Peer Review File

Article information: https://dx.doi.org/10.21037/cco-23-32

**Reviewer A**

This is an up to date comprehensive review of the management of nasopharyngeall carcinoma and would certainly be useful to the international head and neck cancer community. As a review it does not illustrate any new innovative research but does bring what research has taken place together very well with the tables adding a great deal of additional information in a relatively small space. Figure 1 sums up in a nutshell a proposed treatment algorithm.
It is well written with a good narrative style as shown by the approach it takes with the "evolution" of systemic therapy and the paper importantly emphasises that not all metastatic disease in NPC is the same with very different prognoses.
It covers developments in both systemic therapy and immunotherapy and also developments in radiotherapy making it more comprehensive and valuable to the whole head and neck community. The paper usefully looks at the benefit of giving local treatments to metastatic sites.

It could develop further the increasingly important role of circulating DNA, which is mentioned (line 124) as this will undoubtedly become more important in this disease, for example is this technique being used widely at present in NPC and how sensitive and specific is it?
The paper may well benefit from having "Review" somewhere in the title, as this would result in it appearing in more online searches for NPC.

> **Reply:** Thank you for taking the time to assess our manuscript. We appreciate your positive comments and are pleased to hear that you found our article to be valuable and well-presented.
>
> In response to the comments regarding the use of plasma EBV DNA, it is used as part of pre-treatment work-up, monitoring during radical treatment, prognostic testing after completion of radical treatment. Plasma EBV DNA as a screening test has an overall high sensitivity and specificity for early detection of NPC. Although the negative predictive value was close to 100%, the positive predictive value was low. As a tool for disease surveillance, the sensitivity is low for small volume local recurrence. We thank the reviewer for bringing up this point and we have added information on metastatic disease to our manuscript to provide a more comprehensive review (see line 127-134).
>
> As advised, we have modified the title to “Optimal treatment strategy for de novo metastatic nasopharyngeal carcinoma: a literature review.”

**Reviewer B**

Many thanks for the authors’ effort. Mainly, the comments below are used to increase the transparency of your manuscript.

Article Type
1. After reading, we prefer to categorize the manuscript as a Literature review/Narrative Review. The authors thus need to fill out the “Narrative Review Checklist” (https://cdn.amegroups.cn/static/public/18-narrative-review-Checklist.pdf) and revise the manuscript accordingly.

**Reply:** This manuscript has been revised and presented in accordance with the narrative review reporting checklist.

**Changes in text:** The narrative review checklist has been resubmitted.

Structure of the Narrative Review article
2. Due to the Author's Instruction (https://cdn.amegroups.cn/static/public/2.2.3-Structure of Narrative Reviews-template-V2022.11.4.docx?v=1678776164908), please kindly organize the structure of the manuscript. Including the structure of the Abstract and Introduction.

**Reply:** This structure of the manuscript has been organized in accordance with the author's instructions.

**Changes in text:** The abstract and introduction have been revised accordingly (lines 43-96).

Title

3. This article summarizes the new clinical research on the treatment of metastatic nasopharyngeal carcinoma, but the optimal treatment strategy cannot be obtained through the review, it is suggested that the author replace "Optimal".

**Reply:** The word "optimal" has been deleted from the title.

**Changes in text:** Line 2, 17 and Line 28.

Introduction

4. Given that there are some similar reviews in this field (PMID: 37318724, 28477740), please highlight the novelty of this review in the introduction. What does this review add to existing knowledge? How does this review differ from previous reviews?

**Reply:** Thank you for the comment. A recent review (PMID 37318724) discussed ongoing and investigational agents in managing recurrent/metastatic NPC. However, the role of radiotherapy in treating metastatic NPC was only briefly discussed. A previous review published five years ago (PMID28477740) focused mainly on systemic therapy for recurrent and metastatic NPC. This review article discusses the current literature and clinical trials on the risk stratification and treatment of metastatic NPC, focusing on intensifying systemic therapy with immunotherapy and radiotherapy. Based on the evidence, we also made recommendations on treatment strategies for NPC patients with oligometastases and wide-spread metastases.

