Author’s response to reviews

Title: Texture analysis on MR images helps predicting non-response to NAC in breast cancer

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Author’s response to reviews: see over
Dear Dr Paolo Bruzzi,

It is my pleasure to hereby submit the revised version of our manuscript entitled "Texture analysis of MR images helps predicting non-response to NAC in breast cancer" for publication in BMC Cancer.

This letter is keen to provide a point-by-point response to all concerns made by the three reviewers, with a description of the changes made in the text. The text has been reviewed by an English speaker with scientific expertise. For all subsequent correspondence, please write me at the above address.

Yours Sincerely,

Nicolas Michoux, PhD.

Conflict of interest: none in respect to this work and its publication.
Financial interest: none in respect to this work and its publication.
All authors have agreed to the submission to the journal and that the manuscript is not currently under submission in any other journal.
Detailed response

______________________________ Reviewer 1

1. All acronyms, such as pCR and HER2, are not explained in the text.

   As suggested, acronyms are now explained (p4, L69-70).


   The correction has been made.

3. Row 225: “all calculations” refers probably not only to the subtitle Statistical analysis, but is under that title. Please clarify.

   The sentence has been modified as follows: “All calculations (texture computation and statistics) were done with Matlab (Matlab R2011b, MathWorks, Natick, MA, USA).”

4. The tables should be self-explanatory. Please explain all acronyms in the captions or in the table contents in Tables 2, 4 and 5.

   All acronyms are now explained as suggested. For sake of clarity, acronyms of texture parameters given in Table 3 were not repeated in Table 4 and 5.

5. Table 4: the accuracy of texture analysis is probably not four digits. The number of digits should follow the accuracy.

   As suggested, data are now presented in taking into account the number of significant digits only.

6. Give the units for “Dynamics” in Figure2

   The unit has been added to Figure 2.

7. Row 187: what is visual texture? The word “visual” is in general connected with human vision, while texture analysis is based on numbers and expressed numerically.

   In machine vision and image processing, texture refers to the visual characteristics of an image. The term “visual” is generically used because of the parallel with an actual physical object whose surface is interpreted according to its perceived visual and
physical properties. The statistical metrics proposed by Haralick and others are indeed used to translate the “visual” aspect more or less coarse, fine or granular of the image into numbers and expressed numerically.

8. Rows 304 to 306: this sentence is unclear. It is obvious that textures in general differ according to some parameters only.

We agree with this comment. For sake of clarity, the second part of the sentence has been removed.

9. Rows 315 to 316: also this sentence is unclear to me. Please explain.

The sentence has been reformulated as follows: “None of these approaches is superior to the others since their effectiveness basically relies on the visual properties of images to which they are applied. Combining various texture methods may improve the characterization of breast lesions as demonstrated by our data.”

10. You have performed the analysis on subtraction images. Please discuss the application of texture analysis to such processed images. Subtraction can also produce systematic texture errors.

Detection and characterization of breast lesions are routinely performed on subtracted images in clinical practice, due to the attenuation of the normal parenchymal background enhancement. As a result, texture analysis was applied to subtracted images too, with no specific modification of the original algorithms of texture (GLCM or RLM). We agree that the subtraction process may induce error as any image post-processing, which may deserve a specific investigation. However, no obvious error was reported during the consensual review made by the three expert radiologists.

The following sentence has been added to the Limitations: "In this pilot study, a single subtracted MR image was evaluated at a specific time point corresponding to the enhancement peak on intensity time curves. Subtracted images have been chosen because of the attenuation of the normal parenchymal background enhancement.”

As texture analysis is a quite novel approach, it is important to state the software used and the background physics. As this is not the aim of the article, I suggest to state more clearly in the introduction where a complete description of the technique can be found (as in the citations 28-29) and which software was available.

In the Introduction, a sentence (see below, question Pg5, R84) and a reference [31] for a complete and practical description for texture analysis of MR images have been added.
Pg 4, R69: state what pCR stands of (pathological Complete Response)

As suggested, the acronym has been detailed.

