

10/25/2016

Lian-Sheng Ma, MD
President and Company Editor-in-Chief,
Baishideng Publishing Group Inc.,
World Journal of Radiology (WJR)

Reference: Manuscript NO.: **29495**

Dear Dr Lian-Sheng Ma,

Please find attached the revised manuscript, titled “Multimodality functional imaging using DW-MRI and 18F-FDG-PET/CT during radiation therapy for human papillomavirus negative head and neck squamous cell carcinoma: Meixoeiro Hospital of Vigo Experience” by David Aramburu Núñez et al., which we would like to advance for publication as an original research article in the World Journal of Radiology.

We are thankful to Reviewers (R) # 1 (code 00214317) and #2 (code 02439215) for the valuable constructive comments and for the opportunity to further improve the clarity and quality of our manuscript. We have made every effort to address the issues raised and the revised manuscript reflects our changes which are highlighted in yellow. The point wise reply to the critique of Reviewers # 1 and #2 as well as the suggested changes by the Editor (Ed) are pasted below.

Thank you very much for your time and consideration.

Sincerely,

Amita

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Our specific responses are itemized below and the changes in the text are marked accordingly.

Response to Reviewer (R) #1 (code 00214317):

More data about human papillomavirus and its relation to prognosis of HNSCC and why you selective negative patients. Add ref discuss DWI with other prognostic value of HNSCC and post treatment such as 1. NMR Biomed. 2016 Apr;29(4):483-9. 2. Radiol Med. 2013 Jun;118(4):534-9. 3. AJNR Am J Neuroradiol. 2007 Jun-Jul;28(6):1146-52.

Reply: We appreciate the comment about human papillomavirus (HPV) and its relation to prognosis of HNSCC and have added the three references in the discussion section of the revised manuscript (Page 13). The added text reads as follows “In recent years, studies by Razek, et al. have shown that ADC metric has a prognostic value in HNSCC (29-31). They reported a mean ADC value in nasopharyngeal carcinoma (NPC) of $0.99 \pm 0.11 \times 10^{-3} \text{ mm}^2/\text{s}$. The ADC value in this study also correlated inversely with tumor volume (29). In a separate study by the same group, it was reported that the mean ADC value of residual or recurrent lesions ($1.17 \pm 0.33 \times 10^{-3} \text{ mm}^2/\text{s}$) was less than that observed in post-therapeutic changes ($2.07 \pm 0.25 \times 10^{-3} \text{ mm}^2/\text{s}$) (30). They also showed that ADC values with metabolic ratio (Ch/Cr) obtained from ^1H -MRS are well correlated with several prognostic parameters of HNSCC (31)”.

Additionally, the study is based on HPV- as the majority of the patients referred to Meixoeiro Hospital of Vigo, Spain are HPV- HNSCC. This is reflected in the title of the manuscript as the accrual of patients is a Meixoeiro Hospital of Vigo Experience. It appears that the choice is rightly justified as there is very scarce imaging literature on HPV+ or HPV- alone, and it raises an urgent need to study these cohorts independently and assess the value of multimodality imaging for better cancer patient management.

Response to Reviewer (R) #2 (code 02439215):

The sample of the research is really small. It may affect the accuracy of results. As the article mentioned that there were other researches which get the contrary results, it may reduce the reliability of these results, so I think authors should investigate this and explain it in the article. The last I think the data of the result part may could be more simplified and maybe need more explanation about the meaning of each data.

Reply: We agree with the above comment and have added the following lines in the discussion.

On page 14, we have added the line “SUV and ADC remain exploratory imaging metrics yet to be fully explored and understood in HPV-HNSCC patients.” In the same paragraph we have also added the line “Further validation of the correlations with larger patient populations is needed, but was beyond the scope of this study”.

On page 16, the conclusion has been modified and now reads as “These results are preliminary in nature and are indicative, and not definitive, trends rendered by the imaging metrics due to the small sample size of HPV- HNSCC patients in a Meixoeiro Hospital of Vigo Experience.”

The data has been statistically analyzed using Wilcoxon test and Spearman correlation analysis. These are standard statistical approaches for analyzing multi-modality imaging data. Even though our sample size is small, it provides the readers with an insight on how to manage and understand valuable quantitative imaging metrics, such as SUV and ADC for HPV- HNSCC, with the objective of aiding future integration of these imaging metrics into the development of biological adaptive RT.

Response to Editor’s (Ed) comments and edits:

Reply: We have accepted all comments and suggestions made by the editor. The changes are marked in the revised manuscript and listed below:

- 1. We are submitting the revised manuscript with all changes marked in the format of doc file and not pdf.*
- 2. Please find the grant approval notices at the end of the replies to the queries raised.*
- 3. Please find signed pdf files for all the statements listed below:*
 - a. Institutional Review Board statement*
 - b. Informed consent statement*
 - c. Conflict-of-interest statement*
 - d. Data sharing statement*
- 4. We have put the Audio Core Tip file at the assigned manuscript website.*
- 5. We have completed and added the comments section in the revised manuscript. It reads as follows:*

COMMENTS

Background

Human papillomavirus (HPV) negative (-) head and neck squamous cell carcinoma (HNSCC) patients have poor outcomes compared with HPV-positive (HPV+) cancers. Individualization of radiotherapy is especially important in the subgroup of HPV- patients and imaging metrics derived from multimodality imaging can be critical for its implementation.

Research frontiers

In an effort to perform biologically guided adaptive radiotherapy, it is critical to understand how different functional imaging techniques interact and potentially complement each other.

Innovations and breakthroughs

Multimodality imaging in HPV- HNSCC suggests that tumor cell density is inversely proportional to glucose metabolism in a Meixoeiro Hospital of Vigo Experience. These results are promising and need to be validated in larger populations.

Applications

DW-MRI and ^{18}F FDG PET/CT are two valuable imaging techniques that may help build the framework for adaptive radiotherapy based on functional images in future clinical trials by investigating tumor cellularity and glucose metabolism before, during and after RT in HPV- HNSCC.

Terminology

^{18}F -FDG: Fluorine-18 Fludeoxyglucose; ADC: Apparent diffusion coefficient; AWD: Alive with disease; DOC: Dead of other causes; DOD: Dead of disease; DW-MRI: Diffusion-weighted magnetic resonance imaging; HNC: Head and neck cancer; HNSCC: Head and Neck Squamous Cell Carcinoma; HPV-: Human papillomavirus negative; HPV+: Human papillomavirus positive; IMRT: Intensity modulated radiation therapy; MRI: Magnetic resonance imaging; NED: No evidence of disease; PET/CT: Positron emission tomography/computed tomography; ROI: Region of interest; RT: Radiotherapy

Peer-review

This is a well written prospective study conducted in Spain to support the integration of functional imaging in a radiotherapy setting. The authors evaluated multimodality imaging in HPV- HNSCC patients for both primary and neck nodal metastases. Specifically, they observed that pretreatment tumor cellularity is inversely proportional to glucose metabolism in these tumors, which was consistent with the previous literature and appears promising for future clinical trials.

6. *The references have been updated with PubMed citation numbers and DOI citation to NIH style in the revised manuscript.*