Author’s response to reviews

Title: Advantages of using reduced-volume intensity modulated radiation therapy for the treatment of nasopharyngeal carcinoma: a retrospective paired study

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Author’s response to reviews:

Reviewer 1

Comment 1:

I wonder why wide accepted prognostic factors, such as N-stage and chemotherapy are not prognostic in your cohorts. You should at least discuss and try to explain this fact.

Response: Thanks for the referee’s good evaluation and kind suggestion. According to the univariate analyses, there were significant survival differences (OS, P = 0.007; PFS, P = 0.02) between different N category (N0-1 vs. N2-3). However, the multivariate analyses showed that neither T stage nor N stage was significant to predict survival outcomes. In addition, a number of
papers (references 28-31) have also indicated that there was no significant survival difference between each T stage in NPC patients treated with IMRT. However, it should be noted that tumors were staged according to the clinical staging system based on data from conventional 2D-RT in these papers. We suspected that prognostic factors may vary with the progression of diagnostic and treatment techniques. Advanced imaging techniques can early detect occult metastases and accurately define the extent of tumor invasion. The application of IMRT and chemotherapy in the treatment of NPC has improved survival condition obviously. As a consequence, the accuracy and applicability of staging systems should be reevaluated with the rapid development of imaging techniques and therapeutic methods. The latest eighth edition of the UICC/AJCC cancer staging classification was based on data in the IMRT era, which may perform better in predicting survival outcomes. Moreover, the multivariate analyses showed that receiving chemotherapy (concurrent chemotherapy, neoadjuvant or adjuvant chemotherapy) has no predictive value for treatment outcomes. Seemingly, it was not in line with our experience. We noticed that only a tiny proportion of patients included in this study have not received chemotherapy and the majority of which were presented with stage I. Early stage NPC cases treated with radiotherapy alone can be rendered disease-free in the long term. These could lead to the negative result (Lines 309-322, Page 16; Lines 323-333, Page 17).

Comment 2:

Please compare your endpoints (OS, PFS, LCR, DMFS), especially metastases rate with those of Blanchard et al. (Lancet Oncol, 2015). Your recurrence/metastases rates are a bit lower.

Response: Thanks for the referee’s suggestion. The meta-analysis by Blanchard et al. explored the value of chemotherapy in NPC. With a median follow-up of 7.7 years, the 5-year OS, PFS, LRRFS and DMFS rates for patients treated with various chemoradiotherapy protocols were 57.3%-75.7%, 46.9%-71.9%, 70.6%-91.0% and 75.9%-82.3%, respectively. Indeed, the survival rates are a bit lower than those of our study. Patients included in our study were treated with IMRT, however, more than three quarters of the cases in the study by Blanchard et al. were treated with outdated radiotherapy (two-dimensional). As a number of studies have confirmed, IMRT is superior to conventional 2D-RT in local control, progression-free survival and even overall survival. Besides, more patients in the study by Blanchard et al. had a stage III or IV cancer (89.4% vs. 75.6%), which signified poorer survival. We deem that these factors may contribute to the differences. In addition, NPC patients who received RV-IMRT in the study by Lin et al. (reference 16) had similar survival rates with those in our study (3-year OS, 90% vs. 92.2%; 3-year DMFS, 90% vs. 90.0%; 3-year LRFS, 95% vs. 93.3%; 3-year RRFS, 98% vs. 98.9%, respectively)(see in Lines 304-308, Page 16).

Comment 3:

Background, first sentence: "..(NPC) is a malignancy shows high prevalence" Please edit "that" or "which"
Response: Thanks for the referee’s reminder. And we have revised this sentence in Line 52, Page 3.

Comment 4:

Background, second sentence: Add a reference for the leading role of radiotherapy in treating NPC (e.g. a guideline)

Response: Thanks for the referee’s suggestion. We have added this constructive advice in the revised paper (see in Line 54, Page 3).

Comment 5:

Statistics: Which approach did you use for you multivariate analysis (enter, forward, backward?) and how did you select the parameters included? Why did you include parameters not significant in univariate analysis? Are there not too many factors included? See also "rule of ten".

Response: Thanks for the referee’s reminder. In our study, multivariate analyses with the Cox proportional hazards model were used to detect independent predictors by Enter method. The parameters included in the Cox proportional hazards model were selected based on clinical experience and the results of univariate analyses. Univariate analysis often fails to identify the presence of confounding factors, which are likely to interfere with the relationship between survival outcomes and parameters that we are concerned about. Thus, it is possible to exclude important factors by simply including parameters significant in univariate analyses.

Comment 6:

Results, Patient characteristics, line 191: "There were balanced between the CV-IMRT". Please rephrase, what do you mean with "There were"

Response: Thanks for the referee’s reminder. We tried to convey the fact that the matched patients in both arms had balanced characteristics. And we have added this constructive advice in the revised paper (see in Lines 199-200, Page 10).

Comment 7:

Page 13, line 247: "the old showed high risk.." Please rephrase: "Higher age was associated.."

Response: Thanks for the referee’s suggestion. And we have revised this sentence in Line 240, Page 13.
Comment 8:

Discussion. page 14, line 271: "It depended on a wide range of radiation in case of missing". I do not understand the meaning of this sentence, rephrase!

Response: Thanks for the referee’s kind reminder. We are awfully sorry for our vague expression. Over the past decades, traditional radiotherapy was widely used for the treatment of NPC. The radiation technology is simple and imprecise, and radiation field encompassed in a two-dimensional portal is often large. Inevitably, various radiation-induced toxicities negatively affect patients’ quality of life (see in Lines 264-267, Page 14).

Comment 9:

276-277: You state that IMRT and chemotherapy have enhanced survival rates and lengthened survival. This is not completely true, at least not for IMRT. Chemotherapy improved survival compared to RT alone, but there exist no high level evidence for a survival benefit compared at least to 3D-RT (not of course compared to 2D-data, that is obvious). Please comment on that,

Response: Thanks for the referee’s reminder. IMRT is an advanced form of 3D-RT and a major breakthrough in the treatment of NPC. A systematic review and meta-analysis by Zhang et al. (Oral Oncology, 2015, reference 23) has compared clinical treatment outcomes of IMRT with those obtained with 2D-RT or 3D-RT in NPC. The IMRT group was associated with a better 5-year overall survival (OR = 1.51; 95% CI 1.23-1.87; p = 0.0001), and tumor local control (OR = 1.94; 95% CI 1.53-2.46; p < 0.00001). Comparing with conventional radiotherapy, IMRT provides improved long-term tumor local control and overall survival in patients with NPC.

Reviewer 2

Major compulsory revision:

Comment 1:

One main limitation is -as the authors themselves declare- that in this retrospective trial there is "a small amount of patients " (Line 332). In the matched pair analysis the patients are well distributed, however the applicability for the general population should be discussed critically.

Response: Thanks for the referee’s good evaluation and kind suggestion. In spite of the well distributed patients, this study was performed in a nonendemic setting with relatively small amounts of cases. Furthermore, the small number of patients studied may result in an inadequate number of events needed for analysis and limit the accuracy of the research results. Given all these, the generalization of the conclusions has to be carefully considered, and well-designed trials are needed to confirm the findings in the future (Lines 350-356, Page 18).
Comment 2:

The follow-up time was 50 months for the RV-IMRT arm. Thus long term survival condition is not available for analysis. Overall, in nasopharyngeal carcinoma the prognosis is good, which indicates that disparity in overall survival will display after a longer period of time.

Response: Thanks for the referee’s reminder. Since the majority of recurrence occurs in the first two years after the completion of radiotherapy, a median follow-up of 50 months signified that the true incidence of recurrence may approximate our findings. With regard to the long term overall survival rate, further studies are in great need to evaluate the efficacy of RV-IMRT in the treatment of NPC. And long term follow-up studies are ongoing (Lines 357-363, Page 18).

Comment 3:

Late toxicity is only (once) evaluated after 3 months. (page 7, Zeile 151) Is this correct? The authors should critically discuss this fact.

Why is there no evaluation of late toxicity after 6 or 12 months in spite of a median follow-up of 70 months? (Table 4, page 13) -&gt; The main statement that "the RV-IMRT was associated with significantly reduced risk of late xerostomia … and hearing loss…" should be reevaluated after 6 or 12 months.

Response: Thanks for the referee’s kind reminder. We had given a definition of late toxicities in Lines 159-160, Page 8. Late toxicities were defined as symptoms occurred after 3 months after the completion of treatment. In our study, late toxicities were assessed and scored at each follow-up, rather than only being evaluated after 3 months (Lines 161-162, Page 8).

Minor essential revisions:

Comment 1:

The authors do neither describe the doses of chemotherapies which are applied nor the application days of the cycles (Page 7, lines 140-142, Page 9, line 190).

Response: Thanks for the referee’s reminder. We have added this constrictive suggestion in the revised paper and the details could be found in Lines 144-151, Page 7.

Comment 2:

The authors should mention if an MRI scan or PET scan was used for delineation of the target volumes.
Response: Thanks for the referee’s good evaluation and kind suggestion. At our center, computerized optimization was utilized with fusion of MRI with planning CT images to accurately delineate the target volumes (Lines 135-137, Page 7).

Comment 3:
The authors should describe which organs at risk were delineated as critical structures. They only declare that the RTOG protocol was used (Page 6, line 132; Page 7, line 133). Perhaps the authors should demonstrate in a table which organs at risk were classified as critical structures.

Response: Thanks for the referee’s suggestion. Critical normal structures including the spinal cord, brainstem, temporal lobes, hypophysis, optic nerves, chiasm, eyeballs, lens, parotid glands, temporomandibular joints and mandible were set as organs at risk (OARs). The dose received by each OAR was limited according to the RTOG protocol (Lines 131-132, Page 6; Lines 133-135, Page 7).

