OPEN PEER REVIEW

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Iranian Journal of Radiology
Article DOI: 10.5812/iranjradiol.113862
Published in: Iranian Journal of Radiology: 18(3); e113862

Peer Review Report for "Role of FDG-PET/CT in Identification of Histological Upgrade of Ductal Carcinoma in Situ (DCIS) in Needle Biopsy"

Author(s): Na Young Jung, Bong Joo Kang, Sung Hun Kim, Ie Ryung Yoo, Yeon Soo Lim, Won Jong Yoo

Review Timeline:

Submit Date: 16 Feb 2021
Revised Date: 30 Jul 2021
Accepted Date: 2 Aug 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) — 2 Mar 2021

Dear AE,
Totally it must be mentioned that this study was appropriately designed, conducted and written; but according to methodology it needs minor revisions as follows:
1. The study design is a retro-respective cohort, and this term must be added in the abstract and full-text method section.
2. Why use median or some non-parametric tests such as Wilcoxon rank test? Because of the non-normal distribution of some continuous variables? If so, it must be added this point in the statistical analysis; moreover, it must be used of Mann–Whitney U test not Wilcoxon test for correlated data.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 9 Mar 2021

Dear AE,
Thank you very much for inviting me to review the manuscript "Role of FDG-PET/CT in the identification of histologic upgrade of ductal carcinoma in situ of the breast at needle biopsy".

This paper is well written and the results are applicable in better management of breast cancer patients.
Overall I consider this paper interesting enough to be published in your esteemed journal.
Yours sincerely,

Mehrshad Abbasi: Reviewer | **Revision** (0) 6 Apr 2021

Dear AE,
The paper reports the significance of high FDG uptake in the breast lesions to discriminate DCIS from DCIS with invasion. I highly recommend its publication with few following minor revisions:
1- In the abstract, it is mentioned that adjustment for tumor size or ... was done. How was it done? It is not embedded in the method or results of the main text.
2- In the following phrase in discussion: " In this study, the SUVmax and visual analysis were also independent predictors for the upgrade of DCIS to invasive cancer on multivariable analysis"; independent is not supported by the results.
3- I suggest providing a cut point for SUV by using ROC curve analysis and suggesting the shortest distance to the optimal point on the curve (or using the Youden index) as a possible threshold. The sensitivity and specificity at the threshold could be presented.
Regards,

REFEREE: Associate Editor | **Revision** (0) 12 Apr 2021

Dear EIC,
The manuscript needs minor revision.
Thanks.

REFEREE: EIC | **Revision** (0) 12 Apr 2021

Dear authors,
Your article needs Minor Revision.
Regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Replies to Reviewers' Comments:

Reviewer 1:
Totally, it must be mentioned that this study appropriately designed, conducted and written; but according to methodology it needs minor revisions as follows:
Q1. The study design is retro-respective cohort, and this term must be added in the abstract and full-text method section.

→ A: That term was added in the abstract and full-text method section.

Q2. Why used of median or some non-parametric tests such as Wilcoxon rank test? Because of non-normal distribution of some continuous variables? If so, it must be added this point in the statistical analysis; moreover, it must be used of Mann–Whitney U test not Wilcoxon test for correlated data.

→ A: The Kolmogorov-Smirnov test was applied to confirm that continuous variables were normally distributed. Only “age” showed a normal distribution, and the other parameters did not.

The next paragraph has been inserted in the main text.

“To confirm that continuous variables were normally distributed, the Kolmogorov-Smirnov test was applied. Only patient age showed a normal distribution, but the other parameters did not. Comparisons between continuous variables were performed using the Student’s t-test (patient age) or Wilcoxon rank-sum test (SUVmax and tumor size) depending on normality.”

Reviewer 2:
Dear Editorial Team,
The paper reports the significance of high FDG uptake in the breast lesions to discriminate DCIS from DCIS with invasion. I highly recommend its publication with few following minor revisions:

Q1- In the abstract, it is mentioned that adjustment for tumor size or ... was done. How was it done? It is not embedded in the method or results of the main text.

→ A: This means that multivariate analysis was performed adjusted for variables with P value < 0.05 in the univariate analysis. “Multivariable analysis was performed twice in total, one with SUVmax and other significant factors on univariable analysis (model 1), and the other with visual analysis and other significant factors (model 2)”, as mentioned in the main test (method-statistical analysis). I agree that the term “adjusted” is somewhat confusing, so I changed the method in the abstract according to the main text.

Q2- In the following phrase in discussion: "In this study, the SUVmax and visual analysis were also independent predictors for the upgrade of DCIS to invasive cancer on multivariable analysis"; independent is not supported by the results.

→ A: I rewrote the sentence, agreeing that the word “independent” was not statistically clear.

“In this study, the SUVmax and visual analysis were predictors to upgrade DCIS to

invasive cancer in both univariable and multivariable models, as in the previous studies."

Q3-I suggest providing a cut point for SUV by using ROC curve analysis and suggesting the shortest distance to the optimal point on the curve (or using Youden index) as a possible threshold. The sensitivity and specificity at the threshold could be presented.

→ A: In the previous manuscript, the median value of SUV (2.0) was used as the cutoff value in univariable and multivariable analysis. Following the reviewer's advice, we performed the ROC curve analysis, the optimal cutoff value was set to 1.9.

