Role of Sonomammography versus Dynamic Contrast Enhanced magnetic resonance imaging In Post Operative Breast Cancer Surveillance

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Abstract

Background

Breast cancer is a huge public health issue for women all over the world. It is the leading cause of cancer related mortality accounting for 29.1% of the cancer related deaths. Oncologic and reconstructive breast surgery has evolved in the last 20 years. The diagnostic evaluation of the postoperative breast is challenging because of great variability due to surgery and irradiation. Women who have been treated for breast cancer are at risk for second breast cancers, such as ipsilateral recurrence or contralateral metachronous breast cancer. Contrast-enhanced breast imaging as MRI improve the diagnostic accuracy, the per-lesion sensitivity to malignant breast lesions in post operative breast evaluation in comparison with mammography ± US alone.

Aim of work is to detect the additive role of dynamic contrast enhanced MRI in the post operative breast cancer surveillance
Methods

- The study is a prospective study carried over twelve months. The study included 46 patients who had undergone breast operations for breast cancer. Their age ranged from 30 to 80 years (Mean age: 51.9 ± SD). All included patients subjected to postoperative Sonomammography then further evaluation by contrast enhanced MRI breast.

Results

The study population included 46 patients who had undergone breast operations for breast cancer. All included patients subjected to postoperative Sonomammography then further evaluation either contrast enhanced MRI breast. Sonomammography had a sensitivity of 87.50%, a specificity of 23.33%, a positive predictive value of 37.84%, a negative predictive value of 77.78%, positive likelihood ratio 1.14, negative likelihood ratio 0.54 and accuracy of 45.65%. Dynamic MRI had a sensitivity of 93.75%, a specificity of 86.67%, a positive predictive value of 78.95%, a negative predictive value of 96.30%, positive likelihood ratio 7.03, negative likelihood ratio 0.07 and accuracy of 89.13%.

Conclusion

The gold standard modality for initial assessment of post operative surveillance for breast cancers, is mammography with or without adding ultrasound; however conventional methods have been known to be suboptimal in the accurate assessment of certain cases of post operative breast either symptomatic cases or cases with Sonomammographic warranting findings. So further contrast enhanced breast imaging evaluation is required. The choice of surveillance with Breast MRI in women with a personal history of breast cancer requires optimal patient selection. This should be recommended according to identified sonomammography or clinical findings, type of operation, breast density and availability of the modality.
Keywords: Contrast enhanced breast imaging, breast cancer, surveillance, MRI.

Introduction

Breast cancer is a huge public health issue for women all over the world. It is the leading cause of cancer related mortality accounting for 29.1% of the cancer related deaths [1].

Oncologic and reconstructive breast surgery has evolved in the last 20 years. Familiarity with cutting-edge surgical techniques and their imaging characteristics is essential for radiologic interpretation and may help avert false-positive imaging findings. [2]

The diagnostic evaluation of the postoperative breast is challenging because of great variability due to surgery and irradiation [3]

Second breast cancers, ipsilateral recurrence or contralateral metachronous breast cancer, are major risks for women who have been treated for breast cancer. [4]

Current clinical guidelines recommend annual mammography for women after treatment of primary breast cancer. Surveillance imaging in addition to standard digital mammography, such as CESM, breast ultrasound, and MRI, may enhance outcomes [5].

Contrast enhanced magnetic resonance imaging with its high soft tissue contrast, multiplanar sectioning and three dimensional representation of the breast provides high sensitivity in the detection of breast cancer. [6]

We aimed to detect the additive role of dynamic contrast enhanced MRI in post operative breast cancer surveillance

Material and methods
The study is a prospective study carried over twelve months. The study included 46 patients who had undergone breast operations for breast cancer. Their age ranged from 30 to 80 years (Mean age: 51.9 ± SD). All included patients subjected to postoperative Sonomammography then further evaluation by contrast enhanced MRI breast.

