Author's response to reviews

Title: Promising treatment outcomes of intensity-modulated radiation therapy for nasopharyngeal carcinoma patients with N0 disease according to the seventh edition of the AJCC staging system

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Author's response to reviews: see over
Dear Editors,

Thank you very much for your kind decision and reviewer’s comments for our manuscript. We have now revised our manuscript according to the reviewer’s comments. The following is our point-by-point response to their comments. We have also re-submitted the revised manuscript. The changes in the revised manuscript are highlighted in a red font with underlining to make your review easier.

Yours faithfully,

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Regarding the comments of the Reviewer 1 (Frank Wong):

The 5-year survival rates of the whole group, N0 disease, and T4N0 = 83.4%, 93.8%, and 76.9%, respectively, which are much less than their corresponding LRFS, NRFS, and DMFS. It seems that the cause of death of quite a number of patients (esp T4N0) are not related to NPC. Could the authors further explain this – e.g. any treatment related death, death due to other co-morbidities? It may be difficult to justify the conclusion of poor prognostic factor of T4 for OS, if the major cause of death of T4N0 is not related to NPC.

Response: According to the reviewer’s suggestion, we analyzed the causes of death of the T4N0 patients. Of the four patients who died, two deaths were a result of local recurrence or distant metastasis, one was caused by radiation-induced temporal lobe injury, and the fourth was caused by nasopharyngeal hemorrhage.

OS was measured from the date of the first dose of radiotherapy or chemotherapy to death due to any cause. The data of patients who were still alive were censored. To compare the prognosis between T1-3N0 and T4N0 disease, we added disease-specific survival (DSS), which is defined as the time to death as a result of NPC. This event was recorded as death as a result of NPC, or as a result of toxicity from radiotherapy or chemotherapy. Deaths that were unrelated to NPC or treatment were censored. DSS was chosen to provide a more direct inference without adding extra variation because of unrelated deaths. (Page 10, Paragraph 3; Page 11, Paragraph 1)

In T1N0, T2N0, T3N0 and T4N0 disease, the OS and DSS rates were both 97.8%, 100%, and 93.8% and 76.9%; OS and DSS were higher in T1-3N0 patients than T4N0
patients (P<0.01 for both). (Page 13, Paragraph 4)

2. How did the author make a diagnosis of RLN involvement – based on MRI alone? 130 (25.4%) patients also underwent a positron emission tomography-computed tomography (PET-CT) scan. Would the PET findings affect the diagnosis of RLN?

Response: The involvement of RLN was diagnosed on either MRI or PET-CT in this study. On MRI, RLN were considered as metastatic according to the recognized criteria regarding RLN, with a minimal axial dimension of greater than 5 mm, the presence of nodal necrosis, and extracapsular spread \[^1\]. FDG PET images were interpreted visually, and nodes were considered metastatic if they showed prominent FDG uptake against the background with SUV ≥2.5 \[^2\].

Our previous study showed that MRI is better than PET-CT in detecting retropharyngeal lymph node metastasis from NPC, where all of 34 metastatic RLN that were detected by PET-CT (SUV ≥2.5) could be confirmed by MRI (minimal diameter ≥5 mm), and 44 metastatic RLN that were detected by MRI were not confirmed by PET-CT (Table 1) \[^3\]. Ng et al. also found that RLN of approximately 5 mm in diameter were always absent of any FDG uptake \[^4\]. In this study, there were no RLN metastases diagnosed by PET-CT alone.

Table 1: Correlation of the minimal diameter of RLN shown on MRI to the standard uptake value (SUV) of PET-CT in NPC [case (%)].
<table>
<thead>
<tr>
<th>Minimal diameter of MRI</th>
<th>SUV of PET-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 mm</td>
<td>25 (100)</td>
</tr>
<tr>
<td>≥5 mm</td>
<td>44 (56.4)</td>
</tr>
</tbody>
</table>

3. 43.6% N0 disease patients only received prophylactic irradiation to the upper neck lymph drainage region. Could the authors tell us how they choose these 43.6% patients for limited neck field (and why they decide to treat full neck for the rest 56.4%)?

