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Residual Breast Cancer Diagnosed by MRI in Patients Receiving Neoadjuvant Chemotherapy with and without Bevacizumab

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Abstract

Purpose—To investigate the impact of anti-angiogenic therapy with bevacizumab on pathological response and the diagnostic performance of MRI in breast cancer patients.

Methods—Thirty-six patients (age 31-69) with breast cancer were included. Sixteen patients received neoadjuvant chemotherapy (NAC) containing bevacizumab, and 20 patients received the same NAC protocol without bevacizumab. Serial MRI studies were performed to evaluate response. All patients received surgery after completing NAC. The extent of residual disease was examined by histopathology, and classified into three types (pCR-pathologic complete response, confined nodules, and scattered cells). The Fisher's Exact test and the general logistic regression models were applied to analyze differences between two groups.

Results—The pCR rates and residual disease (nodular and scattered cell) patterns were comparable between the two groups. The diagnostic accuracy rate of MRI (true positive and true negative) was 13/17 (76%) for patients with bevacizumab; and 14/20 (70%) for patients without bevacizumab. The size measured on MRI was accurate for mass lesions that shrank down to nodules, showing < 0.7 cm discrepancy from pathological size. For residual disease presenting as scattered cells within a large fibrotic region, MRI could not predict them correctly, resulting in a high false negative rate and a large size discrepancy.

Conclusion—The pathological response and the diagnostic performance of MRI are comparable between patients receiving NAC with and without bevacizumab. In both groups MRI has a limitation in detecting residual disease broken down to small foci and scattered cells/clusters. When MRI is used to evaluate the extent of residual disease for surgical treatment, the limitations, particularly for non-mass lesions, should be considered.

Keywords

Anti-angiogenic therapy; Bevacizumab; Breast MRI; Neoadjuvant chemotherapy; Pathological response

Angiogenesis is an essential process to support development and growth of tumors. In 1971 Folkman first proposed the concept of angiogenesis, suggesting that tumor cells interact with their surrounding tissues to secrete factors stimulating formation of new blood vessels.¹ The vascular endothelial growth factor (VEGF) has been identified as one of the important stimulating mediators.²⁻⁴ VEGF binds to tyrosine kinase receptor on the epithelial cell surface and activates the receptor by transphosphorylation. The activation induces several enzymes stimulating proliferation and migration of endothelial cells, which leads to angiogenic cascade.⁵

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), and it potentially blocks the signal transduction through both the VEGFR-1 and VEGFR-2 receptors.⁶ Therefore, neutralization of VEGF leads to anti-angiogenic effects, which has been shown to result in tumor growth delay and shrinkage.⁷ Clinical efficacy of bevacizumab for treating colorectal cancer, lung cancer, metastatic breast, and other solid tumors has been investigated.⁸⁻¹⁶ It was first approved for treatment of colon cancer by the Food and Drug Administration (FDA) in 2004, then approved for lung cancer in 2006. Based on the result that bevacizumab plus paclitaxel has significantly prolonged progression-free survival as compared to paclitaxel alone,⁹ in February 2008 the FDA granted accelerated approval for bevacizumab to be used in combination with paclitaxel for the treatment of patients with metastatic HER-2 negative breast cancer.

Dynamic contrast enhanced (DCE) MRI is an imaging technique used for diagnosis of breast cancer. Images at several different time frames before and after injection of contrast agents were acquired for characterizing the vascular property of enhanced tissues, and based on that to differentiate between malignant and benign/normal tissues. Compared to other breast imaging modalities, DCE-MRI has been proven as an accurate imaging modality for assessing treatment effect of neoadjuvant chemotherapy (NAC).¹⁷⁻²¹ However, since the treatment effect of bevacizumab is through inhibiting angiogenic vessels, whether the damaged vessels would affect the delivery of MR contrast agents thus leading to under-estimation of residual disease warrants investigation.^{8,21} The purpose of the present work is to study the impact of bevacizumab on the accuracy of MRI in diagnosing residual disease after NAC. Patients receiving NAC regimen with and without bevacizumab were monitored with serial MRI studies. The extent of residual disease was carefully evaluated in pathological examination and correlated with the MRI findings. The pathological response and the diagnostic accuracy of MRI between patients receiving NAC regimen with and without bevacizumab were compared.

