Reviewer’s report

Title: Non-rigid image registration of 4D-MRI data for improved target delineation of moving tumors in radiotherapy

Version: 0 Date: 30 Dec 2019

Reviewer: Andreas Wetscherek

Reviewer's report:

I had a chance to review a previous submission of this manuscript and it has improved and almost all my previously made points were addressed. But I would strongly encourage the authors to acknowledge limitations in the discussion, as it helps the reader to put the work into context and identify remaining challenges. Two points stood out:

1.) From the description of the registration methods (p. 7) I had to come to a different conclusion than the authors, in particular I understand that the respiratory phases in the nn-Reg method do not contribute equally (though it would be possible to realize an nn-Reg scheme with equal contributions by choosing a weighted averaging process, i.e. $4/5\times\{3/4\times[2/3\times(1/2\times p_5 + 1/2\times p_4) + 1/3\times p_3] + 1/4\times p_2\} + 1/5\times p_1\}).$ With the current description I understand that phases 5, 4, 3, 2 and 1 contribute 1/16, 1/16, 1/8, 1/4 and 1/2 to the intensity of the nn-reg image in phase 1, instead. This might be a misunderstanding from my side, but the reader might come to the same conclusion. From this point of view the result that the dir-Reg method leads to a lower CoV, respectively less noise than the nn-Reg method is therefore to be expected. However, potential advantages of the nn-Reg method (in particular in case of large deformations) would be masked by a suboptimal choice of weights. It would be great if the authors could therefore reflect on the methods description and either describe the weighting factors leading to equally contributing phases (if used) or drop this statement and acknowledge it as a limitation in the discussion (e.g. p.12 around l.240).

2.) Considering the intended use case of radiotherapy, there are some additional limitations to this study, e.g. the use of a narrow-bore MRI scanner preventing set up of the patient in radiotherapy treatment position, which makes it unlikely that the images can indeed be compared to 4D CT. Correction for gradient-nonlinearity is essential for accurate localization in radiotherapy.

Are the methods appropriate and well described? If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls? If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown? If not, please explain in your comments to the authors.

Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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