**Response:** Radiation oncologists have previously treated all neck node levels comprehensively with definitive intent radiation therapy or prophylactic irradiation in NPC. However, with the increasingly wide use of MRI, it has been determined that...
nodes are very rarely skipped during metastatic progression in NPC\textsuperscript{[2,3]}. According to these findings, some of radiation oncologists have questioned the necessity of elective irradiation to the lower neck lymph node levels. Several investigators have confirmed that the elective irradiation of levels II, III, and VA is suitable for NPC without lymph node metastasis\textsuperscript{[3,4]}. Therefore, the volume that was to be irradiated in N0 disease varied between different doctors in our center\textsuperscript{[3]}. In this retrospective study, 43.6\% N0 disease patients, who had no cervical lymph nodes or RLN metastases based on MRI, received only prophylactic irradiation to the upper neck lymph drainage region. (Page 15, Paragraph 3; Page 16, Paragraph 1)


4. Page 9 Treatment outcomes. The authors mentioned a total of 38 patients (7.5%) developed disease recurrence, but 74 patients (i.e. >38 patients) developed distant metastases. Do the authors mean that distant metastasis doesn’t belong to disease recurrence?

**Response:** We apologize that this was unclear. Disease recurrence was regarded as locoregional recurrence, including local relapse or cervical nodal relapse. Distant metastases (such as to bone, lung, liver, etc.) were not included in disease recurrence in this study. To avoid confusion, we have revised disease recurrence as ‘locoregional recurrence’. (Page 11, Paragraph 2)

5. For patients with N0, two patients had T4N0 disease developed local recurrence. Are these in-field (NP) failures or marginal (intra-cranial) failures? Note that T4 disease may also be associated with large GTV (in-field failure), in addition to close proximity to critical structures (marginal failure). For the latter, the authors correctly pointed out in the Discussion part that the strategy for the latter could be IGRT, but the strategy for the former could be dose escalation, e.g. SRT boost. The authors could further elaborate these in their Discussion part.

**Response:** We agree with the reviewer’s point. Two patients who had T4N0 disease developed local recurrence. One patient had recurrence in the cavernous sinus, which was considered as a marginal failure, and the other patient had a recurrence in the nasopharynx, which was considered as an in-field failure. We have elaborated on the
dose escalation in the Discussion as follows:

Secondly, another possible explanation is that larger tumors require higher radiation doses for tumor control due to the log-cell-kill principle of radiation treatment. This need could be solved by increasing the physical dose of radiation to an optimal level and/or by administering accelerated fractionation to the tumor. Whole-field simultaneous integrated-boost intensity-modulated radiotherapy with a dose >70 Gy achieved excellent locoregional control, without an excess incidence of severe complications [1]. (Page 17, Paragraph 2; Page 18, Paragraph 1)


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Regarding the comments of the Reviewer 2 (Minh Tam Truong):

1. Is the question posed by the authors well defined?

The question is well defined.

2. Major Compulsory Revisions: Are the methods appropriate and well described?

The population needs to be clarified; on the one hand they report only the outcomes of the N negative patients for nasopharyngeal cancer using the new AJCC staging system. But to validate the question they need to compare the group to the Node positive
Response: We agree with the reviewer’s comments. We mainly reported the outcomes of the N0 patients with nasopharyngeal cancer using the new AJCC staging system, so the population was described as below in the revised paper. We introduced the collection and staging methods of the entire cohort of 506 patients, and then explained the characteristics of the patients with N0 disease in detail. (Page 7, Paragraph 2; Page 8, Paragraph 1)

3. In the abstract, it is not clear what is the sample size used for the whole study. I the abstract they use 110 patients, but in the results the authors report about 191 patients. Please resolve the inconsistencies of sample size. “[We retrospectively reviewed data from 506 biopsy-proven nonmetastatic NPC patients. According to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, 110 patients (21.7%) were staged with N0 disease.” They should mention what percentage of patients were with RLN as well, as they use this population of RLN in the results, yet do not mention it in the methods.

Response: We apologize that this section of the text was unclear. RLN metastasis was also not included in the sixth edition AJCC staging system[1]. The seventh edition of the American Joint Committee on Cancer (AJCC) staging system for NPC includes metastasis of the retropharyngeal lymph nodes (RLN). The classification of negative cervical lymph nodes with RLN metastasis as N0 disease in the sixth edition of the
AJCC staging system has been upgraded to N1 disease in the seventh edition\(^\text{[2]}\).

