Peer Review File

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Reviewer A:

Comment 1: DCIS is a very heterogeneous disease, presenting in different ways as microcalcifications, architectural distortions, small masses or indistinct area of non-mass like enhancement. How do you consider this heterogeneity?

Reply 1: Thanks for your professional comment. DCIS is indeed a highly heterogeneous group of diseases. Different pathological subtypes of DCIS have different radiological manifestations. In mammography DCIS mostly presents as calcification. Due to its high heterogeneity, highly differentiated DCIS (non-comedo, non-high nuclear grade) tend to show clusters of fine polymorphic calcifications, while poorly differentiated DCIS (comedo, high nuclear grade) tend to show linear or segmental distribution of fine linear or fine-linear branched calcifications. A small percentage of DCIS does not develop significant calcifications histopathologically and may show no significant abnormalities on mammography or may only appear as masses, architectural distortions, or limited densities. In MRI, DCIS mostly presents as non-mass-like enhancement (NME). Owing to the heterogeneity of the pathology (e.g. nuclear grading), DCIS also has a diversity of presentation on MRI, which was analyzed in detail for comparison in our study. Non-high nuclear grade (non-HNG) DCIS tend to have a focal distribution of NME, while high nuclear grade (HNG) DCIS tend to have a segmental distribution. Non-HNG DCIS tend to be clustered enhancement, and HNG DCIS tend to be heterogeneous enhancement.

Changes in the text: None.

Comment 2: What kind of lesions have you included? How do you evaluate the shape and the size of the lesions? Since you found that tumor size correlates with the possibility to predict HNG-DCIS, it could be useful to provide more details about this aspect to better understand the clinical application of your results.

Reply 2: Thanks for your professional suggestions. All 159 lesions included in this study were non-mass-like lesions and showed non mass enhancement (NME) in MRI. In assessing lesion shape, we categorized lesions with well-defined borders in dynamic contrast-enhanced MRI (DCE-MRI) as mass-type lesions and those without well-defined borders as NME. In measuring the size of non-mass-type lesions, the largest

section of the tumor was selected by reconstructing the three-dimensional volume of the tumor by three-dimensional maximum intensity projection (3D-MIP) reconstruction of the DCE-MRI images of 1st- and delayed-phase and the largest diameter was used for subsequent analyses.

Changes in the text: We have modified our text as advised (see Page 6, line 130-133).

Comment 3: There are some typos and some sentences are unclear (see lines 226-227, verb tense?).

Reply 3: We are very sorry for our mistake. We have modified the manuscript accordingly in the appropriate places.

Changes in the text: We have modified our text as advised (see Page 10, line 236-237).

Reviewer B:

Comment 1: Its main contribution is the indication that this technique might be of interest in the domain, but there is no evidence of the clinical relevance stated by the authors in the Highlight Box: "A Nomogram constructed by combining these two features is an effective clinical tool for preoperative differentiation of non-HNG DCIS from HNG DCIS and may optimize clinical decision making."

Reply 1: We appreciate your professional comments and have modified the highlight box accordingly. However, after reviewing the literature again and in the context of our clinical work, we consider that it does make sense at the clinical level to distinguish between non-HNG DCIS and HNG DCIS preoperatively. Histological nuclear grading is an important prognostic factor for DCIS. Previous studies have shown that HNG DCIS and non-HNG DCIS develop by different pathways rather than by progressive differentiation. HNG DCIS may progress to high-grade invasive ductal carcinoma, while non-HNE DCIS may progress very slowly or only to certain well-differentiated breast cancers. Therefore, we have attempted to apply non-invasive radiological techniques to assist in differentiating HNG DCIS from non-HNG DCIS and to help individualize clinical treatment plans.

Changes in the text: We have modified our text as advised (see Page 4, Highlight Box).

Comment 2: The authors might improve the paper's novelty by extending the proposed approach beyond its standard use (for instance, exploring the combination of radiomics features coming from different imaging modalities, or

addressing the problem of class unbalancing, which is never considered in the paper). An external validation would be needed for what concerns generality and clinical relevance. If this is not possible, the authors should at least reduce the boldness of their claims, clearly stating that their results must be only considered as a mere suggestion of usefulness.

