Author's response to reviews

Title: Leucopenia and treatment efficacy in advanced nasopharyngeal carcinoma

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Replies to Reviewer of Professor Chaosu Hu:

1. For patients with advanced disease, concurrent chemoradiotherapy should be given. Some of the patients didn’t get chemotherapy, could you give us the reason? Such as the poor conditions. It may affect the results.

Answer: Thank you for your kind advice! As you said, concurrent chemoradiotherapy should be given for patients with advanced disease in nasopharyngeal carcinoma (NPC), which is also recommended by NCCN guidelines. And poor conditions may absolutely affect the prognosis of NPC patients [1].

In our hospital, physicians made the treatment strategy according to the NCCN guidelines, as well as the physical condition of patients, such as Karnofsky performance status, liver function, kidney function, age and so on. Most of our patients received concurrent chemoradiotherapy during 2000s. In current study, we have excluded 113 patients without chemotherapy before analysis. Among those, 41 patients had abnormal liver function (Liver enzyme indicators, eg. ALT, AST, twice more than normal high limit), 25 patients were significantly HBV-DNA positive, 10 patients had abnormal kidney function (Creatinine clearance<60%), 13 patients had diabetes and blood sugar control was not satisfactory, 15 patients had hypertension and blood pressure control was not satisfactory, 9 patients refused to received chemotherapy. So it would make little influence on our study results.

2. In discussion, the author said that G-CSF may affect the treatment results. Please add the relation between usage of G-CSF and outcome.

Answer: Thank you for your suggestion! According to your suggestion, we studied the correlation between usage of G-CSF and outcome complementarily. Because of two-week time limit, we could just randomly review the relative information of 607 patients in those of 3826 patients. In the selected patients, the percentages of patients with no leucopenia, mild leucopenia and severe
leucopenia were 15.0% (91/607), 65.9% (400/607), and 19.1% (116/607), respectively. 404 patients received G-CSF. All patients with severe leucopenia received G-CSF. 72.2% (289/400) patients with mild leucopenia received G-CSF. Patients with no leucopenia didn’t receive G-CSF. We found that the 5-year OS (81.9% VS 77.7%, P=0.842) and 5-year DMFS (79.5% VS 81.3%, P=0.834) made no significant differences between the patients who received G-CSF and who didn’t.

In our discussion, we speculated that G-CSF may affect the treatment results based on the view of G-CSF and GM-CSF stimulating head and neck squamous cell carcinoma cell proliferation and migration in vitro and promote tumor angiogenesis in vivo [38], and radiation-upregulated G-CSF promoting the migratory and invasive properties by triggering the epithelial-mesenchymal cell transition (EMT)[39]. However, there was few clinical data proved the relation between the usage of G-CSF and outcome.

Based on our data, we could not make a conclusion that G-CSF may affect the treatment results. We have reconsidered this matter and delete relative content in our manuscripts.

References:

3. There were lots of expressions not clear as following:
1) Methods: We retrospectively analyzed 3826 patients with ANPC who received radiochemotherapy. Patient background characteristics. It should be basic.

Answer: Thank you for pointing this out; we apologize for this negligence. We have revised this sentence.

Page 2 line 6-8
Original : We retrospectively analyzed 3826 patients with ANPC who received radiochemotherapy. Patient background characteristics and leucopenia were analyzed as prognostic factors.

Revised : We retrospectively analyzed 3826 patients with ANPC who received chemoradiotherapy. Leucopenia was categorised on the basis of worst grade during treatment according to the National Cancer Institute Common Toxicity Criteria version 4.0: no leucopenia (grade 0), mild leucopenia (grade 1-2), and
severe leucopenia (grade 3-4). Associations between leucopenia and survival were estimated by Cox proportional hazards model.

2) Introduction

Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer. Given its unbalanced endemic distribution and pathological and clinical attributes, the incidence rate is high, being 20-30 per 100,000 populations. In radiotherapeutic techniques may add IMRT

Answer: Thank you for pointing this out; we apologize for this negligence. We have revised this sentence.

Page 4 line 1-6
Original: Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer. Given its unbalanced endemic distribution and pathological and clinical attributes, the incidence rate is high, being 20-30 per 100,000 populations in some areas of southern China and Southeast Asia [1-3]. Radiotherapy (RT) is the primary treatment, plus chemotherapy when needed according to clinical stage. With the development of diagnostic imaging, radiotherapeutic techniques (IMRT), chemotherapy regimens, and targeted drugs, survival of NPC has improved significantly [4-6].

Revised: Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer. The incidence rate is as high as 20-30 per 100,000 populations in endemic areas of southern China and Southeast Asia [1-3]. Radiotherapy (RT) is the primary treatment, plus chemotherapy when needed according to clinical stage. With the development of diagnostic imaging, chemotherapy regimens, targeted drugs, and radiotherapeutic techniques, especially the application of IMRT (Intensity Modulated Radiation Therapy), survival of NPC has improved significantly [4-6].

