Author's response to reviews

**Title:** Prognostic significance of the cumulative dose of cisplatin during concurrent chemoradiotherapy for patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy

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

I am very pleased to submit my revised manuscript titled, “Prognostic significance of the cumulative dose of cisplatin during concurrent chemoradiotherapy for patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy”. I feel that the reviewers offered helpful and productive suggestions, and I appreciate the editor and reviewer comments. All of the authors have read and approved the
revised manuscript, which was prepared in accordance with the revised manuscript checklist. We have checked the manuscript and ensured that our manuscript meets BMC Cancer's style requirements, including those for file naming. There are no financial or other relationships that might lead to a conflict of interest.

I hope that the revised manuscript will be accepted for publication. Below, I have restated each esteemed reviewer's comments and have included my point-by-point responses. The changes have been highlighted with red ink in the revised manuscript.

Reviewer #1 Comments:

Major Compulsory Revisions

1) A prognostic factor is a clinical or biologic characteristic that is objectively measurable and that provides information on the likely outcome of the cancer disease in an untreated individual. In contrast, a predictive factor is a clinical or biologic characteristic that provides information on the likely benefit from treatment [for reference see: Antoine Italiano, Prognostic or Predictive? It's Time to Get Back to Definitions!, JCO Dec 10, 2011:4718-4719]. According to this definition, the cumulative cisplatin dose is neither a prognostic nor a predictive factor. In my opinion the authors basically show that suboptimal treatment leads to suboptimal treatment outcome. Unfortunately the authors
did not provide any information why and in how many patients the prescribed dose could not be applied as well as no information about the criteria used to select the excluded, and for this reason it is difficult to draw reliable conclusions concerning the optimal cumulative cisplatin dose or chemotherapy protocol. These limitations should be clearly stated in the manuscript.

Reply: We are very grateful for your constructive suggestions. We apologise for not defining “prognostic factor”. We agree with you on the definition of “prognostic factor” and “predictive factor”, and we agree that the cumulative dose of cisplatin is neither a prognostic factor nor a predictive factor. We have revised the statement about “prognostic factor” with cumulative doses in the manuscript. For example, the statement on Page 12, Para 2, Line 13-16, was revised to, “Multivariate analysis using the Cox proportional hazards regression model demonstrated that the cumulative dose of cisplatin was significantly associated with OS, and the N stage was an independent prognostic factor for OS. Second, we revised the sentence on Page 13, Para 3, Line 15-17 to, “In the subgroup analysis of the low-risk patients (EBV DNA <4000 copies/ml), the cumulative dose of cisplatin was significantly associated with a lower OS”. Third, we revised the sentence on Page 13, Para 3, Line 17-20 to, “In the multivariate analysis, the cumulative dose of cisplatin was significantly associated with OS in the patients of low-risk group (EBV DNA <4000 copies/ml)”. In addition, we revised the sentence on Page 17, Para 2, Line 5-6 to, “In our subgroup analysis of low-risk patients, the cumulative dose
of cisplatin had an impact on prognosis of OS based on the multivariate analysis”.

There were 14 patients who received 100 mg/m$^2$ or less than 100 mg/m$^2$ of cisplatin chemotherapy and 379 patients who received 101-200 mg/m$^2$ of cisplatin chemotherapy. The reasons why the patients did not receive their originally prescribed dose of cisplatin primarily included the patients’ refusal to receive their prescribed dose and side effects experienced by the patients during their treatment, which to the discontinuation or a reduction of their chemotherapy dose.

The study included patients who received either the weekly cisplatin regimen or the three-week cisplatin regimen during IMRT. Both weekly and three-week cisplatin regimens added to radiotherapy had good efficacy[1-3]. However, the weekly cisplatin regimen was not directly compared to the three-week cisplatin regimen in a large prospective trial. There is no evidence demonstrating the difference between the long-term survival of the patients receiving the three-week regimen and the patients receiving the weekly regimen of cisplatin in NPC patients. Until now, only two retrospective studies compared the survival difference between the three-week and weekly regimen of cisplatin in NPC patients. Jagdis A et al. retrospectively analysed 73 patients with locally advanced NPC and found that both OS and DFS did not significantly differ between the three-week regimen and the weekly regimen groups[4]. Tao CJ et al. retrospective reviewed 154 patients with
NPC and found no difference in OS, DFS, LRFS, and DMFS rates between the three-week regimen and the weekly regimen of cisplatin[5]. Because both the three-week and weekly regimen of cisplatin are regarded to be the standard chemotherapy regimen for advanced-staged NPC, the decisions to receive the three-week or weekly regimen of cisplatin were collectively made by the patients and the doctors.

