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Manuscript Type: Opinion Review

Title: The importance of investigating high-risk human papillomavirus in lymph node metastasis of esophageal adenocarcinoma.

Authors: Preeti Sharma, Shweta Dutta Gautam, Shanmugarajah Rajendra

Dear Editor,

Please find enclosed the resubmitted revised manuscript for the opinion-review titled;

The importance of investigating high-risk human papillomavirus in lymph node metastasis of esophageal adenocarcinoma.; Manuscript NO.: 05085716

I am herewith attaching the revised manuscript with track changes and a clean copy. Please find below the point to point replies to the reviewers. Minor grammar and sentence construction amended to read well as shown in track changes.

This is a very minor revision if at all and we hope to have an acceptance decision as soon as possible.

We appreciate the time and effort of the editors and reviewers and hope the changes will provide a favourable outcome.

Thank-you.

Yours sincerely,

Ms. Preeti Sharma, Dr. Shweta Gautam, Professor Shanmugarajah Rajendra

Reviewer #1

1. I salute the impressive amount of work that the authors have performed scrutinizing the current literature available on the subject: HPV-associated esophageal cancers.

Thank-you.

2. I do however not agree that the authors can claim that there are strong evidence of HPV as one of the important risk factors for EAC since only one research-group has been referred to, namely Rajendra et al.

Not true. ALL systematic reviews done on the prevalence of HPV in oesophageal adenocarcinoma have found a positive association. As mentioned clearly in lines 152 to 153 in the index manuscript states; "Systematic reviews found the prevalence of HPV positive DNA in EAC patients of 13%-35%." We have rewritten this with more detail to inform the reader. " A systematic review has reported HPV prevalence rates of 35% in EAC (n=174), which is not much different to our findings. Another systematic review which included 19 studies concluded that the pooled prevalence of HPV in EAC was 13%. The authors suggested that the low prevalence rate may have been caused by small sample sizes and compromised detection methods.' So, clearly, other Groups have validated our findings, contrary to what Reviewer 1 is implying. Nevertheless, we have tempered the association of HPV with esophageal adenocarcinoma as shown in lines 38, 39,134,152-157, 224,225,277,284 (clean copy).

3. Data needs to be reproduced.

Data has been reproduced by at least 19 groups worldwide (excluding our Group)!

4. The authors cite more research groups reporting negative studies.

Yes, we have extensively cited negative studies and possible reasons to give a balanced view; lines 134-151. Therefore, not amended.

5. I do agree that prospective studies are warranted, and I would challenge the authors to adjust and use this manuscript as a protocol for a future trial on whether HPV-positive lymph nodes are predictive for future overall- and disease free survival.

Absolutely. That is what we will be doing.

Reviewer

#2

1. The article titled "The importance of investigating high-risk human papillomavirus in lymph node metastasis of esophageal adenocarcinoma." was reviewed. This topic is very interesting and important. I understand the difficulty of HPV detection in the primary EAC and lymph nodes due to the technical problem as

shown in this review. Hopefully the authors will overcome these problems in near future. This study deserves to be published in priority.

Agree with Reviewer 2.