Reviewer’s report

Title: microRNA-944 Overexpression is a Biomarker for Poor Prognosis of Advanced Cervical Cancer

Version: 0 Date: 30 Dec 2018

Reviewer: Folkert van Kemenade

Reviewer’s report:

In the manuscript, titled "MicroRNA-944 Overexpression is a biomarker for Poor prognosis of advanced cervical cancer", authors demonstrate correlation between mir944 levels and advanced FIGO states, with 5 yr survial as read out (90% vs 60% survival with 66 cases and almost overlapping Confidence Intervals). Selecting only FIGO stage IIb's, the difference is 84% vs 44% but based on (even) less cases (n=37) and, not surprisingly, overlapping CI's. (figs 3 and 4)

As for the biomarker itself: using RTqPCR authors demonstrate with 6 cases that expression is higher in cancer tissue compared to normal tissue from the same cases. In 66 cases, authors demonstrate crosssectionally i.e. 66 cases vs 50 normal cervix controls, that expression is higher in cancer cases. However, values have overlap (high normal vs low cancer) and the ROC shows an AUC of 0.79, which is not very impressive (figs 1a, 1b, 1c). Data are extended by correlating this with hrHPV. in cells in fig 2a and in the aforementioned 66 cases in fig 2b. Actually, only 54 are hrHPV positive and 12 are not. Correlation of mir944 with those 12 cases is less as shown in fig 2b.

The association is supported by demonstrating this in TCGA data, supplied as supplementary data.

Still, I'm not very convinced on the utility of this marker in the presented context.

I have some questions:

Q1: In table 2, association of miR944 low vs high is almost 50%-50% for tumors larger than 4 cm 18 cases low vs 18 cases high miR944), high stage FIGO (19 cases low vs 18 cases high) and in presence of lymph node metastasis (15 cases low vs 16 cases high). Can you explain why this marker is prognostic at all? "you devote exactly one sentence (line 199-201) to this finding. It should be a little more explained to readers in non-statistical terms.

Q2. in abstract 'background': What exactly are authors looking for? In the abstract they state the prognostic value 'in' cervical cancer but then in the next sentence they look for 'prognostic value for' cervical cancer (cxca). It seems to me that those are different things. Either it is a prognostic marker for cxca once it is diagnosed (but it doesn't add much more than FIGO state) or it is a prognostic marker for having cxca? I.e. once you measure mir944 and it is elevated, then you risk having cxca? Please clarify or use consistent phrasing.
Q3. The mir is located on 3q28. What are its targets?

Q4. last sentence of introduction: 'association between miR-944 and E6/E7 was explored'. `In fig 2b this returns as ' HPV neg or HPV pos'. I think it is more appropriate to write this down as E6/E7 mRNA pos or E6/E7 mRNA neg. Alternatively, adapt that last sentence in the introduction.

remarks

line 210: 'which is newly found' --> which is a newly found .

line 219: In advance FIGO stage --> please add n=37.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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