The limitation of the different cisplatin regimens has been added into the manuscript, “Furthermore, the study included patients receiving a three-week regimen or a weekly regimen of cisplatin, which leads to possible bias. We did not provide a suggestive cisplatin delivery regimen or the optimal cumulative cisplatin dose in this study. Further studies are needed to confirm the optimal cumulative cisplatin dose and the preferred delivery cisplatin regimen”. (Page 18, Para 2, Line 6-11).


2) The authors performed a large number of statistical tests. No correction for multiple testing was used. There is an increased probability of type 1 errors. The authors should clearly state that the corresponding results should only be used to generate hypotheses. To reduce the number of statistical tests, the
authors for example could consider to perform a multivariate Cox regression analysis stratified by the risk status of the patients (EBV DNA <4000 versus >= 4000).

**Reply:** We appreciate the helpful advice and apologise for the drawbacks of the statistical tests in the manuscript. We agree with you that no correction for multiple testing was used, and there is thus an increased probability of type 1 errors. To reduce the number of statistical tests, we performed multivariate analyses by using the Cox proportional hazards regression model stratified by the risk status of the patients (EBV DNA <4000 versus >= 4000). The Cox proportional hazards regression model was adjusted for patient gender (1. female, 2. male), age (1. <45, 2. ≥45), T stage (1. T1, 2. T2, 3. T3, 4. T4), N stage (1. N0, 2. N1, 3. N2, 4. N3), Epstein–Barr virus deoxyribonucleic acid (EBV DNA) (1. <4000, 2. ≥4000), and cumulative dose of cisplatin (1. low-, 2. medium-, 3. high-dose group). In the multivariate analysis, the cumulative dose of cisplatin was significantly associated with OS in the low-risk patient group (EBV DNA <4000 copies/ml) (P=0.009). The medium-dose group had reduced odds of death compared with the low-dose group, with an odds ratio of 0.062 (95%CI 0.001–0.347; P=0.002). However, the cumulative dose of cisplatin was not significantly associated with DMFS by multivariate analysis. Moreover, the cumulative dose of cisplatin was not associated with OS or DMFS among the high-risk (EBV DNA ≥4000 copies/ml) patients by multivariate Cox regression analysis. To avoid possible bias due
to pairwise comparison using log-rank test, we deleted the pairwise comparison of OS and DMFS among the low-dose group, the medium-dose group, and the high-dose group and stratified the groups by EBV DNA levels.

Revisions: Page 10, Para 2, Line 19; Page 14, Para 1, Lines 4-5.

3) The authors did not state clearly the design of the study: was it a prospective study or a retrospective analysis of patient data?

Reply: We appreciate the constructive suggestion and apologise for the unclear description about the study design. This study is a retrospective analysis of patient data. We have revised the study description statement on Page 7, Para 4, Line 19-22 to read, “This study retrospectively analysed data from 491 consecutive patients with histologically confirmed NPC that was treated with concurrent chemoradiotherapy between December 2006 and December 2010 at Sun Yat-sen University Cancer Center”.


Minor Essential Revisions

There are plenty unclear or imprecise statements in the manuscript, and the manuscript should be revised by an experienced writer.

Examples:
1) Page 4 line 14: please state the year the overall survival is referred to.

**Reply:** We apologise for the unclear statement in the manuscript, and we revised the statement to, “the 5-year OS” on Page 12, Para 2, Line 11.

**Revision:** Page 12, Para 2, Line 11.

2) Page 5 line 2: I do not agree that the cumulative dose is a prognostic factor.

**Reply:** We apologise for overlooking the definition of prognostic factor. We changed the statement on Page 5, Para 2, Line 3-5 to read, “The cumulative dose of cisplatin is associated with OS and DMFS among NPC patients who received IMRT”.

**Revision:** Page 5, Para 2, Line 3-5.

3) Page 6 line 17: what is a "conformal analysis"?

**Reply:** We apologise for the misleading statement. This was a clerical error. We revised the statement to read, “three-dimensional conformal technique”.

**Revision:** Page 6, Para 1, Lines 17-18.

4) Page 8 line 9: "stage IV disease": does it include M1? Or do you mean IVa
and IVb?

**Reply:** Thank you very much for pointing out this misleading statement. As we mentioned on Page 8, Para 1, Line 11, the patients whom we included had no distant metastases. Therefore, “stage IV disease” does not include M1, it means IVa-b. We revised the statement to, “stage IVa-b disease” in the manuscript.

**Revisions:** Page 8, Para 1, Line 11; Table 1.

5) Page 8 line 10: "PTV of the involved cervical lymph nodes" not "PTV of the GTV for the involved cervical lymph nodes"

**Reply:** Thank you for the kind advice for our manuscript. We revised the statement on Page 9, Para 1, Line 12-13 to, “PTV of the involved cervical lymph nodes”.

**Revision:** Page 9, Para 1, Line 12-13.

6) Page 9 line 18: "or" instead of "and" 30-40 mg/m2...

