Correlation of E-cadherin Immunohistochemical Expression with Histopathological Grading of Oral Squamous Cell Carcinoma

Abstract
Objectives: The current research was undertaken with an aim to correlate the expression of E-cadherin with histopathological grading in oral squamous cell carcinoma (OSCC) patients. Further, the objectives of the study were to evaluate the qualitative and quantitative expressions of E-cadherin in OSCC and to correlate the number of tumor cells of OSCC, immunopositive for E-cadherin with histopathological grading of OSCC. Materials and Methods: Immunohistochemistry of E-cadherin expression was evaluated in previously diagnosed, paraffin-embedded sections of 20 tissues each of well-differentiated and moderately differentiated OSCC, 17 tissues of poorly differentiated OSCC, and 10 tissues of normal oral mucosa; Chi-square test, analysis of variance, and Tukey’s honestly significant difference test were employed for statistical analysis. Results: E-cadherin immunoreactivity was inversely correlated to the loss of cell differentiation. There was a significant decrease in expression of E-cadherin (P < 0.0001) in advanced cases of OSCC. Furthermore, there was a significant reduction in intensity of E-cadherin expression with advancing histological grades of OSCC. Conclusion: From the present study, it is concluded that the reduced expression of E-cadherin may be a reliable indicator of increase in the invasiveness of OSCCs.

Keywords: E-cadherin, immunoreactive score, oral squamous cell carcinoma, prognosis

Introduction
Despite an ever-expanding fund of knowledge regarding the etiology and pathogenesis of malignant neoplasms, oral squamous cell carcinoma (OSCC) is still considered as a deadly disease. OSCC when clubbed with pharyngeal cancer, constitutes to be the sixth most common cancer around the globe with a vast variation in its incidence depending on the geographical areas. The annual estimated incidence is around 275,000 and 130,300 for oral and pharyngeal cancers, respectively (excluding nasopharynx), of which two-thirds of cases have been reported from the developing countries. WHO grades the epithelium of OSCC into well, moderately, and poorly differentiated types, wherein the grades define the patient survival as well.

Most of the invasive OSCCs are preceded by a preinvasive stage that lasts for years. During this period as the condition progresses, subsequently, cohesion is lost which is a result of deficiency at the molecular level. E-cadherin is the most important molecule in cell-to-cell adhesion in epithelial tissues. It is responsible for adhesion of epithelial cells and promoting cell polarity and also in the formation of cell-to-cell junction, as it has been found to be expressive in most of the epithelial cells.

E-cadherin is a 120 kDa transmembrane glycoprotein and has been considered to be the main cell-to-cell adhesive molecule. The cytoplasmic moiety of E-cadherin binds to β- and γ-catenin, linked to cytoskeleton through α-catenin, whereas the extracellular moiety is a calcium-dependent receptor responsible for homophilic interactions. Classical or Type I cadherins were first to be discovered, which include E-cadherin which prompts cell-to-cell adhesion.

Now, it is a well-known fact that they not just act as “biological glue,” but from the cell surface they generate signals that help in carrying out a number of functions such as apoptosis, growth factor receptor activation, tumor development, and metastasis. Loss of expression of E-cadherin is suggestive of its role in
inhibiting tumor invasion or metastasis, as the activity of tumor differentiation decreases and the probability of metastasis increases.\(^6\)\(^8\)

Although, the level of E-cadherin is maintained in cases of OSCC, its level and patient survival seem to follow an inverse relationship.\(^6\)\(^7\)\(^9\)\(^10\)\(^11\) It has been observed in most of the cases of OSCC that as the disease progresses, there is a decrease in expression of E-cadherin which is because of the epigenetic mechanisms.\(^12\) In vitro studies demonstrate that lack of E-cadherin production and loss of epithelial phenotype are dependent on each other.\(^13\)

In this background, the current research was carried out with an aim to correlate the immunohistochemical (IHC) expression of E-cadherin with histopathological grading in OSCC. Further, the objective of the study was to evaluate the qualitative and quantitative expressions of E-cadherin in OSCC and to correlate the number of tumor cells of OSCC, immunopositive for E-cadherin with histopathological grading of OSCC.

