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Original Research

Assessment of the impact of residual tumors at different sites post-neoadjuvant chemotherapy on prognosis in breast cancer patients and development of a disease-free survival prediction model

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Hanzhao Yang, Yuxia Ruan, Yadong Sun, Peili Wang, Jianghua Qiao, Chengzheng Wang and Zhenzhen Liu

Abstract

Background: Residual disease after neoadjuvant chemotherapy (NAC) in breast cancer patients predicts worse outcomes than pathological complete response. Differing prognostic impacts based on the anatomical site of residual tumors are not well studied.

Objectives: The study aims to assess disease-free survival (DFS) in breast cancer patients with different residual tumor sites following NAC and to develop a nomogram for predicting 1- to 3-year DFS in these patients.

Design: A retrospective cohort study.

Methods: Retrospective analysis of 953 lymph node-positive breast cancer patients with residual disease post-NAC. Patients were categorized into three groups: residual disease in breast (RDB), residual disease in lymph nodes (RDN), and residual disease in both (RDBN). DFS compared among groups. Patients were divided into a training set and a validation set in a 7:3 ratio. Prognostic factors for DFS were analyzed to develop a nomogram prediction model.

Results: RDB patients had superior 3-year DFS of 94.6% *versus* 85.2% for RDN and 81.8% for RDBN ($p < 0.0001$). Clinical T stage, N stage, molecular subtype, and postoperative pN stage were independently associated with DFS on both univariate and multivariate analyses. Nomogram integrating clinical tumor-node-metastasis (TNM) stage, molecular subtype, pathological response demonstrated good discrimination (C-index 0.748 training, 0.796 validation cohort), and calibration.

Conclusion: The location of residual disease has prognostic implications, with nodal residuals predicting poorer DFS. The validated nomogram enables personalized DFS prediction to guide treatment decisions.

Plain language summary

Understanding the impact of residual tumor location on prognosis after breast cancer treatment

After receiving neoadjuvant chemotherapy, a treatment to shrink tumors before surgery, some breast cancer patients may still have residual tumor cells. Our study focuses on how the location of these remaining tumors – whether in the breast, lymph nodes, or both – affects the likelihood of the cancer not returning within the next 1 to 3 years. This likelihood is known as 'disease-free survival' (DFS). We analyzed data from 953 breast cancer patients who underwent neoadjuvant chemotherapy and still had residual tumors. By comparing

Correspondence to:
Zhenzhen Liu
Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, No. 127, Dongming Road, Zhengzhou 450008, China
zlyyliuzhenzhen0800@zzu.edu.cn

Hanzhao Yang
Yuxia Ruan
Yadong Sun
Peili Wang
Jianghua Qiao
Chengzheng Wang
Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

DFS among patients with tumors remaining in different locations, we discovered that the specific location of the residual tumor significantly impacts the patient's long-term health and recovery. Additionally, we developed a predictive tool called a 'nomogram' to help doctors and patients assess the risk of cancer recurrence in the next 1 to 3 years. This tool considers various factors such as the size and type of the tumor, as well as the location and extent of the residual tumor after chemotherapy. Our research offers new insights into understanding the risk of recurrence after breast cancer treatment. This work not only enhances our comprehension of breast cancer management but also aids in devising more personalized and effective treatment strategies for patients in the future.

Keywords: breast cancer, neoadjuvant chemotherapy, nomogram, residual disease, survival

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Introduction

Breast cancer is one of the most common malignant tumors in women. For patients initially diagnosed with locally advanced breast cancer, neoadjuvant chemotherapy (NAC) is often considered.[1] The NSABPB-18 trial[2] has shown that NAC is equally effective in treating breast cancer when contrasted with postoperative adjuvant chemotherapy. Patients undergoing NAC can experience reduced tumor size, increased rates of breast conservation, and less extensive axillary staging, thus avoiding unnecessary axillary lymph node dissection.[3] More importantly, NAC allows for the assessment of the tumor's response to systemic therapy.[4,5] Studies[6–8] indicate that patients achieving complete remission in both the breast and lymph nodes after NAC exhibit significantly improved event-free survival and overall survival (OS) rates compared to those with residual disease.

Although it is known that residual tumors are related to prognosis risk, research on the specific impact of the location and size of residual tumors on prognosis is still limited. Current studies[9–11] mainly focus on pathological complete response (pCR), while patients with residual disease are considered a homogeneous group. Due to a lack of understanding of the heterogeneity of such patients, clinicians often face challenges in formulating follow-up treatment plans for patients with residual disease. There has not yet been a systematic study on the impact of residual tumors in different locations (breast, lymph nodes, or both) on long-term prognosis. Therefore, there is no unified understanding of this issue in clinical practice.[12–16] To fill this gap, it is necessary to conduct more research on subgroup analysis of patients with residual disease, to provide a basis for individualized treatment strategies based on the characteristics of residual tumors.

Therefore, in this study, to better understand the distinct prognostic implications of residual disease locations, we conducted a retrospective analysis of the clinical and pathological data of lymph node-positive breast cancer patients who did not achieve pCR after NAC. We assessed the disease-free survival (DFS) for these different types of remission and analyzed clinical and pathological factors affecting DFS. Concurrently, we developed a nomogram model to predict the 1- to 3-year DFS of these patients.

Methods

Patient selection criteria

We conducted a retrospective study at The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital. From 2015 to 2020, we reviewed the breast cancer database, which included 2930 female patients diagnosed with primary invasive breast cancer and treated with NAC. Among them, 1238 patients were diagnosed with lymph node metastasis, including axillary and/or ipsilateral supraclavicular lymph node involvement, through core needle biopsy prior to NAC. We excluded patients who (1) achieved pCR ($n = 220$); (2) had missing pathological information ($n = 34$); (3) were lost to follow-up ($n = 26$); or (4) progressed to distant metastasis ($n = 5$). Ultimately, 953 patients who received preoperative NAC and were confirmed

to have residual tumor tissue in the postoperative pathological examination were included for analysis (Figure 1).