Pg5, R84: revise English in the sentence “…distribution of the grey levels in the image; both resulting…”

In the *Introduction*, the paragraph introducing texture analysis has been reformulated as follows: “Texture analysis allows describing the MR appearance of the tissues and of their changes in terms of fineness, coarseness, smoothness, granularity, homogeneity or periodicity [29]. These attributes are related to the local spatial distribution of the grey levels in the image matrix and can be captured by using metrics, called texture parameters. In texture analysis of MR images, it is assumed that the distribution of the grey levels results from the underlying ultrastructural properties of tissues affected by the disease processes; an assumption that has been validated by finding correlation between MRI texture patterns and tissue changes at histology [30]. Numerically, texture can be described by using $n^{th}$-order statistics, spatial frequency or structural primitives, the first two approaches being the most commonly used. A practical description of the concepts and methodologies for texture analysis of MR images has been proposed in [31]. First studies in breast MRI, while remaining to be validated, showed that certain pre-treatment texture parameters (based on high order statistics) may help evaluating breast tumor response to NAC [32-34].”

Pg5, R87-88: the classification of texture analysis should be stated more clearly.

As suggested, the type of texture analysis that can be performed has been detailed (see above).

Pg5, R93-95: I suggest to leave all the comments on statistical approach in Materials and Methods. Also the comment on the analysis of biological parameters is not well integrated in the context of the explanation of the study.

As suggested, the comments on the statistical approach were removed from the introduction.

Pg 6: What is the study period? State more clearly weather only pure IDC or also IDC with DCIS were included. To clarify the overall number of tumors diagnosed and how many of them were IDC and were included could be interesting. Why did all patients undergo MRI? A diagnosis of IDC is not an indication.

All details are now given in p7, in the *Methods*. Precisely: “This two-years retrospective study was approved by our institutional ethical committee (Comité
Written informed consent from the patients was not required. All patients had an invasive carcinoma diagnosed on core-biopsy specimen. To obtain a homogeneous histologic sample for texture analysis, only invasive ductal carcinomas (IDC) with and without ductal carcinoma in situ (DCIS) were included in this pilot study. A baseline MRI as well as a pre-operative MRI to evaluate response to NAC was performed in all patients.

Pg 8: there are some imprecisions in the technical parameters. To perform breast MRI a dedicated breast coil is essential. From images and given parameters, I believe a dedicated coil was used but this is not clearly specified. Slice thickness is 1.25 mm? Please specify also the matrix and fat suppression technique. Did the MRI study include also T2w sequences and DWI? Even is this sequences were not analysed in this work, I suggest to specify the whole protocol (it is not necessary to specify parameters of the sequences not analysed in this work). Bracco is an Italian company, and the dose according to published data is 0.1 mmol/kg.

As suggested, all details have been given in the paragraph MRI sequence (p9).

Why is the third post-contrast image used? Usually first or second post contrast image should be used for the analysis (see Kuhl, Radiology 2007 and EUSOMA guidelines).

Image analysis was indeed performed on the post-contrast image corresponding to the maximum enhancement peak on intensity time curves. This time point corresponded to the second (third dynamics) post-contrast images. We corrected this imprecision in the text.

BI-RADS lexicon uses the definitions “mass enhancement” and “non mass enhancement”. I suggest to use these definitions, rather than “pattern”.

As suggested, the terminology has been updated.

Table 2 does not show only mass or non mass. I suggest not to cite it like it is now.

The second paragraph in the Results has been reformulated for sake of clarity.

Pg 14: insert reference number for cited articles (Uematsu, Pickles – 24, 257). Also, cite authors names and not only citation number.

References have been added.
TITLE: Please modify the title to match the methods and results

The title has been modified as follows: “Texture analysis on MR images helps predicting non-response to NAC in breast cancer”.

ABSTRACT: Change “Pathological response was defined as .....” to “Pathological complete response was defined as .....”

As suggested, the sentence has been modified.

INTRODUCTION: 1. The authors should more clearly state why there was a need for this study. 2. What is the biological basis of textural analysis on NAC prediction?

The purpose of the study is stated on page 4, line 73-75. The biological basis of textural analysis on NAC prediction remains to be investigated. However, the relevance of texture analysis of MR images to characterize tissues changes with disease or therapeutic intervention has been proved (see reference 30). The paragraph introducing texture analysis has been reformulated to better show the relevance of the technique (see response to reviewer 2).