The analysis using SUVmax (≥1.9, cutoff value by ROC analysis) was added in methods and results section of abstract and methods (statistical analysis), results and discussion section of full-text (all highlighted).

Reviewer 3:

Dear editor

Thank you very much for inviting me to review the manuscript "Role of FDG-PET/CT in the identification of histologic upgrade of ductal carcinoma in situ of breast at needle biopsy".
This paper is well written and the results are applicable in better management of breast cancer patients.

Overall I consider this paper interesting enough to be published in your esteemed journal.

Thank you very much for your review.

Sincerely,

Corresponding author of this manuscript

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 5 May 2021

Dear AE,
Thanks to the dear authors for applying comments in the manuscript.
But, a point that was also mentioned in the first time review, it was not corrected properly. In the statistical analysis section and footnote of table 1, it was written that the Wilcoxon test was used, while the Mann-Whitney test should be used; because the data are independent. In addition, the type of t-test should be modified as an independent t-test.
Thanks.

REFEREE: Associate Editor | **Revision** (1) 26 Jun 2021

Dear EIC,
The manuscript could be accepted.
Thanks.

REFEREE: Reviewer | **Revision** (1) 30 Jun 2021

Dear AE,
The study is reviewed carefully. According to comments and revisions by the author, this manuscript is accepted.
Thanks

REFEREE: Associate Editor | **Revision** (1) 22 Jul 2021

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (1) 24 Jul 2021

Dear authors,

Your article needs Minor Revision.

Regards

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

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Replies to Reviewers' Comments:

Reviewer 1:

Thanks to the dear authors for applying comments in the manuscript.

But, a point that was also mentioned in the first time review, it was not corrected properly. In the statistical analysis section and footnote of table 1, it was written that the Wilcoxon test was used, while the Mann-Whitney test should be used; because the data are independent. In addition, the type of t-test should be modified as an independent t-test.

→ As you said, the nonparametric method for independent samples is the Mann-Whitney U test. There seems to have been some confusion, because the Wilcoxon Rank Sum test is numerically the same as the Mann-Whitney U test.

(https://www.lexjansen.com/nesug/nesug04/an/an10.pdf)

The text and footnote of Table 1 have been corrected as your comment.

Reviewer 2:

This paper is ok.

Associate Editor's Comments:

Associate Editor 1:

Dear authors,

The manuscript could be accepted.

Associate Editor 2:

1-please separate the objective part from background in paper.

→ I separated the objective part from background.

2-this part should be written better: "a Biograph Duo or a Biograph True Point (Siemens Medical Solutions, Knoxville, TN, USA)." For example, please write: "…… dedicated PET/CT scanner including a Biograph Duo or a Biograph True Point (Siemens Medical Solutions, Knoxville, TN, USA)."

→ I corrected this as you mentioned.

3-at the beginning of statistical analyses session, the authors mentioned "Form receiver operating characteristic (ROC) analysis," this part is meaningless. Please correct.

→ This sentence was added from Reviewer 2's comments on previous revision. (Previous reviewer's comments : "I suggest providing a cut point for SUV by using ROC curve analysis and suggesting the shortest distance to the optimal point on the curve (or using Youden index) as a possible threshold. The sensitivity and specificity at the threshold could be presented.")

The later paragraph in "Statistical Analysis" contains the ROC analysis, so this sentence has been deleted according to your comment.

4-the following sentence could be written better: "Differences in the biopsy methods; tumor grade on biopsy; high and low SUVmax groups divided by the cutoff value; visual analysis of primary tumor and axillary LNs on FDG-PET/CT; axillary LN metastasis on pathology; ER and PR status; HER2 expression; Ki-67 index; EGFR between the pathologic groups were compared using the χ 2 test and Fisher's exact test." For example, for example, we can write: "different groups determined based on biopsy methods; tumor grade on biopsy; …….. were compared using the χ 2 test ……."

→ I corrected this as you mentioned.

5-In this sentence: "Multivariable analysis was performed twice in total, one with SUVmax and other significant factors on univariable analysis (model 1), and the other with visual analysis and other significant factors (model 2)." it is better the authors mention that the upgrade to invasion is the dependent variable and the regression is logistic [??? I guess so] and the above mentioned variables are independent variables or predictive factors.

→ This sentence has been corrected as follows: "Univariate and multivariate logistic regression analyses were performed to analyze the effect of independent variables on upgrade to invasion. Multivariate models were performed separately for SUVmax and PET cancer detection with other factors showing $p<0.05$ in univariate analysis (SUVmax + age + tumor size for model 1 and PET cancer detection + age + tumor size for model 2)."

For uniformity of terminology, the "univariable" was changes to "univariate" and "multivariable" as "multivariate" throughout the paper.

6-the authors mentioned: "In practical clinical practice" is this appropriate? We have two "practice" word here.

→ I corrected this as "In actual clinical practice"

7-please correct in table 1 the word cufoff

→ I corrected this as you mentioned.

8-what is the meaning of "between Recurrence" in table 1 footnote? It is correct here?

→ Thank you for pointing out the error. I edited it as "between DCIS and IDC".

9-in table 2, it is better the author determine in the column headers which results are univariate analysis and which one are multivariate analysis.

→ The headers have been added.

Thank you for your attentive review.

Sincerely,

Corresponding author of this manuscript

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (2) 1 Aug 2021

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (2) 2 Aug 2021

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