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OPEN PEER REVIEW

Value of a ^{18}F-FDG PET/CT Semi-quantitative Parameter (SUV_{max}) in Predicting the Survival of Patients with Esophageal Cancer Subtypes

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 8 Jun 2022

Editor-in-Chief

MINOR REVISION 8 Jun 2022

Dear authors,
Before the review process for your article begins, it is necessary to clarify the following items:

Given the importance of clarifying “conflict of interest”, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

Regards

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Point by point answer to the reviewer's comment:

EIC Decision:

Dear authors,

Before starting the review processing of your article, it is necessary to clarify the following items:

Regarding the importance of "conflict of interest" clarification, the corresponding author should fill out the "ICMJE form" form and upload in the submission process. (The form exists in "conflict of interest" section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

Answer: The ICMJE form is filled and uploaded per your request.

Best regards

Corresponding author

Dr. A.D.

2 Revision 1

2 comments · 30 Jul 2022 – 9 Aug 2022

Referee 1 Reviewer

MINOR REVISION 30 Jul 2022

Thank you for submitting your valuable manuscript to the Iranian Journal of Radiology.
The main goal of this study was to assess the predictive value of the 18F-FDG PET/CT semi-quantitative parameter (SUVmax) for the short-term survival of patients diagnosed with esophageal cancer, including both SCC and adenocarcinoma subtypes. In this retrospective study, 36 patients with esophageal SCC and 15 patients with esophageal adenocarcinoma were enrolled. The authors concluded that the SUVmax of distant metastasis in patients with esophageal SCC could predict short-term survival.
The main strength of this study is its interesting subject with limited data available in the literature. The manuscript is also well written.
The major limitation of the manuscript is the small sample size, particularly for the esophageal adenocarcinoma subtype (15 patients), which could affect the results. I would suggest adding the 'limitation' subsection and mentioning this study's small sample size.

MATERIALS AND METHODS:
When discussing the measurement of SUVmax, the authors did not mention anything about patients with multifocal distant metastasis. Please add some information.

Editor-in-Chief

MAJOR REVISION 9 Aug 2022

Dear authors,
Your article needs Major Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:
I have received the manuscript titled (Value of 18F-FDG PET/CT semi-quantitative parameter (SUVmax) in esophageal cancer subtypes to predict patients’ survival)

This is a cross sectional study on a total number of 51 newly diagnosed patients with esophageal cancer (36 patient with esophageal SCC and 15 patients with esophageal adenocarcinoma).
The results suggest that 18F-FDG107 PET/CT scan has high potential to predict prognosis and survival of patients with esophageal squamous cell carcinoma compared to esophageal adenocarcinoma.
The paper is well written and there are no major problems with the English language.
The method is well structured and the results are reasonable.
It would be valuable to mention that there were no confounder risk factors (unrelated to underlying malignancy) in deceased patients of the two SCC and adenocarcinoma groups. **Answer**: Thank you for your comments. Your comment was mentioned in the material and method section.
There should be at least three key words using MESH. **Answer**: The key words are added.
Please update your references (last 5 years). **Answer**: We edited a few older references to last 5 years. But it is clear that we still need to cite some older valuable articles.

Reviewer 2:
Thank you for submission of your valuable manuscript to the Iranian journal of radiology.
The main goal of this study was to assess the predictive value of 18F-FDG PET/CT semi-quantitative parameter (SUVmax) in the short-term survival of patients diagnosed with esophageal cancer, including both SCC and adenocarcinoma subtypes. In this retrospective study, 36 patients with esophageal SCC and 15 patients with esophageal adenocarcinoma were enrolled. The authors concluded that the SUVmax of distant metastasis in patients with esophageal SCC could predict short-term survival.
The main strength of this study is its interesting subject with limited data available in the literature. The manuscript is also well written.
The major limitation of the manuscript is the small sample volume, particularly of the esophageal adenocarcinoma subtype (15 patients), which could affect the results. I would suggest adding the 'limitation' subsection and mentioning this research's small sample volume. **Answer:** Thank you for your comment. This has been already mentioned in the final part of “discussion”. Per your advice we separated it under “limitations”.

MATERIALS AND METHODS:
When discussing the measurement of SUVmax, the authors did not mention anything about patients with multifocal distant metastasis. Please add some information. **Answer:** Thank you for your comment. We clarified it in material and method section.

