Original Article

Evaluation of immunohistochemical expression of E-cadherin in pleomorphic adenoma and adenoid cystic carcinoma

Bhavani Nagendra Sangala[1], Vandana Raghunath[2], Pratibha Kavle[1], Anish Gupta[3], Swati Shrikant Gotmare[4], Venkata Subhash Andey[5]

[1]Department of Oral Pathology and Microbiology, Bharati Vidhyapeeth Dental College and Hospital, [4]Department of Oral Pathology and Microbiology, DY Patil University, Navi Mumbai, Maharashtra, [2]Department of Oral Pathology and Microbiology, Narayana Dental College and Hospital, Nellore, [5]Department of Dentistry, Gayathri Medical College and Hospital, Marikivalasa, Vishakapatnam, Andhra Pradesh, [3]Department of Oral Pathology and Microbiology, People's Dental Academy, People's university, Bhopal, Madhya Pradesh, India

Abstract

Background: Pleomorphic adenoma (PA) and adenoid cystic carcinoma (ADCC) are benign and malignant salivary gland tumors, respectively, with distinct behavior. They have similar origins and cell components. E-cadherins are the main homophilic cell adhesion molecules, which play a central role in maintaining epithelial integrity, functioning in intercellular adhesion and differentiation. Hence, changes in E-cadherin function are reflected in the morphologic events associated with the cellular arrangement, movement and wound healing.

Aim: To study and compare the expression of E-cadherin immunostaining in PA and ADCC.

Materials and Methods: Fifteen cases of each PA and ADCC were immunohistochemically stained with E-cadherin. Five cases of normal salivary gland tissues were taken as the positive control.

Mann–Whitney *U*-test was used for statistical analysis.

Results: About 86.6% of PA cases showed homogeneous staining. 66.6% of cases of ADCC showed heterogeneous staining. PA, cribriform and tubular patterns of ADCC predominantly showed moderate immune-staining and solid patterns of ADCC exhibited predominantly mild immunostaining. Depending on the intensity of staining, we found a significant *P* value between PA and the solid variant of ADCC.

Conclusion: E-cadherin proved to be a better marker for epithelial phenotypes in PAs. In ADCC difference in staining intensity between different histological subtypes suggests that further studies should be done to assess the usefulness of an immuno-marker to know the aggressive behavior of ADCC.

Keywords: Adenoid cystic carcinoma, E-cadherin, immunohistochemistry, pleomorphic adenoma

Address for correspondence: Dr. Bhavani Nagendra Sangala, Department of Oral Pathology and Microbiology, Bharati Vidyapeeth Dental College and Hospital, CBD Belapur, Navi Mumbai - 400 614, Maharashtra. India.
E-mail: drbhavani21@yahoo.com

Submitted: 19-Sep-2021, **Revised:** 24-Dec-2021, **Accepted:** 30-Dec-2021, **Published:** 31-Mar-2022

INTRODUCTION

Salivary glands are the most histo-pathologically heterogeneous group of tumors and have the greatest diversity of morphologic features among their cells and tissues.[1,2] Pleomorphic adenoma (PA) and adenoid cystic carcinoma (ADCC) are benign and malignant epithelial

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_337_21

How to cite this article: Sangala BN, Raghunath V, Kavle P, Gupta A, Gotmare SS, Andey VS. Evaluation of immunohistochemical expression of E-cadherin in pleomorphic adenoma and adenoid cystic carcinoma. J Oral Maxillofac Pathol 2022;26:65-71.

salivary neoplasms respectively with distinct behavior but of similar origin and cell components. Many studies have been conducted to compare PA with ADCC using markers like Mcm-2, Ki-67, Gemeinin, PCNA, P53, Maspin, α – SMA, adhesion molecules such as NCAM, HCAM, PECAM-1, ICAM and P120 catenin.[3-9]

E-cadherin, a 120 kDa glycoprotein is the main homophilic cell adhesion molecule, which plays a central role in maintaining epithelial integrity, functioning in intercellular adhesion and differentiation, as well as in establishing and maintaining cell polarity and tissue architecture.[10,11] A mechanical linkage at the zonula adherens between E-cadherin and cytoskeleton actin filaments mediated by catenins is critical for normal E-cadherin function.[12,13] Failure of E-cadherin/catenin complex assembly and failure of proper actin cytoskeleton connection results in loss of adhesion.[14] Thus, changes in E-Cadherin functions are reflected in the morphogenic events associated with cellular rearrangement, movement and wound healing.[15]