The final diagnosis was either by pathological diagnosis including core biopsy, fine needle aspiration, surgical excision or radical surgery (for lesions assigned BIRADS 4 or 5) or by close follow up (for lesions assigned BIRADS 2 or 3). The study was approved by the ethical committee and informed written consent was taken from all subjects. Image interpretation was done by two consultant radiologists with more than 10 years of experience in advanced breast imaging mammography techniques.

Subjects:

Inclusion criteria:

- All cases presented for post operative breast cancer surveillance.

Exclusion criteria:

1- Contraindication to mammography e.g. : Pregnant women
2- Contraindication to IV Contrast e.g. : patients with renal impairment, allergic patients or those known to have history of anaphylactic reaction from contrast media
3- Contraindication to MRI e.g. cardiac pacemaker, aneurismal clips, bone growth stimulators.

The technique of conventional mammography:

Bilateral conventional mammography was performed in both cranio-caudal (CC) and medio-lateral oblique (MLO) views are taken using full Field Digital
Mammography was performed for all patients using GE Senograph 2000 Machine.

**The technique of breast ultrasound:**

Ultrasound examination was performed using for all the cases using 8–12 MHz linear array transducer (General Electric (GE), Logic 7 machine). By radial scanning of the entire breast and axillary tail of both sides while, the patient’s arm relaxed and flexed behind the head. Medial lesions were scanned in the supine position, and lateral lesions, including the axilla, were scanned with the patient in the contralateral oblique position. Longitudinal and transverse images of breast lesions were obtained.

**The technique of contrast enhanced magnetic resonance imaging:**

Examination will be performed on a 1.5 T MRI system using a bilateral breast surface coil with the patient in the prone position. The imaging studies will include:

A-Localizer: scout views in the sagittal or coronal orientations.

B-Pre-contrast series: axial T1-weighted turbo spin echo (TR/TE= 307/4.6 ms), axial T2-weighted turbo spin echo (TR/TE= 4.3 s /91ms) and axial short T1 inversion recovery (STIR) (TR/TE= 5.2s /71 ms; inversion time= 170ms) as well as sagittal T2 turbo spin echo weighted sequences.

C-Post-contrast series: seven dynamic acquisitions, one before and sex after intravenous injection 0.1mmol/kg body weight of contrast material (gadolinium-diethylene tri amino penta acetic acid; Gd-DTPA), using the dynamic THRIVE sequence (T1 High Resolution Isotropic Volumetric Examination) (TR/TE = 5/2 ms).

D- Subtraction images were generated.

**Possible Risk:**

1- Risk of allergic reaction to contrast media

2- Minimal risk of developing swelling, pain or hematoma at site of contrast injection that are easily managed by cold fomentation and some topical ointment.

**Imaging Analysis and interpretation:**

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In mammographic studies, the lesions were evaluated regarding size, site, shape, margin, definition, density and calcifications. We assigned each lesion a BIRADS category according to the 2013 BIRADS Atlas.

**B-mode ultrasound examination** of lesions was evaluated regarding, shape, boundary, orientation, margin, echo pattern and posterior acoustic features. Surrounding tissue condition was also included in the final assessment. We assigned a BIRADS category for each lesion according to Ultrasound BIRADS atlas 2013.

In post contrast studies (DCE-MRI) the lesions were evaluated regarding size and pattern of enhancement. We assigned a BIRADS category for each lesion according to 2013 MRI BIRADS lexicon morphology descriptors.

Comparison with histopathological examinations: Lesions were biopsied (if indicated) under US guidance using fine needle aspiration, true cut needle biopsy (via 14 -18-gauge needles) or referred for surgical excision. Results of histopathological examinations of surgical or biopsy specimens were obtained and served as a reference.

**Follow up** for patients when pathology and cytology were not indicated.

**Statistical analysis:**
- Data were statistically described in terms of range, mean standard deviation (SD), frequencies (number of cases), and percentages when appropriate.
- Accuracy was represented using the terms sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy, the likelihood ratio of a positive test, and the likelihood ratio of a negative test.

**Results**

The current study population included 46 patients who had undergone breast operations for breast cancer.

