Reviewer's report

Title: Different protein expression associated with chemotherapy response in oropharyngeal cancer according to HPV status

Version: 2
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Reviewer: Volker Rudat

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In this retrospective study the authors assessed the impact of multiple biomarkers on the outcome of HPV-positive and -negative patients with oropharyngeal cancer treated with neoadjuvant chemotherapy followed by concomitant radiochemotherapy. More than 60 statistical tests were performed to evaluate factors in dependence of the HPV- and p16-status, and their impact on the treatment response after induction chemotherapy and on the 3-year PFS and OS. No correction for multiple testing was performed. Distinct protein expression patterns were found depending on the HPV-status and an association of certain expression profiles with the treatment outcome was observed. The authors concluded that further development of biomarkers could be used in the design of individualized treatment strategies for OPC.

Major Compulsory Revisions

More than 60 statistical tests were performed without correction for multiple testing. If correction for multiple testing would have been applied (for example the Bonferroni correction) presumably no statistical test would have been significant. In other words the authors obviously present an exploratory analysis. This should be more clearly indicated in the "Methods" and "Discussion" section as well as the limitations of an exploratory analysis. The objectives of an exploratory analysis are to (i) suggest hypotheses about the causes of observed phenomena, (2) assess assumptions on which statistical inference will be based, (3) support the selection of appropriate statistical tools and techniques and (4) to provide a basis for further data collection through surveys or experiments. The conclusions of the authors should correspond to the goals and meaning of an exploratory analysis.

Furthermore, interpretation of the findings is difficult because recognized important impact factors were not considered in the analysis. These factors include the N-status, stage, tumor volume, total dose, overall treatment time, histologic differentiation, age, EGFR expression, Ku80 expression. This limitation should also be stated in the manuscript.

Minor Essential Revisions

The multivariate analysis has not been adequately described. Which factors were entered into the model and what was the selection criterion for the factors? How
was the model optimized? Why were results presented in table 4 "Multivariate analysis for survival" for the “3Y PFS HR (95% CI)” but not for the “3Y-OS HR (95% CI)” and vice versa?

What radiation technique was used: 3D-CRT or IMRT? Was the same technique used for all patients?

Was there a significant prolongation in the overall treatment time?

Was a salvage neck dissection routinely performed in patients with a PR in the neck after radiochemotherapy?

**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