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BREAST

Prediction of axillary response by monitoring with ultrasound and MRI during and after neoadjuvant chemotherapy in breast cancer patients

Na Lae Eun[1] · Eun Ju Son[1] · Hye Mi Gweon[1] · Jeong-Ah Kim[1] · Ji Hyun Youk[1]

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Abstract

Purpose To investigate whether monitoring with ultrasound and MR imaging before, during and after neoadjuvant chemotherapy (NAC) can predict axillary response in breast cancer patients.

Materials and methods A total of 131 breast cancer patients with clinically positive axillary lymph node (LN) who underwent NAC and subsequent surgery were enrolled. They had ultrasound and 3.0 T-MR examinations before, during and after NAC. After reviewing ultrasound and MR images, axillary LN features and tumour size (T size) were noted. According to LN status after surgery, imaging features and their diagnostic performances were analysed.

Results Of the 131 patients, 60 (45.8%) had positive LNs after surgery. Pre-NAC T size at ultrasound and MR was different in positive LN status after surgery ($p < 0.01$). There were significant differences in mid- and post-NAC number, cortical thickness (CxT), T size and T size reduction at ultrasound and mid- and post-NAC CxT, hilum, T size and T size reduction, and post-NAC ratio of diameter at MR ($p < 0.03$). On multivariate analysis, pre-NAC MR T size (OR, 1.03), mid-NAC ultrasound T size (OR, 1.05) and CxT (OR, 1.53), and post-NAC MR T size (OR, 1.06) and CxT (OR, 1.64) were independently associated with positive LN ($p < 0.004$). Combined mid-NAC ultrasound T size and CxT showed the best diagnostic performance with AUC of 0.760.

Conclusion Monitoring ultrasound and MR axillary LNs and T size can be useful to predict axillary response to NAC in breast cancer patients.

Key Points

- *Monitoring morphologic features of LNs is useful to predict axillary response.*
- *Monitoring tumour size by imaging is useful to predict axillary response.*
- *The axillary ultrasound during NAC showed the highest diagnostic performance.*

Keywords Breast cancer · Lymph nodes · Ultrasound · Magnetic resonance imaging · Neoadjuvant therapy

Abbreviations

ALND	Axillary lymph node dissection
AUC	The area under the receiver operating characteristic curve
ER	Oestrogen receptor
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
LN	Lymph node
NAC	Neoadjuvant chemotherapy
NPV	Negative predictive value
pCR	Pathologic complete response
PR	Progesterone receptor
SLNB	Sentinel lymph node biopsy
US	Ultrasound

✉ Ji Hyun Youk
jhyouk@yuhs.ac

[1] Department of Radiology, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, South Korea

Introduction

Neoadjuvant chemotherapy (NAC) has been widely used for large or locally advanced breast cancers, allowing breast-conserving surgery by reducing cancer size, and treatment response after NAC is known to offer prognostic information [1, 2]. For patients with breast cancer undergoing NAC,

axillary lymph node (LN) status is crucial to determine axillary management and has been reported to be associated with disease-free survival [3–5].

Currently, axillary LN dissection (ALND) is regarded as a standard-of-care management for clinically positive LNs in breast cancer patients. However, it requires a major surgery for the axilla and can cause long-term morbidity, including lymphedema or paraesthesia [6]. To overcome this, sentinel LN biopsy (SLNB) is used as an effective method in node-negative breast cancer patients with much less complication. Regarding axillary management after NAC, two prospective observational trials—the Alliance Z1071 and SENTINA trials—were conducted to evaluate the feasibility of SLNB for the negatively converted LN group after NAC in initially node-positive breast cancer patients and reported 12.6% and 14.2% of false-negative rates, respectively, which were above the accepted cut-off value of 10% [7, 8]. Interestingly, axillary ultrasound (US) after NAC was found to reduce false-negative rates to 4~9.8% [9, 10]. In this context, axillary imaging for predicting axillary pCR becomes very important for surgeons to decide axillary management after NAC.

As breast imaging is routinely performed for monitoring response to NAC, US and MR imaging are also used for monitoring axillary response in clinical practice. Previous studies reported that the sensitivity and specificity of axillary imaging after NAC are 50–70% and 58–77% for US and 57–72% and 54–72% for MR [11–14]. To the best of our knowledge, however, specific US or MR imaging features associated with axillary pCR by sequential monitoring of axillary response to NAC—before, during and after NAC—were not investigated. In particular, monitoring axillary response during NAC could be beneficial to identify responders to reduce overtreatment and non-responders to be directed to change ineffective treatment or to earlier surgical intervention [15]. Therefore, we performed the current study to investigate whether monitoring with US and MR imaging can predict axillary response in breast cancer patients before, during and after NAC.