All Included patients subjected to postoperative Sonomammography then further evaluation by contrast enhanced MRI breast.
Final diagnosis:

We classified the 46 cases with post operative Sonomammography positive findings into 3 groups according to the lesion location and further according to their final diagnosis either by pathological assessment of biopsy and surgical samples, fine-needle aspiration cytology or close follow up.

Out of the 46 cases, the **operative bed lesions** were 28/46 lesions (61%),

- The newly developed **ipsilateral lesions** were 10/46 lesions (21.7%).
- **Contralateral breast lesions** were 8/46 lesions (17.3%).
- **Collectively** the **benign** lesions group included 37/46 (80.4%) while the **malignant** lesions group included 9/46 (19.6%) lesions

❖ **Final diagnosis according to sono-mammography**:

30/46 (65.2%) lesions were considered benign (BIRADS 1,2and3) and 16/46 (34.8%) lesions were considered malignant (BIRADS 4 and 5).

**Diagnostic Indices Of sono-mammography among studied population:**

- Upon correlating the sono-mammography findings to the final diagnoses, 14 lesions were true positives, 23 lesions were false positive, 2 lesions were false negatives and 7 lesions were true negatives, Table 1
- Based on the previous findings, sono-mammography had a **sensitivity** of 87.50%, a **specificity** of 23.33%, a **positive predictive value** of 37.84%, a **negative predictive value** of 77.78%, **positive likelihood ratio** 1.14, **negative likelihood ratio** 0.54 and **accuracy** of 45.65%. Table 2

❖ **Dynamic MRI Findings:**

- 46/46 (100%) performed post operative Sonomammography followed by dynamic MRI.
- **Contrast uptake:**
- 29/46 (63 %) lesions showed contrast uptake and 17/46 (37%) lesions showed no contrast uptake.

✓ Final diagnosis according to Dynamic MRI revealed 27/46 (58.7%) lesions were benign (BIRADS 1,2 and 3) and 19/46 (41.3%) lesions were malignant (BIRADS 4 and 5).

**Diagnostic Indices of Dynamic MRI:**
- Upon correlating the MRI findings to the final diagnoses 15 lesions were true positives, 4 lesions were false positives, 26 were true negatives and 1 lesion was false negative, table 3
- Based on the previous findings, Dynamic MRI had a sensitivity of 93.75%, a specificity of 86.67%, a positive predictive value of 78.95%, a negative predictive value of 96.30%, positive likelihood ratio 7.03, negative likelihood ratio 0.07 and accuracy of 89.13%. Table 4
- ROC curve for MRI compared to both US and Mammography show its superiority over both (with same sensitivity, specificity, ppv, npv values mentioned before). With P-Value =0.0085 (less than 0.05); statistically significant.

**Discussion**

The diagnostic evaluation of the postoperative breast is challenging because of the great variability due to surgery and irradiation. Distinguishing treatment related findings from breast cancer recurrence in the operative bed site is extremely challenging [3]

The current clinical guidelines are consistent in supporting annual mammography for women after treatment of primary breast cancer. Surveillance imaging beyond standard digital mammography, including breast ultrasound and MRI, may improve outcomes [5]

Contrast enhanced magnetic resonance imaging with its high soft tissue contrast, multiplanar sectioning and three dimensional representation of the breast, provides
a high sensitivity in the detection of breast cancer. The main additional diagnostic value of MRI relies on detecting foci of multifocal, multicentric or contralateral disease unrecognized on conventional assessment [6].

Fallenberg et al. [7] hypothesized that MRI is more accurate in lesion detection and size assessment than digital MG. Their study has shown that bilateral MRI are superior to MG in breast tumor detection. They found an increase in lesion detection using MRI reaching 17.5% compared to MG.

Our study population included 46 patients who underwent breast operations for breast cancer. 10/46 (21.7%) patients underwent MRM, 36/46 (78.3%) patients had underwent BCT. All patients performed post operative MG and breast US then further evaluation either by contrast enhanced MRI breast was done.

