Reviewer’s report

Title: EpCAM Nuclear Localization Identifies Aggressive Thyroid Cancer and is a Marker for Poor Prognosis

Version: 1 Date: 29 January 2010

Reviewer: Wendy Van Veelen

Reviewer’s report:

Major Compulsary Revisions:
1. In the more aggressive types of TC, nuclear Ep-ICD expression correlates with nuclear beta-catenin. The authors should mention the relation of nuclear beta-catenin with patient prognosis in the Introduction. In the Discussion the authors implicate a causal relationship between nuclear Ep-ICD and nuclear beta-catenin expression. This is states too strong as the authors have only observed concomitant nuclear expression of these proteins. Could both proteins serve (equally well) as biomarkers for diagnosis of aggressive TC? Could nuclear Ep-ICD expression (and/or nuclear beta-catenin expression) be used in addition or instead of standard pathological characteristics to improve discrimination between well- and poorly differentiated TC?

2. At pag. 15 nuclear EpEx is mentioned as an ideal candidate diagnostic marker and therapeutic target for most well- and poorly differentiated TCs, however, EpEx is also expressed in normal thyroid tissue. Therefore, membranous EpEx would not serve as an ideal marker. Instead, nuclear Ep-ICD is specifically expressed in poorly differentiated TCs, like ATC. Therefore, I would say that nuclear Ep-ICD could serve as an ideal target for diagnostic and therapeutic strategies for aggressive TC.

3. The scoring system used for IHC by the authors and shown in fig 3A,B,C is not conventional. Staining intensities on archived paraffin material are not reliable. The data should be presented in a table or diagram (e.g. +/-, +, ++ or percentages), like Fig 3D. There, the percentages of nuclear beta-catenin could be included.

Minor Essential Revisions:
1. The IHC pictures in Fig. 1 and 2 should be of a higher magnification. Preferably all at 40x.

2. The n, m, and c are not explained in the figure legends of fig 1 and 2 and are not visible in the pictures.

3. fig.3. Asterixes with numbers are shown. What do they indicate? Typo in title fig. 3D.

4. fig.4. Lines are not visible.

5. pag.9. A correlation between beta-catenin and overall survival is not shown in figure 4.
6. pag.9/10. The results mentioned in the text would be clearer in a table.
7. pag.14. beta-catenin is not a marker for proliferation.
8. pag.19. Panel CI depicts membranous staining and CIII depicts nuclear staining.

Discretionary Revisions:
1. It would be interesting to show whether the activity of the proteases TACE or Presenilin-2 is increased in aggressive TC.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests