

The Validity of MRI in Evaluation of Tumor Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

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Abstract

Background: Physical Examination (PE) and breast MRI are two of the current methods which have usually used in diagnosis of primary breast cancer. Their accuracy in detection of: either complete response or presence of residual tumor, however, has not yet been established in patients who have been received Neoadjuvant Chemotherapy (NAC).

The purpose of this study was to evaluate the diagnostic accuracy of breast MRI in assessment of residual neoplastic tissue after NAC in patients with Locally Advanced Breast Cancer (LABC).

Methods: Twenty patients with LABC have undergone contrast-enhanced MRI before and after the NAC. Considering histology as the gold standard, the tumor sizes in MRI and PE have compared with the histology results. We have calculated for all below: the accuracy, sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for each of MRI and physical examination, as well as Pearson's correlation coefficients between the results of MRI and PE, and their histology results.

Results: We have found an accuracy of 85% for MRI with a sensitivity of 100%, a specificity of 50%, a PPV of 83.3%, and an NPV of 100%. In addition, the accuracy for PE was 70% with a sensitivity of 71.4%, a specificity of 66.6%, a PPV of 83.3%, and an NPV of 50%. In this study, the calculated Pearson's correlation coefficient for MRI and histology was 0.817 ($p < 0.0001$) versus 0.26 ($p = 0.26$) for correlation between PE and histology.

Conclusion: MRI has higher sensitivity but less specificity than PE for detection of residual tumor after NAC in locally advanced breast carcinoma. Also, the tumor size that has measured by MRI had highly correlation with the histology.

Keywords: Locally advanced; Breast cancer; Magnetic Resonance Imaging (MRI); Neoadjuvant; Chemotherapy

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Introduction

Locally Advanced Breast Cancer (LABC) represents about 30-60% of breast cancer population in low-resource countries. Nowadays the current treatment for LABC could be Neoadjuvant Chemotherapy (NAC) that has followed by locoregional therapy (surgery and/or radiotherapy) and subsequent postoperative systemic chemotherapy [1].

Several advantages could be achieved by NAC in LABC patients: tumor downstaging with higher

chances for breast conserving surgery; evaluation of tumor sensitivity to the selected chemotherapeutic regimens; and early control of micrometastatic disease[2].Using NAC, we could even attained the complete elimination of invasive tumor, from the breast tissue and axillary lymph nodes before surgery in a number of patients [3],which is associated with improved disease-free and overall survival in these patients [4].

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About 25-40% of locally advanced breast cancers have complete histopathologic response after neoadjuvant chemotherapy [5] and breast conserving surgery is possible in 10%-40% of LABC patients [1].

Meantime histopathological complete response is not predictable exactly by any of the current diagnostic modalities [5]. All of the diagnostic methods (physical examination, mammography, sonography, and MRI) have been associated with both false positive and false negative results. In spite of these limitations, there relative accuracy of these modalities should be defined as present basis for clinical practice that guided the treatment [6].

The purpose of this study was evaluation of diagnostic accuracy of breast MRI in assessment of residual neoplastic tissue after NAC locally advanced breast carcinoma. The gold standard was pathology after radical mastectomy or conservative surgery.

Materials and Methods

From August 2010 to April 2012, 20 patients with clinical and histopathologic diagnosis of locally advanced breast cancer that have scheduled for NAC before surgery, have participated in our study. Before the initiation, and after the completion of chemotherapy, each patient has fully evaluated clinically by both medical and surgical oncologists who were specialist in breast cancer treatment. A contrast-enhanced MR study from both breasts has performed within 1 week after the initiation of NAC for each patient. After the completion of neoadjuvant courses and before the surgery, MR study has repeated. This study has approved by the Ethics Committee of Mashad University of Medical Sciences and was in compliance with Helsinki Declaration. Written informed consent has been obtained from all patients.

MRI Technique

All MR examinations have performed on a 1.5-T system (Symphony, Siemens Healthcare, Erlangen, Germany) with a dedicated breast coil in prone position. For each patient an axially oriented Turbo Inversion Recovery Magnitude (TIRM) sequence (TR=70, TE=6010, TI=150, slice thickness=1.5mm, matrix size=256*256) followed by six series of axial three-dimensional (3D) Fast Low-Angle Shot (FLASH) T1-weighted sequence (TR=12, TE=5, flip angle=25, slice thickness=2.2mm, matrix size=512*512 with 80 s acquisition time per volume), once before the administration of contrast and five times after intravenous injection of 0.1mmol

GD-DTPA/kg of body weight (Magnevist; Schering Berlin, Germany) have obtained. Also, a sagittally oriented fat-suppressed T1-weighted sequence (TR=31, TE=7, slice thickness=2mm, matrix size=256*256) has performed after 3D FLASH T1-weighted images. Semi-quantitative analysis of the enhancing areas has performed with creating signal intensity to time curves of the region of interest.

