

Peer Review File

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Reviewer A

Comment #1 Do the authors have any data on the use of radiomics in female breast cancer for lymph node staging, which is much more common, particularly in older women for whom sentinel node biopsy may be completely omitted if the axilla is clinically node negative? It is influenced by breast density?

Reply to Comment#1

There are several studies evaluating mammography, MRI and US to evaluate axillary node status in female breast cancer. For example, Tan¹ et al developed a mammogram-based radiomics nomogram by integrating radiomic metrics with clinical risk factors to predict preoperative axillary metastasis and reported an AUC 0.876 and 0.862 in the primary and validation cohorts. Dong et al⁶ showed that using radiomics in DWI and joint Fat Sat T2 MRI can preoperatively predict sentinel lymph node metastasis in female breast cancer with an AUC of 0.80 in the validation set. Using deep learning in combination with radiomic metrics from the ultrasonography of 1280 patients breast cancer patients Guo⁴⁸ et al identified patients with positive sentinel node metastasis with a sensitivity of 98.4% and those without metastasis with a 97% negative predictive value. To our knowledge, there have been no studies evaluating omitting sentinel node biopsy based on radiomic nodal assessments.

Radiomic features have been used to classify mammographic breast parenchymal complexity. These radiomic features in combination with breast density and BMI have been shown to help stratify breast cancer risk assessment.³⁸

Changes in Text

Lines 98-112 above text added

Comment #2 The following sentence is unclear. Please clarify what you mean. Incidence of what? Are you saying that 26% of male cancers present at an advanced stage? What about women?

29 the USA and less than 0.1% of cancer related deaths in men¹. Although the incidence has risen to
30 26% over the last 25 years with men being diagnosed at more advanced stages compared to
31 women², MBC research is limited. Some of the hurdles include the lack of sizable patient cohort

Reply to Comment#2

Changes made to text (below)

Changes in Text

Revised to read, see lines 29-32.

While the incidence of female breast cancer has been decreasing since the year 2000, the juxtaposed incidence of male breast cancer has risen by 26% over the last 25 years. Dedicated breast cancer research in males would be valuable²⁶

Comment#3

“Under staging” should be “understaging” “Hx” should be “history” “Her2” should be “HER2” or “HER2/neu”

There are various places where a line space is omitted or added, or where the font size changes. Please review the document and make these edits.

Reply to Comment#3

Changes made to text (below)

Changes in Text

line 46 corrected under staging changed to understaging

line 74 corrected to history

Comment#4

Did you determine the sensitivity and specificity of radiomics and compare it to axillary ultrasound?

Reply to Comment#4

A systematic review estimated the average sensitivity for positivity of US in patients with nonpalpable axillary nodes to be 44–61% and specificity for positivity at 75–86% in all patients³⁹. Currently, if clinical and US evaluation suggest nodal metastases on the basis of size or abnormal morphology, US-guided biopsy (FNAC or Core biopsy) of abnormal nodes is undertaken, which detects 45% of metastases³⁹. However, there are a significant number of false negatives.

The current study evaluates only the primary tumor to identify radiomic metrics capturing a variety of tumor phenotypes such as size, shape and radiological texture from mammograms which could predict the presence of nodal metastases. We report a reasonable performance (AUC=0.71) in discriminating pathologically node negative vs node positive male patients. Currently, we are limited by the nonavailability of nodal imaging in a large proportion of our retrospective cohort. However, we hope to address this in future and prospective studies.

Change to Text

Added text 47-59

Comment#5

Does the technology work if you change the ROI to the axilla as opposed to the primary lesion?

Reply to Comment#5

According to Huang's and Dong's study^{6,35}, a radiomics signature was concluded by radiomics features that extracted from primary tumor, which was used to predict lymph nodes metastasis and show a significant performance. Therefore, it is reasonable that we choose the primary tumor as the segmentation region. In future and prospective studies when we have access to dedicated nodal imaging, we will address this specific issue.

The evaluation of the axilla by mammography can be limited due to the body habitus of most men, lack of the ability to identify the SLN amongst the number of potentially visualized nodes by mammography and lack of specific guidelines to include the entire axilla during mammographic examinations. Therefore, we were unable to directly address this question from the reviewer. This topic may be better addressed in the future using MRI or US where the entire axilla could be visualized.

Change to Text

We added this to lines 175-186.

Comment#6

What is STARD reporting checklist? It should be referenced.

Reply to Comment#6

STARD (Standard's for Reporting of Diagnostic Accuracy Studies)

Change to Text

Reference added lines 500-502

Comment#7

It should be stated why only 2D mammograms were used.

