Research Square

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Dual-Region Ultrasound Radiomics for the Non-Invasive Prediction of HER2 Status in Breast Cancer Patients with Equivocal Immunohistochemistry

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Abstract

Objective

To assess the potential of ultrasound (US) radiomics, incorporating intratumoral and peritumoral regions, in predicting human epidermal growth factor receptor 2 (HER2) status in breast cancer patients with uncertain immunohistochemical (IHC) results.

Methods

This retrospective study included 410 breast cancer patients with an IHC HER2 score of 2+, confirmed by fluorescence in situ hybridization (FISH). US images were analyzed using 3D Slicer software to delineate regions of interest (ROI) in the tumor and surrounding peritumoral areas. Radiomics features were extracted from intratumoral regions and peritumoral areas (3mm, 6mm, 9mm) and divided into four groups. Feature selection was conducted via Spearman correlation, Mann-Whitney U test, and least absolute shrinkage and selection operator (LASSO) regression. Six machine learning classifiers were trained and validated. The best-performing model was evaluated in an independent test cohort, and SHAP (SHapley Additive exPlanations) analysis was used to interpret predictions.

Results

The logistic regression (LR) model, utilizing intratumoral and 6mm peritumoral features, achieved the highest area under the curve (AUC) of 0.794 in the training set and 0.712 in the test set. Decision curve analysis demonstrated net benefit across a range of thresholds, particularly at lower levels. SHAP analysis highlighted key radiomics features in predicting HER2 status.

Conclusion

US radiomics, particularly when incorporating both intratumoral and peritumoral regions, offers a promising approach for predicting HER2 status in breast cancer patients with equivocal IHC results, potentially aiding clinical decision-making.

Clinical trial number

Not applicable.

Introduction

Breast cancer remains one of the most prevalent malignancies among women worldwide, accounting for a significant proportion of cancer-related morbidity and mortality[1]. HER2 is a key molecular marker in breast cancer, playing a crucial role in prognosis and guiding treatment. HER2-positive breast cancers, characterized by HER2 protein overexpression, are associated with more aggressive disease but respond well to targeted therapies like trastuzumab [2–4]. Accurate HER2 status determination is therefore essential for optimizing treatment strategies and improving patient outcomes.

The standard methods for assessing HER2 status, including IHC and FISH, are widely used in clinical practice[5]. However, IHC, a semi-quantitative technique, often yields equivocal results, complicating clinical decision-making [6, 7]. This uncertainty can have significant implications for initiating HER2-targeted therapies, which are costly and carry potential side effects. As a result, there is a growing need for non-invasive, reliable methods to predict HER2 status, especially when IHC results are inconclusive.

Radiomics, an emerging field that extracts high-dimensional data from medical images, offers a promising solution by capturing tumor heterogeneity and other characteristics not visible in conventional imaging [8]. Temporal and spatial heterogeneity of HER2 expression correlates with prognosis and treatment outcomes options [9]. US radiomics, in particular, has shown potential in evaluating breast cancer, providing insights into tumor morphology, texture, and other intrinsic properties [10, 11]. Studies have demonstrated its utility in predicting molecular subtypes, therapy response, and prognostic factors [12–14]. However, its application for predicting HER2 status in cases with IHC uncertainty remains underexplored.

This study introduces a novel approach by analyzing both intratumoral and peritumoral regions. While intratumoral features reflect the characteristics within the tumor, peritumoral features capture the tumor's interaction with surrounding tissue, offering additional insights into tumor biology and behavior. This dual-region analysis could enhance the accuracy of radiomics-based predictions by providing a comprehensive view of the tumor environment.

The primary objective of this study is to develop and validate a US radiomics model for accurately predicting HER2 status in breast cancer patients with uncertain IHC results. By integrating intratumoral and peritumoral radiomics features, this approach aims to offer a non-invasive tool that improves HER2 prediction reliability and supports clinical decision-making. The findings from this study could lead to more precise and personalized treatment strategies, improving outcomes for breast cancer patients.

Materials and methods

This study followed the ethical standards of the Declaration of Helsinki. The retrospective study allowed for anonymization without requiring written informed consent and was approved by the Medical Ethics Committee of our hospital (IRB-2024-872).

Patients

Two radiologists collected patient data from the picture archiving and communication system (PACS) at our hospital. The study included patients who underwent preoperative breast US between January 2017 and December 2018, meeting the following inclusion criteria: (a) breast cancer diagnosed via surgery or core needle biopsy; (b) breast US conducted within one month prior to surgery; (c) HER2 IHC score of 2+; (d) presence of a solitary mass-based tumor; and (e) HER2 status confirmed via FISH.

Exclusion criteria included: (a) prior treatment such as chemotherapy or radiotherapy before the preoperative US; (b) incomplete pathological data; and (c) poor-quality US images (evaluated by two radiologists in agreement). In total, 410 eligible patients were randomized into training (70%) and testing (30%) groups.

Clinical data collection and pathological assessment

Clinical data included patient age, tumor size (< 2mm or ≥ 2mm), menopausal status, tumor laterality, family history, and levels of estrogen receptor (ER), progesterone receptor (PR), and Ki-67 expression. All patients underwent surgery followed by IHC to assess ER, PR, HER2, and Ki-67. HER2 status was based on IHC, with scores of 3 + considered positive, 0 or 1 + negative, and 2 + equivocal, requiring FISH to confirm gene amplification. A HER2/CEN-17 ratio of ≥ 2 indicated amplification, while < 2 indicated no amplification [15].

US Image Acquisition

Experienced sonographers performed standardized breast US examinations, maintaining consistent imaging parameters (gain ~ 50%, imaging depth 3–5 cm, and lesion-focused adjustments). US devices used included LOGIQ E9, Toshiba Aplio 400, Philips iU22, and Siemens S2000 with high-frequency linear probes. The cross-sectional images recorded the largest tumor sections.

Segmentation of Intratumoral and Peritumoral Regions

Preoperative US images (DICOM format) were exported from PACS and processed using 3D Slicer software (version 5.0.3). Tumor boundaries were manually contoured by two experienced radiologists, defining intratumoral ROIs. It has been found that the 3- to 9-mm region surrounding a tumor can provide biological information related to heterogeneity [16]. Peritumoral regions were automatically and proportionally expanded by 3mm, 6mm, and 9mm using the extension tools in 3D Slicer software to encompass tumor-adjacent tissues. Figure 6 illustrates example maps of US radiomics extraction for intratumoral and peritumoral regions at 3mm, 6mm, and 9mm distances. ROIs were manually delineated on US images using 3D Slicer software by a radiologist with 7 years of experience in US diagnostics, who was blinded to the histopathological results. Radiomic features were then extracted from these ROIs. ROIs were delineated independently by a second radiologist with 5 years of experience, also blinded to

the histopathological outcomes, on a random subset of 50 lesions to ensure consistency, and intraclass correlation coefficient (ICC) values > 0.8 confirmed high reproducibility.

Radiomics feature extraction

Radiomics features were extracted using the PyRadiomics plugin in 3D Slicer. Features were calculated for intratumoral and peritumoral regions (3mm, 6mm, and 9mm), including: (1) first-order statistics, (2) gray-level co-occurrence matrix (GLCM), (3) gray-level difference method (GLDM), (4) gray-level run-length matrix (GLRLM), (5) gray-level size zone matrix (GLSZM), and (6) neighborhood gray-tone difference matrix (NGTDM).

Radiomics feature selection

Radiomics features were grouped based on the ROIs: (1) intratumoral features, (2) intratumoral + 3mm peritumoral, (3) intratumoral + 6mm peritumoral, and (4) intratumoral + 9mm peritumoral. Features were standardized using z-score normalization. To handle the class imbalance, we applied synthetic minority oversampling (SMOTE) to increase the number of minority class samples, thus achieving a more balanced dataset. Feature selection was performed in three steps: (a) Spearman correlation to remove highly correlated features ($|\rho| > 0.9$), (b) Mann-Whitney U test to retain significant features ($p < 0.05$), and (c) LASSO regression to select the most predictive features. A 5-fold cross-validation was used to select the optimal λ value.

Model construction and testing

Six machine learning classifiers—LR, decision tree (DT), support vector machine (SVM), XGBoost, K-nearest neighbors (KNN), and random forest (RF)—were trained using the radiomics features from the four ROI groups. Hyperparameters were fine-tuned using 10-fold cross-validation and grid search, with performance evaluated using AUC from receiver operating characteristic (ROC) curves. After model development, an internal validation protocol was conducted to assess discriminative ability. AUCs of four training sets were compared to identify the optimal model and radiomic region. The selected model was further evaluated in an independent test cohort, assessing its discrimination and clinical utility to provide deeper insights into its predictive power.

Model interpretability

To enhance model interpretability, we used SHAP to identify the most influential radiomics features. SHAP values were calculated across the training set, offering insights into feature contributions and improving the model's transparency.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) for normal distributions and median (interquartile range) for skewed data. Group differences were assessed using chi-square tests, Mann-Whitney U tests, and independent-samples t-tests. Model performance was evaluated using ROC curves, with AUC as the primary metric. Decision curve analysis (DCA) was used to assess the model's clinical relevance and prediction accuracy. A p-value of < 0.05 was considered statistically significant. All analyses were performed using Python version 3.12.5.

Results

Basic clinicopathologic features of the patient

Figure 1 shows the study's flowchart. A total of 410 consecutive breast cancer cases (from January 2017 to December 2018) were included, all with HER2 2 + IHC results, and final HER2 status confirmed by FISH. Of these, 337 (82.2%) were HER2 positive, and 73 (17.8%) were HER2 negative. Basic clinicopathologic characteristics of both groups are summarized in Table 1. No significant differences were observed between the HER2-positive and HER2-negative groups regarding age, menstrual status, family history, tumor diameter, lesion laterality, ER, and PR expression levels ($P > 0.05$). However, a significantly higher proportion of patients in the HER2-positive group had Ki-67 expression ≥ 14% compared to the HER2-negative group (86.3% vs. 65.3%), while more HER2-negative patients had Ki-67 expression < 14% (34.7% vs. 13.7%). This difference in Ki-67 expression was statistically significant ($P < 0.001$). The majority of patients (389, 94.9%) had invasive ductal carcinoma (Table 2). For subsequent analysis, patients were randomly assigned to a training set (n = 287) and a test set (n = 123) in a 7:3 ratio. Of these, 51/287 (17.8%) in the training set and 22/123 (17.9%) in the test set were HER2 negative. Clinical variables between the training and test sets were compared, confirming no statistically significant differences, thus ensuring the model's generalizability and validity.

Table 1
Basic clinicopathologic information in patients with HER2 2 + breast cancer (n = 410).

Characteristics	FISH results		*P* Value
	HER2-negative (n = 337) (82.2%)	HER2-positive (n = 73) (17.8%)	
Age (years, mean ± SD)	53.0 ± 10.2	51.6 ± 10.9	0.293[a]
Range	26–82	28–74	
Age (%)			1.000[b]
< 50	132 (39.2)	28 (38.4)	
≥ 50	205 (60.8)	45 (61.6)	
Maximum tumor diameter			0.057[b]
< 2mm	117 (34.7)	34 (46.6)	
≥ 2mm	220 (65.3)	39 (53.4)	
Menopausal status (%)			1.000[b]
Premenopausal	145 (43.0)	31 (42.5)	
Postmenopausal	192 (57.0)	42 (57.5)	
Family history (%)			0.107[b]
Yes	86 (25.5)	26 (35.6)	
No	251 (74.5)	47 (64.4)	
Laterality of lesion (%)			0.718[b]
Left	163 (48.4)	33 (45.2)	
Right	174 (51.6)	40 (54.8)	
ER (%)			0.166[b]
Positive	276 (81.9)	54 (74.0)	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization.

[a] Independent samples t-test.

[b] Chi-square test.

The bolded data represent statistically significant differences.