MRI Interpretation

MR images have assessed and the findings have reported based on criteria previously described for interpretation of breast imaging [7-9].

All MRI images have then reevaluated by one radiologist expert in breast imaging interpretation. The dimension of the abnormally enhancing lesion or lesions has measured and the maximum dimension has registered as the size of the tumor. If the lesion has consisted of multiple adjacent abnormalities, the maximum dimension has considered as a single measurement encompassing the lesions farthest apart. Also, the abnormally enhancing lesions have characterized as focal (single discrete mass) or decentralized (segmental, regional or diffuse).

Neoadjuvant Chemotherapy

Patients have undergone one of the following regimens: 10 patients have received 6 cycles of TAC (Taxotere=Docetaxel) 75mg/m², Adriamycin 60 mg/m², Cyclophosphamide 600 mg/m²) and 10 patients have received 4 cycles of AC (Adriamycin 60 mg/m², Cyclophosphamide 600 mg/m²) followed by 4 cycles of Taxol (paclitaxel) 175 mg/m².

Based on clinical and imaging findings, using the measurements have obtained with PE and MRI and according to the "Response Evaluation Criteria in Solid Tumors (RECIST)" [10], the responses to chemotherapy have classified into the following categories:

- 1- Responders
 - Complete Response (CR): no clinical evidence of residual tumor
 - Partial Response (PR): reduction in size of the tumor more than 30%
- 2- No Responders
 - Stable Disease (SD): reduction in size of the tumor inferior than 30%
 - Progressive Disease (PD): increase in size of tumor or presence of new lesions

Statistical Analysis

Histology has considered as the gold standard and the size of the tumor on MRI and clinical

Table 1. Physical examination and MRI findings before and after neoadjuvant chemotherapy, compared with pathologic results

Patient No.	Distribution	Size of lesion (cm)					Final histologic result
		Before neoadjuvant chemotherapy		After neoadjuvant chemotherapy			
		Physical examination	MRI	Physical examination	MRI	Pathology	
1	Focal	10	11	3	3.1	0	
2	Focal	7	4.5	1.5	1	2	Invasive ductal carcinoma
3	Focal	6	3.9	4	2.7	2.5	Invasive ductal carcinoma
4	Decentralized	0	10	0	5	7	Invasive ductal carcinoma
5	Focal	6	4.7	4	3	4	Invasive ductal carcinoma
6	Decentralized	8	8	0	0	0	
7	Decentralized	10	8	3	4	7	Invasive ductal carcinoma
8	Focal	8	4.5	0	4.5	0	
9	Decentralized	9	7	3	4.6	5	Invasive lobular carcinoma
10	Decentralized	11	8	0	0	0	
11	Focal	8	5	2	3.5	5	Invasive ductal carcinoma
12	Focal	6	1.8	4	1.5	0	
13	Focal	8	6	0	1.5	3	Invasive ductal carcinoma and DCIS
14	Focal	8	5	0	3	2	Invasive ductal carcinoma
15	Decentralized	10	6	0	0	0	
16	Focal	11	3.7	5	2.5	2.5	Invasive ductal carcinoma
17	Focal	12	12	4	16	16	Invasive ductal carcinoma and DCIS
18	Decentralized	9	9	5	8	3.5	Invasive ductal carcinoma
19	Focal	12	5.5	6	4.5	5	Invasive ductal carcinoma
20	Decentralized	14	7	0	1.5	7	Invasive ductal carcinoma

Note.—Decentralized distribution includes: segmental, regional, or multicentric distribution.

^a Based on MRI findings before treatment.

examination has compared with the result of histopathologic assessment.

The accuracy, sensitivity, specificity, PPV and NPV for each of MRI and PE has calculated.

We also have calculated Pearson's correlation coefficients to determine the association between the size of the tumor on MRI and PE and that of histology.

Results

Twenty patients with mean (±SD) age of 44.7 ± 9.5, with maximum age of 64y and minimum age of 30y, have included in our study. The histology of the tumor was invasive ductal carcinoma in 19 patients and invasive lobular carcinoma in one patient.

