

April 29, 2021

Dear Editor:

We are grateful for the time you and the reviewers spent thoroughly reviewing our work entitled "Effects of radiation and chemotherapy on adipose stem cells: Implications for use in fat grafting in cancer patients". We have thoroughly considered all the comments of the reviewers and the major revised portions are 1) we have revised figures, improved the figure clarity, and provided the original PowerPoint documents. 2) We have made the suggested changes and added the future directions as part of the summary, 3) we have confirmed that the figure 4 image has been never used before and added a detailed description of the image to the figure legend. 4) We have reviewed the entire reference section carefully to confirm that there are 4 self-cited references (self-referencing rate is 6.9%). Finally, we have reviewed the entire manuscript carefully to improve the language concerning grammar, typos and clarity. We believe that we have addressed each of your concerns and have made the appropriate changes needed. We remain enthusiastic about this report and hope that you agree that it is now worthy of publication in your esteemed journal.

Sincerely,

Ping Zhang, DMD, PhD  
Assistant Professor of Surgery  
Cooper University Hospital  
Cooper Medical School of Rowan University  
401 Haddon Avenue  
Camden, New Jersey 08103 U.S.A.  
E-mail: zhang-ping@cooperhealth.edu

## Answering Reviewers

### **Reviewer #1 (05925555):**

Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Dear authors, Has been a pleasure to read this manuscript on one of the most interesting tool for breast reconstruction. I have outlined the comments and suggestions as follows:

Introduction You stated "The use of ASCs is also thought to produce less donor-site morbidity than conventional vascularized tissue transfer used in tissue reconstruction". Talking about breast reconstruction, I wouldn't compare free flap transfer to fat transplantation procedure, since the indications for those procedures are different.

We thank the reviewer for these insightful comments and suggestions and in direct response have made the suggested changes and thus deleted the part about donor site morbidity and rephrased our opinions as “The use of ASCs is also thought to improve the survival of fat grafting because it can boost angiogenesis via ASCs differentiation into endothelial cells and vascular endothelial growth factor (VEGF) secretion”.

Radiation effect on ASCs endothelial differentiation Your study asserted radiation therapy has deleterious effects on ASC differentiation capacity towards endothelial cells after comparing ASCs harvested from irradiated and no-irradiated breast tissue. However, it's important to highlight how the main donor sites for adipose tissue harvesting are: abdomen, flanks, thighs; usually not irradiated areas. I would placed stress on the effect of radiation therapy on the breast recipient site, which could affect more fat graft survival.

We agree with the reviewer about the importance of the effect of radiation therapy on the breast recipient site, which could affect more fat graft survival. However, the effects of radiation on ASC cells in patients post-radiation remain largely unknown. Our goal here was simply to demonstrate whether ASCs, as a practical source of autologous mesenchymal adult stem cells, can be obtained and used for tissue engineering purposes in patients post-radiation treatment. Interestingly, our study indicated that the number of stem cells harvested did not appear to be affected by radiation as there was no significant difference in the number of ASCs obtained between the radiated and non-irradiated breast tissue. However, the radiation therapy has deleterious effects on ASC differentiation capacity towards endothelial cells which may represent the root cause of chronic wounding and poor fat graft survival in patients. This finding requires further study to determine whether fat grafting assisted with ASC differentiated to a functional EC phenotype can be achieved following post-radiation therapy. This will likely depend upon ASCs' ability to neovascularize secondary to improved graft survival and healing of damaged tissues. We have added this exact point to the “Summary and Future Directions” of our revised manuscript. We hope that this is now acceptable to the reviewer.

**Reviewer #2 (05685573)**

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

In “Availability and growth rate of ASCs in patients treated with radiation” There are no specifics data on the subjects considered in the study (unpublished):

- how many are they, their age, what kind of radiation treatment have they done?

- Please specify the methodology: which procedure was used to isolate the ASCs?
- From the attached figure only it is known that the ASCs are in percentage with respect to the SVF: How did they calculate the doubling time? How many in vitro steps have they performed? Fig. 1 reports the differentiation in adipocytes, osteocytes and endothelial cells, anyway this is not mentioned in the text. In this case also, it would be necessary to add more methodological details. In “Availability of ASCs in patients receiving chemotherapy” We read that ASCs isolated from the breast would be a cellular source for cell-assisted lipotransfer. Wouldn't it still be better to isolate them from the subcutaneous or visceral adipose tissue of the same subject? Do they have data to support this procedure?

