Author’s response to reviews

Title: Prognostic value of the distance between the primary tumor and brainstem in the patients with locally advanced nasopharyngeal carcinoma

Authors:

Yuxiang He (heyuxiang88@163.com)
Yin Wang (wylionking@163.com)
Lin Shen (linshen2014@yeah.net)
Yajie Zhao (yajie_zhao@yeah.net)
Pengfei Cao (caopengfei66@163.com)
Mingjun Lei (mingjunlei@yeah.net)
Dengming Cheng (cdm888@sina.com)
Tubao Yang (1064960669@qq.com)
Liangfang Shen (lfshen2008@yeah.net)
Shousong Cao (shousongc@gmail.com)

Version: 1 Date: 30 Oct 2015

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Response to the reviewers' comments (MS ID: BCAN-D-15-00363)

Reviewer #1:

This manuscript studied association of prognostic value of the distance between the primary tumor and brainstem in locally advanced nasopharyngeal carcinoma. It is an interesting study. However, there are three questions.

1. Material and methods: You should offer the dose constraints for the critical structure, especially for the brain stem.

   Response: Thanks for the excellent comment. The dose constraints for the critical tissue structures have been provided in the revisal manuscript as the reviewer suggested (Page 7, lines 18-19).
2. Results: How many cases in these two group (Dbs > 4.75mm & Dbs ≤ 4.75mm), and how is the comparability?

Response: There were 220 patients in the Dbs > 4.7 mm group and 138 patients in the Dbs ≤ 4.7 mm group (Page 10, lines 18-19, and Table 1). Comparison of the two groups were included the characteristics of age, gender, N classification, histological type, chemotherapy, prescribed radiation dose. The related information is provided in the revisal manuscript (Page 13, lines 11-19, and Table 5).

3. Discussion: You should give more specific information for why do you choose 4.75mm as a definition.

Response: This is an excellent comment. Cut-off point is usually determined by receiver operator characteristic (ROC) curve. The determination of ROC cut-off value is always complied with the principle of maximization in the sensitivity plus (1-specificity) or the maximization of the sum of the true positive rate and false negative rate. Therefore, we calculated the cut-off value of Dbs as 4.75 mm by ROC curve analysis. Because we only could accurately detect the Dbs to 0.1 mm, we changed the cutoff value of Dbs from 4.75 mm to 4.7 mm in the revisal manuscript.

Reviewer #2:

This is an article analyzed the prognostic value of the distance between the primary tumor and brainstem in locally advanced nasopharyngeal carcinoma, however, it cannot be published in its present form, as some important issues must be demonstrated clearly.

Major revision:

1. On the basis of geometry, the distribution of the isodose curves were correlated with both the distance between two objects and the contact area. The cutoff value of Dbs was 4.75mm, how the authors accurately detected Dbs to 0.05mm? The authors did not analyzed the PGTV in different Dbs groups for those had a radiation dose lower than 66Gy.

Response: This is an important point brought up by the reviewer and we appreciate the input. It is true that the distribution of the isodose curves were correlated with both the distance between two objects and the contact area. But the contact area is just the product of the transverse diameter and the conjugate diameter. Dsb is the conjugate diameter. The reviewer is right; the measurement of Dbs was only accurate to 0.1 in this study, so the cutoff value of Dbs has been changed from 4.75 mm to 4.7 mm in the revised manuscript. In addition, we have provided the data for analysis of the PGTV in different Dbs groups for those had a radiation dose lower than 66 Gy (Page 12, lines 16-20, Table 5, and Fig. 1B & 3I-L).
2. In the Introduction part, the authors defined lower dose as less than \( \leq 66.5 \text{Gy} \), however, \( 66 \text{Gy} \) was demonstrated as the prescription dose of PGTVnx in the Method part (2.4)

Response: In the Introduction part, the lower dose as less than \( \leq 66.5 \) Gy was referred from the results of Ng et al. and was equal to 95\% of their prescription dose of 7 0 Gy (reference #5). In our studies, 66.0-75.9 Gy was the range of prescription dose of PGTVnx. Because 66.0 Gy always represents the minimum radical cure dose, so we selected a GTVnx Dmin of 66.0 Gy as the divided dose to analysis the radiation dose for prognosis.

3. The chemotherapy given in this cohort irregular, was 21 patients did not received chemotherapy. It is not reasonable to decide the necessity of neoadjuvant chemotherapy according to the waiting time. In addition, the authors did not indicated clearly the chemotherapy details of the whole group and how many patients had not complete adequate chemotherapy. OS and DMFS should be analyzed after excluded other factors (i.e. chemotherapy).

Response: Yes, there were 21 patients did not received chemotherapy because they were unwilling to receive or could not tolerate it. We did not use the waiting time to decide the necessity of neoadjuvant chemotherapy but we did give chemotherapy to the patients for long waiting time. We have provided the chemotherapy details which showed that there were 193 patients received 2 cycles and 153 patients received more than 3 cycles of chemotherapy in the revised manuscript (page 8, lines 10-11). In addition, we had added the univariate analysis of prognostic factors in these patients. The cycles of chemotherapy had be included for the analysis (new Table 5).

4. Dbs could had great influence on the results of TPS, which could induce the underdose of GTV, then further influence the local control. Since different physicists may yield different radiation protocols in the same patient, false positive result results may be produced. The distance of Dbs was correlated to T category and the volume of tumor, both are factors of primary site, and may have more influence on local control. The difference of 3-year OS should be analyzed further, as local control of NPC patients in IMRT era was superior, distant metastasis was the main failure pattern.

Response: It is correct that different physicists may yield different radiation protocols in the same patient and it may produce false positive result. However, most of treatment protocols were within the range of acceptable error. We also found that Dbs was correlated to T category and the volume of tumor (Table 1). However, Dbs have more influence on OS/LRFS/DFS and it may be due to different mechanisms to influence the treatment outcome. Dbs produced poor outcome not only due to tumor volume but more important due to its effect on tumor dose and related complications, because the D95\% and V95\% decrease as the Dbs becomes smaller (Fig. 2 and Tables 3 & 4). Therefore, Dbs
has its specific clinical application. The effect of Dbs on OS still has statistical significance after justifying the effect of T classification by multivariate analysis. We also further analyzed the difference of 3-year OS and have addressed the issues raised by the reviewer in the revisal manuscript (Page 17, lines 12-16).

5. It was not sufficiently rigorous that the authors analyzed the impact of Dbs on treatment outcomes without considering other factors, yield limited reference significance in clinic of this study.

Response: We had added other factors such as age, clinic stage on prognosis of NPC for analysis of the impact of Dbs on treatment outcomes in the revisal manuscript (Page 18, lines 20-22, page 19, lines 1-5, and Table 5).