Reviewer's report

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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Reviewer: Minh Tam Truong

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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

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 patients by the old staging system.

3. In the abstract, it is not clear what is the sample size used for the whole study. In the abstract they use 110 patients, but in the results the authors report about 191 patients. Please resolve the inconsistencies of sample size. 

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.

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.

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.

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?

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.

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.

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.

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.

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.

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.
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.

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?

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

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

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

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.