Nomogram Based on Clinicopathologic and US Characteristics: Axillary Nodal Evaluation Following Neoadjuvant Chemotherapy in Patients with Biopsy-Proven Node-Positive Breast Cancer

Jia-Xin Huang
Sun Yat-sen University Cancer Center
Jia-Hui Huang
Guangzhou University
Yi-Jie Chen
Fujian Medical University Cancer Hospital, Fujian Cancer Hospital
Xue-Yan Wang
Sun Yat-sen University Cancer Center
Yan-Fen Xu
Sun Yat-sen University Cancer Center
Ming-Jie Wei
Sun Yat-sen University Cancer Center
Li-Na Tang
Fujian Medical University Cancer Hospital, Fujian Cancer Hospital
Xiao-Qing Pei (peixq@sysucc.org.cn)
Sun Yat-sen University Cancer Center

Research Article

Keywords: breast neoplasm, chemotherapy, lymph node, ultrasound

Posted Date: June 1st, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1699310/v1

Nomogram Based on Clinicopathologic and US Characteristics: Axillary Nodal Evaluation Following Neoadjuvant Chemotherapy in Patients with Biopsy-Proven Node-Positive Breast Cancer

Authors

Jia-Xin Huang[*1], Jia-Hui Huang [*2], Yi-Jie Chen[3], Xue-Yan Wang[1], Yan-Fen Xu[1], Ming-Jie Wei[1], Li-Na Tang[3], Xiao-QingPei[1]

Affiliations

1 Department of Medical Ultrasound, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, 510000, China
2 Institute of Artificial Intelligence and Blockchain, Guangzhou University, Guangzhou, 510000, China
3 Department of Medical Ultrasound, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, Fuzhou, 350014, China
[*]These authors contributed equally to this work.

Corresponding author

Li-Na Tang, BD, Department of Medical Ultrasound, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, No. 420 Fuma Road, Fuzhou, Fujian Province, China, 350014
Phone number:86+13625079386
E-mail address: tanglina@fjzlhospital.com
Xiao-Qing Pei, PhD, Department of Medical Ultrasound, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, No. 651 Dongfeng Road East, Guangzhou, Guangdong Province, China, 510000
Phone number:86+13560172209
E-mail address: peixq@sysucc.org.cn

Abstract

Objective: To avoid surgical over-treatment of the axilla in patients with lymph node (LN) conversion following neoadjuvant chemotherapy (NAC), high-performing axilla staging procedures are needed. This study is designed to develop a convenient modality to predict the axillary response to NAC in breast cancer patients.

Methods: In this retrospective study, a total of 1046 patients with breast cancer who received NAC followed by axillary lymph node dissection (ALND) between 2015 and 2021 were identified from a maintained database. The training set included 607 breast cancer patients with biopsy proven positive LNs at initial diagnosis, and receiving NAC followed by ALND. Clinicopathologic and ultrasound (US) characteristics were analyzed, and a nomogram was generated to predict the probability of axillary LNs residual metastasis. The predictive performances of models were assessed using multivariate logistic regression and receiver operator characteristic curve (ROC) analyses. The nomogram integrating clinicopathological and US characteristics was validated with an external cohort of 242 patients.

Results: In this study, 49.75% and 32.23% patients achieved axillary pathological complete response (pCR) after NAC in the training and external validation sets, respectively. Multivariate analysis indicated that expression of estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), Ki-67 score, and clinical nodal stage were independently significant factors for predicting the nodal response to NAC. Location and radiological response of primary tumors, cortical thickness and shape of LNs on US were also significantly associated with nodal pCR. The area under the ROC curve (AUC), estimating the ability of clinicopathologic model to determine axillary status after NAC, was 0.72 and that of US model was 0.81 in the training cohort. AUCs of the nomogram based on clinicopathologic and US characteristics for the training and validation sets were 0.86 and 0.82, respectively.

Conclusions: Nomogram incorporating routine clinicopathologic and US characteristics can predict nodal pCR in node-positive breast cancer patients receiving NAC and may be a feasible modality to aid clinicians in treatment decisions.

Key words: breast neoplasm; chemotherapy; lymph node; ultrasound

Background

Neoadjuvant chemotherapy (NAC) followed by surgery is the recommended treatment for patients with node-positive breast cancer [1]. Breast cancer patients with pathological complete response (pCR) of the lymph node (LN) after NAC have improved prognosis outcomes [2]. Over the past decades, patients with pathologically confirmed nodal involvement have undergone axillary lymph node dissection (ALND) following NAC regardless of the nodal response. However, only 50–60% of breast cancer patients with initially node-positive disease who received NAC, presented residual axillary nodal disease [3]. Moreover, extensive axillary surgery may lead to considerable morbidity such as lymphedema, arm pain, and decreased range of motion [4]. Thus, over the last decades, the management of axilla disease following NAC in patients with node-positive breast cancer has become gradually less radical and invasive [5,6].

There is an ongoing discussion of alternative treatment strategies to ALND for patients with nodal pCR following NAC. Several prospective, multicenter studies have investigated the SLNB performance for axilla LNs evaluation after NAC in patients with biopsy-proven node-positive breast cancer. This showed the unacceptable FNR of 12.6-14.1% [3,7] with various detection rates [8]. In addition, several groups have been working on ways to remove the clipped LNs using targeted axillary dissection [9-11]. From the surgery perspective, accurate prediction of axillary pCR is of utmost interest to enable the omission of ALND.