Materials and methods

Study population

After approval of the institutional review board, the requirement of informed consent was waived. We retrospectively identified 1382 breast cancer patients who underwent surgery of the breast and axilla in our institution from January 2014 to October 2017. Of them, 172 patients received NAC and obtained US and MR imaging before, during and after NAC. The US and MR monitoring during NAC was performed after 3~4 cycles of NAC. Among them, we excluded 41 patients because of the following: (a) images were obtained in a 1.5-T MR system ($n = 3$), (b) MR imaging was not obtained at our hospital ($n = 2$), (c) axillary regions were insufficiently included on MR imaging ($n = 12$) and (d) axillary LNs did not show any suspicious feature, including cortical thickening more than 3 mm, round or irregular shape, or loss of fatty hilum at presentation ($n = 24$) [16]. We finally enrolled 131 women (mean age, 48 ± 10 years; range, 26–75 years) who demonstrated clinically positive LNs by US or MR imaging (cortical thickening more than 3 mm, round or irregular shape, or loss of fatty hilum) [16]. Of them, representative LNs of 88 patients were confirmed malignant by fine-needle aspiration biopsy.

The NAC regimen administered to all patients was according to the standard protocols of our institution, including adriamycin with docetaxel, adriamycin with cyclophosphamide, adriamycin with cyclophosphamide plus docetaxel or human epidermal growth factor receptor 2 (HER2)/neu monoclonal antibody-based chemotherapy. After NAC, all patients underwent breast-conserving surgery or mastectomy. Axillary LNs were surgically removed by SLNB ($n = 22$), ALND ($n = 34$) and both ($n = 75$). The results of SLNB were accepted if at least three SLNs were removed.

US technique

US examinations were performed before, during and after NAC for breast cancer and axilla by one of six radiologists with 6 to 20 years of experience in breast imaging. All patients were assessed with real-time US using a 5–12-MHz linear-array transducer (iU22; Philips Medical Systems) or a 4–15-MHz linear-array transducer (SuperSonic Imagine).

MR imaging technique

MR examinations were performed using a 3.0-T system (Achieva; Philips Medical Systems and Discovery MR750; General Electric Medical Systems) with a dedicated, four-channel breast coil. The baseline protocol consisted of turbo spin-echo T1/T2-weighted sequences and T2-weighted spin-echo series with fat suppression (repetition time/echo time ms, 5506/70; matrix, 564 × 261; field of view, 20–34 cm; sliced thickness, 3 mm). Dynamic contrast-enhanced MR examination was undergone with one pre-contrast and five post-contrast series using a fat-suppressed T1-weighted gradient echo sequence (repetition time/echo time ms, 5/2.5; matrix, 340 × 274; flip angle, 12°; field of view, 34 cm; sliced thickness, 2 mm). Gadobutrol (Gadovist, Bayer Healthcare) was injected with a dose of 0.1 mmol/kg using an automated injector (Nemoto; Nemoto Kyorindo) at a rate of 2 mL/s, followed by a 20-mL saline flush.

Image interpretation

US and MR images of the index breast cancer and axillary LN obtained before, during and after NAC were retrospectively reviewed by two radiologists in consensus. For the index breast cancer, the tumour size was determined by the largest dimension of it. For the axillary LNs with suspicious features, their number was counted. If the axillary LNs were identified two or more, the index LN was determined as the LN with the most suspicious feature which exhibits the largest cortical thickness [17]. Imaging features of the index LN were assessed as follows: longitudinal diameter, ratio of short/long diameter, cortical thickness, shape (oval, round or irregular) and hilum (normal-appearing, no or displaced hilum). Invisible LNs at US and MR during and after NAC were not included in the analysis.

Histopathologic assessment

The histologic result was assessed by one pathologist with 30 years' experience in breast pathologic evaluation. The histologic type was assessed from histopathologic reports of US-guided core biopsies before NAC. The expression of oestrogen receptor (ER), progesterone receptor (PR) and HER2 was evaluated by the standard avidin-biotin complex immunohistochemical (IHC) staining method [17, 18]. ER and PR positivity were assessed by the Allred score, which rates the proportion of positive cells (on a 0–5 scale) and the staining intensity (on a 0–3 scale). Tumours were considered ER or PR positive if the Allred score exceeded 3. Tumours with 3+ score at IHC examination were defined as HER2 positive. If HER2 status was equivocal (2+ score) at IHC examination, gene amplification using fluorescence in situ hybridisation analysis or silver in situ hybridisation analysis was performed to determine HER2 status.

