Author’s response to reviews

Title: Radiomic features from MRI distinguish myxomas from myxofibrosarcomas

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Version: 1 Date: 01 Mar 2019

Author’s response to reviews:

Dear Editor,

We appreciate the comments from the reviewers. We have revised the manuscript incorporating the comments by the reviewers, which have improved the manuscript. Please see our responses below inline.

Reviewer reports:

I-M. Noebauer-Huhmann (Reviewer 1): In this single-center, retrospective case-control study, radiomic parameters and conventional MR imaging features of 27 patients with myxofibrosarcomas are compared with those of 29 patients with myxomas.

The topic is clinically important, as myxofibrosarcomas are often considerably heterogeneous, and biopsy specimen may not contain the most representative areas. The study is very interesting, as the use of radiomic parameters is evolving, may revolutionize MR interpretation, and has hardly been investigated in soft tissue tumors so far.

Specific comments:

1) The title is adequate.
2) Abstract:

- The text is clear.

- I very much agree to the first parts of the conclusion. The last part ("Radiomic texture features best differentiate myxofibrosarcomas from myxomas using T1-weighted sequences…") does not completely follow from what has been tested; T2w sequences and T1w sequences post contrast agent administration or others could not be investigated in comparison to T1w sequences.

=> Authors’ response: We thank the reviewer because the statement could be misunderstood. We meant radiomic features performed best for differentiating myxomas from myxofibrosarcomas compared to T1-weighted signal intensity and tumor volume features. We have revised the conclusion to state this.

3) Keywords:

Keywords should be added.

=> Authors’ response: Keywords have been added.

4) Approval:

Institutional review board approval and HIPAA compliance: approved/compliant.

5) Introduction:


- In the very nice article of Kaya et al. Skeletal Radiol. 2008; 37(12):1085-90, dealing with the growth pattern of myxofibrosarcoma, MFS is described as "hypointense", but in fact is almost isointense to skeletal muscle in their fig 1 (in their figure 3, the legend might be slightly mixed); so the reference is correct. Otherwise, you could use the reference of Petscavage-Thomas RadioGraphics 2014; 34:964-980 (wonderful article, however a review).

=> Authors’ response: We have included the Petscavage-Thomas reference in addition to the Kaya reference as suggested by the reviewer.

- Page 11, line 220: do you mean fluid sensitive fat saturated sequences? If so, please replace "T2/STIR" by "T2w FS/STIR"; otherwise, differentiation of muscle with fatty atrophy may be an issue.
Authors’ response: Adjacent normal muscle had to have no signal abnormality on fluid-sensitive sequences (T2w FS/STIR) because tumor cells have been found in the peritumoral edema and these tumor cells may affect the T1 signal intensity measured.

6) Materials and Methods:

- The total number of patients is impressive for this entity.

Authors’ response: We thank the reviewer for recognizing the difficulty in accruing a sample of this size given how rare these diagnoses are.

- As the authors mention correctly in the discussion, the main limitation of the study is the non-uniform pre-treatment MRI technique, with inconsistent use of T2w sequences. Also, the T1w contrast may vary with different field strength and sequence parameters. Please mention that the T1 contrast was comparable, or could be used, as the contrast vs. muscle was similar (I personally have got no experience with a field strength of 0.6T) if applicable.

Authors’ response: We did not analyze the contrast-enhanced T1-weighted sequences because the injection delay time was not uniform across patients (~2-10 minute delays) and we thought this would introduce more noise into the analysis and not be definitive.

- Histopathology: one of the criteria for the grading of MFS is the presence of necrosis. MFS Grade 1 and Grade 3 differ significantly (please also see discussion).

Authors’ response: Agree with the reviewer that necrosis is important for the histological diagnosis of Grade 3 MFS. What we have noted is that diagnosis from core needle biopsy is highly dependent on the area sampled within the tumor. We have noted just within the last 3 months at our institution a case where a patient had to have a repeat biopsy because the senior author thought the lesion was grade 3, but the histological diagnosis from a biopsy performed at an outside institution was grade 1. The repeat biopsy showed grade 3 MFS. We have made this change as suggested by the reviewer.

- Radiomics:

The radiomics approach of the paper is sound. The authors extracted radiomics features, and used a random forest classifier to classify tumors. They evaluated if this classification is better than more simple features such as volume, and use cross validation to separate training and test sets.

One comment regarding the feature importance: this is an interesting result of the paper. A possible added value would be to repeat this feature selection with random sub-samples of the data set to test up to which top ranked feature it is stable.
7) Results:

- It would be important to discriminate between solid tissue and necrosis. Were there differences in Normalized T1-weighted signal intensity between G1, G2, and G3? Presumably, the number of patients in each group would be too small for statistics, but it may be interesting to visualize this result. This is also interesting for subtle differences in homogeneity measurements and the normalized T1-weighted signal intensity. Please comment.

=> Authors’ response: We have now included a diagram of the normalized T1-weighted signal intensity between G1, G2 and G3 as a new figure as suggested by the reviewer.

There is no difference regarding the normalized T1 signal intensity between groups (p=0.88 by Kruskal-Wallis rank sum test).

- If you combined the information of volume measurement and T1w signal intensity, and calculated the AUC, would the results using radiomics features still be better than the combination of conventional parameters?