Unfortunately, even if patients with excellent response to chemotherapy may be potential candidates for procedures instead of ALND, it is still not clear how the status of axillary LNs should be determined, with several institutes depending on clinical examination only and others using additional imaging means like ultrasound (US) [12-13]. Several studies have developed clinicopathologic models for predicting nodal response to NAC with AUC of 0.65 - 0.79 [14,15]. However, US has been a preferred choice for axilla assessment in breast cancer patients due to its practicality, accessibility, dynamic observation, and lack of radiation [16-18]. According to the current guidelines, the most appropriate imaging modality in the assessment of residual disease in axillary LNs after NAC is US [19]. However, its moderate sensitivity and low specificity make conventional US alone insufficient to determine axillary status after NAC and guiding clinicians in treatment decisions [16]. Overall, how LNs status is assessed after NAC for breast cancer remains undefined. High-performing assessment for axillary LNs after NAC is warranted to minimize the surgical overtreatment of the axilla in breast cancer patients.

This study was designed to assess clinicopathologic and imaging predictors of nodal response to NAC for patients with pathologically confirmed node-positive breast cancer at initial diagnosis. We also aimed to develop a nomogram predicting the likelihood of the conversion of axillary LNs that might aid clinicians in treatment decisions.

Materials and methods

Study population

Patients with breast cancer who received NAC followed by ALND between 2015 and 2021 at the Sun Yat-Sen University Cancer Center (SYSUCC; n=783) and Fujian Medical University Cancer Hospital (FMUCH; n=263) were identified from our maintained database. 197 patients were excluded because of (i) no nodal metastases confirmed by needle biopsy before treatment (n=98), (ii) distant metastasis (13), (iii) history of previous axillary surgery (n=16), (iv) recurrence (n=18) and (v) no US examination for breast and axilla before NAC (n=23) or surgery (n=29). As a result, a total of 849 cases including 607 cases at the SYSUCC and 242 cases at the FMUCH were included in this study. The ethics committee of the institutional review board approved the study design and protocol. The requirement of informed consent was waived due to its retrospective nature.

US examination and image analysis

About 2-3 weeks after the last course of NAC, patients underwent pre-operative US examination for the breast and axilla. The US examinations were performed with a 7.0-12.0 linear array transducer [Siemens S2000 (Siemens Medical Solutions, Mountain View, CA, USA), GE Logiq 9, GE Logiq S8 (Healthcare, Milwaukee, WI, USA) or Philips iU 22 (Philips Healthcare, Bothell, WA, USA)]. During the US examination before surgery, US features of the breast lesions based on BI-RADS lexicon and axillary LNs were recorded by radiologists with at least 3 years of experience in breast US and with the knowledge of US images at initial staging. For the evaluation of US characteristics of breast tumors and axillary LNs in this study, two board-certified radiologists retrospectively reviewed US images to reach a consensus. First, the location of breast tumors on US was recorded. Second, the largest diameters of breast tumors on US before NAC and surgery were recorded and the radiological response to NAC was determined according to RECIST 1.1[20]. In case of multifocality, we only evaluated the largest tumor as index. Finally, for US features of axillary LNs, the long diameter (mm), the short diameter (mm), the ratio of long/short diameter, the cortical thickness (≤3 mm or >3 mm), the shape (oval, round or irregular), the margin condition (clear or obscure), and the fatty hilum and microcalcification status were recorded [21-23].

Pathological evaluation

The pre-NAC pathological diagnosis of breast tumors and axillary LNs was determined using US-guided core needle biopsy. The hormonal receptor (HR) expressions including estrogen receptor (ER) and progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 were detected by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) [24]. After NAC, all patients underwent mastectomy or breast-conserving surgery accompanied by ALND. LNs were stained with hematoxylin and eosin (HE) to observe malignant cells and to confirm the presence or absence of metastasis. Pathological complete response (pCR) was defined as the absence of residual metastasis in all LNs of a case. All pathological results were determined in consensus by two board-certified

pathologists.

Data collection

Clinical and pathology reports have been reviewed to record the clinicopathologic characteristics of all cases, including age, menopausal status, IHC characteristics of breast tumor, breast tumor stage, nodal stage, and pathological status of axillary LNs postoperatively. Tumor and nodal staging were performed at initial diagnosis using the criteria of the 8th American Joint Committee on Cancer [25]. US characteristics of breast tumor have been recorded retrospectively including the location of breast tumor, the largest diameters of breast tumors before NAC and surgery as assessed by US, and the radiological response to NAC. For US characteristics of axillary LNs, the long diameter, the short diameter, the ratio of long/short diameter, the cortical thickness, the shape, the margin condition, and the fatty hilum and microcalcification status were also recorded.