After surgery, the excised LNs were fixed in formalin, embedded in paraffin, and stained with haematoxylins and eosin. They were routinely sectioned to 2–3-mm thickness and examined. Each node was classified according to the staging system of the American Joint Committee on Cancer, and we defined benign and isolated tumour cells (≤ 0.2 mm) as axillary pCR and micro- (> 0.2–2.0 mm) and macrometastasis (> 2.0 mm) as axillary non-pCR. For the index breast cancer, pCR was defined as the absence of any invasive cancer with or without ductal carcinoma in situ.

Data and statistical analysis

Univariate analysis was performed for US and MR features of axillary LNs and the tumour size before (pre-NAC), during (mid-NAC) and after NAC (post-NAC) according to the response of axillary LN to NAC, by using independent *t* test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Multiple logistic regression analysis using the backward elimination method was performed for identifying independently associated features with axillary non-pCR. Receiver operator characteristic curve analysis was performed to assess the diagnostic performance of US and MR imaging features. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), accuracy and the area under the receiver operating characteristic curve (AUC) were obtained at the cut-off value yielding the largest Youden index and compared using generalized estimating equations and the DeLong method. Statistical analyses were performed using SAS ver. 9.2 (SAS Institute Inc.) with a value of $p < 0.05$ considered to be significant.

Results

Patients' characteristics

Among 131 patients who underwent SLNB in 22 (16.8%) and ALND in 109 (83.2%), 71 (54.2%) achieved axillary pCR. Patients' characteristics according to axillary response are listed in Table 1. For clinical characteristics, the non-pCR group showed a higher proportion of initial clinical stage III (58%, $p = 0.048$), NAC regimen of adriamycin with docetaxel (22%, $p = 0.021$) and the operation method of mastectomy (68%, $p = 0.002$) or ALND (95%, $p < 0.0001$) than the pCR group. For histopathologic characteristics, the non-pCR group showed a higher proportion of ER positivity (65%, $p = 0.0002$), hormone-positive cancer subtype (65%, $p = 0.0009$) and tumour non-pCR (87%, $p < 0.0001$) than the pCR group. The pCR group showed a higher rate of PR negativity (79%, $p = 0.002$). Age and tumour histologic type showed no significant difference between the two groups.

Univariate and multivariate analyses

For the univariate analysis of US features (Table 2), only larger tumour size was associated with axillary non-pCR before NAC (45 mm vs. 33 mm, $p = 0.004$). During NAC, larger tumour size (29 mm vs. 17 mm, $p < 0.0001$), reduction in tumour size (51% vs. 34%, $p = 0.0002$), larger number of LNs (2.2 vs. 1.6, $p = 0.033$) and thicker cortex of LNs (5.3 mm vs. 2.9 mm, $p < 0.0001$) were associated with axillary non-pCR. After NAC, larger tumour size (22 mm vs. 12 mm, $p = 0.0001$), larger number of LNs (1.7 vs. 1.0, $p = 0.003$) and thicker cortex of LNs (3.9 mm vs. 2.5 mm, $p = 0.002$) were associated with axillary non-pCR.

For the univariate analysis of MR features (Table 3), only larger tumour size was associated with axillary non-pCR before NAC (50 mm vs. 37 mm, $p = 0.002$). During NAC, larger tumour size (30 mm vs. 15 mm, $p < 0.0001$), reduction in tumour size (59% vs. 41%, $p = 0.0005$), thicker cortex of LNs (6.6 mm vs. 3.7 mm, $p < 0.0001$) and higher proportion

Table 1 Clinicopathologic characteristics according to the response of axillary lymph nodes after neoadjuvant chemotherapy

Characteristics	Axillary pCR ($n = 71$)	Axillary non-pCR ($n = 60$)	p value
Age (years)	47.1 ± 10.2	48.6 ± 10.2	0.423
Clinical stage			0.048
II	41 (57.7)	25 (41.7)	
III	30 (42.3)	35 (58.3)	
Regimens of neoadjuvant chemotherapy			0.021
AT	4 (5.6)	13 (21.7)	
AC	1 (1.4)	1 (1.6)	
AC-T	38 (53.5)	31 (51.7)	
HER2/neu monoclonal antibody-based	28 (39.5)	15 (25.0)	
Tumour surgery type			0.002
Breast-conserving surgery	41 (57.7)	19 (31.7)	
Mastectomy	30 (42.3)	41 (68.3)	
Axillary surgery type			< 0.0001
SLNB	19 (26.8)	3 (5.0)	
ALND	52 (73.2)	57 (95.0)	
Tumour histologic type			0.367
Ductal	69 (97.2)	55 (91.7)	
Lobular	1 (1.4)	2 (3.3)	
Others	1 (1.4)	3 (5.0)	
ER status			0.0002
Negative	48 (67.6)	21 (35.0)	
Positive	23 (32.4)	39 (65.0)	
PR status			0.0019
Negative	56 (78.9)	32 (53.3)	
Positive	15 (21.1)	28 (46.7)	
HER2 status			0.107
Negative	40 (56.3)	42 (70.0)	
Positive	31 (43.7)	18 (30.0)	
Subtype			0.0009
Hormone-positive	23 (32.4)	39 (65.0)	
HER2-positive	20 (28.2)	8 (13.3)	
Triple-negative	28 (39.4)	13 (21.7)	
Tumour pCR			< 0.0001
Non-pCR	30 (42.3)	52 (86.7)	
pCR	41 (57.7)	8 (13.3)	