Immunohistochemical (IHC) expression of E-cadherin, has been studied in a variety of carcinomas of the head and neck.[16-21] Its under expression or deficiency leading to changes in cell motility, intercellular adhesion and cell morphology, has been correlated to aggressive behavior, high proliferation, dedifferentiation, invasion, metastasis, and poor prognosis. Thus, it's considered to have a tumor suppressor function.[12] However, its expression in human epithelial salivary neoplasms have been little studied. Few studies exist pertaining to salivary gland tumors [5,6,9,22-32] Studies reported that loss of E-cadherin expression in relation to the progression from an ordered polarized ductular/glandular structure to a more malignant disorganized architecture.[33-36] The present study aimed at studying in detail and comparing the expression of E-cadherin in two common salivary pathologies, i.e., PAs and ADCCs.

MATERIALS AND METHODS

In the present study, buffered formalin-fixed, paraffin-embedded tissues sections of 15 cases of PA and 15 cases of ADCC were evaluated for IHC E-cadherin expression. Super Sensitive™ Polymer-HRP IHC Detection system (Bio-Genex, India), Monoclonal anti-E-cadherin and Ethylenediamine tetracetic acid (EDTA) buffer were used in the study. Two to three serial sections of 4–5 μm thickness were taken on the slide, deparaffinized and rehydrated. Antigen retrieval was done in the microwave oven (EZ-Retriever® System v. 2) and IHC staining continued. Tissue sections of normal salivary glands were used as positive controls. TBS solution was used instead of the primary antibody as negative control. Immunoreactivity for E-cadherin was assessed by two observers independently using microscope (Olympus BX 51). The mean of two observers is taken for statistical analysis. The specimens were classified according to localization (membrane or cytoplasmic), distribution of staining (homogeneous, heterogeneous or isolated foci) and intensity of staining among the various cells and stromal patterns.

The staining intensity was classified as:[25]

- 0 – Negative/absent (no staining)
- + – Mild but definite positive staining
- ++ – Moderate staining
- +++ – Intense staining.

Statistical analysis

Significant differences in the overall intensity of E-cadherin expression in PAs and ADCCs were analyzed using Mann–Whitney *U*-test. $P < 0.05$ were considered statistically significant.

RESULTS

Distribution of cases

A total of 15 cases of PA and 15 cases of ADCC were included in the study. Five normal salivary gland tissues served as positive controls.

Expression of E-cadherin was evaluated for the presence or absence of staining, all the cases of PA, ADCC and normal salivary gland, showed the presence of staining. Further, positive cases were studied with respect to localization, distribution and intensity of staining in various cells and stromal patterns, in both PAs and ADCCs and their intensity graded as mild, moderate and intense.

Expression of E-cadherin in lesional tissue and control group:

Homogeneous immunostaining was observed in all the cases of normal salivary gland tissues, 86.6% of PA and only in 20% of ADCC cases. Heterogenous immunostaining was predominantly observed in ADCC (66.6%) and only 13.3% of PA cases. 13.3% of ADCC cases exhibited immunostaining in isolated focal areas [Table 1].

All five normal salivary gland specimens, all 15 cases of PAs and all 15 cases of ADCCs exhibited membrane immuno-staining. It was predominantly confined to the basolateral membrane of the cells. Only 02 cases of PAs and 04 cases of ADCCs exhibited diffuse mild cytoplasmic immunostaining.

Among 5 cases of normal salivary tissue, serous acini depicted predominantly moderate intensity of staining, i.e., 03/05 cases (60%), followed by one case (20%) each in mild and intense staining categories. Mucous acini showed predominant mild staining intensity in 03/05 cases (60%) and 02/05 cases (40%) moderate intensity. Ducts showed predominantly intense staining intensity (03/05 cases [60%]) [Figure 1] followed by 02 cases (40%) in the moderate category.