Comment 4:
On page 3, line 52 there is a typing error: ….that shows….

Response: Thanks for the referee’s reminder. We have revised this sentence in Line 52, Page 3.

Comment 5:
"LV-IMRT arm". (Page 6, line 117) Is this a typing error?

Response: Thanks for the referee’s kind reminder. And we have revised this sentence in Line 116, Page 6.

Comment 6:
The patients included in this study present with stage II-IVb (page 7, line 139) respectively I,II,III and IV (page 9, line 189). The authors should critically discuss the limited validity in this broad spectrum.

Response: Thanks for the referee’s suggestion. In this revised paper, we performed subgroup analyses to evaluate the effects of subgroups on survival rates in nasopharyngeal carcinoma underwent CV-IMRT versus RV-IMRT (Table 3). None significant survival difference was shown between the CV-IMRT and RV-IMRT arms, irrespective of T stage, N stage and clinical stage (Lines 233-234, Page 12; Lines 235-236, Page 13). In terms of the radiation toxicity, the advantage of RV-IMRT was mainly observed in patients with T1-2 stage, N0-1 stage and I-II stage. Generally, patients with T1-2 stage, N0-1 stage and I-II stage disease particularly benefit
from RV-IMRT with similar survival rates and lower toxicity incidence (Lines 341-344, Page 17).

Comment 7:

The authors should critically discuss the limitation of the propensity score matching method (page 8, line 157)

Response: Thanks for the referee’s friendly reminder. We have added this constrictive suggestion in the revised paper (Lines 363-366, Page 18; Lines 367-369, Page 19).

Comment 8:

In the multivariate COX regression analysis for prognostic factors only the age showed a high risk ratio for OS (page 13, line 247). Is this correct?

Response: Thanks for the referee’s good evaluation and kind suggestion. According to the univariate analyses, there were significant survival differences (OS, P = 0.007; PFS, P = 0.02) between different N category (N0-1 vs. N2-3). However, the multivariate analyses showed that neither T stage nor N stage was significant to predict survival outcomes. In addition, a number of papers (references 28-31) have also indicated that there was no significant survival difference between each T stage in NPC patients treated with IMRT. However, it should be noted that tumors were staged according to the clinical staging system based on data from conventional 2D-RT in these papers. We suspected that prognostic factors may vary with the progression of diagnostic and treatment techniques. Advanced imaging techniques can early detect occult metastases and accurately define the extent of tumor invasion. The application of IMRT and chemotherapy in the treatment of NPC has improved survival condition obviously. As a consequence, the accuracy and applicability of staging systems should be reevaluated with the rapid development of imaging techniques and therapeutic methods. The latest eighth edition of the UICC/AJCC cancer staging classification was based on data in the IMRT era, which may perform better in predicting survival outcomes. Moreover, the multivariate analyses showed that receiving chemotherapy (concurrent chemotherapy, neoadjuvant or adjuvant chemotherapy) has no predictive value for treatment outcomes. Seemingly, it was not in line with our experience. We noticed that only a tiny proportion of patients included in this study have not received chemotherapy and the majority of which were presented with stage I. Early stage NPC cases treated with radiotherapy alone can be rendered disease-free in the long term. These could lead to the negative result (Lines 309-322, Page 16; Lines 323-333, Page 17).

Comment 9:

In this study the tolerability and the toxicity of chemotherapy is not investigated. Which toxicity is associated to chemotherapy? The authors should eliminate the cases with chemotherapy-
associated toxicity when indicated because they falsify the comparison of RV-IMRT to CV-IMRT.

Response: Thanks for the referee’s suggestion. This study was performed to investigate the clinical treatment outcomes and toxicities of using IMRT with reduced-volume CTV for the treatment of NPC. Therefore, the toxicities of chemotherapy was not investigated. In addition, the matched patients in both arms had balanced characteristics, including the use of chemotherapy (concurrent chemotherapy, neoadjuvant or adjuvant chemotherapy). The similar toxicities from chemotherapy in the two arms were expected. If we had eliminated the cases with chemotherapy induced toxicities, the sample size would be largely reduced and selection bias would come along with.

Comment 10:

Did all the patients receive the same radiation concept? (33 x 2,12Gy (70Gy) PTVs of GTV-P, GTV-N, 33x1,82Gy (60Gy) PTV of CTV1,33x1,7Gy (56Gy) of the PTV of CTV-2)

How many patients did receive a lower dose? If patients did receive less than 60Gy total dose, was it converted to the biologic equivalent dose?

Response: Thank for the referee’s kind reminder. At our cancer center, the prescribed dose was 70 Gy in 33 fractions to the PTVs of GTV-P and GTV-N, 60 Gy in 33 fractions to the PTV of CTV-1, 56 Gy in 33 fractions to the PTVs of CTV-2 and CTV-N. All patients included in our study received the same radiation concept. And no patient received less than 60Gy total dose.