The time interval between the performance of MRI after the completion of chemotherapy and final surgery was 2-30 days, except for one patient who

had a delay of about 85 days to present herself for surgery.

The average post-chemotherapy tumor size has predicted by MRI and PE was 3.49 cm (SD= 3.5 cm, range= 0-16 cm) and 2.2 cm (SD=2.1 cm, range=0-6 cm), respectively, in comparison with the mean size at histopathology of 3.57 cm (SD=3.83 cm, range=0-16 cm).

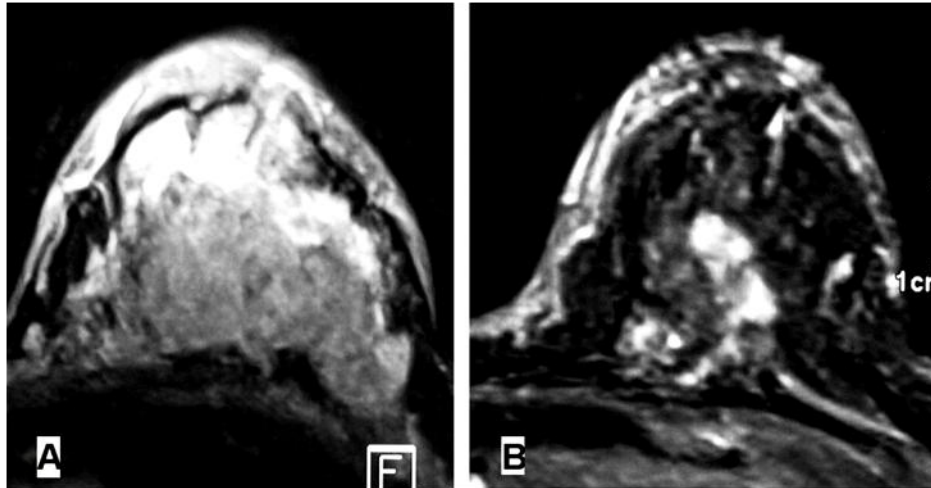
The findings of MRI, PE and histopathologic assessment of all patients have provided in Table 1.

The accuracy, sensitivity, specificity, PPV and NPV for each of MRI and PE have outlined in Table 2.

The calculated Pearson's correlation coefficient for MRI and histology was 0.817 (95% Confidence Interval [CI] = 0.58 – 0.92) (P < 0.0001) versus 0.26 (95% Confidence Interval [CI] = -0.20- 0.62) (P =0.26) correlation between PE and histology.

Table 2. Accuracy, Sensitivity, Specificity, PPV and NPV for each of MRI and physical examination

Characteristic	Physical examination	MRI
Accuracy	70%	85%
Sensitivity	71.4%	100%
Specificity	66.6%	50%
PPV	83.3%	83.3%
NPV	50%	100%

**Figure 1.** A 42-year-old woman with left breast invasive ductal carcinoma (tumor size underestimated by MRI)

A. Contrast-enhanced MRI before chemotherapy shows a 7-cm irregular mass in upper part of the breast. B. After completion of chemotherapy CE-MRI shows a 1.5-cm area of regional enhancement at the site of previous tumor. Pathology showed a 7cm residual tumor.

MRI could predict the residual tumor size from 1cm, in 11 out of 20 patients, however, overestimation and underestimation the size of the tumor by more than 1 cm for one, then for five patients respectively. On PE in 7 out of 20 patients, the size of the tumor has precisely predicted from 1cm, for 3 patients the size has overestimated and in 4 patients, it has underestimated.

In one case with significantly underestimated tumor size on MRI examination (Figure 1), MRI has demonstrated a 1.5cm residual mass, but a 7 cm invasive ductal carcinoma has reported at pathology. This patient had an interval of about 85 days between the performance of MRI and breast surgery, so the discrepancy between the MRI and histopathologic findings might somehow be related to tumor regrowth during this delay. Two of the three patients with false-positive MRI examinations had areas of decentralized regional enhancement on MR images, and in one of them MRI has shown

peripheral nodular enhancement at a mass margin of corresponding to the main primary tumor site.

According to RECIST criteria, in MRI complete response has seen in 3 (Figure 2), partial response in 13 (Figures 3), stable disease in 3 (Figure 4), and progressive disease in 1 of the patients. On PE, 8 patients had complete response, but 12 patients had partial ones.