Characteristics	FISH results		*P* Value
	HER2-negative (n = 337) (82.2%)	HER2-positive (n = 73) (17.8%)	
Negative	61 (18.1)	19 (26.0)	
PR (%)			0.134[b]
Positive	249 (73.9)	47 (64.4)	
Negative	88 (26.1)	26 (35.6)	
Ki-67 (%)			**< 0.001[b]**
≥ 14	220 (65.3)	63 (86.3)	
< 14	117 (34.7)	10 (13.7)	
ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; FISH, fluorescence in situ hybridization.			
[a] Independent samples t-test.			
[b] Chi-square test.			
The bolded data represent statistically significant differences.			

Table 2
Pathologic typing of breast cancer cases (n = 410).

Pathogical Results	Number (%)
Invasive ductal carcinoma	389 (94.9)
ductal carcinoma in situ	5 (1.1)
Invasive lobular carcinoma	4 (1.0)
Mucinous carcinoma of the breast	4 (1.0)
Invasive micropapillary carcinoma	4 (1.0)
Others	4 (1.0)

Intratumoral and peritumoral feature selection

ROIs were delineated on US images. After removing unanalyzable features, 3348 features per case remained. A total of 837 radiomics features were extracted, including 162 first-order features, 216 GLCM features, 126 GLDM features, 144 GLRLM features, 144 GLSZM features, and 45 NGTDM features for intratumoral, peritumoral 3mm, 6mm, and 9mm regions. The features were divided into four groups: (1) intratumoral, (2) intratumoral + peritumoral 3mm, (3) intratumoral + peritumoral 6mm, and (4)

intratumoral + peritumoral 9mm. Feature selection followed three steps: first, Spearman correlation was used to remove highly correlated features ($|\rho| > 0.9$) within each group to reduce redundancy. Second, the Mann-Whitney U test was applied to retain features that significantly distinguished between HER2-positive and HER2-negative cases ($p < 0.05$). Finally, LASSO regression with 5-fold cross-validation was used to select the most predictive features (Fig. 2). After these three steps of feature screening, 6, 11, 11, and 9 features were selected from the four groups, respectively.

Training and testing of the model

Using the selected features from the four regions, six machine learning models were built: LR, DT, SVM, XGBoost, KNN, and RF. Figure 3 (A–D) shows the performance of these models across the four training sets through ROC curves. To optimize model robustness and mitigate overfitting, 10-fold cross-validation and grid search were used during training. The LR model, using intratumoral and 6mm peritumoral features, was identified as the best-performing model with an AUC of 0.794 (95% CI: 0.723–0.865) in the training set. Table 3 and Fig. 4 display the LR model's evaluation on the test set, where it achieved an AUC of 0.712 (95% CI: 0.624–0.801). The model's accuracy (Acc) was 0.747, with a sensitivity (Sen) of 0.545, specificity (Spe) of 0.792, positive predictive value (PPV) of 0.364, and negative predictive value (NPV) of 0.889. These results demonstrate the model's strong capability in class differentiation, characterized by high specificity and NPV, despite its relatively lower sensitivity. The LR model effectively discriminated between HER2-positive and HER2-negative cases. Decision curve analysis (DCA) confirmed the model's clinical utility, showing a net benefit over the "Treat All" and "Treat None" strategies, particularly at lower threshold probabilities (up to ~ 0.2). However, the benefit decreases as threshold probabilities increase, with negligible utility observed at higher thresholds (Fig. 4). These findings highlight the model's potential in predicting HER2 status in breast cancer patients, particularly in scenarios where lower threshold probabilities are clinically relevant.

Table 3
Optimal model performance (LR) in the testing set.

Model	AUC	95% CI	Acc	Sen	Spe	PPV	NPV
Intra + 6mm peri-radiomics	0.712	0.624–0.801	0.747	0.545	0.792	0.364	0.889

AUC, area under the curve; CI, confidence interval; Acc, accuracy; Sen, sensitivity; Spe, specificity; PPV: positive predictive value; NPV: negative predictive value.

SHAP model interpretation

The SHAP bar plot (Fig. 5A) illustrates the overall importance of each feature, with longer bars indicating greater impact on model predictions. The SHAP summary plot (Fig. 5B) displays how individual features influence predictions, with color indicating feature values (high in red, low in blue). In our LR model, which used radiomics features from intra-tumoral and 6mm peritumoral regions, the SHAP analysis identified Peri_wavelet-HHL_firstorder_Mean as the most impactful feature, with a mean absolute SHAP

value of 0.18. Higher values of this feature were associated with HER2-positive predictions, while lower values indicated HER2-negative status. Other important features, such as Peri_wavelet-LLH_firstorder_Kurtosis and Peri_wavelet-HLH_firstorder_Uniformity, also contributed significantly, highlighting the potential of radiomics in predicting HER2 status.

Discussion

This study investigated the potential of US radiomics to predict HER2 status in breast cancer patients with equivocal IHC results, focusing on both intratumoral and peritumoral features. The results show that incorporating features from the tumor and surrounding tissue improves predictive Acc, especially in ambiguous IHC cases. The LR model, utilizing intratumoral and 6mm peritumoral features, demonstrated the highest performance, achieving an AUC of 0.712 in the test set, highlighting the promise of this approach.

The performance improvement observed by combining intratumoral and peritumoral features underscores the importance of considering the tumor microenvironment in radiomics analyses. While intratumoral features reflect tumor characteristics like texture and morphology, peritumoral features provide insights into the tumor's interaction with surrounding tissue, which may influence its behavior and aggressiveness. Our findings are consistent with previous studies showing that peritumoral regions hold valuable biological information contributing to tumor heterogeneity [17, 18]. Notably, the inclusion of a 6mm peritumoral margin was particularly effective in predicting HER2 status, likely capturing key microenvironmental changes linked to HER2 expression. Similarly, Hua Qian et al. demonstrated that combining intratumoral and peritumoral MRI-based radiomics effectively assessed immune cell infiltration in breast cancer, providing critical insights into the tumor microenvironment and aiding prognosis [19].

