Reviewer's report

Title: Mitogen Activated Protein Kinase Kinase Kinase 3 (MEKK3) overexpression is an early event in Esophageal Tumorigenesis and is a predictor of poor disease prognosis

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Reviewer: Huan Ren

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The study examined MEKK3 expression mainly by immunohistochemistry in archived formalin fixed and paraffin embedded tissue sections from 93 ESCCs, 47 histologically normal and 61 dysplastic esophageal tissues to evaluate the significance between the MEKK3 expression and clinicopathological parameters, and its prognostic relevance for ESCC patients. Although the patients’ materials and related examinations were of value and significance, the analysis on the work appeared superficial, and the manuscript was poorly organized.

- Major Compulsory Revisions
  1. Discrepancies in the manuscript. In the abstract results section, the manuscript stated that, the accumulation of MEKK3 and node positivity emerged as important predictors of reduced disease free survival, where there were only one set of p value, HR, and 95% CI; However, in the Results section under the subtitle (MEKK3 overexpression as a prognostic marker for ESCC) of the first paragraph, it stated that, MEKK3 overexpression, or nodal metastasis was an independent parameter of the prognostic relevance for ESCC patients, as each had a set of p value, HR, and 95% CI. Whether there was a combination effect between the MEKK3 expression and nodal positivity on the prognostic significance for ESCC patients, such discrepancies in the manuscript were misleading.
  2. Lack of detailed analysis and description on the clinicopathological parameters. Besides the follow up study on collection of relevant patients’ survival data, the manuscript failed to provide relevant description and selection criteria for other important parameters such as nodal positivity or metastasis, etc.
  3. The cell culture section was unnecessary and irrelevant to the present manuscript;
  4. Irrelevant paragraphs in the Discussion section. The present study mainly focused on the MEKK3 expression by immunohistochemistry and its relevance of prognostic significance for ESCC patients, the discussion on the relationship of MEKK3 expression with other factor expression in ESCC samples or cell lines, such as NF-kB, was unnecessary.
  5. The authors needed to clarify the exact cellular location of MEKK3 expression in the relevant chapters across the manuscript. Most of the staining positivity in the manuscript was shown as nuclear/cytoplasmic on expression of MEKK3, however, some of the description on that was indicated as only nuclear MEKK3
expression (The Results section under the subtitle MEKK3 overexpression as a prognostic marker for ESCC of the 2nd paragraph).

- Minor Essential Revisions
  Minor spelling errors.

- Discretionary Revisions
  None.

**Level of interest:** An article of limited interest

**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.