1. How the tumor size in pathology was measured should be detailed, for example, in case of scattered tumor foci or diffuse lesions.

When only one tumor lesion is present, the size of the foci is measured histologically. The overall dimension of the foci is given when they are adjacent and part of a single lesion pre-chemotherapy. When the foci are distant, each of them is measured. In diffuse tumor lesions, the overall size again is given. These comments have been added to the text (p7, L133-137).

2. How was tumor cells density measured?

The density of tumor cells, compared to the previous biopsy, was analyzed, allowing the classification of the tumor following the grading system of Miller-Payne (5 grades). The tumor grade was evaluated with the Nottingham score (p8).

3. Please confirm if breast MRI was performed with breast coil or body coil.

See response to reviewer 2.
4. Image analysis: please use the correct lexicon for the description of “Lesions were categorized into mass pattern and non-mass pattern”.

See response to reviewer 2.

5. In Table 1, how the tumors were graded?

The tumor grade was evaluated with the Nottingham score (p8).

RESULTS: 1. Please add subtitles to the results to make them clearer.

As suggested, subtitles have been added.

2. Many numbers in Table 1 and Table 2 did not match. For example, PR-positive was 42 in Table 1 but was 41 in Table 2.

This imprecision in Table 2 has been corrected.

3. The percentages shown in Table 2 were very confusing.

In order to be consistent with the approach of the paper (i.e. the search for a predictive model of response), proportions are now estimated as follows: % of NR patients with a given feature within all patients (NR+PR+CR) having this feature. The same calculation is undertaken for CR, PR and CR+PR patients.

Then, \( p \)-values assess the statistical significance of the relationship between response (NR or PR+CR) and features. If a \( p \)-value < 0.05 is observed for a given feature, then we can conclude that patients’ response is associated to that feature. If a \( p \)-value > 0.05 is observed, then the null hypothesis that there is no association, cannot be rejected.

Reformulated as described above, and with a detailed legend, we think that Table 2 is understandable.

4. In Table 3, please add an illustration for kinetic definition.

As suggested, the definition of the kinetic parameters has been added to Figure 2.

5. In Table 3, references should be provided for the definition of textures.

As suggested, references [29] and [40] have been added.

6. In Table 4, so many numbers were presented for the textural parameters. What did these numbers mean? Unless the readers can understand, it made no sense to present in this way.
Data are presented for a potential comparison with other study such as the one performed by Gibbs et al [33], and may be used in a reproducibility analysis of texture parameters. However, the table has been reformatted for sake of clarity.

7. What were the technical and biological factors affecting the measured numbers in the textural analysis?

Mainly, the values of the texture parameters depend on the spatial resolution of MR images, on the signal to noise ratio, as well as on the type of contrast enhancement achieved by the MR sequence. This obvious dependence is not reminded in the text. However, the reader may now refer to the reference [31] for a practical description of texture analysis of MR images. The way biological factors affect the values of texture parameters is complex. As shown by Zhang et al [30] in brain white matter lesions, MRI texture patterns and tissue changes on histological analysis are correlated. To date, changes in texture parameters induced by NAC remain to be investigated. We agree that this question should be central in any future study of texture analysis in a context of assessment of response to treatment. A study design including histological analysis would thus seem mandatory.

8. Similarly, Table 5 was with too many numbers. Please consider how to convert the table message into text.

Table 5 has been reformatted. AUC and cut-offs values have been preserved as they are essential in ROC analysis.

9. More detailed caption is needed for Figure 4.

Legend of Figure 4 has been detailed as follows: “Pixel-level analysis of breast MRI texture in a CR patient with a mass enhancement. Are respectively displayed, a) the axial subtracted image and the maps based on b) contrast, c) correlation, d) difference variance, e) energy, f) entropy, g) inverse differential moment (which is correlated with the homogeneity parameter), h) sum average and i) sum variance from the GLCM, with mean value estimated on a 3x3 neighbourhood around the pixel of interest then normalized on the 0-255 range. Individual texture parameters reveal different local and regional statistical properties of the grey level intensity between (and respectively within) breast lesions and normal parenchyma. Combination of all or parts of the texture parameters helps classifying patients according to their response to NAC.”