In the test set, the LR model demonstrated a high AUC (0.712), specificity (Spe: 0.792), and negative predictive value (NPV: 0.889), indicating its potential utility for risk stratification and clinical decision-making in HER2 2 + cases. However, the model showed lower sensitivity (Sen: 0.545) and positive predictive value (PPV: 0.364). The high specificity and NPV make it particularly useful for accurately identifying HER2-negative breast cancer, which is increasingly important with the emergence of the HER2-low classification [20]. As therapies like trastuzumab deruxtecan (T-DXd) target HER2-low patients [21], accurate differentiation is essential. By reliably excluding HER2-negative cases, the model reduces overtreatment and conserves resources. Though Sen is low, the model complements other diagnostic tools by excluding non-HER2 cases, improving diagnostic accuracy. Future refinements in feature selection and model optimization could further enhance its performance. Overall, the model serves as a useful filter, especially for screening HER2-negative cases.

Approximately 90% of HER2 overexpressing breast cancers are caused by gene amplification. Accurately predicting HER2 status is crucial for guiding breast cancer treatment. While traditional methods like IHC and FISH are effective, they sometimes yield inconclusive results, complicating clinical decisions [22].

FISH, considered the gold standard for detecting HER2 gene amplification, is time-consuming and typically reserved for HER2-IHC-2 + cases. The 2013 ASCO/CAP guidelines lowered the critical HER2/CEP-17 ratio to 2.0 [15] (compared with 2.2 in 2007 [23]), increasing the identification of gene amplification in HER2-IHC-2 + tumors [24]. Our model, with its high specificity, offers a valuable complement to existing assays by accurately excluding HER2-negative cases, reducing the need for FISH and streamlining diagnostics. This aids in directing patients to appropriate therapies, improving resource allocation and supporting personalized treatment strategies. Moreover, it has value as a complementary tool in distinguishing true HER2-negative cases, reducing overtreatment and unnecessary diagnostic costs.

Our study builds on the existing literature on radiomics for breast cancer characterization by emphasizing the combined value of intratumoral and peritumoral features. While prior research has demonstrated radiomics' utility in predicting molecular subtypes [13], most have focused solely on intratumoral features [25, 26], often overlooking the peritumoral region. Recent evidence, however, underscores the importance of peritumoral features in refining HER2 status prediction. For instance, a radiomics nomogram incorporating multiregional DWI and ADC features with clinical factors achieved robust predictive accuracy (AUC: 0.883/0.848) [27]. Similarly, mammographic radiomics combined with clinical characteristics achieved AUCs up to 0.838 in training but did not assess peri-tumoral features. The application of US radiomics for HER2 prediction, particularly in IHC-uncertain cases, remains limited. Our findings demonstrate that combining intratumoral and peritumoral radiomics offers a powerful tool for HER2 status prediction, with better performance over traditional methods. Additionally, we found a positive correlation between HER2 positivity and high Ki-67 index ($p < 0.001$), consistent with prior studies [28, 29]. US radiomics offers practical advantages such as accessibility, cost-effectiveness, and non-invasiveness, making it suitable for widespread clinical use. Integrating radiomics into routine US could provide clinicians with real-time insights, enabling more personalized treatment planning. Additionally, using SHAP analysis to interpret the model’s predictions enhances transparency, offering clear explanations for decisions and facilitating the integration of such models into clinical practice. Additionally, we employed SHAP analysis to interpret the model’s predictions, enhancing transparency and providing clinicians with clear explanations for the decision-making process. This interpretability is critical for fostering trust in AI-driven tools and facilitating their seamless integration into routine clinical workflows. Our findings underscore the potential of radiomics, particularly the combination of intratumoral and peritumoral features, to advance the precision and accessibility of HER2 prediction in breast cancer care.

Despite promising results, this study has several limitations. The use of various US equipment may have introduced differences in image quality and radiological feature extraction. Although a standardized imaging protocol was followed, the retrospective design limits control over equipment variation and operator experience. Future research should use a prospective design with uniform equipment or multicenter image coordination to reduce variability and improve generalizability. Another limitation is the reliance on manual ROI segmentation, which can introduce variability; automated segmentation techniques could enhance reproducibility and efficiency. Exploring peritumoral distances beyond 9mm

and incorporating other imaging modalities, like MRI, could further improve predictive accuracy. Lastly, while SHAP analysis provided insights into feature importance, future studies should investigate more advanced interpretability techniques to better understand the relationships between radiomics features and HER2 status.

Conclusion

In conclusion, our study highlights the potential of US radiomics, particularly integrating intratumoral and peritumoral features, in predicting HER2 status in breast cancer patients with equivocal IHC results. This non-invasive approach could complement traditional diagnostics and reduce reliance on procedures like FISH. Future research should validate these findings in larger, multi-center cohorts and explore the integration of radiomics into routine clinical practice to enhance personalized breast cancer management.

Abbreviations

HER2	Human Epidermal Growth Factor Receptor 2
US	Ultrasound
IHC	Immunohistochemistry
FISH	Fluorescence in Situ Hybridization
ROI	Region of Interest
SHAP	SHapley Additive exPlanations
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic
ICC	Intraclass Correlation Coefficient
GLCM	Gray-Level Co-occurrence Matrix
GLDM	Gray-Level Difference Method
GLRLM	Gray-Level Run-Length Matrix
GLSZM	Gray-Level Size Zone Matrix
NGTDM	Neighborhood Gray-Tone Difference Matrix
LR	Logistic Regression
DT	Decision Tree
SVM	Support Vector Machine
XGBoost	Extreme Gradient Boosting
KNN	K-Nearest Neighbors
RF	Random Forest
SMOTE	Synthetic Minority Over-sampling Technique
DCA	Decision Curve Analysis
ER	Estrogen Receptor
PR	Progesterone Receptor
Acc	Accuracy
Sen	Sensitivity
Spe	Specificity
PPV	Positive Predictive Value
NPV	Negative Predictive Value

Declarations

Ethics approval and consent to participate

This study followed the ethical standards of the Declaration of Helsinki. The retrospective study allowed for anonymization without requiring written informed consent and was approved by the Medical Ethics Committee of our hospital (IRB-2024-872).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

X.L. Li designed the study, collected the data, and performed the statistical analyses. L. Huang contributed to data analysis and statistics. Y. Sun collected and curated the data. W. Li revised the manuscript. C. Yang contributed to study conception and design. H.P. Song contributed to study design and critical review. M.Y. Yan contributed to study design and critical review. X.L. Li, L. Huang, and Y. Sun contributed equally to this work and share first authorship. H.P. Song and M.Y. Yan are co-corresponding authors. All the authors read and approved the final manuscript.

