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OPEN PEER REVIEW

Association of Tumor Metabolic Activity on PET/CT Scan with Pathological Characteristics in Patients with Malignant Melanoma

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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.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

1 comment · 18 Mar 2022

Editor-in-Chief

MAJOR REVISION 18 Mar 2022

Dear authors,
Your article needs Major Revision.
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 comments:

Reviewer 1:

Dear Prof. Salahshour,

I reviewed the paper which aimed to instruct a correlation between the metabolic activity of the melanoma primary and metastatic tumors based on the PET study and pathologic features. In general, the topic is interesting for the radiologists and nuclear physicians as may provide further insight on the tumor aggressiveness and prognosis of the patient, based on the imaging. Nevertheless, the researchers missed certain aspects of the main question particularly in the discussion section. I believe the paper merits the publication with few changes as follows:

1- In the result section of both abstract line 1 "without" should be changed to "with". Same change is demanded in main text result section. **Answer:** Thank you for your comment. We applied the necessary change in the text. However, line 2 abstract was wrong. Patients with free margin are less aggressive tumors and SUVmax was lower in them.
2- In the result of abstract the Ki67 related phrase should be omitted as it does not correlate with the main research question. **Answer**: We agree with your comment and related sentence was omitted from abstract/result.
3- Main body introduction section is rather undirected to the research question (i.e. association of the tumor thickness and metastasis metabolic activity) and is long. The first half of first paragraph could be deleted. Instead, the indication of the FDG PET for staging or re-staging may be introduced. **Answer**: We agree with your comment and requested edition was applied in "introduction" section.
4- In main body method section, the method for calculation of SUV for regional LNs in non-metastatic patients (i.e. normal LNs?) should be defined. **Answer**: We appreciate your comment. We added briefly the method for SUV calculation. However, there was no reason to calculate normal LNs SUV value.
5- In the result section of main text, the presentation of the prevalence of the metastases is confusing. Please provide the data orderly based on the most common to less encountered. **Answer**: Thank you for your comment. We applied this suggested revision.
6- In the result section of main text, it should be stated that the metastasis statistics are provided based on the PET findings only or other previous patient's data are also included. **Answer**: Metastatic statistics are only based of current patient's PET/CT and no previous date are included, we stated this in the text.
7- Abdominopelvic metastasis, in result section, should be previously defined in the methods. What do authors mean by abdominopelvic metastasis? Is hepatic metastasis included? Skeletal? Skin? LNs? **Answer**: We agree that the term "abdominopelvic metastasis" is unclear and therefore deleted all related correspondence from the text and also tables.
8- Clark related data should be provided by median and interquartile or range instead of mean and SD. The analysis also should be changed from parametric to nonparametric or rank analysis. **Answer**: Since the "Clark" classification" is also less commonly used in the recent literature, we rather to omit "Clark" and all related information from text and tables.
9- Discussion needs to be re-written: authors should consider that the discussion is not a restatement of the results, but should provide reasoning and possible causes for their finding. What their finding regarding the association of Clark and SUV in metastatic sites mean? What would be the

correlation of higher SUV with prognosis? Do I when interpret a PET should search for more metastases when the primary tumor SUV is higher? or not? **Answer**: We agree with your comment. We did our best to revise the “discussion” section.

10- In conclusion, “and other pathological results and FDG PET/CT” should be changed to “with either other pathological results or FDG PET/CT”. **Answer**: We changed the sentence per your suggestion.

11- I suggest the limitation part be omitted from the conclusion; I disagree that the sample size is low to answer the main study question. Nevertheless, the suggestion for multicenter and community based similar studies may be kept. **Answer**: We agree with your comment and applied the changes.

Reviewer 2:

Thanks from authors for their submission to the IJR.

It can be said that this manuscript is relatively appropriate according to designing and scientific writing; but it needs some revisions as follows:

1- The design of the study is cross-sectional and the retrospective and descriptive words should be omitted throughout the text. **Answer**: We applied your comment to the best we could.

2. The method section should be written as a subheading. **Answer**: Thank you for comment. We followed.

3. In the method, a section should be added as a classification of variables and described about the calcification and measurement of variables (such as Tables 1 and 2). **Answer**: The suggested edition is applied in the text and a table added.

4. The Ethical considerations section should be added to the method. **Answer**: Ethical consideration and code are added.

