Author’s response to reviews

Title: Long-term Results of Intensity-Modulated Radiotherapy Concomitant with Chemotherapy for Hypopharyngeal Carcinoma Aimed at Laryngeal Preservation

Authors:

Wen-Shan Liu (p53_tw@yahoo.com.tw)
Chung-Han Hsin (hsin@csmu.edu.tw)
Ying-Hsiang Chou (hideka@pixnet.net)
Jung-Tung Liu (cshy654@csh.org.tw)
Ming-Fang Wu (mfwu@csmu.edu.tw)
Szu-Wen Tseng (doc1952b@yahoo.com.tw)
Jong-Kang Lee (jklee@csmu.edu.tw)
Hsien-Chun Tseng (rad.tseng@msa.hinet.net)
Tzu-Hwei Wang (tzuhwei@yahoo.com.tw)
Mao-Chang Su (smc@csmu.edu.tw)
Huei Lee (hl@csmu.edu.tw)

Version: 2 Date: 9 December 2009

Author’s response to reviews:

Dear Editor-in-chief:

We are grateful to you for the opportunity to submit our revised manuscript (MS: 1619482514295179). We are also grateful to Dr. Harold Lau and Dr. Andreas Dietz for their suggestions in refining this manuscript entitled “Long-term Results of Intensity-Modulated Radiotherapy Concomitant with Chemotherapy for Hypopharyngeal Carcinoma Aimed at Laryngeal Preservation”. Modifications have been made based on the reviewers’ comments and are described point by point below:

Response to Dr. Harold Lau:

1. Include explanatory note why 2 different chemotherapy regimens were used
Response: We have added an explanation as to why there are two different chemotherapy regimens. However, this is a retrospective study so there are some limitations in terms of treatment uniformity.

2. Include how many patients had follow-up MRI and the time interval from RT completion to MRI and assessment of response?
Response: We have added this information. Every patient received both fibrescopic laryngoscopy and MRI examination two to three months after completion of radiotherapy.

3. How was complete response defined? By clinical assessment only?
Response: The complete response was defined by clinical assessment both by
fiberscopic laryngoscopy and MRI examination. However, if the ENT experts found a suspicious lesion, biopsy was performed for further confirmation.

4. Were any PET scans done for assessment of response?
Response: Yes, 12 patients received PET scan 4 to 6 months after the completion of radiotherapy. However, the main assessment methods were MRI, physical examination and fiberscopic laryngoscopy examinations.

5. Please include any additional information on late side effects - ie. what was the specific complication in the "one patient died of pharyngeal late effects 10 months after treatment"
Response: Thank you for your comment! We have added the description of the cause of death of that particular patient. In addition, we have included more comprehensive discussion of the late effects comparing our data to other experiences of IMRT treatment for hypopharyngeal cancer.

6. The 7 patients who required tracheostomy should be scored as NOT retaining a functional larynx.
Response: We have revised our data and recorded these patients as not retaining a functional larynx.

Response to Dr. Andreas Dietz:

General comments:

1. The paper lacks of the fact that this is only a retrospective case description without character of a trial. So the comparison of the data with published randomized trials is difficult or better spoken not possible.
Response: Thank you for your comment! We have revised the Discussion section and Conclusion section. In the revision we have removed most of the local control and survival comparisons between our data and the data from clinical trials.

2. We do not know about the reversibility of the tracheostomies?
Response: There were two patients with closure of the tracheostomy, and we have added this information to the Results section.

3. Authors should not focus on comparison to randomized trials. They should give more attention to feasibility and toxicity. Functional outcome should be described much more comprehensive.
Response: In the revised paper, most of the local control and survival comparisons between our data and the data from randomized trials have been removed. As the most common late effect was laryngeal stricture in our series, this grade 3 late effect was imperative to the management of tracheostomy. So, we analyzed the risk factors that may correlate with the procedure of tracheostomy. We found that patients belonging to high risk group (5/8) had significantly higher risk of receiving tracheostomy when compared to the patients of low risk group (2/16) (Fisher exact test, p=0.014). We defined the high risk
group as follows: having two or more factors including GTV dose more than 76 Gy, gross tumor more than 37 ml and primary tumor location other than the pyriform sinus. Those with one or none of the above risk factors were defined as the low risk group.

Specific comments:
1. Is the question posed by the authors well defined? The question is well defined but incomplete.
   Response: We have made major revisions to this manuscript. We have focused our results on long-term toxicity and functional outcome.
2. Are the methods appropriate and well described? Yes
3. Are the data sound? If the data are described more comprehensive, long term outcome after this new regimen would be interesting.
   Response: We revised the Method and Results sections extensively. We added more statistical analysis focused on finding the risk factors for prediction of late effect. This has been described in the general comments section.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? No
   Response: As there has been very little experience with IMRT for laryngeal preservation, we added further discussion comparing our data to the early experiences of other researchers in the Discussion section.
5. Are the discussion and conclusions well balanced and adequately supported by the data? No
   Response: We revised the original Discussion and Conclusion sections. The original discussion of the local control and survival comparing our data to the results of clinical trials has been removed. In the revised manuscript the discussion concerns both the acute and late effects of IMRT. We also reminded the readers of the risk group that may be associated with higher risk of receiving tracheostomy which was imperative for both acute and late grade 3 laryngeal stricture side-effect.
6. Are limitations of the work clearly stated? No
   Response: We believe the character of the retrospective study is the main limitation of this work. We remind readers of the need for further prospective studies.
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
8. Do the title and abstract accurately convey what has been found? No
   Response: We revised the abstract. We added the finding that the high risk group had significantly higher risk of tracheostomy procedure.
9. Is the writing acceptable? Yes

In conclusion, we have majorly revised the manuscript. The revision focuses more on the feasibility, toxicity and functional outcome of this new treatment modality. All authors approved this manuscript. We have no conflict of interest in this study.

Yours sincerely,

Wen-Shan Liu, MD, PhD
Department of Radiation Oncology
Chung Shan Medical University Hospital
No.110, Sec. 1, Chien-Kuo N. Road, Taichung, Taiwan
Tel: +886-4-2205-9019
E-mail: p53_tw@yahoo.com.tw