**Changes in text:** This has been highlighted in lines 94-96.

5. Please point out current problems and bottlenecks in the treatment for metastatic NPC.

**Reply:** Metastatic NPC is a complex and heterogeneous disease. The prognosis of patients with metastatic NPC differs considerably. Several crucial factors impact the prognosis, including tumor burden, EBV-DNA levels, location of involvement, timing of metastasis, and treatment strategies. Patients with oligometastases may benefit from more aggressive treatment. Therefore, treatment for de novo metastatic NPC should be individualized to achieve optimal outcomes.

**Change in text:** Lines 90-96.

Methods

6. Also please add a Methods section in the paper, that should briefly describe the search strategy, including databases, time frame, and language considerations. We also recommend adding an independent supplement table to present a detailed search strategy. Here is an example of our sister journal for your reference: https://atm.amegroups.com/article/view/91974/html (See Table 1). This part is essential as it reflects the sources of evidence (even though it is not a systematic review). This is to transparently report the process, not to judge it.

**Reply:** The Method section has been added to describe the search strategy.

**Changes in text:** Lines 98-110.

Main body

7. We recommend authors provide a detailed interpretation of Figure 1 in a separate paragraph.

**Reply:** Thank you. A new paragraph detailing our recommendation on treatment strategy for de novo metastatic NPC has been added.

**Changes in text:** Lines 316-327.

8. We suggest authors also consider discussing these included studies in depth with an objective perspective. Specifically, which are more trustworthy while others are not? Have authors considered some (even the simplest/most obvious) limitations/quality of this evidence?

**Reply:** Thank you for the comments. The retrospective nature and sample size of the studies may lead to potential bias. Due to the lack of randomized controlled trials evaluating the role of radiotherapy in treating de novo metastatic NPC, the retrospective approach can provide valuable insights. Further studies

should include randomized controlled trials to confirm the current evidence and provide more reliable insights.

**Changes in text:** Lines 331-339.

9. Line 80: "There are variations in the recommendation by different major guidelines". The authors list three guideline-recommended treatments. Could the authors clarify which are consistent with certain guidelines and which are not, what are the reasons for the inconsistencies, and what are the authors' experiential recommendations in the subsequent subsections?

**Reply:** All three guidelines recommended chemotherapy in combination with a PD-1 inhibitor as first-line therapy for de novo metastatic NPC. However, different anti-PD1 antibodies were recommended with varying levels of evidence. Based the two randomized controlled trials (JUPITER-02 and CAPTAIN-1st), the Chinese Society of Clinical Oncology (CSCO) recommends GP with or without camrelizumab or toripalimab (evidence 1A). However, the NCCN recommends dual chemotherapy as the preferred first-line regime. Cisplatin/gemcitabine in combination with a PD-1 inhibitor (eg, pembrolizumab or nivolumab) has been added as a category 2A recommendation, as camrelizumab and toripalimab are not available in the United States. The combination with an available PD-1 inhibitor was based on extrapolation. Similarly, all guidelines made a recommendation for adding locoregional radiation to systemic therapy with varying level of evidence.

**Changes in text**: Our recommendations on the treatment strategy for de novo metastatic NPC has been summarized in lines 316-327.

10. Accordingly, when the authors refer to "standard" (e.g., line 132), please specify the country or guideline, if available.

**Reply:** The standard first-line chemotherapy referred to NCCN recommendation.

**Changes in text:** The text has been modified to “The preferred first-line chemotherapy regimen recommended by NCCN guideline” (line 172).

11. Though it is a review, a separate section on the STRENGTHS and LIMITATIONS of this review is highly recommended. We think this could promote a more intellectual interpretation.

**Reply:** A separate paragraph has been added to discuss the strengths and limitations of this review article.

**Changes in text:** Lines 331-339.

Other concerns

12. Please delete the abbreviation AJCC and UICC in the abstract as they only show once.

**Reply:** The abbreviations have been deleted as advised.

**Changes in text:** Lines 45-46.

13. Line 88-90 “NCCN recently added GP plus a PD-1 inhibitor (pembrolizumab or nivolumab) as an "other recommended regimen" for the first-line treatment of recurrent and metastatic NPC, even though no phase 3 data supported the use of these two immune-checkpoint inhibitors.” The corresponding references should be cited.

**Reply:** This corresponding reference has been added.

**Changes in text:** Lines 123.