MRI patterns of tumor regression after neoadjuvant chemotherapy in breast cancer patients: correlation with pathologic response grading system based on tumor cellularity

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Purpose

The purpose of this study was to analyze the tumor shrinkage pattern on MRI after neoadjuvant chemotherapy and to evaluate whether there is any difference in shrinkage pattern between pathologic responder and nonresponder groups. In addition, we wanted to compare tumor diameter obtained from MRI with histological diameter according to the tumor shrinkage pattern.
Methods and Materials

Patients

Our Institutional Review Board approved this study. Between January 2008 and December 2010, 63 consecutive patients with breast cancer underwent breast MRI before and after neoadjuvant chemotherapy. Of 63 patients, 2 patients were excluded because malignant lesions were not well visualized on MRI due to weak contrast enhancement, 2 patients due to poor image quality, and 4 patients because they did not undergo curative surgery. Ultimately, 56 lesions in 55 patients were enrolled in our study. One patient had bilateral breast cancers. The mean patient age was 46 years old (range 29-63). Forty-six patients (84%) received taxane plus anthracycline regimens, whereas 9 patients (16%) received an anthracycline-based regimen. All patients had undergone a core needle biopsy for diagnosis and two separate breast MRI examinations; one examination was done prior to neoadjuvant chemotherapy, and the other examination was performed after completion of chemotherapy and prior to final surgery. The mean interval between the second MRI examination and surgery was 4.1 days (range, 1-16 days).

MR imaging technique

Patients underwent MR imaging before chemotherapy and after they had completed three or four cycles of chemotherapy. MR images were acquired on a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, WI, USA) or 3-T system (Achieva; Philips Healthcare, Best, the Netherlands) with the use of a dedicated breast coil. Patients underwent imaging in the prone position with the breasts immobilized. Contrast material was injected (0.1 mmol/kg gadopentetate dimeglumine [Magnevist; Schering, Berlin, Germany]) and followed by a 20 mL saline flush at a rate of 2 mL/s.

The imaging protocol of a 1.5-T scanner consisted of fat suppressed axial fast spin-echo T2-weighted images (TR/TE, 4,000/74; slice thickness, 3 mm) and three-dimensional, T1-weighted fast spoiled gradient-echo sequence with bilateral axial images (6.5/2.5; flip angle, 0°; image matrix, 320 × 160; field of view, 200 × 200 mm; section thickness, 1.5 mm; and section gap, 0 mm).

The imaging protocol of a 3-T scanner consisted of fat suppressed axial fast spin-echo T2-weighted images (TR/TE, 7,562/70; slice thickness, 3 mm) and dynamic unenhanced and contrast-enhanced fat saturated 3D gradient-echo T1-weighted imaging (7.6/3.9; flip angle, 10°; slice thickness, 3 mm). Sagittal and coronal reformatted images were obtained using raw data. Standard subtraction images were obtained by subtracting the precontrast images from the early peak postcontrast image on a pixel-by-pixel basis. Reverse subtraction images were obtained by subtracting the last postcontrast image from the early peak postcontrast image.
Interpretation of MR findings

Two breast imaging radiologists (D.K.K. and T.H.K) who had experience of 12 and 3 years, respectively, performed a consensus review of the breast MRI examinations. They were blind to the pathology results. The longest dimension of the lesion based on the response evaluation criteria in solid tumors (RECIST) criteria was measured.

The initial contrast enhancement pattern of breast cancer was classified into four categories by modifying Tozaki's classification: solitary lesion, grouped lesion (localized mass with adjacent linear or spotty enhancement), separated lesion (multifocal or multicentric masses), and replaced lesion (diffuse contrast enhancement in whole quadrants). The shrinkage pattern was classified into four categories: type I, concentric shrinkage without surrounding lesion; type II, concentric shrinkage with surrounding lesions; type III, shrinkage with residual multinodular lesions, and type IV, diffuse contrast enhancement in whole quadrants (Fig 1).

Histologic Evaluation

Histopathologic tumor regression was semiquantitatively graded by one pathologist (H.Y) based on the Miller-Payne grading system (Table 1). Patients were divided into two groups: pathologic responders and nonresponders. Patients showing Miller-Payne grades 3, 4, and 5 were categorized as responders, and patients showing grades 1 and 2 were nonresponders. Histologic measurement of tumor size included not only the invasive foci but also in situ ductal carcinoma.

Statistical Analysis

The Fisher's exact test was used to compare shrinkage patterns between responders and nonresponders. Tumor diameter obtained by MRI was correlated with histologic diameter using the Spearman rank correlation test. All analyses were performed using the SPSS 11.0 statistical software package (Chicago, IL, USA), with a value of $P < 0.1$ considered to be significant.
Fig. 1: Classification of tumor shrinkage pattern

Table 1: Miller-Payne grading system

<table>
<thead>
<tr>
<th>Miller-Payne System</th>
<th>Histopathologic findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No change or some alteration to individual malignant cells, but no reduction in overall cellularity</td>
</tr>
<tr>
<td>Grade 2</td>
<td>A minor loss of tumor cells, but overall cellularity still high; up to 30% loss</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Between an estimated 30% and 90% reduction in tumor cells</td>
</tr>
<tr>
<td>Grade 4</td>
<td>A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; &gt;90% loss of tumor cells</td>
</tr>
<tr>
<td>Grade 5</td>
<td>No malignant cells identifiable in sections from the site of the tumor; only vascular fibroelastotic stroma remains, often containing macrophages; however, ductal carcinoma in situ may be present.</td>
</tr>
</tbody>
</table>
Results

A solitary lesion was seen in 26 cases, grouped lesion in 18, separated lesion in 7, and replaced lesion in 5 cases. After neoadjuvant chemotherapy, 21 (81%) of 26 solitary lesions showed type I, and 9 (50%) of 18 grouped lesions showed type II (Table 2). In cases that showed separated enhancement pattern before neoadjuvant chemotherapy, we evaluated only the largest index tumor. Five (71%) of 7 separated lesions showed type I shrinkage pattern. Four (80%) of 5 replaced lesions showed type IV shrinkage pattern.

We analyzed the pathologic regression grading score according to the shrinkage pattern (Table 3). Of 3 lesions that were not visualized on MRI, 2 lesions were grade 5, suggesting pathologic complete remission (CR). However, 1 lesion was grade 4, representing the false negative case on MRI. Pathologic finding of this false negative case was two microscopic clusters of invasive cancer cells without mass formation.

Of 29 lesions with type I shrinkage pattern, grade 3 was most frequently observed (34%), followed by grade 4 (21%). Miller-Payne grade 5 was found in 3 cases, suggesting false positive case on MRI. Pathologic findings of these false positive cases were sparsely scattered foci of ductal carcinoma in situ, focal lobular lymphocytic infiltration with adenosis, and fibrous stroma containing numerous foamy histiocytes, respectively.

Of 13 lesions with type II shrinkage pattern, grade 3 was most frequently observed (46%), followed by grade 2 (38%). Only 1 case showed grade 4, and there was no case of grade 5.

Of five lesions with type III, 2 lesions were grade 3, and 2 lesions were grade 5. There were 2 false positive cases, and histologic findings were scattered DCIS with marked fibrosis and a few microscopically scattered DCIS, respectively.

Of 4 lesions with type IV, 3 lesions (75%) showed pathologic grade 2. The 2 lesions showing increased size on MRI were pathologic grade 1.

Shrinkage patterns of pathologic responder and nonresponder groups are listed in Table 4. Nineteen (66%) lesions with type I, 7 (54%) lesions with type II, and all 5 lesions with type III were present in pathologic responders. All 4 lesions with type IV were present in nonresponders. There was a statistically significant difference in the shrinkage pattern between pathologic responder and nonresponder groups (P=0.017).

When the tumor size measured by MRI was correlated with the histologic size, the overall correlation was 0.619 (P < 0.0001). According to the shrinkage pattern, lesions with type I, II, and IV showed significant correlation with the histologic diameter (Table 5). Among them, the correlation factor was highest in type IV (# = 0.94, P < 0.001), followed by type I (# = 0.67, P < 0.01) and type II (# = 0.502, P = 0.08). However, in type III shrinkage
pattern, tumor size measured on MRI was not significantly correlated with histologic size ($P = 0.87$).

Typical MRI findings of tumors with different scores of histologic regression and shrinkage pattern are illustrated in figures 2, 3, 4 and 5.
### Table 2: Initial enhancement pattern before chemotherapy and shrinkage pattern after chemotherapy

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<table>
<thead>
<tr>
<th>Shrinkage pattern</th>
<th>Solitary (n=26)</th>
<th>Grouped (n=18)</th>
<th>Separated (n=7)</th>
<th>Replaced (n=5)</th>
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<tr>
<td>Non-visualization (n=3)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type I (n=29)</td>
<td>21</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Type II (n=13)</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type III (n=5)</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type IV (n=4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Increased (n=2)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 3: Correlation of tumor shrinkage pattern with pathologic regression grading score

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<table>
<thead>
<tr>
<th>Shrinkage pattern</th>
<th>Miller-Payne grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Non-visualization (n=3)</td>
<td>0</td>
</tr>
<tr>
<td>Type I (n=29)</td>
<td>5</td>
</tr>
<tr>
<td>Type II (n=13)</td>
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</tr>
<tr>
<td>Type III (n=5)</td>
<td>0</td>
</tr>
<tr>
<td>Type IV (n=4)</td>
<td>1</td>
</tr>
<tr>
<td>Increased (n=2)</td>
<td>2</td>
</tr>
<tr>
<td>Shrinkage pattern</td>
<td>Responder</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Type I (n=29)</td>
<td>19</td>
</tr>
<tr>
<td>Type II (n=13)</td>
<td>7</td>
</tr>
<tr>
<td>Type III (n=5)</td>
<td>5</td>
</tr>
<tr>
<td>Type IV (n=4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 4: Comparison of shrinkage patterns between pathologic responder and nonresponder groups

