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Prediction of nipple-areolar complex involvement by breast cancer: role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

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Abstract

Background: Skin-sparing and nipple-sparing mastectomies were considered as alternative techniques for modified radical mastectomy. In patients who are candidates for nipple-sparing mastectomy, preoperative assessment of the nipple-areolar complex (NAC) is essential for adequate surgical planning. Breast MRI is highly sensitive for cancer detection and has an important role in disease staging. The aim of this study was to estimate the role of DCE-MRI in predicting malignant NAC invasion by underlying breast cancer and assess the best predictors on MRI that can suspect malignant NAC invasion.

Results: Out of the 125 patients with breast cancer, 33 patients (26.4%) showed malignant NAC invasion. On basis of multivariate analysis, abnormal nipple enhancement, tumor nipple enhancement, tumor nipple distance ≤ 2 cm, and abnormal and asymmetric nipple morphology were all significant predictors of malignant NAC invasion ($P < 0.001$) with abnormal unilateral nipple enhancement as the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, $P < 0.001$). When combining more than positive suspicious MRI features, DCE-MRI had 66.6% sensitivity, 76% specificity, 50% PPV, 86.4% NPV, and 73.6% accuracy in prediction of malignant NAC invasion.

Conclusion: DCE-MRI could predict malignant NAC invasion with abnormal unilateral nipple enhancement as the most important independent MRI predictor.

Keywords: Dynamic contrast enhanced, Magnetic resonance imaging, Nipple-areolar complex, Breast cancer

Background

Breast cancer is considered as the second commonest cause of cancer-related death in women [1]. Great efforts were performed in order to introduce more conservative surgeries for the treatment of breast cancer [2]. Skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) were considered as alternative techniques for modified radical mastectomy (MRM) [3]. They provide better cosmetic outcomes resulting in improved body image and more patient satisfaction with more cosmetic results obtained by NSM due to preservation of the NAC [4]. In SSM, the recurrence rate was equivalent to that of MRM; however, in NSM, a small amount of ductal tissue was left behind the nipple, and this could result in an increased risk of local recurrence [5].

In patients who are candidates for NSM, preoperative assessment of the nipple-areolar complex (NAC) is essential for adequate surgical planning [6]. Several clinical and pathological factors are suspected to be associated with occult invasion of the NAC by the underlying breast cancer such as tumor size, multicentric tumor, central location of the tumor, and proximity of the tumor to the nipple base [7]. Mammography and breast

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ultrasound can be used to predict the malignant invasion of the NAC by underlying breast cancer; however, they have limited sensitivity and specificity. Breast MRI is highly sensitive for cancer detection and has an important role in disease staging. It is considered the imaging modality of choice for the assessment of malignant invasion of the NAC [8].

Several previous studies investigated the role of breast MRI in the prediction of malignant invasion of the NAC [6–13]. However, there is still debate on what is the most important MRI predictor of malignant NAC invasion by underlying breast cancer.

Aim of the study

The aim of this work was to estimate the role of DCE-MRI in predicting malignant NAC invasion by underlying breast cancer and assess the best predictors on MRI that can suspect malignant NAC invasion.

Methods

Patient's demographic data

This retrospective study was approved by our institution's ethics committee. The medical records and the preoperative MRI studies of 125 female patients with primary breast cancer and prepared for surgery (MRM, SSM, or NSM) were reviewed from the period of August 2018 till September 2020. Their age ranged from 28 to 70 years (mean ± SD = 44.8 ± 8.96). Out of the 125 female patients, 77 patients underwent MRM, 30 patients underwent SSM, and 18 patients underwent NSM. After reviewing the pathological reports, we found that 33 cases (26.4%) showed malignant NAC invasion and 92 cases (73.6%) showed free NAC. We had 9 cases with DCIS, 109 cases with IDC, and 7 cases with invasive lobular carcinoma.

Inclusion criteria

Inclusion criteria included female patients with primary breast cancer and prepared for surgery (MRM, SSM, or NSM).

Exclusion criteria

Exclusion criteria included patients who were referred to other hospitals and their pathological reports were not available, patients who received neoadjuvant chemotherapy, and patients with advanced disease stage (stage IV) because they were not amenable for surgery.

MRI technique

MRI breast for 125 female patients was performed using 1.5 T MR imaging unit (Philips Ingenia). All patients were examined in the prone position by using a dedicated breast coil. All patients underwent the following: (A) localizing sagittal protocol (scout view); (B) axial non-fat-suppressed T1W fast spin-echo images, with the following parameters: TR/TE 450/14 ms, slice thickness 3 mm, field of view (FOV) 300–360 mm, and matrix 307 × 512; (C) axial non-fat-suppressed T2W turbo spin-echo images with the following parameters: TR/TE 4500/97 ms, slice thickness 3 mm, and matrix 384 × 512; (D) axial STIR images with the following parameters: TR/TE 7000–9000/70 ms, TI 150 ms, slice thickness 3–4 mm, inter-slice gap 1 mm, FOV 300–360 mm, and matrix 307 × 512; and (E) dynamic MR images were obtained in the axial plane with fat suppression. The sequence used was FLASH 3-D GRE-T1WI with the following parameters: TR/ TE 4–8/2 ms, flip angle 20–25, slice thickness 2 mm, no inter-slice gap, FOV 300–360 mm, and matrix 307 × 512. Dynamic MR images were obtained after injecting a bolus of gadopentetate dimeglumine at a dose of 0.2 mmol/kg using an automated injector at a rate of 3–5 ml/s. This was followed by a bolus injection of saline (total of 20 ml at 3–5 ml/s).

Image post-processing includes (A) image subtraction obtained by subtracting each of the pre-contrast images from each post-contrast series image and (B) maximum intensity projection (MIP) images obtained through each orthogonal plane, producing sagittal, coronal, and axial projection.

Image interpretation

Using a secondary workstation (Phillips Advantage windows workstation with functional tool software), MR images were analyzed by two radiologists (ME, DE) with breast imaging experience for 14 and 9 years. They were blinded to the clinical and pathological data of the patients. The two radiologists joined and reached a correspondence for controversial cases.

The assessed signs on dynamic MR images were (A) malignant mass pattern (mass lesion or non-mass enhancement); (B) tumor size (TS) (maximum diameter of the lesion, if multiple lesions present we took the maximum diameter of the largest lesion); (C) nipple morphology (NM) (normal or retracted nipple) was assessed on axial T1WI and axial STIR image; (D) symmetry of nipple morphology was assessed on MIP images; (E) tumor nipple enhancement (TNE) (presence of enhancement between tumor and nipple base assessed on early subtraction MR images); (F) tumor nipple distance (TND) (measured from the tumor margin to the base of the nipple on early subtraction MR images); (G) abnormal asymmetric nipple enhancement assessed on early subtraction MR images; and (H) thickening of the periareolar skin when compared with the contralateral NAC, it was assessed on early subtraction MR images.

Final diagnosis

The pathological reports after surgery were reviewed and the following data were collected: (1) presence of malignant NAC invasion (malignant NAC invasion was defined on pathology as the presence of IDC, DCIS, or invasive lobular carcinoma within the retro-areolar tissue), (2) histologic tumor type, (3) tumor grade, (4) presence of lymphovascular metastasis, (5) presence of lymph node metastasis, and (6) hormone receptor status (ER, PR, Her 2, and Ki67).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Corp., released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum), interquartile range for non-parametric data, and mean and standard deviation for parametric data after testing normality using the Shapiro-Wilk test. The significance of the obtained results was judged at the (0.05) level. Student t test was used to compare 2 independent groups. The diagnostic performance (accuracy) of a test to discriminate diseased cases from non-diseased cases is evaluated using receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity were detected from the curve. PPV, NPV, and accuracy were calculated through cross-tabulation. The multivariate logistic regression model was done to determine the best combined parameters for the prediction of malignant NAC invasion by generating AUC with 95% confidence intervals.