Reply to Comment#7

While a subset of patients (n=7) had a 3D mammogram, a 2D radiomic analysis was conducted to maximize the cohort sample size. Consequently, the ROI was marked on the 2D component of the mammogram or reconstructed 2D mammogram. All tumors were detectable on 2D mammograms. This cohort was acquired retrospectively before 3D mammo was widely available.

Change to Text

154-158

Comment#8

Regarding the exclusion of “suspicious” lymph nodes. Was suspicion based on mammography and exam alone or was axillary ultrasound routinely included in that assessment?

Reply to Comment#8

As advised, added mammographically suspicious lymph nodes in line 167.

Comment#9

This statement is not accurate. Ultrasound does this.

247 Non-invasive prediction of axillary lymph node metastasis preoperatively has significant clinical impact.

248 Currently, there is no method to reliably, cost effectively and non-invasively obtain this information.

Reply to Comment#9

Currently, ultrasound has a specificity for positivity of 75-86% in all patients and is non-invasive. However, an US study identifying a suspicious node would prompt a US guided biopsy which requires additional time delay due to the need for another appointment and a false negative rate up to 30%⁴².

Change to Text

Text added to lines 302-305. Currently, there is no method to reliably, cost effectively and non-invasively obtain this information has been deleted.

Comment#10

Did the authors make an effort to compare the predictive value of radiomics or genomics? Or the combined value of both?

Reply to Comment#10

We have reported the predictive value of radiomics in terms of the Area Under the Curve (AUC) metric in Figure 3. We report an AUC of 0.71 in discriminating pathologically node negative vs node positive male patients using radiomic-metrics derived from mammograms. Genomic information was not available for this cohort of patients therefore not evaluated in this study.

Change to Text

Text added to lines 316-320.

Comment#11

Can the authors express “histogram” or “intensity” in clinical or biological terms?

Reply to Comment#11

First order statistical features describe the distribution of individual voxel values without concern for spatial relationships. These are histogram-based properties reporting the mean, median, maximum, minimum values of the voxel intensities on the image, as well as their skewness (asymmetry), kurtosis (flatness), uniformity, and randomness (entropy).

These radiomic features assess different imaging characteristics. They may be representative of or be surrogates for specific biologic processes but these would also be dependent on clinical and patient specific factors. Radiomics therefore may potentially enhance or nuance the clinical and pathological data available for treating physicians to make patient specific decisions.

Change to Text

Text added to lines 204-213.

Comment#12

This is “hypothetical”. The authors did not actually study patients treated with neoadjuvant therapy.

- 2 MBC patients due to the small number of cases in individual centers. Accurate nodal status could
- 3 allow consideration of downstaging the axilla in clinically node positive patients leading to
- 4 limited axillary surgery with less morbidity if the negative predictive value was high.

Reply to Comment#12

Yes, we did not study neoadjuvant therapy, the sentence is a hypothetical statement in the discussion section to highlight the potential clinical impact if validated.

Change to Text

In line 360, added hypothetically

Comment #13

I'm not sure what this means in the context of male breast cancer.

7 MBC patients tend to have more comorbidities than their female counterparts. Further validation
8 would be needed in patients who had negative axilla by radiomics if sentinel node biopsy could
9 be omitted. As 50% of MBC patients are node negative, only 18-25% of MBC patients undergo

Reply to Comment#13

Change to Text

Deleted MBC patients tend to have more co-morbidities than their female counterparts.

Reviewer B

Your study was performed between the years 2009 and 2020. Your report states that you only analyzed 2-D digital mammograms. Did, in fact, any of the men undergo 3-D digital tomographic mammograms? If yes, why did you not also evaluate this technology with their 3-D digital mammograms?

The mammographic images utilized in your study involved standard 2-D digital mammograms. Since most breast centers are now converting to 3-D digital tomographic mammograms is the CaPTK toolkit equally as effective in the 3-D images?

Reply to Comment from Reviewer B

CaPTK can be used to mark ROI on 3D images. A 3d dataset was not available for all the cases included in this cohort. Though 3D tomosynthesis is the primary modality being used for screening in many centers, there are logistical issues that arise when using it in radiomics. As this was a multicenter study, there was no consistent imaging protocol that was adopted. While 3D evaluation may improve the accuracy of radiomic evaluation, in some instances 2D evaluation may produce similar accuracy^{42,43,44}.

Change to Text

Text added to lines 158-163.