Materials and Methods

Patients

The breast MRI research study database from 2004 to 2007 was reviewed. Only patients with histological-proven invasive ductal cancer (IDC) and infiltrating lobular cancer (ILC) were included in the analysis. During this time period, a total of 16 patients received the NAC treatment protocol with bevacizumab (Avastin®, provided by Genentech Inc., San Francisco, CA); and 20 earlier patients (before Genentech Inc. agreed to provide the drug) received the same treatment protocol without addition of bevacizumab. The age range was 31-64 years old (46 ± 12 [standard deviation], median 43) for patients receiving Avastin; and from 31-69 years old (47 ± 9 [standard deviation], median 46) for patients not receiving Avastin. One patient receiving Avastin had bilateral disease, which was analyzed separately; therefore increasing the total number of Avastin-treated lesions to 17. All patients had received serial MRI monitoring studies before, during, and after the NAC, and then received definitive surgery. This study was approved by the Institutional Review Board and was HIPAA-compliant. All patients gave written informed consent to participate in the study, including receiving the treatment protocol and undergoing the serial MRI study for response monitoring.

The patient characteristics and lesion information is summarized in Table 1 for patients with Avastin, and in Table 2 for patients without Avastin. All cancers were known to be HER-2 negative before receiving NAC. For the Avastin-treated group, the pre-treatment size in the longest dimension was 1.0 to 9.6 cm (median 4.7 cm), the time from the last treatment to the last MRI was 4 to 74 days (median 14 days), and from the last MRI to surgery was 28 to 120 days (median 41 days). For the group without Avastin, the pre-treatment size in the longest dimension was 1.5 to 11.6 cm (median 3.2 cm), the time from the last treatment to the last MRI was 0 to 43 days (median 10 days), and from the last MRI to surgery was 1 to 65 days (median 34 days). None of the characteristic variables was significantly different between the two groups.

Neoadjuvant Chemotherapy Treatment Protocol

The neoadjuvant chemotherapy protocol consisted of AC-sensitivity-adapted first-line regimen followed by a taxane-based second-line regimen. The AC regimen containing doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) was given every 2 weeks for 2 to 4 cycles intravenously. After 2 cycles, the response was evaluated by imaging and/or clinical examination, and along with consideration of patient's tolerability the treating oncologist decided whether the patient should continue to receive 2 additional cycles of AC, or be switched to the taxane-based regimen. All patients received growth factor support, either granulocyte-macrophage colony-stimulating factor (GM-CSF) or pegylated granulocyte colony-stimulating factor (peg-G-CSF). The taxane-based regimen included paclitaxel (80 mg/m²) or Nab-paclitaxel (90 mg/m²) combined with carboplatin (area under the curve AUC=2), weekly for 3 weeks on followed by 1 week off, for a total of 9-12 doses. Patients in the bevacizumab-treated group also received bevacizumab (10 mg/kg body weight) alongside the taxane-regimen, every 2 weeks for 5 doses.

Breast MRI Protocol

The MRI study was performed using a 1.5 T scanner using a dedicated breast coil (Philips Medical Systems, Best, Netherlands). The dynamic contrast enhanced (DCE) sequence was RF-FAST (Fourier Acquired Steady State) with 16 frames, including four pre- and 12 post-contrast sets. The parameters were TR = 8.1 ms, TE = 4.0 ms, flip angle = 20°, slice thickness = 4mm, matrix size = 256 × 128, FOV = 32-38 cm. The scan time was 42 seconds per frame. Eight patients had some follow-up MRI studies performed on a 3.0 T scanner using a dedicated breast coil (Philips Medical Systems, Best, Netherlands). The dynamic sequence was Fast Field Echo (FFE) sequence with 10 frames, including 2 pre- and 8 post contrast sets. The parameters were TR = 12.0 ms, TE = 4.0 ms, flip angle = 40°, slice thickness = 3mm, matrix size = 512 × 512, FOV = 38 cm. The scan time was 70 seconds per frame. The contrast agent (Omniscan®, 0.1 mmole/kg body weight) followed by saline was injected after the pre-contrast frames were acquired.

Processing and Interpretation of MRI

All imaging analysis was performed on a workstation. To ensure consistency in evaluation of the lesion extent, images from previous MRI studies of the same patient were displayed in multiple windows for comparison. Subtraction images at 1 to 2 minutes post injection and the maximum intensity projection (MIP) images were used for interpretation of the MR scan. Two radiologists evaluated the status of residual tumor on MRI and reached a consensus diagnosis for each lesion. They were blind to the pathology results. The longest dimension of the lesion based on the RECIST (Response Evaluation Criteria in Solid Tumors) criteria was measured.²² When there was no residual enhancement, or the residual enhancement was equal or lower compared to the normal glandular tissue enhancements elsewhere, the case was determined as a clinical complete responder, with residual lesion size=0. In order to study whether tumor

presenting as the mass lesions or the non-mass lesions (NML, showing diffuse contrast enhancements on MRI) show different response patterns, they were classified based on the morphological descriptors defined in BI-RADS (Breast Imaging-Reporting and Data System) breast MRI lexicon.

Pathological Diagnosis

All patients received definitive surgery after completing NAC. The specimen was processed for histological examination, by cutting into approximately 5mm thin sagittal slices and submerging the slices in 10% neutral buffered formalin for fixation. After fixation and processing, the slides were stained with hematoxylin and eosin (H&E) for evaluation. Based on the distribution of residual disease, the cases were categorized into three types (Figure 1), including: 1) pCR (pathologic complete response)- no residual invasive cancer;²³ 2) Nodular pattern- with confined cancer nodules; and 3) Scattered cell pattern- with small cancer nodules and scattered cancer cells/clusters distributed in a large fibrotic region. In cases with residual invasive cancer nodules, the pathological size was determined as the longest dimension (Figure 1b). For the scattered cell pattern, the longest dimension was estimated from the location of tissue specimens containing scattered cancer cells/nests, based on the number of involved blocks from the most medial to the most lateral slices.

Statistical Analysis

The clinical characteristics between the two groups of patients with and without Avastin were compared. The normality of all clinical characteristics was examined using Shapiro-Wilk test. Two-tailed t-test was used to compare age; and the two-way Mann-Whitney non-parametric test was used to compare the tumor type, stage, hormonal receptor status, pre-treatment size, and time from the last MRI to surgery. The Fisher's Exact test was used to compare the pCR response rate, the pathological residual disease pattern, and the diagnostic performance of MRI between the two groups. A value of $P < 0.05$ was regarded as statistically significant. Furthermore, all patients in the two groups were combined, and the univariate logistic regression was applied to analyze whether the pCR rate and the diagnostic accuracy rate were associated with any clinical variable.

Results

Pathologic Response between 2 Groups

The pathological response and the residual disease evaluated on the last MRI after completing NAC is listed in Table 1 (with Avastin) and Table 2 (without Avastin). The clinical characteristics between the two groups were compared, and no significant difference was found. Of the 17 lesions receiving Avastin, 5 lesions were pCR (5/17, 29%), 5 lesions showed scattered cell residual disease pattern (5/17, 29%), and 7 lesions shrank down to nodules. Of the 20 lesions without receiving Avastin, 8 lesions were pCR (8/20, 40%), 4 lesions showed scattered cell residual disease pattern (4/20, 20%), and 8 lesions shrank down to nodules. The rates of different pathological response patterns between the two groups were comparable, not significantly different analyzed by the Fisher's Exact test.

Diagnostic Accuracy of MRI between 2 Groups

The diagnostic performance of MRI is listed in Table 1 and Table 2 as “true positive”, “true negative”, “false positive”, and “false negative”. Of the 17 lesions receiving Avastin, 9 were true positive, 4 were true negative, 1 was false positive, and 3 were false negative. The overall accuracy was 13/17 (76%). Among 7 lesions that were diagnosed as complete clinical response (no residual disease, lesion size on MRI = 0), 4 were pCR thus as true negative, and 3 were false negative. Therefore, the pCR prediction accuracy was 4/7 (57%). Figure 2 demonstrates

an IDC case with true negative diagnosis (lesion #11 in Table 1); and Figure 3 demonstrates an ILC case with false negative diagnosis (lesion #16 in Table 1).

Of the 20 lesions not treated with Avastin, 7 were true positive, 7 were true negative, 1 was false positive, and 5 were false negative. The overall accuracy was 14/20 (70%). Twelve lesions were diagnosed as complete clinical response, and 7 were pCR as true negative, and 5 were false negative. The pCR prediction accuracy was 7/12 (58%). The overall diagnostic accuracy of MRI (76% vs. 70%) and the pCR prediction accuracy (57% vs. 58%) were comparable between the two groups with and without Avastin, not significantly different. In a previous publication we have reported a cohort of patients with HER-2 positive cancer receiving a similar NAC protocol containing trastuzumab (Herceptin®, Genentech, Inc.).²¹ The pCR rate and the diagnostic performance of these 3 groups of patients are summarized in Table 3 for comparison. The pCR rate was much higher in HER-2 positive patients (19/25, 76%), and MRI had a higher overall diagnostic accuracy (19/25, 92%) and accuracy for predicting pCR (18/19, 95%).

Residual Disease in Mass vs. Non-Mass Lesions

Of the 11 mass lesions treated with Avastin (in Table 1), 4 cases were correctly diagnosed as pCR (true negative), and 6 cases were true positive, with size discrepancy between MRI and pathology ranging from 0.1 to 0.7 cm. The other case was false positive. Figure 4 shows an IDC case with residual size of 0.8 cm on MRI, and 0.2 cm on pathology (lesion #2 in Table 1). Of the 14 mass lesions not treated with Avastin (in Table 2), 5 cases were correctly diagnosed as pCR (true negative), and 5 cases were true positive diagnosis by MRI, with size discrepancy ranging from 0 to 0.5 cm between MRI and pathology. Three cases were false negative, and one was false positive.

There were 6 non-mass lesions in both groups. In patients receiving Avastin, there were 2 false negative cases, and the remaining 4 cases (lesion #12, 13, 14, 15 in Table 1) had a large size discrepancy between the residual size measured on MRI (4.9, 4.0, 5.6, and 3.2 cm) and the pathological disease extent (0.3, 0.8, 1.9, and 5.3 cm, respectively). Four of 6 NML lesions presented the scattered cell residual disease pattern, which was significantly higher compared to only 1 case in 11 mass lesions (4/6, 67% vs. 1/11, 9%, $p=0.03$). In patients not treated with Avastin, there were 2 true negative and 2 false negative cases. There was also one case (lesion #20 in Table 2) showing a large size discrepancy (0.5 cm on MRI, but pathology shows residual scattered cells in a 6 cm region).

Univariate Logistic Regression Analysis

Lastly whether the pCR rate and the diagnostic accuracy of MRI were associated with the use of Avastin, lesion morphology type (mass vs. NML), hormonal receptor status (positive vs. negative), and all other clinical variables were evaluated using the univariate logistic regression analysis. The pCR rate was significantly associated with hormonal receptor status ($p=0.01$, with 82% power based on post-hoc power analysis), but not significantly with the use of Avastin (yes vs. no), lesion morphology type (mass vs. NML), pre-treatment size, stage, grade, or any other variables listed in Tables 1 and 2. For patients not receiving Avastin, 5 of 6 patients with hormonal receptor negative cancer achieved pCR (5/6, 83%); and only 3 of 14 patients with hormonal receptor positive cancer achieved pCR (3/14, 21%, $p=0.02$). The diagnostic accuracy of MRI (as True or False) was not affected by any clinical variable either.

