Supplementary

Response to "A balanced view of imaging and molecular markers for predicting axillary lymph node metastasis in T1 breast cancer"

Cong Shang

Department of Ultrasound, Shengjing Hospital of China Medical University, Shenyang, China

Correspondence to: Cong Shang, MD. Department of Ultrasound, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Heping District, Shenyang 110004, China. Email: shangc@cmu.edu.cn.

We sincerely appreciate Dr. Zhao and colleagues for their insightful and constructive comments (1) regarding our recently published article (2). Their valuable feedback has prompted us to further reflect on the strengths and limitations of our study. We would like to respond to the raised points as follows:

Regarding comparison with conventional imaging modalities

We appreciate the suggestion to compare our proposed approach with traditional imaging methods such as mammography, conventional ultrasound, and magnetic resonance imaging (MRI). As stated in our Discussion section, although conventional imaging modalities are widely used for axillary assessment, they have inherent limitations in the preoperative evaluation of axillary lymph nodes (ALNs), particularly in T1 breast cancer. Our study aimed to explore the value of novel functional imaging techniques—diffuse optical tomography (DOT) and strain elastography (SE)—combined with molecular markers (e.g., Ki-67) for the preoperative prediction of axillary lymph node metastasis (ALNM), focusing on biomarkers reflecting tumor microenvironment and cellular characteristics. Although this study did not directly compare with mammography or MRI, we acknowledge the necessity for future prospective research to conduct head-to-head comparisons between predictive models and traditional imaging methods, or to evaluate the incremental diagnostic benefit and cost-effectiveness of integrating them with conventional approaches. Such studies would further validate and clarify their clinical value.

Regarding the higher observed ALNM rate (45.9%) in our T1 cohort

We acknowledge that the ALNM rate observed in our cohort exceeds that reported in larger population-based registries. Potential contributing factors include:

(I) Our center is a tertiary referral hospital. A proportion of enrolled patients presented with subtle clinical or sonographic signs suggestive of nodal involvement, potentially enriching the cohort with a relatively higher-risk population (i.e., introducing possible referral bias).

(II) While we excluded patients with multifocal or larger lesions, patients with clinically suspicious lymph nodes on imaging were not excluded if they met the inclusion criteria.

We addressed the potential for selection bias arising from the single-center setting in the "Limitations" section of our original manuscript. We fully concur that external validation through multicenter studies is crucial for enhancing the generalizability of our findings. We thank Dr. Zhao and colleagues for this suggestion; we will provide a more explicit description of preoperative axillary imaging findings in future studies.

Regarding technical limitations of DOT and single-center sample size

We fully acknowledge the technical limitations of DOT, particularly its restricted penetration depth and challenges in imaging symmetric lesions, as detailed in the "Discussion" section of our manuscript. To mitigate the impact of depth, we strictly adhered to the study

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flowchart, excluding lesions located too superficially (<0.5 cm) or too deeply (>3.5 cm). Regarding the sample size and single-center nature of the study, we recognize that these factors limit the generalizability of our model. External validation in prospective, multicenter settings is therefore essential to assess its clinical applicability. Future technical improvements and multicenter collaborative studies are planned to help overcome these current limitations.

Regarding lack of other predictive pathological factors [e.g., lymphovascular invasion (LVI)]

We appreciate Zhao *et al.* highlighting LVI as a well-established predictor of ALNM. However, definitive assessment of LVI requires pathological examination of the surgically excised specimen and cannot be accurately assessed preoperatively. Our study focused specifically on developing a *non-invasive preoperative predictive model* based on variables accessible before surgery (imaging biomarkers and molecular markers) to inform surgical decision-making. Consequently, LVI was not included as a preoperative predictor in our model. Nevertheless, we recognize the importance of LVI in postoperative risk stratification. Integrating LVI and other emerging biomarkers into future research models represents an important direction.

Regarding collection of long-term outcome data

We agree that long-term outcome measures, such as axillary recurrence-free survival and overall survival, would enhance the clinical significance of our findings. However, our study was designed as a cross-sectional investigation (imaging-pathology correlation analysis), and this retrospective dataset lacks sufficient longitudinal follow-up data for meaningful survival analysis. We are currently considering initiating a prospective cohort study with standardized follow-up to enable future longitudinal assessment of these critical endpoints.

Conclusions

We once again extend our sincere gratitude to Dr. Zhao and colleagues for their insightful comment. Their points accurately identify key areas for future research and refinement of non-invasive predictive strategies for ALNM. We are confident that continued exploration of integrating multimodal information will contribute to personalized surgical decision-making in early-stage breast cancer.

References

1. Zhao J, Chen X, Zhang Z, et al. A balanced view of imaging and molecular markers for predicting axillary lymph node metastasis in T1 breast cancer. Quant Imaging Med Surg 2025. [Epub ahead of print]. doi: 10.21037/qims-2025-1293.
2. Shang C, Zhang J, Huang Y. Prediction of axillary lymph node metastasis in T1 breast cancer using diffuse optical tomography, strain elastography and molecular markers. Quant Imaging Med Surg 2025;15:2162-74.

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