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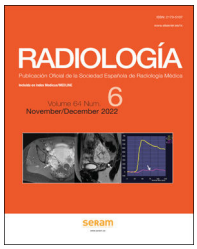

ORIGINAL ARTICLES

Contrast-enhanced mammography and preoperative magnetic seed placement in breast cancer patients for the detection of residual disease following neoadjuvant systemic therapy

A. Mariscal Martínez[a,*], E. Iglesias Bravo[b], H. Peris Alvà[a], P. Rodríguez Martínez[c], M. Luna Tomás[d], I. Pascual Miguel[e], P. Puyalto de Pablo[f]

[a] *Unidad de Diagnóstico por la Imagen de la Mama, Servicio de Radiología, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[b] *Servicio de Ginecología, Hospital Virgen de Valme, Sevilla, Spain*
[c] *Servicio de Anatomía Patológica, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[d] *Servicio de Ginecología y Obstetricia, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[e] *Servicio de Cirugía General, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*
[f] *Servicio de Radiología, Hospital Universitario Germans Trias i Pujol, Badalona, Barcelona, Spain*

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KEYWORDS
Contrast-enhanced mammography;
Magnetic seed;
Neoadjuvant therapy;
Breast neoplasms

Abstract
Purpose: Assess whether contrast-enhanced mammography (CEM) enables an evaluation of the residual size of breast tumours following neoadjuvant systemic therapy (NAST) in patients initially marked with magnetic seed.
Materials and methods: This single-centre prospective study was performed between March 2022 and April 2023 with patients with invasive breast carcinoma and lesional marking with magnetic seed. CEM was performed before and after NAST. The lesion size in CEM after NAST was compared to the pathological examination after surgery. Differences between sizes were evaluated and we determined the diagnostic capability indices.
Results: The breast lesions marked with magnetic seed were successfully localised in the pre-operative stage for the 42 patients included in the study and selective surgical excision was also achieved in all cases. Tumour diameter after NAST was determined by comparing enhancement on combined CEM images from before and after NAST. The mean diameter was 13.6 mm while post-surgical pathological examination determined the mean diameter to be 12.9 mm. There were therefore no statistically significant differences between the measurements.

* Corresponding author.
E-mail address: mariscal.germanstrias@gencat.cat (A. Mariscal Martínez).

Conclusions: There is a positive correlation and similarity between CEM and pathological examination with regards to the detection of residual disease after NAST, with high specificity and PPV.

PALABRAS CLAVE
Mamografía con contraste;
Semilla magnética;
Tratamiento neoadyuvante;
Cáncer de mama

Mamografía con contraste y marcaje con semilla magnética para la detección de enfermedad residual en el cáncer de mama tras tratamiento neoadyuvante

Resumen
Objetivo: Valorar si la mamografía con contraste (MC) permite evaluar el tamaño tumoral residual en la mama tras realizar tratamiento sistémico neoadyuvante (TSN) en pacientes con cáncer de mama, marcado inicialmente con semilla magnética.
Materiales y métodos: Se realizó un estudio prospectivo unicéntrico entre marzo 2022 - abril 2023 con pacientes con cáncer de mama infiltrante y marcaje lesional con semilla; se realizó MC antes y después del TSN. Se comparó el tamaño lesional en MC posterior al TSN respecto al de la valoración anatomopatológica tras cirugía, se evaluaron las diferencias de los tamaños y se determinaron los índices de capacidad diagnóstica.
Resultados: En las 42 pacientes incluidas se consiguió con éxito la localización preoperatoria y la exéresis quirúrgica selectiva de las lesiones mamarias marcadas con semilla magnética. La media del diámetro mayor tumoral tras TSN, determinado por el realce en las imágenes recombinadas de la MC, fue de 13,6 mm vs 12,9 mm en el examen patológico postquirúrgico, no hallándose diferencias estadísticamente significativas entre las medias de las mediciones.
Conclusiones: La MC presenta una buena correlación y concordancia con la histopatología para detectar la enfermedad residual tras TSN, con elevada especificidad y VPP.

Introduction

Neoadjuvant systemic therapy (NST) is the current first-line treatment for advanced breast cancer. It reduces or eliminates the tumour burden in a significant percentage of patients, and increases the proportion of surgery that is breast- and/or axilla-conserving. The primary goal of NST is to achieve pathological complete response (pCR), which is associated with a more favourable prognosis.[1] But some patients are NST-resistant (10–35% of cases).[2] A reliable and non-invasive radiological method that can assess early pathological response to NST is necessary to enable proper surgical planning at a later stage.

Magnetic resonance imaging (MRI) is the gold standard modality for predicting the pathological response of breast cancer to NST.[3,4] It assesses changes in tumour size and morphology. However, its high cost, lengthy imaging times and contraindications in some patients mean that it is not always suitable for routine use.

Therefore, a novel alternative is contrast-enhanced mammography (CEM), an imaging technique that has developed rapidly over recent years. Some studies have shown that CEM is effective in monitoring pathological response to NST, and may even be as effective as MRI.[5,6] It is important to mark breast lesions and/or metastatic lymph nodes (MLNs) in the axilla prior to NST so that they can be localised later. This is especially true in cases of pCR, in which the marker placed prior to treatment might be the only reliable reference point for pre-operative localisation.[7] Different breast tissue markers have been used, and each type has different advantages and complications.[8] The main disadvantage is that after NST, they require repeat identification and labelling prior to surgery. Furthermore, most are poorly visualised on ultrasound and can move around during placement or surgery.[9,10]

Recently, some new markers, such as magnetic seed (Magseed®), enable lesions in the breast and/or axillary lymph nodes to be marked before NST and localised during targeted surgery, thus avoiding a second pre-surgical localisation procedure. It has proven to be as reliable and effective as guidewire for the localisation and excision of non-palpable breast tumours with free margins.[11,12] It has also been useful for the presurgical localisation of MLNs after NST.[13,14] However, due to the fact that MRI produces significant signal void artifacts in the breast, this imaging technique cannot be used in conjunction with magnetic seed to assess the response to NST.[15] If CEM is used to assess the response to NST, magnetic seed can be used to mark lesions without causing artifacts in the CEM study.

The main objective of this study is to assess the diagnostic accuracy of CEM, together with baseline magnetic seed marking of the breast lesion, to assess the extent of residual disease and predict the pCR in breast cancer patients treated with NST. We will also evaluate the safety and effectiveness of magnetic seeds in the intraoperative localisation and excision of residual breast lesion(s) and/or marked MLNs.

Materials and methods

A prospective longitudinal cohort study was conducted as a single-centre substudy of the prospective multicentre MAGMA (Magseed® in the Breast) study. The MAGMA study is led by the University Hospital of Nuestra Sra. De Valme in Seville, with the participation of the University Hospital of Germans Trias i Pujol in Badalona, the University Hospital of Cáceres, the University Hospital of Miguel Servet in Zaragoza and the Child and Maternity University Hospital of the Canary Islands in Las Palmas.

The study was approved by the research ethics committees of all centres (our hospital's investigational ethics committee ref. PI-22-090). All patients gave written informed consent.

Study population

We included patients with invasive breast cancer, with or without axillary lymph node involvement and with no other metastatic sites, with clinical stage T1–3, N0/N1 or M0 who agreed to participate in the study and signed the informed consent form. All underwent NST and subsequent surgical treatment. We excluded patients with inflammatory carcinoma, extensive microcalcifications and those for whom metastasis was detected in studies carried out to assess the spread of disease. The patient enrolment period for the multicentre study was between January 2022 and April 2023. In our centre, patients were enrolled between March 2022 and April 2023.

Study protocol

First, a baseline diagnostic CEM was carried out for all patients, followed by magnetic seed marking of the lesion. Then, NST was performed, the response to NST was evaluated by CEM, and surgical treatment was carried out before the surgical specimen was submitted for pathological examination.

CEMs were performed using an AMULET Innovality FDR (Fujifilm®, Japan) machine and CEM software. CEM was performed with the dual-energy technique and automated post-processing of the obtained images. The study was performed with 2D mammography and bilateral CEM in the four projections after intravenous administration of 1.5 ml/kg of body weight of iodine-based contrast, Iomeprol (Iomeron®, Bracco, Italy), with a concentration of 350 mg/ml, maximum 100 ml, at a flow rate of 2.5–3 ml/s. Low- and high-energy images were obtained and recombined to generate subtraction images (recombined images), highlighting areas of the breast that uptake contrast. Four images were taken of each breast, the first being the craniocaudal view of the pathological breast, followed by the craniocaudal view of the contralateral breast, the mediolateral oblique (MLO) view of the pathological breast and finally the MLO view of the contralateral breast. The studies took as long as the CEM itself, between two and ten minutes.

Analysis of contrast-enhanced mammographies

Three radiologists from our breast imaging unit, with more than 15 years of experience and more than five years of experience performing CEMs, participated in the reading of the CEMs.

The baseline CEM served to assess the radiological characteristics of the breast lesion, to measure the size of the lesion and to study local spread. The CEM performed after completion of NST and a few days before surgery made it possible to assess the response to NST by measuring the residual lesion and check the correct localisation of the seed(s) in the breast and/or MLNs.

The response to NST was assessed by comparing the larger lesion size on CEM after NST, taking the longest diameter of the enhanced residual lesion in the recombined images and comparing it to the longest diameter of the enhanced lesion in the baseline diagnostic CEM. The Response Evaluation Criteria for Solid Tumours (RECIST) were used to assess tumour response to treatment.[16]

We also assessed the presence of background parenchymal uptake both in the baseline CEM and in the CEM performed after completion of NST, classifying it into four grades: none, minimal, moderate and intense. We visually compared the difference in background parenchymal uptake between the CEM after NST and the baseline CEM.

Marking and localisation technique

After the baseline CEM was performed, breast lesion(s) and/or MLNs were marked using ultrasound-guided magnetic seed placement. In cases of multifocality, different tumour foci were marked at a distance of not less than 2 cm from each other to avoid possible interference of the intraoperative detection probe signal. When there was more than one pathological axillary lymph node, only the most suspicious lymph node was marked, determined by its size and morphology regardless of its location. Later, a mammography was performed to check the correct position of the seed(s) in the breast lesion and MLN.

Possible complications were evaluated from the point of seed placement through to its intraoperative removal and possible displacements during magnetic seed placement within the tumour lesion. The latter was achieved by comparing measurements of the location of the seed inside the tumour lesion in the three axes (anteroposterior, craniocaudal and transverse) between the baseline CEM and that performed after NST. To our knowledge, there is no standardised reference that determines at what point displacement is considered significant. Therefore, in this study, significant displacement was recorded when the difference between the baseline location of the seed inside the lesion and its final location after NST was greater than 15 mm in any of its axes.

Surgical treatment and pathological study

All patients underwent conservative or radical surgery after completion of NST. During surgery, the residual breast lesion(s) and/or MLN were located and excised using a magnetic detection probe (Sentimag®). A sentinel lymph node (SLN) biopsy was performed at the same time. We also checked the percentage of cases in which MLNs corresponded with SLNs. Radiography checked that the residual breast lesion—and/or MLN marked with seed—was included in the surgical specimen. During surgery, we studied the MLN together with the SLNs, obtained by targeted axillary dissection (TAD), using the One-Step Nucleic Acid Amplification (OSNA) method, as well as the margins of the residual breast lesion. Lumpectomy specimens in which a radiological complete response had previously been observed were excluded from the intraoperative pathological study.

Later, a deferred pathological study was performed on the residual breast lesion in all cases, and on the axillary lymph nodes in those cases in which axillary lymphadenectomy was indicated due to positive intraoperative TAD. Gross examination of the breast resection specimens was carried out in a standardised manner according to international recommendations.[17] Microscopic study of the tumour bed and MLN after NST made it possible to calculate the residual tumour size. The longest tumour diameter provided by the pathologist was used in the comparative study with the CEM.

Pathological response to treatment was determined according to the Miller-Payne grading system for histological response. Following these criteria, we define pCR as the absence of invasive breast cancer, irrespective of the presence of ductal carcinoma in situ or axillary lymph node involvement (ypT0/is).

The response, estimated by CEM and assessed with RECIST criteria, was compared with the pathological response, assessed according to the Miller-Payne grading system. The longest diameter of the residual tumour in the CEM after NST was compared with the longest pathological tumour diameter, the latter being the reference standard. Concordance between measurements was evaluated using the intraclass correlation coefficient.

Data collection and statistical analysis

The Shapiro-Wilk test was used to check the normal distribution of the data and Levene's test was employed to assess the homogeneity of differences. Qualitative data were described using absolute and relative frequencies. Quantitative data, which follow the law of normality, were described using measures of central tendency such as mean and standard deviation. The mean difference of the residual tumour size was calculated using CEM and the pathological study using the paired Student's t-test parametric, given the normal distribution of the data and the homogeneity of variance. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to assess the diagnostic capacity of CEM to detect residual disease after completion of NST. The PPV (True Positives [TP]/TP + False Positives [FP]) was defined as the diagnostic accuracy of CEM to detect residual disease and NPV (True Negatives [TN]/TN + False Negatives [FN]) as the accuracy of the test in predicting pCR. Statistical analysis was carried out with Stata® software version 14.2 (StataCorp, Texas, USA).

Results

Patient and tumour characteristics

Forty-two women with a mean age of 57 years were included, of whom 29 were postmenopausal and 13 premenopausal. Seventy-four percent of patients had a palpable breast tumour at diagnosis and only three percent had a palpable tumour after completion of NST.

Most cases involved the invasive ductal histological type (97.6%). In 22 cases, the invasive carcinoma was grade II and in 20 cases it was grade III. The most common tumour subtype was luminal B-like (HER2-negative), affecting 21 cases. In the remaining cases, one was luminal A-like, seven were luminal B-like (HER2-positive), 11 were triple-negative and three were HER2-enriched. Prior to treatment, the clinical stage group was IIA in 21 cases, IIB in 18 cases and IIIA in three cases. A total of 78.6% of cases were T2 tumours.

Multifocality was detected in 21.4% of cases, requiring magnetic seed marking in the different tumour foci (Fig. 1). No artifacts were produced during the ultrasound-guided placement or intraoperative localisation, and radiographs verified that the surgical specimen included all the seeds. Axillary lymph node involvement (N1) was detected in 22 out of 42 cases. Most frequently, ultrasound revealed a single pathological lymph node (68.2%).

The clinical/pathological findings and treatment are shown in Table 1.

Evaluation of contrast-enhanced mammography findings and magnetic seed marking

In 42.9% of cases, mammographic density was type c or d according to the ACR guidelines. The most commonly detected mammographic finding was a nodule (24 out of 42), followed by architectural distortion (7 out of 42), density asymmetry (4 out of 42) and the remaining cases had a combination of the three (7 out of 42). Of the 42 cases, two were classified as BI-RADS 4A, eight as BI-RADS 4B, 21 as BI-RADS 4C and 11 as BI-RADS 5. The type of enhancement in the breast lesions in the recombined images from the baseline CEM corresponded mostly to mass-like enhancement in 40 out of 42 cases. The lesion size was taken from the longest diameter of the lesion in any of its axes measured in the recombined images. Background parenchymal uptake was classified into four grades: none, minimal, moderate and intense. CEM prior to NST revealed minimal background uptake in 21 cases, moderate in 19 cases and intense in two cases. A decrease in parenchymal enhancement in post-NST CEM images compared to baseline images was observed in 28.6% of cases.

All lesions were marked during ultrasound by implanting a magnetic seed, with no complications in its placement. All three multifocal cases required the placement of more than one seed, with no artifacts seen in any of the CEM follow-ups

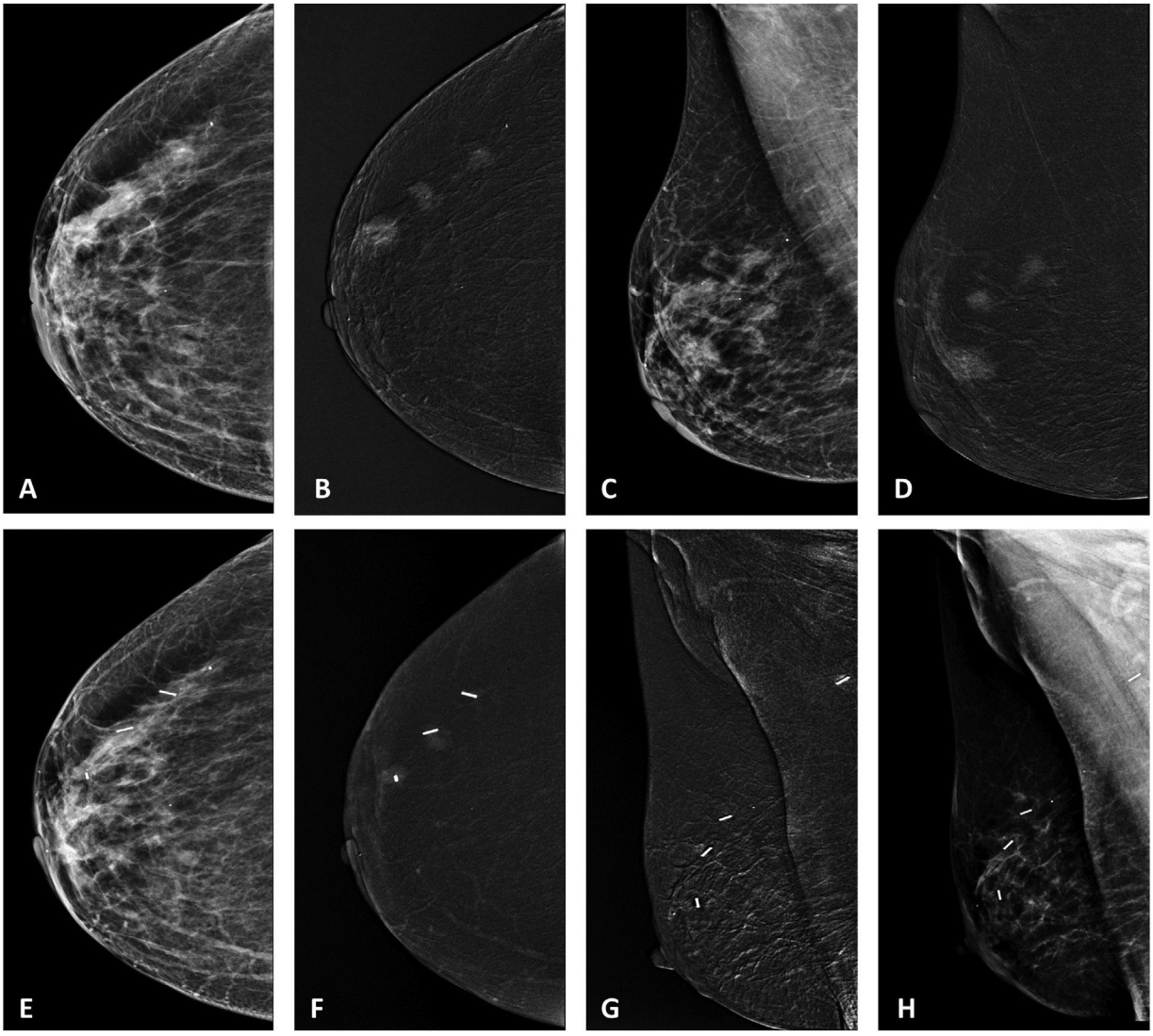

Figure 1 Fifty-seven-year-old woman diagnosed with multifocal neoplasm in the right breast. A–D) Baseline contrast-enhanced mammography (CEM), prior to neoadjuvant systemic therapy (NST): three nodules with irregular contours and increased uptake, measuring 10, 13 and 15 mm in UOQ. E–H) CEM after NST: signs of partial tumour response with decrease in size of the three nodules marked with magnetic seeds.

(Fig. 1). Only one case involved seed displacement (21 mm), but this did not affect its localisation or surgical excision.

The seed was seen inside the breast lesion(s) on mammographic projections in all cases. In cases with lymph node involvement (22 of the 42), the MLN was marked with magnetic seed and no complications were observed. We checked the seed was inside the MLN in the MLO projection. In three cases, the MLN could not be seen on mammography, due to its far posterior location. Radiographs confirmed that the surgical specimen included the MLN in all cases.

Evaluation of surgical treatment

After NST, breast-conserving treatment was performed in 39 of the 42 cases (Table 1). In all patients, selective surgical excision of the residual breast lesion(s) and MLN after completion of NST was possible with magnetic seed guidance. In most cases, this was easy and quick, with no complications.

In all cases, the radiograph of the surgical specimen of the breast and/or axilla verified that the magnetic seed was inside the lesion. The seed was observed within the centre of the surgical specimen in 34 cases and in the margins in eight cases. Only one case required a second surgical procedure due to affected margins. Pathological complete response of the breast was achieved in 33.3% of cases. Pathological complete response of the axilla was achieved in 50% of cases, while an MLN was found in conjunction with an SLN in 63.6% of cases. Radiographs of the axillary surgical specimens showed that the MLN was excised in all 22 cases. Pathological complete response of the breast and axilla was achieved in nine of the 42 cases (Table 1). There were no problems or complications during the targeted surgical excision of the seeds in the breast and/or axilla.

Table 1 Clinical/pathological findings.

Characteristics	
No. of patients	42
Mean age (range), days	57 (36–79)
Hormonal status, no. (%)	
Postmenopausal	29 (69)
Premenopausal	13 (31)
Clinical presentation, no. (%)	
Palpable tumour	31 (74)
Non-palpable tumour	11 (26)
Histological type, no. (%)	
Ductal	41 (97.6)
Lobular	1 (2.4)
Histological grade, no. (%)	
Grade II	22 (52.4)
Grade III	20 (47.6)
Tumour subtype, no. (%)	
Luminal A-like	1 (2.4)
Luminal B-like (HER2-negative)	21 (50)
Luminal B-like (HER2-positive)	6 (14.3)
HER2-enriched	3 (7.1)
Triple-negative	11 (26.2)
Clinical T, no. (%)	
T1c	4 (9.5)
T2	33 (78.6)
T3	5 (11.9)
Tumour stage group, no. (%)	
IIA	21 (50)
IIB	18 (42.9)
IIIA	3 (7.1)
No. of pathological lymph nodes on US, no. (%)	
1	15 (68.2)
2	4 (18.2)
3	1 (4.5)
≥ 4	2 (9.1)
Coincidence of MLN with SLN, no. (%)	14/22 (63.6%)
Type of surgical treatment, no. (%)	
Lumpectomy	39 (92.9)
Mastectomy	3 (7.1)
Breast pCR, no. (%)	
Complete	14 (33.3)
Partial	28 (66.7)
Axillar lymph node involvement, no. (%)	22/42 (52.4)
Axillar pCR, no. (%)	
Complete	11/22 (50)
Partial	11/22 (50)
Breast and axillar pCR, no. (%)	9/22 (40.9)

MLN: metastatic lymph node; pCR: pathological complete response; SLN: sentinel lymph node; US: ultrasound.

Table 2 Mean differences, based on Student's t-test parametric test, between residual tumour lesion size on CEM vs. pathological size.

Difference in means	CI 95% Upper/lower limit	p-Value
0.75	−6.24/7.74	0.83

CI 95%: confidence interval of 95%; CEM: contrast-enhanced mammography.

Comparative evaluation of residual tumour size assessed by contrast-enhanced mammography and pathological study

The distribution of the tumour size measurements followed the law of normality with homogeneity of variance both for the measurements established by the CEM and those of the surgical specimen. The mean pathological tumour size after NST was 12.9 mm (range: 0–64 mm and standard deviation: 15.2) compared to 13.6 mm (range: 0–71 mm and standard deviation: 17.0) for the CEM. There is a mean difference of 0.75 mm between the sizes measured by mammography and those of the surgical specimen (CI: −6.2 to 7.7) which is not statistically significant, recording a p value of 0.83 (Table 2).

The final tumour size measured by CEM was different to the pathological result by ≤ 10 mm in 39 of the 42 patients. This correlation was considered precise. By contrast, it overestimated tumour size by more than 10 mm in three patients, predicting disease progression in one case.

Of the 28 patients that presented with pathological residual disease, 25 were TPs in the CEM (Fig. 2). In the remaining three cases, the CEM showed no residual disease, corresponding to FN cases (Fig. 3). Disease progression was correctly described by CEM for two patients.

Pathological complete response was achieved in 14 of the 42 cases, of which six were triple-negative, four were luminal B-like (HER2-negative), two were HER2-positive and two were luminal B-like (HER2-positive). Of the 14 patients with pCR, CEM showed complete remission in 13 cases, corresponding to TNs (Fig. 4). Only one case was positive on CEM for residual disease (FP), with non-mass enhancement (Fig. 5).

Sensitivity, specificity, NPV and PPV of CEM for the detection of residual disease were 89.3, 92.8, 81.2 and 96.1%, respectively (Table 3).

Discussion

Preoperative NST can reduce the stage group of locally advanced breast cancer and in turn increase rates of breast- and axilla-conserving surgery. Early assessment of pathological response to NST can guide clinicians to optimise the treatment plan for each patient while avoiding unnecessary toxicity. Pathological complete response findings after NST have proved that this therapy is associated with improved prognostic outcomes and is a surrogate marker of survival. Currently, pCR after NST is achieved for 20% of patients.[1,2]

MRI is considered the gold standard modality for monitoring response to NST in breast cancer patients. Furthermore,

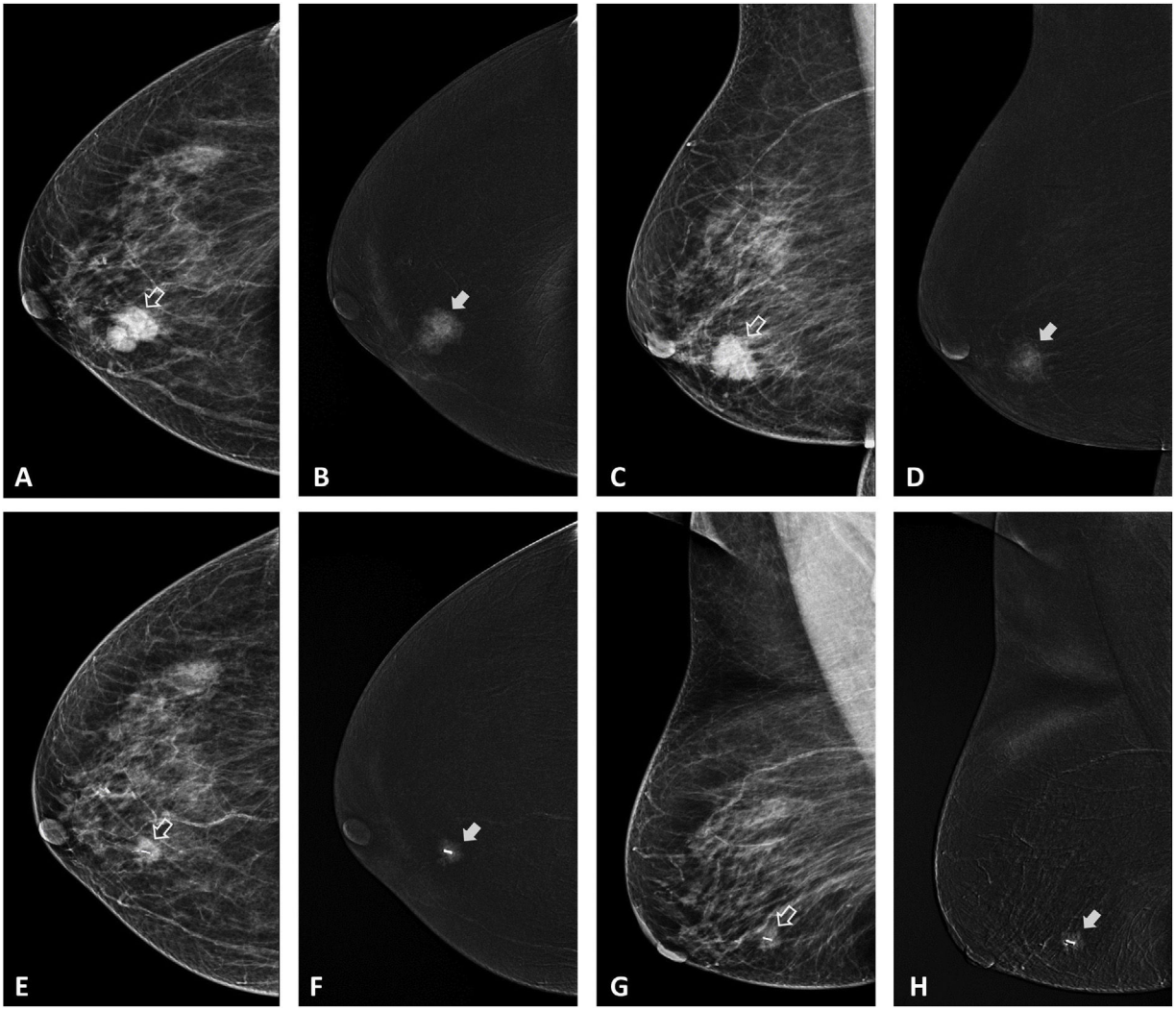

Figure 2 Seventy-two-year-old woman diagnosed with invasive ductal carcinoma of the right breast, with partial tumour response after neoadjuvant systemic therapy (NST). A–D) Contrast-enhanced mammography (CEM) and low-energy mediolateral oblique (MLO) view (A and C) at diagnosis, showing a dense nodule with irregular contours in the right breast (hollow arrow). Recombined CEM and MLO images (B and D) show mass-like contrast uptake with irregular contours (solid arrow). E–H) Imaging after completion of NST showed signs of partial tumour response with decrease in size and uptake of the tumour nodule marked with magnetic seed.

many studies have upheld the comparison of the residual tumour diameter on MRI with the pathological result as gold standard.[3,4] Correlation coefficients were good to excellent. Although these correlation coefficients are high, they do not necessarily mean that the concordance between measurements is good, and both over- and underestimation of tumour size on MRI was often observed.[3] Moreover, its application is limited due to its lengthy examination times, high cost and the intolerance of some patients.

CEM has developed rapidly in recent years. Some studies have shown that CEM has the potential to be an alternative to MRI for the pCR assessment of breast cancer in patients undergoing NST, showing a high correlation in the assessment of residual lesion size after NST.[5,6] Prospective studies have shown a high correlation of MRI and CEM in the assessment of pCR after NST. Consequently, CEM may be an alternative if MRI is contraindicated or unavailable.[18–20] Lotti V et al. show that CEM has greater sensitivity and specificity than MRI (100% and 84% vs. 87% and 60%).[18] Ramos F et al. demonstrate that CEM has a good correlation and concordance with histopathology for measuring residual disease after NST, comparable to MRI, showing high PPVs and specificity for detecting residual disease.[19] Tang S et al. carried out a meta-analysis of 24 studies (2,528 patients), in which they analysed the diagnostic performance of the pCR analysis following NST by CEM and MRI. Their findings showed that CEM has the same specificity as, and higher sensitivity than, MRI. Moreover, it is more accurate, cheaper and better tolerated.[21]

The main objective of our study was to assess the usefulness of CEM for the detection of residual disease after NST. Our study showed slightly higher sensitivity, specificity, NPV and PPV results than previous studies.[19–21] Pathological complete response was achieved in 33.4% of the breasts. The results described in the literature for the detection of pCR may vary depending on how it is defined. In our study, we

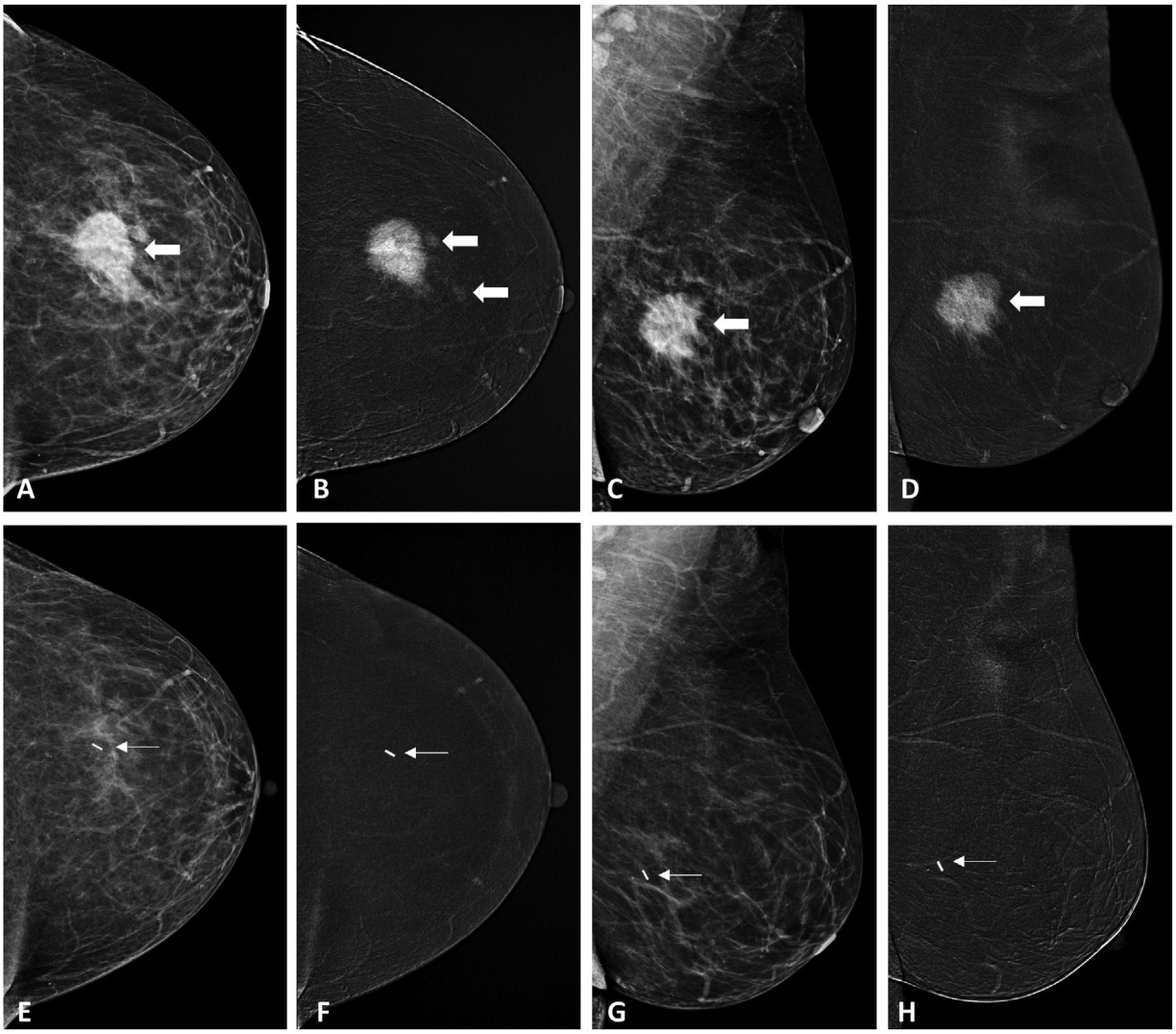

Figure 3 Sixty-nine-year-old woman with invasive ductal carcinoma of the left breast, with contrast-enhanced mammography (CEM) revealing complete response after neoadjuvant systemic therapy (NST) and the presence of residual tumour in the pathological study (false negative). A–D) Baseline diagnostic CEM showing a 5 cm spiculated nodule in UOQ, with homogeneous contrast uptake and nodular foci of enhancement adjacent to the anterior and medial location (thick arrows). E–H) CEM after completion of NST showing complete tumour response, with magnetic seed visible and no nodules or areas of pathological uptake (thin arrows). Pathological examination after surgery revealed residual tumour.

defined pCR as the absence of invasive carcinoma. Pathological complete response of the axilla was achieved in 50% of cases (Table 1), and these findings correspond to those published in the literature.[1,13,14]

Tumours may shrink significantly and be hidden on imaging after NST. In patients who opt for breast-conserving treatment, it is imperative that a marker is placed during staging prior to NST, as this marker may be the only reliable reference point for preoperative localisation. The literature demonstrates that the use of a marker is associated with a lower rate of affected surgical margins and better local control of disease, regardless of the stage group or other clinical and pathological findings.[7,8]

Complications can occur, such as displacement of the marker during placement, which is more common in stereotactic biopsies and surgery.[9,10] They can also be difficult to visualise on ultrasound and can cause difficulties in surgery.[8] Preoperative re-localisation of the marker is therefore required to ensure excision of the residual lesion.

The magnetic seed makes it possible to mark lesions before NST and to localise them during surgery after NST, thus avoiding the need for the preoperative marking of residual lesions. This stainless steel device measures approximately 1×5 mm and is housed in a 7, 12 or 20 cm $\times$ 18 G needle. The magnetic seed has proven to be as reliable and effective as guidewire in terms of lesion identification and excision.[11,12]

Its major drawback is that it causes significant artifacts on MRI. Therefore, it cannot be used to mark breast lesions prior to NST.[15] In our work we have found that in contrast to MRI, no magnetic seed artifacts have been produced when using CEM,[15] nor have there been any complications in its

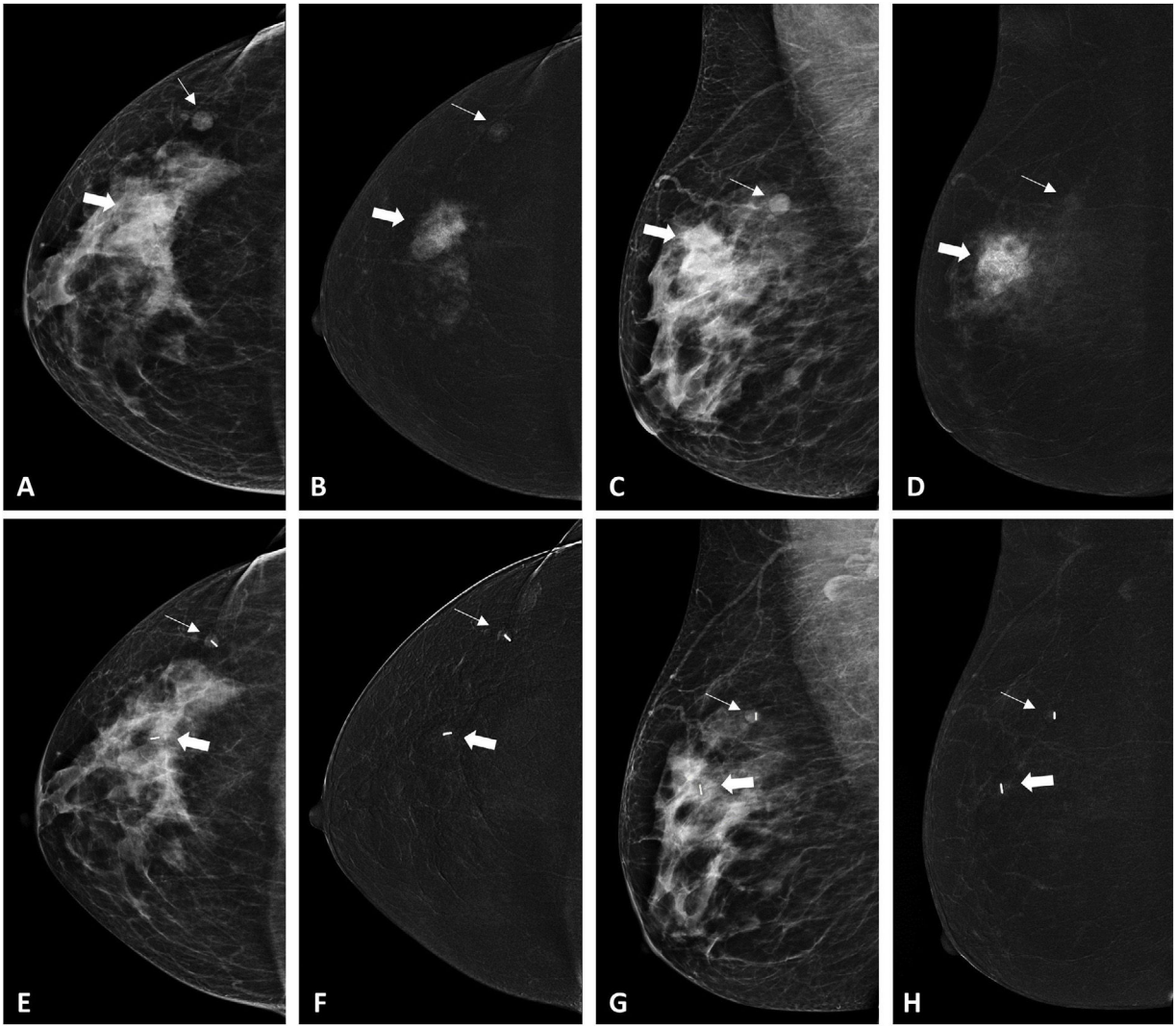

Figure 4 Fifty-five-year-old woman diagnosed with invasive ductal carcinoma in the right breast, with complete response shown by contrast-enhanced mammography (CEM) and pCR. A–D) Diagnostic CEM showing an area of extensive focal asymmetry, with irregular contours and associated microcalcifications located in the UOQ of the right breast (thick arrows), with heterogeneous internal enhancement of irregular morphology measuring 26 × 31 × 34 mm, and non-mass-like uptake adjacent to the lesion. Another round nodule measuring 11 mm was seen in the right tail of Spence, corresponding to intramammary lymph node metastasis (thin arrows). E–H) CEM after completion of neoadjuvant systemic therapy. Imaging shows a magnetic seed in UOQ, with loss of focal assymetry/distortion (thick arrow) and the magnetic seed with no intramammary lymph node disease (thin arrow). The pathological study after surgery revealed pCR.

placement. It has been very well accepted by patients. Displacement of the magnetic seed was detected in only one case, but this did not prevent its excision. The magnetic seed made it possible to locate and carry out the excision of all marked breast lesions during surgery in an easy and uncomplicated manner. Our results are in line with those obtained in previous studies.[11,12]

Magnetic seed has been useful for preoperative localisation and the guided excision of MLNs, as seen in our previously published work, and similar results have been obtained in studies by Mariscal A et al.[13] and Greenwood HI et al.[14] In all cases, radiographs of the surgical specimens verified that the magnetic seed was inside the lesion and/or MLN. Only one case required a second surgical procedure due to affected margins.

This study has some possible weaknesses, which include the small sample size and the fact it was conducted in a single centre, which may limit the applicability of the results. Furthermore, the NST regimen performed was not taken into account, and no interobserver variability study was conducted on the radiologist readers who participated in the study.