Statistical analysis

Data have been summarized using standard descriptive statistics and frequency tabulation. Univariate assessment was performed using a logistic regression model. Multivariate logistic regression analysis was further performed to identify independent predictors of axillary response to NAC. Statistically significant characteristics in the multivariate logistic regression stepwise analysis have been used to create the clinicopathologic model and US model, respectively. A combined model was subsequently developed by integrating the clinicopathologic and US characteristics. Receiver operator characteristic (ROC) curve analysis was performed to assess the predictive performance of these models. The area under the ROC curve (AUC) was calculated to quantify the ability to rank patients by risk. The predictive value of each model was also represented by the sensitivity and specificity. Multivariate logistic regression analysis was used to generate a nomogram to predict the nodal response to NAC in node-positive breast cancer patients. Variables with $p < 0.05$ on multivariable analysis were included in the nomogram. Finally, the nomogram was validated with the external cohort. A calibration curve was generated to show the association between the observed outcome frequencies and the predicted probabilities by categorizing patients on the basis of their predictive probability of residual metastasis of axillary LNs. All statistical analyses were performed using R version 3.2.0 software (Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The characteristics of the training and validation cohorts are summarized in Table 1. and Table 2. The axillary pCR rates were 49.75% (302/607) in the training set and 32.23% (78/242) in the external validation set, respectively. At the SYSUCC, we found a significantly higher pCR rate of axillary LN (302 patients, 49.75%) than that of breast tumor (173 patients, 25.2%). The axilla response to NAC was also significantly superior to breast in the external validation cohort (pCR, 32.23% vs.

22.31%), as shown in Table 2. Kappa values between the NAC response of breast and axilla were 0.42 and 0.26 in the training and external validation cohort, respectively.

Univariate analyses

Table 3 summarizes the univariate analyses for the training cohort to identify predictive characteristics of axillary pCR. Except for the menopausal status, clinical tumor stage and size of breast tumor on US before NAC, clinicopathologic and US characteristics had statistical significance for predicting nodal response to NAC. The odds of nodal residual metastasis were significantly improved for cases with: advanced age, high nodal stage, tumors with ER+, PR+, HER2-, low Ki-67 score, tumor on the lateral part of the breast, multifocal disease, large breast tumor after NAC, poor response to NAC on US, and LN with large size, small ratio of long/short diameter, oval or irregular shape, absence of fatty hilum, ill-defined margin and presence of microcalcification on US.

Clinicopathologic model

Significant clinicopathologic characteristics in the univariate analysis were incorporated into multivariate logistic regression analysis. Multivariate analysis revealed that clinical nodal stage, expression of ER, HER2 and Ki-6 were independently significant factors for predicting the nodal response to NAC, as shown in the Appendix A. The final model equation was then designed to calculate patient-specific probabilities of having residual nodal metastasis after NAC. AUC for the ability of clinicopathologic characteristics to determine axillary status after NAC was 0.72, with a sensitivity of 73.13% and a specificity of 62.83% in the training cohort, while AUC was 0.68 with a sensitivity of 74.50% and a specificity of 53.15% in the validation cohort.

US model

Location and radiological response of breast tumors, cortical thickness, and shape of LNs on US were significantly associated with the pathological response of LNs to NAC in the multivariate analysis, as presented in Appendix B. A US model was constructed with independent US predictors. The AUC for the ability of US characteristics including primary tumors and axillary LNs features to determine axillary status after NAC was 0.81, with a sensitivity of 74.38% and a specificity of 78.44% in the training cohort. While in the validation cohort, AUC was 0.76 with a sensitivity of 68.46% and a specificity of 74.77%.

Combination model

The aforementioned factors including clinicopathologic and US characteristics were included in the multivariate analysis and combined models, as shown in Table 4. The clinical nodal stage before treatment, expression of ER, HER2 and Ki-67, the location and radiological response of breast tumor, cortical thickness, and shape of LNs on US were significantly associated with nodal response to NAC in the multivariate analysis.

A combined model was developed by integrating all independent predictors for nodal restaging after NAC. AUC of the combined model for predicting nodal status after NAC was 0.86 with a sensitivity of 85.94% and a specificity of 76.58% at the SYSUCC, as shown in Table 5. Appendix C summarizes pCR and non-pCR rates of breast or axillary node after NAC at the SYSUCC. And Appendix D shows the predictive performance of the combined model in the different subtypes. The highest nodal pCR (55 patients, 71.43%) were found in the HR- HER2- subtype (77 patients). The greatest performance of the combined model for predicting nodal response to NAC was achieved in the HR- HER2- subtype, as shown in Fig 1. In the HR- HER2- subtype, AUC of the combined mode for predicting nodal status after NAC was 0.97 with a sensitivity of 95.45% and a specificity of 94.55%. Table 6 shows the performance of the combined model for predicting nodal status after NAC in the external validation cohort. AUC of the combined model was 0.82 with a sensitivity of 81.88% and a specificity of 62.16% in the validation cohort.

Nomogram based on combined clinicopathologic and US characteristics

The independently associated predictors, including clinicopathologic and US characteristics, have been used to create the nomogram model aiming to predict the likelihood of nodal residual disease after NAC (Fig 2). Calibration curves of the nomogram model in the training and validation cohorts were plotted to assess the consistency between the predicted probability of residual metastasis following NAC and actual results (Fig 3). The bias curves for the training and validation sets are both close to the ideal line, and substantial agreement can be observed between the predictions and observations. The ROC curve also demonstrated a great performance of the nomogram of the combined model for predicting the nodal response to NAC in both the training and validation cohorts (Fig 4).