Values are expressed as the mean ± standard deviation or number (%)

AT adriamycin with docetaxel, *AC* adriamycin with cyclophosphamide, *AC-T* adriamycin with cyclophosphamide plus docetaxel, *SLNB* sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *ER* oestrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor 2, *pCR* pathologic complete response

of abnormal hilum (30.5% vs. 12.7%, $p = 0.013$) were associated with axillary non-pCR. After NAC, larger tumour size (24 mm vs. 10 mm, $p < 0.0001$), reduction in tumour size (74% vs. 53%, $p < 0.0001$), larger ratio of short/long diameter of LNs (0.6 vs. 0.5, $p = 0.021$), thicker cortex of LNs (4.5 mm vs. 2.6 mm, $p < 0.0001$) and higher proportion of abnormal hilum of LNs (26% vs. 6%, $p = 0.002$) were associated with axillary non-pCR.

For the multivariate analysis, pre-NAC MR tumour size (odds ratio [OR], 1.03; $p = 0.002$), mid-NAC US tumour size (OR, 1.05; $p = 0.004$), mid-NAC US cortical thickness of LNs (OR, 1.53; $p = 0.0002$), post-NAC MR tumour size (OR, 1.06; $p = 0.004$) and post-NAC MR cortical thickness of LNs (OR, 1.64; $p = 0.002$) were independently associated with axillary non-pCR (Table 4) (Figure 1, 2).

Diagnostic performance for predicting axillary lymph node status

With respect to the diagnostic performance of imaging features independently associated with axillary non-pCR (Table 5), combined mid-NAC US tumour size and cortical thickness of LNs showed the highest AUC value (0.760; 95% confidence interval, 0.680–0.841) and significantly higher sensitivity and NPV than pre-NAC MR tumour size, mid-NAC US cortical thickness of LNs and post-NAC MR tumour size ($p < 0.02$) which showed no significant difference in the AUCs. Post-NAC MR cortical thickness of LNs had no significant difference in diagnostic performance from combined mid-NAC US tumour size and cortical thickness of LNs.

Table 2 Ultrasound features of tumour size and axillary lymph nodes before, during and after neoadjuvant chemotherapy according to the response of axillary lymph nodes after neoadjuvant chemotherapy

Ultrasound features	Before NAC			During NAC			After NAC		
	Axillary pCR ($n = 71$)	Axillary non-pCR ($n = 60$)	p value	Axillary pCR ($n = 60$)	Axillary non-pCR ($n = 54$)	p value	Axillary pCR ($n = 45$)	Axillary non-pCR ($n = 46$)	p value
T size (mm)	33.3 ± 12.2	44.8 ± 27.9	0.004	16.5 ± 10.7	29.4 ± 22.3	< 0.0001	12.0 ± 9.8	22.1 ± 17.4	0.0001
Reduction in T size (%)	–	–	–	50.6 ± 25.3	33.5 ± 25.4	0.0002	65.3 ± 21.7	57.7 ± 25.3	0.128
Number of nodes	3.3 ± 2.3	3.9 ± 2.6	0.132	1.6 ± 1.4	2.2 ± 1.6	0.033	1.0 ± 1.0	1.7 ± 1.5	0.003
Longitudinal diameter (mm)	18.1 ± 8.9	20.7 ± 8.6	0.09	11.6 ± 4.7	13.3 ± 6.7	0.14	10.6 ± 4.6	12.2 ± 5.8	0.155
Ratio of short/long diameter	0.6 ± 0.2	0.5 ± 0.2	0.46	0.5 ± 0.2	0.5 ± 0.1	0.054	0.5 ± 0.2	0.5 ± 0.2	0.508
Cortical thickness (mm)	8.4 ± 5.2	9.7 ± 4.5	0.136	2.9 ± 1.6	5.3 ± 3.3	< 0.0001	2.5 ± 1.8	3.9 ± 2.4	0.002
Shape									
Oval	60 (84.5)	53 (88.3)	0.526	56 (93.3)	49 (90.7)	0.433	42 (93.3)	43 (93.5)	> 0.99
Round/irregular	11 (15.5)	7 (11.7)		4 (6.7)	5 (9.3)		3 (6.7)	3 (6.5)	
Hilum									
Normal	42 (59.2)	35 (58.3)	0.924	51 (85.0)	39 (72.2)	0.095	40 (88.9)	36 (78.3)	0.172
No/displaced hilum	29 (40.8)	25 (41.7)		9 (15.0)	15 (27.8)		5 (11.1)	10 (21.7)	

