 (12%) case of moderately differentiated and 5 (45.45%) cases of poorly differentiated carcinoma had cytoplasmic staining. 1 (9.09%) case of poorly differentiated carcinoma showed nuclear staining. While 3 (12%) cases of moderately differentiated carcinoma and 1 (9.09%) case of poorly differentiated carcinoma showed absent staining (Figure 3c). Thereby indicating that as the tumour grade increases from well to poorly differentiated OSCC, β-catenin membranous and cytoplasmic positivity decreases and nuclear positivity increases. Chi square test showed a p-value of <0.001, which was statistically significant.

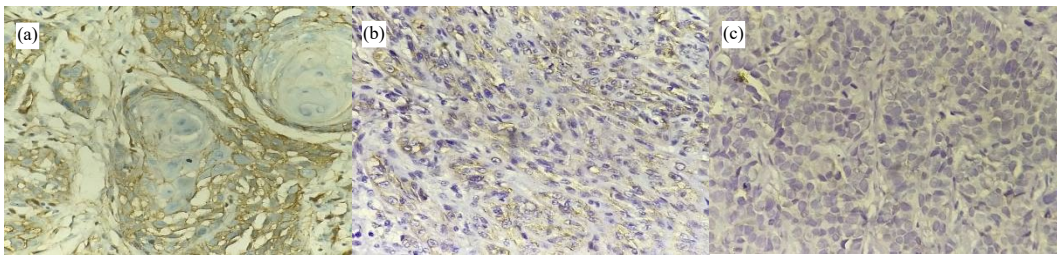

Figure 3(a) WDSCC: Shows membranous positivity of β-catenin (2+) in tumour cells (IHC β-catenin X 400); (b) MDSCC: Shows both membranous and cytoplasmic positivity of β-catenin (1+). (IHC β-catenin X 400); (c) PDSCC: Shows absence of staining (IHC β-catenin X 400)

In our study, lymphnode metastasis was present in 29 (40.8%) cases of OSCC. Out of these, 19 (26.8%) cases showed low immunoreactivity and 10 (14.1%) cases showed high immunoreactivity for E-cadherin expression which was statistically significant. While, 15 (21.1%) cases showed low immunoreactivity and 14 (19.7%) cases with high immunoreactivity for β-catenin expression, which was statistically non-significant. The present study showed a statistically significant difference in the expression of E-cadherin in patients who had lymph node metastasis showing decreased expression in these patients, indicating loss of E-cadherin is associated with more lymph nodes metastasis and more invasions. However, there was no statistically significant expression of β-catenin in patients with lymph node metastasis.

Table 8 Comparision of E-cadherin and β-cateninimmunoexpression in OSCC with or without lymphnode metastasis

Groups	E-cadherin		p-value	β-catenin		p-value
	≤ 4 (%)	5 to 12 (%)		≤ 4 (%)	5 to 12 (%)	
OSCC without Lymphnode metastasis [n=42]	16 (22.5)	26 (36.6)	0.031	20 (28.2)	22 (31.0)	0.733
OSCC with Lymphnode metastasis [n=29]	19 (26.8)	10 (14.1)		15 (21.1)	14 (19.7)	

This table showed that there was a significant difference in E- cadherin expression at the primary site of OSCC, with or without lymph node metastases but no significant difference observed in β-catenin expression (Table 8).

DISCUSSION

Adhesion molecules play a central role in pathogenesis and progression of malignant tumours [11]. Therefore, it is important to evaluate the role of cell adhesion molecules like E-cadherin and β-catenin in tumour metastasis of oral squamous cell carcinoma [12].

In the present study, we evaluated the immune-histochemical expression of E-cadherin and β-catenin in oral squamous cell carcinoma, and compared its change with different grades of tumour, age, gender, site, lymph node metastasis etc.

In our study, we found WDSCC constituted the maximum number of cases (48.3%) followed by MDSCC (45.6%); Ahluwalia *et al.*, 2001 found 65.97% well differentiated, 24.49% moderately differentiated, and 9.53% poorly differentiated squamous cell carcinoma [13]. Similarly, Patel *et al.*, 2004 also found 60.12% well differentiated, 38.7% moderately differentiated, and 1.18% poorly differentiated squamous cell carcinoma [14].