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<table>
<thead>
<tr>
<th>Shrinkage pattern</th>
<th>Histologic diameter Median (min~max)</th>
<th>MRI diameter Median (min~max)</th>
<th>Correlation coefficient (ρ)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>1.7 (0~7.0)</td>
<td>1.7 (0.4~6.0)</td>
<td>0.67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Type II</td>
<td>1.8 (0.3~4.0)</td>
<td>2.0 (0.6~3.5)</td>
<td>0.502</td>
<td>0.08</td>
</tr>
<tr>
<td>Type III</td>
<td>0.5 (0~1.8)</td>
<td>2.6 (1.0~3.6)</td>
<td>0.103</td>
<td>0.87</td>
</tr>
<tr>
<td>Type IV</td>
<td>9 (6.0~13.0)</td>
<td>8 (5.5~13.0)</td>
<td>0.94</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 5: Correlation of tumor diameter obtained from MRI with histological tumor diameter according to the shrinkage pattern after neoadjuvant chemotherapy

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**Fig. 2:** Figure 2 MR images in a 48-year old woman with invasive ductal carcinoma. (a) Contrast-enhanced sagittal image obtained 2 minutes after contrast injection shows an irregular shape enhancing mass with adjacent ductal enhancement and satellite nodules in right breast. This lesion was classified into the grouped pattern. (b) Contrast-enhanced sagittal image obtained after chemotherapy shows decreased size of irregular enhancing mass and adjacent satellite nodules. Tumor shrinkage pattern was interpreted as type II. (c) On microscopic examination (original magnification x200, hematoxylin and eosin stain) obtained after chemotherapy, overall cellularity was slightly decreased (about 10%) with prominent nuclear pleomorphic change induced by chemotherapy representing Miller-Payne System Grade 2. Tumor size measured by MRI (2.6 cm) and histopathology (2.8 cm) were identical within a few millimeters.

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**Fig. 3:** Figure 3 MR images in a 54-year old woman with invasive ductal carcinoma. (a) Contrast-enhanced sagittal image obtained 2 minutes after contrast injection shows an irregular shape enhancing mass with adjacent satellite nodules at 4-o'clock position in left breast. This lesion was classified into the grouped pattern. (b) Contrast-enhanced sagittal image obtained after chemotherapy shows multiple small residual nodules in the original tumor site. Tumor shrinkage pattern was interpreted as type III. (C) The histopathological examination revealed a few microscopically scattered foci of ductal carcinoma in situ (DCIS) without invasive ductal focus representing Miller-Payne grade 5. There were foam cells and lymphocytic infiltration around the ducts. Residual DCIS and reactive changes could contribute to the remaining contrast enhancement observed by MRI and result in an overestimation of tumor size (3.6 cm).

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**Fig. 4:** Figure 4 MR images in a 61-year old woman with invasive ductal carcinoma (a) Contrast-enhanced sagittal image obtained 2 minutes after contrast injection shows irregular enhancing mass in right breast. There is associated skin thickening and pectoralis major invasion. This lesion was classified into the solitary enhancement pattern. (b) Contrast-enhanced sagittal image obtained after chemotherapy shows irregular shape mass in right breast showing minimal contrast enhancement. Tumor shrinkage pattern was interpreted as type I and the diameter was 4.5cm on MRI. (c) On microscopic examination (original magnification x200, hematoxylin and eosin stain) obtained after chemotherapy, there was no residual malignant cells. Tumor bed showed fibrous stroma containing numerous foamy histiocytes consistent with complete response to neoadjuvant chemotherapy. The remaining contrast enhancement in the original tumor site is probably predominantly caused by the histologically observed reactive changes, and the tumor size was therefore overestimated by MRI.

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**Fig. 5:** Figure 5 MR images in a 43-year old woman with invasive ductal carcinoma (a) Contrast-enhanced sagittal image obtained 2 minutes after contrast injection shows an irregular shape infiltrative mass in whole quadrants of right breast. This lesion was classified into the replaced pattern. (b) Contrast-enhanced sagittal image obtained after chemotherapy shows slightly decreased size of irregular mass in whole quadrants of right
breast. Tumor shrinkage pattern was interpreted as type IV. (c) The histopathological examination (original magnification x100, hematoxylin and eosin stain) revealed a minor loss of tumor cells. However, overall cellularity was still high representing Miller-Payne grade 2. There was foamy histiocytes infiltration and interstitial fibrosis within the tumor. Tumor size measured by MRI (5.9 cm) and histopathology (6 cm) were identical within a few millimeters.

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Conclusion

In conclusion, there was significant difference in the shrinkage pattern between pathologic responders and nonresponders. Type I and III shrinkage patterns were more frequently observed in the pathologic responder group and type IV in the nonresponder group. Type II pattern showed similar frequencies between the two groups and moderate correlation between sizes obtained from MRI and histology. While tumors with type III shrinkage pattern showed better chemo-responsiveness but poor correlation between sizes obtained by MRI and histology, tumors with type IV shrinkage pattern showed chemo-resistance but strong correlation between sizes obtained by MRI and histology.
References


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