**Materials and Methods**

The research was initiated after obtaining clearance from the institutional ethical committee. The inclusion criteria was based on the retrospective selection of tissue block previously diagnosed as OSCC histopathologically. Exclusion criteria was based on patients who had received neoadjuvant cancer therapy, necrosed/scanty tissues, and poorly fixed paraffin blocks.

The present study was undertaken by retrieving previous records and paraffin-embedded tissue blocks of histopathologically diagnosed cases of OSCC (57 cases) and normal mucosa.\(^10\) As control, a specimen of normal oral mucosa (Group I) was obtained from the patient’s buccal flap that was raised during surgical removal of impacted mandibular third molars. Fifty-seven cases of OSCC were included, of which 20 cases were of well-differentiated carcinoma (Group II), 20 cases were of moderately differentiated carcinoma (Group III), and 17 cases were of poorly differentiated carcinoma (Group IV).

Two fresh sections of 3-µm thickness were cut from each formalin-fixed and paraffin-embedded tissue blocks. One set of sections was stained with hematoxylin and eosin. The histological grading of malignancy was carried out using a light microscopy according to criteria proposed by Byrne.\(^14\) Subsequently, another set of sections was taken onto polylysine-coated (slide adhesive) microslides for immunohistochemical staining.

**Immunohistochemical procedure**

The sections were deparaffinized, and then, xylene and descending grades of alcohol were used to rehydrate the section. Retrieval of antigen was carried out in a microwave in 10-mM citrate buffer (pH 6.0) at high power for 15 min and at low power for 10 min and then washed in Tris-buffered saline. Afterward, sections were incubated by covering them with 4% hydrogen peroxide for 30 min, which would help in blocking endogenous peroxidase activity. Further, the slides were incubated with primary anti-E-cadherin monoclonal antibody (Biogenex Life Sciences Private Limited, CA, USA, 6 ml, ready to use) for 60 min at 37°C in a humid chamber.

Further, the sections incubated along with secondary-linking antibody (biotinylated anti-immunoglobulins/super-enhancer) at room temperature, in a humid chamber for 30 min, which would enhance the effect of subsequent polymer step. These sections were then incubated with prediluted secondary antibody, i.e., conjugate(enzyme-conjugated streptavidin) at room temperature for 30 min. This was followed by incubation with diaminobenzidine chromogen and counterstained with Mayer’s hematoxylin. For negative control tissue, sections were treated with all the reagents except the primary antibody. Positive control tissue (i.e., the normal mucosa) sections were used to determine homogeneous, accurate, and reproducible staining.

**Immunohistochemical analysis**

All the immunohistochemically stained slides from the study Groups I, II, III, and IV were evaluated for the expression of E-cadherin. E-cadherin immunopositivity was defined as the presence of a brown color immunostaining of the cell membrane and cytoplasm. E-cadherin expression pattern in all the groups was recorded based on their localization as membranous expression, cytoplasmic expression, and both cytoplasmic and membranous expression. The immunoreactivity of E-cadherin in all the groups was assessed semi-quantitatively by calculating the immunoreactive score (IRS)\(^15\) as follows: IRS = percentage of immunopositive cells (A) \(\times\) intensity of immunostaining (B) [Table 1].\(^15\)

The E-cadherin immunoposession patterns and E-cadherin immunoreactivity calculated from the IRS were compared, by statistical methods, between normal oral epithelium (NOE) and three grades of OSCC and also, among the three grades of OSCC. The statistical analysis was done using SPSS (Statistical Package Inc., Chicago, Ill., USA) Version 20.0. Chi-square test was employed to evaluate the gender distribution among different study groups (NOE and three grades of OSCC). Tukey’s -honestly significant difference technique was used to compare within the four groups, the variance in the IRS of E-cadherin and the variance in age distribution among the study groups. \(P < 0.05\) was considered to be statistically significant.