Clinicopathological characteristics

Patients were categorized into three groups based on the anatomical location of the residual tumor: residual disease in the breast (RDB, $n = 294$), residual disease in the lymph nodes (RDN, $n = 97$), and residual disease in both breast and lymph nodes (RDBN, $n = 562$). The RDB group did not include residual ductal carcinoma *in situ*, as this was defined as pT0 if present in the breast. Lymph nodes considered included axillary and ipsilateral supraclavicular lymph nodes and isolated tumor cells in lymph nodes were regarded as lymph node tumor residue. Clinical and pathological data were collected from patients' records, including age at diagnosis, breast cancer molecular subtype [based on hormone receptor (HR) and the human epidermal growth factor receptor-2 (Her2) status], preoperative clinical staging and postoperative pathological staging (according to the American Joint Committee on Cancer/Union for International Cancer Control TNM staging[17]), NAC regimen, type of surgery, and radiation therapy information. Estrogen receptor (ER) and progesterone receptor (PR) were considered negative if the nuclear staining of tumor cells was less than 1%. Her2 negativity was defined as a Her2 score of 0 or 1+ in immunohistochemistry, or no Her2 amplification in fluorescence *in situ* hybridization. Triple-negative breast cancer (TNBC) was defined as simultaneous negativity for ER, PR, and Her2.

Outcome measurement and follow-up

DFS was defined as the time from the date of surgery to local-regional recurrence, distant metastasis, or contralateral breast cancer occurrence. Postoperative treatment was managed according to the latest guidelines at the time. For the first 2 years post-surgery, patients were followed up every 3 months in the outpatient clinic, and then every 6 months thereafter, and annually after 5 years. When patients were unable to attend the clinic, follow-up information was collected *via* telephone. All patients were followed up until December 2022, and patients without DFS events at the last follow-up were censored. This study was approved by the Ethics Review Committee of the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital (No. 2017407). The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement[18] (Supplemental Table 1).

Statistical analysis

For categorical variables, frequencies and proportions were reported as descriptive statistics, while for continuous variables, means (standard deviations) were used. We estimated DFS periods using the Kaplan–Meier method and assessed differences in DFS among groups with the log-rank test. To ensure robust statistical analysis, patients were divided into a training set and a validation set in a 7:3 ratio. Differences between the training and validation sets were evaluated using the independent sample *t*-test or chi-square test. In the training set, univariate analyses were conducted using the Cox proportional hazards regression model. Variables with a p value less than 0.1 in univariate analysis were included in the multivariate analysis to identify independent predictors significantly associated with DFS. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each variable. Based on the results of the multivariate analysis, we developed a nomogram for predicting 1-year, 2-year, and 3-year DFS in patients. To assess the predictive accuracy of our nomogram, we utilized the concordance index (C-index) and receiver operating characteristic (ROC) curves. The C-index was calculated to quantify the nomogram's ability to correctly predict DFS, with values closer to 1.0 indicating higher accuracy. Calibration of the model was assessed using a bootstrap method with 1000 resamples to compare the predicted DFS with the observed DFS. Finally, the clinical utility of the predictive model was evaluated using decision curve analysis (DCA), quantifying the net benefit at various threshold probabilities. All analyses were performed using R version 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria), with a two-tailed p value < 0.05 considered statistically significant.

Results

Patient baseline characteristics

The study ultimately included 953 patients: 294 in the RDB group, 97 in the RDN group, and 562 in the RDBN group. The median age of the study population was 49 ± 10 years. Among them, 476 patients (49.9%) had HR+Her2− molecular

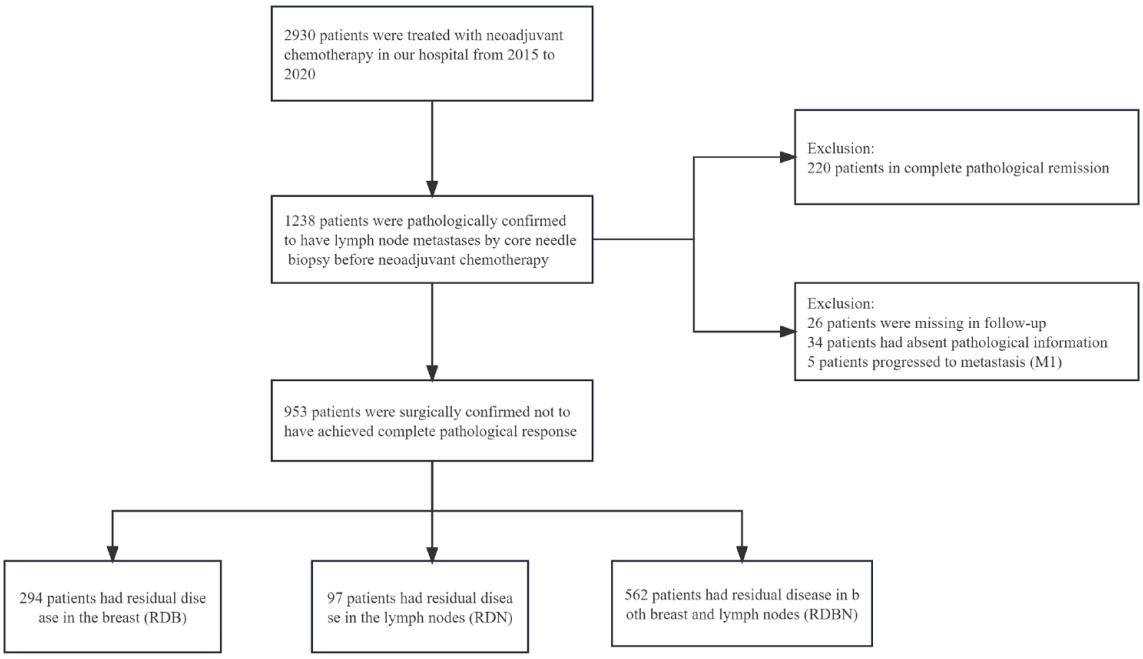

Figure 1. Patients' enrollment and exclusion flow chart.

subtype, 317 (33.3%) were HR+Her2+, 81 (8.5%) were HR−Her2−, and 79 (8.3%) were HR−Her2+. Overall, 608 patients (63.8%) received an anthracycline combined with a taxane chemotherapy regimen, 318 (33.4%) received a taxane-based regimen, and only 27 (2.8%) received an anthracycline-based regimen. Regarding surgical choice, 81 patients (8.5%) opted for breast-conserving surgery, while 872 (91.5%) underwent mastectomy. Other patient characteristics are detailed in Table 1.