In PA, histologically the cells are categorized into Cohesive and noncohesive cells.[37] Among cohesive cells in the tubulo-glandular area, inner/luminal/ductal cells predominantly showed (73%) intense immunostaining and nonluminal cells predominantly showed moderate (40%) and negative (40%) immunostaining [Figure 2]. Large ducts predominantly exhibit (75%) intense immunostaining. Among cohesive nonluminal cells, islands predominantly exhibit (45%) moderate immunostaining, strands (35%) and (45%) sheets predominantly exhibit negative immunostaining. Areas of squamous metaplasia predominantly exhibit intense immunostaining and plasmacytoid areas predominantly exhibit (63%) negative immunostaining. Within the stroma chondroid (75%) and myxoid areas (87%) predominantly exhibit negative immunostaining [Table 2]. Expression of E-cadherin in ADCC was evaluated in various histological variants which include tubular, cribriform and solid types. Tubular pattern predominantly exhibited mild (40%) and moderate (40%) immunostaining, cribriform pattern predominantly exhibited moderate immunostaining (74%) and mild-to-negative staining was observed in all the cases of solid variant (100%) Both hyalinized and fibro-cellular stroma exhibited negative immunostaining [Figure 3 and Table 3].

When the overall intensity of all the cases of PA was accessed, we observed predominantly moderate staining intensity (46.6%). In ADCC combined tubular and cribriform variant exhibited predominantly moderate immunostaining (60%) and mild staining in solid pattern (100%) [Table 4].

Statistical analysis performed using Mann–Whitney *U*-test comparing the E-Cadherin immunostaining intensities between PA and ADCC did not yield any significant *P* value, when all the histologic variants of ADCC was considered as a whole [Table 5] Statistical analysis of E-cadherin immuno-stained cases between PA and combined cribriform and tubular histological patterns of ADCC did not yield any significant *P* value [Table 6]. However, statistical analysis showed significant $P = 0.01$, when the comparison of E-cadherin immunostaining intensity was analyzed between PA and more malignant solid variant of ADCC [Table 7]. Similarly, statistical analysis of E-Cadherin between the histological variants, i.e., tubular and cribriform combined as one entity and solid variant as one entity, yield a significant $P = 0.03$ [Table 8].

Table 1: Distribution of E - cadherin immunostaining in normal salivary glands and in positive cases of pleomorphic adenoma and adenoid cystic carcinoma

	Total number of positive cases	HM (%)	HT (%)	IF (%)
NSG	5	5 (100)	Nil	Nil
PA	15	13 (86.6)	2 (13.3)	Nil
ADCC	15	3 (20.0)	10 (66.6)	2 (13.3)

HM: Homogeneous, HT: Heterogeneous, IF: Isolated foci, NSG: Normal salivary gland, PA: Pleomorphic adenoma, ADCC: Adenoid cystic carcinoma

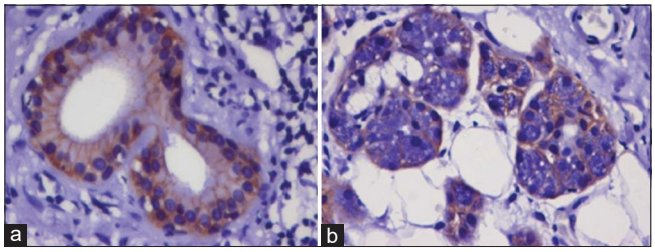

Figure 1: (a) Photomicrograph showing moderate staining of E-cadherin in the striated duct, localized on the basolateral membrane of the normal salivary gland (immunohistochemical, ×400). (b) Photomicrograph showing moderate staining of E-cadherin in serous acini, localized on the basolateral membrane of normal salivary gland (immunohistochemical, ×400)

DISCUSSION

Cell adhesion molecules (CAMs) participate in cell to cell and cell–matrix interactions. By coupling such interactions to intracellular signaling mechanisms, they play an important role in tissue morphogenesis, development, integrity and maintenance. Its alternative expression is however associated with pathogenesis and progression of benign

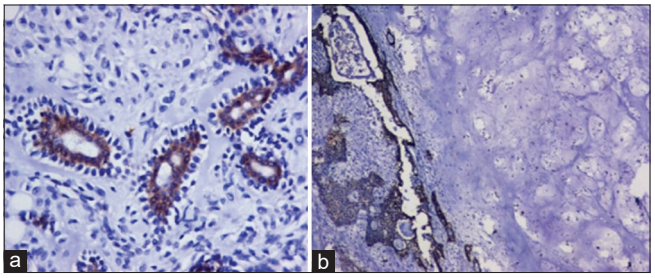

Figure 2: (a) Photomicrograph showing intense staining of E-cadherin in inner ductal cells and negative staining of outer cells in pleomorphic adenoma (immunohistochemical, ×200). (b) Photomicrograph showing intense staining of E-cadherin in tubuloglandular area, moderate staining in sheets and negative staining in myxochondroid areas in pleomorphic adenoma (immunohistochemical, ×50)

