OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
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- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Iranian Journal of Radiology
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Peer Review Report for "Evaluating Changes of Tumor Hypoxia Using $^{99}Tc^{m}$-MNLS Hypoxic Imaging"

Author(s): Yujing Hu, Dayong Wu, Congna Tian, Wenyan Zhang, Qiang Wei, Yanzhu Bian

Review Timeline:

Submit Date: 6 Nov 2018
Revised Date: 9 Aug 2019
Accepted Date: 18 Aug 2019

Revision (0)

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** (0) 9 Nov 2018

Daer EIC,
This interesting report examines Changes of Tumor Hypoxia using 99Tcm-MNLS Hypoxic imaging in a rat model. This content review focuses on suggestions I believe the authors may want to address prior to journal submission.
* While this paper is a valuable contribution to its field, that importance is not made apparent enough in the Introduction.
* The Introduction can be more described the field of study and importance.
* The Methods are carefully described; however, some issues in statistical Analysis, which might benefit from rewriting.
* IJR Authors guideline should be checked carefully and all the paper especially titles of abstract and main text rewrite according to it.
In Fact, the paper needs major revision to consider for publication in IJR.
Best Regards

REFEREE: Reviewer | **Revision** (0) 12 Dec 2018

Dear AE,
The manuscript "Evaluating Changes of Tumor Hypoxia using 99Tcm-MNLS Hypoxic Imaging" is research on an interesting topic. It is well performed and well written and I consider it acceptable for publishing.
Yours sincerely,

REFEREE: Reviewer | **Revision** (0) 4 Jan 2019

Dear AE,
There are some comments which should be addressed by the author:
1- Please add a brief background to abstract according to journal format.
2- It is better the method of Quality control 99 Tc m –MNLS part is documented by a reference.
3- How many operators or researchers did draw the ROIs and what was their reliability in drawing ROI? [interrater and intrarater reliability]
4- The highest concentration of 99 Tc m –MNLS after injection is seen in 1 h after injection while the authors selected 2 h after injection. This is confusing [0.365 in 1 h and 0.359 in 2 h]. please clarify.
5-The authors mentioned: “There was a positive correlation between T/NT ratio and the expression of HIF-1α in the radiotherapy groups” it is unknown which time is the basis for this analysis? did the authors use all data in all times for this analysis? please clarify.
6- Please add in the stat method that the normality of data was assessed before analysis and in case of normality, the parametric tests have been used.
7- It is better the authors compare important baseline characteristics between mices to show their similar conditions such as weight.
8- The authors mentioned method of expression of HIF-1α by counting the cell number expressing HIF-1α
In each field [totally 5 regions] but they did not mention how many fields have been used for this counting? Did they use only one field? Or more? Please add the data to the paper.
9- It is better the authors add a diagram for easy visual comparison of 99 Tc m –MNLS and HIF1- α in different times and different groups. It would help to readers to better compare the values in these subgroups.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 2 Feb 2019

Dear EIC,
According to the reviewers, the article needs major revision.
Best Regards

REFEREE: EIC | **Revision** (0) 2 Feb 2019

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

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.

Dear Prof. Kavous Firouznia and reviewers,

We greatly appreciate the editor and reviewers' positive and constructive comments and suggestions on our manuscript. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration. Many thanks for your continued attention.

Yours sincerely,

Reply to Reviewers' comments:

Reviewer 1

Comments 1: **The manuscript "Evaluating Changes of Tumor Hypoxia using 99Tcm-MNLS Hypoxic Imaging" is a research on an interesting topic. It is well performed and well written and I consider it acceptable for publishing.**

Reply: Thank you very much for your efforts on our work.

Reviewer 2:

Comments 1: **please add a brief background to abstract according to journal format.**

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "Hypoxia is an important cause of recurrence and metastasis of malignant tumors. Noninvasive detection of the extent of hypoxic areas of tumors is essential for delineation of radiotherapy target areas and dose." Thanks.

Comments 2: **it is better the method of Quality control 99 Tc m –MNLS part is documented by a reference.**

Reply: The information has been supplied and reference 5 has been added. Thanks.

Comments 3: **how many operators or researchers did draw the ROIs and what was their reliability in drawing ROI? [interrater and intrarater reliability]**

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "Two doctors with over 10-year experience delineated the coverage of ROI independently and compared, if there was any big difference, they would re-delineate to determine ROI." Thanks.

Comments 4: **the highest concentration of 99 Tc m –MNLS after injection is seen in 1 h after injection while the authors selected 2 h after injection. This is confusing [0.365 in 1 h and 0.359 in 2 h]. please clarify.**

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "The retention of imaging agents in tumors (T) and non-tumorous tissues (NT) was highest at 1 hour, and excreted with time which was more significant in non-tumorous tissues." Thanks.

Comments 5: **the authors mentioned: "There was a positive correlation between T/NT ratio and the expression of HIF-1α in the radiotherapy groups" it is unknown which time is the basis for this analysis? did the authors use all data in all times for this analysis? please clarify.**

Reply: Since we have had the results as "The ratio of % ID/g in tumor and muscle (T/M) was increased significantly over time within 2 h, and reached 5.36±2.62% ID/g at 2h, then it began to decrease gradually over time from 3h.", so the ratio of T/NT at 2h was highest, and the correlation between T/NT and HIF-1α was analyzed based on the T/NT ratio of 2h.

Comments 6: **please add in stat method that the normality of data were assessed before analysis and in case of normality, the parametric tests have been used.**

Reply: According to your kind suggestion, the relevant contents have been added in the revised manuscript: "Data were expressed as mean±standard deviation (SD) and analyzed using statistical software SPSSv17.0. The normality of data were assessed before analysis. If the data were normality， comparisons of measurement data were carried out using one-way ANOVA, pairwise comparison LSD-t test, two independent sample *t*-test and non-parametric Spearman analysis. If not, the Rank sum test was used." Thanks.

Comments 7: **it is better the authors compare important baseline characteristics between mices to show their similar conditions such as weight.**

Reply: Indeed, the baseline between mice was similar with the same weight and sexual ratio. Thanks.

Comments 8: **the authors mentioned method of expression of HIF-1α by counting the cell number expressing HIF-1α， In each field [totally 5 regions] but they did not mention how many fields have been used for this counting? Did they use only one field? Or more? Please add the data to the paper.**

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "Every field was counted twice, and the average percentage of HIF-1α positive cells was taken as the expression of HIF-1α in this field." Thanks.

Comments 9: **it is better the authors add a diagram for easily visual comparison of 99 Tc m –MNLS and HIF1- α in different times and different groups. It would help to readers to better compare the values in these subgroups.**

Reply: Table 2 has been supplied. Thanks.

The updated Table 2:

Table 2 The T/NT of $^{99}Tc^{m}$-MNLS hypoxic imaging and the expression of hypoxia inducible factor-1α in different subgroups.

	$^{99}Tc^{m}$-MNLS hypoxic imaging			hypoxia inducible factor-1α		
	Radiotherapy group	Control group	P	Radiotherapy group	Control group	P
24 h before	2.17±0.19	2.68±0.12	>0.05	45.43%±2.36%	48.26% ±1.70%	>0.05
immediatel y	3.38±0.23	2.78±0.29	< 0.05	87.52%±0.84%	40.52% ±3.24%	< 0.05
24 h	2.78±0.37	2.98±0.16	>0.05	49.12%±3.78%	62.38% ±0.89%	>0.05
48 h	2.22±0.43	3.17±0.76	< 0.05	21.58%±0.89%	74.57% ±2.98%	< 0.05

Associate Editor's Comments:

Associate Editor 1:

Comments 1: **This interesting report examines Changes of Tumor Hypoxia using 99Tcm-MNLS Hypoxic imaging in a rat model. This content review focuses on suggestions I believe the authors may want to address prior to journal submission.**

Reply: It has been supplied in the background: "Hypoxia is an important cause of recurrence and metastasis of malignant tumors. Noninvasive detection of the extent of hypoxic areas of tumors is essential for delineation of radiotherapy target areas and dose."

Comments 2: The Introduction can be more described the field of study and importance.

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "Noninvasive detection of the extent of hypoxic areas of tumors is essential for delineation of radiotherapy target areas and dose. In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells, and then until hypoxic cells get enough oxygen due to the apoptosis of oxygen-enriched cells and when transformed into oxygen-enriched cells, enough doses could be given too. Therefore, monitoring the range and extent of hypoxic area can guide the radiation dose segmentation and the timing of radiotherapy."

Thanks.

Comments 2: **While this paper is a valuable contribution to its field, that importance is not made apparent enough in the Introduction.**

Reply: According to your kind suggestion, the relevant content has been added in the revised manuscript: "Hypoxia is an important cause of recurrence and metastasis of malignant tumors. Noninvasive detection of the extent of hypoxic areas of tumors is essential for delineation of radiotherapy target areas and dose.....Noninvasive detection of the extent of hypoxic areas of tumors is essential for delineation of radiotherapy target areas and dose. In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells, and then until hypoxic cells get enough oxygen due to the apoptosis of oxygen-enriched cells and when transformed into oxygen-enriched cells, enough doses could be given too. Therefore, monitoring the range and extent of hypoxic area can guide the radiation dose segmentation and the timing of radiotherapy." Thanks.

Comments 3: **The Methods are carefully described; however, some issues in statistical Analysis, which might benefit from rewriting.**

Reply: The methods have been revised, especially the statistical analysis: "Two doctors with over 10-year experience delineated the coverage of ROI independently and compared, if there was any big difference, they would re-delineate to determine ROI..... Every field was counted twice, and the average percentage of HIF-1α positive cells was taken as the expression of HIF-1α in this field..... The normality of data were assessed before analysis. If the data were normality， comparisons of measurement data were carried out using one-way ANOVA, pairwise comparison LSD-t test, two independent sample *t*-test and non-parametric Spearman analysis. If not, the Rank sum test was used." Thank you.

Comments 4: **IJR Authors guideline should be checked carefully and all the paper especially titles of abstract and main text rewrite according to it.**

Reply: We have double checked according to your kind suggestion. Thank you very much for your continued attention again.

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) — 3 Apr 2019

Dear AE
The manuscript is now acceptable to publish in IJR.
Best Regards

REFEREE: Reviewer | **Revision** (1) — 6 Apr 2019

Dear AE,
The authors have corrected many points. there is two other points to be clarified:
1- This sentence that has been added in new version is unclear: “In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells, and then until hypoxic cells get enough oxygen due to the apoptosis of oxygen-enriched cells and when transformed into oxygen-enriched cells, enough doses could be given too.” It seems they mean: “In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells; then oxygen-enriched cells experience an apoptotic die and hypoxic cells get enough oxygen and transformed into oxygen-enriched cells, in which, enough doses could be given too.” [????] or something similar [??]. please correct and clarify.
2- The authors mentioned: “….., if there was any big difference, they would re-delineate to determine ROI.” This is questionable the meaning and definition of big difference. in addition, I ask them if there were mismatch between two radiologists [big difference], which one re-delineate the ROI? Both of them? And if they drew a ROI by consensus? It is better the authors clarify and explain these points in paper.
Thanks.

REFEREE: Associate Editor | **Revision** (1) — 8 Apr 2019

Dear EIC,
The article needs minor revision.
Best Regards

REFEREE: EIC | **Revision** (1) — 8 Apr 2019

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.

Thanks.

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.

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

Dear Prof. Kavous Firouznia and reviewers,

We greatly appreciate the editor and reviewers' positive and constructive comments and suggestions on our manuscript. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration. Many thanks for your continued attention.

Yours sincerely,

Style Checking:

[Article Standard: Not OK]

Your manuscript did not follow the journal's standards, please make it as standard according to the journal terms and bellow Instructions.

- Authorship Manipulation

The list of authors in the current revision is different from Revision 0. Please note that any "Authorship Changes" (i.e., order, addition, and deletion of authors) after initial submission should be approved by all authors. Any such changes made after a manuscript has been submitted should be explained to the journal. For more information about the journal policy regarding “Authorship Changes” see the following link.

Click here to read more.

Reply: We haven't changed the author.

Reply to Reviewers' comments:

Reviewer 1

the authors have corrected many points. there is two other points to be clarified:

Comments 1: **this sentence that has been added in new version is unclear: “In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells, and then until hypoxic cells get enough oxygen due to the apoptosis of oxygen-enriched cells and when transformed into oxygen-enriched cells, enough doses could be given too.” It seems they mean: “In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells; then oxygen-enriched cells experience an apoptotic die and hypoxic cells get enough oxygen and transformed into oxygen-enriched cells, in which, enough doses could be given too.” [????] or something similar [??]. please correct and clarify.**

Reply: Thank you very much for your efforts on our work. We are very sorry because of imprecise description, and we have revised it according to your kind suggestion: "In Oxygen-enriched area, enough radiation doses could be given to kill malignant tumor cells; then

oxygen-enriched cells experience an apoptotic die and hypoxic cells get enough oxygen and transformed into oxygen-enriched cells, in which, enough doses could be given too." Thanks.

Comments 2: **the authors mentioned: "….., if there was any big difference, they would re-delineate to determine ROI." This is questionable the meaning and definition of big difference. in addition, I ask them if there were mismatch between two radiologists [big difference], which one re-delineate the ROI? Both of them? And if they drew a ROI by consensus? It is better the authors clarify and explain these points in paper.**

Reply: Yes, this sentence is questionable, and we are so sorry. We have revised it according to your kind suggestion: "If the ROIs were mismatch between the two doctors, they would discuss and reach a consensus about the ROI; then one of the doctors re-delineated the ROI according to the consensus." Thank you very much for your continued attention again.