Survival analysis

During a median follow-up of 37.7 [36.3–39.1] months among all women, 148 patients (15.5%) experienced a recurrence. The overall cohort's 3-year DFS was 84.5%. According to the pathological response status post-NAC, the 3-year DFS for RDB, RDN, and RDBN patients were 94.6%, 85.2%, and 81.8%, respectively ($p < 0.0001$) [Figure 2(a)]. There was no significant difference in the 3-year DFS between patients with pT0 and those with residual breast disease post-treatment ($p = 0.9692$) [Figure 2(b)]. For lymph node pathological response status, patients with pN0 had a better 3-year DFS than those with residual lymph node disease ($p < 0.0001$) [Figure 2(c)]. Clinical T stage, N stage, molecular subtype, and postoperative pN stage were independently associated with DFS on both univariate and multivariate analyses (Table 2). Higher clinical T stage conferred markedly worse DFS hazards, with cT3 and cT4 tumors bearing 2.53-fold (95% CI, 1.05–6.13) and 4.50-fold (95% CI, 1.62–12.50) greater risks of events compared to cT1 tumors, respectively. Nodal involvement was also adversely prognostic, as cN3 status conveyed a 1.87-fold (95% CI, 1.30–2.70) higher hazard than node-negative disease. Molecular subtype was similarly predictive, with HR−HER2− and HR−HER2+ cancers experiencing significantly worse DFS than HR+HER2− tumors, with respective hazards of 2.13 (95% CI, 1.17–3.90) and 3.42 (95% CI, 2.05–5.69). Extensive residual disease after surgery also correlated with poorer outcomes, as pN2 and pN3 nodal stage carried 4.04-fold (95% CI, 2.29–7.14) and 5.17-fold (95% CI, 2.94–9.11) greater risks of events relative to pN0 status.

Development and validation of prognostic nomogram

Patients were divided into a training set and a validation set in a 7:3 ratio, with 667 patients in the training set and 286 in the validation set. Table 3 summarizes the clinical and pathological

Table 1. Clinicopathologic characteristics of the study patients.

Characteristic	Total ($n=953$)	RDN group ($n=97$)	RDB group ($n=294$)	RDBN group ($n=562$)	*p*
Age, year					
Mean ± SD	49 ± 10	49 ± 10	48 ± 10	49 ± 10	0.261
<50	499 (52.4%)	47 (48.5%)	172 (58.5%)	280 (49.8%)	0.039
⩾50	454 (47.6%)	50 (51.5%)	122 (41.5%)	282 (50.2%)	
Clinical T category					0.161
cT1	109 (11.4%)	18 (18.6%)	36 (12.2%)	55 (9.8%)	
cT2	643 (67.5%)	64 (66.0%)	201 (68.4%)	378 (67.3%)	
cT3	165 (17.3%)	11 (11.3%)	47 (16.0%)	107 (19.0%)	
cT4	36 (3.8%)	4 (4.1%)	10 (3.4%)	22 (3.9%)	
Clinical N category					0.003
cN1	723 (75.9%)	76 (78.4%)	242 (82.3%)	405 (72.1%)	
cN2	66 (6.9%)	9 (9.3%)	19 (6.5%)	38 (6.8%)	
cN3	164 (17.2%)	12 (12.4%)	33 (11.2%)	119 (21.2%)	
Biologic subtype					<0.001
HR+/Her2–	476 (49.9%)	57 (58.8%)	96 (32.7%)	323 (57.5%)	
HR+/Her2+	317 (33.3%)	31 (32.0%)	126 (42.9%)	160 (28.5%)	
HR–/Her2–	81 (8.5%)	4 (4.1%)	42 (14.3%)	35 (6.2%)	
HR–/Her2+	79 (8.3%)	5 (5.2%)	30 (10.2%)	44 (7.8%)	
Chemotherapy received					<0.001
Anthracycline based	27 (2.8%)	3 (3.1%)	6 (2.0%)	18 (3.2%)	
Taxane based	318 (33.4%)	24 (24.7%)	141 (48.0%)	153 (27.2%)	
Anthracycline and taxane	608 (63.8%)	70 (72.2%)	147 (50.0%)	391 (69.6%)	
Surgery type					<0.001
Mastectomy	872 (91.5%)	79 (81.4%)	261 (88.8%)	532 (94.7%)	
Breast conserving	81 (8.5%)	18 (18.6%)	33 (11.2%)	30 (5.3%)	
Pathologic T category					<0.001
T0	97 (10.2%)	97 (100.0%)	0 (0.0%)	0 (0.0%)	
T1	565 (59.3%)	0 (0.0%)	213 (72.4%)	352 (62.6%)	
T2	258 (27.1%)	0 (0.0%)	75 (25.5%)	183 (32.6%)	
T3	23 (2.4%)	0 (0.0%)	4 (1.4%)	19 (3.4%)	
T4	10 (1.0%)	0 (0.0%)	2 (0.7%)	8 (1.4%)	

(Continued)

Table 1. (Continued)

Characteristic	Total ($n=953$)	RDN group ($n=97$)	RDB group ($n=294$)	RDBN group ($n=562$)	p
Pathologic N category					<0.001
N0	294 (30.8%)	0 (0.0%)	294 (100.0%)	0 (0.0%)	
N1	276 (29.0%)	55 (56.7%)	0 (0.0%)	221 (39.3%)	
N2	200 (21.0%)	24 (24.7%)	0 (0.0%)	176 (31.3%)	
N3	183 (19.2%)	18 (18.6%)	0 (0.0%)	165 (29.4%)	
Radiation					0.074
Yes	842 (88.4%)	81 (83.5%)	254 (86.4%)	507 (90.2%)	
No	111 (11.6%)	16 (16.5%)	40 (13.6%)	55 (9.8%)	

Her2, human epidermal growth factor receptor 2; HR, hormone receptor; RDB, residual disease in breast; RDBN, residual disease in breast and lymph nodes; RDN, residual disease in lymph nodes; SD, standard deviation.

characteristics of both groups, with no significant statistical differences between them. Univariate survival analysis indicated that clinical T stage, N stage, molecular subtype, and postoperative pN stage were associated with poorer DFS prognosis (Table 4). Variables with a p value less than 0.1 in univariate analysis were further included in multivariate Cox regression analysis. Clinical T stage, N stage, molecular subtype, and postoperative pN stage were identified as independent variables associated with poorer DFS outcomes (Table 4).

Based on prognostic factors identified in the Cox regression analysis, a nomogram model for predicting 1-year, 2-year, and 3-year DFS was developed [Figure 2(d)]. This model integrates multiple prognostic factors to provide a more personalized risk assessment for each patient. The specific scores of these prognostic variables were summarized to obtain the corresponding survival probabilities for each patient. Regarding the predictive performance of the nomogram, the C-index for predicting DFS in the training cohort was 0.748 (0.695–0.801) and 0.796 (0.730–0.863) in the validation cohort, indicating good discriminative ability. Calibration plots for 1-year, 2-year, and 3-year DFS showed good consistency between predicted and actual survival probabilities in both training and validation cohorts (Figure 3). ROC curves for 1-year, 2-year, and 3-year DFS were plotted in the training and validation cohorts. The area under the curve (AUCs) for predicting 1-year, 2-year, and 3-year DFS were 0.754, 0.749, and 0.768, respectively, in the training cohort, and 0.815, 0.804, and 0.805 in the validation cohort (Figure 4). These high AUC values reinforce the model's reliability in predicting DFS. Decision curves for 1-year, 2-year, and 3-year nomograms in both training and validation cohorts demonstrated good consistency between predicted probabilities and actual clinical outcomes (Supplemental Figure 1).