Table 2: Total number and percentage distribution of cases reflecting the pattern and staining intensities of E-cadherin immuno-staining in 15 cases of pleomorphic adenoma

Various parenchymal and stromal patterns	Total number of positive cases	Mild (%)	Moderate (%)	Intense (%)	Negative (%)
Cohesive cells					
Tubulo - glandular	15				
Inner cells		Nil	4 (27)	11 (73)	Nil
Outer cell		3 (20)	6 (40)	Nil	6 (40)
Large ducts	8	1 (13)	1 (13)	6 (75)	Nil
Islands	11	2 (18)	5 (46)	Nil	4 (36)
Strands	14	3 (22)	5 (35)	Nil	6 (43)
Sheets	12	4 (33)	3 (25)	Nil	5 (41)
Squamous metaplasia	11	2 (18)	3 (27)	6 (55)	Nil
Plasmacytoid	8	3 (IF) (37)	Nil	Nil	5 (63)
Noncohesive/stromal cells					
Chondroid	8	2 (IF) (25)	Nil	Nil	6 (75)
Myxoid	15	2 (IF) (13)	Nil	Nil	13 (87)
Stroma					
Hyalinized	10				10 (100)
Myxoid	15				15 (100)
Chondroid	8				8 (100)

IF: Isolated foci, NL: Nonluminal cells, L: Luminal cells

Table 3: Total number and percentage distribution of cases reflecting the pattern and staining intensities of E-cadherin immunostaining in 15 cases of adenoid cystic carcinoma

Histological patterns in adenoid cystic carcinoma	Total number of positive cases	Mild (%)	Moderate (%)	Intense (%)	Negative (%)
Parenchymal patterns					
Tubular	10	1 (10)	4 (40)	4 (40)	1 (10)
Cribriform	15	2 (13)	11 (74)	2 (13)	Nil
Solid	5	5 (100)	Nil	Nil	Nil
Stromal patterns					
Fibro cellular	15				15 (100)
Hyalinized	15				15 (100)

Table 4: Distribution of cases based on the intensity of immuno-staining in pleomorphic adenoma cases and adenoid cystic carcinoma cases

	Total number of cases	Mild (%)	Moderate (%)	Intense (%)	Negative (%)
Pleomorphic adenoma	15	4 (26.6)	7 (46.6)	4 (26.6)	Nil
Adenoid cystic carcinoma					
Predominantly cribriform and tubular	10	1 (10)	6 (60)	3 (30)	Nil
Predominantly solid	5	5 (100)	Nil	Nil	Nil

Table 5: Comparison of the intensity of E-cadherin immunostaining between pleomorphic adenoma (PA) and adenoid cystic carcinoma using Mann-Whitney U-test

Tumors	Sum of ranks	Mann-Whitney U-value	*Z*	*P*	Significance
Benign	249	96.0	−0.734	0.463	Not
Malignant	216				significant

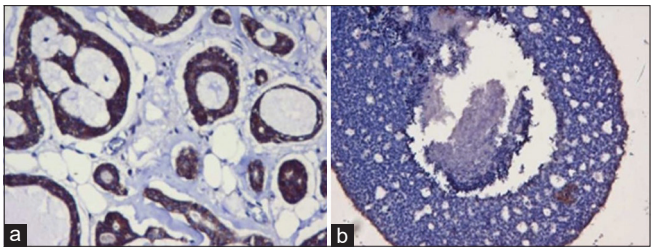

Figure 3: (a) Photomicrograph showing intense staining of E-cadherin in the cribriform pattern of adenoid cystic carcinoma (immunohistochemical, ×200). (b) Photomicrograph showing mild-to-negative staining of E-cadherin in the solid pattern of adenoid cystic carcinoma (immunohistochemical, ×100)

and malignant neoplasms of various tissues.[12] E-cadherin in adherens and desmoglein-2 (the main desmoglein expressed in salivary glands) in desmosomal junctions, beta-4 integrin in alpha6 beta4 laminin receptor of hemidesmosomes, HCAM (CD44s) associated with hyaluronan and ICAM-1 – member of Ig superfamily is implicated in normal tissue epithelial architecture and/ immune responses.[26]

