Reviewer's report

Title: Evaluation of chemiluminescence, toluidine blue and histopathology for detection of high risk oral precancerous lesions: a cross-sectional study

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Reviewer: Darren Roblyer

Reviewer's report:

Summary:

The manuscript describes a comparison between several oral cancer diagnosis methods in subjects with clinically identified premalignant lesions in a tertiary-care setting. The manuscript attempts to deal with an extremely important aspect of emerging diagnostic techniques, namely the repeatability and accuracy of histopathological diagnosis, especially when used as a gold standard against which other methods are compared. Although there are several significant limitations of the study, including a patient population from which results may generalize poorly to a true screening setting and a small number of pathologists (2) used for comparison, the results are still likely to be of significant interest to researchers and physicians studying oral cancer diagnostics and the manuscript provides a methodological framework for future, larger studies. Additionally, these limitations are clearly and appropriately stated in the text. The possibility of using the single more cost effective test (TBLU) instead of the CHEM test is also of significance if it can be corroborated in the future. There are several statistical issues that must be addressed before publication. Additionally, if more pathologists can be included in this analysis the manuscript would be greatly strengthened.

Discretionary Revisions:

PATIENTS AND METHODS, Histopathological evaluation, in reference to figure 1H, in this image of a severe dysplasia, the basement membrane is not visible. I recommend replacing this image with an example where the full thickness of the epithelium is visible in order to demonstrate the histopathological diagnostic procedure.

Major Compulsory Revisions:

RESULTS, Composite histopathological evaluation: The authors should justify the choice of threshold of their binary separation of diagnostic categories. At this institution, are there significant differences in how patient with 0 and 1 scores are treated compared to patients with 2 and 3? Is there a more logical threshold based on clinical practice?

RESULTS, Composite histopathological evaluation: In figure 1 E, it appears that the “total category score” is a summation of the 0-3 risk category codes for the
three evaluations by pathologists. The score only ranges between 1 and 7 however instead of between 0 and 9. Please clarify this point and alter the figure if necessary.

ABSTRACT, Conclusion: The statement: “There exists substantial variability in the histopathologically evaluation of oral precancerous lesions” is too strongly worded and too generalized based on the fact that only two pathologists were included in the study. This sentence, along with paragraph 2, sentence 4, should be modified to indicate that substantial variability existed within the context of this study. This will allow the reader to draw his or her own conclusions based on the presented data.

RESULTS, Variability in reference standard evaluation: It appears the Kappa statistic was performed on repeated observations from one pathologist + a single observation from a second pathologist. This is potentially confounding two aspects of the data, the intra and inter-pathologist correlation. The authors should justify this point.

RESULTS, Comparison of diagnostic performance: The authors should better define the HPMV as it is unclear. Is this the majority vote among the 3 readings (2 from the same pathologist and 1 from a different pathologist)? As mentioned before, it seems atypical to combine repeated observations with singular observations for a single consensus. The authors should justify this point.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests