

Peer Review File

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Reviewer A:

Question 1: Introduction: Too long. Some of the basic issues could be summarized.

Response: Thanks for your constructive suggestion. We have summarized some of the basic issues, and greatly shortened the introduction section (Pages 5-6 lines 77-122, in introduction section).

Question 2: Introduction: Study emphasis to differentiate malignant from benign circumscribed lesion.

Response: Thanks for your suggestion very much. We have summarized some of the basic issues, and focused on the identification of round-like tumors with circumscribed or obscured margins in our study (Pages 5 lines 86-91, in introduction section).

Question 3: Introduction: I would like to point out that current imaging protocol undertakes ultrasound and/or MRI, or contrast-enhanced mammography in almost all lesions primarily seen in mammography since biopsy may be required. Therefore, more effort to analyze the lesion seen in mammography does not play a significant role except in microcalcification.

Response: We are very grateful for your comments. Digital mammography (DM) is a cost effective and commonly used method for detecting breast tumors in clinical practice, so we want to explore the value of DM-based radiomics for the differential diagnosis of round-like breast tumors.

Question 4: Introduction: In relation to the second objective of identifying triple negative cancer from non-triple negative cancer, I would like to explain that the current imaging aim is to identify smaller and smaller node negative cancers in all modalities including in mammography to promote early diagnosis of breast

cancer. As you also mentioned, triple negative cancers are often large and palpable. They frequently have large positive axillary nodes. These factors help to identify them even when they have circumscribed outline in mammography.

Response: Thanks for your suggestions. Your opinion is very reasonable. Triple negative breast cancer (TNBC) is really very characteristic. In daily work, some TNBCs are usually large when they are found and accompanied by positive axillary lymph nodes, in this case, these lesions are easily diagnosed as malignant lesions. It is necessary to increase the early detection rate due to their poor prognosis. The cases in our study also included many TNBCs without positive axillary lymph nodes(16/23) on mammogram and larger NTNBCs. At present, radiomics has become a hot topic in the preoperative lesions classification and etc. Therefore, we want to explore whether DM-based radiomics can distinguish round-like TNBC from NTNBC. In view of your comments, I have revised this section again (Page 5 lines 92-100, in introduction section).

Question 5: Methodology: Very disappointing to note that 31 cases of dense breasts were excluded in the study. These are the cases at risk for breast cancer and are of great interest to mammographers.

Response: We also deeply regret it. It is really difficult to recognize the lesions on mammograms of dense breasts, so the ROIs cannot be determined, and the radiomics analysis of which cannot be carried out. Anyway, we still appreciate your comments, and we will pay attention to these cases in the future.

Question 6: Methodology: No analysis of the initial digital mammograms to compare with the radiomic analysis.

Response: Thanks for your constructive suggestions. In the method section, we have added the analysis of the initial DM characteristics for the identification of benign and malignant tumors, and for TNBC and NTNBC (Page 8 lines 161-174). Meanwhile, we have added the corresponding results (Page 11 lines 237-241, Page 12 lines 258-260, in result section) including 2 tables (Page 21 lines 442-444, Page 23 lines

454-456). The initial DM characteristics analysis was performed by SPSS software, and the radiomic analysis was performed by R Software, therefore, we added the statistical analysis softwares at the end of the method section (Page 10 lines 222-224, in method section).

We have also made corresponding modifications in the abstract section (Page 3 lines 53-54, pages 3-4 lines 63-66, in abstract section).

Question 7: Conclusion: The first sentence is not part of the study.

Response: Thanks for your comments, and we have deleted this sentence.

Question 8: Conclusion: The conclusion compares with a non-available result of the original mammograms without ultrasound or MRI with the outcome of the digital mammographic radiomic.

Response: We are very grateful for your comments. We have added the analysis and result of the original mammograms in method and result sections (Please refer to the response of the question 5).

Reviewer B:

Question 1: It is a well-performed study. One of my general comment is that, in academic writing, it is not common to use ‘... the literature (ref.)’ although it is acceptable. For example, it would be more scientific to use ‘consist with one previous study....’ rather than ‘consist with the literature...’.

Response: We are very thankful for your suggestion. We have modified ‘ literature’ to ‘study’ (Page 6 line 101, in introduction section), ‘ the literature’ to ‘one previous study’ (Page 13 line 293, in discussion section), and ‘previous results’ to ‘one previous study’ (Page 14 line 307, in discussion section).

Question 2: Abstract: Results: ‘The study cohort included 79 patients with malignant masses and 33 patients with pathologically confirmed benign tumors (training cohort: n=79; testing cohort: n=33).’ Why Malignant patients are in training cohort and benign patients are in testing cohort?

Response: Thanks for your comments. 112 lesions were enrolled into the study, of which 79 malignant masses and 33 benign tumors. The cases were randomly separated into training cohort and testing cohort at a ratio of 7:3. In order to ensure the balance of random grouping, we adopted a stratified random sampling method. Finally, there are 79 cases in the training group and 33 cases in the testing cohort. Both the training cohort and the testing cohort contained benign and malignant lesions.

Question 3: Introduction:1st paragraph: ‘The diagnosis of a breast mass from DM images depends on the shape, margin, density, and calcification of the lesion, as well as other indirect signs containing architectural distortion, thickened skin, and retracted nipples’. ‘signs’ is not an appropriate medical imaging terminology. These are mammographic findings or lesion characteristics. Also, where is the reference for this sentence, why ‘shape, margin, density, and calcification’ are ‘direct’ and the others are ‘indirect’?

Response: We greatly appreciate your suggestion. We have summarized introduction

section, and the word ‘signs’ (not an appropriate medical imaging terminology) and the corresponding sentence have been deleted.

The reference for this sentence mentioned above is “Li Z, Yu L, Wang X, et al. Diagnostic Performance of Mammographic Texture Analysis in the Differential Diagnosis of Benign and Malignant Breast Tumors. Clin Breast Cancer 2018;18:e621-e7.”. It is obvious that ‘associated’ is better than ‘indirect’ in this section. However, we didn’t cite the reference because we have summarized the introduction section in this updated revision.

Question 4: Introduction: 1st paragraph: ‘Digital mammography (DM) is a proposed imaging method...’ DM is not an imaging modality or technology rather than a ‘method’. Same issues exist in the rest of the manuscript.

Response: We are very thankful for your suggestion. We have made corresponding changes (Page 5 line 81, Page 5 line100, in introduction section).

Question 5: Introduction: 1st paragraph: ‘With these direct and indirect signs, breast tumors may be interpreted by the Breast Imaging-Reporting and Data System (BI-RADS) (6,7).’ I can’t see the point of this sentence at the end of this paragraph. It is not logic. Please re-write it.

Response: We are very thankful for your suggestion. We apologize for our inaccurate expression, and we have modified corresponding section (Page 5 lines 82-84, in introduction section).

Question 6: Introduction: 2nd paragraph: ‘Although DM plays an important role in the evaluation of breast masses...’. DM does not ‘evaluate’ a lesion. Instead, DM is to detect or diagnose a lesion.

Response: Thanks for your comments. We apologize for the improper wording. We have revised “evaluation” to “detection” (Page 5 line 84, in introduction section).

Question 7: Introduction: 2nd paragraph: same comments as above for ‘signs’.

Response: Thanks for your suggestions. We have summarized the introduction section in this updated revision, and the word 'signs' and the corresponding sentence has been deleted.

Question 8: Introduction: 2nd paragraph: 'The mass is easily classified as long as one of the following signs is present: spiculated margins, architectural distortion, and suspicious calcifications'. The classification of mass here is mixed up with architectural distortion and calcifications, which is not a common classification. Please add reference.

Response: We are very grateful for your suggestion. We apologize for the inaccurate description. In order to summarize the introduction section, we have deleted the sentence.