3) the categories of evidence for induction or adjuvant chemotherapy of NPC has declined. In NCCN guideline, induction chemotherapy followed by concurrent chemoradiotherapy is recommend.

Answer: Thank you for pointing this out. We apologize for this confusion. We would like to express that the categories of evidence for induction chemotherapy of NPC changed from category 2A to category 3 and adjuvant chemotherapy “cisplatin+ RT followed by cisplatin/5-FU change from category 1 to category 2A and “cisplatin+ RT followed by carboplatin/5-FU change from category 2A to category 2B. We were very sorry for this confusion. And revised this sentence.

Page 4 line 13-18
Original: the categories of evidence for induction or adjuvant chemotherapy of NPC has declined. In nccn guideline, induction chemotherapy followed by concurrent chemoradiotherapy is recommend.

Revised: In 2014 version of NCCN guidelines, the categories of evidence for induction or adjuvant chemotherapy of NPC has changed [7]. Category of induction chemotherapy of NPC changed from category 2A to category 3.
Category of adjuvant chemotherapy “cisplatin+ RT followed by cisplatin/5-FU changed from category 1 to category 2A and “cisplatin+ RT followed by carboplatin/5-FU changed from category 2A to category 2B.

4) We retrospectively collected 3826 newly diagnosed ANPC samples from January 2005 to December 2010 from patients at the Nasopharyngeal Carcinoma Department of Sun Yat-Sen University Cancer Center. Samples should be patients. Treated in Department of Nasopharyngeal Carcinoma. Answer: thank you for pointing this out. We apologize for this mistake. We have revised this sentence.

Page 5 line 13-17

Original: We retrospectively collected 3826 newly diagnosed ANPC samples from January 2005 to December 2010 from patients at the Nasopharyngeal Carcinoma Department of Sun Yat-Sen University Cancer Center.
Revised: We retrospectively collected 3939 newly diagnosed ANPC patients from January 2005 to December 2010 treated in the Nasopharyngeal Carcinoma Department of Sun Yat-Sen University Cancer Center. 113 patients were excluded owing to different reasons, abnormal liver function, abnormal kidney function, unsatisfactory blood sugar control and so on. 3826 patients were involved in the study.

5) Informed consent was obtained from all patients, The study was retrospective. As a retrospective study, it is impossible to get all informed consent in such large number of patients. Answer: thank you for pointing this out. We apologize for the lack of strictness. We have revised this sentence.

Page 5 line 17-20

Original: the Sun Yat-Sen University Cancer Center Institutional Review Board (IRB) and ethics committee reviewed and approved the study. Informed consent was obtained from all patients. The study was retrospective. Patient records were anonymized and de-identified prior to analysis.
Revised: the Sun Yat-Sen University Cancer Center Institutional Review Board (IRB) and ethics committee reviewed and approved the study. The study was retrospective. Patient records were anonymized and de-identified prior to analysis.

6) Examining them with Kaplan–Meier methods and comparing them using the log-rank test examining should be test.
Answer: thank you for pointing this out. we apologize for this confusion. We have revised this sentence.

Page 7 line 13-14
Original: examining them with Kaplan–Meier methods and comparing them using the log-rank test examining should be test.
Revised: Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

7) Induced chemotherapy- should be induction
Answer: Thank you for pointing this out; we apologize for this mistake. We have revised the word “induced” to “induction”.
Page 8 line 6
Original: Induced chemotherapy (IC) was administered to 1073 patients.
Revised: Induction chemotherapy (IC) was administered to 1073 patients.

8) patients using paclitaxel were likelier—likely
Answer: Thank you for pointing this out; we apologize for this negligence. We have revised the word “likelier” to “likely”.
Page 8 line 17
Original: patients using paclitaxel were likelier to develop severe leucopenia.
Revised: patients using paclitaxel were likely to develop severe leucopenia.

9) The overall median OS—omit overall
Answer: Thank you for pointing this out; we apologize for this negligence. We have omitted the word “overall”.
Page 8 line 18
Original: The overall median OS was 52.6 months (range 3.07-113.0 months)
Revised: The median OS was 52.6 months (range 3.07-113.0 months)

10) We performed multivariate analysis to investigate whether leucopenia could be a predictive marker of improved OS and DMFS. Omit the predictive
Answer: Thank you for pointing this out; we apologize for this negligence. We have omitted the word “predictive”.
Page 9 line 16
Original: We performed multivariate analysis to investigate whether leucopenia could be a predictive marker of improved OS and DMFS.
Revised: We performed multivariate analysis to investigate whether leucopenia could be a marker of improved OS and DMFS.