Reply 2: Thank you very much for your professional advice, which addresses the issue of evaluating the generality of prediction models, while these are indeed problems in our study. We have carefully evaluated the conditions and possibilities for external independent validation and feel that the appropriate number of additional multicenter case collections cannot really be completed in a short time currently. Because of the difficulties in collecting cases with surgical pathology of DCIS and with preoperative breast MRI in actual clinical practice. Our institution, as the Key Laboratory of Breast Cancer Prevention and Therapy, collected only 159 cases of DCIS in the time period of 2015-2020. At the same time, we feel that the scope of work of the current study is still able to support the arguments of this paper. But we did describe our conclusions a bit too boldly in the writing of the paper. As you suggested, we have revised the conclusions. In summary, we plan to continue collecting multicenter DCIS cases based on your suggestions, combining other breast imaging modalities, constructing nomograms based on a larger dataset and performing external validation. This will go on to be done in another follow-up paper.

In addition, the radiomics method used in this study is indeed fully standardized, but it is also the one with relatively high stability at present. There are few studies on the use of MRI-based radiomics features to predict the nuclear grading of DCIS, and we consider this to be an innovative point in this study. In our future work, we will also continue to explore new algorithms to improve the stability and reliability of the radiomics model.

Changes in the text: We have modified our text as advised (see Page 13, line 333-337).

Reviewer C:

Comment 1: The study overlooked the consideration of therapeutic aspects such as surgery, radiation therapy, and hormone therapy in the analyzed DCIS patients. As a result, it becomes challenging to attribute validity to the nomogram without taking into account these subtypes and therapeutic considerations.

Reply 1: Thanks for your precious comments. We strongly agree with the reviewers

that this is indeed a problem in our article. The prognosis of the DCIS patients is influenced by multiple factors, including the surgical approach, neoadjuvant therapy, and other aspects suggested by the reviewers, of which the histopathological features are also an important part. However, these are some of the information that can be obtained only after the operation. Instead, the original aim of this study was to investigate the feasibility of using non-invasive radiological techniques to predict the nuclear grading of DCIS preoperatively. Therefore, we established a nomogram based on MRI radiomics features as well as semantic features to predict DCIS nuclear grading preoperatively and achieved a good predictive ability. Unfortunately in the writing of the original manuscript we overemphasized the relevance of this nomogram to clinical decision making and treatment outcomes for DCIS patients. This was a mistake on our part and we are very sorry for bringing these misunderstandings to the reviewers. In response to the reviewers' suggestions, we have revised the introduction and the conclusion sections of the manuscript accordingly.

Changes in the text: We have modified our text as advised (see Page 4, line 78-80；Page 5, Line 94-97; Page 13, Line 333-337; Page 3, Line 42-45; Page 3, Line 63-65).

Comment 2: It is difficult to establish the extent of correlation between predicting nuclear grade through imaging and its relevance to patient treatment outcomes. Hence, instead of focusing on completing the nomogram, the paper should have placed more emphasis on predicting detailed pathologic features using diagnostic imaging and exploring the underlying principles of these predictions.

Reply 2: We appreciate your professional comments and agree with the points you have made. Indeed, it is difficult to establish a clear correlation between radiologically predicted nuclear grading and patient prognosis. However, it has been clearly established in previous literature that predicting nuclear grading of DCIS is of some clinical relevance, and several large clinical trials are currently exploring the feasibility of conservative active surveillance disease management for non-HNG DCIS to avoid over-surgical treatment. After careful consideration, we believe that this study is also of some clinical value. Unfortunately, however, we misrepresented the purpose and conclusions of this study in the original manuscript, which made the reviewers confused. This was a mistake on our part and we apologize for it. The main purpose of this study was to investigate the feasibility of predicting a specific pathological feature of DCIS

based on the radiomic features of MRI, i.e., nuclear grading. It is concluded that MRI-based radiomic features can be used as potential biomarkers reflecting tumor heterogeneity and have clinical value and feasibility in assessing nuclear grading of DCIS. The nomogram constructed by radiomic features combined with semantic features has the ability to discriminate between non-HNG and HNG DCIS. In future work, we hope that the results of this study can help optimize clinical treatment decisions. According to the reviewers' comments, we have modified the title, introduction, and conclusion of the original manuscript.

Changes in the text: We have modified our text as advised (see Page 1, Line 2-3; Page 4, Line 78-80；Page 5, Line 94-97; Page 13, Line 333-337; Page 3, Line 42-45; Page 3, Line 63-65).