=> Authors’ response: The classification model built upon radiomic features obtained an AUC of 0.885 (accuracy=0.839, sensitivity=0.852, specificity=0.828), which outperformed the classification model built upon the T1SI values (p=0.039, DeLong test), the classification model built upon volume features (AUC=0.838, p=0.285 by DeLong test), and also the classification model built upon combined T1SI and volume features (AUC=0.867, p=0.508) as shown in Figure 3.

8) Discussion:

- The study is very interesting, and the results are novel.

It would have been interesting to correlate the T1 signal of different intralesional areas with the final histology within this area. The hypothesis of protein content and hemorrhage is interesting but a bit speculative; necrotic areas may have variable content. Please comment.

=> Authors’ response: This study was a retrospective study and it was not possible to evaluate the gross resected specimen. Prospective studies would be needed to evaluate this, and is a future line of research in our lab. In addition, at our institution neoadjuvant radiation therapy is used – which changes the degree of hemorrhage and necrosis within the post-treated tumor compared to the pretreatment tumor.
- In the discrimination of MFS and Myxoma by MRI, the AUC comparison of conventional MR features (please also see section "results") and radiomics it would have been desirable to include several crucial conventional MR parameters: T2w signal (without FS) and T1w post contrast series would have been helpful.

=> Authors’ response: T2w signal was available in ~ 50% of patients and STIR sequences were available in approximately 50% of patients. Losing 50% of the sample size dramatically decreases the power to detect any association and may result in false conclusions. We chose to not analyze the T2w sequences for this reason. We thought it was more scientifically appropriate to comment on the sequence we had the most power to evaluate.

We also did not evaluate T1w post contrast series. Not all patients had T1w post-contrast sequences. This was because the mass was incidentally discovered by MRI and the ordering clinician did not order a contrast enhanced MRI study after the initial MRI study because he/she thought biopsy was needed and the contrast enhanced MRI study would just delay the inevitable biopsy. This is because the imaging characteristics of a lesion with contrast enhanced MRI is often not pathognomonic and would not preclude biopsy.

The second reason we did not analyze T1w post contrast studies was because the interval between injection of contrast and imaging was not standard. These patients are often hand-injected with between 2 and 10 minutes of delay. Introducing this noisy T1w post-contrast studies could result in erroneous conclusions.

The study very nicely shows, however, that even in cases of incomplete or inconsistent preoperative MRI examinations, radiomics can help to predict whether a lesion is more likely to be myxoma or MFS (irrespective of the grade).

- Page 15, Line 314: the references of Kaya, of Murphey and of Abdelwahab do not really report the capability of T1w sequence to differentiate between benign and malignant myxoid tumors. Please replace by another reference.

=> Authors’ response: We have changed this to the reference of Petscavage-Thomas et al.

- Page 15, Line 318: core biopsies should be image-guided, and MR sequences seem helpful for intralesional targeting also of MFS (we have seen that targeting is very accurate, and that inclusion of necrotic tissue in one of the samples may even add to the correct grade specifically in MFS (Eur Radiol 2015; 25:2041-204)).

=>Authors’ response: We agree with the reviewer. Unfortunately, a fair number of biopsies are still performed by surgeons without imaging guidance. We have included that targeted biopsy of necrosis may add to correct grade and the reference in the revised manuscript.

- Page 16, Line 323: The sentence "We have shown that MRI image-derived radiomic features can quite accurately differentiate two extremely rare tumor types (myxomas and myxofibrosarcomas) which are challenging for pathologists and radiologists" represents the conclusion and could be moved there.
However, the present study represents an excellent radiomics feasibility study. An issue is the comparison of a selection of conventional MR parameters with radiomics. The conclusion could focus on the strength of the study, which is the novel method; radiomics may also be used to better use discriminatory information out of suboptimal MRI (e.g. from teleradiology…).


Authors response:

The Corino manuscript is an interesting manuscript. It was not significant and based on a small sample size, which they attempted to split into 60-30-10 % datasets for training, validation and testing. This sample is too small to have any power and the result observed is what was expected. One challenge we have noted is that several different sarcoma histologies are grouped together. Today, we would not group pancreatic adenocarcinoma with neuroendocrine tumor of the pancreas with intraductal papillary mucinous neoplasms of the pancreas because they are different tumors with different histologies and different behaviors. We wanted to focus on a single tumor type to really elucidate the relationship between imaging and the tumor biology.

The Crombe manuscript is also an interesting manuscript. However, in the aggregation of tumor types they include known chemosensitive sarcomas (myxoid round cell liposarcoma and synovial sarcoma) with those that are usually less chemosensitive sarcomas (MPNST). Here, our concern is that the findings are not treatment findings, but findings related to differences in sarcoma subtypes and potentially their responses to chemotherapy.

9) References:

Some of the references mentioned above could be added. Otherwise, the references are adequate.

11) The text of the article is clear.

=> Authors’ response: Thank you.

12) The nomenclature is correct.

=> Authors’ response: Thank you.

13) Tables:

The tables are adequate
=> Authors’ response: Thank you.

14) Figures/ figure legends:

Fig.1 is very impressive and informative. Please submit it in higher resolution.

Fig. 2 please see above

Fig. 3 please see above.

=> Authors’ response: We have revised the figures and included high resolution figures (600 dpi)