Results

This retrospective study included 125 female patients with primary operable breast cancer. After reviewing the pathological reports, we found that 33 cases (26.4%) showed malignant NAC invasion and 92 cases (73.6%) showed free NAC (Fig. 1).

On univariate analysis, tumor size, tumor nipple distance, abnormal nipple enhancement, nipple morphology, symmetry of nipple morphology, tumor nipple enhancement, and periareolar skin thickening were all important predictors of malignant NAC invasion (Fig. 2a–c). The mean TS for cases of malignant NAC invasion was 5.5 ± 2.34 cm versus 3.55 ± 1.67 cm for free NAC (P < 0.001). The mean TND for cases of malignant NAC invasion was 2.28 ± 1.94 cm versus 3.89 ± 2.63 cm for free NAC (P = 0.032). Abnormal nipple enhancement was observed in 19 (57.6%) out of 33 cases with malignant NAC invasion; however, it was observed only in 2 (2.2%) cases out of 92 cases with free NAC (P < 0.001). Abnormal nipple morphology was observed in 21 (63.6%) out of 33 cases with malignant NAC; however, it was observed only in 6 (6.5%) cases out of 92 cases with free NAC (P < 0.001). TNE was observed in 24 (72.7%) out of 33 cases with malignant NAC invasion; however, it was observed in 22 (23.9%) out of 92 cases with free NAC. Regarding pathological features, tumor type, HER 2 status, and PR state were significant predictors for malignant NAC invasion; P values were 0.006, < 0.001, and 0.014, respectively (Table 1).

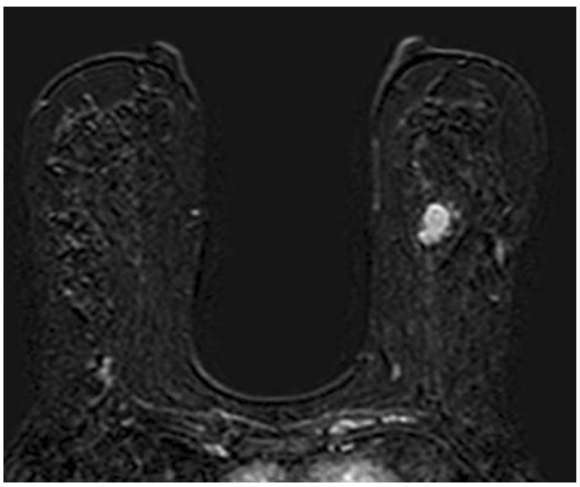

Fig. 1 Axial early subtraction MR image shows heterogeneously enhancing mass with speculated borders seen in the left breast. The nipple morphology appears normal and symmetrical on both sides, no tumor nipple enhancement, no periareolar skin thickening with tumor nipple distance of about 5.2 cm, and no abnormal nipple enhancement. Pathological diagnosis revealed grade II IDC with free NAC. ER, positive; PR, negative; Her 2, positive and high Ki67

Other radiological features as lesion pattern (P = 0.09) and other pathological features as tumor grade (P = 0.105), lymph node status (P = 0.510), Ki67 state (P = 0.970), and ER state (P = 0.262) could not be considered as predictors for malignant NAC invasion (Table 1).

On multivariate analysis, abnormal unilateral nipple enhancement was the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, P < 0.001) (Fig. 3). Other MRI predictors as TND ≤ 2 cm, abnormal nipple morphology, asymmetry of nipple morphology, and tumor nipple enhancement were also significant (P < 0.001). Also, HER2 status (P = 0.001) and PR state (P = 0.016) remained significant (Table 2).

Abnormal nipple enhancement had 57.6% sensitivity, 97.8% specificity, and 87.2% accuracy in the prediction of malignant NAC invasion. Abnormal nipple morphology had 63.6% sensitivity, 93.4% specificity, and 85.6% accuracy. The symmetry of nipple morphology had 63.6% sensitivity, 96.7% specificity, and 88% accuracy. TNE had 72.7% sensitivity, 76.1% specificity, and 75.2% accuracy. TND ≤ 2cm had 63.6% sensitivity, 72.8% specificity, and 54.4% accuracy (Table 3).