Values are expressed as the mean ± standard deviation or number (%)

NAC neoadjuvant chemotherapy, *pCR* pathologic complete response, *T* tumour, *CR* complete response

Table 3 MR features of tumour size and axillary lymph nodes before, during and after neoadjuvant chemotherapy according to the response of axillary lymph nodes after neoadjuvant chemotherapy

MR features	Before NAC			During NAC			After NAC		
	Axillary pCR ($n = 71$)	Axillary non-pCR ($n = 60$)	p value	Axillary pCR ($n = 71$)	Axillary non-pCR ($n = 59$)	p value	Axillary pCR ($n = 66$)	Axillary non-pCR ($n = 58$)	p value
T size (mm)	36.5 ± 16.4	49.8 ± 27.8	0.002	15.4 ± 14.0	29.9 ± 23.7	< 0.0001	9.5 ± 11.5	23.7 ± 21.3	< 0.0001
Reduction in T size (%)	–	–	–	59.4 ± 31.6	41.2 ± 26.2	0.0005	74.3 ± 28.6	53.3 ± 29.0	< 0.0001
Number of nodes	5.9 ± 3.1	6.6 ± 3.0	0.227	3.9 ± 1.9	4.5 ± 2.6	0.139	3.7 ± 2.2	4.0 ± 2.5	0.458
Longitudinal diameter (mm)	18.5 ± 9.7	21.4 ± 9.8	0.096	11.9 ± 6.7	13.7 ± 7.0	0.14	11.8 ± 6.7	12.0 ± 6.9	0.873
Ratio of short/long diameter	0.7 ± 0.2	0.6 ± 0.1	0.419	0.6 ± 0.2	0.6 ± 0.1	0.139	0.5 ± 0.2	0.6 ± 0.2	0.021
Cortical thickness (mm)	10.0 ± 5.7	11.7 ± 5.5	0.077	3.7 ± 2.3	6.6 ± 4.3	< 0.0001	2.6 ± 1.3	4.5 ± 3.3	< 0.0001
Shape									
Oval	63 (88.7)	52 (86.7)	0.719	68 (95.8)	56 (94.9)	> 0.99	63 (95.5)	53 (91.4)	0.472
Round/irregular	8 (11.3)	8 (13.3)		3 (4.2)	3 (5.1)		3 (4.5)	5 (8.6)	
Hilum									
Normal	38 (53.5)	29 (48.3)	0.554	62 (87.3)	41 (69.5)	0.013	62 (93.9)	43 (74.1)	0.002
No/displaced hilum	33 (46.5)	31 (51.7)		9 (12.7)	18 (30.5)		4 (6.1)	15 (25.9)	

Values are expressed as the mean ± standard deviation or number (%)

NAC neoadjuvant chemotherapy, *pCR* pathologic complete response, *T* tumour, *CR* complete response

Table 4 Multivariate analysis using the backward elimination method of ultrasound and MR imaging features of tumour size and axillary lymph nodes before, during and after neoadjuvant chemotherapy according to the response of axillary lymph nodes

	Variables	Univariate		Multivariate	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Before NAC	US T size (mm)	1.03 (1.01–1.05)	0.006	–	–
	MR T size (mm)	1.03 (1.01–1.05)	0.002	1.03 (1.01–1.05)	0.002
During NAC	US T size (mm)	1.06 (1.03–1.09)	0.0003	1.05 (1.02–1.09)	0.004
	US reduction in T size (%)	0.97 (0.96–0.99)	0.0005	–	–
	US number of nodes	1.30 (1.02–1.65)	0.037	–	–
	US cortical thickness (mm)	1.53 (1.25–1.88)	< 0.0001	1.53 (1.22–1.91)	0.0002
	MR T size (mm)	1.05 (1.02–1.07)	0.0002	–	–
	MR reduction in T size (%)	0.98 (0.97–0.99)	0.0009		
	MR cortical thickness (mm)	1.34 (1.16–1.53)	< 0.0001	–	–
	MR hilum				
	Normal	–	–	–	–
	No/displaced	3.02 (1.24–7.38)	0.015	–	–
After NAC	US T size (mm)	1.06 (1.03–1.10)	0.0003	–	–
	US reduction in T size (%)	0.98 (0.96–0.99)	0.001	–	–
	US number of nodes	1.57 (1.15–2.13)	0.004	–	–
	US cortical thickness (mm)	1.46 (1.12–1.90)	0.005	–	–
	MR T size (mm)	1.06 (1.03–1.09)	< 0.0001	1.06 (1.02–1.11)	0.004
	MR reduction in T size (%)	0.98 (0.96–0.99)	0.0001	–	–
	MR ratio (short/long diameter)	12.77 (1.39–117.13)	0.024	–	–
	MR cortical thickness (mm)	1.55 (1.22–1.96)	0.0003	1.64 (1.20–2.24)	0.002
	MR hilum			–	–
	Normal	–	–	–	–
	No/displaced	5.41 (1.68–17.41)	0.005	–	–

NAC neoadjuvant chemotherapy, *OR* odds ratio, *CI* confidence interval, *T* tumour, *US* ultrasound

Discussion

In the present study, we identified pre-NAC MR tumour size, mid-NAC US tumour size, mid-NAC US cortical thickness of LNs, post-NAC MR tumour size and post-NAC MR cortical thickness of LNs as imaging features independently associated with axillary response (Figs. 1 and 2). Regarding the prediction of axillary response, combined mid-NAC US tumour size and cortical thickness of LNs showed the best diagnostic performance with an AUC of 0.760, a sensitivity of 81.5% and an NPV of 80.8%.

A previous study reported that a false-negative result was associated with higher pre-NAC clinical T stage [19]. Similarly, we found that pre-NAC MR tumour size was positively associated with axillary non-pCR. The explanation for the association of larger tumour size with axillary non-pCR could be that patients with higher tumour burden may have higher probability of metastatic LNs [19]. Regarding tumour response to NAC, post-NAC MR reduction in tumour size was found to be an important independent predictor in previous reports [20, 21]. Although reduction in tumour size was not independently associated in our study, mid- and post-NAC tumour size reflecting tumour response showed independent association, which could be useful in monitoring axillary response. Regarding axillary LN features, mid- and post-NAC cortical thickness were independent predictors with higher ORs, which is comparable with post-NAC studies [22, 23]. The size, shape or hilum of LN would be related to how tumour cells infiltrate within the cortex, and even when the tumour deposit is reduced by NAC and not enough to cause LN enlargement or effacement of the hilum, the cortical thickness could reflect the tumour burden within LN [22].

With respect to minimising treatment morbidity and improving cancer-related outcome, it is critical to select candidates who would benefit from SLNB and to avoid ineffective or overtreatment [15, 24]. To predict axillary response to NAC, therefore, several studies suggested prediction models using clinical, pathological or imaging features before or after NAC [12, 20, 21, 23, 25]. However, our

