Author's response to reviews

Title: Impact of late toxicities on quality of life for survivors of nasopharyngeal carcinoma

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Response to Reviewer 1 (Tony J Wang)

1. **Methods Paragraph 1:** The authors mention that informed consent was obtained twice (Page 6: line 2 and Lines 16-17).

   **Answer:** Thanks for reminding. The duplicated sentence has been deleted.

2. **Background Paragraph 1:** It is unclear what the author's mean by "radiation, if given above an individual's tolerance level". There is no safe dose of radiation and the decision to treat with radiation is based on the benefits outweighing these risks. If they are referring to specific dose-tolerance limits (i.e., QUANTEC) this should be stated.

   **Answer:** Thanks for your suggestion. We change the sentence to “If the individual organ received the radiation dose above the specific dose-tolerance limit, the so called late complications, which are usually chronic, irreversible and progressive, would be induced.” The citation about QUANTEC was added in the Reference.

3. The authors assume that the hearing loss reported by their patients is due to "radiation-induced otitis media [which] can cause conductive deafness, presenting with ear stuffiness, tinnitus, and hearing loss", though 66% of the patients in the study also received chemotherapy which may have been a confounding factor. Do the authors know what the doses to the cochlea was?

   **Answer:** Thanks for your suggestion. We could not exclude the possibility of some confounding factors such as aging process, and the combination of chemotherapy would contribute the cause of hearing problems. We have stated this in our study limitations in the last paragraph of Discussion: “….Also, about two thirds of our patients were treated with a combination of chemotherapy, and we could not exclude the morbidity being related to chemotherapy.” Further, we could not precisely know the doses to the cochlea because of the heterogeneous treatment techniques of the study cohort. This has also been stated in our study limitation: “….Third, the study cohort included the evolved heterogeneous radiotherapeutic components from 2D, 3D conformal to IMRT techniques at different time periods and the dosimetric data were not provided in the cohort; therefore, it was difficult to establish the specific variables of the RT technique and survival years that might have confounded the analysis.”
1. Were clinical stage IV NPC patients associated with poor QoL, and high score of neuropathy?

Answer: Thanks for your question. We did not find a statistically significant trend that those with clinical stage IV had a worse global QoL or a higher CTCAE neuropathy grading in our cohort. Concerning the global QoL, the mean score was 60.2 for the 40 cases with stage IV, compared with 56.0 for the 202 cases with stage I-III (p value=0.24). The incidence of CTCAE neuropathy grading was 77.5% in grade 0, 10.0% in grade 1, 10.0% in grade 2; and 2.5% in grade 3 respectively for the 40 cases with stage IV, compared with 81.7 in grade 0, 5.0% in grade 1, 6.9% in grade 2; and 6.4% in grade 3 for the 202 cases with stage I-III (p value=0.41).

2. For the patients with the same stage, will the IMRT technique improve the QoL and neuropathy?

Answer: Thanks for your question. The comparison of IMRT and non-IMRT technique was not the endpoint in this study, however, we did find a statistically significant trend (p value < 0.01) that those treated with IMRT technique had a better global QoL and a lower CTCAE neuropathy grading in the whole cohort. The comparison of mean score for IMRT versus non-IMRT group after stratifying the clinical stage was 60.2 versus 47.9 (p value=0.11) in stage I, 66.7 versus 51.0 (p value < 0.01) in stage II, 59.6 versus 52.1 (p value=0.18) in stage III, and 63.5 versus 58.0 (p value=0.28) in stage IV, respectively. Meanwhile, the comparison of the incidence of symptomatic (≧ grade 2) CTCAE neuropathy for IMRT versus non-IMRT group after stratifying the clinical stage was 0.0% versus 8.3% (p value=0.57) in stage I, 2.8% versus 19.7% (p value=0.013) in stage II, 5.3% versus 25.0% (p value=0.23) in stage III, and 11.8% versus 13.0% (p value=0.90) in stage IV, respectively.
Response to Reviewer 3 (Sen-Tien Tsai)

1. Fatigue is a common symptom which is related to the late toxicity of nasopharyngeal carcinoma patients with long term survival. Because the thyroid gland and pituitary gland were included in the radiation field, the possibility of hypothyroidism will occur. The discussion section may reflect this situation and the way to resolve it.

Answer: Thanks for your suggestion. In the Discussion, we have added some statement about radiation induced hypothyroidism and cited the reference.

2. For dizziness or vertigo is frequently encountered in patients with nasopharyngeal carcinoma with long term survival. Carotid artery stenosis is one of the major cause. Aggressive management such as stent insertion of the carotid artery for such patients is recommended to prevent the possibility of ischemic change of the brain. It is advised to emphasize such a late complication in discussion section.

Answer: Thanks for your suggestion. As the above question, we have added some statement about radiation induced carotid arterial stenosis and cited the reference. We stated them as the followings: “We found that, in contrast to other anatomic sites of HNC, NPC survivors presented some specific but common late sequelae related to the irradiation field, such as otitis media, hypothalamic-pituitary-thyroid dysfunction, and neuropathy related from temporal lobe necrosis, cranial nerve palsy, or carotid arterial stenosis, etc [21-23]. Besides parotid sparing for the prevention of xerostomia or dysphagia, the modern conformal radiation technique should place more emphasis on the anatomic structures that are involved in these late complications, e.g. cochlea, thyroid and pituitary gland, temporal lobe, and carotid artery. Furthermore, regular examinations such as carotid duplex scanning or evaluation of thyroid function for early detection and possibly intervention of these potential late complications should be kept in mind in routine clinical practice especially for those with high risk factors and long term survival [22, 23].”