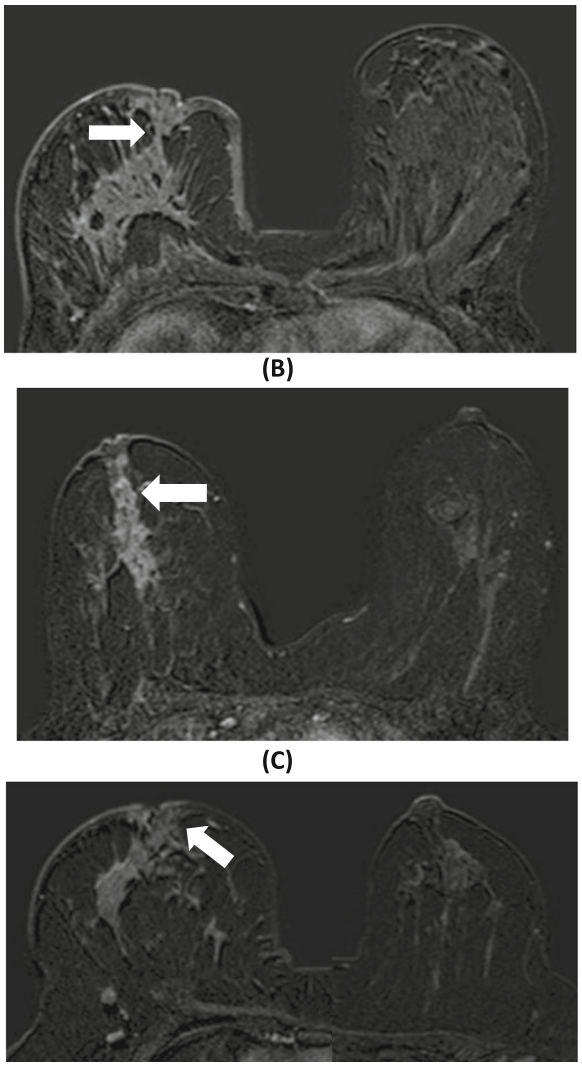

Fig. 2 Cases with pathologically proven malignant nipple infiltration. **a** Axial early subtraction MR image shows irregularly shaped heterogeneously enhancing mass with speculated margins in the retroareolar region of the right breast, the nipple appears retracted with abnormal unilateral nipple enhancement, and there is thickening in the periareolar skin with evidence of tumor nipple enhancement (linear non-mass enhancement extending from the mass to the nipple base) (arrow). Pathological diagnosis revealed stage IIIC; grade II IDC with nipple infiltration; ER and PR: negative; and HER2: positive and high ki67. **b** Axial early subtraction MR image shows heterogeneous linear non-mass enhancement seen in the retroareolar region of the right breast (arrow). The right nipple appears retracted with the linear non-mass enhancement continuous with the nipple base. No periareolar skin thickening. No abnormal unilateral nipple enhancement. Pathological diagnosis revealed grade II IDC with nipple infiltration, ER: positive, PR: positive, and HER2: positive with high ki67. **c** Axial early subtraction MR image shows heterogeneous segmental non-mass enhancement is seen in the retroareolar region of the right breast (arrow). The right nipple appeared retracted showing abnormal unilateral nipple enhancement with thickening in the periareolar skin. The non-mass enhancement is seen continuously with the nipple base. Pathological diagnosis revealed grade II IDC with malignant nipple infiltration, ER: negative, PR: negative, and HER2: positive with high ki67

When combing more than two positive suspicious MRI features, we found that DCE-MRI had 66.6% sensitivity, 76% specificity, 50% PPV, 86.4% NPV, and 73.6% accuracy in the prediction of malignant NAC invasion by underlying breast cancer (Table 4).

Discussion

The incidence of malignant NAC invasion by underlying breast cancer varies in different studies from 5.6 to 24.6% [14–16]. One study showed that malignant invasion of the NAC by underlying breast

Table 1 Univariate analysis of clinical, pathologic, and MRI findings associated with NAC invasion by underlying breast cancer

	Free NAC n = 92	Malignant NAC invasion n = 33	Test of significance
Age/years Mean ± SD	43.82 ± 9.61	45.12 ± 8.42	t = 0.691 p = 0.491
TS/cm Mean ± SD	3.55 ± 1.67	5.51 ± 2.34	t = 4.30 p < 0.001*
	n = 72	n = 21	
≤ 2cm	13 (18.1)	0 (0.0)	χ^2 = 4.41
> 2 cm	59 (81.9)	21 (100.0)	p = 0.036*
TND/cm Mean±SD	3.89 ± 2.63	2.28 ± 1.94	t = 4.71 p = 0.032*
≤ 2cm	25 (27.2)	21 (63.6)	χ^2 = 13.88
> 2 cm	67 (72.8)	12 (36.4)	p < 0.001*
LP			
Mass	72 (78.3)	21 (63.6)	χ^2 = 2.73
Non-mass	20 (21.7)	12 (36.4)	p = 0.09
Abnormal nipple enhancement			
Present	2 (2.2)	19 (57.6)	χ^2 = 53.33
Absent	90 (97.8)	14 (42.4)	p < 0.001*
NM (Nipple morphology)			
Normal	86 (93.5)	12 (36.4)	χ^2 = 46.78
Abnormal (inverted or retracted)	6 (6.5)	21 (63.6)	p < 0.001*
Sym NM (symmetry of nipple morphology)			
Symmetric	89 (96.7)	12 (36.4)	χ^2 = 57.07
Asymmetric	3 (3.3)	21 (63.6)	p < 0.001*
TNE (tumor nipple enhancement)			
Present	22 (23.9)	24 (72.7)	χ^2 = 24.88
Absent	70 (76.1)	9 (27.3)	p < 0.001*
PST (peri-areolar skin thickening)			
Present	0 (0.0)	22 (66.7)	χ^2 = 74.43
Absent	92 (100.0)	11 (33.3)	p < 0.001*
TT (tumor type)			
DCIS	3 (3.3)	6 (18.2)	MC
IDC	82 (89.1)	27 (81.8)	p = 0.006*
Invasive lobular carcinoma	7 (7.6)	0 (0.0)	
TG (tumor grade)			
Low or intermediate	67 (72.8)	19 (57.6)	χ^2 = 2.63
High	25 (27.2)	14 (42.4)	p = 0.105
LNS (lymph node state)			
Positive	54 (58.7)	17 (51.5)	χ^2 = 0.510
Negative	38 (41.3)	16 (48.5)	p = 0.475
PR (progesterone receptor) state			
Positive	50 (54.3)	26 (78.8)	χ^2 = 6.09
Negative	42 (45.7)	7 (21.2)	p = 0.014*
HER 2			
positive	51 (55.4)	31 (93.9)	χ^2 = 15.96
negative or equivocal	41 (44.6)	2 (6.1)	p < 0.001*
KI 67			
High	70 (76.1)	25 (75.8)	χ^2 = 0.001
Low	22 (23.9)	8 (24.2)	p = 0.970
ER (estrogen receptor) state			
Positive	63 (68.5)	26 (78.8)	χ^2 = 1.26
Negative	29 (31.5)	7 (21.2)	p = 0.262

χ^2 Chi-square test, *MC* Monte Carlo test, *t* Student's t test
*Statistically significant