Discussion

Traditionally, ALND is indicated in patients with pathologically confirmed nodal involvement prior to NAC, leading to considerable complications such as lymphedema, arm pain, and restricted arm movement. Just as NAC can eradicate disease in the breast, it also can eradicate nodal disease in breast cancer patients [26]. Many studies, including ours, have shown very high pCR rates of axillary LN [3,7,26]. Our study suggested a significantly higher pCR rate of axillary LN than that of breast tumor at both institutes. And the less invasive approach of axillary surgery is increasingly being considered for patients with nodal pCR [3,5-8]. Unfortunately, accurate identification of these patients likely to have a nodal pCR has been difficult.

Among the clinicopathologic characteristics, we identified low nodal stage before treatment, ER negativity, HER2 positivity and high Ki-67 score as factors associated with nodal pCR in breast cancer patients receiving NAC. On the other hand, US was also proved to play a significant role in the axilla management of breast cancer patients receiving NAC [12,13,18]. In our study, none of the residual disease on the lateral part of the breast, the excellent response of primary tumor on US, cortical

thickness of ≤ 3 mm and oval shape of axillary LNs were independent predictors for nodal pCR. The cortical thickness of LNs was the strongest predictor [odds ratio (OR), 5.93; 95% confidence interval (CI), 4.11-8.57]. Furthermore, we developed a nomogram integrating clinicopathologic and US predictors that estimate the likelihood of axillary residual disease following NAC in breast cancer patients.

Our study showed that the nodal response to NAC varies according to the tumor biology. ER negativity, HER2 positivity, high Ki-67 score were identified as predictors of nodal pCR in breast cancer patients receiving NAC. These results are consistent with studies reporting higher pCR rates of breast cancer among basal-like and HER2+/ER- subtypes compared with luminal subtypes [26,27]. The clinicopathologic model integrating the above mentioned characteristics and clinical nodal stage can be developed prior to treatment and may be used as an adjunct to clinical decision making. Specifically, the use of NAC often is driven to downstage the primary breast tumor, increasing the chances of surgery or breast-conserving surgery. Considering the omission of extensive axillary surgery in patients with nodal disease eradicated by chemotherapy, NAC may be considered as a route to downstage the axilla as well. Therefore, this clinicopathologic model may aid clinicians in chemotherapy regimen decisions, as well as provide information to surgeons regarding surgical management of the axilla after NAC. However, similar to previous studies [14,15], our study proved that clinicopathologic model alone was not sufficient to identify the remaining nodal metastasis in breast cancer patients receiving NAC.

While a large number of studies focused on the performance of US in the evaluation of axillary LNs prior to treatment [28, 29], only a few studies have investigated the value of axillary US following NAC [12,13,16-18] and not all of them reported performance data [9,21]. In addition, prediction of axillary response to NAC on US depended on various standards set by radiologists in the previous studies [16]. The lack of consensus on scoring systems for abnormal LNs on US might be responsible for diverse sensitivity and specificity of US for predicting axillary response to NAC, ranging from 37 to 100% and 37 to 92%, respectively [16]. Our study assessed the US characteristics of both axillary LN and primary tumor, and then developed a US model using multivariate logistic regression analysis. Among the US characteristics, the cortical thickness of LN was the strongest predictor of axillary response to NAC. The tumour cells drain into LN through the afferent lymphatic vessel, infiltrate into the marginal sinuses, accumulate in the cortex of LN. In generally, therefore, the cortex of the metastatic LNs is thicker than that of benign LNs on US. In addition to axillary LN, US characteristics of primary tumor, including the location of breast tumor and tumor response to NAC, also were significant independent predictors of axillary response to NAC.

Our study found that the combined model incorporating clinicopathologic and US characteristics had a higher AUC for the prediction of nodal response to NAC compared with the clinicopathologic model (training cohort, 0.86 vs. 0.72, $p < 0.001$; validation cohort, 0.82 vs. 0.68, $p < 0.001$). The sensitivity of the combined model for predicting nodal response to NAC (85.94% and 81.88% in the training cohort and

validation cohort, respectively) was higher than that of the clinicopathologic model (73.13% and 74.50% in the training cohort and validation cohort, respectively), suggesting that the combined model might benefit from US characteristics to reduce FNR for the predictive ability. In the training cohort, the combined model showed a FNR of 14.06%, comparable to that of SLNB [3,7]; furthermore, the FNR of the combined model was 4.55% in the HR - HER2 - subtype which achieved the highest nodal pCR of 71.43%. Our study used valuable pathological data through the core needle biopsy of the breast tumor, a standard procedure before NAC. On the other side, US is a routine examination in breast cancer patients before surgery at our institute and it is recommended to assess the axillary LNs after NAC by the ACR. Therefore, this combined model does not require additional procedures and serves as a more convenient, lower-cost, less time-consuming, and non-invasive approach compared to SLNB. Moreover, the specificity of the combined model to predict the axillary status after NAC (76.58% and 62.16% in the training cohort and validation cohort, respectively) was higher than that of the clinicopathologic model (62.83% and 53.15% in the training cohort and validation cohort, respectively). This suggests that the combined model can be used to stratify more patients with nodal pCR. The combined model with US restaging for axilla may help to screen out patients who are eligible for SLNB and thereby avoid ALND [12,30,31].