Loss of E-cadherin seems to be related to progression from an ordered polarized ductal/glandular architecture to a more malignant disorganized architecture especially in breast and colon tumors.[33-36] However studies pertaining to salivary gland neoplasm concluded that the same does not appear to exist for salivary gland neoplasm in which the diversity of architectural patterns precludes detection of any simple relationship and that E-cadherin expression

Table 6: Comparison of the intensity of E-Cadherin immunostaining between benign pleomorphic adenoma and malignant combined predominantly cribriform and tubular variants of adenoid cystic carcinoma by Mann-Whitney U-test

Tumors	Sum of ranks	Mann-Whitney U-value	*Z*	*P*	Significance
Pleomorphic adenoma	184	64.0	−0.669	0.503	Not significant
Combined predominantly cribriform and tubular	141				

Table 7: Comparison of the intensity of E-cadherin immunostaining between benign pleomorphic adenoma and the malignant solid variant of adenoid cystic carcinoma

Tumors	Sum of ranks	Mann-Whitney U-value	*Z*	*P*	Significance
Pleomorphic adenoma	185.0	10	−2.588	0.01	Significant
Solid variant	25.0				

should be studied in detail to know its importance in diagnosis or prognosis of salivary neoplasm in general. Only a limited number of researchers have focussed in the role of CAMs in salivary gland architecture and their neoplasm with conflicting results.[23]

PA, the commonest salivary gland tumor is noted for its cytologic and histomorphological variations. Histomorphologically, the cells (both inner/luminal/ductal and outer/nonluminal) of tubulo-glandular areas and nonluminal cells of islands, sheets and strands remained cohesive or loosely cohesive and were grouped under the category of "cohesive cells.". Some of the nonluminal cells were widely separated amidst lots of stroma and these were grouped under the category of "non-cohesive cells." Since squamous metaplastic cells and plasmacytoid cells also remained cohesive they were also grouped under "cohesive cells." Thus, the cells in the parenchymal areas were considered as cohesive cells as they were grouped/linked together. Whereas the cells in the stromal areas were considered as noncohesive cells as they were separated from each other.[37] Thus, its an admixture of epithelial and myoepithelial cells consisting of gland-like structures, ducts, sheets, cell nests, cords, spindle and plasmacytoid cells and mesenchymal-like chondromyxoid tissue. ADCC is an uncommon malignant salivary gland tumor, most commonly involving the minor salivary glands. It is characterized by locally invasive growth and has affinity for perineural and perivascular invasion. It exhibits a high tendency of local recurrence and metastasis to distant site.[38] Ko *et al.* in their study observed that patients with solid histological patterns showed a significant ($P = 0.026$) correlation with local recurrence compared to distant metastasis.[39]

Expression of E – Cadherin in normal salivary gland tissues

E-cadherin expression was noted in all five samples of normal salivary gland tissues and homogeneously, immuno-localized to the cell membranes. The baso-lateral membranes showed a more distinct staining which was in accordance with Furuse *et al.*[24] The serous acini displayed predominantly moderate intensity of staining, i.e., 03/05 cases (60%), followed by one case (20%) each in mild and intense staining categories. On the contrary mucous acini showed predominant mild and moderate staining intensity in 03/05 cases (60%) and 02/05 cases (40%) respectively. Moderate intensity of staining was noted in the emptied serous acini compared to mild or absent staining in acinar cells with abundant cytoplasm and secretory granule which was similar to that of Furuse *et al.*[24] Both the striated and excretory ducts showed predominant intense staining intensity 03/05 cases (60%) followed by 02 cases (40%) in mild category which was similar to Shibuya *et al.* and Ekarat study.[9,40] In Sudeendra prabhu *et al.*'s observation only intense staining in normal salivary gland epithelium was reported without any details.[25] All the myoepithelial cells were immuno-stained in Shibuya *et al.*'s study,[40] contrary to our's and that of Economopoulou *et al.*'s[23] observation.

