Author’s response to reviews

Title: Development and validation of a novel MR imaging predictor of response to induction chemotherapy in locoregionally advanced nasopharyngeal cancer: a randomized controlled trial substudy (NCT01245959)

Authors:

Di Dong (di.dong@ia.ac.cn)
Fan Zhang (zhangfan26@mail.sysu.edu.cn)
Lian-Zhen Zhong (zhonglianzhen2018@ia.ac.cn)
Meng-Jie Fang (fangmengjie2015@ia.ac.cn)
Cheng-Long Huang (huangchl6@mail2.sysu.edu.cn)
Ji-Jin Yao (yaojj@sysucc.org.cn)
Ying Sun (sunying@sysucc.org.cn)
Jie Tian (jie.tian@ia.ac.cn)
Jun Ma (majun2@mail.sysu.edu.cn)
Ling-Long Tang (tangll@sysucc.org.cn)

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Author’s response to reviews:

Dear Editors and Reviewers:

We would like to thank the editors and the reviewers for their careful perusal of our revised manuscript and for the insightful comments and suggestions, which have helped to improve our paper markedly. We have carefully addressed the reviewers’ concerns and revised the manuscript accordingly. Our detailed point-by-point responses to the reviewers’ comments and suggestions are appended below. The line, page, section, and equation numbers correspond to the where the revisions are made in the manuscript. The revisions are denoted in red font in the revised manuscript.

Reviewers' comments to the authors:
Reviewer: 1
Reviewer #1:
1. P12 - Line 8: We used the Greenwood's formula to obtain the 95% CI for 3 year and 5 year FFS.
   [Response]: We thank the reviewer for the valuable advice. Following your suggestion, we have corrected the sentence.
   “We used the Greenwood’s formula to obtain the 95% CI for 3-year and 5-year FFS.”

2. P13 - Line 14: were instead of was
   [Response]: We thank the reviewer for the astute observations and valuable advice. Following your suggestion, we have corrected all the same mistakes:
   “In the matched training cohort, 3-year and 5-year FFS were 68.2% …”
   “In the high ICTOS group, 3-year and 5-year FFS were 69.3% …”
   “While in the low ICTOS group, 3-year and 5-year FFS were 67.1% …”
   “The 3-year and 5-year FFS were 82.4% (95% CI = 0.76-0.89) vs. 69.9 (95% CI = 0.62-0.79);”
   “In the high ICTOS group (n = 73/248), 3-year and 5-year FFS were 89.7% …”
   “While in the low ICTOS group (n = 175/248), 3-year and 5-year FFS were 79.1% …”

3. - P14 - Line 16: Please split the sentence into 2. A word is missing for correct understanding
   [Response]: We thank the reviewer for the valuable advice. Following your suggestion, we have split the sentence into 2.
   “In the high ICTOS group (n = 73/248), 3-year and 5-year FFS were 89.7% (95% CI = 0.81-1.00) and 89.7% (95% CI = 0.81-1.00) in ICT+CCRT; and 61.8% (95% CI = 0.47-0.81) and 52.8% (95% CI = 0.38-0.73) in CCRT alone subgroups (HR = 0.17, 95% CI = 0.06-0.51, p < 0.001, Figure 3E). Therefore, in the high ICTOS group, there were 27.9% absolute benefit at 3 year in favor of ICT+CCRT vs. CCRT alone, and 36.9% absolute benefit at 5 year.”

- P19 - Lines 8 to 11: The two sentences can be better formulated.
   [Response]: We thank the reviewer for the astute observations and good advice. Following your suggestion, we have rephrased the two sentences:
   “While for the patients with low ICTOS and low risk, CCRT alone already had a good 5-year FFS of 86.3% and the introduction of ICT generated no significant benefit. Therefore, CCRT alone might be preferred for patients in this subgroup to avoid unnecessary ICT-related expense and toxicity, as well as the prolonged wait before definitive radiotherapy.”

Reviewer 2
1. Table 1: would it be possible for the authors to better explain this Table: Is the aim to estimate any difference in the clinical variables between the two groups (low ICTOS and high ICTOS ?) how the p values are computed ? Which test is used? I assume that some different tests are used depending on the type of the associated clinical variable. However due to binary cut-off shown in the table even for continuous variables (for instance age and so on), it is unclear. Finally, could the authors check all the p-values that are reported in Table 1 ?
   [Response]: We thank the reviewer for the astute observations and valuable advice. Yes, table 1 was used to estimate any difference in the clinical variables between the low ICTOS and high ICTOS groups. We updated the legend of table 1 for clarity “Table 1. Association of baseline characteristics with ICTOS in both training and validation sets.”
   In table 1, all continuous variables were truncated to categorical variables using mean value. For
categorical variables, group comparison was performed by either the Pearson’s χ^2 test or the Fisher’s exact test, which have been mentioned in the “Statistics” section of the revised manuscript: “Categorical variables were expressed as percentages, and group comparison was performed by either the Pearson’s χ^2 test or the Fisher’s exact test.” Therefore, all the p values in Table 1 were computed using either the Pearson’s χ^2 test or the Fisher’s exact test. Following your suggestion, we have checked and confirmed all the p values reported in Table 1.

Sincerely,
Jie Tian, PhD
Fellow of IAMBE, AIMBE, ISMRM, IEEE, SPIE, OSA, IAPR
Director of the CAS Key Laboratory of Molecular Imaging, Institute of Automation, Chinese Academy of Sciences, No. 95 Zhongguancun East Road, Hai Dian District, Beijing, 100190, China
Telephone: +86-10-82618465
Email: jie.tian@ia.ac.cn

Jun Ma, MD
Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, People’s Republic of China
Telephone: +86-20-87343469
Fax: +86-20-87343295
E-mail: majun2@mail.sysu.edu.cn

Ling-long Tang, MD
Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, 651 Dongfeng Road East, Guangzhou 510060, People’s Republic of China
Telephone: +86-20-87343096
Fax: +86-20-87343295
E-mail: tangll@mail.sysu.edu.cn