Dear Editor,

I have reviewed the manuscript titled "The Accuracy of Fiber-Optic Raman Spectroscopy in the Detection and Diagnosis of Head and Neck Neoplasm in Vivo: A Systematic Review and Meta-Analysis" by Dr. Chen and the research group with great interest. The authors have undertaken a comprehensive evaluation of the accuracy of Fiber-Optic Raman Spectroscopy in the in vivo detection and diagnosis of head and neck neoplasms. The potential of this technology in detecting such neoplasms is promising and holds significance in clinical applications.

The authors have made a lot of effort in this research, including multiple subgroups analysis. They have also shown great understanding of Raman Spectroscopy and have investigated the causes of the heterogeneity in the included studies appropriately. In addition, the authors have pointed out the limitations of their work. However, to enhance the scientific rigor and reliability of this meta-analysis, there are certain methodological concerns that must be addressed before considering the publication of this work (major revisions). I have indicated the major revisions that must be addressed. Additionally, there are some minor concerns that, when addressed, would further improve the overall quality of the manuscript.

Basic Reporting

1- (Major) In the introduction, the authors must mention what is unique about this meta-analysis compared to previously published meta-analyses on this topic (reference no. 7 in this paper and PMID: 35992884). Otherwise, concerns on the originality of this research might arise. After addressing this concern, please revise the statement in line 218-219 and check if it needs an update or not. “This meta-analysis assessed the accuracy of fiber-optic Raman spectroscopy in the diagnosis of head and neck carcinomas in vivo **for the first time**.”

2- (Major) Authors should add a statement on the data availability in the main text. (are the raw data shared? or Table 2 or in supplementary material or only available with the corresponding author?)

3- Please add a contribution statement as well.

4- The sentence in line 193-195 is incoherent and should be rephrased. “In addition, the Q test values of the sensitivity and specificity were 106.23 (P=0.00) and I2 = 85.88 (95% CI 79.99-91.77), respectively, and the I2 index of the sensitivity and specificity were 64.21 (P=0.00) and I2 =76.64 (95% CI 65.45- 196 87.83), respectively.”

Experimental design

1- (Major) Prospective registration of systematic reviews (for example in PROSPERO) is considered important to prevent authors from repeating undergoing reviews and limit reporting bias (e.g. reporting only significant results). This systematic review did NOT provide details regarding its' registration. Suggestion: If the authors did not Prospectively register this review, they should explicitly indicate that in the methods section and provide an appropriate justification. Check item #24 of PRISMA checklist to see which details exactly should be mentioned on this part

2- (Major) In line 60, the authors claim that they use the random effect model for analysis. However, this is insufficient, and the authors should provide more details (what module was used STATA: maten? How is the SROC curve created?)

3- Authors should identify the authors who performed the search strategy (within their Methods section).

4- The authors should also describe the screening process (both title/abstract and full-text screening). Please indicate which authors screened, was it blinded or not and mention if a software/website was used in the process.

5- Authors should provide the reasons for excluding articles at the full text screening (preferably in the PRISMA flowchart). This part of item 16b in the PRISMA checklist, which has not been appropriately addressed.

6- If possible, the authors should provide confidence interval for the AUC.

Validity of the findings

1- Authors should expand on the conclusion section and include **their own** conclusion from the subgroup analysis and discussion.

2- In lines 285-295, the authors discuss some of the limitations of Raman spectroscopy (RS). Those limitations are for RS and not limitations to this study. I suggest that this part becomes a separate paragraph and placed before the meta-analysis limitations section.

3- In the results section (line 186-187), authors mention the process of quality assessment instead of the result of the quality assessment (the included studies was evaluated independently by two

reviewers etc.). This part is more appropriate in the methods section. In the results section instead, the authors must mention the results of the quality assessment (overall risk of bias, how many studies were had high risk of bias, which domains of QUADAS-2 were mostly affected, etc.)

General comments

1- Abbreviations use has been inconsistent. For example, line 18 Raman spectroscopy abbreviation “RS” was not introduced and has been use inconsistently thereafter.

2- **Table 2** lacks the appropriate cation that includes the abbreviations used within it.

3- **Figure 1** shows records after duplication removed are 324. However, it shows that only 86 has been screened. Authors should fix the PRISMA flowchart and make it more coherent.

4- **Figure 2A** is missing the labels for the 3 bars on the right side (patient selection, index test, reference standard).

5- Figures are of poor quality. Hopefully the authors can provide clearer figures.