Six patients (30%) had pathologic complete response to neoadjuvant chemotherapy. MRI has precisely shown complete response in 3 of them, however, for 3 patients MRI was falsely positive (Figure 5).

On PE, 4 out of the six patients with pathologic complete response had no palpable tumor, yet the 2 other patients had false-positive examination. PE has shown no palpable mass in 5 patients with pathologic result of residual tumoral mass, indeed in these 5 patients PE was falsely negative.

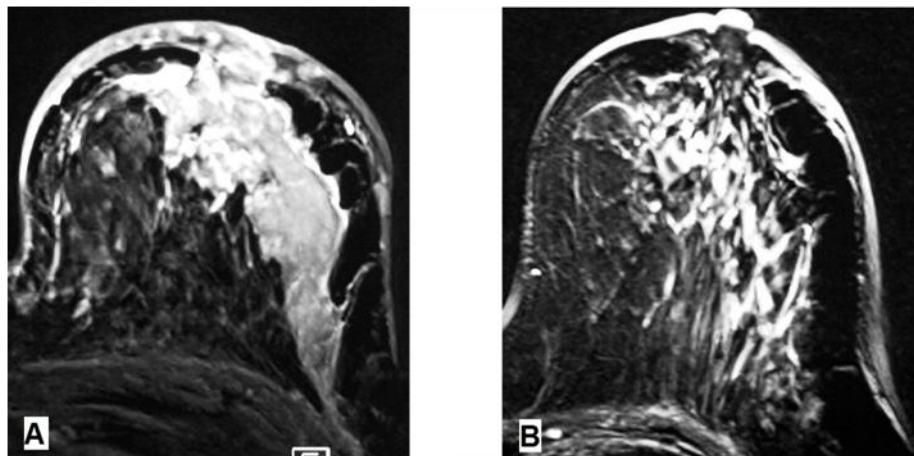


Figure 2. A 48-year-old woman with left breast invasive ductal carcinoma, complete response to neoadjuvant chemotherapy and true-negative MRI

A. Contrast-enhanced T1-weighted MRI before chemotherapy shows a 8-cm area of regional enhancement at the central and lateral portion of the left breast. B. After completion of chemotherapy at CE-MRI there is no visible abnormal enhancement. At pathology there was complete response to chemotherapy.

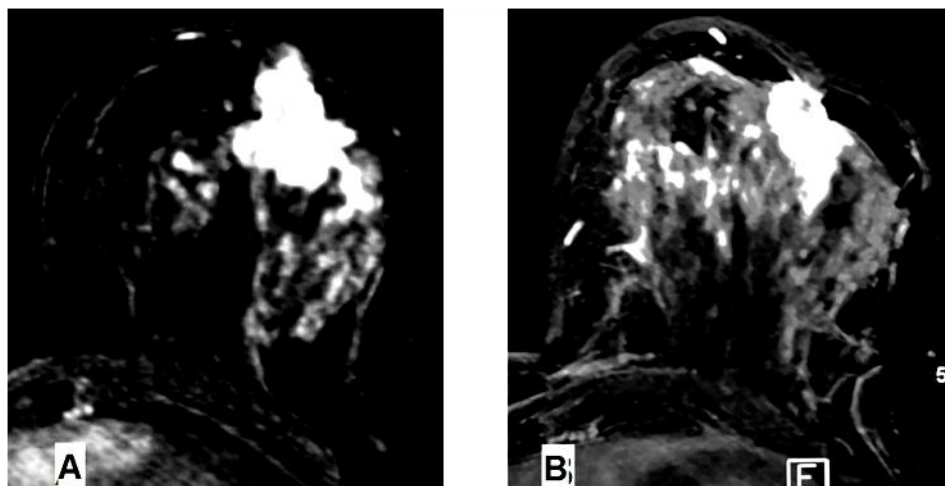


Figure 3. A 30-year-old woman with the left breast invasive ductal carcinoma, partial response to neoadjuvant chemotherapy

A. Contrast-enhanced T1-weighted MRI before chemotherapy shows a retroareolar enhancing round mass measuring 4.7-cm in diameter. B. After completion of chemotherapy CE-MRI shows a 3-cm round mass at previous tumor site. Pathology showed a 4cm residual mass.