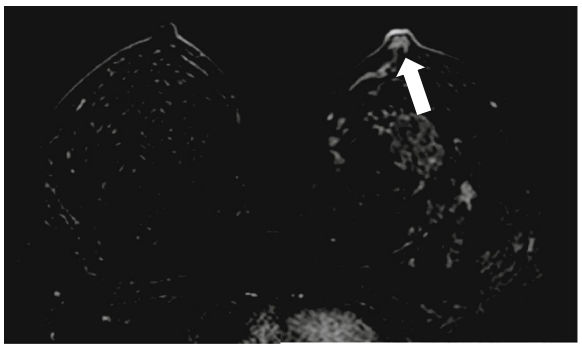

Fig. 3 Axial early subtraction MR image shows irregularly shaped heterogeneously enhancing mass with speculated borders seen in the retroareolar region of the left breast. It is seen surrounded by multiple satellite nodules. The nipple morphology appears normal and symmetrical on both sides, no tumor nipple enhancement, and no periareolar skin thickening with tumor nipple distance of about 3.4 cm. The only sign that could suspect nipple invasion is the presence of abnormal unilateral nipple enhancement (arrow). Pathological diagnosis revealed grade III IDC with malignant nipple infiltration. ER, positive; PR, positive; Her 2, positive and high ki67

cancer was found in 37 (21.8%) out of 170 mastectomy specimens [16]. Another study showed that malignant NAC invasion was found in 71 (35.5 %) out of 200 patients [3]. In this work, malignant NAC invasion by underlying breast cancer was reported in 26.4% of patients.

Several previous studies investigated the role of DCE-MRI in predicting malignant NAC invasion by underlying breast cancer [1, 3, 7–16]. It was stated that both tumor nipple distance and abnormal enhancement extending from the tumor to the nipple base were the most important predictors of malignant NAC invasion on MRI [9, 10]. One stated that TND with cutoff value of 10 mm had high sensitivity and specificity in predicting malignant NAC [3]. Another study stated that Continuity to NAC and unilateral NAC enhancement were all important MRI predictors of malignant NAC invasion [12]. This is in agreement with our study where we found that MRI predictors such as abnormal nipple morphology, asymmetry of nipple morphology, abnormal unilateral nipple enhancement, TNE, and TND ≤ 2cm were all significant predictors of malignant NAC invasion.

In the present study, abnormal unilateral nipple enhancement was the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, P < 0.001) (specificity = 97.8% and diagnostic accuracy = 87.2%). This in agreement with Liao et al. [7] who stated that abnormal unilateral nipple enhancement was the most significant independent image predictor of malignant NAC invasion (odds ratio = 4.86, 95% CI 1.76–13.80, $P \leq .01$). Also, our results are in agreement with a study performed by Lee et al. [17], and they found that MR images displaying inhomogeneous and diffuse enhancement in areas of thickened skin and the parenchyma of the NAC were indicative of NAC invasion. Another study performed multivariate logistic regression analysis for pathologic diagnosis of NAC involvement and concluded that NAC enhancement and NAC enhancement thickness were the two most important factors related to NAC invasion ($P < .001$) [18], and this is in agreement with our results.

The sensitivity and specificity of DCE-MRI in the prediction of malignant NAC invasion is variable among different studies. One study stated that the combination of more than one suspicious MRI feature had 60.5% sensitivity, 87.5% specificity, and 84.6% accuracy in predicting malignant NAC invasion [12]. Another study performed interobserver agreement about the ability of DCE-MRI to predict malignant NAC invasion; the first observer found that DCE-MRI had 71.4% sensitivity, 81.6% specificity, and 80.8% accuracy; and the second observer found that it had 78.6% sensitivity, 88.1% specificity, and 87.4% accuracy [7]. In this study combination of more than two suspicious MRI features, it could result in 66.6% sensitivity, 76% specificity, and 73.6% accuracy in predicting malignant NAC invasion.

The limitations of this study were that its retrospective nature, no interobserver agreement was performed, and also the MRI examinations were performed on 1.5 Tesla MRI.

Conclusion

DCE-MRI could predict malignant NAC invasion with abnormal unilateral nipple enhancement as the most important independent MRI predictor.

