

**To the BGP Editorial Office**  
**Reviewer answering form**

Reviewer #1

We highly appreciate your positive feedback and are very pleased with your constructive comments. Thank you.

Reviewer #2

Thank you for your interesting remarks. Please find below a response to your comments:

- 1) We started this systematic review with the negative impact of radiotherapy on tissues in mind since we are confronted with this on a daily clinical base. We do agree with the reviewer that in the manuscript we generalize our analysis towards sclerosis rather than particularly radiotherapy. Therefore following your suggestion we modified the title.
- 2) Although the topic of this manuscript seems particularly focused, there is a multitude of interactions of ADSCs and their bioactive molecules with surrounding matrix elements and cells. Each of these interactions are widely described by fascinating papers and reviews, amongst which the excellent review by Shukla, Lipi et al., amongst others. Since we particularly focused on the impact of ADSCs on sclerosis, we integrated those papers we found to be most related to this perspective.
- 3) In this review we mention that the complex and sometimes even contradicting nature of some ADSC effects, can be a limitation to the ADSC treatment. In a clinical context we extensively use ADSC transplantation after tumor resection and radiotherapy. This clinical transfer of fatgrafts and the intrinsic ADSCs is extensively reported in literature (and beyond the scope of our study) Although there are minimal adverse effects (for instance, activation of oncologic sleeper cells by the ADSCs in the fatgrats have not be reported), the major drawback of these transfers though, is the relatively high percentage of fatgraft absorption and the unpredictable outcome. It is not clear yet, whether the cause is due to the technique used, or the number and quality of the ADSCs involved. The suggestion of the reviewer is great and we surely will look further into the use of the secretome of ADSCs to overcome cell transplantation limitations.
- 4) Indeed, inflammatory cells can be diagnosed in histological sections, but not 'the increase of IL6-and IL8'. We have removed this section of the sentence.
- 5) We corrected this in the manuscript.
- 6) Thank you for your remark – we changed this.
- 7) We mentioned the role of MMP-2 and MMP-9 in the accumulation of the ECM. We focused on the overall interactions not so much on the particular detailed pathways.
- 8) Keywords were added.

Reviewer #3

We thank the reviewer for the interesting remarks. Please find below the response to the comments:

- 1) ADSCs produce these bioactive molecules, followed by the secretion ('release') in the wound environment. As a result the expression is increased for instance in tissues after treatment with fatgrafts.
- 2) This is a great suggestion indeed. The downregulation of TGF-B1 by high concentrations of HGF, could be one of the effects underlying the decrease of TGF-B1 concentrations when administering ADSCs. We have added this in the paragraph.
- 3) In the review, we encountered several contradicting effects when discussing the anti-fibrotic mechanisms of ADSCs, depending on the perspective of the key factors. However, this was indeed not explicitly highlighted in the section about angiogenesis. We have therefore added your suggestion at the end of that section.