Expression of E-cadherin in pleomorphic adenoma

All 15 cases of PAs showed positive E-cadherin immuno-staining with the immune-stain localized to the membranes (especially the basolateral surfaces).[22-25] Two cases also displayed diffuse mild cytoplasmic immuno-staining which was not reported earlier and probably could be due to methodological error. However cytoplasmic expression of E-cadherin was reported in the cytoplasm of thyroid cells according to Mitselou *et al.*'s study.[41] Majority of our cases 07 (46.6%) showed moderate, followed by intense and mild staining (04, 26.6% each) which was in contrast to intense staining (05/10, 50%) followed by moderate (03/10, 30%) and mild staining (02/10, 20%) in Sudeendra *et al.*'s study. However, the differences were not by large.[25]

Expression of E-cadherin in adenoid cystic carcinoma

In ADCC all 15 (100%) cases of ADCC s displayed positive E-cadherin immunostaining, closer to the observation of positive staining in 21/24 (87.5%) cases in Prabhu *et al.* 's study[25] and in contrast to the finding of only (37/60) 62% positivity Zhang *et al.*[31] The immuno-stain was localized predominantly to the basolateral membranes similar to the findings of Economopoulou *et al.*, Furuse *et al.*, Shibuya *et al.*'s study (plasma membranes at interdigitations).[23,24,40]

Table 8: Comparison of the intensity of E-cadherin immunostaining between combined predominantly cribriform and tubular variant and the solid variant of adenoid cystic carcinoma

Tumors	Sum of ranks	Mann-Whitney U-value	*Z*	*P*	Significance
Combined predominantly cribrifrorm and tubular	102.5	2.5	−2.958	0.003	Significant
Solid variant	17.5				

Majority showed moderate and mild intensity (12/15) followed by intense (03/15) in contrast to Prabhu *et al*.'s observation of majority (10/24) in intense followed by 4/24 in moderate and 07/24 in mild. This could be attributed to the varying proportions of the histological patterns as solid areas stain mild or negative as seen in our cases and that of Prabhu *et al*.'s, Zhang *et al*.'s and Franchi *et al*.'s [25,27,31] observations or conflicting as in Daa *et al*.'s observation.[30]

In predominantly combined cribriform and tubular variants (10 cases), majority, i.e., six (06) showed moderate, three (03) showed intensely and one (01) showed mild staining. In predominantly solid pattern all five (05) cases showed mild staining. Studies on ADCCs have grouped the total number of cases based on the intensity of staining but have not done the same with respect to each histologic variant of ADCCs though they have discussed about the variations in the intensity of staining. Hence, no comparisons could be made in each histologic variant.

In our study, we couldn't find statistical significance of staining intensities between PA and ADCC (all histological patterns combined). Our results were similar to the findings of Prabhu *et al*.[25] Similarly, we couldn't find any statistical significance when only combined cribriform and tubular variants of ADCC were compared with PA. However, a $P = 0.01$ was noticed on comparing PAs with the solid variant of ADCCs and a $P = 0.03$ was noticed on comparing within the histologic variants of ADCCs. This clearly showed that E-cadherin expression got downregulated in the solid variant of ADCCs similar to the observations of Franchi *et al*.[27] who also correlated the downregulation of E-Cadherin staining with the histological grade of the tumor. However, in contrast Wu *et al*.'s study the expression of combined E-cadherin catenin complex was found not to correlate with the histological grade of the tumor.[28] Thus, its better to classify the ADCCs based on the predominant variant and then to assess the statistical significance as it's a known fact that the solid type is more malignant with more potential for recurrence and metastases and is associated with poor prognosis.

SUMMARY AND CONCLUSION

In the present study, IHC expression of E-cadherin between PAs and ADCCs (all the variants combined) did not show any statistical significance. When the comparison is done considering all the histological subtypes of ADCCs individually, we observed a significant loss of E-cadherin expression in solid growth pattern. It helps to correlate decreased E-cadherin expression along with the decrease in cellular differentiation and thus signifies its role in the complex mechanism of progression of salivary gland pathologies. Hence, all future studies aiming to assess the usefulness of an immuno-marker should aim at classifying the ADCCs depending on the predominant histologic pattern.

