Correlations between Apparent Diffusion Coefficient Values and Prognostic Factors of Breast Cancer

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Purpose: We investigated possible correlations between apparent diffusion coefficient (ADC) values and prognostic factors of breast cancer.

Methods: We retrospectively evaluated 81 patients who underwent magnetic resonance (MR) imaging of the breast and were diagnosed pathologically with invasive ductal carcinoma (IDC) not otherwise specified with invasive foci one cm or larger. We excluded ductal carcinoma in situ and IDC with invasive foci smaller than one cm because small lesions decrease the reliability of signal intensity of diffusion-weighted imaging (DWI). We also excluded special type cancers. We used t-test to compare the mean ADC values of cancers of Stage pT1 (≤ 2 cm) versus pT2 or 3 (> 2 cm), cancers with versus without vascular invasion, axillary lymph node (N)-positive versus N-negative cancers, estrogen receptor (ER)-positive versus ER-negative cancers, and progesterone receptor (PgR)-positive versus PgR-negative cancers. We analyzed correlations between the ADC value with nuclear grade (NG) and human epidermal growth factor receptor 2 (HER2) score by rank test using Spearman’s correlation coefficient.

Results: The mean ADC value was significantly higher for N-positive (n = 28; 0.97 ± 0.20 × 10⁻³ mm²/s) than N-negative cancers (n = 53; 0.87 ± 0.17 × 10⁻³ mm²/s) (P = 0.017); significantly lower for ER-positive (n = 63; 0.88 ± 0.15 × 10⁻³ mm²/s) than ER-negative cancers (n = 18; 1.01 ± 0.21 × 10⁻³ mm²/s) (P = 0.005); and significantly lower for PgR-positive (n = 47; 0.88 ± 0.16 × 10⁻³ mm²/s) than PgR-negative cancers (n = 34; 0.95 ± 0.18 × 10⁻³ mm²/s) (P = 0.048). Tumor size, vascular invasion, NG, and HER2 status showed no significant correlation with ADC values.

Conclusion: ADC values were higher for N-positive and ER-negative breast cancers than N-negative and ER-positive cancers.

Keywords: ADC, breast cancer, prognostic factor

Introduction

Prognostic risk factors in patients with breast cancer are axillary lymph node (N)-positive status, larger tumor size (> 2 cm), high nuclear grade (NG), presence of peritumoral vascular invasion, overexpression of human epidermal growth factor receptor type 2 (HER2), and younger age (< 35). In addition, N status greatly influences choice of operative procedure (sentinel lymph node biopsy [SLNB] or axillary dissection [Ax]) and the decision to administer neoadjuvant chemotherapy. Hormone receptor and HER2 expressions are also im-
important factors in choosing treatment. Although some authors have correlated these factors with findings of dynamic magnetic resonance (MR) imaging, we believe only a few studies have reported correlations with apparent diffusion coefficient (ADC) value.

Many reports have described the usefulness of both diffusion-weighted MR imaging (DWI) and ADC value for evaluating primary breast lesions. DWI is now widely used in routine clinical MR imaging studies. However, DWI and ADC value have been used mainly to differentiate benign and malignant lesions; only a few reports address correlations between ADC value and prognostic factors.

We therefore investigated possible correlations between ADC values and prognostic factors of breast cancer.

**Materials and Methods**

**Patients**

Our institutional committee on clinical study approved this retrospective study, and informed consent was waived. We enrolled 130 consecutive patients who underwent MR imaging of the breast including DWI at our institute between May 1, 2006 and May 31, 2007 who were subsequently proven histopathologically to have breast cancer. We excluded 49 patients, including 25 with ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC) with invasive foci of less than one cm (because of the poor reliability of the signal intensity of the ADC map with slightly low spatial resolution), 13 who received neoadjuvant chemotherapy or endocrine therapy, 6 with special type cancer (mucinous carcinoma, 3; invasive lobular carcinoma, 2; metaplastic carcinoma, 1), 4 patients for whom axillary lymph nodes were not sampled, and one patient with low image quality of DWI. As a result, we included 81 patients with 81 breast cancers with invasive foci of one cm or more in this study. All patients were female and aged 34 to 82 years (mean age, 54.3 years). The numbers of cancers by pathological stage were: pT1, 58 (T1b, 4; T1c, 54); pT2, 22; and pT3, one (Union for International Cancer Control [UICC] 2002). Forty cancers were diagnosed as negative for lymph node metastasis by SLNB and 13, by Ax. The remaining 28 cancers were diagnosed as positive for lymph node metastasis; four underwent only SLNB, 15 underwent SLNB followed by Ax, and nine underwent Ax.