As regards the sono-mammographic findings; 30/46 (65.2%) lesions were considered benign (BIRADS 1, 2 and 3) and 16/46 (34.8%) lesions were considered malignant (BIRADS 4 and 5). Upon correlating the sono-mammography findings to the final diagnoses, 14 lesions were true positives, 23 lesions were false positive, 2 lesions were false negatives and 7 lesions were true negatives. The high number of false positive cases was due to the architectural distortion and increased breast density at the lumpectomy site as well as post-treatment edema. And the cases which were false negative, they were small denovo lesions masked by dense breast tissue. They were non-visualized by MG and missed at operator dependent US.

Based on the previous findings, sono-mammography had a sensitivity of 87.50%, a specificity of 23.33%, a positive predictive value of 37.84%, a negative predictive value of 77.78%, positive likelihood ratio 1.14, negative likelihood ratio 0.54 and accuracy of 45.65%.
The low diagnostic indices in the current study goes in accordance with Yalcinkaya et al. [8] who concluded that it is difficult to assess the breast with mammography and US in patients who have had breast conservative surgery and radiotherapy because of parenchymal distortion and edema. MRI is recommended as the screening modality of choice for these patients as well as high risk patients with genetic predispositions. For mammography the false-negative diagnosis rate which is up to 15% in the general population is even higher for this group.

The American Society of Clinical Oncology Clinical Practice Guidelines recommended a post-treatment MG one year after initial diagnosis or at least 6 months after completion of radiation therapy, and yearly MG follow-up thereafter (Khatcheressian et al., 2013).

In current study regarding DCE-MRI findings: 29/46 (63%) lesions showed contrast uptake and 17/46 (37%) lesions showed no contrast uptake. Enhancing lesions were classified into enhancing focus 8/29 (27.6%), enhancing mass lesions 20/29 (68.9%) and enhancing non mass lesions 1/29 (3.5%).

In reference to the ACR 2013 MRI morphology descriptors, DCE-MRI characterized: 27/46 (58.7%) lesions were benign (BIRADS 1,2 and 3) and 19/46 (41.3%) lesions were malignant (BIRADS 4 and 5). Upon correlating the MRI findings to the final diagnoses 15 lesions were true positives, 4 lesions were false positives, 26 were true negatives and 1 lesion was false negative.

The false negative case was misdiagnosed as it was diagnosed as axillary carcinoma by ultrasound then histopathology, but the axillary lesion was showing a benign contrast uptake curve on MRI.

Our four false positive cases were misdiagnosed due to the following causes:
Two cases revealed a contra-lateral breast nodular enhancement but were proven as benign adenosis by histopathology and the other two cases showed non mass enhancement at the operative bed site and was proven as benign inflammatory changes by subsequent close follow up resolution.

The false positive operative bed cases in our study were due to enhancing delayed post-surgical changes. This goes in accordance with Chae et al [9] hypothesis which states that early post-operative MRI may be useful before non-neoplastic contrast enhancement from post-surgical changes becomes radiologically apparent.

The single false negative case in our study goes in accordance with Belli et al. [10] who reported high negative predictive values of breast MRI in women who had BCT. He also concluded that the absence of enhancing foci in the post-treatment breasts has very high reliability for predicting the absence of tumor recurrence.

Based on the previous findings, Dynamic MRI had a sensitivity of 93.75%, a specificity of 86.67%, a positive predictive value of 78.95%, a negative predictive value of 96.30%, positive likelihood ratio 7.03, negative likelihood ratio 0.07 and accuracy of 89.13%. Upon comparing MRI to both US and Mammography, it showed its superiority over both with statistically significant higher diagnostic indices with P-Value =0.0085 (less than 0.05).

This goes in accordance with Belli et al [10] who also reported that there may be no need for additional invasive procedures such as biopsy if there are no enhancing operative bed foci in breast MRI. Patients may benefit from screening MRI, with its high negative predictive value, by reducing many benign biopsies.
Supporting our study results; Delille et al. [11] reported that it has been accepted that breast MRI with contrast enhancement indicates a high degree of sensitivity ranging from 95% to 100% and a variable specificity up to 97% to detect breast cancers.