Discussion

Our study encompassed 953 breast cancer patients with residual tumors post-NAC. Based on the anatomical location of tumor residuals, they were categorized into three groups: residual in the breast, in the lymph nodes, and both. Interestingly, it was observed that post-NAC, the breast was more likely to retain tumor tissue, while lymph node metastatic lesions were more likely to achieve pathological complete remission compared to primary breast lesions. This aligns with findings from previous studies.[12,14,19]

Samiei *et al.*[20] found that among cN1 patients, those without breast tumor residuals were more likely to achieve ypN0 compared to those with residuals (45% *versus* 9.4%, $p<0.001$). This correlation was notably significant in Her2 and TNBC patients, providing a basis for future clinical trials in this patient group. Other studies[21,22] have indicated that patients with Her2-positive and TNBC subtypes respond better to NAC, achieving higher rates of pCR. These findings are corroborated by our study, where among patients with tumor residuals, HR+Her− patients were the most common at 49.9%, followed by HR+Her2+ at 33.3%, and the least being HR−Her2+ and HR−Her2− at 8.5% and 8.3%,

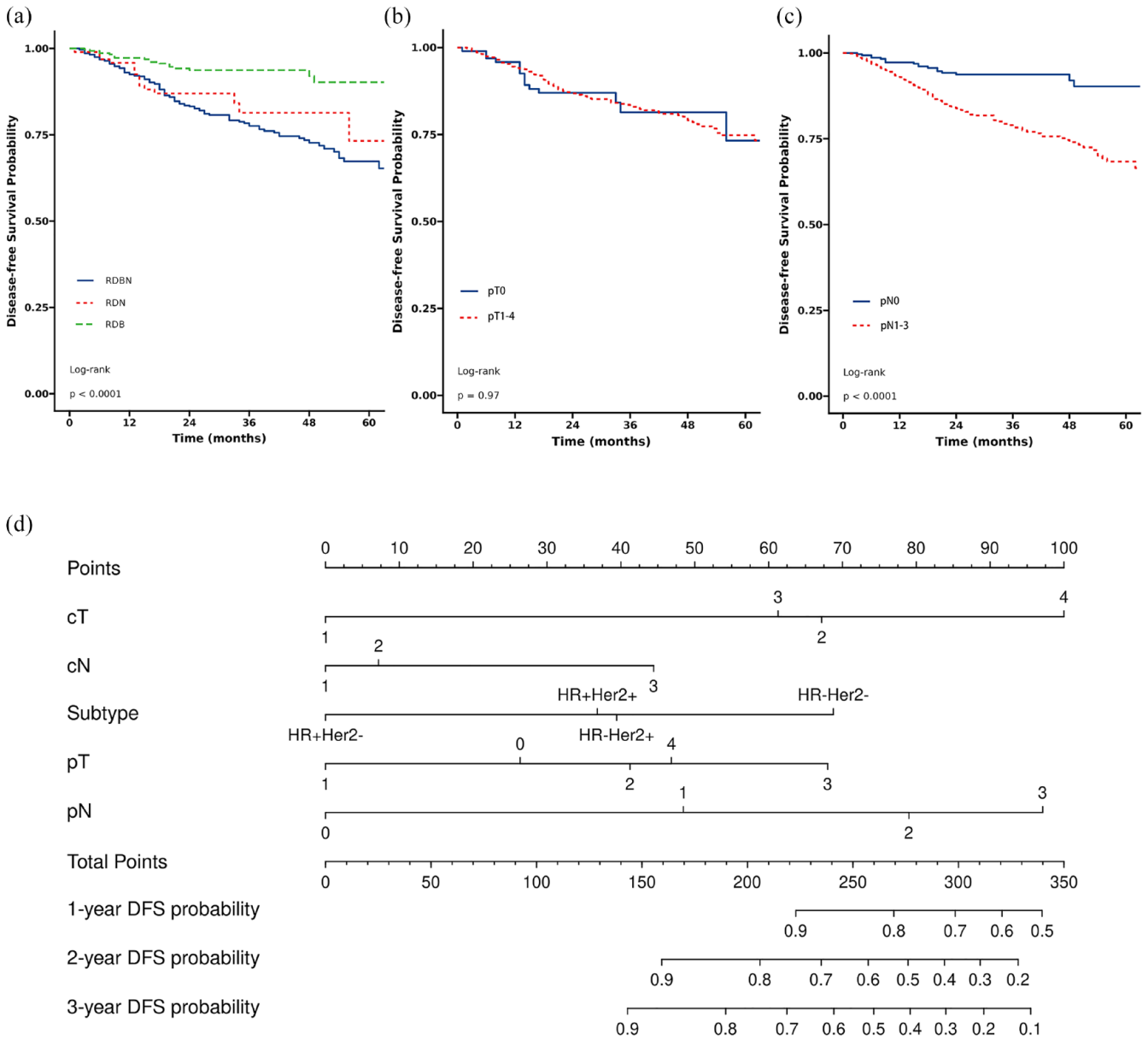

Figure 2. DFS post-NAC. (a) 3-Year DFS by residual tumor site. (b) 3-Year DFS: pT0 *versus* residual breast tumor. (c) 3-Year DFS: pN0 *versus* residual lymph node tumor. (d) Nomogram for predicting 1-, 2-, and 3-year DFS.
DFS, disease-free survival; NAC, neoadjuvant chemotherapy.

respectively. In terms of lymph node pathological remission, compared to HR+Her2− patients (20.2%), those with Her2+ (HR+Her2+ at 39.7%, HR−Her2+ at 51.9%) and TNBC patients (38.0%) had higher probabilities of lymph node pCR.

Goorts *et al.*[23] found in a study of 2366 patients that the pCR rate was 21%, and the cT stage was a significant independent predictor of pCR rate in breast cancer patients. However, our study, excluding patients with pCR, found that in patients who did not achieve pathological remission post-NAC, the probability of achieving pCR in breast tumors was not significantly different across initial breast tumor stages, with cT1–4 being 16.5%, 10.0%, 6.7%, and 11.1%, respectively ($p = 0.157$). Among patients with tumor residuals, there was no significant correlation between cT stage and breast pCR.