Discussion

Bevacizumab is designed to neutralize VEGF and blocks signal transduction of tyrosine kinase receptors located on the surface of endothelial cells to decrease the angiogenic activity.²⁴⁻²⁶

The therapeutic mechanism of bevacizumab on tumor has been studied in different animal models; either through damage of vascular supply thus cutting off the delivery of nutrients, or through vascular normalization to decrease tumor vascular permeability and tumor interstitial fluid pressure thus facilitating the delivery of systemic chemotherapeutic agents.²⁷⁻³⁰ Tumor vasculature normalization provides a “window” for optimizing the effects of adjuvant cytotoxic therapy, which is an emerging concept in design of anti-angiogenic therapy.

Bevacizumab was first approved by FDA for colorectal cancer in 2004, then for lung cancer in 2006. The addition of bevacizumab has been shown to improve overall survival or progression free survival for colorectal cancers.^{12,32-33} Similar findings were also noted for non-small-cell lung cancer.³⁴ For breast cancer, Miller et al. studied 722 metastatic breast cancer and found that paclitaxel plus bevacizumab significantly increased the objective response rate and prolonged progression-free survival as compared with paclitaxel alone. The overall survival rate, however, was similar in the two groups (median, 26.7 vs. 25.2 months; $P=0.16$).⁹ This result was used as the basis for the FDA to grant accelerated approval of bevacizumab for treating metastatic HER-2 negative breast cancer. In this study we set out to investigate the accuracy of MRI for evaluation of the treatment response in preoperative setting in stage II-IV breast cancer, so the information may be better utilized for pre-surgical planning.

Studies reporting evaluation of bevacizumab treatment effect using MRI have been emerging in recent years. Wedam et al. and Thukral et al. studied inflammatory and locally advanced breast cancer treated with one cycle of bevacizumab using DCE-MRI, and reported decrease in the DCE rate constants.^{11,35} Raatschen et al. studied human breast cancers implanted in rats using MRI, and found slower tumor growth in all bevacizumab-treated cancers and the acute change in vascular leakiness $K(PS)$ was correlated with tumor growth response.³⁶ Norden et al. found that bevacizumab might alter the recurrence pattern of malignant gliomas by suppressing tumor areas that showed contrast enhancements.³⁷ These results suggested that MRI is a suitable imaging modality for evaluating changes in vascular response after bevacizumab treatment, in addition to evaluating size changes. However, given the rapid change of temporal events starting from damage of angiogenic vessels, followed by normalization of vasculature and sustained vascular damage,²⁸ it is expected that the measured changes in DCE kinetics using MRI will be time-sensitive, and will be dependent on these combined effects. While vascular changes were reported, to date no study has been published yet to evaluate the diagnostic accuracy in patients receiving Avastin-containing regimen.

In the present study the pathological responses in patients with and without Avastin were compared. To better describe the different residual disease patterns, they were classified into three types: pCR, nodular pattern, and scattered cell pattern with cells/clusters within a large fibrotic region. The pCR rates were comparable between patients receiving Avastin vs. those without Avastin. Five patients with Avastin (5/17, 29%) and 4 patients without Avastin (4/20, 20%) had residual disease presenting as scattered cell pattern, which was not significantly different either. The results suggest that the scattered cancer cells/clusters pattern was not specific for patients receiving Avastin.

Next, we evaluated the diagnostic performance of MRI, focusing on the correlation of the residual disease measured by MRI vs. that determined by pathological examination. The overall accuracy was comparable (13/17, 76% for Avastin-treated patients, and 14/20, 70% for patients without Avastin). The true diagnosis of pCR based on complete clinical response on MRI was also comparable (4/7, 57%, for Avastin-treated patients, and 7/12, 58% for patients without Avastin). The results suggest that treatment with Avastin does not compromise the diagnostic performance of MRI. Avastin is expected to reduce the neovasculature from angiogenic activity, however, it is not expected to affect the mature vasculature. As such, and as long as

the vascular supply is present, the MRI contrast agent can still be delivered to show contrast enhancements for detection of residual disease.