**Results**

According to mean, the percentage of immunopositive cells was higher in well-differentiated squamous cell carcinoma (WDSCC, 3.7300%) followed by moderately
differentiated squamous cell carcinoma (MDSCC, 2.6800%) and poorly differentiated squamous cell carcinoma (PDSCC, 1.6588%) [Table 2]. There is a significant variation between all OSCC grades and control group (P < 0.05), and pairwise comparison also shows a significant difference between each group. The intensity of immunostaining was higher in WDSCC and NOE, followed by MDSCC and PDSCC [Figures 1-4 and Table 3]. IRS was higher in WDSCC (10.4800) and NOE (9.5800), followed by MDSCC (6.2500) and PDSCC (2.5529) [Table 4]. E-cadherin showed a strong homogeneous membranous expression in NOE [Figure 1] and cells of WDSCC [Figure 2]. It was heterogeneous (both membranous and cytoplasmic) in MDSCC [Figure 3], whereas it attained a weak cytoplasmic or negative expression (n = 3) in cells of PDSCC [Figure 4], with a significant P < 0.05 [Table 5].

E-cadherin expression was significantly reduced from NOE through WDSCC to MDSCC and PDSCC, a reduction that was found to be statistically significant. It could also be used in estimating the invasiveness and aggressiveness of the disease, hence significantly predicting the behavior of the disease more accurately.

**Discussion**

One of the features of malignancy is invasion into the stroma and surrounding tissues. Cancer invasion is initiated by the dissociation of cells, due to a loosened intercellular adhesion. The release of tumor cells from the primary nest of cancer may be triggered by the suppression of cell-to-cell adhesion which benefits the invasive properties on a tumor. The E-cadherin expression level is frequently reduced or may be absent in a variety of epithelial cancers, and the loss of intercellular junctions is believed to precede a tumor invasion and metastasis. The loss or reduction of E-cadherin-mediated adhesion defines the staging of invasion and metastasis in many epithelial carcinomas, including head-and-neck carcinomas. Experiments carried out in vitro show that E-cadherin acts as an invasion suppressor in human cancers.

The growth and differentiation pertaining to stratified squamous epithelium is regulated by the cell-to-cell adhesion molecules for which E-cadherin being the primary mediator, the role of which is to help in the tissue morphogenesis (segregation and differentiation). Under normal conditions, it is present in the divided and segregated cells.

For maintenance of intracellular adhesion, an intact E-cadherin/β-catenin complex is necessary. Any disturbance in functioning of this complex leads to loss of adhesion. This loss of adhesion can be either due to mutations in E-cadherin or its associated complex (including catenins and actins).

### Table 1: Immunoreactive score

| Description | n | Mean (per sample) | SD    | F     | P       |
|-------------|---|------------------|-------|-------|---------|
| I Normal    | 10| 3.2800           | 0.47329 | 96.995 | <0.0001 |
| II WDSCC    | 20| 3.7300           | 0.25361 |       |         |
| III MDSCC   | 20| 2.6800           | 0.42748 |       |         |
| IV PDSCC    | 17| 1.6588           | 0.38578 |       |         |
| Total       | 67| 2.8239           | 0.87975 |       |         |

WDSCC: Well-differentiated squamous cell carcinoma; MDSCC: Moderately differentiated squamous cell carcinoma; PDSCC: Poorly differentiated squamous cell carcinoma; SD: Standard deviation

### Table 2: Mean percent of E-cadherin immunopositive cells in the control and study groups

| Description | n | Mean (per sample) | SD    | F     | P       |
|-------------|---|------------------|-------|-------|---------|
| I Normal    | 10| 2.9000           | 0.31623 | 31.108 | <0.0001 |
| II WDSCC    | 20| 2.8000           | 0.41039 |       |         |
| III MDSCC   | 20| 2.3000           | 0.47016 |       |         |
| IV PDSCC    | 17| 1.5294           | 0.51450 |       |         |
| Total       | 67| 2.3433           | 0.68650 |       |         |

WDSCC: Well-differentiated squamous cell carcinoma; MDSCC: Moderately differentiated squamous cell carcinoma; PDSCC: Poorly differentiated squamous cell carcinoma; SD: Standard deviation

## Conclusion

Considering E-cadherin as an invasion suppressor gene, we have examined the expression of E-cadherin in NOE and different grades of OSCC (well-differentiated, moderately differentiated, and poorly differentiated).
Age matching and gender matching of the samples are conducive to arrive at a bias-free conclusion in any comparative study that examines variables other than age or gender. In our study, E-cadherin immunopositivity, its intensity of staining, and location of expression were the variables that were compared between the three study groups.

