The Apparent Diffusion Coefficient in Invasive Breast Carcinoma: Correlation with the Biological Markers and Enhancement Patterns on Dynamic MRI

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Aims and objectives

In recent years, the treatment strategy for breast carcinoma has been evolving based on analysis of various biological features of each lesion. By performing a combined modality treatment including molecular targeting drug, hormonal therapies and anti-human epidermal growth factor receptor 2 (HER2: c-erb 2) therapies, the treatment options are becoming suitable for the individual patients with breast carcinoma. In order to plan the most adequate treatment strategy for each patient, correct evaluation of the biology of each tumor is essential. The proliferative potential of tumor cells which reflects the aggressiveness of each tumor is one of the most important biomarkers for the evaluation of neoplastic characteristics of breast carcinoma.

Ki-67 (MIB-1) is one of the nuclear antigens, and is expressed in the growth or synthesis phases of cell cycles. The antigen is not expressed in resting phase [1]. Therefore, Ki-67 has been used as a tumor proliferation marker on various neoplasms. The 13th St. Gallen International Breast Cancer Conference Expert Panel is including the values for Ki-67 (‘high’ and ‘low’) in surrogate definitions of intrinsic subtypes of breast cancer [2].

Based of the intrinsic subtypes of breast cancer, systemic treatment recommendations is constructed [2].

On the other hand, magnetic resonance imaging (MRI) has become an important method for correct and detailed diagnosis of breast cancer. Diffusion-weighted imaging (DWI) uses the variability of "Brownian motion" of water molecules in the tissues. Various studies have shown the usefulness of detection and evaluation of breast tumor extension and differentiating malignant and benign tumors [3-7]. Additionally, the apparent diffusion coefficient (ADC) based on DWI reflect the cellular density [8-11] and also reflect the growth pattern including the proliferative potential of the tumor.

In breast cancer, hormone receptors (estrogen and progesterone receptor) and degree of expression of HER-2 protein is also important biomarkers, and these factorshas been implicated in thedevelopmentof breast cancerinmutually influence one another.

The Purpose of this study is in order to investigate the correlation of the apparent diffusion coefficient (ADC) values in invasive breast carcinomas with the cell proliferative marker (MIB-1labeling index: Ki-67), the expression of hormone receptors, HER2 protein and the enhancement patterns on dynamic MRI.
This study clarifies the biological characteristics of each breast carcinoma by non-invasive method based on the MR images and these results contribute to selecting the most appropriate treatment for each case.
Methods and materials

Patients

Fifty-one consecutive females (51 lesions) with invasive ductal breast carcinoma who underwent partial or total mastectomy after MR imaging at our institution between April 2013 and October 2013 were selected for examination. The lesion was initially detected by physical examination, mammography, or ultrasonography. None of the patients had undergone chemotherapy or large-core needle biopsy for tissue sampling before the MR examination.

The institutional review board approved this retrospective study, and therefore no individual patient consent was required. Written informed consent was obtained from each patient before surgical treatment.

Methods

1. MR imaging.

MR imaging was performed using a 1.5T whole-body imager (Magnetom Symphony; Siemens AG, Erlangen, Germany). The affected side in each patient was examined using a dedicated breast coil with the patient in the prone position. DW images were acquired using a multisection single-shot short tau inversion recovery (STIR) echoplanar sequence in the transverse or sagittal plane. Following DWI, fat-suppressed T2- and T1-weighted and dynamic images were obtained. Subtraction images were produced from dynamic images for identification of enhancement. The imaging parameters were as follows: DWI (TR/TE/TI = 5400/80/180 msec, matrix = 50 x 128, slice thickness (SL) = 5 mm, FOV = 131 x 300 mm, b factor =0 and 1000 s/mm², with a motion probing gradient (MPG) applied along the X, Y, and Z axes), 2D fat-suppressed T2-weighted turbo spin-echo pulse sequence (TR/TE =4500/84 msec, matrix = 460 x 512, SL = 5 mm, field of view (FOV) = 200 x 200 mm), and a three-dimensional fat suppressed T1-weighted FLASH pulse sequence (TR/TE =5.9/2.4 msec, matrix = 141 x 256, SL = 1.5 mm, FOV = 150 x 220 mm). The latter sequence was performed before and during intravenous contrast enhancement with 0.1 mmol gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) per kilogram of body weight. A bolus of contrast agent was injected intravenously using a dedicated infusion pump at a rate of 1 ml/s, followed by a 20-ml saline solution flush. Sequential multisection, whole-breast images were obtained in
the sagittal plane at 60-second intervals for 5 minutes. In all patients, late sagittal T1-weighted (TR/TE =420/10 msec, matrix = 384 × 512, SL = 5 mm, FOV = 200 ×200mm) and transverse T1-weighted (TR/TE = 420/10 msec, matrix = 384 × 512, SL = 5 mm, FOV = 131 × 300mm) images were obtained for the bilateral breasts.

2. Image Analysis

Interpretation of MR Images.

Two radiologists of the authors (R.M and K.T) interpreted the MR images separately. Then, if there were discrepancies of findings between two radiologists, final finding was determined after discussions to reach an agreement. We recorded the size, shape, and enhancement patterns of each lesion based on ACR MRI BI-RADS (5th edition) classification.

Measurement of the ADC.

Based on the DW images, we measured the ADC values of 51 carcinomas. ADC values were calculated with b-factors of 0 and 1000 s/mm² using echoplanar DW images. A region of interest (ROI) of as large a size as possible was positioned over the tumor to avoid necrosis or scar (non-enhanced area) and artifacts, based on dynamic MR images (Figures 1(a) and 1(b)). Positioning of the ROI of each lesion was performed by a radiologist (R. M. and K.T.) under the consensus.

When the lesions were ring-like on DW images, we positioned the ROI in the peripheral portion. The signal intensities in the ROI corresponded to the two different b values.

3. Histopathologic Analysis.

Patients were divided intrinsic subtypes as follows (2):

1. Luminal A
'Luminal A-like' all of: ER and PgR positive HER2 negative Ki-67 'low' a Recurrence risk 'low' based on multi-gene-expression assay (if available)

2. Luminal B

'Luminal B-like (HER2 negative)' ER positive HER2 negative and at least one of: Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)

'Luminal B-like (HER2 positive)' ER positive HER2 over-expressed or ampli#ed Any Ki-67 Any PgR

3. Erb-B2 overexpression

'HER2 positive (non-luminal)' HER2 over-expressed or ampli#ed ER and PgR absent

4. Basal-like

'Triple negative (ductal)' ER and PgR absent HER2 negative


Statistical comparisons were performed using Fisher's protected least significant difference test or Spearman's log rank test. The correlations of ADC values with the MIB-1 labeling index, degree of expression of estrogen or progesterone receptor (ER and PR), and HER 2 protein were examined. ADC values were also compared between intrinsic subtypes. Additionally, we correlated the ADC values with the enhancement patterns based on BI-RADS^5th^ MRI. A $P$-value of less than .05 was considered to be statistically significant. Data are expressed as means ± SD (standard deviation). Statistical analysis was performed using Stat View software program (SAS Institute, North Carolina, USA).
Images for this section:

**Image Analysis**

A region of interest (ROI) of as large a size as possible was positioned over the tumor to avoid necrosis or scars (non-enhanced area) and artifacts.

**Fig. 1:** Measurement of the ADC. Based on the DW images, we measured the ADC values of 51 carcinomas. ADC values were calculated with b-factors of 0 and 1000 s/mm² using echoplanar DW images. A region of interest (ROI) of as large a size as possible was positioned over the tumor to avoid necrosis or scar (non-enhanced area) and artifacts, based on dynamic MR images. Positioning of the ROI of each lesion was performed by a radiologist (R. M. and K.T.) under the consensus. When the lesions were ring-like on DW images, we positioned the ROI in the peripheral portion. The signal intensities in the ROI corresponded to the two different b values.

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Results

The median age of the patients was 58 years old (range; 37 to 87 years old). The mean ADC was 1.112±0.297× 10⁻³ mm²/sec.

<table>
<thead>
<tr>
<th>Correlation Between the Factors</th>
<th>P-value (significance level &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC/ MIB-1 labeling index</td>
<td>0.0355</td>
</tr>
<tr>
<td>ADC/ ER (+/-)</td>
<td>NS</td>
</tr>
<tr>
<td>ADC/ PR (+/-)</td>
<td>NS</td>
</tr>
<tr>
<td>ADC/ HER-2</td>
<td>NS</td>
</tr>
<tr>
<td>MIB-1 labeling index/ ER (+/-)</td>
<td>0.0019</td>
</tr>
<tr>
<td>ER (+/-)/ PR (+/-)</td>
<td>0.0021</td>
</tr>
<tr>
<td>BI-RADS</td>
<td></td>
</tr>
<tr>
<td>Mass ADC/ shape</td>
<td>NS</td>
</tr>
<tr>
<td>ADC/ margin</td>
<td>NS</td>
</tr>
<tr>
<td>ADC/ mass enhancement</td>
<td>NS</td>
</tr>
<tr>
<td>ADC/ kinetic curve</td>
<td></td>
</tr>
<tr>
<td>initial fast/ slow</td>
<td>NS</td>
</tr>
<tr>
<td>initial moderate/ fast</td>
<td>NS</td>
</tr>
<tr>
<td>initial moderate/ slow</td>
<td>0.0037</td>
</tr>
<tr>
<td>delayed persistent/ plateau</td>
<td>NS</td>
</tr>
<tr>
<td>delayed persistent/ wash out</td>
<td>NS</td>
</tr>
<tr>
<td>delayed plateau/ wash out</td>
<td>NS</td>
</tr>
<tr>
<td>Non-mass</td>
<td></td>
</tr>
</tbody>
</table>
The MIB-1 (Ki-67) labeling index was significantly correlated with the ADC values ($P = 0.0355$). Additionally, the MIB-1 (Ki-67) labeling index was significantly correlated with the degree of expression of the ER ($P = 0.0019$).