One of the strengths of the study is the impact this new tool might have in radiology services. It speeds up schedule management in breast radiology departments, gives surgical teams more independence when planning operations and improves patient satisfaction by eliminating the need to place a harpoon on the day of the surgery. To our knowledge, no previous articles have analysed the usefulness of CEM in conjunction with breast lesion marking for the assessment

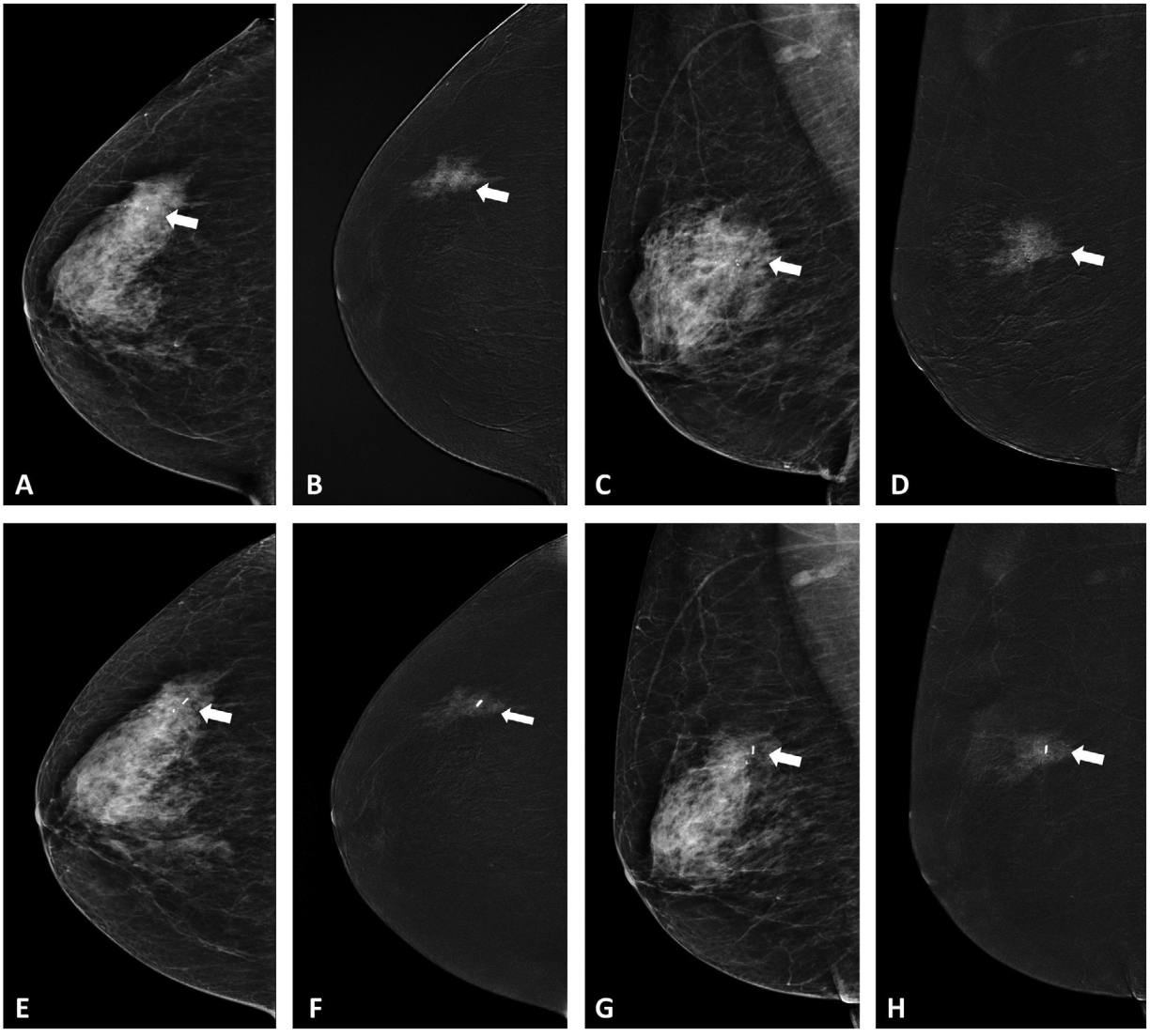

Figure 5 Sixty-nine-year-old woman diagnosed with invasive ductal carcinoma of the right breast, with partial tumour response shown on contrast-enhanced mammography (CEM) and complete response in the pathological study after surgery (false positive CEM). A–D) Initial CEM showing an area of microcalcifications with underlying focal density of irregular and imprecise contours (A and C), with mass-like uptake and intense internal enhancement, located in the UOQ of the right breast (B and D), 43 mm in greatest diameter (arrows). E–H) CEM after completion of neoadjuvant systemic therapy showing a discrete decrease in lesion size with persistent microcalcifications associated with focal density and magnetic seed inside, associated with a persistence of irregularly shaped mass-like uptake, about 38 mm in size (arrows). In the end, the pathological examination following surgical treatment (mastectomy) revealed extensive intraductal carcinoma.

of response to NST in breast cancer patients. We must now await the results of larger studies, such as the MAGMA multicentre study, to see if they confirm the good results obtained in our study, thus allowing the findings to be applied in clinical practice.

Conclusions

The conclusions drawn from this study are that CEM is highly accurate in assessing residual breast cancer disease after NST. When used with CEM, magnetic seed makes it possible to correctly locate and excise a residual tumour and/or metastatic lymph nodes without producing artifacts. These findings are encouraging as CEM could be used in conjunction with magnetic seed marking in the assessment of tumour response to NST for patients with contraindications to MRI, in centres with limited MRI availability or even as a replacement for MRI.

Author contributions

- Research coordinators: AMM and EIB.
- Study concept: AMM and EIB.
- Study design: AMM and EIB.
- Data collection: AMM, HPA, PPP, PCM, MLT and IPM.
- Data analysis: AMM, EIB, PRM, MLT and IPM.

Table 3 Assessment of residual tumour detection following NST by CEM.

Result from CEM	Pathological result	
	Residual tumour	No residual tumour (pCR)
Positive CEM	25 TP	1 FP
Negative CEM	3 FN	13 TN

Sensitivity: TP/TP + FN = 89.3%; Specificity: TN/TN + FP = 92.8%; NPV: TN/FN + TN = 81.2%; PPV: TP/TP + FP = 96.1%.
FN: false negatives; FP: false positives; CEM: contrast-enhanced mammography; NST: neoadjuvant systemic treatment; TN: true negatives; TP: true positives; NPV: negative predictive value; PPV: positive predictive value.

- Statistical processing: PPP.
- Literature search: AMM, HPA and PRM.
- Drafting of article: AMM.
- Critical review of the manuscript with intellectually relevant contributions: EIB and HPA.
- Approval of final version: AMM, EIB, HPA, PRM, MLT, IPM and PPP.

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Conflicts of interest

The authors declare there are no conflicts of interest.

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