In this study, E-cadherin expression appeared in 3.7300% of the cells in well-differentiated OSCC (WDOSCC), 2.6800% of moderately differentiated OSCC (MDOSCC), and 1.6588% of poorly differentiated OSCC (PDOSCC) [Table 2]. The percentage of immunopositive cells was higher in WDOSCC, followed by MDOSCC and PDOSCC, respectively. There is a significant variation between all OSCC grades. Our findings are in concordance with Lopes et al.,[26] Zhai et al.,[27] and Rosado et al.[28] Further, similar to the observations of Chen et al.[18] and Zaid,[6] we have observed a significant reduction of E-cadherin expression in OSCC against the normal oral mucosa. However, a reduction of E-cadherin expression with an increase in the histological grades of OSCC was not in concordance with Liu et al.[26] They used different staining methods and had different standards for the assessment of the expression. With respect to the intensity of E-cadherin immunostaining [Table 3], we observed that WDOSCC expressed E-cadherin often as strong as normal stratified squamous epithelium, whereas in PDOSCC, expression of E-cadherin is lost or cytoplasmic, and in MDOSCC, it is expressed in a heterogeneous fashion.
Similar were the results of Kaur et al.\cite{11} and Tanaka et al.\cite{30} who observed a significant relationship between reduced E-cadherin and invasiveness of OSCC. Bagutti et al.\cite{31} have shown that least differentiated tumors showed a reduced expression of E-cadherin in later stages, and these tumor cells are said to acquire invasive phenotype. However, studies on E-cadherin by Shinohara et al.\cite{32} reported a nonsignificant relation between degree of differentiation and expression of E-cadherin.

The main factor, which helps to provide a scientific question with a clear answer, is the use of good scoring criteria. We specifically chose IRS as a scoring system in the present study as IRS is one of the widespread combined scoring systems, which is considered to be the gold standard in IHC evaluation and presentation. It is also one of the widely accepted and recommended scoring criteria by various associations and organizations.

We could not come across any literature regarding assessment of E-cadherin immunoreactivity by IRS method. We assessed the immunoreactivity of E-cadherin in all the groups semi-quantitatively by calculating the IRS, which is the result of percentage of immunopositive cells and intensity of immunostaining.

There was a significant variation in the mean of IRS [Table 4] between all OSCC grades and the control group (P < 0.05). It was higher in WDO SCC (10.4800) and NOE (9.5800), followed by MDOSCC (6.2500) and PDOSCC (2.5529). In pairwise comparison, no significant difference was found between NOE and WDO SCC, but a significant difference was observed between MDOSCC and PDOSCC.

In the NOE, we observed that the E-cadherin membranous expression [Table 5] was present mainly in the basal and lower parts of the spinous layers. With respect to the superficial layers, the expression of E-cadherin was reduced. Although the mechanisms of regulation of E-cadherin expression in the upper layers of the epithelium are not understood, it is thought that the loss of expression may play a role in normal desquamation of the epithelium.

In the present research, a moderate-to-strong E-cadherin expression was observed for the well-differentiated cases, whereas on the contrary, a negative or weak E-cadherin expression was observed for poorly differentiated cases, which are similar to the observations made by Bánkfalvi et al.\cite{25}

A MDOSCC resulted in heterogeneous staining, where the E-cadherin staining was observed in the differentiated central tumor island, whereas among the differentiated peripheral cells only expressed cytoplasmic staining.

From this, we can infer that E-cadherin expression was significantly reduced from NOE through well-differentiated to poorly differentiated OSCCs, a reduction which was found to be statistically significant [Table 5]. Huber et al.\cite{33} found that the downregulation of E-cadherin expression in cancer cell is associated with occult metastasis in oral cavity and oropharyngeal squamous cell carcinomas. These findings are supportive of the fact that E-cadherin plays a role in tumor suppression in vivo.

Along with downregulation of E-cadherin, Bryan and Tselepis\cite{34} had sketched a phenomenon, i.e., “cadherin switching,” which relates to the upregulation of members other than E-cadherin from the cadherin family such as N-cadherin or P-cadherin, that are associated with more worse condition such as bladder carcinoma. Similarly, there was a significant observation of expression of N-cadherin with malignant behavior.\cite{11}

As it is clear now that the adhesive function of E-cadherin crucially depends on their association with cytoplasmic catenins, additional studies focusing on (ITF) invasive tumor front need to be carried out on a larger sample and along with these related cell adhesion molecules, which, in turn, is necessary to evaluate the biological value of loss of E-cadherin in the progression of neoplasm. Further, this could aid in designing new strategies for the diagnosis and treatment of OSCC.