Financial support and sponsorship

Self-supported.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ellis GL, Auclair PL, Gnepp DR. Surgical Pathology of Salivary Glands. Vol. 25. Philadelphia: W B Saunders; 1991. p. 165-82 & 333-49.
2. Dardick I. Color Atlas/Text of Salivary Gland Tumor Pathology.New York: Igaku Shoin Publishers; 1996. p. 75-83 & 149-60.
3. Vargas PA, Cheng Y, Barrett AW, Craig GT, Speight PM. Expression of Mcm-2, Ki-67 and geminin in benign and malignant salivary gland tumours. J Oral Pathol Med 2008;37:309-18.
4. Alves FA, Pires FR, De Almeida OP, Lopes MA, Kowalski LP. PCNA, Ki-67 and p53 expressions in submandibular salivary gland tumours. Int J Oral Maxillofac Surg 2004;33:593-7.
5. Enescu A, Enescu AŞ, Florou C, Petrescu F. E-cadherin and α-SMA expression in the epithelial-mesenchymal transition of salivary glands pleomorphic adenomas. Rom J Morphol Embryol 2014;55:1383-7.
6. Perschbacher K, Jackson-Boeters L, Daley T. The adhesion molecules NCAM, HCAM, PECAM-1 and ICAM-1 in normal salivary gland tissues and salivary gland malignancies. J Oral Pathol Med 2004;33:230-6.
7. Schwarz S, Ettl T, Kleinsasser N, Hartmann A, Reichert TE, Driemel O. Loss of Maspin expression is a negative prognostic factor in common salivary gland tumors. Oral Oncol 2008;44:563-70.
8. Charalabopoulos K, Gogali A, Kostoula OK, Constantopoulos SH. Cadherin superfamily of adhesion molecules in primary lung cancer. Exp Oncol 2004;26:256-60.
9. Phattarataratip E, Kositkittiwanit N, Kajornkiatkul P, Yeunyong P, Ratanapitak R. P120 catenin expression and its correlation with E-cadherin in salivary gland neoplasms. J Oral Biol Craniofac Res 2019;9:57-62.
10. Takeichi M. Cadherin and adhesion receptors as a morphogenic regulator. Science 1991;251:145-5.
11. Takeichi M. Morphogenetic roles of classic cadherins. Curr Opin Cell Biol 1995;7:619-27.
12. Charalabopoulos K, Binolis J, Karkabounas S. Adhesion molecules in carcinogenesis. Exp Oncol 2002;24:249-57.
13. Mittari E, Charalabopoulos A, Batistatou A, Charalabopoulos K. The