In agreement with previous studies [14-17], our study suggested that the model incorporating tumor clinicopathologic characteristics demonstrated moderate performance in predicting nodal pCR while axillary US still limitedhas limitations in the accurate assessment of the nodal response to NAC for breast cancer. Therefore, a nomogram based on US and clinicopathologic characteristics was developed in this study among which the variables are easily achieved without complicated processes. Nomogram is a simple tool for decision-making that have been widely used to predict medical outcomes by combining multiple risk factors. It obtained a good performance with an AUC of 0.86 in the training cohort and 0.82 in the validation cohort. Moreover, the FNR of this nomogram model was comparable to that of SLNB. Regretfully, even with the combined model through integration of clinicopathologic and US characteristics, the FNR was still dissatisfactory, and the specificity was also moderate. Thus, this nomogram based on the combined model was not aimed to substitute the SLNB but might be an adjunct to axillary management decisions. For example, it might help reduce the FNRs of SLN surgery in a further study. As shown in the previous studies axillary US after NAC was found to reduce the FNRs of SLNB to 4~9.8% using a strategy where patients with normal LNs on US underwent SLNB [12,13]. In addition, for patients with node-positive breast cancer who convert to negative nodes following NAC, targeted axillary dissection may be considered as a substitution for ALND [9-11]. The nomogram role in such scenario is expected to be defined. We analyzed the value of clinicopathologic and US characteristics of primary tumor and axillary LN, which are readily available in the routine practice, in predicting nodal response to NAC. This study was based on a relatively large sample, and the models in our study had the added advantage of the external validation. The integration of clinicopathologic and US characteristics was proved to be superior to

clinicopathologic model in the prediction of axillary status after NAC, whose FNR might be comparable to SLNB.

Our study has several limitations. The first is the unavoidable bias due to the retrospective design. The selection of index axillary LNs on US might depend on the radiologist experience. Second, this nomogram did not include the number of suspicious axillary LNs on US which was not available in this retrospective study. Third, the LNs assessed on US were not always those biopsied before NAC as no clip was placed within the biopsied LNs.

Conclusion

In conclusion, US characteristics of primary tumor and axillary LN were independently associated with axillary status post-NAC. The nomogram constructed with readily available clinicopathologic features and US characteristics improved the predictive capability. The nomogram can be used to predict the nodal response to NAC in patients with pathologically node-positive breast cancer to aid clinicians in treatment decisions.

Acknowledgments

The authors would like to express their gratitude to EditSprings (https://www.editsprings.cn) for the expert linguistic services provided. We also thank all the patients involved in the study.

Funding information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

XQP and LNT conceived and designed the project. JXH, YJC and XYW collected the data. JXH drafted the manuscript. JHH provided data analysis. JHH, YFX and MJW prepared the figures and tables. XQP critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Availability of data and material

The datasets supporting the conclusions of this study are included within the manuscript and its additional files.

Ethics approval and consent to participate

The study design and protocol were approved by the ethics committee of the institutional review board at the Cancer Center of Sun Yat-Sen University. Written informed consent was waived by the Institutional Review Board for this retrospective study.

References

1. Teshome M, Hunt KK (2014) Neoadjuvant therapy in the treatment of breast cancer. Surgical Oncology Clinics 23:505-523. doi: 10.1016/j.soc.2014.03.006.

2. Hennessy B, Hortobagyi G, Rouzier R et al (2005) Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 23:9304–9311. doi: 10.1200/JCO.2005.02.5023.

3. Boughey JC, Suman VJ, Mittendorf EA et al (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 310:1455-1461. doi: 10.1001/jama.2013.278932.

4. Galimberti V, Cole BF, Viale G et al (2018) Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 19:1385-1393. doi: 10.1016/S1470-2045(18)30380-2.

5. de Bellefon M, Lemanski C, Ducteil A et al (2018) Management of the axilla in the era of breast cancer heterogeneity. Front Oncol 8:84. doi: 10.3389/fonc.2018.00084.

6. Yan M, Abdi MA, Falkson C (2018) Axillary Management in Breast Cancer Patients: A Comprehensive Review of the Key Trials. Clin Breast Cancer 18(6):e1251-e1259. doi: 10.1016/j.clbc.2018.08.002.

7. Kuehn T, Bauerfeind I, Fehm T et al (2013) Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14:609-618. doi: 10.1016/S1470-2045(13)70166-9.

8. Fu JF, Chen HL, Yang J, Yi CH, Zheng S (2014) Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: A meta-analysis. PloS ONE 9:e105316. doi: 10.1371/journal.pone.0105316.

9. Choy N, Lipson J, Porter C et al (2015) Initial results with preoperative tattooing of biopsied

axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. Ann Surg Oncol 22:377–382. doi: 10.1245/s10434-014-4034-6.

10. Donker M, Straver ME, Wesseling J et al (2015) Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Ann Surg 261:378–382. doi: 10.1097/SLA.0000000000000558.

11. Caudle A, Yang W, Krishnamurthy S et al (2016) Improved axillary evaluation following neoadjuvant therapy for patients with nodepositive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol 10:1072–1078. doi: 10.1200/JCO.2015.64.0094.

