Author's response to reviews

Title: Cytokeratin 8/18 expression indicates a poor prognosis in squamous cell carcinomas of the oral cavity

Authors:

Thomas Fillies (fillies@uni-muenster.de)
Richard Werkmeister (Rwerkmeis@aol.com)
Jens Packeisen (ipackeisen@pathoweb.de)
Burkhard Brandt (brandt@uni-muenster.de)
Philippe Morin (p.morin@katharinenhospital.de)
Dieter Weingart (weingart.mkg@katharinenhospital.de)
Ulrich Joos (joos@uni-muenster.de)
Horst Buerger (burgerh@uni-muenster.de)

Version: 2 Date: 14 September 2005

Author's response to reviews: see over
Comments to revision:

We appreciate the comments of the reviewers and tried to include the criticism and the suggestions in the revised paper.

Reviewer 1:

We added possible therapeutic strategies of our results to the discussion. These include monoclonal antibodies against cytokeratin 19 or chemotherapy in the Ck 8-18 positive subgroup.

Reviewer 2:

Ad 1: This investigation was primarily focussed on the expression of cytokeratins which are rather untypical for oral mucosa and in consequence with the clinical outcome. There are definitely a multitude of further immunohistochemical markers which would be worth to investigate. However, our eligibility criterion of studied intermediate filaments was to investigate the rarely expressed cytokeratins in oral mucosa - Ck 8/18, Ck19, Ck1 and Ck10 and as typical expressed cytokeratins we used Ck 5/6 and Ck 14. Ck 5/6 and Ck 14 which are typically expressed in oral mucosa showed no correlation to the survival time / tumour prognosis therefore we have not seen the necessity to investigate a third typical expressed intermediate filament. Under this primary hypothesis we did not investigate CK13 expression.

Ad 2: First part of point 2: Cytokeratin 14 expression showed in various studies an inhomogeneous expression pattern in squamous cell carcinoma. Chu et al. (Histopathology. 2001 Jul;39(1):9-16) described that 90 % of head and neck tumours show a positive (n=30) Cytokeratin 14 reaction. Ibrahim et al. (APMIS. 1998 Oct;106(10):959-69) described different cytokeratin 14 expression for snuff dippers K14 (86%; 12/14) and non-snuff dippers K14 (43%; 32/74). Sesterhenn et al. (Anticancer Res. 2005 Jul-Aug;25(4):2675-80) described an expression level of CK14 in 73% of the investigated cases. Our results are therefore within the range of previous results - especially if we take into account that tissue
arrays have been used. The latter may have contributed to a lower than expected frequency since Ck 14 expression is rather inhomogeneous.

The second part of remark 2: The diagnosis of the squamous cell carcinoma have been reviewed during the preparation several times from different investigators. First, the initial diagnosis have been done by the evaluating pathologists during the initial diagnosis making. The diagnosis was confirmed without the knowledge of any protein expression patterns or other clinical data by one of the coauthors (H.B.) in the primary tumour block, before the preparation of the tissue microarray. All tumours have been constantly reviewed during the evaluation of the tissue array sections and therefore, we can exclude with certainty that other than squamous cell carcinomas are included in the TMA´s.

Ad 3 : We are aware that the expression of cytokeratins in cell cultures have to be interpreted with caution. However, to our opinion we didn´t compare the expression of Cytokeratin 8/18 in solid tumours with cell culture results. Hannsson et al. (Eur J Oral Sci. 2003) described a spontaneous induction of Ck’s 8 and 18 expression in immortalized buccal mucosa cells, which we interpreted as partial support of our findings which pinpointed a subgroup of oral squamous cell carcinoma with a poor prognosis

Ad 4: We inserted immunohistochemical illustrations to evaluate the morphology of the tumour and the quality of reactions.