Table 2. Univariate and multivariate Cox regression analyses for disease-free survival of the patients.

Characteristic	Univariate		Multivariable	
	Hazard ratio (95% CI)	***P***	**Hazard ratio (95% CI)**	***p***
Age				
<50	Reference			
⩾50	0.85 (0.61–1.18)	0.330		
Clinical T category				
cT1	Reference		Reference	
cT2	2.54 (1.11–5.79)	0.027	2.41 (1.05–5.54)	0.038
cT3	3.85 (1.63–9.13)	0.002	2.53 (1.05–6.13)	0.039
cT4	5.56 (2.05–15.06)	0.001	4.50 (1.62–12.50)	0.004
Clinical N category				
cN1	Reference		Reference	
cN2	1.35 (0.70–2.60)	0.376	1.18 (0.60–2.31)	0.631
cN3	2.80 (1.99–3.94)	<0.001	1.87 (1.30–2.70)	0.001
Biologic subtype				
HR+/Her2–	Reference		Reference	
HR+/Her2+	1.21 (0.84–1.76)	0.309	1.62 (1.10–2.37)	0.014
HR–/Her2–	1.50 (0.84–2.68)	0.171	2.13 (1.17–3.90)	0.014
HR–/Her2+	2.58 (1.57–4.23)	0.001	3.42 (2.05–5.69)	<0.001
Chemotherapy received				
Anthracycline and taxane	Reference			
Taxane based	1.05 (0.73–1.50)	0.794		
Anthracycline based	1.56 (0.78–3.10)	0.208		
Surgery type				
Mastectomy	Reference			
Breast-conserving	0.52 (0.24–1.12)	0.094		
Pathologic T category				
T0	Reference		Reference	
T1	0.67 (0.38–1.18)	0.166	0.72 (0.40–1.28)	0.263
T2	1.69 (0.96–2.98)	0.070	1.49 (0.83–2.68)	0.182
T3	3.22 (1.30–7.93)	0.011	2.25 (0.89–5.73)	0.087
T4	3.47 (1.15–10.49)	0.027	1.96 (0.63–6.10)	0.244

(Continued)

Table 2. (Continued)

Characteristic	Univariate		Multivariable	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*p*
Pathologic N category				
N0	Reference		Reference	
N1	1.78 (1.00–3.19)	0.051	1.88 (1.04–3.40)	0.038
N2	3.82 (2.21–6.62)	<0.001	4.04 (2.29–7.14)	<0.001
N3	5.83 (3.42–9.94)	<0.001	5.17 (2.94–9.11)	<0.001
Group				
RDN	Reference			
RDB	0.38 (0.19–0.76)	0.006		
RDBN	1.36 (0.79–2.33)	0.265		
Radiation				
Yes	Reference			
No	0.93 (0.54–1.58)	0.776		

CI, confidence interval; Her2, human epidermal growth factor receptor 2; HR, hormone receptor; RDB, residual disease in breast; RDBN, residual disease in breast and lymph nodes; RDN, residual disease in lymph nodes; SD, standard deviation.

Table 3. Clinicopathologic characteristics in the training set and validating set.

Characteristic	Total (*n* = 953)	Training set (*n* = 667)	Validating set (*n* = 286)	*p*
Age, year				
Mean ± SD	49 ± 10	49 ± 10	48 ± 10	0.314
<50	499 (52.4)	342 (51.3)	157 (54.9)	0.305
⩾50	454 (47.6)	325 (48.7)	129 (45.1)	
Clinical T category				0.152
cT1	109 (11.4)	66 (9.9)	43 (15.0)	
cT2	643 (67.5)	459 (68.8)	184 (64.3)	
cT3	165 (17.3)	117 (17.5)	48 (16.8)	
cT4	36 (3.8)	25 (3.8)	11 (3.9)	
Clinical N category				0.479
cN1	723 (75.9)	513 (76.9)	210 (73.4)	
cN2	66 (6.9)	43 (6.5)	23 (8.0)	
cN3	164 (17.2)	111 (16.6)	53 (18.5)	

(Continued)

Table 3. (Continued)

Characteristic	Total ($n = 953$)	Training set ($n = 667$)	Validating set ($n = 286$)	p
Biologic subtype				0.705
HR+/Her2−	476 (50.0)	325 (48.7)	151 (52.8)	
HR+/Her2+	317 (33.2)	227 (34.0)	90 (31.5)	
HR−/Her2−	81 (8.5)	59 (8.9)	22 (7.7)	
HR−/Her2+	79 (8.3)	56 (8.4)	23 (8.0)	
Chemotherapy received				0.438
Anthracycline based	608 (63.8)	418 (62.7)	190 (66.4)	
Taxane based	318 (33.4)	231 (34.6)	87 (30.4)	
Anthracycline and taxane	27 (2.8)	18 (2.7)	9 (3.2)	
Surgery type				0.234
Mastectomy	872 (91.5)	615 (92.2)	257 (89.9)	
Breast conserving	81 (8.5)	52 (7.8)	29 (10.1)	
Pathologic T category				0.611
T0	97 (10.2)	64 (9.6)	33 (11.5)	
T1	565 (59.3)	394 (59.1)	171 (59.8)	
T2	258 (27.1)	188 (28.2)	70 (24.5)	
T3	23 (2.4)	14 (2.1)	9 (3.2)	
T4	10 (1.1)	7 (1.1)	3 (1.1)	
Pathologic N category				0.254
N0	294 (30.8)	217 (32.5)	77 (26.9)	
N1	276 (29.0)	189 (28.3)	87 (30.4)	
N2	200 (21.0)	141 (21.2)	59 (20.6)	
N3	183 (19.2)	120 (18.0)	63 (22.0)	
Group				0.198
RDN	97 (10.2)	64 (9.6)	33 (11.5)	
RDB	294 (30.9)	217 (32.5)	77 (26.9)	
RDBN	562 (59.0)	386 (57.9)	176 (61.5)	
Radiation				0.773
Yes	111 (11.7)	79 (11.8)	32 (11.2)	
No	842 (88.4)	588 (88.2)	254 (88.8)	

Her2, human epidermal growth factor receptor 2; HR, hormone receptor; RDB, residual disease in breast; RDBN, residual disease in breast and lymph nodes; RDN, residual disease in lymph nodes; SD, standard deviation.

Table 4. Univariate and multivariate Cox regression analyses for disease-free survival in the training set.

