Author’s response to reviews

Title: Quantification of Heterogeneity Observed in Medical Images

Authors:

Frank J Brooks (kkerns@radonc.wustl.edu)
Perry W Grigsby (pgrigsby@radonc.wustl.edu)

Version: 3 Date: 11 January 2013

Author’s response to reviews:

Dear Editor,

We again thank you and the reviewers for your hard work. In addition to addressing the remaining minor concerns of the reviewers, we’ve taken this opportunity to address some minor wording/clarification issues as well as to correct a few niggling grammatical and typographical errors. These changes have been detailed below.

Sincerely,

Frank J Brooks and Perry W Grigsby

REVIEWER GG - MINOR REVISIONS

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1) "There have several previous attempts to objectively quantify tumor heterogeneity [6–10]"

Changed to "Several attempts to objectively quantify tumor heterogeneity have been published previously [6–10]."

2) "Table 2: the mean value of the p-values for the oncologist is still incorrect."
One of the table values was incorrect and has been corrected. Thanks again.

REVIEWER GT - MINOR REVISIONS

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1) "In the first version of the paper the authors claimed that they used FBP for reconstruction. In the second version they mentioned OSEM. Which is correct?"

OSEM is the correct method. The statement about FBP in the original manuscript was totally incorrect.

2) "The CSI statistics introduced in eq.3 is sometimes referred to as CSISA (shape aware), sometimes as CSI. It is better to start using the SA subscript in eq.3 and use in all the manuscript. Also when they introduce CSISU (lines 182-195) the authors should use this symbol (CSISU) and use it throughout the manuscript. Note that lines 202 and 203 the authors used CSIA and CSIU, which should be corrected to CSISA and CSISU,"

In an effort to keep the notation as clean as possible, in Equation 3 we define our statistic with no subscript and then consistently refer to it throughout the manuscript as being shape aware. In the first paragraph of the Results and Discussion, we denote a shape unaware version of our statistic with a lowercase "u" subscript. This notation appears in this paragraph and in only one other sentence (3rd paragraph of the Results and Discussion section). We hope this adequately abates any confusion or inconsistencies in notation while employing as few subscripts as possible.

3) "line 242. Please report the p-value corresponding to that value of ro."

Suggestion accepted as given.
We disagree. This paragraph speaks to an anatomical concern that will become important when our statistic is employed clinically. In short, the extremes of shape (e.g., rings vs blobs) correspond to tumors in different anatomical locations and orientations relative to the PET scanner. We believe that it is important for the oncologist to clearly understand that, for example, all ring-like objects do not yield a certain value of our heterogeneity statistic nor does a given value always imply a ring-like shape.

2) "The discussion on the application to 3D images is important and should be expanded. For instance the strategy of using the Euclidean line could in theory be used also for a 2D image. Also, the two different strategies (Bresenham algorithm vs. Euclidean line+interpolation) should be discussed a little bit better. The details of the type of interpolation necessary for the Euclidean line could be discussed."

The point is well taken and we've struggled with deciding how much additional consideration of three dimensions should be included here. Our original intent was solely to introduce our ranking statistic, not to prove it's clinical value (which is where the extension to 3D manifests). In an effort to keep the paper focused and brief, we grudgingly truncated the discussion of three dimensions to an admittedly incomplete status. We have, however, included a bit more text about some key concerns when handling 3D images. Please see the discussion subsection, "Extension to Three Dimensions", highlighted in blue.

MINOR ADDITIONAL REVISIONS BY THE AUTHORS

1) The first five sentences of the Background section have been re-ordered and
slightly re-worded in an effort to improve the flow of the text. These changes are highlighted in blue.

2) Corrected a split-infinitive in the second-to-last paragraph of the Background. This change is highlighted in blue.

3) Corrected the word "hydric" to "hybrid" in the 3rd sentence of the "Test image database" subsection.

4) For clarity, we added the word "grayscale" to the first sentence of the "Test of shape dependence" subsection of the Methods section.

5) In the 3rd paragraph of the Results and Discussion section, as well as in the caption for Table 2, we replaced superfluous wording with the symbol $\zeta_u$.

6) At a reviewer's request, we added a p-value to rho in the 5th paragraph of the Results and Discussion section. In spirit, this rendered the "approximately zero" redundant and we thus removed it.

7) Added an omitted "the" after "However," in the 3rd sentence of the "Handling large images" sub-subsection.

8) Added "for" before "magnetic" in the 2nd sentence of the "Vectorization of $\zeta$ within one image" sub-subsection.

9) For clarity, we added a sentence to the 1st paragraph of the "Applications & Future Work" subsection which specifies the dimension of the application. This change is highlighted in blue.

10) A few superfluous words have been removed from the 5th sentence of the Conclusion. This change is highlighted in blue.

11) Corrected the values of local homogeneity for image set A to be given to four
significant figures as is in the rest of the table.

12) All table values were scrutinized for accuracy and several typographical errors have been corrected. We note that these corrections in no way changes our results or conclusions.