> Associate Editor's Comments:

Associate Editor 1:
The manuscript was studied by two reviewers and by me. I agree with the reviewers’ comments. Other

concerns that need to be addressed are as follows:

1- The study lacks technical detail and information about how the images have been analyzed. How many metastatic lymph nodes or distant metastases have been included in case of multifocal disease? **Answer**: Thank you for your comment. It has been briefly explained that PET/CT images are analyzed using an ADW4.5 work station and all primary tumor (T), regional lymph nodes (N) and distant metastatic sites (M) are included in analysis.
2- How many readers have evaluated the images? What about the experience and intra and inter-observer variabilities? **Answer:** We added this explanation to the text with details. The images have been reviewed by two readers simultaneously. One experienced nuclear medicine and one experienced radiologist with specific PET training reviewed all images and final conclusion was based on their consensus.
3- The definition of treatment response is vague, and it seems all items of T, N or M should be in line to be responsive or non-responsive. What about the patients with complete or partial response in the primary tumor (T), but progressive disease in N or M? This needs to be clarified. **Answer**: You are correct. We clarified it in the text and we added this explanation “Any new lesion or any increase in size or metabolic activity of any of T,N or M components was considered progressive disease”.
4- There is no data that whether two groups of patients can be basically compared in terms of SUV values and outcomes, because they may differ significantly with respect to T, N or M stages. The results of analyses for T, N and M stages between the two groups should be added. **Answer**: This might be a limitation of our study due to different number of patients between the 2 groups (36 versus 15) which unfortunately we had no control over. However we have mentioned and compared the T,N,M data between the 2 groups in tables2 and 3.
5- The pathologic subtype of mucinous adenocarcinoma might be PET negative. Is there any data about the pathologic subtypes of the tumors? **Answer**: MA of esophagus is very rare and comprises only 1.4% of esophageal cancer cases. Therefore among only 15 cases of adenocarcinoma we did not consider this subtype differential. Also you may agree that most pathology reports are not detailed enough to include all subtypes especially for such rare cases.
6- In the abstract, result section, 0.60% should be corrected as 60%. **Answer**: Thank you. We made the correction.
7- Two figures from the samples of two groups can better show the main message of this study. **Answer**: Thank you. We also agree and added an image for each subtype.

Associate Editor 2:
Thanks to the authors for their submission to the IJR.
Although, according to clinically the topic of study is interesting and important; but, methodologically there are some major concerns. In this study, at first, two subtypes (SCC vs. Adenocarcinoma) of esophageal cancer compared; and then, two groups of respondent vs. non-respondent to the treatment compared; and finally, two dead vs. alive groups compared. While, the most important factor that determines the study design is objective of research; and so, the study design is determine the sample size formula and appropriate sample size. Therefore, this diversity in outcome of study is inappropriate and must be focused on one of them. Detailed comments are attached in the manuscript file. It is advisable that all editions marked in the draft; and also, in a separate file as response to the reviewers described about the comments one by one. **Answer**: Thank you for this comment. We also have mentioned that small sample size and also different number of patients between the 2 groups is a limitation that

unfortunately we had no control over and should be addressed in future studies with larger sample size. But regarding your note, In the Table-1, SCC and adenocarcinoma patients are compared separately regarding demographics, tumor location, PET findings and treatment and outcome.

In Table 2, the SUV value for each subtype in responders and non-responders and in Table 3, the SUV value for each subtype in alive and death patients are analyzed to our best of knowledge. We came to an interesting finding that SUV of SCC patients with distant metastasis is significantly different between alive and deceased patient (higher in deceased patients). Actually we compared the details of SUV, pathology subtype and outcome of esophageal cancer patients very detailed and had an interesting finding as was mentioned.

I believe our finding can add to the literature. We are able to say that “Higher SUV values for metastases in SCC of esophagus are associated with poorer outcome”.

Yours sincerely

Dr. A.D

Corresponding author

3 Revision 2

2 comments · 10 Sep 2022 – 29 Oct 2022

Referee 2 Reviewer

ACCEPT 10 Sep 2022

Currently, this manuscript is relatively appropriate in terms of methodology, and it can be accepted for publication in the IJR.

Editor-in-Chief

MINOR REVISION 29 Oct 2022

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Reviewer 1:

Currently, this manuscript is relatively appropriate according to methodology, and it can accepted for publication in the IJR. **Answer**: Thank you

Associate Editor's Comments:

Associate Editor 1:

The suggested corrections and modifications have been made by the authors in the revised manuscript as far as possible. **Answer**: Thank you

Associate Editor 2:

Thanks to the authors of the article for sending their paper to Iran J Radiol. There are some issues that should be corrected:

1-It seems the SUV is standardized uptake value not semi-quantitative parameter. The author can write instead: "…. to assess the value of PET/CT semi-quantitative parameter (maximum standardized uptake value -SUVmax) to determine ……." [please apply such correction in body of paper too]. In addition, when you introduce abbreviated form, in next usage, please don't use complete form and add only abbreviated form. [for example, SUV max in line 7 of abstract]. **Answer:** SUV stands for Standard uptake value and also is a well-known semi-quantitative parameter of FDG PET/CT imaging. It is very well described in literature. We made the change. Thank you for your comment.

2-Please add objective to the abstract. **Answer**: Objective added

3-This part is unclear: "between both groups". Please clarify. **Answer**: we changed it to "adenocarcinoma and SCC groups" to be clearer.