12. Boughey JC, Ballman KV, Hunt KK et al (2015) Axillary Ultrasound After Neoadjuvant Chemotherapy and Its Impact on Sentinel Lymph Node Surgery: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance). J Clin Oncol 33:3386-3393. doi: 10.1200/JCO.2014.57.8401.

13. Peppe A, Wilson R, Pope R et al (2017) The use of ultrasound in the clinical re-staging of the axilla after neoadjuvant chemotherapy (NACT). Breast 35:104-108. doi: 10.1016/j.breast.2017.05.015.

14. Vila J, Mittendorf EA, Farante G et al (2016) Nomograms for predicting axillary response to neoadjuvant chemotherapy in clinically nodepositive patients with breast cancer. Ann Surg Oncol 23: 3501–3509. doi: 10.1245/s10434-016-5277-1.

15. Kim HS, Shin MS, Kim CJ et al (2017) Improved model for predicting axillary response to neoadjuvant chemotherapy in patients with clinically node-positive breast cancer. J Breast Cancer 20:378–385. doi: 10.4048/jbc.2017.20.4.378.

16. Banys-Paluchowski M, Gruber IV, Hartkopf A et al (2020) Axillary ultrasound for prediction of response to neoadjuvant therapy in the context of surgical strategies to axillary dissection in primary breast cancer: a systematic review of the current literature. Arch Gynecol Obstet 301:341-353. doi: 10.1007/s00404-019-05428-x.

17. Chang JM, Leung JWT, Moy L, Ha SM, Moon WK (2020) Axillary Nodal Evaluation in Breast Cancer: State of the Art. Radiology 295:500-515. doi: 10.1148/radiol.2020192534.

18. Almerey T, Villacreses D, Li Z et al (2019) Value of Axillary Ultrasound after Negative Axillary MRI for Evaluating Nodal Status in High-Risk Breast Cancer. J Am Coll Surg 228:792-797. doi:

10.1016/j.jamcollsurg.2019.01.022.

19. Expert Panel on Breast Imaging:, Slanetz PJ, Moy L, et al (2017) ACR Appropriateness Criteria® Monitoring Response to Neoadjuvant Systemic Therapy for Breast Cancer. J Am Coll Radiol 14:462-475.. doi: 10.1016/j.jacr.2017.08.037.

20. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205-16. doi: 10.1093/jnci/92.3.205 [published Online First: 2000/02/03]

21. Shin K, Weaver O, Wei W et al (2020) Sonographic features of benign and malignant axillary nodes post-neoadjuvant chemotherapy. Breast J 26:182-187. doi: 10.1111/tbj.13488.

22. Morency D, Dumitra S, Parvez E et al (2019) Axillary Lymph Node Ultrasound Following Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Breast Cancer: Results from the SN FNAC Study. Ann Surg Oncol 26:4337-4345. doi: 10.1245/s10434-019-07809-7.

23. Skarping I, Förnvik D, Zackrisson S, Borgquist S, Rydén L (2021) Predicting pathological axillary lymph node status with ultrasound following neoadjuvant therapy for breast cancer. Breast Cancer Res Treat 189:131-144. doi: 10.1007/s10549-021-06283-8.

24. Goldhirsch A, Winer EP, Coates AS et al (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 24(9):2206-2223. doi: 10.1093/annonc/mdt303.

25. Giuliano AE, Edge SB, Hortobagyi GN (2018) Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer. Ann Surg Oncol. 25(7):1783-1785. doi: 10.1245/s10434-018-6486-6.

26. Chen SC, Yu CC, Chang HK et al (2021) Discrepancy of Breast and Axillary Pathologic Complete Response and Outcomes in Different Subtypes of Node-positive Breast Cancer after Neoadjuvant Chemotherapy. J Cancer 12(17):5365-5374. doi: 10.7150/jca.62830.

27. Yang TJ, Morrow M, Modi S et al (2015) The Effect of Molecular Subtype and Residual Disease on Locoregional Recurrence in Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Postmastectomy Radiation. Ann Surg Oncol 22 Suppl 3(Suppl 3):S495-501. doi: 10.1245/s10434-015-4697-7

28. Alvarez S, Anorbe E, Alcorta P et al (2006) Role of sonography in the diagnosis of axillary lymph node metastases in breast cancer: a systematic review. Am J Roentgenol 186(5):1342 –

1348. doi: 10.2214/AJR.05.0936.

29. Marino MA, Avendano D, Zapata P, Riedl CC, Pinker K (2020) Lymph node imaging in patients with primary breast cancer: concurrent diagnostic tools. Oncologist 25(2):e231 – e242. doi: 10.1634/theoncologist.2019-0427.

30. Le-Petross HT, McCall LM, Hunt KK et al (2018) Axillary Ultrasound Identifies Residual Nodal Disease After Chemotherapy: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance). AJR Am J Roentgenol 210:669-676. doi: 10.2214/AJR.17.18295.

31. Peppe A, Wilson R, Pope R et al (2017) The use of ultrasound in the clinical re-staging of the axilla after neoadjuvant chemotherapy (NACT). Breast 35:104-108. doi: 10.1016/j.breast.2017.05.015.