Therefore, all of the 110 patients that were staged as N0 disease had no RLN metastasis. Of the entire cohort of 506 patients, a total of 81 patients with negative cervical lymph nodes (16.0\%) were reclassified with N1 disease due to the presence of RLN metastasis. (Page 7, Paragraph 2)


4. They mention that T3N0 are no longer locally advanced, yet a significant proportion of the study population still received concurrent chemotherapy, BY the Alsarraf data, patients with the old T2b would have qualified for concurrent chemo. Therefore, is chemotherapy still warranted in this patient population of Non T4 patients. They should study the effect of chemotherapy in the T2T3N0 patients in order to make this statement about “no longer locally advanced”. If the authors are still giving chemotherapy in 81\% of patients, then it is still locally advanced and they authors cannot make this conclusion. If T3N0 by the new staging system is considered early stage disease, then need to consider whether these patients can do without
chemotherapy.

Response: We agree with the reviewer's comments. In this study, chemotherapy was administered to 82.3% (28/34) of the patients with T3-4N0 disease. Besides the improved outcomes after IMRT treatment, excellent locoregional control of T3N0 disease was also attributed to the intensive use of chemotherapy.

Our conclusions that T3N0 disease was no longer locally advanced were mainly based on the treatment outcomes, and whether these patients can do without chemotherapy still needs to be confirmed by prospective clinical trials. Therefore, we deleted the sentences that described how T3N0 disease was no longer locally advanced. (Page 16, Paragraph 3)

5. Why was prophylactic irradiation to only the upper neck lymph drainage region, including the Level II, III and VA upper neck lymph nodes was administered to 43.6% (48/110) of the patients with N0 disease; This is considered undertreatment by standard practice. If the recurrence rates are so low, when elective nodal irradiation is underutilized then the question of optimal radiation fields in these N0 patients could be answered in this paper.

Response: Radiation oncologists have previously treated all neck node levels comprehensively with definitive intent radiation therapy or prophylactic irradiation in NPC\(^1\). However, with the increasingly wide use of MRI, it has been determined that nodes are very rarely skipped during metastatic progression in NPC\(^2,3\). According to
these findings, some of radiation oncologists have questioned the necessity of elective irradiation to the lower neck lymph node levels. Several investigators have confirmed that the elective irradiation of levels II, III, and VA is suitable for NPC without lymph node metastasis\(^3\,^4\). Therefore, the volume that was to be irradiated in N0 disease varied between different doctors in our center\(^3\). In this retrospective study, 43.6% N0 disease patients, who had no cervical lymph nodes or RLN metastases based on MRI, received only prophylactic irradiation to the upper neck lymph drainage region. (Page 15, Paragraph 3)

Only one patient received prophylactic irradiation of all neck node levels and then developed level II lymph node recurrence, and no nodal recurrence occurred in patients who received prophylactic irradiation of the upper neck lymph nodes. Therefore, our data support the finding that elective irradiation of levels II, III, and VA was suitable for the treatment of nasopharyngeal carcinoma in patients classified with N0 disease, according to the seventh edition of the AJCC staging system using MRI. (Page 16, Paragraph 2)


6. Their fractionation schema is slightly high dose per fraction, than is done is USA: a total dose of 68 Gy in 30 fractions at 2.27 Gy per fraction. Can they provide data for its use? If long term toxicity is to be mentioned “Therefore, it will be increasingly important to pay attention to the long-term complications of treatment in T1-3N0 NPC patients.” Then they need to consider the effect of their fraction size.