**Conclusion**

Thus, from the present study, it can be concluded that the specific expression of E-cadherin, intensity, and site staining in different histopathological grades of OSCC can be used in estimating the invasiveness and aggressiveness of the disease, hence significantly predicting the behavior of the disease more accurately.

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Nil.
Conflicts of interest

There are no conflicts of interest.

References

1. Papagerakis S, Pannone G. Epithelial-mesenchymal interactions in oral cancer metastasis. In: Og Burke KE, editor. Oral Cancer. London: InTech; 2012.
2. Warnaikusuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309-16.
3. Schipper JH, Scharfen BA, Behrens J, Unger A, Jahnke K, Birchmeier W. E-cadherin expression in squamous cell carcinomas of head and neck: Inverse correlation with tumor dedifferentiation and lymph node metastasis. Cancer Res 1991;51:6328-37.
4. Thompson LD. Squamous cell carcinoma variants of the head and neck. Curr Diagn Pathol 2003;9:384-96.
5. Yuwani MB, Tupkari JV, Avadhani A. Expression of E-cadherin in oral epithelial dysplasia and oral squamous cell carcinoma: An in vivo study. J Clin Exp Invest 2011;2:347-53.
6. Zaid KW. Immunohistochemical assessment of E-cadherin and β-catenin in the histological differentiations of oral squamous cell carcinoma. Asian Pac J Cancer Prev 2014;15:8847-53.
7. Bringuer PP, Umbas R, Schaalma HE, Karthaus HF, Debruyne FM, Schalken JA, et al. Decreased E-cadherin immunoactivity correlates with poor survival in patients with bladder tumors. Cancer Res 1993;53:3241-5.
8. Deng QW, He BS, Pan YQ, Sun HL, Xu YQ, Gao TY, et al. Roles of E-cadherin (CDH1) genetic variations in cancer risk: A meta-analysis. Asian Pac J Cancer Prev 2014;15:3705-13.
9. Hiroshi S. Inactivation of the E-cadherin-mediated cell adhesion system in human cancers. Am J Pathol 1998;153:333-9.
10. Kaur G, Carmelo S, Rao N, Rao L. Expression of E-cadherin in primary oral squamous cell carcinoma and metastatic lymph nodes: An immuno-histochemical study. Indian J Dent Res 2009;20:71-6.
11. Nguyen PT, Kudo Y, Yoshiha M, Kamata N, Ogawa I, Takata T. N-cadherin expression is involved in malignant behavior of head and neck cancer in relation to epithelial-mesenchymal transition. Histol Histopathol 2011;26:147-56.
12. Kudo Y, Kitajima S, Ogawa I, Hiraoka M, Sargolzaei S, Keikhaee MR, et al. Invasion and metastasis of oral cancer cells require methylation of E-cadherin and/or degradation of membranous beta-catenin. Clin Cancer Res 2004;10:5455-63.
13. Behrens J, Marcel MM, Van Roy FM, Birchmeier W. Dissecting tumor cell invasion: Epithelial cells acquire invasive properties after the loss of uvomorulin-mediated cell-cell adhesion. J Cell Biol 1989;108:2435-47.
14. Bryne M, Stromme H, Lilleng R, Stene T, Bang G, Dabelsteen E, et al. New malignancy grading is a better prognostic indicator than Broder’s grading in oral squamous cell carcinoma. J Oral Pathol Med 1989;18:432-7.
15. Fedchenko N, Reifenrath J. Different approaches for interpretation and reporting of immunohistochemistry analysis results in the bone tissue – A review. Diagn Pathol 2014;9:221.
16. Sun H, Chu J, Cho E, Lee D, Min M, Lee S, Cho N. Methylation status and expression of E-cadherin in oral squamous cell carcinomas compared to benign oral epithelial lesions. Int J Oral Biol 2006;31:27-32.
17. Pittella F, Katsube K, Takemura T, Hashimoto T, Kawano T, Garrod D, et al. Perinuclear and cytoplasmic distribution of desmoglein in esophageal squamous cell carcinomas. Pathol Res Pract 2001;197:85-91.