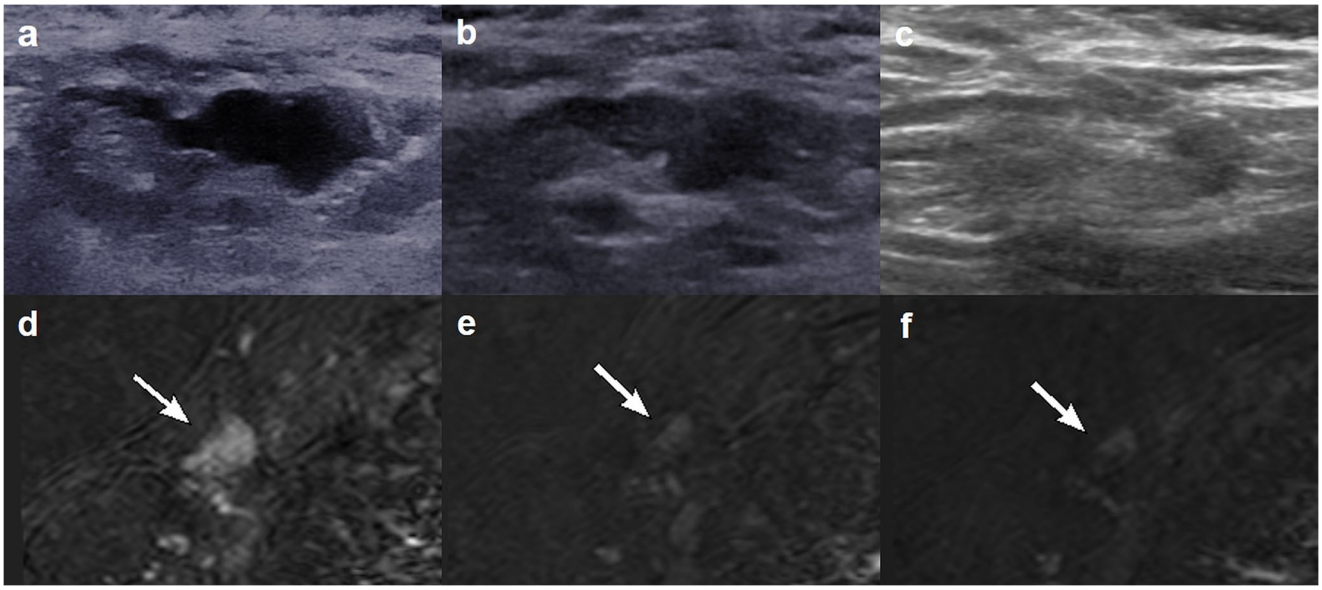

Fig. 1 Axillary ultrasound and MR images of a 31-year-old woman given diagnosis of ER/PR-positive/HER2-positive breast carcinoma with a fine-needle aspiration-proven metastatic lymph node in the right breast and axilla. Ultrasound image before neoadjuvant chemotherapy (**a**) shows a metastatic lymph node with cortical thickening of 7.7 mm and displaced hilum, which were assessed as positive findings. The lymph node shows cortical thickening of 4.7 mm and 4 mm at US during (**b**) and after (**c**) neoadjuvant chemotherapy. The MR image before neoadjuvant chemotherapy (**d**) shows a metastatic lymph node with cortical thickening of 9 mm and displaced hilum. The lymph node shows cortical thickening of 5 mm and 3 mm at MR during (**e**) and after (**f**) neoadjuvant chemotherapy. The final pathology after axillary lymph node dissection revealed a residual metastatic deposit of 2 mm; therefore, this was included in the axillary non-pCR group

study encompassed pre-, mid- and post-NAC US and7 MR imaging features, and identified mid-NAC US features combined tumour size with cortical thickness of LN as the best predictor of axillary response with AUC of 0.760, comparable with previous results, ranging from 0.617 to 0.788 [12, 20, 25]. It should be emphasised that our mid-NAC US features

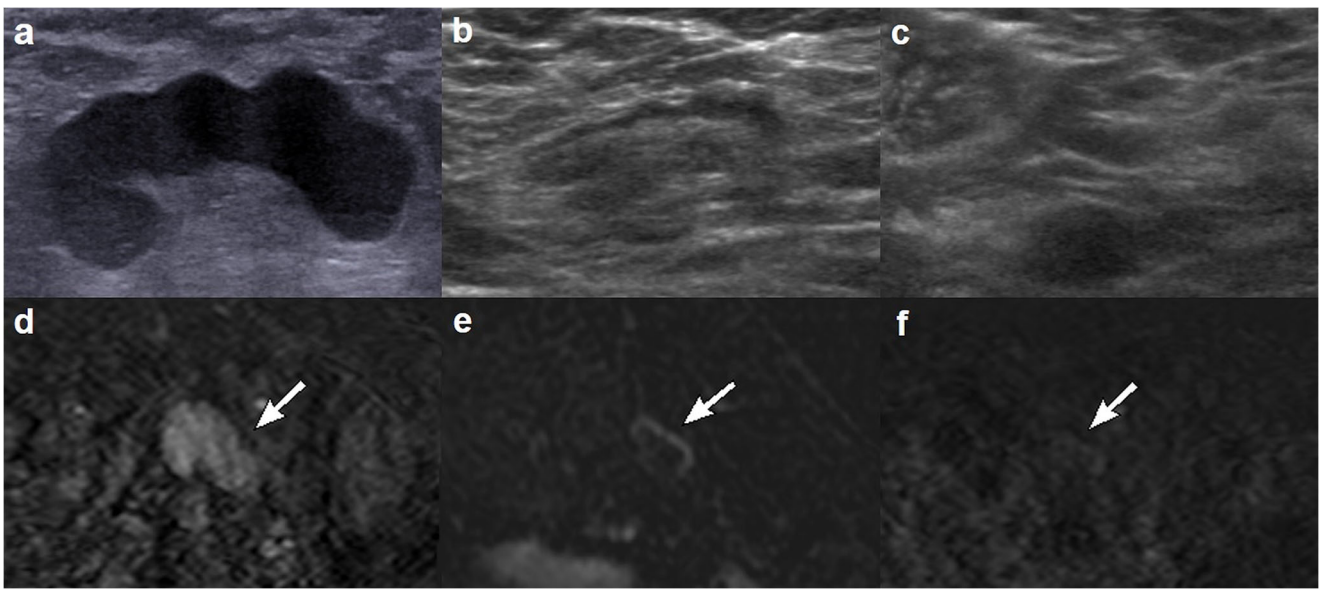

Fig. 2 Axillary ultrasound and MR images of a 61-year-old woman given diagnosis of ER-negative/PR-positive/HER2-negative breast carcinoma with a fine-needle aspiration-proven metastatic lymph node in the left breast and axilla. Ultrasound image before neoadjuvant chemotherapy (**a**) shows a metastatic lymph node with cortical thickening of 10 mm with displaced hilum, which were assessed as positive findings. The lymph node shows cortical thickening of 3.1 mm during neoadjuvant chemotherapy (**b**) and disappears at US after neoadjuvant chemotherapy (**c**). The MR image before neoadjuvant chemotherapy (**d**) shows a metastatic LN with cortical thickening of 15 mm with displaced hilum. The lymph node shows cortical thickening of 2.5 mm at MR during neoadjuvant chemotherapy (**e**) and normal appearance at MR after neoadjuvant chemotherapy (**f**). Axillary lymph node dissection revealed 0.05 mm metastasis on final pathology, and this was included in the axillary pCR group