Characteristic	Univariate		Multivariable	
	Hazard ratio (95% CI)	***p***	**Hazard ratio (95% CI)**	***p***
Age				
<50	Reference			
⩾50	0.85 (0.57–1.27)	0.438		
Clinical T category				
cT1	Reference		Reference	
cT2	3.02 (0.95–9.62)	0.061	2.96 (0.92–9.50)	0.068
cT3	3.79 (1.13–12.67)	0.030	2.69 (0.79–9.17)	0.114
cT4	6.30 (1.67–23.77)	0.007	5.02 (1.28–19.65)	0.020
Clinical N category				
cN1	Reference		Reference	
cN2	1.27 (0.55–2.95)	0.580	1.12 (0.47–2.67)	0.793
cN3	3.00 (1.98–4.55)	<0.001	2.05 (1.29–3.25)	0.002
Biologic subtype				
HR+/Her2−	Reference		Reference	
HR+/Her2+	1.34 (0.86–2.09)	0.202	1.81 (1.14–2.87)	0.011
HR−/Her2−	1.28 (0.60–2.73)	0.527	1.89 (0.86–4.15)	0.113
HR−/Her2+	2.53 (1.38–4.67)	0.003	3.04 (1.61–5.71)	<0.001
Chemotherapy received				
Anthracycline and taxane	Reference			
Taxane based	1.17 (0.76–1.78)	0.474		
Anthracycline based	1.43 (0.57–3.59)	0.442		
Surgery type				
Mastectomy	Reference			
Breast conserving	0.47 (0.17–1.27)	0.136		
Pathologic T category				
T0	Reference		Reference	
T1	0.63 (0.31–1.25)	0.182	0.65 (0.32–1.34)	0.244
T2	1.45 (0.72–2.89)	0.296	1.27 (0.62–2.62)	0.515
T3	2.68 (0.84–8.58)	0.097	1.96 (0.59–6.55)	0.275
T4	2.26 (0.49–10.31)	0.294	1.39 (0.30–6.56)	0.676

(Continued)

Table 4. (Continued)

Characteristic	Univariate		Multivariable	
	Hazard ratio (95% CI)	***p***	**Hazard ratio (95% CI)**	***p***
Pathologic N category				
N0	Reference		Reference	
N1	2.20 (1.13–4.31)	0.021	2.19 (1.10–4.35)	0.026
N2	3.46 (1.79–6.68)	<0.001	3.58 (1.80–7.12)	<0.001
N3	5.67 (2.99–10.79)	<0.001	4.80 (2.39–9.63)	<0.001
Group				
RDBN	Reference			
RDB	0.29 (0.16–0.51)	<0.001		
RDN	0.81 (0.42–1.56)	0.525		
Radiation				
Yes	Reference			
No	0.88 (0.46–1.70)	0.714		

CI, confidence interval; Her2, human epidermal growth factor receptor 2; HR, hormone receptor; RDB, residual disease in breast; RDBN, residual disease in breast and lymph nodes; RDN, residual disease in lymph nodes; SD, standard deviation.

Currently, the main drugs in NAC include anthracyclines and taxanes. Our study found that among patients with residual tumors post-NAC, 48% who received anthracycline- and taxane-free treatments achieved lymph node pCR. This finding suggests that anthracycline-free treatment might be sufficient for some patients. The KRISTINE study[24] further confirmed the efficacy and safety of the TCbHP regimen in NAC. The TRAIN-2 study[11] results showed that compared to anthracycline-based regimens, the TCbHP regimen achieved the same pCR rates with significantly reduced toxicity, such as neutropenia. Therefore, TCbHP could be considered a preferred preoperative treatment option. According to the neoCART study,[25] compared to the 8-cycle AC-T regimen, the 6-cycle TP regimen made progress in improving the pCR rate in TNBC patients undergoing neoadjuvant treatment. Hence, it is necessary to further research to explore those subgroups that do not require anthracycline treatment, to mitigate the potential toxicity of anthracycline therapy.

In our study, we found that the DFS differed significantly among patients with tumor residuals at different sites ($p < 0.0001$). Specifically, those with tumor residuals in the breast were more likely to have better DFS, while those with tumor residuals in the lymph nodes had similar DFS, regardless of whether there was residual primary breast tumor post-NAC ($p = 0.9692$). This observation suggests that the anatomical location of residual disease plays a crucial role in patient prognosis. This finding is consistent with Hennessy *et al.*,[16] who also observed that the absence of tumor residuals in the axillary lymph nodes was associated with a favorable prognosis, and the presence of residual primary tumor did not affect the prognosis of patients with pCR in the axillary lymph nodes. This could imply that the residual tumor cells in the breast are likely removed during surgery, whereas lymph node tumor residuals may represent other potential distant metastatic sites not eradicated by NAC.

The prognostic implications of lymph node metastasis in cancer patients are a topic of keen clinical interest. Tumor cells in lymph nodes not only reflect the metastatic capability of the primary tumor but can also migrate to other sites.[26] Several preclinical studies[27–29] have confirmed that lymph node tumor cells can migrate to distant sites. Studies[30,31] have shown that the