**MR imaging**

Patients underwent MR imaging in prone position using a 1.5-tesla system (Intera Achieva Nova Dual, Philips Medical Systems, Best, The Netherlands) with body coil. Axial DWIs of both breasts were obtained at b values of 0, 500, and 1000 s/mm² with parameters: repetition time (TR), 4600 to 6800 ms; echo time (TE), 51.0 ms; number of excitations (NEX) 2; flip angle, 90°; field of view (FOV), 360 × 360 mm; matrix, 128 × 88; slice thickness, 5.0 mm; slice gap, 1.5 mm. Fat suppression was applied using a spectral attenuated inversion recovery (SPAIR) technique. ADC maps were automatically generated on the operating console by the methods of least squares using all 3 images with b values of 0, 500 and 1000 s/mm². We placed regions of interest (ROI), maximum-sized circles, within the primary lesions on the ADC maps and obtained ADC values, avoiding apparent necrotic or cystic components by referring to other MR images. Figures 1 to 3 show representative MR images.

**Histopathologic assessment**

Nuclear grade was classified according to the General Rules for Clinical and Pathological Recording of Breast Cancer 2005. We assessed ER and PgR using mouse monoclonal antibody (Dako, Glostrup, Denmark). We defined receptor status using the Allred score, with a total score of 3 or more considered positive. The HER2 score was analyzed by immunohistochemistry using the Hercep Test (Dako, Glostrup, Denmark).

**Statistical analysis**

We used t-test to compare the mean ADC values of Stage pT1 (≤ 2 cm) versus pT2 or 3 (> 2 cm) cancers, cancers with versus those without vascular invasion, N-positive versus N-negative cancers, ER-positive versus ER-negative cancers, and PgR-positive versus PgR-negative cancers. We analyzed correlations between the ADC value with NG and the HER2 score by rank test using Spearman’s correlation coefficient. We did not analyze age statistically because all patients but one were at least 35 years old. For multivariate analysis, we used multiple linear regression to assess factors that showed significant differences in the univariate analysis. P ≤ 0.05 was considered statistically significant. Statistical analyses were performed using Statcel (OMS, Tokorozawa, Japan).

**Results**

Univariate analysis demonstrated significantly higher mean ADC value for N-positive (0.97 ± 0.20...
Fig. 1. A 46-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-negative, nuclear grade (NG) 2, estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2) score 0. (A) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI) (arrow). (B) The apparent diffusion coefficient (ADC) value was found to be $0.73 \times 10^{-3} \text{mm}^2/\text{s}$ on the ADC map.

Fig. 2. A 56-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-positive, nuclear grade (NG) 3, estrogen receptor (ER)-negative, progesterone receptor (PgR)-negative, and human epidermal growth factor receptor 2 (HER2) score 3+. (A) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI). (B) The apparent diffusion coefficient (ADC) value was $1.10 \times 10^{-3} \text{mm}^2/\text{s}$ on the ADC map.

Mean ADC values did not differ significantly between breast cancers with $0.92 \pm 0.11 \times 10^{-3} \text{mm}^2/\text{s}$ for those with score 2 + (n = 17), and $0.86 \pm 0.13 \times 10^{-3} \text{mm}^2/\text{s}$ for those
Fig. 3. A 49-year-old woman with left breast cancer diagnosed as axillary lymph node (N)-positive, nuclear grade (NG) 1, estrogen receptor (ER)-positive, progesterone receptor (PgR)-positive, and human epidermal growth factor receptor 2 (HER2) score 0. (A) A nodule with high signal intensity was detected in the left breast on diffusion-weighted imaging (DWI) (arrow). (B) The apparent diffusion coefficient (ADC) value was $1.24 \times 10^{-3}$ mm$^2$/s on the ADC map.