The diagnostic performance of MRI is highly dependent on the distribution of residual disease. When the disease is broken down to cells or cell clusters (Figure 1c), the cells may not need vascular supply to survive, and it is difficult to detect such residual disease based on MRI contrast enhancements. For mass lesions that shrink down to nodules, the size measured by MRI is very close to the pathological size. In contrast, for non-mass lesions the size discrepancy is worse, particularly for Avastin-treated patients. Of the 6 NML patients in Table 1, the size discrepancy ranged from 2.1 to 8.5 cm. For the non-mass lesions (such as in Figure 3), the pre-treatment size is already difficult to assess, and that adds uncertainty in determination of the post-NAC size. Furthermore, the NML is more likely to present with post-NAC residual disease as the scattered cell pattern, and that leads to additional difficulty in evaluating the treatment response with MRI.

We have shown that the false negative diagnosis is mainly related to the distribution of scattered residual disease, and is not specific to the use of Avastin. Since MRI relies on contrast enhancements to detect the residual disease; it cannot detect small foci or scattered cancer cells/clusters that do not need vascular supply to survive. In Table 3 we have shown that the diagnostic accuracy for pCR in HER-2 positive cancer receiving Herceptin was higher (18/19, 95%) compared to Avastin-treated patients (4/7, 57%,) or patients not treated with Avastin (7/12, 58%). In patients who achieve pCR, the treatment is very effective in eliminating scattered residual cancer cells, and therefore, the negative predictive value of MRI is high.

For a patient who is mis-diagnosed by MRI with false negative findings, if the results are used to plan for breast conservation surgery, it might lead to positive margin. However, as long as a negative margin can be achieved by re-excision, the prognosis of patients with this type of minimal residual disease with very low cellularity may still be favorable, despite of its large extent of distribution. Recently, the concept of quantifying residual cancer burden (RCB) was proposed, calculated as a continuous index combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size).³⁸ This study found that patients with minimal residual disease (defined as RCB-I) had the same prognosis as pCR, thus it was concluded that RCB was a significant predictor of distant relapse-free survival, and can be used to define the category of near-complete response. Similarly, the outcome of patients in the present study presenting with residual disease as scattered cells/clusters with low cellularity should be followed and compared with those achieving pCR. In fact, in follow-up of patients with hormone-receptor negative breast cancer, we have shown high survival outcome not only related to high pathologic complete response but also related to minimal residual disease³⁹.

These findings have to be interpreted in the context of the small subject number. Enrolling patients to participate in NAC treatment protocol with serial MRI monitoring studies is difficult to perform, and most similar studies in the literature did not report a large subject number.^{11, 35} The use of serial MRI studies to assess the sequential changes of the tumor size (Figures 2-4) strengthened our confidence in diagnosis of residual disease.

In conclusion, our results indicate that overall MRI is an appropriate imaging modality in the evaluation of neoadjuvant chemotherapy containing the anti-angiogenic agent, bevacizumab. In mass lesions where the tumor boundary is clear and when the tumor shows concentric shrinkage to nodular pattern, MRI is highly accurate in diagnosis of residual disease. When the residual cancer cells present as small foci or scattered cells/clusters, these receive nutrients via diffusion, not from vascular perfusion; thus MRI may not detect these small foci. This problem is due to the intrinsic limitations of MRI, not specific to patients receiving Avastin.

The overall diagnostic accuracy is comparable in patients receiving chemotherapy with or without Avastin. This limitation of MRI in detecting small cancer foci or scattered cells and clusters should be considered when planning for breast conservation surgery after NAC.

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Figure 1.

Three different pathological response patterns on hematoxylin and eosin staining slides.

Photomicrograph original magnifications = 200×. (a) The pathologic complete response (pCR) showing a few macrophages in acellular stroma. No invasive cancer cells can be identified. (b)

The nodular pattern showing a single nodule with cancer cells intermingled with fibrotic stroma. (c) The scattered cell pattern showing scattered cancer cells and cell nests (indicated by arrows) in a large fibrotic region.

Figure 2.

A true negative case in a 33-year-old woman with invasive ductal carcinoma (subject #11 in Table 1). Baseline MRI prior to NAC shows a primary lesion of 4.0 cm enhanced mass (left column). After 4 cycles of AC treatment, the tumor only shows a faint enhancement (middle column). After all NAC treatment, no enhancement is noted in the previous tumor bed, thus a complete clinical responder determined by MRI (right column). Pathological examination of surgical specimen reveals pCR without invasive cancer. Upper row: pre-contrast non-fat-sat T1-weighted image. The patient has bilateral implants. Lower row: gray-scale subtraction image at 1.5 min after contrast injection.