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Data Availability

Data may be made available on reasonable request to the authors.

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Figures

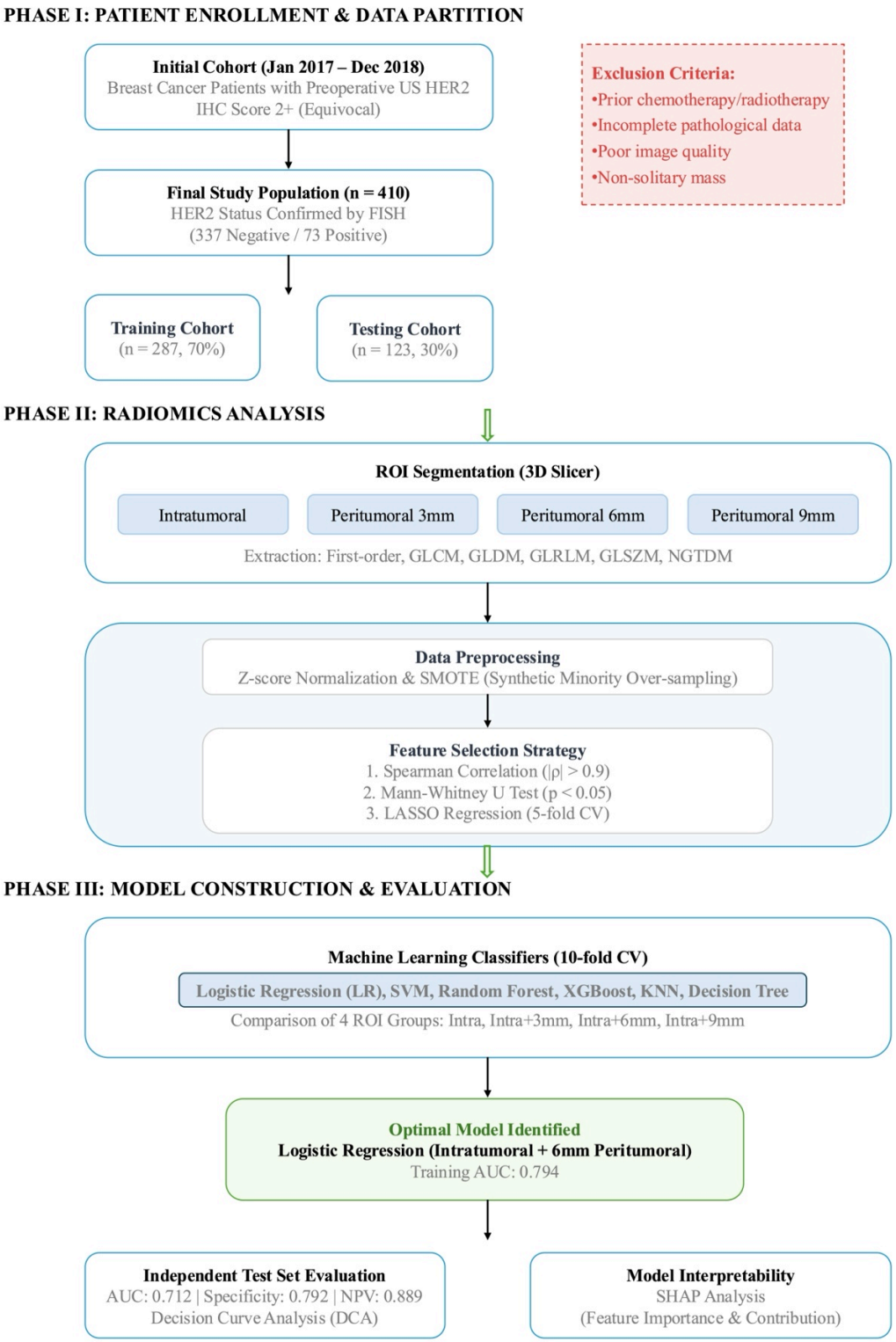


Figure 1

Overall workflow of the study for predicting HER2 status in breast cancer patients with IHC 2+ results. ROI, regions of interest; SMOTE, synthetic minority over-sampling technique; LASSO, least absolute shrinkage and selection operator; LR, logistic regression; DT, decision tree; SVM, support vector machine; XGBoost, extreme gradient boosting; KNN: k-nearest neighbor; RF, random forest; SHAP, Shapley additive explanations.