Reviewer 2:

Comments 1: **Dear Authors: The manuscript is now acceptable to publish in IJR.**

Reply: Thanks for your continued attention again.

Associate Editor's Comments:

Associate Editor 1:Dear editor in chief, The article needs minor revision.

Reply: The current version has been carefully checked and revised, and thanks for your continued attention again.

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: Reviewer | **Revision** (2) — 11 Jun 2019

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

REFEREE: Associate Editor | **Revision** (2) — 12 Jun 2019

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

REFEREE: Associate Editor | **Revision** (2) — 24 Jul 2019

Dear EIC,
The authors should respond to all comments one by one.
1- In “4.2. 99Tcm-MNLS imaging and its biological distribution in tumor-bearing mice”,” 99Tcm-MNLS could be absorbed quickly by tumor (0.68±0.44 % ID/g at 30 min). The percentages of injected dose per gram tumor (% ID/g) at different time points were compared with that at 2 h (Table 1). 99Tcm-MNLS was mainly excreted via the kidneys (mean: 2.98±0.53% ID/g). The ratio of % ID/g in tumor and muscle (T/M) was increased significantly over time within 2 h, and reached 5.36±2.62% ID/g at 2 h, then it began to decrease gradually over time from 3 h.”
None of the underlined numbers are mentioned in this table. Please clarify.
2- In “4.4. Expression of HIF-1α”:
The expression of HIF-1α in A24 h before, Aimmediately, A24 h and A48 h groups was 45.43±2.35%, 87.52±0.84%, 49.12±3.78%, and 21.58±0.89%, respectively; while in the C24 h before, Cimmediately, C24 h and C48 h groups, it was 40.52±3.24%, 48.26±1.70%, 62.38±0.89%, and 74.57±2.98%, respectively (Figure 2)”. The underlined numbers don’t match.
Please clarify
Thank you.

REFEREE: EIC | **Revision** (2) 27 Jul 2019

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (3)

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.

Dear editor and Reviewers,

We greatly appreciate the editor and reviewers' positive and constructive comments and suggestions on our manuscript. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration.

Many thanks for your continued attention.

Yours sincerely,

Reply to the reviewers' comments

Associate Editor 1:

Accept.

Associate Editor 2:

Comments 1 In "4.2. 99Tcm-MNLS imaging and its biological distribution in tumor-bearing mice"," 99Tcm-MNLS could be absorbed quickly by tumor (0.68±0.44 % ID/g at 30 min). The percentages of injected dose per gram tumor (% ID/g) at different time points were compared with that at 2 h (Table 1). 99Tcm-MNLS was mainly excreted via the kidneys (mean: 2.98±0.53% ID/g). The ratio of % ID/g in tumor and muscle (T/M) was increased significantly over time within 2 h, and reached 5.36±2.62% ID/g at 2 h, then it began to decrease gradually over time from 3 h."

None of the underlined numbers are mentioned in this table. Please clarify.

Reply: Thanks for your comments. According to your advice, we have edited it in the revised manuscript: "$^{99}Tc^{m}$-MNLS could be absorbed quickly by tumor (0.243±0.026 % ID/g at 30 min) …The ratio of % ID/g in tumor and muscle (T/M) was increased significantly over time within 2 h, and reached 5.368±2.624 at 2 h, then it began to decrease gradually over time from 3 h."

Comments 2 In "4.4. Expression of HIF-1α": The expression of HIF-1α in A24 h before, Aimmediately, A24 h and A48 h groups was 45.43±2.35%, 87.52±0.84%, 49.12±3.78%, and 21.58±0.89%, respectively; while in the C24 h before, Cimmediately, C24 h and C48 h groups, it was 40.52±3.24%, 48.26±1.70%, 62.38±0.89%, and 74.57±2.98%, respectively (Figure 2)". The underlined numbers don't match.

Reply: Thanks for your comments. We have edited the Table 2 in the revised manuscript: "while in the $C_{24\ h\ before}$, $C_{immediately}$, $C_{24\ h}$ and $C_{48\ h}$ groups, it was 40.52±3.24%, 48.26±1.70%, 62.38±0.89% and 74.57±2.98%, respectively (Table 2, Figure 2)."

OPEN PEER REVIEW

Revision (3)

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** (3) 17 Aug 2019

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

REFEREE: EIC | **Revision** (3) 18 Aug 2019

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.