Figures

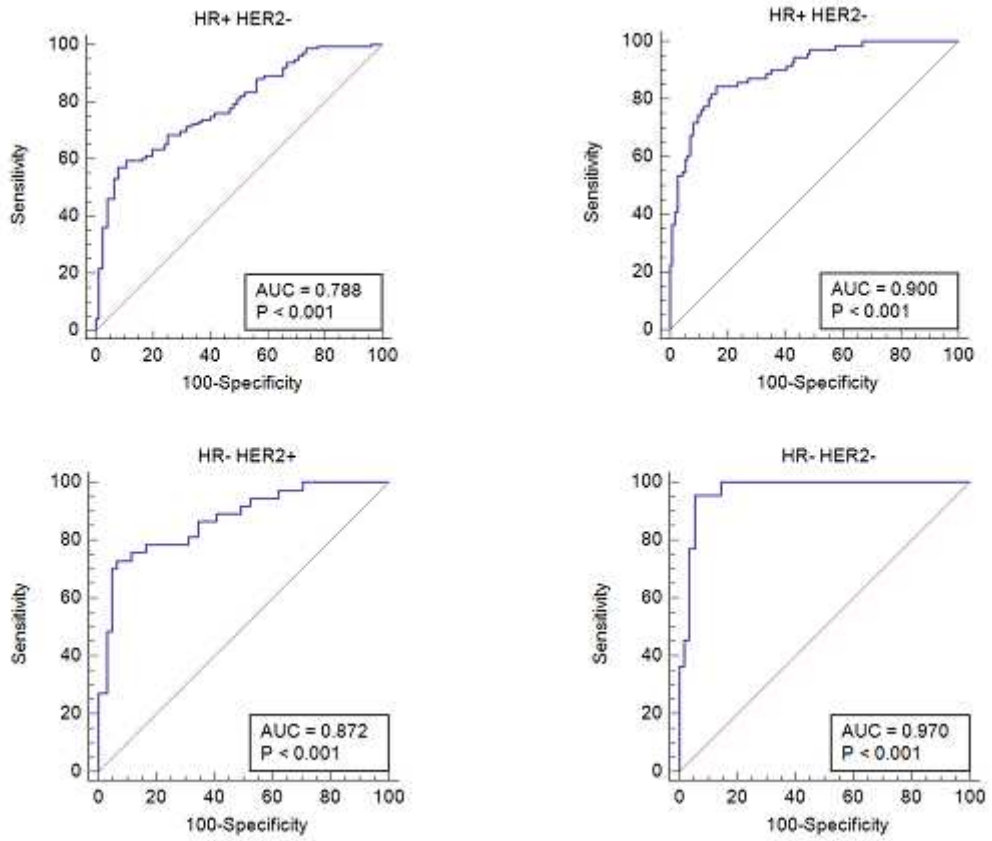

Figure 1

The receiver operating characteristic (ROC) curves of the combined model for determining axillary status after NAC in the different subtypes