We appreciate this point brought up by the reviewer. We would note that this a review article intended to summarize our interesting research findings. We agree that more data such as the characteristics of the experimental population, methodological and results for multipotency differentiation of ASCs would add to this part (Availability and growth rate of ASCs in patients treated with radiation); however, given our recent work on the full manuscript in preparation (will be submitted soon), we chose to not provide more detailed data in this mini-review. We hope that this is acceptable to the reviewer, and acknowledge this within the paragraph discussing these results.

Regarding the ASCs isolation, many of the original studies evaluating fat as a source of stem cells examined liposuction specimens obtained from young, healthy plastic surgery patients. Our group also studied the availability of ASCs from the arm, abdomen, flank, and thigh and found that the harvesting site does appear to make a difference in ASCs yield in the patients. However, little is known about the cell yield and viability of ASCs from patients after exposure to cancer treatment. In these studies, we are focusing specifically on this stem cell's availability as a source of autologous stem cells in cancer patients after receiving radiation or chemotherapy treatment. We hope that this is acceptable to the reviewer.

Fig. 1 Missing data: 1) The number of subjects 2) The standard deviation of each measurement Also, you can't put a “p” value associated with (+) and (-), it takes numbers. The percentages in the columns are misread, they must provide a higher resolution figure.

Thank you for pointing this out; we have revised figure 1 in direct response to the reviewer's concerns and removed the *p*-value and improved the figure clarity.

Fig. 3 The number of subjects taken into consideration is missing.

We appreciate the reviewer's viewpoint here and have added the number of subjects into figure 1 and figure 3.

Fig. 4 Is it an already published figure? If so, the source should be cited, otherwise they must add details about:

- the ASCs.
- which rats were used
- where they injected the ASCs
- which anti-CD-31 antibodies
- what does it mean "human nuclear stain"
- X of magnification shown, etc.

We appreciate this point brought up by the reviewer. The study has been published but the image has been never used before. We have cited this study in the reference list. We have added a detailed description of the image to the figure legend to address the reviewer's concerns and to improve clarity.

**Reviewer #3:** (00504362)

Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

This is a very interesting and well-written review on a topic where the authors have important contributions. The title reflects the main subject of the manuscript and the abstract correctly summarize the content of the manuscript. The only concern this reviewer has is in regards to adding an extra section such as Future directions, highlighting the new directions in which current research on this topic is moving on.

We very much thank the reviewer for these insightful suggestions; we have further discussed this interesting point and added the future directions into the summary part of the manuscript.

## **Science editor**

### **(1). Scientific quality:**

The manuscript describes a review of the Effects of radiation and chemotherapy on adipose stem cells. The topic is within the scope of the WJSC.

(1) Classification: Grade B, Grade C and Grade B;

(2) Summary of the Peer-Review Report: The authors found a very interesting and well-written review on a topic where the authors have important contributions. However, the questions raised by the reviewers should be answered; and

(3) Format: There are 4 figures.

(4) References: A total of 59 references are cited, including 2 references published in the last 3 years;

(5) Self-cited references: There are 7 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated; and

We have checked that there were 5 self-cited references. However, we have removed one more self-cited reference (total is now 4). The self-referencing rate now is 6.9%. Just to be clear the self-references we identify remaining in the manuscript are references 22, 24, 44 and 51.

(6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

## **(2) Language evaluation:**

Classification: Grade B, Grade B and Grade B.

## **(3) Academic norms and rules:**

No academic misconduct was found in the Bing search.

## **(4) Supplementary comments:**

This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC.

## **(5) Issues raised:**

(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

We have revised figures, improved the figure clarity, and provide the original PowerPoint documents.

(2) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights.

The image showed in figure 4 has been never used before it's not a published figure. We have cited this study in the reference list. We have revised the figure legends to improved clarity.

For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]".

And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable; and

(3) The column should be minireviews.

**(6) Recommendation:**

Conditional acceptance.