Table 2 Multivariate analysis of clinical, pathologic, and MRI findings associated with NAC invasion by underlying breast cancer

	Free NAC n = 92	Malignant NAC invasion n = 33	β	P	Odds ratio (95% CI)
TS/cm	n =7 2	n = 21			
≤ 2cm	13 (18.1)	0 (0.0)	20.51	0.99	Undefined
> 2 cm	59 (81.9)	21 (100.0)			
TND/cm					
≤ 2 cm	25 (27.2)	21 (63.6)	1.54	< 0.001*	4.69 (2.02–10.92)
> 2 cm (R)	67 (72.8)	12 (36.4)			Reference group
Abnormal nipple enhancement					
Present	2 (2.2)	19 (57.6)	4.12	< 0.001*	61.07 (12.81–291.22)
Absent (R)	90 (97.8)	14 (42.4)			Reference group
NM (nipple morphology)					
Normal (R)	86 (93.5)	12 (36.4)			Reference group
Abnormal	6 (6.5)	21 (63.6)	3.22	< 0.001*	25.08(8.43-74.6)
Sym NM (symmetry of nipple morphology)					
Symmetric (R)	89 (96.7)	12 (36.4)			Reference group
Asymmetric	3 (3.3)	21 (63.6)	3.95	< 0.001*	51.92 (13.44–200.58)
TT (tumor type)					
DCIS(R)	3 (3.3)	6 (18.2)	−1.80	0.015*	Reference group
IDC	82 (89.1)	27 (81.8)	-	0.99	0.165 (0.039–0.704)
Invasive lobular carcinoma	7 (7.6)	0 (0.0)	21.89		Undefined
TNE (tumor nipple enhancement)					
Present	22 (23.9)	24 (72.7)	2.14	< 0.001*	8.48 (3.44–20.94)
Absent (R)	70 (76.1)	9 (27.3)			Reference group
PST (peri-areolar skin thickening)					
Present	0 (0.0)	22 (66.7)			
Absent	92 (100.0)	11 (33.3)	23.32	0.999	Undefined
PR (Progesterone receptor state)					
Positive	50 (54.3)	26 (78.8)			3.12 (1.23–7.91)
Negative(R)	42 (45.7)	7 (21.2)	1.14	0.016*	Reference group
HER 2					
Positive	51 (55.4)	31 (93.9)	2.523	0.001*	12.46 (2.71–55.17)
Negative or equivocal	41 (44.6)	2 (6.1)			Reference group

Table 3 Diagnostic performances of tumor-nipple enhancement, abnormal nipple morphology, symmetry of nipple morphology, abnormal nipple enhancement and tumor-nipple distance in prediction of NAC invasion by underlying breast cancer

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Abnormal nipple enhancement	57.6	97.8	90.5	86.5	87.2
Abnormal nipple morphology	63.6	93.4	77.7	87.7	85.6
Symmetry of nipple morphology	63.6	96.7	87.5	88.1	88
TNE (tumor nipple enhancement)	72.7	76.1	52.2	88.6	75.2
TND/cm ≤ 2 cm	63.6	72.8	45.7	84.8	54.4

NPV negative predictive value, *PPV* positive predictive value

Table 4 Diagnostic performance of DCE-MRI when combing more than two positive MRI features in the prediction of malignant NAC invasion by underlying breast cancer

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
DCE-MRI	66.6	76	50	86.4	73.6

NPV negative predictive value, *PPV* positive predictive value

Abbreviations

DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging; NAC: Nipple-areolar complex; TS: Tumor size; TNE: Tumor nipple enhancement; TND: Tumor nipple distance; NSM: Nipple-sparing mastectomy; SSM: Skin-sparing mastectomy; IDC: Invasive duct carcinoma; DCIS: Duct carcinoma in situ; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor

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Not applicable.

Declarations

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Authors' contributions

AA revised the collected data and the manuscript. DM and ME analyzed the MRI images of all patients. DM wrote the manuscript. ME performed the statistical analysis. The authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

The study was approved by our institution's ethics committee (Mansoura Faculty of Medicine Institutional Research Board) (ethics committee reference number is R. R.19.05.513), and all patients gave their written informed consent before inclusion in the study.

Consent for publication

This study is a retrospective study, so there is no need for patient consent.

Competing interests

The authors declare that they have no competing interests.

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