

Peer Review File

Article information: <https://dx.doi.org/10.21037/anpc-21-10>

Comment 1: I suggest the authors to inform in title what does NPC means.

Reply 1: Nasopharyngeal carcinoma has been informed in the title.

Changes in the text: We have modified our text as advised (see Page 1, line 1).

Comment 2: The authors should clarify how this literature review was carried out.

Reply 2: This review aimed at classifying the major subpopulations in tumor microenvironment (TME) and summarizing the well-documented gene signatures and specific cell type compositions that were correlated with clinical outcomes. In the first part of this review that illustrates the composition of TME, we used “nasopharyngeal carcinoma”, “tumor microenvironment” and “clinical outcome” as keywords to collect related literature. As for the second part, we summarized the survival and prognosis evaluation using the platform of scRNA-seq with the addition of “single-cell RNA sequencing” as keywords.

Comment 3: It makes no mention of how this new information can be used in patient stratification (for treatment), or how it can be used to develop novel "immune-based" therapies.

Reply 3: Recent studies conducted by Gong et al. (Nat Comm, 2021) and Jin et al. (Cell Res, 2020) stratified NPC patients according to the activation status of tumor immune microenvironment and the differences in tumor microenvironment composition, respectively. These studies proved that both specific gene signatures and subpopulation components in NPC TME significantly affected the progression-free survival outcomes. Indeed, there is still a lack of representative clinical models for prognostic risk stratification, survival prediction and therapeutics and drug treatment evaluation in NPC so far, but a bright future can be seen with the current advancement.

Comment 4: There are a small number of typographical errors (mainly spelling mistakes). Also, there are instances where acronyms are used prior to their full explanation.

Reply 4: Full explanation has been added before the used of acronyms.

Changes in the text: We have modified our text as advised (e.g., see Page 4, line 23 and Page 6, line 38).

Comment 5: Sections 1.1 & 1.2: information described were not derived from NPC studies. The authors should clarify the purpose of those statements and how they are relevant to NPC.

Reply 5: NPC studies has been related in these sections.

Changes in the context: We have modified our text as advised (see Page 3, line 4 to Page 4, line 4).

Comment 6: The implication of “a large number of CD45+ TILs in the tumour stroma of NPC” should be further elaborated.

Reply 6: More description is added into this implication of lymphocyte infiltration.

Changes in the context: Another study shows that among infiltration lymphocytes, CD3+ T lymphocytes usually account for more than 50%. The massive infiltration of leukocytes has been shown to be a shared characteristics of primary NPC tissues tumors, but it is less frequently in metastatic lesions. This phenomenon suggests that the infiltration of leukocytes may have a more important role in the development of primary NPC development, whereas lymphocyte infiltration may have less effects on late and metastatic NPC lesions.

Comment 7. NK cell clinical trials in NPC and a recent paper in Nat Comm by Ding et al (2021; 12:3046) are not described. Could the authors relate that information to enhance the current understanding on the prognosis of NPC patients?

Reply 7: NK cell clinical trial (case report) and recent study by Ding et al (Nat Comm, 2021) has been described.

Changes in the context: We have added some data as advised (see Page 5, line 10 to 13 and Page 15, line 12 to 17).

Comment 8. The manuscript mainly describes what have been reported in the literatures. It will be more informative to provide some insightful comments and/or concluding remarks on the current knowledge and future perspectives.

Reply 8: The section of “Conclusions and outlook” was added.

Changes in the context: We have added some description as advised (see Page 14, line 23 to Page 16, line 4).

Comment 9: There are some careless mistakes:

(i) Wrong references (e.g. Reference 8) or no references are cited when needed. The authors should carefully check correct references are cited and statements are supported by appropriate references.

(ii) Figure 1 is referred.

(iii) A big table is embedded in the middle and appears at the end of the manuscript, and it is not referred in the text.

(iv) There are some English issues at places and the manuscript will benefit from a language check.

Reply 9:

(i) Reference citation has been carefully reviewed.

(ii) Figure 1 is not referred in the text.

(iii) Table 1 is Referred

(iv): Language check was performed.

Changes in the context: We have modified our text as advised (see Page 2, line 31, and Page 11, line 2).