Response:

In our center, IMRT was used in 2002, and the prescribed radiation dose was applied as follows: a total dose of 68 Gy to the planning target volume (PTV) of the gross tumor volume of the primary tumor (GTV-P), 60–64 Gy to the PTV of the nodal gross tumor volume (GTV-N), 60 Gy to the PTV of CTV-1 (i.e., the high-risk regions), and 54 Gy to the PTV of CTV-2 (i.e., the low-risk regions) and CTV-N (i.e., the neck nodal regions) [1,2] (Figure 1). To ensure the PTV2 (CTV2+margin) at 1.8-2 Gy per fraction, 30 fractions were required; therefore, 2.27 Gy (68 Gy in 30 fractions) fractions were used for the GTV-P. Bakst et al. also reported that IMRT was prescribed to deliver 70.2 Gy using 2.34-Gy fractions to the gross tumor volume for the primary and nodal sites while simultaneously delivering 54 Gy in 1.8-Gy fractions to regions at risk of microscopic disease [3].
Excellent locoregional control was achieved in this study (LRFS, 93.7%; NRFS, 97.2%). However, there is a lack of data regarding the long-term complications of the patients in this study. Bakst et al. reported that 12% of patients treated on this protocol developed radiation necrosis, one of whom required surgery. In contrast, standard fractionation in the IMRT series did not result in any complications \[4\]. Therefore, we will pay more attention to the long-term complications of treatment considering the effect of fraction size (2.27 Gy per fraction). At this point, we have also changed the prescribed radiation dose to 70 Gy in 33 fractions at 2.12 Gy per fraction in our center.

![Fig.1. The Definition and Dose of Target Volumes](image)


7. If the authors can answer how should the treatment between RLN positive and negative patients be different? Is it the nodal coverage that needs to be changed with IMRT or the administration of chemotherapy?

**Response:** In patients with negative cervical lymph node involvement, the presence of RLN metastasis was found to affect DMFS negatively, but not to affect the rate of locoregional recurrence. Therefore, we hypothesize that the administration of effective chemotherapy might be considerable for patients with positive RLN. However, the benefits of chemotherapy for patients with RLN disease should be confirmed by prospective clinical trials.

8. In their study if such a low recurrence rate was noted in the neck, is this attributed
to the elective nodal irradiation (ENI) or not. Since there are only 2 papers on this topic, as referenced, but standard practice still dictates this. Can this paper address the utility of ENI in the study population since there was only a 43.6% utilization rate.

Response: In this study, only one patient received prophylactic irradiation of all neck node levels and then developed level II lymph node recurrence, and no nodal recurrence occurred in patients who received prophylactic irradiation of the upper neck lymph nodes. Therefore, our data support the finding that elective irradiation of levels II, III, and VA was suitable for the treatment of nasopharyngeal carcinoma in patients classified with N0 disease, according to the seventh edition of the AJCC staging system using MRI, which is attributed to the elective nodal irradiation. (Page 16, Paragraph 2)

Radiation oncologists have previously treated all neck node levels comprehensively with definitive intent radiation therapy or prophylactic irradiation in NPC \[1\]. Several investigators have confirmed that the elective irradiation of levels II, III, and VA is suitable for NPC without lymph node metastasis\[3,4\]. Therefore, the volume that was to be irradiated in N0 disease varied between different doctors in our center\[3\]. In this retrospective study, 43.6% N0 disease patients, who had no cervical lymph nodes or RLN metastases based on MRI, received only prophylactic irradiation to the upper neck lymph drainage region. We addressed this issue in the revised paper. (Page15, Paragraph3)

\[1\]. Carkos A.Perez. Nasopharynx. In:Luther W.Brady. Principle and practice of


9. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?

6. Are limitations of the work clearly stated? Limitations of the study are not clearly stated.

Response: We have added a section regarding the limitations of the current study in the revised paper. Most importantly, this was a retrospective study, and our conclusions needs to be confirmed by prospective studies. (Page 18, Paragraph 1)
10. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes

8. Do the title and abstract accurately convey what has been found? No, the study population needs to be clarified, in the results they mention “Group 1 included the 110 patients without RLN metastasis, and Group 2 included the 81 patients with RLN metastasis”. Which is not mentioned in abstract.

Response: According to the reviewer’s suggestion, we have added these details into the Abstract, as follows: There were 191 patients with negative cervical lymph node involvement. According to the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, 110 patients (21.7%) were staged with N0 disease, and 81 patients (16.0%) were reclassified with N1 disease due to the presence of RLN metastasis. (Page 3, Paragraph 3)

11. I would be interested in knowing the regional recurrence rate of group one compared to group 2, and also the role of ENI in both groups. This would better answer the question regarding validation of the new staging system to show that they are different with regards to local, regional and distant control.