**Reply:** Thank you for the suggestion. We revise the word to “or” on Page 9, Para 2, Line 20.

**Revision:** Page 9, Para 2, Line 20.
7) Page 12 line 5: which "two groups" do you mean?

Reply: We apologise for the misleading statement. It was a clerical error. We mean to say, "NPC patients received low- ($\leq 100$ mg/m$^2$), medium- (101–200 mg/m$^2$), or high-doses (>200 mg/m$^2$) of cumulative cisplatin. The clinical characteristics and treatment factors for the three groups ($\leq 100$ mg/m$^2$, 101–200 mg/m$^2$, >200 mg/m$^2$) were well balanced." This was revised in the manuscript.

Revision: Page 12, Para 2, Lines 8-11.

8) Page 12 line 20: I do not understand the sentence: "For other prognostic factors...."

Reply: We were referring to other prognostic factors that could potentially effect the clinical outcome such as N stage and EBV DNA level. To make it more clear, we revised the sentence to, “In addition, a significant difference in OS was observed based on the N stage and EBV DNA administration”.


9) Page 12 line 22: what "ratios" you are referring to?

Reply: We apologise for the misleading statement in the manuscript. When
was stated “ratios”, we were referring to “odds ratios”. We have revised “ratios” to “odds ratios” in the manuscript.

Revision: Page 12, Para 2, Lines 22.

10) Page 12 line 7: please state the year the overall survival is referred to.

Reply: Thank you for your kind advice for the manuscript. We revised the statement to “5-year overall survival” in the manuscript. In addition, we revised the statement of “DMFS rate” to “5-year DMFS rate”.


11) Page 13 line 3: what do you exactly mean by “DMFS values”?

Reply: We apologise for the misleading statement regarding “DMFS values”. It was a clerical error. We revised the sentence to, “The 5-year DMFS rates of the low-, medium- and high-dose groups were 69.2%, 88.7%, and 88.6%, respectively”.

Revision: Page 13, Para 2, Lines 2.
Reviewer #2 Comments:

1) In Introduction, please insert the recently published paper by Blanchard et al. in Lancet Oncology 2015, “Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis” (minor)

Reply: Thank you for your advice. We inserted the recently published paper by Blanchard et al. in Lancet Oncology 2015, “Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis” into the revised manuscript.

Revisions: Page 6, Para 1, Line 14, Reference 11.

2) In Ethic statements, please explain what do you mean with “…informed consent was given by participants for their clinical records to be used in this study”. Please specify the retrospective characteristic of the study (major)

Reply: Thank you very much for your careful suggestion. We apologise for the misleading statement in the manuscript. We changed the statement in the Ethics section. We mean to say that “This retrospective study was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center, and all the participants provided written informed consent before treatment.” We changed the sentence on Page 7, Para 2, Line 13-15. In addition, we specified the retrospective characteristic of the study in this
sentence, “The study retrospectively analysed data from 491 consecutive patients with histologically confirmed NPC that were treated with concurrent chemoradiotherapy between December 2006 and December 2010 at Sun Yat-sen University Cancer Center” on Page 7, Para 2, Line 19-22.


3) It is stated that patients who received neoadjuvant chemotherapy were ineligible; specify when the use of induction chemotherapy was adopted (advanced N stage, time period, ..) (major)

Reply: Thank you for your good advice. We would like to sincerely apologise for this misunderstanding in the manuscript. Induction chemotherapy is used on patients with extensive primary tumours, such as widespread cranial invasion. In these cases, induction chemotherapy can shrink the primary tumour to give a wider margin for radiotherapy, which is an advantage that is particularly needed for patients whose tumour borders critical neural structures. In addition, induction chemotherapy is also delivered to patients who are enrolled in clinical trials that compare the efficacy of induction chemotherapy plus concurrent chemoradiotherapy with concurrent chemoradiotherapy.

The effect of induction chemotherapy for clinical outcomes for patients with nasopharyngeal carcinoma is not clear until recently. Therefore, we did
not include patients who received induction chemotherapy plus CCRT (concurrent chemoradiotherapy). The recently updated results of the MAC-NPC meta-analysis concluded that the benefits of induction chemotherapy added to concomitant chemoradiotherapy still need further assessment[6]. The preliminary results of Trial NPC-0501 also indicated that the benefit of changing to an induction-concurrent sequence remains uncertain[7]. A phase II/III trial comparing concurrent chemoradiotherapy with or without induction gemcitabine, carboplatin, and paclitaxel in locally advanced NPC showed no significant difference in OS, DFS, and DMFS[8]. Several phase III trials comparing sequential regimens with concurrent chemoradiotherapy alone are ongoing. For example, Sun Yat-sen University is studying induction TPF followed by concurrent cisplatin plus RT compared with RT plus concurrent cisplatin without induction in stage III-IVB disease (NCT01245959). The status of this study is ongoing. Another phase III trial is a multi-centre trial comparing induction chemotherapy followed by CCRT (concurrent chemoradiotherapy) vs. CCRT alone in stage IV nasopharyngeal carcinoma (NCT00201396), which is sponsored by The Taiwan Cooperative Oncology Group. This study has been completed, but the results are not published yet. The unpublished data from phase III trials are expected to clarify the effect of induction chemotherapy plus CCRT.