An important perspective is that the standard modality for the initial assessment of the post operative surveillance for breast cancers is MG with or without complementary ultrasound. However, conventional methods have been known to be suboptimal in the accurate assessment of certain cases of post operative breast either symptomatic cases or cases with sonomammographic suspicious findings. So further contrast enhanced breast imaging evaluation is required.

Following this concept, the approach of further more advanced imaging should be dependent upon whether the patient is symptomatic or not and upon the sonomammographic findings which require further assessment.

The choice of surveillance with Breast MRI in women with a personal history of breast cancer requires optimal patient selection. This should be recommended according to identified sono-mammography or clinical findings. It also should be tailored according to type of operation, breast density, availability of the modality. MRI is an effective tool for increasing sonomammography sensitivity, improving size estimation and staging. MRI is considered the exam of choice whenever we have mastectomy bed recurrence, in deeply seated lesions or lesions located at mammographically hidden areas, and it is also superior in detection of post operative changes as operative bed seroma or fat necrosis.

**Conclusion**

To conclude the standard modality for initial assessment of post operative surveillance for breast cancers, is MG with or without adding ultrasound; however
conventional methods have been known to be suboptimal in the accurate assessment of certain cases of post operative breast either symptomatic cases or cases with Sonomammographic warranting findings. So further contrast enhanced breast imaging evaluation is required. The choice of surveillance with Breast MRI in women with a personal history of breast cancer requires optimal patient selection. This should be recommended according to identified sono-mammography or clinical findings. It also should be tailored according to type of operation, breast density, availability of the modality.

**List of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Radiology</td>
</tr>
<tr>
<td>BIRADS</td>
<td>Breast Imaging and Reporting Data System</td>
</tr>
<tr>
<td>CC</td>
<td>Cranio-Caudal</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Dynamic contrast enhanced magnetic resonance imaging</td>
</tr>
<tr>
<td>FN</td>
<td>False negative</td>
</tr>
<tr>
<td>FP</td>
<td>False positive</td>
</tr>
<tr>
<td>MG</td>
<td>Mammogram</td>
</tr>
<tr>
<td>MLO</td>
<td>Medio-lateral oblique</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>TN</td>
<td>True negative</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>WI</td>
<td>Weighted images</td>
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</table>

**Conflict of interest**: No

**References**


Table 1: TP, TN, FP and FN results of sono-mammography.

<table>
<thead>
<tr>
<th>Sono-mammography</th>
<th>Final Diagnosis</th>
<th>Final Diagnosis</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>Malignant</td>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>14 TP (a)</td>
<td>23 FP (b)</td>
<td>37/46</td>
</tr>
<tr>
<td>Benign</td>
<td>2 FN (c)</td>
<td>7 TN (d)</td>
<td>9/46</td>
</tr>
<tr>
<td>Total</td>
<td>16 (a+c)</td>
<td>30 (b+d)</td>
<td>46 (a+b+c+d)</td>
</tr>
</tbody>
</table>
Table 2: Diagnostic Indices of sono-mammography among studied population:

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>87.50%</td>
<td>61.65% to 98.45%</td>
</tr>
<tr>
<td>Specificity</td>
<td>23.33%</td>
<td>9.93% to 42.28%</td>
</tr>
<tr>
<td>Positive Likelihood Ratio</td>
<td>1.14</td>
<td>0.87 to 1.50</td>
</tr>
<tr>
<td>Negative Likelihood Ratio</td>
<td>0.54</td>
<td>0.13 to 2.28</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>37.84%</td>
<td>31.71% to 44.38%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>77.78%</td>
<td>45.09% to 93.72%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>45.65%</td>
<td>30.90% to 60.99%</td>
</tr>
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</table>