Discussion

Pre-operative or neoadjuvant chemotherapy has gained a real accepted and underlying role in treatment of stage II and III breast cancer [11]. Obviously the most significant effect of this treatment is its potential to clear the neoplastic tissue completely from the breast and axillary region. Complete response makes the conservative surgery feasible with an improved expected survival [12]. In

recent years, determining the best diagnostic modality, which could precisely predict "the complete pathologic breast tumors response" to neoadjuvant chemotherapy, has reformed into a favorite research topic. However, there is still no general consensus on this issue and the results have been controversial. MRI has been stated as a superior modality in comparison to the others, in tumor response assessment by several authors [13-17].

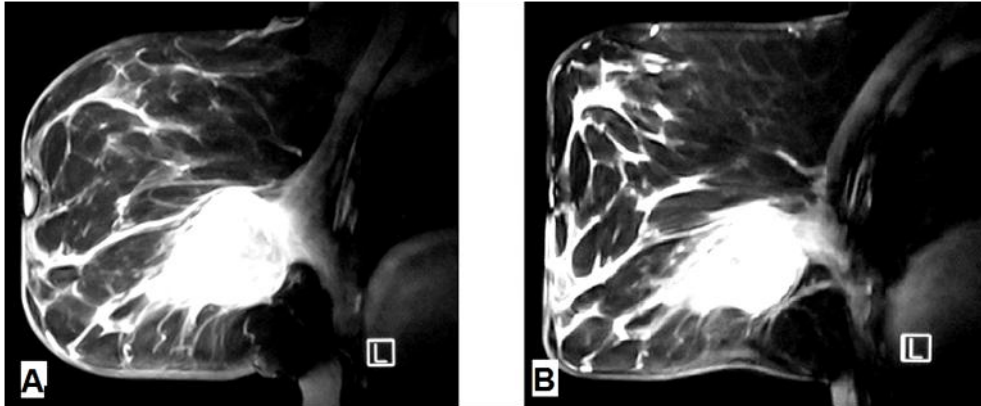


Figure 4. A 30-year-old woman with the right breast invasive ductal carcinoma with stable disease

A. Contrast-enhanced T1-weighted MRI before chemotherapy shows a 5.5-cm round mass in posterior central part of the breast. B. After completion of chemotherapy CE-MRI shows a 4.5-cm round mass at the site of previous tumor. At pathology there was a 5cm residual mass.

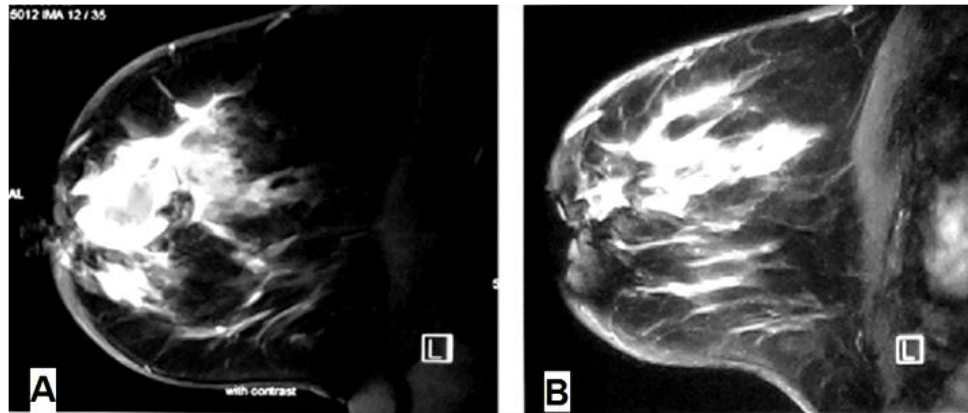


Figure 5. A 48-year-old woman with invasive ductal carcinoma of the left breast with complete response to neoadjuvant chemotherapy and false-positive MRI

A. Contrast-enhanced T1-weighted MRI before chemotherapy shows a retroareolar oval mass measuring 4.5-cm in diameter. B. After completion of chemotherapy CE-MRI shows a 4.5-cm area of decentralized regional enhancement at the site of previous tumor, which makes the false impression of the stable disease at mind. Pathologic examination has shown no residual tumor.

By meta-analysis assessment in thirty four studies, that have performed to assess the diagnostic validity of Diffusion-Weighted MR Imaging (DW-MRI) and Contrast-Enhanced MR Imaging (CE-MRI) for predicting the pathological response to NAC in breast cancer, Wu and associates (2012) have found a high sensitivity (93%) for DW-MRI and a high specificity (91%) for CE-MRI [18].

In another recent study, DCE-MRI and histopathological standards have reported highly correlated; a fact which has approved by MRI accuracy assessment for estimating the efficiency of

NAC in 91 patients with locally advanced breast cancer [19].