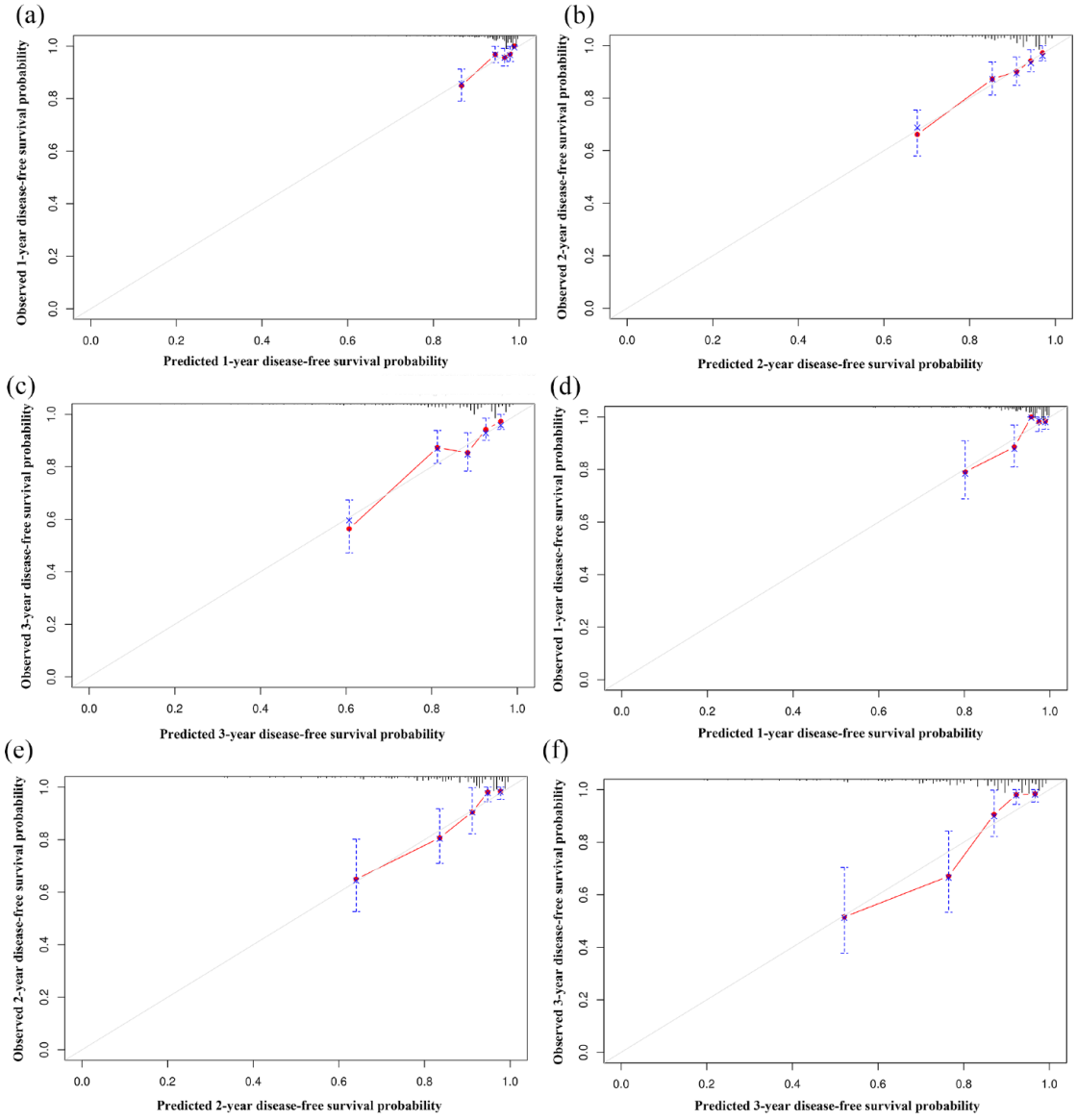

Figure 3. The graph shows calibration plots for DFS predictions using the nomogram. Panels (a–c) illustrate the calibration plots for 1-year, 2-year, and 3-year DFS in the training set, respectively. Panels (d–f) present these plots for the corresponding timeframes in the validation set.
DFS, disease-free survival.

presence of circulating tumor DNA post-NAC is associated with poorer DFS. About one-third of early-stage patients have lymph node metastasis, which predicts a worse prognosis compared to lymph node-negative status.[32] This aligns with Mougalian *et al.*,[13] who suggested that axillary pCR post-NAC is associated with improved 10-year OS and relapse-free survival (RFS). Consistent with our findings, the CTNeoBC pooled analysis[6] indicated that patients with persistent lymph node positivity post-NAC have poorer OS. Hence, our study reinforces that patients with residual tumor cells in the lymph nodes post-NAC had significantly worse 3-year DFS compared to those without lymph node tumor residuals ($p < 0.0001$), further supporting axillary tumor-free status as an important indicator of long-term prognosis.

Lee *et al.*[12]'s study pointed out that in lymph node-positive patients undergoing NAC, any pathological remission, regardless of the site, can improve prognosis, with no significant differences in OS ($p = 0.18$) and DFS ($p = 0.12$)

