Reviewer’s report

Title: P-cadherin expression and survival rate in oral squamous cell carcinoma: an immunohistochemical study.

Version: 1 Date: 5 April 2005

Reviewer: Miguel Angel Gonzalez-Moles

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Major compulsory revisions.

1) The objectives in the Abstract differ from those stated in the Introduction.

2) Comments on controls:
   a. Healthy margins of the tumour and skin sections are used as controls. The use of the mucosa adjacent to the tumour with a normal clinical and histopathologic appearance may have some drawbacks. First, it has been demonstrated that numerous early molecular markers of progression to cancer can be altered at a very early stage, even in mucosa of normal clinical and pathological appearance. The alteration may consist of total loss of the normal expression of the marker. If the present study uses mucosa adjacent to the carcinoma as control, although it has a normal appearance, the authors cannot rule out that a loss of p-cad expression in this mucosa indicates an early oncogenic disorder in the epithelium that has probably given rise to the carcinoma and affords invasive advantages to cells that are undergoing malignant transformation. In fact, the author cites in the Discussion a report (39) of the loss of p-cad expression in dysplasias adjacent to infiltrating carcinomas, which can be interpreted as a pre-invasion event. This can also be taking place in normal or hyperplastic epithelia adjacent to the tumour. It is very important in my view to take this into account in a marker like p-cad that has been little studied. More appropriate controls could be obtained from patients with no mucosal disease who do not receive oncogenic stimuli such as tobacco and alcohol. For example, patients coming to Schools of Dentistry for tooth extractions, whose consent could be sought to obtain a small sample of mucosa while under anaesthesia. Healthy skin could be a good control and indeed is used by these authors. Nevertheless, they should clarify where they obtained the healthy skin from, how many controls they used, and what results were obtained in the controls.

3) The authors make a cell count and establish a percentage. Based on this, they classified the tumours into only two groups (< 5% of +cells; > 5% of +cells):
   a) One of these groups should be ≤ or ≥.
   b) Why only two groups? The reason for this decision should be given as well as the previous analysis on which it was based. This type of assessment leads to the interesting result that when p-cad expression is lost the prognosis is worse. However, within the p-cad-positive tumours there are probably behavioural and biologically significant differences between tumours with 80% positive and 20% positive cells. Using the author’s approach, they are considered to be the same.

4) According to the photographs I received, different types of immunohistochemical techniques appear to have been used: phosphatase and peroxidase. If this is so, it should be clearly stated in Material and Methods. Otherwise, at least in the photographs I have, image 1d appears to correspond to a negative tumour. This clarification should be given in both Figure Legends and Material and Methods.

5) In the Results section, the term ‘dysplastic transformation’ is used in the p-cad+ve tumour group. In my opinion, this terminology is confusing in the setting of invasive oral carcinomas. The term dysplasia, inevitably associated with the term ‘dysplastic’ by readers with knowledge of oral cancer and precancer, refers, as I am sure the authors know, to premalignant epithelial changes...
from alterations in cell proliferation and maturation/differentiation. When these epithelia undergo unequivocal malignant transformation we speak of invasive carcinoma, so that in these cases the term dysplasia or dysplastic transformation should not be used. The term should be removed from the text or, if not, it should be fully clarified by the authors.

6) At the beginning of page 9 the authors argue that "normal P-cad or up-regulation." It should be clarified in the text what is understood by normal p-cad expression in oral squamous cell carcinoma and what is understood by over-regulation of p-cad.

7) The authors mention that the anomalous expression of p-cad in the epithelium underlying the tumour can be a biological marker of keratinocyte atypia and/or premalignant changes (page 10, para 2):

a. Who makes this affirmation? If it is the authors, they should give their results on p-cad expression in these epithelia. If they refer to interpretations by other authors, these should be cited.

8) Finally, I found the Discussion to be long, difficult to read and not well connected. It should be made easier to read and more attractive, perhaps offering interpretations derived from the personal reflection of the authors on the reasons why p-cad loss behaves as a factor of poor prognosis.

Final decision: this study presents a little-known and interesting phenomenon. It should be published if corrections are made in line with my comments

Level of interest: high.

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no conflict of interests