18. Chen HC, Chu FY, Hsu PN, Hsu PI, Lu JY, Lai KH, et al. Loss of E-cadherin expression correlates with poor differentiation and invasion into adjacent organs in gastric adenocarcinomas. Cancer Lett 2003;201:97-106.
19. Kajiyama H, Kikkawa F, Khin E, Shibata K, Ino K, Mizutani S. Desipradipyl peptide IV overexpression induces up-regulation of E-cadherin and tissue inhibitors of matrix metalloproteinases, resulting in decreased invasive potential in ovarian carcinoma cells. Cancer Res 2003;63:2278-83.
20. Luo J, Lubaroff DM, Hendrix MJ. Suppression of prostate cancer invasive potential and matrix metalloproteinase activity by E-cadherin transfection. Cancer Res 1999;59:3552-6.
21. Saito T, Masuda N, Miyazaki T, Kanoh K, Suzuki H, Shimura T, et al. Expression of EphA2 and E-cadherin in colorectal cancer: Correlation with cancer metastasis. Oncol Rep 2004;11:605-11.
22. Mehandiratta M, Solomon MC, Boaz K, Gudattu V, Mohindra A. Clinico-pathological correlation of E-cadherin expression at the invasive tumor front of Indian oral squamous cell carcinomas: An immunohistochemical study. J Oral Maxillofac Pathol 2014;18:217-22.
23. Wang X, Zhang J, Fan M, Zhou Q, Deng H, Aisharif MJ, et al. The expression of E-cadherin at the invasive tumor front of oral squamous cell carcinoma: Immunohistochemical and RT-PCR analysis with clinicopathological correlation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:547-54.
24. 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.
25. Bánkfalvi A, Krassost M, Buchwalow IB, Végh A, Felszeghy E, Pillé J. Gains and losses of adhesion molecules (CD44, E-cadherin, and beta-catenin) during oral carcinogenesis and tumour progression. J Pathol 2002;198:343-51.
26. Lopes FF, da Costa Miguel MC, Pereira AL, da Cruz MC, de Almeida Freitas R, Pinto LP, et al. Changes in immunoeexpression of E-cadherin and beta-catenin in oral squamous cell carcinoma with and without nodal metastasis. Ann Diagn Pathol 2009;13:22-9.
27. Zhai JW, Yang XG, Yang FS, Hu JG, Hua WX. Expression and clinical significance of Ezrin and E-cadherin in esophageal squamous cell carcinoma. Chin J Cancer 2010;29:317-20.
28. Rosado P, Lequerica-Fernández P, Fernández S, Alonza E, Villallain L, de Vicente JC, et al. E-cadherin and β-catenin expression in well-differentiated and moderately-differentiated oral squamous cell carcinoma: Relations with clinical variables. Br J Oral Maxillofac Surg 2013;51:149-56.
29. Liu LK, Jiang XY, Zhou XX, Wang DM, Song XL, Jiang HB, et al. Upregulation of vimentin and aberrant expression of E-cadherin/beta-catenin complex in oral squamous cell carcinomas: Correlation with clinicopathological features and patient outcome. Mod Pathol 2010;23:213-24.
30. Tanaka N, Odajima T, Ogi K, Ikeda T, Satoh M. Expression of E-cadherin, alpha-catenin, and beta-catenin in the process of lymph node metastasis in oral squamous cell carcinoma. Br J Cancer 2003;89:557-63.
31. Bagutt 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.
32. Shinohara M, Hiraki A, Ikebe T, Nakamura S, Kurahara S, Shirasu K, et al. Immunohistochemical study of desmosomes
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in oral squamous cell carcinoma: Correlation with cytokeratin and E-cadherin staining, and with tumour behaviour. J Pathol 1998;184:369-81.

33. Huber GF, Züllig L, Soltermann A, Roessle M, Graf N, Haerle SK, et al. Down regulation of E-cadherin (ECAD) – A predictor for occult metastatic disease in sentinel node biopsy of early squamous cell carcinomas of the oral cavity and oropharynx. BMC Cancer 2011;11:217:1-8.

34. Bryan RT, Tselepis C. Cadherin switching and bladder cancer. J Urol 2010;184:423-31.