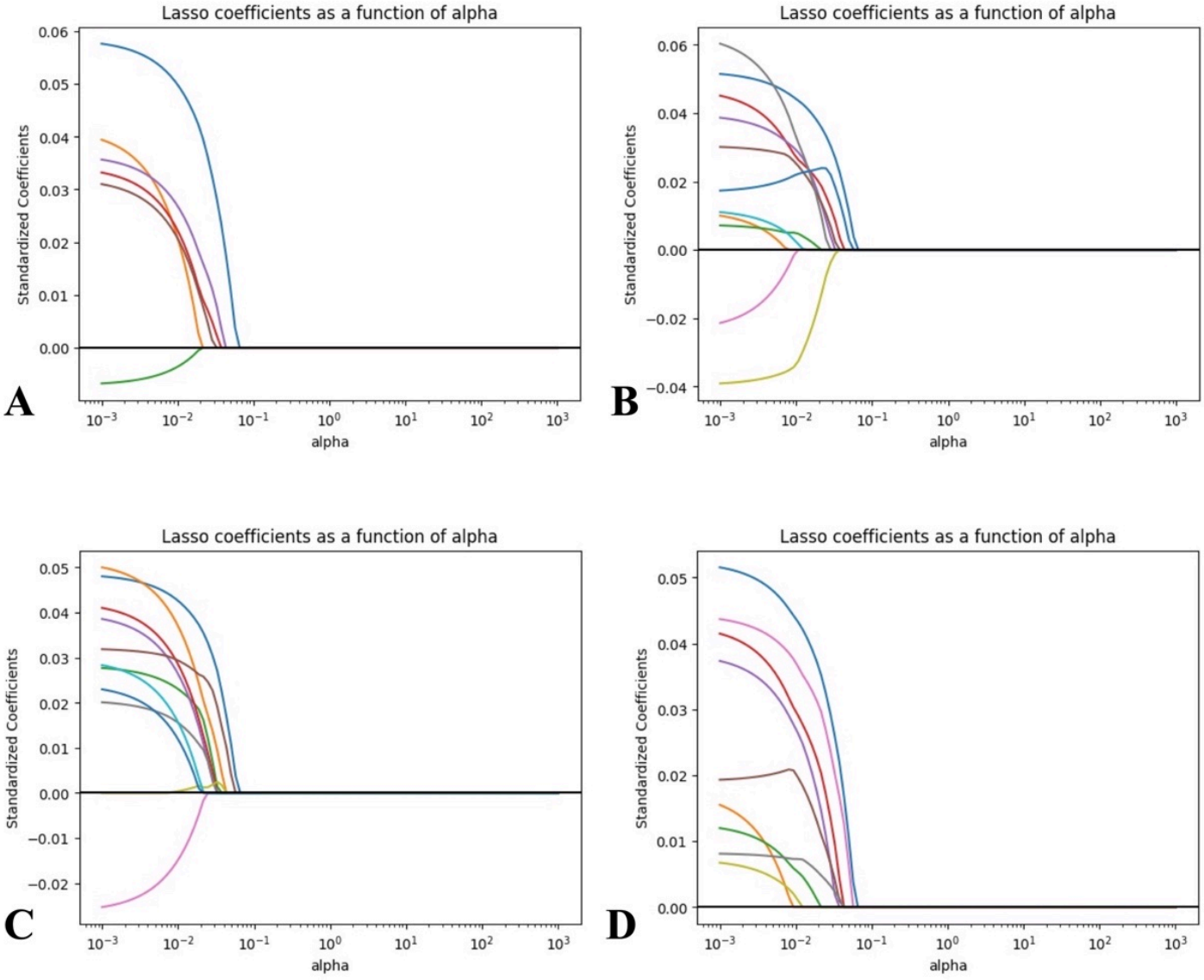


Figure 2

The LASSO (least absolute shrinkage and selection operator) regression results for four groups of radiomics region groupings in the training sets. (A). Intratumoral radiomics group; (B). Intra- + peritumoral 3mm radiomics group; (C). Intra- + peritumoral 6mm radiomics group; (D). Intra- + peritumoral 9mm radiomics group.