Fig. 4. Comparison of apparent diffusion coefficient (ADC) values between axillary lymph node (N)-negative and N-positive cancers. The mean ADC value of the N-positive cancers was significantly higher than that of the N-negative cancers ($0.97 \pm 0.20 \times 10^{-3}$ mm$^2$/s vs. $0.87 \pm 0.17 \times 10^{-3}$ mm$^2$/s) ($P = 0.017$).

Fig. 5. Comparison of apparent diffusion coefficient (ADC) values between estrogen receptor (ER)-negative and ER-positive cancers. The mean ADC value of the ER-positive cancers was significantly lower than that of the ER-negative cancers ($0.88 \pm 0.15 \times 10^{-3}$ mm$^2$/s vs. $1.01 \pm 0.21 \times 10^{-3}$ mm$^2$/s) ($P = 0.005$).

Discussion

The inverse correlation of tumor ADC values with tumor cellularity has been reported.\textsuperscript{6,7} In this study, we observed higher ADC values for N-positive than N-negative cancers, and we speculate that the high ADC values in N-positive cancers may be attributable to a relatively large number of micro-necroses or fibroses. The presence of fibrotic focus or necrosis is an important clinicopathological parameter associated with a higher degree of malignancy in IDCs.\textsuperscript{13-16} One study reported significant association between the presence of nodal metasta-
Fig. 6. Comparison of apparent diffusion coefficient (ADC) values between progesterone receptor (PgR)-negative and PgR-positive cancers. The mean ADC value of the PgR-positive cancers was significantly lower than that of the PgR-negative cancers (0.88 ± 0.16 × 10⁻³ mm²/s vs. 0.95 ± 0.18 × 10⁻³ mm²/s) (P = 0.048).

Table. Multivariate analysis by multiple linear regression analysis

<table>
<thead>
<tr>
<th>Status</th>
<th>Regression coefficient</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary node</td>
<td>0.11</td>
<td>0.005</td>
<td>0.03 – 0.18</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>-0.12</td>
<td>0.026</td>
<td>-0.23 – -0.01</td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>-0.01</td>
<td>0.83</td>
<td>-0.10 – 0.08</td>
</tr>
</tbody>
</table>

also affect the results, but Kim’s group did not detail tumor size. We excluded patients with DCIS or IDC with invasive foci smaller than one cm because we thought the signal intensity of small lesions was unreliable on the ADC maps with the low resolution. In addition, the larger size of our study population than Kim’s might account for the significant difference between our study findings.

In contrast, Razek and colleagues reported the opposite result.22 They associated lower ADC values with the presence of axillary lymph nodes metastasis. These disparate results may be explained by the difference in study populations because larger tumor size is a risk factor for lymph node metastasis. Their study included many large (>5 cm) cancers, whereas the number of large cancers in our study was small because we excluded patients who had received neoadjuvant chemotherapy or endocrine therapy.

We observed lower ADC values for ER-positive than ER-negative cancers. Other authors reporting the same result19,23–25 have inferred that ER inhibited the angiogenic pathway and induced a decrease in perfusion, thus affecting the ADC value. In addition, ER-positive tumors have shown high cellularity.26–28 These results also support our finding of lower ADC values of ER-positive cancers. Despite a significant difference in the univariate analysis, PgR positivity and negativity showed no significant difference in the multivariate analysis. ER appears to have been the confounding factor that influenced PgR in the univariate analysis because it is known that most ER-positive cancers are also PgR-positive, and this applied to our series.

In this study, we did not analyze the prognosis itself, but prognostic factors. Further study evaluating recurrence or survival rate by long-term follow-up is required to clarify prognoses.

Our study has several limitations. Because SLNB has been reported to yield some false negatives,29–31 some of our patients with lymph node metastasis may have been judged negative for metastasis based on their assessment by SLNB alone. Secondly, we did not include fluorescence in situ hybridization (FISH) analysis in this study for HER2 evaluation because it was not performed in some patients in the early period. According to recent guidelines, FISH analysis should be performed when the score is 2+ at immunohistochemistry. However, we believe this did not likely significantly influence our results because there were only minor differences among ADCs of 0, 1+, and 3+.
Conclusion

ADC values were significantly higher for N-positive than N-negative breast cancers and significantly lower for ER-positive than ER-negative breast cancers.

References

24. Martincich L, Deantoni V, Bertotto I, et al. Corre-