4) Please avoid the time “patients enrolled”, as this is a retrospective trial
(minor)

**Reply:** Thank you for your kind advice. We apologise for the misleading statement. We have changed this statement to “all of the patients” instead of “For all enrolled patients”.

**Revision:** Page 9, Para 2, Line 17.

5) The multivariate analysis lacks the performance status and the comorbidities, that could be an important factor in determining the possibility or not to receive full dose chemotherapy. The fact that the cumulative dose of cisplatin was not significantly associated with DFS or LRFS, but only with OS could represent an indirect evidence of this bias. Comment on this or report these factors (major)

**Reply:** Thank you very much for this suggestion. We apologise for not including the performance status and the comorbidities in the multivariate analysis. We added the Eastern Cooperative Oncology Group (ECOG) performance status score and the Adult Comorbidity Evaluation-27 (ACE-27) score to the multivariate analysis by Cox proportional hazards regression model. We used the ECOG performance status score to evaluate performance status of the patients, and we used the ACE-27 system to assess comorbidity
of the patients. The ACE-27 system was developed to assess the comorbidity for cancer patients, specifically for patients with head and neck cancer. We added the ACE-27 information to Table 1 to compare the ACE-27 between groups. We did not find a statistically significant difference among the low-dose, medium-dose, and high-dose group regarding the ACE-27 values ($P=0.159$), as shown in Table 1. In addition, the ECOG score is well balanced among the low-dose, medium-dose, and high-dose groups, with a $P$ value of 0.859, as presented in Table 1. After adding the ECOG performance status scores and ACE-27 scores into multivariate analysis, we found that the cumulative dose of cisplatin was significantly associated with OS but not DFS or LRFS. And the $P$ value and odds ratio did not change in the Cox proportional hazards regression model. We concluded that there are no significant correlations between the performance statuses and the comorbidities on clinical outcomes among the low-dose, medium-dose, and high-dose groups in this study.

Revision: Table 1.

6) Median follow up in Table 1 should be months (not yr) (minor)

Reply: Thank you for your careful critique. We apologise for this oversight. We have corrected this error in Table 1.
Revision: Table 1.

7) A dose of cisplatin lower than 100 mg/sm is composed by only 8 patients; please comment about the possible bias of this and specify the causes of death in this group. Comment also more extensively about the fact that the cumulative dose of cisplatin was not associated with OS or DMFS among the high-risk group (minor).

Reply: Thank you very much for your thoughtful suggestion. The low-risk group receiving a dose of cisplatin lower than 100 mg/m² was composed of only 8 patients. Two patients died in the low-risk group, which received a dose of cisplatin lower than 100 mg/m². Both of the patients died from distant metastases. The reasons why the patients did not receive their originally prescribed dose of cisplatin primarily included the patient’s refusal to receive their prescribed dose and side effects during treatment, which led to the discontinuation or reduction of their chemotherapy dose. Therefore, there is the possibility of bias. There is an unavoidable bias because of the small sample size in the low-risk group. Increasing the sample size of this patient cohort is needed to reduce bias. We added this limitation on Page 17, Para 2, Line 8-13 in the manuscript.

We further discussed the fact that the cumulative dose of cisplatin was not associated with OS or DMFS among the high-risk group by adding the
sentence on Page 17, Para 2, Lines 16-22, Page 18, Para 1, Line 1-2, “There were 191 high-risk patients in our study, which is not a very large sample size. Thus, there is possible bias due to the small sample size in the high-risk patient group. Increasing the sample size in future studies will enable the further evaluation of the cumulative dose of cisplatin among high-risk patients with NPC with reduced bias. In addition, the high-risk patients were usually with high tumour burden, which probably progressing to tumour distant metastasis. Therefore, for these high-risk patients, concurrent chemoradiotherapy may not be very effective.”


8) The suggestion about de-intensification of dose number of concurrent cycles from three to two, reducing the dose of concurrent cisplatin to #200 mg/sm, without affecting efficacy should be mitigated (minor)

Reply: Thank you for your good advice about our manuscript. We revised the sentence to, “Further clinical studies are required to investigate the balance between clinical outcomes and the compliance with concurrent cisplatin chemotherapy and thereby identify the appropriate dose of
concurrent cisplatin that is required to improve NPC patient outcomes.”

Revision: Page 16, Para 2, Lines 12-16.

References


I look forward to your favourable reply.

Sincerely yours,

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Professor and Director
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