TCR TRANSLATIONAL CANCER RESEARCH
ADVANCES CLINICAL MEDICINE TOWARD THE GOAL OF IMPROVING PATIENTS' QUALITY OF LIFE
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Peer Review File

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Reviewer A

This manuscript is probably the first Meta-analysis of Raman spectroscopy for lung cancer detection since there are not that many papers published in this regard. So it will be interesting to the readers of TCR. However, the following issues have to be resolved before considering for publication.

A total of 12 studies are included in this meta-analysis. And the authors divided them into three subgroups according to the sample types: Lung tissue (5 studies), blood sample (4 studies), and saliva sample (3 studies). But they failed to realize that the different Raman methods (spontaneous Raman vs. SERS) preferably detect different biochemical compositions, thus should not be mixed together in diagnostic performance analysis. In vivo tissue and ex vivo tissues are at different physiology status and their measurements have different sample volume/geometry, thus their Raman spectra/detected biochemical composition are quite different and should not be mixed together in diagnostic performance analysis either. Lumping all the 12 studies together for diagnostic performance analysis is also not appropriate for the same reasons. I suggest the following way of grouping:

1) In vivo tissue – spontaneous Raman [17]
2) Ex vivo tissue – spontaneous Raman [1], [16], [23]
3) Ex vivo tissue – SERS [22]
4) Blood – SERS [5], [18], [21]
5) Blood – spontaneous Raman [20]
6) Saliva – SERS [3], [4], [19]

The authors interpreted “lung cancer diagnosis” as differentiating “cancer” from “normal”. This is misleading. In clinical diagnosis, it is way more important to differentiate “cancer” form various “benign lesions” than just differentiate “cancer” from “normal”. The later is often an easier task. Ref [17] is the only study that included various “benign lesions”, thus the most meaningful study, not as the authors said that it exists bias (page 8, line 207).

Table 1. For the row starting with “McGregor,2017 (17)” “NA” should be changed to “80”. Study [17] clearly stated that 80 patients were enrolled in the study.

Reply: Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “The Accuracy of Raman Spectroscopy in the Diagnosis of Lung

Cancer: A Systematic Review and Meta-Analysis" (ID: TCR-21-515). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction point to point which we hope meet with approval.

1. Your suggestions on the subgroups analysis of our article are very pertinent. We also considered the grouping method as you mentioned. However, considering that this grouping methods will result in a smaller number of articles included in each subgroup. Some subgroups even included only one article, which would not be conducive to aggregate analysis. Therefore, we adopted the grouping methods in the manuscript after careful consideration. Thank you for your valuable suggestions. I also hope that our consideration can be understood and adopted by the reviewers.
2. Thank you for your comments. We re-read the article carefully, and all of our authors also discussed about your suggestions. Your suggestions are very pertinent, so we deleted the relevant inappropriate sentences.
3. We have revised the table1. Thank you for your comment.

Reviewer B

I disagree with the conclusion statement that Raman spectroscopy can be treated as an alternative option for lung cancer diagnosis. It may be further investigated and evaluated, yet this is NOT an option in terms of EBM.

Reply: Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "The Accuracy of Raman Spectroscopy in the Diagnosis of Lung Cancer: A Systematic Review and Meta-Analysis" (ID: TCR-21-515).
Many studies have shown that Raman has a certain value in the diagnosis of malignant tumors including colorectal cancer, breast cancer, esophageal cancer and so on. Now, it is less used in clinical diagnosis. However, the value of Raman spectroscopy in the diagnosis of malignant tumors cannot be denied. Maybe Raman spectroscopy can be applied in the diagnosis of malignant tumors in the future.

Reviewer C

This review article which conducted meta-analysis on the overall performance of Raman Spectroscopy in the diagnosis of lung cancer is well organized and summarized covering nearly all articles on these issues. The authors demonstrated that pooled sensitivity was 0.90 indicating that Raman spectroscopy had a high identification of lung cancer samples and can distinguish them from normal samples respectively regardless of sample types.
In addition, they briefly explained how Raman spectroscopy could distinguish lung cancer from normal tissues and suggested future direction of Raman spectroscopy including the integration work with machine learning to increased sensitivity and

specificity.

I have one question in real world setting.

Thoracic surgeons or physicians are sometimes encountering the patients with inflammatory lung lesion mimicking lung cancer. I think whether Raman spectroscopy can tell inflammatory lung lesion from lung cancer should be addressed in this article if possible.

Reply: Thank you for your valuable suggestion. Your idea of Raman spectroscopy in identifying tumor and inflammation is very good. However, since there are no articles on Raman diagnosis of lung cancer and inflammation, we have not conducted relevant research and discussion. However, your idea opens up a new direction for the application of Raman in the diagnosis of tumor in the future. Thank you very much.