Author's response to reviews

Title: The impact of the cumulative dose of cisplatin during concurrent chemoradiotherapy on the clinical outcomes of patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy

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

I am very pleased to submit my revised manuscript titled, “The impact of the cumulative dose of cisplatin during concurrent chemoradiotherapy on the clinical outcomes of patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy”. I feel that the reviewers offered helpful and productive suggestions. 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 carefully 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.

**Reviewer #1 Comments:**

1) Results: "Analysis of the prognostic implications of the cumulative dose of cisplatin among all patients stratified by EBV DNA levels" The added sentence: "In the subgroup analysis for low-risk group patients (EBV DNA <4000 copies/ml), the cumulative dose of cisplatin was significantly associated with a lower OS based on univariate analysis (P<0.001; Figure 3). 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) (P=0.009)." could be shortened and simplified, not to be confusing for the reader. (minor)

**Reply:** Thank you for the helpful advice. We revised the sentence into “In the subgroup analysis for low-risk group patients (EBV DNA <4000 copies/ml), the cumulative dose of cisplatin was significantly associated with a lower OS based on univariate analysis (P<0.001; Figure 3). After multivariate analysis
using the Cox proportional hazards regression model, the cumulative dose of
cisplatin was significantly associated with OS (P=0.009). "


2) Discussion. After the sentence "The patterns of failure after IMRT
predominantly result from distant metastases rather than local control.
Therefore, the optimal cisplatin dose in CCRT regimes for NPC warrants
further exploration" it could be interesting to discuss the fact that it is possible
that induction/adjuvant chemotherapy may cooperate with IMRT + cisplatin in
reducing the risk of distant metastatization. The results of ongoing trials will
help in answering this question. (minor)

Reply: Thank you for your kindly suggestion. We added the discussion into the
manuscript: “It is possible that combined use of induction chemotherapy or
adjuvant chemotherapy with cisplatin-based CCRT results in reducing the
DMFS rate on NPC patients treated with IMRT. Although the answer for this
question is still unclear, the results of ongoing trials are expected to point out
the benefits on DMFS by using induction chemotherapy or adjuvant
chemotherapy combined with CCRT compared to cisplatin-based CCRT
alone.”
3) Discussion. The sentence: “The low-risk group, which received a dose of cisplatin, was composed of only 8 patients, and therefore could be biased. Among the low-risk group receiving a dose of cisplatin #100 mg/m2, the cause of death for both was distant metastases” is not clear (major)

Reply: Thank you for your carefully advice. Sorry for the unclear statement in the manuscript. We revised the statement into “The low-risk group, which received a dose of cisplatin $\leq 100\text{mg/m}^2$, was composed of only 8 patients, and therefore could be biased. In the low-risk group, only 2 patients died. Both of the patients died from distant metastases.”

Reviewer #2 Comments:

1) The authors agreed that according to the definition by Antoine Italiano [Prognostic or Predictive? It's Time to Get Back to Definitions!, JCO Dec 10, 2011:4718-4719] the cumulative cisplatin dose is not a prognostic factor and implemented corresponding changes in the manuscript. Consequently, the
authors should also replace the term "Prognostic significance..." in the title of the manuscript, in the Abstract (page 4 line 2) and in the Discussion.

"Prognostic significance..." could be for example replaced with "Impact of...".

**Reply:** Thank you for your kindly suggestion. We are sorry for the ignorance of the term “Prognostic significance…” in the title, in the Abstract and in the Discussion. We revised the title into “The impact of the cumulative dose of cisplatin during concurrent chemoradiotherapy on the clinical outcomes of patients with advanced-stage nasopharyngeal carcinoma in an era of intensity-modulated radiotherapy”. We revised the statement in the Abstract into “The impact of cumulative dose of cisplatin on clinical outcomes of nasopharyngeal carcinoma (NPC) patients who received intensity-modulated radiotherapy (IMRT) was evaluated.” and “For the low-risk patients, the cumulative dose of cisplatin significantly associated with a lower OS (P<0.001).” In addition, we revised the statements in the Discussion as:

“Therefore, it is necessary to re-evaluate the impact of the cumulative dose of cisplatin on the clinical outcomes for NPC in this new era of IMRT.”; “Currently, to the best of our knowledge, no report has addressed the impact of the dose of cisplatin on the clinical outcomes on patients with NPC who were treated with IMRT. Several studies have analysed the impact of the dose of cisplatin on clinical outcomes of NPC using conventional 2D and 3D conformal radiotherapy technology.”; “The impact of the cumulative dose of cisplatin on clinical outcomes of NPC remains unknown in this era of IMRT.” and “In our
subgroup analysis of low-risk patients, the cumulative dose of cisplatin had an impact on OS based on the multivariate analysis."

Revised on Tittle; Page 4, Para 1, Line 2-4; Page 4, Para 3, Line 19-20; Page 14, Para 2, Line 10-12; Page 14, Para 3, Line 13-17; Page 14, Para 3, Line 22, Page 15, Para 1, Line 1; Page 17, Para 2, Line 5-6.

2) I do not agree that the major drawback of this study is the single-center study design (page 18, line 3). In my opinion the major drawback of the study are the limitations of the retrospective study design, in particular the variability of the chemotherapy regimen applied and the comparatively low patient number in the low-dose chemotherapy group.

    Reply: Thank you for your helpful advice. We agree with you on the major drawback of the study. We revised the statement in the manuscript as “The major drawback of this study is the limitations due to the retrospective design. For example, the number of patients in the low-dose group was too small. And the study included patients who received 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. In
addition, it was a single-centre study; therefore, these results need to be validated in other data sets."

Revised on Page 18, Para 2, Line 2-10.

3) Page 13 line 17: "...was significantly associated..." Instead of "...was significantly was associated...".

Reply: Thank you very much for your helpful suggestion. We revised the statement into "...was significantly associated...".

Revised on Page 13, Para 3, Line 17.

I look forward to your favourable reply.

Sincerely yours,