Figure 3.

A false negative case in a 62-year-old woman with infiltrating lobular carcinoma (subject #16 in Table 1). Baseline MRI shows a 7.6 cm linearly enhanced lesion in the left breast, consistent with the feature of lobular cancer (left column). After 4 cycles of AC, the tumor appears as a linear faint enhancement (middle column). After all NAC treatment, although a faint enhancement is still visible in the tumor bed (right column), the intensity is only comparable to that of normal tissue enhancement elsewhere, thus this case is determined as a complete clinical responder. Final pathology, however, reveals residual disease with scattered invasive cancer cells/clusters within a 8.0 cm region. Upper row: pre-contrast non-fat-sat T1-weighted image. Lower row: gray-scale subtraction image at 1.5 min after contrast injection.

Figure 4.

A true positive case in a 41-year-old woman with invasive ductal cancer (subject #2 in Table 1). Baseline MRI prior to NAC shows a 3.4 cm enhanced mass in the right breast (left column). After 4 cycles of AC treatment, the tumor shrinks down to 1.2 cm (middle column). After all NAC, the tumor is further reduced to 0.8 cm, thus a partial responder diagnosed by MRI (right column, lesion noted by an arrow). Pathology after surgery reveals a 0.2 cm residual invasive cancer. Upper row: pre-contrast non-fat-sat T1-weighted image. Lower row: gray-scale subtraction image at 1.5 min after contrast injection.

Table 1

Clinical characteristics, pre-, post-NAC MRI, and pathological findings in 17 lesions receiving Bevacizumab

MRI Phenotype	Lesion #	Age	Cancer Type	Stage	Tumor Grade	Hormonal Receptor	Pre-size (cm)	Post-size (cm)	MRI diagnosis	Pathology type	Pathological size (region) ^a	Last C/T to MRI (days)	Last MRI to Surgery (days)
Mass (N=11)	# 1	50	IDC	II	4/9	POS	2.2	2.1	True +	nodular	2 cm	6	44
	# 2	41	IDC	II	9/9	NEG	3.4	0.8	True +	nodular	0.2 cm	13	28
	# 3	49	IDC	III	8/9	POS	4.8	1.2	False +	pCR	0	28	28
	# 4	51	IDC	III	9/9	POS	4.8	2.7	True +	scattered	(3.3 cm)	21	61
	# 5	38	IDC	II	5/9	POS	2.4	1.3	True +	nodular	1.1 cm	7	35
	# 6	64	IDC	II	8/9	POS	2.2	0.7	True +	nodular	0.4/0.2 cm	30	89
	# 7	34	IDC	III	8/9	NEG	9.1	0	True -	pCR	0	4	30
	# 8	63	IDC	II	9/9	POS	1.0	0	False -	nodular	0.7 cm	74	56
	# 9	36	IDC	II	7/9	NEG	1.5	0	True -	pCR	0	14	120
	# 10	64	IDC	III	8/9	POS	3.5	0	True -	pCR	0	30	89
	# 11	33	IDC	II	7/9	POS	4.0	0	True -	pCR	0	12	34
NML ^b (N=6)	# 12	63	IDC	IV	8/9	NEG	7.0	4.9	True +	nodular	0.3 cm + inflammation	9	63
	# 13	33	IDC+ILC	III	6/9	POS	6.4	4.0	True +	nodular	0.8 cm	22	33
	# 14	37	IDC	IV	7/9	NEG	9.6	5.6	True +	scattered	(1.9 cm)	9	36
	# 15	43	ILC	III	ND ^c	POS	4.7	3.2	True +	scattered	(5.3 cm)	28	37
	# 16	62	ILC	II	ND	POS	7.6	0	False -	scattered	(8 cm)	44	41
	# 17	31	IDC	II	ND	POS	8.4	0	False -	scattered	(8.5 cm)	7	48

^aThe residual tumor size is given when the lesion presents as nodule; (Region): the distribution of residual disease that present as scattered tumor cells or clusters in a large fibrotic region.