Table 3: TP, TN, FN and FP results of MRI.
<table>
<thead>
<tr>
<th>MRI</th>
<th>Final Diagnosis</th>
<th>Final Diagnosis</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Malignant</td>
<td>Benign</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>15 TP (a)</td>
<td>4 FP (b)</td>
<td>19/74</td>
</tr>
<tr>
<td>Benign</td>
<td>1 FN (c)</td>
<td>26 TN (d)</td>
<td>27/74</td>
</tr>
<tr>
<td>Total</td>
<td>16 (a+c)</td>
<td>30 (b+d)</td>
<td>46(a+b+c+d)</td>
</tr>
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</table>

Table 4: Diagnostic Indices of MRI among studied population:

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>93.75%</td>
<td>69.77% to 99.84%</td>
</tr>
<tr>
<td>Specificity</td>
<td>86.67%</td>
<td>69.28% to 96.24%</td>
</tr>
<tr>
<td>Positive Likelihood Ratio</td>
<td>7.03</td>
<td>2.80 to 17.66</td>
</tr>
<tr>
<td>Negative Likelihood Ratio</td>
<td>0.07</td>
<td>0.01 to 0.48</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>78.95%</td>
<td>59.89% to 90.40%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>96.30%</td>
<td>79.50% to 99.43%</td>
</tr>
<tr>
<td>Accuracy</td>
<td>89.13%</td>
<td>76.43% to 96.38%</td>
</tr>
</tbody>
</table>
Figure (1)

(a) Mammography CC view and MLO view

(b) Complementary ultrasound
(C) Dynamic MRI: Axial T1, T2, STIR and 3d dynamic subtraction.
Figure 1: 40 year-old asymptomatic female patient underwent right CBS for papillary carcinoma, presenting for her follow up. Mammography revealed: Bilateral well circumscribed masses are seen and right peri-areolar UOQ post operative parenchymal distortion(a). Complementary ultrasound revealed: Large operative bed seroma, bilateral thin wall anechoic cysts and a well defined isoechoic mass is seen deeply seated at left 12 o'clock (b). Dynamic MRI revealed: Bilateral scattered non enhancing cysts apart from the one seen in the left one showing rim enhancement measuring 12mm. RT BREAST: Large operative bed seroma with no operative bed definitive residual or recurrent lesions seen. LT BREAST: Shows oblong shaped mass lesions showing a bright T2 signal seen at 12 o'clock location (corresponding to previously described in sonomammogram). Multiple other irregular shaped intensely enhancing lesions are also seen taking a segmental distribution in the left UOQ. All lesions show a type 2 and type 3 high peak malignant curves. Final Diagnosis: Right operative bed seroma, Bilateral fibrocystic mammary changes. And left breast highly suspicious multicentric mass lesions (BIRADS4). Pathology papillary carcinoma (contra lateral newly developed lesion). Final comment: In this case sonomammography couldn't confirm the contralateral newly developed lesion; while DCE-MEI revealed contralateral multicentric newly developed mass lesions.

Figure (2)
(a) Mammography CC view and MLO view.
(b) Complementary ultrasound.
(c) Dynamic MRI: Axial T1, T2, STIR, 3d dynamic subtraction and dynamic curve.

✓ **Figure 2:** 65 year-old asymptomatic female patient underwent left mastectomy for IDC, presenting for post operative follow up.

**Mammography revealed:** Right breast: Scattered fibroglandular densities (ACR). No speculated mass lesions or microcalcific clusters.

**Complementary ultrasound revealed:** The operative bed is a seat of two hypoechoic lesions; suspicious operative bed nodules. **Dynamic MRI revealed:** Post left mastectomy status. The left operative bed sub-mammary region show two partially circumscribed subcutaneous nodules eliciting isointense signal on T2 & high signal on STIR with faint post contrast enhancement. On plotting the time intensity curves, they showed a high peak washout (type 3) curve. No right enhancing lesions are seen. **Final Diagnosis:** Left mastectomy status showing two left operative bed subcutaneous nodules (BIRADS4) >> Pathology >> IDC (operative bed recurrence). No right breast suspicious masses (BIRADS1). **Final comment:** In this case DCE-MEI confirmed mastectomy bed recurrence and excluded contralateral lesions.