In present study, the accuracy of MRI in tumor response prediction to NAC in 20 patients with locally advanced breast cancer has evaluated. An accuracy of 85% for MRI with a sensitivity of 100%, a specificity of 50%, a PPV of 82% and a NPV of 100% has touched. The accuracy, sensitivity, specificity, PPV, and NPV for PE were 70%, 71%, 66%, 83%, and 50% respectively.

In a similar study Croshaw et al has reported an accuracy of 84%, a sensitivity of 86%, a specificity of 79%, a PPV of 93% and a NPV of 65% for MRI.

In their study accuracy for PE was 57%, sensitivity was 50%, specificity was 82%, PPV was 91% and NPV was 31% [20]. The results of Croshaw et al study fairly corresponds to our findings, however, we have found a sensitivity of 100% and a NPV of 100% for MRI in detection of residual tumor, whereas in Croshaw's study sensitivity has been 86% and NPV 65%. This difference might be related to small sample size which was one of these study limitations.

Despite the fact that, in present research MRI could show the residual tumor with a high sensitivity (100%) and an intermediate specificity (50%) due to some discrepancy between the MRI size measurement, and histologic reports, then we also have calculated a Pearson's correlation coefficient, need to be calculated for assessing two results correlation.

The correlation between MRI and histology, then the correlation between PE and histology was 0.817 ($P < 0.0001$) and 0.26 ($P = 0.269$), respectively, which means that a good correlation exists between MRI and histology; however, it reveals an unfavorable correlation between PE and histology.

In contrast to our findings, Prati et al and Rosen and associates by assessment of the correlation coefficients between PE and pathology have reported correlation values of 0.655 and 0.61, respectively, [6, 21] which have higher coefficients than the one that has been achieved in this study.

Such a contrast could be attributed to differences about native size and breast tissue consistency between the patients groups in these studies, which made the PE unreliable in our population. The mean age of patients in present study was about 5 years younger than Prati's et al study and the more compact texture of breast in younger patients might be associated with difficulty in physical examination.

In comparison with Positron Emission Tomography (PET) study, some investigators have shown that MRI is more efficient in evaluating complete pathologic response to neoadjuvant chemotherapy [22-24].

By applying a threshold SUV of 2.0, Dose-Schwarz and colleagues have shown that the sensitivity of FDG-PET was 32.9% (specificity, 87.5%) for detection of residual tumor, which increased to 57.5% (specificity, 62.5%) at a threshold SUV of 1.5 [22]. In comparison to these results, a higher sensitivity (100%) and a lower specificity (50%) for MRI has attained in the present study.

On the other hand, the sensitivity and NPV for PET in Park et al study have been 100% [25,26], which

are comparable to the present study results for MRI (sensitivity and NPV of 100%).

Moreover, by meta-analysis of nineteen studies relating to accuracy of (18)F-FDG PET in predicting responses to neoadjuvant therapies, Wang and colleagues have reported a sensitivity of 84%, a specificity of 66%, a PPV of 50% and a NPV of 91% for PET imaging[25]. In present study, higher sensitivity, PPV and NPV have obtained for MRI (100%, 83.3% and 100%, respectively).

Conclusion

In conclusion, in our study MRI has shown a higher sensitivity but a lower specificity than PE in detection of residual tumor after NAC in locally advanced breast carcinoma. Although MRI has underestimated the size of the residual tumor in five of the patients, the overall correlation between the tumor sizes measured on MRI, and histopathology was high. According to the findings of present study, MRI has an NPV of 100% in pathologic complete response prediction, thus, one might conclude that breast conserving surgery could accomplish based on MRI results, however, due to the small sample size used in our study, such a conclusion must infer cautiously. Further studies with greater sample sizes need to validate these results.

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Conflict of Interest

The authors indicate no potential conflict of interest.

Authors' Contribution

Mahboobeh Abedi has contributed in data acquisition and manuscript drafting.

Donya Farrokh has contributed in data interpretation.

Fatemeh Homaei Shandiz has contributed in study conception and design.

Azadeh Jolaei has participated in study design.

Robab Anbiaee has participated in data acquisition.

Behrooz Zandi has contributed in data interpretation.

Masoumeh Gity has contributed in interpreting the MR images.

Hamid Reza Sayah has participated in MR imaging performance.

Mohammad Sadegh Abedi has participated in statistical analysis.

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