5. About statistical analysis:

5.1. Delete these sentences: Quantitative data were analyzed using descriptive test and presented as Mean ± SD. Crosstabs program and Chi Square test were used to compare percentages or frequencies of data between groups. **Answer**: The sentences are deleted.

5.2. It should be exactly written that each test was used to examine the association of what variables, and with what strata or statistical nature. Also, the names of each tests should not be repeated. **Answer**: your comment is accepted and applied to the best we could.

5.3. The Chi-square test and multiple linear regression results not presented. **Answer**: This part is edited.

6. In the case of Tables 4-6

6.1. Merge them into one table

6.2. Reverse row and column variables

6.3. Only columns related to the variables of mean, standard deviation and significant level should be presented

6.4. The columns should contain CT variables and the row related to qualitative pathology variables.

6.5. Tables 4 and 5, which measure the relationship between pathology variables, should be omitted, because they are not in line with the objectives of the study.

6.6. When a star-like symbol is used in the table, it should be explained below the table. **Answer**: We greatly appreciate your comment. We the authors believe that contents of these tables are very important and their statistical significance is different as is stated in the tables. Therefore, we rather to keep these tables, however their content is revised. We greatly appreciate your understanding

7. Sentences should not start with a number. **Answer**: Your comment is appreciated.

Reviewer 3:
Dear editor
I read the manuscript,
- English writing is poor and the manuscript needs a professional English writing edit. **Answer**: Language is edited by a professional person per your request.
- The title is not comprehensive and did not focus on a specific subject. **Answer**: The title is edited.
- The objective of the study is interesting. **Answer**: Thank you.
- Line 121: The study is cross-sectional but not "retrospective". **Answer**: Change applied.
- Method is suboptimal with many biases in the study design. **Answer**: The method section is edited.
- There are many uncertainties in the results, some of the issues are as follow:
o The author used "relationship" all over the manuscript; however, the relationship could not be used in this study and it should be changed to "association". **Answer**: change applied.
o Line 202: "Comparison of the median of PET and pathology factors" what does it mean?!!!! **Answer**: The sentence changed to: Association between primary location and SUV values is shown in Table-6
o The author mentioned that many factors such as ulceration, tumor thickness, margin and … correlated to metastases SUVmax, this is not a true correlation because there are many confounding factors, including tumor size and partial volume effect on SUV calculation. The factors could be correlated with presence of regional/distant metastases. **Answer**: we agree with your comment and changes are applied in the text. All "relationships" are changed to "association".
o Lines 209-210: "lung metastasis was significantly increased from 0.0 in non-metastasis group to 0.79 and finally 4.16 in single and multiple metastasis groups, respectively" it is obvious that when there is no lesion the SUV is zero!!! Also again the results should be adjusted for confounding factors, including tumor size, location, partial volume effect and …**Answer**: This part is edited.
o Tumor location definition is vague for eye lesions, what did the author means about "eye" if the tumor is in the palpebral is should be categorize as skin, if the tumor is originated from conjunctiva it should be categorize as mucosa and finally if the tumor originated from the retina it should be categorize as third and separate category. **Answer**: requested edition is applied.
o Finally, the most important point is the missing DATA in statistical analysis which makes the results unreliable, for example in the tables 4 and 6 there are many valid numbers less than 10 and even as low as 2. The statistical analysis in these instances is not relevant and should not be reported. **Answer**: we edited and merged table's information to resolve this issue.

oThe discussion is disappointing and did not include above mentioned study limitations.
Answer: the discussion section is also edited.

Reviewer 4:
Dear author

Please mention ethical code with the link address. **Answer**: This will be appreciated during revision submission.
Please clarify the financial resource and mention the number grant. **Answer**: This will be appreciated during revision submission. The COI form will be uploaded.
Regarding the importance of “conflict of interest” clarification, corresponding author should fill the “ICMJ 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).

The references you used are old. Please use references that are from the 5 last years. **Answer**: Studies with our topic are few. We updated references.

Best Regards

Dr. A.D.

Corresponding author

2 Revision 1

1 comment · 15 Jun 2022

Editor-in-Chief

MINOR REVISION 15 Jun 2022

Dear authors,
Your article needs Minor 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.