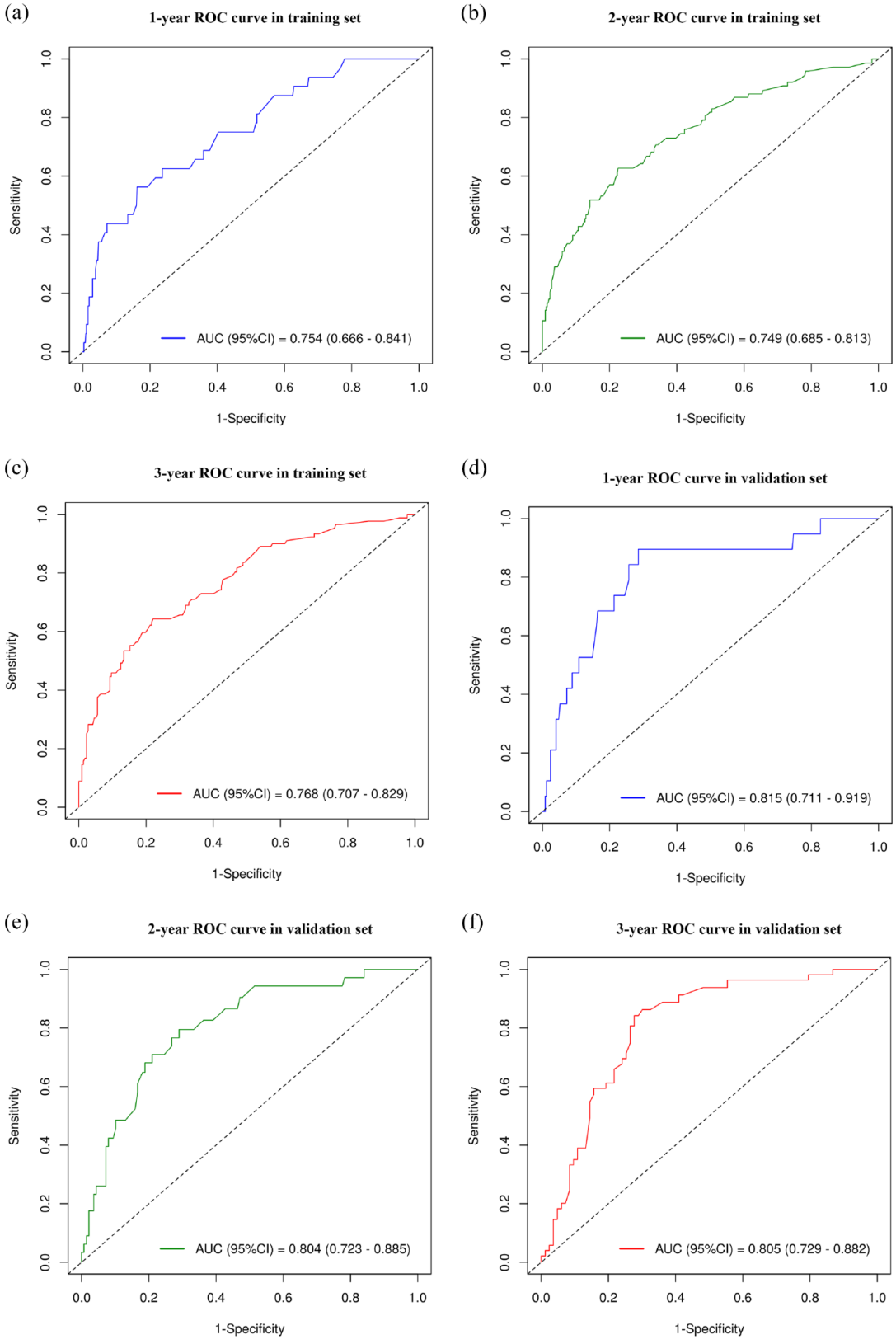

Figure 4. The graph shows ROC curves for DFS predictions at various intervals. Panels (a–c) show 1-year, 2-year, and 3-year DFS predictions in the training set, respectively. Panels (d–f) present these curves for the same timeframes in the validation set.
DFS, disease-free survival; ROC, receiver operating characteristic.

across different types of pathological remission. By contrast, our study results demonstrate that in patients with residual breast tumor tissue post-NAC, the presence or absence of lymph node tumor residuals does not significantly impact long-term DFS ($p = 0.97$). A key difference from Lee's study is that in our research, lymph node metastasis was pathologically confirmed, not just clinically positive. In addition, our study had a larger sample size and included more patients without breast tumor residuals (97 *versus* 5). In our cohort, a higher proportion of patients were HR+, whose long-term outcomes depend more on the long-term response to endocrine therapy than chemotherapy,[33] pCR may not be particularly crucial for the long-term outcomes of these patients.[6] This distinction highlights the importance of considering HR status when evaluating the impact of residual disease on DFS.

Patients with residual tumors post-NAC have been confirmed to have a significantly worse prognosis compared to those achieving pCR. Therefore, for this patient group, an effective scoring system is crucial for prognostic assessment. To better tailor this system to the unique needs of these patients, the traditional AJCC staging system[17] reflects the tumor burden at a single time point and may not fully represent the different tumor types' response to NAC, potentially failing to accurately predict post-NAC survival rates in patients. To overcome these limitations, we combined the molecular subtype of the tumor and changes in TNM staging before and after NAC to construct a more comprehensive nomogram for predicting DFS, thereby aiming to more accurately predict the prognosis of patients with residual tumors post-NAC. Compared to the traditional AJCC staging system, our nomogram is based on five variables: cT, cN, molecular subtype, pT, and pN, offering a more comprehensive reflection of the response of different tumor types to NAC and thus allowing for more accurate assessment and prediction in both training and validation cohorts.

The results showed that the validation cohort's C-index and calibration curves were favorable, indicating that the model has good discriminative ability and reliability. These results underscore ROC results clearly demonstrated that our predictive nomogram had better specificity and sensitivity. In our nomogram, pN received a higher risk score, underscoring its substantial influence on DFS. With HRs of 2.19 (1.10–4.35) for pN1, 3.58 (1.80–7.12) for N2, and 4.80 (2.39–9.63) for N3, as compared to N0, the data unequivocally demonstrate that increased lymph node involvement is significantly associated with an elevated risk of adverse DFS outcomes. This is similar to the findings of Zhang *et al.*,[34] where in non-pCR patients, the 3-year DFS rates for ypN0, ypN0-1, and ypN2-3 patients were 98%, 91%, and 56%, respectively ($p < 0.05$). In addition, DCA showed that our nomogram had a wide range of threshold probabilities, reflecting its good clinical utility. This innovation marks the first time a model for predicting DFS has been established for patients with residual tumors post-NAC by integrating easily accessible parameters such as TNM changes and molecular subtypes before and after neoadjuvant therapy. The results demonstrate that this model has good predictive ability. This provides a foundation for quantifying the recurrence risk of individual patients with residual tumors and guiding the design of appropriate subsequent treatment strategies. Especially for patients with HR-positive residual tumors, these findings can guide the development of new drug treatments.

We acknowledge several limitations in our study. First, as a retrospective study based on a single-center database, the scope and applicability of our findings is limited. Second, our database lacks some potentially important prognostic information, such as the family history of breast cancer, histological grade, vascular invasion, and anti-Her2 therapy data. This omission could influence the comprehensiveness of our conclusions. Third, the exclusion of patients with missing data variables may have introduced selection bias. This factor might affect the accuracy of our findings. Fourth, the follow-up period was not sufficiently long, potentially undermining the reliability of our findings. Lastly, our nomogram has undergone internal validation, but we anticipate future external validation from other centers to further strengthen the credibility of the model. In future research, we aim to address these limitations by expanding the sample size, collecting more comprehensive patient information, extending the follow-up period, and conducting external validation. These measures are crucial to more thoroughly understand the performance of our model and ensure its generalizability across different patient populations.

Conclusion

This study assessed the impact of tumor residuals in different locations post-NAC on the prognosis of breast cancer. We found that lymph node tumor residuals predicted poorer DFS. Our analysis reveals the anatomical location of the residual tumor is significant in assessing individualized prognostic risks. Moreover, we have developed a DFS prediction model with excellent internal validation performance. This nomogram more comprehensively considers the biological behavior of tumors than traditional staging systems and is expected to become an important tool for assessing the efficacy of NAC and formulating subsequent treatment strategies. Our findings preliminarily clarify the different impacts of residual tumors at different sites on the long-term survival of breast cancer, thereby providing theoretical support for achieving precision medicine.

Declarations

Ethics approval and consent to participate

The Ethics Review Committee of the Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital approved this retrospective analysis of anonymous data (No. 2017407). Informed consent from patients was waived owing to the retrospective nature of this study and the anonymized data analysis.

Consent for publication

Not applicable.

Author contributions

Hanzhao Yang: Conceptualization; Data curation; Methodology; Writing – original draft.

Yuxia Ruan: Conceptualization; Data curation; Writing – review & editing.

Yadong Sun: Conceptualization; Writing – review & editing.

Peili Wang: Conceptualization; Writing – review & editing.

Jianghua Qiao: Conceptualization; Writing – review & editing.

Chengzheng Wang: Conceptualization; Investigation; Methodology; Writing – review & editing.

Zhenzhen Liu: Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ORCID iDs

Hanzhao Yang https://orcid.org/0009-0003-5253-4813

Zhenzhen Liu https://orcid.org/0000-0002-3878-1258

Supplemental material

Supplemental material for this article is available online.

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