Question 9: Methods: Patients: Exclusion Criteria (1): DM screening should be 'DM examination' because these patients were not selected form any screening program. Same issue in Figure 1.

Response: Thanks for your suggestions. We have modified "DM screening" to "DM examination" (Page 7 lines 127, 130 and 140, in methods section and Figure 1) .

Question 10: Methods: Patients: Exclusion criteria (3)-(6): 'Tumor' should be 'Tumors'.

Response: We appreciate your suggestions. We apologize for our carelessness. We have modified "Tumor" to "Tumors" (Page 7 lines 142, 144 and 145, in methods section).

Question 11: Methods: Feature extraction, selection and model construction: 'Participants were randomly separated into a training cohort and testing cohort at a ratio of 7:3'. Except for the ratio, it is important to specify the exact number of patients in each cohort.

Response: Thanks for your suggestion. We have added the exact number of patients in

each cohort: a training cohort (n = 79) and testing cohort (n = 33) (Page 9 lines 188-189, in methods section).

Question 12: Discussion: 1st paragraph: ‘Therefore, the differential diagnosis of benign or malignant lesions may be difficult based only on DM if masses have regular shapes but do not have architectural distortion, spiculated margins, or suspicious malignant or benign macrocalcification’. I would recommend to have reference here.

Response: Thanks for your suggestion. We apologize for our carelessness, and we have modified ‘regular’ to ‘round-like’ (Page 13 lines 278, in discussion section). We have added reference “Jung Lim Yoo OHW, Yoon Kyung Kim, Kyu Ran Cho, etc. Can Mr Imaging Contribute in Characterizing Well-circumscribed Breast Carcinomas? Radiographics 2010 Oct; 30(6):1689-702.” for the sentence mentioned above (Page 13 line 280, in discussion section).

Question 13: Discussion: ‘Radiomics provides massive features extracted from images to quantify tumors and allows the possibilities for uncovering the differences that the human eye cannot recognize’. It would be more convincing to add references, such as previous studies similar to yours. E.g. Gandomkar, Z., Brennan, P., Mello-Thoms, C. (2018). A framework for distinguishing benign from malignant breast histopathological images using deep residual networks. 14th International Workshop on Breast Imaging (IWBI 2018), Bellingham: Society of Photo-Optical Instrumentation Engineers (SPIE).

Response: Thanks for your constructive suggestion. We have added references for the sentence mentioned above, including the reference “Gandomkar, Z., Brennan, P., Mello-Thoms, C. (2018). A framework for distinguishing benign from malignant breast histopathological images using deep residual networks. 14th International Workshop on Breast Imaging (IWBI 2018), Bellingham: Society of Photo-Optical Instrumentation Engineers (SPIE).”, and made some corresponding changes (Page 13 lines 283-285, in discussion section).

Question 14: Discussion: You may want to add one paragraph regarding the application or translational purpose of your study since the benefits in each paragraph is piece-by-piece, which is difficult for readers to follow.

Response: We really appreciate your constructive suggestion. We have added one paragraph regarding the application of our study (Page 12 lines 270-273, in discussion section).

Question 15: Tables: Table 5: why it doesn't contain 95% CI for each metric?

Response: Thanks for your question. Due to the addition of 2 tables in result section, the original table 5 has been changed to table 7. In the study, the number of invasive ductal carcinoma cases was 54 (TNBC 23/ NTNBC 31), and because of the relatively small sample size, the multivariate regression prediction model was constructed based on the whole data set, which was not divided into training and test groups. Therefore, 100 times repeated cross-validation was applied to prove that the model was valuable in discriminating one group from another group and the result was not due to overfitting. Table 7 is the mean result of the 100 times cross-validation, therefore, it doesn't contain 95% CI. Due to our carelessness, we previously provided the inaccurate result (Fig.5 and the AUC value). We apologize for this mistake. Now we have revised (page 12 line 265, in result section; page 3 line 63, in abstract section) and updated Figure 5. In addition, we added the accuracy, sensitivity, specificity of the predictive model (page 12 lines 265-266, in result section).