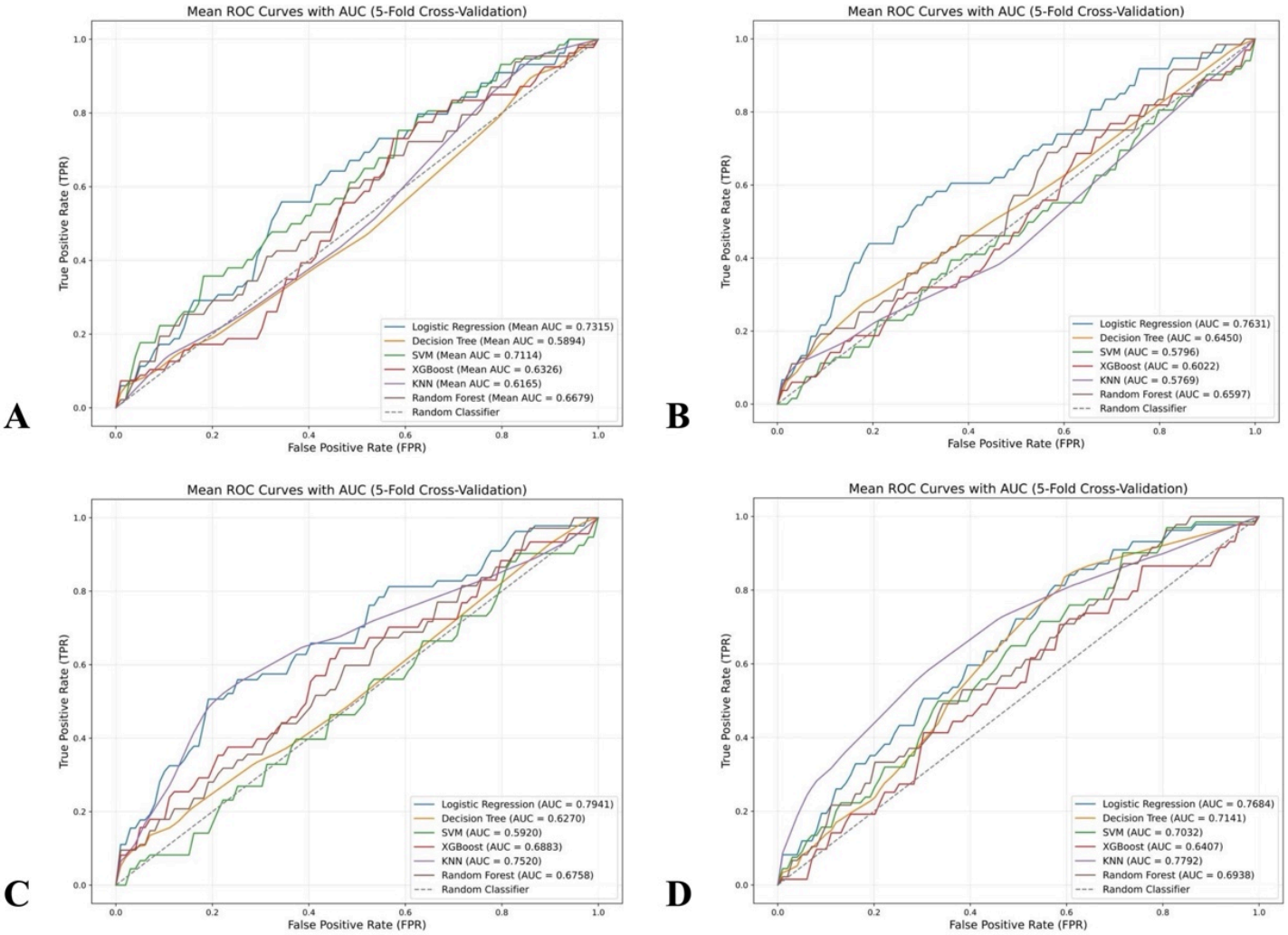


Figure 3

Comparative analysis of receiver operating characteristic (ROC) curve results for the training set of six machine learning models in predicting HER2 status in breast cancer. (A). Intratumoral radiomics group; (B). Intra- + peritumoral 3mm radiomics group; (C). Intra- + peritumoral 6mm radiomics group; (D). Intra- + peritumoral 9mm radiomics group. SVM, support vector machine, KNN, K-nearest neighbors.

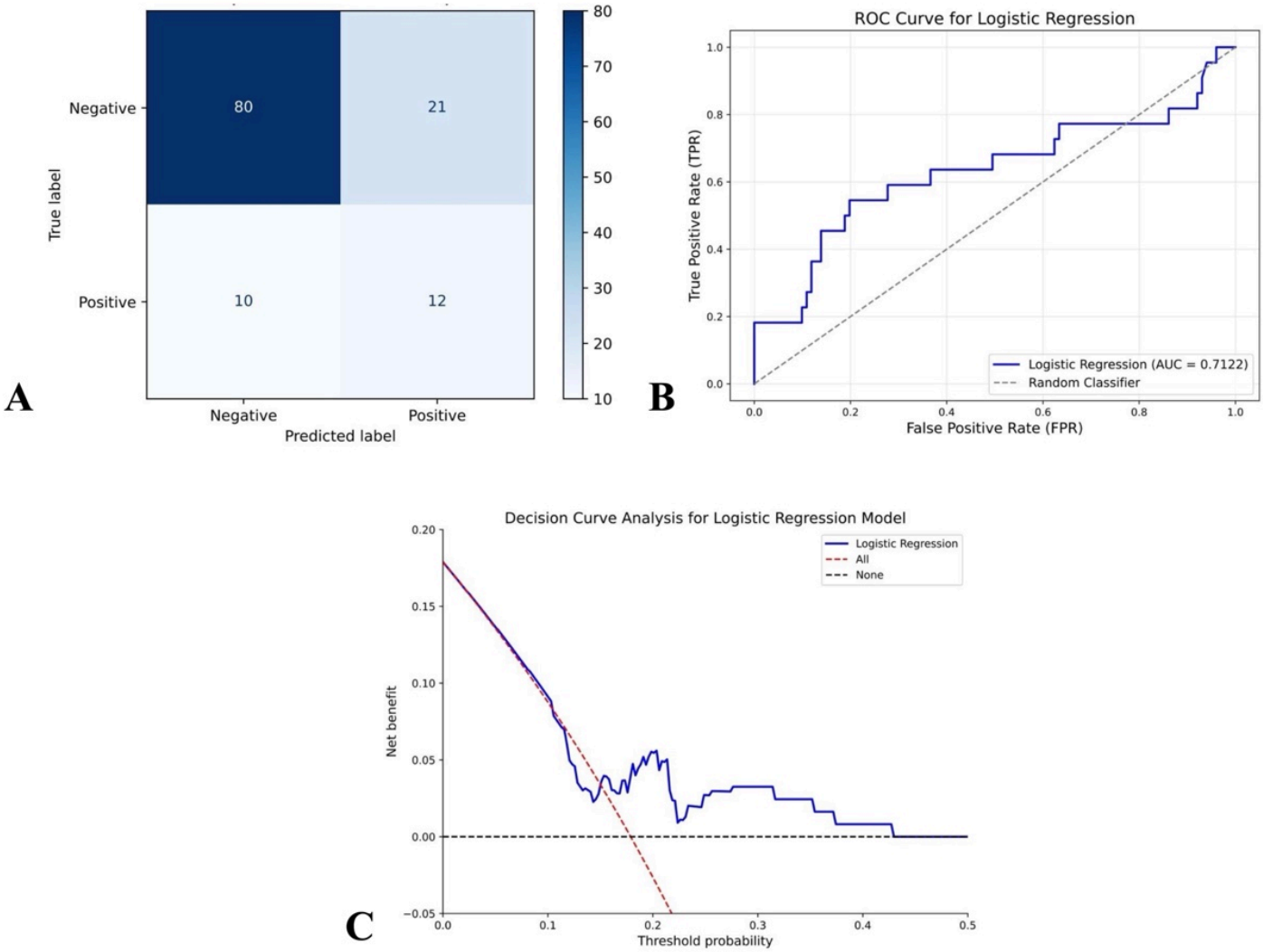


Figure 4

Evaluation of the logistic regression (LR) model on the testing set. (A) Confusion matrix displaying the classification results of the LR model, with true negatives (80), false positives (21), false negatives (10), and true positives (12). (B) Receiver operating characteristic (ROC) curve illustrating the predictive performance of the LR model, with an area under the curve (AUC) of 0.712. (C) Decision curve analysis (DCA) showing the net benefit of the LR model across a range of threshold probabilities, with higher net benefit observed at lower thresholds and diminishing returns at higher thresholds.