Response: Only 43.6% N0 disease patients, who had no cervical lymph nodes or
RLN metastasis based on MRI, received prophylactic irradiation to the upper neck lymph drainage region in this study, and ENI was not used in Group 2.

Of the 110 patients in Group 1 (N0 disease according to the seventh edition of AJCC staging system), one patient received prophylactic irradiation of all neck node levels developed level II lymph node recurrence, and no node recurrence occurred in patients who received ENI.

DMFS (distant metastasis-free survival) was significantly higher in Group 1 than Group 2 (5-year DMFS: 95.9% vs. 88.1%, P = 0.04). No significant difference was observed in the LRFS (local relapse-free survival) and NRFS (nodal relapse-free survival) of Group 1 and Group 2 (5-year LRFS: 97.1% vs. 95.0%, P = 0.40; 5-year NRFS: 99.1% vs. 97.4%, P = 0.38).

According to the sixth edition of the AJCC staging system, Tang et al. [1] and Tham et al. [2] proved that N0 NPC patients with RLN alone have a similar risk of distant metastasis to patients with N1 disease. The proposal that patients with RLN should be classified with N1 disease formed the basis of the revisions to the N0/N1 classifications in the seventh edition of the AJCC staging system. In this study, all patients underwent magnetic resonance imaging (MRI) examinations and received IMRT as their primary treatment. In patients with negative cervical lymph node involvement, the presence of RLN metastasis was found to negatively affect both DMFS, indicating it is still appropriate to classify RLN metastasis as N1 disease, even in the era of improved NPC treatment and diagnosis.


12. Discretionary:

Discussion, they mention EBV in discussion but no mention in the paper, they should remove this as this is not the focus of the paper

Response: We have removed this from the revised paper.

13. “In practice, locoregional control in T1-T3 patients should no longer be a major problem due to the improved outcomes after IMRT treatment, accurate geographic coverage of tumors assisted by CT-guided radiation treatment planning, increased diagnostic accuracy provided by MRI and PET and the intensive use of chemotherapy, and T3N0 disease can no longer be regarded as locally advanced disease.” I do not think the authors can make such a strong statement from a retrospective review. This needs to be validated in a randomized prospective setting.

Response: We agree with the reviewer’s suggestion. As the response to comment 4, our conclusions that T3N0 disease was no longer locally advanced were mainly based
on the treatment outcomes, and whether these patients can indeed do well without chemotherapy still needs to be confirmed by prospective clinical trials. Therefore we have deleted the related sentence that stated T3N0 disease is no longer locally advanced.

Furthermore, it needs to be emphasized that this was a retrospective study, and our conclusions needs to be confirmed by prospective studies. We added this to the limitations of the study description in the Discussion of the revised paper. (Page 18, Paragraph 1)

Minor Revisions:

14. Methods, they report only WHO grade I and II, but the WHO staging system uses a grading system from I, II and III, I am assuming that grade II in this paper implies grade II and III, in which they should break down the latter. In the table they mention grade II/III, but not in the text.

Response: We have corrected it in the revised paper. (Page 8, Paragraph 1)

15. Table 1 describes the whole 506 patient cohort, but the study only looks at the N0 patients, the details of table 2 chemotherapy refers to which population of patients?

Response: We mainly reported the outcomes of the N0 patients with nasopharyngeal cancer using the new AJCC staging system, and so Table 1 was revised to describe
only N0 patients in the revised paper. Table 2 refers to T3-4N0 stage disease.

16. Table 3 refers to which population, the new AJCC staging N0 patients?

Response: Table 3 refers to N0 nasopharyngeal carcinoma patients according to the seventh edition of AJCC staging system. The title of Table 3 has been revised to the following: “Five-year survival rates for N0 nasopharyngeal carcinoma patients according to the different T-classification of the seventh edition of AJCC staging system.”

17. Figures, on the y axis should read from 0-100%, it starts at about 70% which is visually deceiving.

Response: We have revised the y-axis in the figures.

18. Is the writing acceptable? correct: “associated professor” to associate professor.

Response: We have revised this. (Page 19, Paragraph 2)