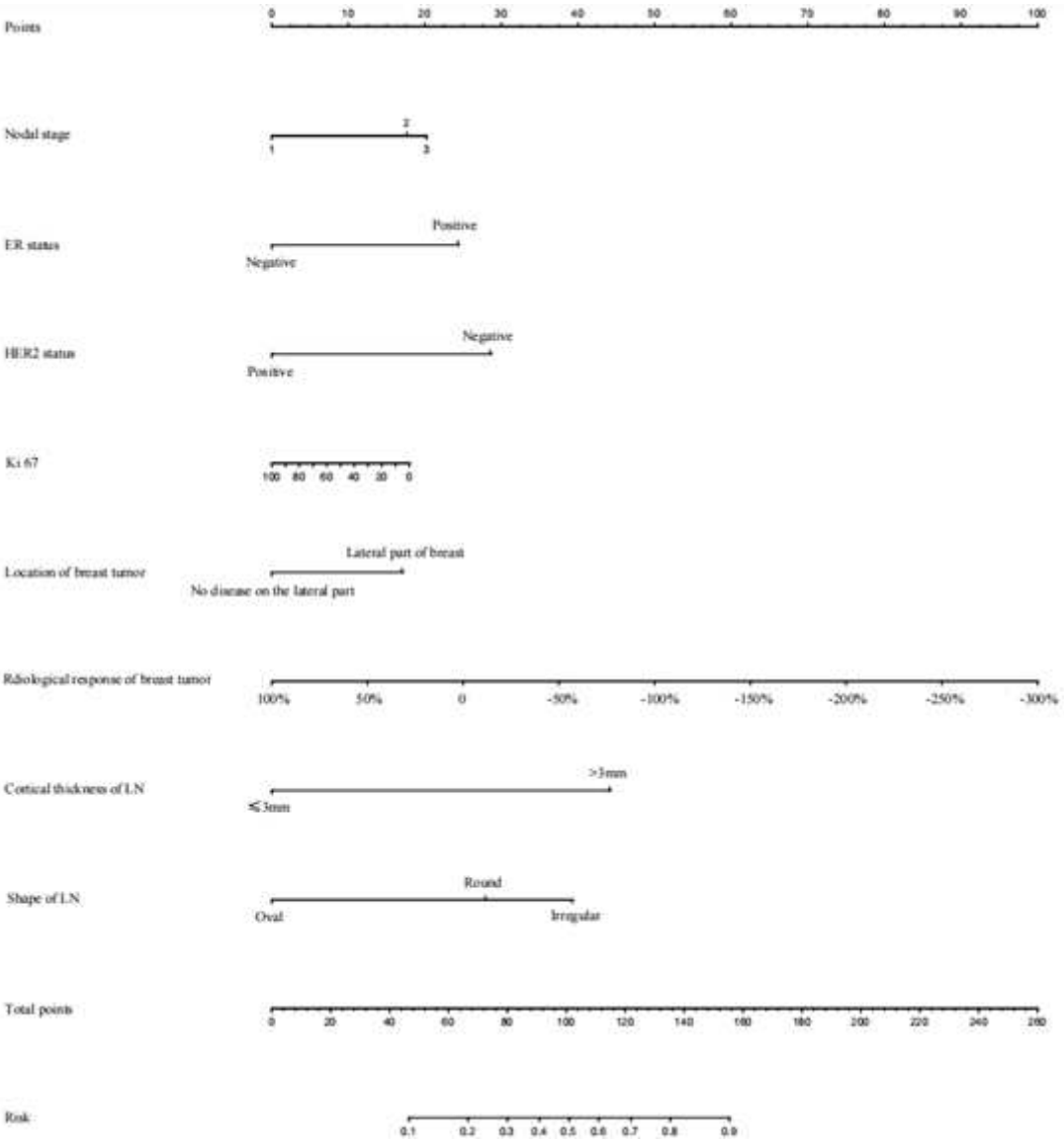

Figure 2

Nomogram for predicting axillary residual disease following NAC in breast cancer patients

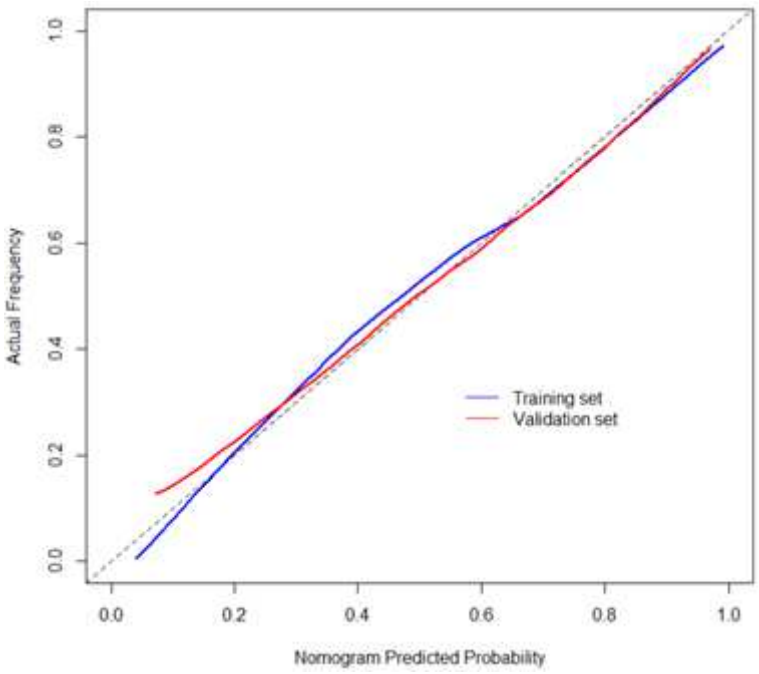

Figure 3

Calibration curve of nomogram

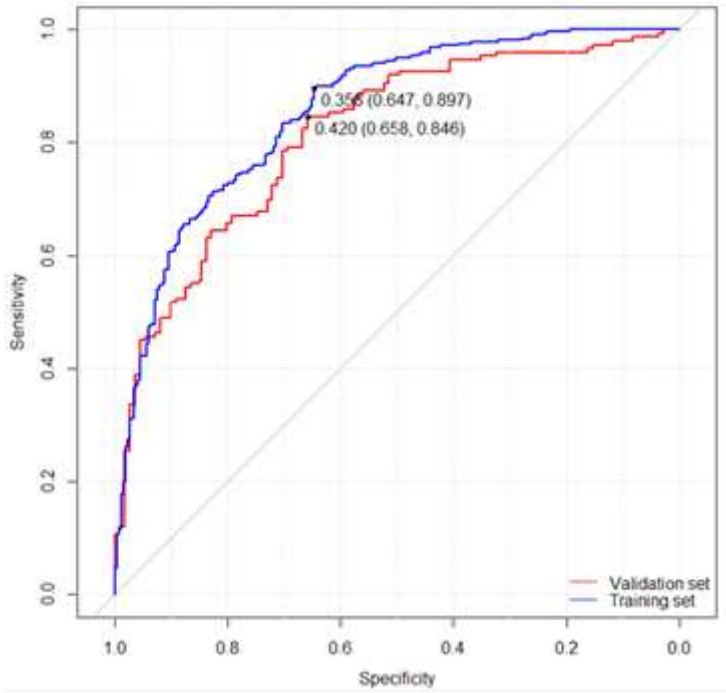

Figure 4

The receiver operating characteristic (ROC) curve of the nomogram for determining axillary status after NAC

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendixes.docx