role of Ecadherin – Catenin complex in laryngeal cancer. Exp Oncol 2005;27:257-61.
14. Semb H, Christofori G. Insights from model systems: The tumor-suppressor function of E-cadherin. Am J Hum Genet 1998;146:219-24.
15. Le TL, Yap AS, Stow JL. Recycling of E-cadherin: A potential mechanism for regulating cadherin dynamics. J Cell Biol 1999;146:219-32.
16. Bagutti C, Speight PM, Watt FM. Comparison of integrin, cadherin, and catenin expression in squamous cell carcinomas of the oral cavity. J Pathol 1998;186:8-16.
17. Bánkfalvi A, Krassort M, Végh A, Felszeghy E, Piffkó J. Deranged expression of the E-cadherin/beta-catenin complex and the epidermal growth factor receptor in the clinical evolution and progression of oral squamous cell carcinomas. J Oral Pathol Med 2002;31:450-7.
18. Sakaki T, Tamura I, Kadota H, Kakudo K. Changing expression of E- and P-cadherin during rat tongue carcinogenesis induced by 4-nitroquinoline 1-oxide. J Oral Pathol Med 2003;32:530-7.
19. Diniz-Freitas M, García-Caballero T, Antúnez-López J, Gándara-Rey JM, García-García A. Reduced E-cadherin expression is an indicator of unfavourable prognosis in oral squamous cell carcinoma. Oral Oncol 2006;42:190-200.
20. Menezes MB, Lehn CN, Gonçalves AJ. Epidemiological and histopathological data and E-cadherin-like prognostic factors in early carcinomas of the tongue and floor of mouth. Oral Oncol 2007;43:656-61.
21. Mahomed F, Altini M, Meer S. Altered E-cadherin/beta-catenin expression in oral squamous carcinoma with and without nodal metastasis. Oral Dis 2007;13:386-92.
22. Yamada K, Namba M, Kudeken W, Takai Y, Mori M, Yang L, *et al*. Comparitive expression of E-cadherin, ALPHA. And BETA. Catenin in salivary gland tumors. Acta histochemica et cytochemica 1999;32:305-13.
23. Economopoulou P, Hanby A, Odell EW. Expression of E-cadherin, cellular differentiation and polarity in epithelial salivary neoplasms. Oral Oncol 2000;36:515-8.
24. Furuse C, Cury PR, Altemani A, dos Santos Pinto D Jr., de Araújo NS, de Araújo VC. Beta-catenin and E-cadherin expression in salivary gland tumors. Int J Surg Pathol 2006;14:212-7.
25. Prabhu S, Kaveri H, Rekha K. Benign, malignant salivary gland tumors: Comparison of immunohistochemical expression of e-cadherin. Oral Oncol 2009;45:594-9.
26. Andreadis D, Epivatianos A, Poulopoulos A, Nomikos A, Christidis K, Papazoglou G, *et al*. Immunohistochemical detection of the expression of the cell adhesion molecules E-cadherin, desmoglein-2, beta4-integrin, ICAM-1 and HCAM (CD44s) in Warthin's tumour of the parotid gland. Oral Oncol 2005;41:799-805.
27. Franchi A, Gallo O, Bocciolini C, Franchi L, Paglierani M, Santucci M. Reduced E-cadherin expression correlates with unfavorable prognosis in adenoid cystic carcinoma of salivary glands of the oral cavity. Am J Clin Pathol 1999;111:43-50.
28. Wu YQ, Zhang WG, Tian Z, Zhang ZY. The expression of E-cadherin-catenin complex in human salivary adenoid cystic carcinoma. Shanghai Kou Qiang Yi Xue 1999;8:163-5.
29. Zhang ZY, Wu YQ, Zhang WG, Tian Z, Cao J. The expression of E-cadherin-catenin complex in adenoid cystic carcinoma of salivary glands. Chin J Dent Res 2000;3:36-9.
30. Daa T, Kaku N, Kashima K, Nakayama I, Yokoyama S. Expression of beta-catenin, E-cadherin and cyclin D1 in adenoid cystic carcinoma of the salivary gland. J Exp Clin Cancer Res 2005;24:83-7.
31. Zhang CY, Mao L, Li L, Tian Z, Zhou XJ, Zhang ZY, *et al*. Promoter methylation as a common mechanism for inactivating E-cadherin in human salivary gland adenoid cystic carcinoma. Cancer 2007;110:87-95.
32. van Boxtel W, Uijen MJ, Verhaegh GW, Willems SM, Jonker MA; PALGA Group, *et al*. Prognostic value of PSMA, c-MET and E-cadherin in salivary duct carcinoma. Oral Oncol 2020;110:105018.
33. Mayer B, Johnson JP, Leitl F, Jauch KW, Heiss MM, Schildberg FW, *et al*. E-cadherin expression in primary and metastatic gastric cancer: Down-regulation correlates with cellular dedifferentiation and glandular disintegration. Cancer Res 1993;53:1690-5.
34. Becker KF, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, *et al*. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res 1994;54:3845-52.
35. Smith ME, Pignatelli M. The molecular histology of neoplasia: The role of the cadherin/catenin complex. Histopathology 1997;31:107-11.
36. Tan DS, Potts HW, Leong AC, Gillett CE, Skilton D, Harris WH, *et al*. The biological and prognostic significance of cell polarity and E-cadherin in grade I infiltrating ductal carcinoma of the breast. J Pathol 1999;189:20-7.
37. Triantafyllou A, Thompson LD, Devaney KO, Bell D, Hunt JL, Rinaldo A, *et al*. Functional histology of salivary gland pleomorphic adenoma: An appraisal. Head Neck Pathol 2015;9:387-404.
38. Jaso J, Malhotra R. Adenoid cystic carcinoma. Arch Pathol Lab Med 2011;135:511-5.
39. Ko YH, Lee MA, Hong YS, Lee KS, Jung CK, Kim YS, *et al*. Prognostic factors affecting the clinical outcome of adenoid cystic carcinoma of the head and neck. Jpn J Clin Oncol 2007;37:805-11.
40. Shibuya Y, Ri S, Umeda M, Yoshikawa T, Masago H, Komori T. Ultrastructural localization of E-cadherin and alpha-/beta-catenin in adenoid cystic carcinoma. Histopathology 1999;35:423-31.
41. Mitselou A, Ioachim E, Peschos D, Charalabopoulos K, Michael M, Agnantis NJ, *et al*. E-cadherin adhesion molecule and syndecan-1 expression in various thyroid pathologies. Exp Oncol 2007;29:54-60.