4-It is better the authors introduce the abbreviations in first time usage for example 18F-FDG-PET/CT, …… [separately in abstract and body paper] **Answer**: we added to full term: fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography

5-This sentence is somehow unclear: "Significant difference was observed in SUVmax of distant metastatic lesions in patients with esophageal SCC and higher SUVmax values were detected in deceased patients versus cancer survivors." The first part seems unclear; the authors mentioned "Significant difference was observed in SUVmax of distant metastatic lesions in patients with esophageal SCC …" maybe, better version is: "In patients with esophageal SCC, a statistically higher SUVmax values of distant metastatic lesions were detected in deceased patients versus cancer survivors". Or something like this. **Answer**: Thank you for your comment. The change applied.

6- ---**Answer**: Your comment is empty

7-Please add objective part for paper based on the journal format. **Answer**: Objective part added.

8-Please change MATERIALS AND METHODS to Patients and Methods **Answer**: Thank you for your comment. The change applied.

9-Please add numbers for titles and sub-titles **Answer**: Thank you for your comment. The change applied.

10-please complete the SPSS manufacturer data based on the following address: https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss **Answer**: Thank you for your comment. The change applied.

11-In table 1, some points should be corrected:

I-the percents of gender distribution have been calculated based on the whole population [36+15], while it is better the percents will be calculated based on the tumor type [for example, in SCC, male percent will be 58.3% (21 out of 36)]. Please follow such approach in all tables. **Answer**: Change applied.

II-Please delete (percent) in table 1 and notify in footnote that the data have been mentioned as Mean±SD or No. (%). **Answer**: Change applied.

III-Precents of treatment outcome are based on whole 36+15 patients that is not good style. Please follow the above-mentioned style. **Answer**: Change applied.

IV-In table 1 and 2, the word index is not appropriate. Please replace by a better word or delete. **Answer**: Change applied.

V-There are two P-Values under the variable treatment outcome each one in front of Responder to treatment and non-Responder to treatment, while as the variable treatment outcome has two possible situations [responder and non-responder], so if we assess the relationship of tumor type with treatment outcome, we will have one single chi-square table and only one P-Value will be calculated. **Answer**: Your comment is correct. We discussed it with our statistician and put only one P-value

VI-In fact, the variables responder and non-responder are two possible conditions of more general variable that is response to treatment. Please arrange the layout of table based on this point. **Answer**: We discussed it with our statistician and per his advice we think to leave the table in current format. It still is enough clear to understand. Thank you for the comment.

VII-Please add unit of time for Mean time between diagnosis to death [month???] **Answer**: Change applied.

VIII-Please introduce full term of abbreviations in tables as footnote; for example, SUV, SCC, PET/CT, …… [please follow this recommendation for all tables] **Answer**: Change applied.

IX-in variable response to treatment, number of SCC is 37 [25+12] and the number of adenocarcinoma is 14 [8+6] that are wrong. Please correct. **Answer**: Change applied.

13-please correct the axis legends of figure 1 and 2 as Follow up and Cumulative survival. **Answer**: Thank you for your comment. The change applied.

14-the authors mentioned: “Death occurred in 36.1% of SCC and 40.0% of adenocarcinoma patients respectively with no significant difference (p = 0.103).” while 0.103 is P-value of Mean time between

diagnosis to death in table 1. PLEASE completely revise carefully all the paper and tables for similar mistakes and correct them. **Answer**: Thank you for your comment. The change applied.

15- in lines 96-8, we can write the part better. For example: “Comparing responders and nom-responders subgroups; no difference was found in the mean SUVmax of primary tumor, SUVmax

of lymph node and SUVmax of distant metastasis between these subgroups in both groups of SCC and adenocarcinoma” **Answer**: Thank you for your comment. The change applied.

16-Please delete title Limitation. **Answer**: In the previous revision we were requested to add this. Now we delete that per your request.

17-abbreviated journal name of reference 1 is wrong. [Radit Oncol; I think it is Radiat Oncol]. Please carefully revise the references based on the standard format. **Answer**: Revised if indicated per your advice.

Yours sincerely

Dr. A.D

Corresponding author

4 Revision 3

1 comment · 7 Nov 2022

Editor-in-Chief

MINOR REVISION 7 Nov 2022

Dear authors,
Your article needs Minor Revision.
Regards

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewers' Comments:

Associate Editor 1:

The authors have corrected many parts. There are some minor issues that should be corrected:

1-In table 1, the relationship of gender variable [that have two subgroups of male and female] with tumor type should have only one P-Value. [not two P-Values]. **Answer**: Change applied.

2-By the question “10-please complete the SPSS manufacturer data based on the following address: https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss” I did not mean that the authors add web address in paper. I mean please check this web address and complete the manufacturer data of SPSS based on data of this page. **Answer**: Change applied.

3-Regarding limitation, I did not mean that the authors delete limitations. They are necessary and useful. I requested to delete only the title limitation [not the part related to limitations]. So please add the limitation part to the paper again. **Answer**: Change applied.

Yours sincerely

Dr. A.D

Corresponding author

5 Revision 4

1 comment · 15 Nov 2022

Editor-in-Chief

ACCEPT 15 Nov 2022

Dear authors,
Your article is acceptable for publication in IJR.
Regards