Point by point answer to the reviewer's comments:

Reviewers' Comments:

Reviewer 1:

No public comments. **Answer:** Thank you for accepting our article.

Reviewer 2:

Currently, this manuscript is edited appropriately; but the Table 1 is not necessary and, it must be deleted. **Answer:** We deleted Table-1 per your comment.

Reviewer 3:

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:** We uploaded related ICMJE form per your request.

Best regards

Dr. A.D.

Corresponding author

3 Revision 2

2 comments · 18 Jun 2022 – 2 Jul 2022

Referee 1 Reviewer

ACCEPT 18 Jun 2022

At present, this manuscript has been edited appropriately according to the suggested comments.
Therefore, it is suitable for publication in the IJR from a methodological point of view.

Editor-in-Chief

MINOR REVISION 2 Jul 2022

Dear authors,
Your article needs Minor Revision.
Regards

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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.

Point by point answer to reviewer comments:

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1-in line 37 abstract, it seems the verb “consider” is better to be changed to “assess” or “evaluate”. **Answer:** The change applied.

2-please introduce full term of abbreviations in the first time [in abstract and paper separately]; for example SUV. **Answer:** The change applied.

3-please separate the objective [art in paper based on journal format. **Answer:** The change applied.

4-please add full data of PET CT machine manufacturer. **Answer:** Full data of PET/CT manufacturer added.

5-please add the data of SPSS manufacturer [based on IBM site data]. **Answer:** data of SPSS manufacturer added.

6-please add numbers for titles and sub-titles. **Answer:** The change applied.

7-the term abnormal distribution seems incorrect. It is better to be written as without normal distribution or something like this. **Answer:** The change applied.

8-the authors mentioned: “Independent t-test was used to compare the mean of SUVmax and the number of metastases between pathology groups.” It seems number of metastasis is not a continuous variable and should be analyzed by non-parametric methods. **Answer**: This section was deleted to avoid any further confusion.

9-the authors mentioned two times the use of t-test in stat analysis part. It could be summarized. **Answer:** The change applied. T-test is stated once.

10-in line 150, metastatic evaluation should be metastasis evaluation. [similar point in line 154]. **Answer:** The change applied.

11-in sentence of line 180m the verb [shown] seems wrong. **Answer:** Shown changed to demonstrated.

12-please unify the writing style of beta-tubulin in paper. [beta-tubulin and β-tubulin] **Answer:** The change applied.

13-please introduce full term of abbreviations in tables in footnote of tables [for example ALL in table 1] **Answer**: We decided to delete (ALL) because it might be confusing. I think table-1 in clear to understand.

14-please change LIMB, SCALP, …. In table 1 to Limb, Scalp, …… **Answer:** The change applied.

15-n table 3, there are three row variables of pathology features while there are 4 row variables for N. please clarify. **Answer**: The N in first row reflects total number for each column. Subsequent Ns reflect number in each row, corresponding to its column.

16-please add abbreviations in figure legend [such as HMB45] **Answer:** The change applied.

17-it is recommended the authors add notifications to figure 2 parts [A, B, …..J] and address these parts in figure 2 legend. **Answer:** We think this might neither be necessary nor helpful. Because figure-2 is only a sample patient with extensive metastases. You can see the MIP image on the left and select axial and coronal images on the right merged together. However we have clarified that in the related figure legend.

18-analysis in table 5 needs one way ANOVA or kruskal wallis test. It is better the authors add this method in statistical analysis section. **Answer:** The edition applied.

Sincerely yours

Dr. A.D.

Corresponding author

4 Revision 3

1 comment · 6 Jul 2022

Editor-in-Chief

MINOR REVISION 6 Jul 2022

Dear authors,
Your article needs Minor Revision.
Regards

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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.

Point by point answer to reviewer's comments:

Associate Editor 1:

1-Based on IBM site, the SPSS 22 should be cited as: "IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp." **Answer**: The requested change applied. Thank you.

2-please separate objective part in paper before method section. **Answer**: The requested change applied. Thank you.

3-please add full term of abbreviations SUV, IHC, … in tables as footnotes. **Answer**: The requested change applied. Thank you.

Dr. A.D.

Corresponding author

5 Revision 4

1 comment · 11 Jul 2022

Editor-in-Chief

ACCEPT 11 Jul 2022

Dear authors,
Your article is acceptable for publication.
Regards