Table 5 Diagnostic performances of ultrasound and MR imaging features of tumour size and axillary lymph nodes before, during and after neoadjuvant chemotherapy in the prediction of axillary non-pCR

		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
Before NAC	MR T size[1]	56.7* (44.1–69.2)	77.5 (67.8–87.2)	68 (55.1–80.9)	67.9* (57.7–78.1)	67.9 (60.0–75.9)	0.655 (0.567–0.744)
During NAC	US T size[2]	50* (37.4–62.7)	85.9* (77.8–94.0)	75 (61.6–88.4)	67.0* (57.4–76.7)	69.5 (61.6–77.4)	0.673* (0.589–0.757)
	US cortical thickness[3]	57.4* (44.2–70.6)	81.7* (71.9–91.5)	73.8 (60.5–87.1)	68.1* (57.3–78.8)	70.2 (61.8–78.6)	0.702 (0.617–0.786)
	US T size[2] + cortical thickness[3]	81.5 (71.1–91.8)	70 (58.4–81.6)	71 (59.7–82.3)	80.8 (70.1–91.5)	75.4 (67.5–83.3)	0.760 (0.680–0.841)
After NAC	MR T size[4]	55* (42.4–67.6)	80.3 (71.0–89.5)	70.2 (57.1–83.3)	67.9* (57.9–77.9)	68.7 (60.8–76.6)	0.674 (0.587–0.761)
	MR cortical thickness[5]	72.4 (60.9–83.9)	65.2 (53.7–76.7)	64.6 (53.0–76.2)	72.9 (61.5–84.2)	68.6 (60.4–76.7)	0.678 (0.591–0.765)
	MR T size[4] + cortical thickness[5]	87.9 (79.6–96.3)	50* (37.9–62.1)	60.7* (50.3–71.2)	82.5 (70.7–94.3)	67.7 (59.5–76.0)	0.662* (0.585–0.739)

Values in parentheses are 95% confidence intervals

NAC neoadjuvant chemotherapy, *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the receiver operating characteristic curve, *T* tumour

*$p < 0.05$, compared with US T size + cortical thickness during NAC

[1] Cut-off, 44.5 mm

[2] Cut-off, 27.5 mm

[3] Cut-off, 3.85 mm

[4] Cut-off, 18.5 mm

[5] Cut-off, 2.75 mm

could be helpful to guide axillary management earlier than post-NAC features of previous models. Tumour size and cortical thickness of LN as measured values can provide objective and quantitative data for the prediction of axillary response. Moreover, axillary US has advantages of wide availability, low cost, lack of contrast administration and short acquisition time over MR imaging, which can be easily accepted as mid-NAC evaluation. Further investigation is needed to validate the mid-US features for the clinical outcome and cost-benefit analysis.

We acknowledge several limitations to our study. First, this study is of a retrospective design and enrolled patients with clinically positive LNs by US or MR imaging and undergoing subsequent follow-up imaging. Fine-needle aspiration or core needle biopsy for lymph nodes showing suspicious imaging features was recommended but not mandated, and 88 of 131 (67.2%) were confirmed malignant by fine-needle aspiration biopsy. Thus, the results may have suffered from selection bias. Second, interpretation of axillary LN was based on the most suspicious finding among the axillary LNs and node-to-node evaluation could not be performed. Although we did not use special marking techniques, we assumed that the index LN with the most suspicious imaging finding represents the clinically suspicious LN. Third, the diagnostic accuracy of axillary US might be underpowered by operator dependency, which is an inherent nature of US. Lastly, the assessment of US axillary imaging was based on the captured images and real-time US evaluation of tumour size and imaging features of suspicious LNs could not be analysed, although the imaging features were assessed in consensus by two radiologists.

In conclusion, pre-NAC MR tumour size, mid-NAC US tumour size and cortical thickness of LNs, and post-NAC MR tumour size and cortical thickness of LNs were independently associated with axillary response. Combined mid-NAC US tumour size and cortical thickness of LNs can be useful to predict axillary response in breast cancer patients.

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Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

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