Our study revealed increase prevalence of OSCC in the males with 161 cases (89.4%) as compared to females with only 19 cases (10.6%) with male to female ratio of 8.5:1. Sharma *et al.*, 2010 have also documented a male to

female ratio of 2.2:1 in OSCC cases in their study [15]. Cervical lymph node metastasis was observed in 52 cases (28.9%) of OSCC. Singh *et al*., 2003 have demonstrated that metastatic behaviour was critical to survival, since patients with distant disease have three times less five-year survival rate than patients with local spread to lymph nodes [16].

In our study, degree of E-cadherin and β-catenin expression decreased as the grade of the tumour was increased and depicts a poor prognosis. Similar findings were seen in a study conducted by Mehendiratta *et al*., 2014 on Indian population where they observed absent E-cadherin membranous staining in 0%, 10% and 30% cases of well, moderately and poorly differentiated oral squamous cell carcinomas respectively. It was concluded that loss of E-cadherin expression at the invasive tumour front is an important event in the progression of oral squamous cell carcinomas and tumours with a loss of expression of E-cadherin are those which had a poor prognosis [17]. Afrem *et al*., 2014 documented a decrease E-cadherin reactivity in parallel with decreasing tumour differentiation and with the increase of invasion pattern of tongue carcinoma [18]. Similar study done by Zaid *et al*., 2014 also documented β-catenin expression in different histological grades of oral squamous cell carcinoma and reported the expression of β-catenin in 87.3% of the cells in WDOSCC, 68.7% of MDSCC and 43.4% of PDSCC [19].

In the present study, we analysed that E-cadherin expression changed from membranous to cytoplasmic to complete absrent staining pattern as tumour grade increased from well to poorly differentiated oral squamous cell carcinoma. A study by Kaplanis *et al*., 2004 showed loss of membranous staining and a progressive increase in cytoplasmic staining of E-cadherin, as the disease progressed from dysplasia to carcinoma in situ to invasive squamous cell carcinoma [20]. Another similar study by Mattijssen *et al*., 1993 however, found no correlation between tumour differentiation and E-cadherin expression [21].

Similarly, β-catenin membranous and cytoplasmic positivity decreased and nuclear positivity increased as the tumour grade increased from well to poorly differentiated OSCC. Our findings were in concordance with the study done by Barakat *et al.*, 2015 who analysed more than 56% of the tumour cells in the whole sample showed abnormal expression for β-catenin, in 14.7% cytoplasmic expression was noticed whereas the nuclear expression appeared in 5% of the cells [22]. Zhi-gang *et al*., 2008 also found different degrees of reduced expression of β-catenin at the cell membrane in 54 (71%) cases with squamous cell carcinoma. Cytoplasmic β-catenin expression was seen in 17 tumors (22.4%). Three cases were found with nuclear β-catenin expression. The cytoplasm and nuclear β-catenin expression was only seen in the tumours with poor differentiation. They concluded that reduced expression of β-catenin may constitute a hallmark of aggressive biological behaviour of squamous cell carcinoma [23].

Study done by Balasundaram *et al*., 2014 who also analysed the down regulation of molecular markers E-cadherin and β-catenin in oral squamous cell carcinoma. However, they did not show any significant difference in the expression of E-cadherin as well as β-catenin in oral squamous cell carcinoma with and without lymphnode metastases [24]. It is likely that these discrepancies may be due to variation in the experimental model or tissue used, clinico-pathological characteristics of the patients, sample size, and methodology.

There was a direct correlation of E-cadherin and β-catenin expression in oral squamous cell carcinoma. Anneroth *et al*., 1986 and Crissman *et al*., 1984, have shown a positive correlation between the degree of histological malignancy and prognosis of the disease [25,26]. So we may suggest that the reduced expression of E-cadherin and β-catenin is an indicator of a poor prognosis in oral squamous cell carcinoma. Loss of expression of both E-cadherin and β-catenin are frequent events in oral squamous cell carcinoma of all histological grades, and both proteins are thus likely participants in the pathogenesis of oral squamous cell carcinoma.

CONCLUSION

The main characteristics of oral squamous cell carcinoma are invasion and the tendency to metastasize. Escape from the primary tumour site is the initial step of invasion and metastasis of cancers by the disruption of normal cell-cell adhesion. The major goal of cancer research is to identify the crucial pathways involved in the growth regulation of normal cells and to understand how tumour cells escape these control mechanisms. Thus, the present study concluded that loss of expression of both the proteins is of diagnostic and prognostic significance with respect to the histologic grades of OSCC.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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