^bNML: Non-mass lesions, referring to lesions that do not show clear tumor boundary, presenting non-mass like enhancements on MRI.

^cND: no data

Table 2

Clinical characteristics, pre-, post-NAC MRI, and pathological findings in 20 patients without receiving Bevacizumab

MRI Phenotype	Lesion #	Age	Cancer Type	Stage	Tumor Grades	Hormonal Receptor	Pre-size (cm)	Post-size (cm)	MRI diagnosis	Pathology type	Pathological size (region) ^a	Last C/T to MRI (days)	Last MRI to Surgery (days)
Mass (N=14)	# 1	64	IDC	II	5/9	POS	1.5	1.5	True +	nodular	1.4 cm	5	36
	# 2	45	IDC	II	5/9	POS	2	1.2	True +	nodular	1.4 cm	27	30
	# 3	46	IDC	II	ND ^c	POS	3.1	3.1	True +	nodular	2.6 cm	10	51
	# 4	56	IDC+ papillary	IV	6/9	POS	2.6	0	False -	scattered	(1.5 cm)	6	34
	# 5	52	IDC	III	7/9	POS	2.8	1.3	True +	nodular	1.7 cm	10	65
	# 6	48	IDC	II	9/9	POS	2.7	0	False -	nodular	1.4 cm	8	34
	# 7	38	IDC	II	6/9	NEG	5.4	0	True -	pCR	0	20	1
	# 8	48	IDC	II	9/9	POS	3.2	0	True -	pCR	0	21	43
	# 9	37	IDC	III	9/9	NEG	3.9	0	True -	pCR	0	8	59
	# 10	64	IDC	II	8/9	POS	3.4	0	False -	scattered	(2.2 cm)	36	58
	# 11	42	IDC	III	8/9	POS	3.6	0.4	True +	nodular	0.4 cm	7	51
	# 12	31	IDC	II	8/9	NEG	3.1	0	True -	pCR	0	8	30
	# 13	49	IDC	III	9/9	NEG	6.1	0	True -	pCR	0	12	19
	# 14	46	IDC	II	9/9	NEG	3.3	1.0	False +	pCR	0	7	29
NML ^b (N=6)	# 15	49	IDC	II	7/9	POS	2.9	0	False -	nodular	3 × 1.5 mm	8	65
	# 16	41	IDC	II	7/9	POS	2.4	0	True -	pCR	0	43	26
	# 17	50	IDC	III	ND	POS	11.6	0	True -	pCR	0	16	26
	# 18	43	IDC+ILC	II	6/9	POS	2.4	0	False -	scattered	(1.2 cm)	0	4
	# 19	45	IDC	IV	7/9	POS	9.3	0.3	True +	nodular	0.5	11	29
	# 20	69	ILC	III	5/9	POS	4.9	0.5	True +	scattered	(6.0 cm)	1	36

^aThe residual tumor size is given when the lesion presents as nodule; (Region): the distribution of residual disease that present as scattered tumor cells or clusters in a large fibrotic region.

^bNML: Non-mass lesions, referring to lesions that do not show clear tumor boundary, presenting non-mass like enhancements on MRI.

^cND: no data

Table 3

The pCR rate and MRI diagnostic performance of the two HER-2 negative groups compared to one HER-2 positive group

Regimen	pCR	True Negative	False Negative	True Positive	False Positive	Prediction of pCR ^b	Overall Accuracy ^c
Bevacizumab (N=17)	5/17 (29%)	4	3	9	1	4/7 (57%)	13/17 (76%)
No bevacizumab (N=20)	8/20 (40%)	7	5	7	1	7/12 (58%)	14/20 (70%)
Trastuzumab ^a (N=25)	19/25 (76%)	18	1	5	1	18/19 (95%)	23/25 (92%)

^aThe results were taken from reference [21].

^bThe accuracy fr prediction of pCR is calculated as = True Negative / (True Negative + False Negative)

^cThe overall diagnostic accuracy is calculated as = (True Positive + True Negative) / all cases