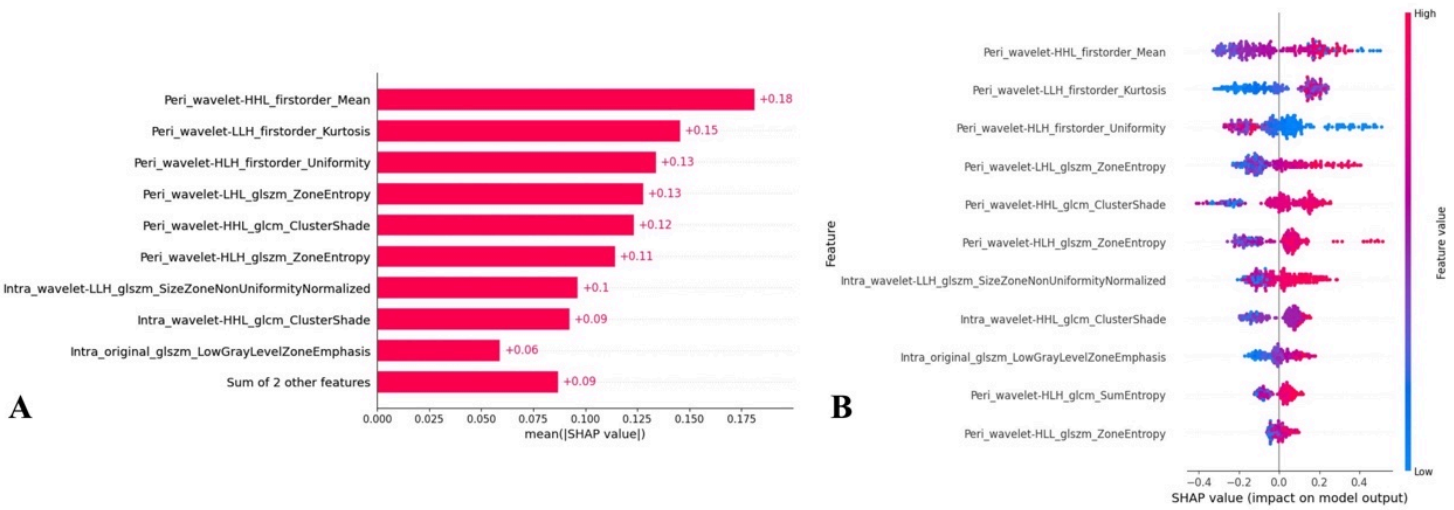


Figure 5

SHAP analysis of the LR model. (A) Displays the overall importance of each feature, with longer bars indicating features that have the most impact on the model's predictions; (B) The SHAP summary plot provides how each feature influences individual predictions, with dots representing samples and color indicating whether the feature value is high (red) or low (blue). The horizontal position of the point indicates the SHAP value; positive values indicate a higher likelihood of HER2 positivity, and negative values indicate the opposite. SHAP, Shapley additive explanations.

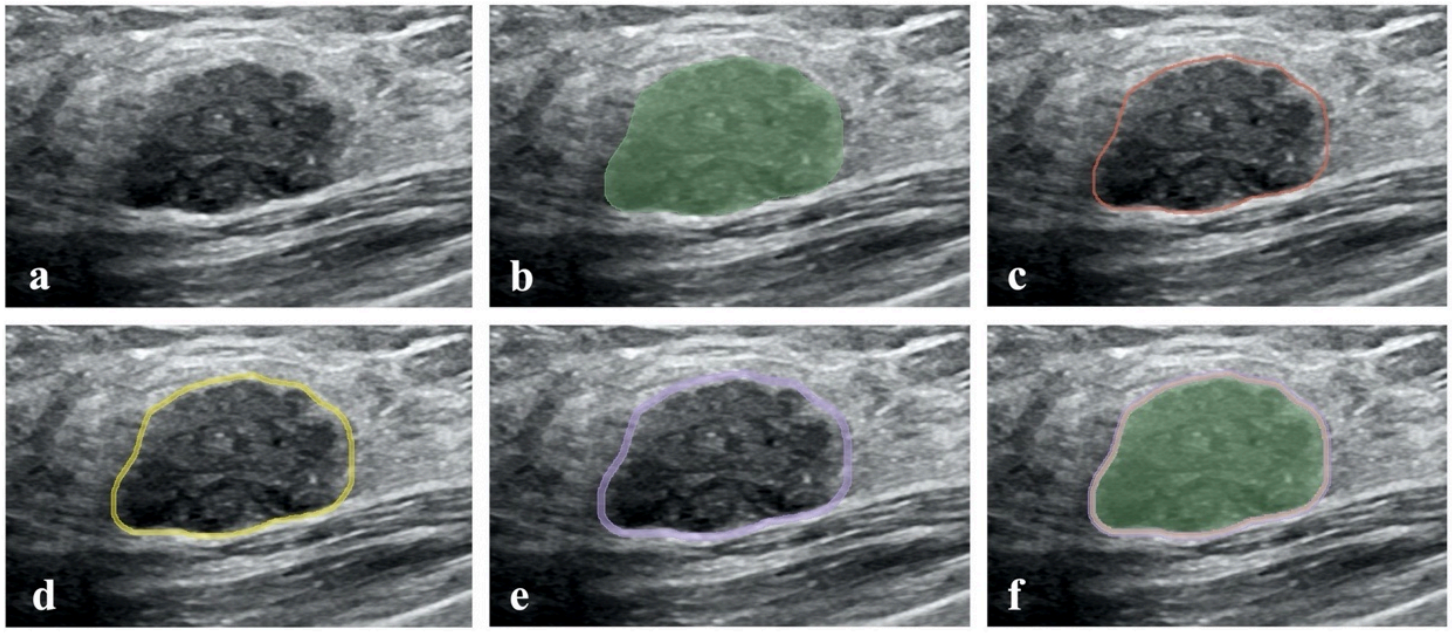


Figure 6

(a-f) Demonstration of breast US lesions and corresponding peritumor areas in a patient with pathologic findings of invasive ductal carcinoma HER2 positive. (a) Gray-scale US image of the lesion; (b) Depicted

intratumoral region of interest; (c) Peri-tumor 3mm region of interest; (d) Peri-tumor 6mm region of interest; (e) Peri-tumor 9mm region of interest; (f) Intra- and peritumoral combined region of interest.