There was no correlation between the expression of hormone receptors and the ADC values.

There were significant correlations between the expression of the PR and age ($P = 0.0028$) and the expression of the PR and the ER ($P = 0.0021$).

The ADC values were significantly correlated with the initial rise (fast/slow) ($P = 0.0133$) and delayed phase enhancement (persistent /plateau) ($P = 0.0037$) on the kinetic curve assessment in BI-RADS MRI.

**Fig. 2**: The MIB-1 (Ki-67) labeling index was significantly correlated with the ADC values ($P = 0.0355$). Additionally, the MIB-1 (Ki-67) labeling index was significantly correlated with the degree of expression of the ER ($P = 0.0019$). There was no
correlation between the expression of hormone receptors and the ADC values. There were significant correlations between the expression of the PR and age (P = 0.0028) and the expression of the PR and the ER (P = 0.0021). The ADC values were significantly correlated with the initial rise (fast/slow) (P= 0.0133) and delayed phase enhancement (persistent /plateau) (P=0.0037) on the kinetic curve assessment in BI-RADS MRI.

**References:** Radiology, Breast Care Center, National Hospital Organization Kyushu Medical Center - Fukuoka/JP

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**Fig. 3:** The MIB-1 (Ki-67) labeling index was significantly correlated with the ADC values (P = 0.0355).

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**Fig. 4:** The ADC values were significantly correlated with the initial rise (fast/slow) (P = 0.0133) on the kinetic curve assessment in BI-RADS MRI.

**References:** Radiology, Breast Care Center, National Hospital Organization Kyushu Medical Center - Fukuoka/JP
**Fig. 5:** The ADC values were significantly correlated with the delayed phase enhancement (persistent /plateau) (P=0.0037) on the kinetic curve assessment in BI-RADS MRI.

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Fig. 3: The MIB-1 (Ki-67) labeling index was significantly correlated with the ADC values ($P = 0.0355$).

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**Fig. 4:** The ADC values were significantly correlated with the initial rise (fast/slow) (P=0.0133) on the kinetic curve assessment in BI-RADS MRI.

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Fig. 5: The ADC values were significantly correlated with the delayed phase enhancement (persistent /plateau) (P=0.0037) on the kinetic curve assessment in BI-RADS MRI.

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Conclusion

Discussion

Three molecular biomarkers (ER, PR and HER2) have mainly been used to assess the tumor characteristics of invasive breast cancer.

The 'intrinsic subtypes' of breast cancer reflect the biological characteristics, including the status of these three biomarkers in each case, and it is standard to choose the most effective treatment based on the specific subtype [2].

Anti-estrogen drugs (e.g. tamoxifen) block the ER, as a result, the patients with ER-positive cancer show significantly longer survival than those with ER-negative cancer. The PR is also routinely assessed, because the presence of the PR indicates that the estrogen-ER pathway is intact and functional.

The HER2 gene encodes a growth factor receptor expressed on the surface of normal breast epithelia. HER2-expressing invasive breast cancers respond to therapies that target the HER2 protein, such as trastuzumab.

On the other hand, DWI can visualize the microscopic characteristics, including tissue cellularity. We previously showed the correlation between the growth patterns of invasive breast cancers and ADC.

The ADC values in the present study also significantly correlated with the initial rise and delayed phase enhancement on the kinetic curve assessment in BI-RADS MRI. The kinetic assessment can reflect the vascularity and tissue architectural characteristics of each breast cancer, and we previously revealed that the enhancement patterns of breast cancers affected the expression of vascular endothelial growth factor (VEGF), tumor angiogenesis, fibrosis and tissue architectural features, including the cancer nests and stroma [12]. Based on these facts, ADCs can reflect the biological aggressiveness of invasive breast cancer.

Conclusion

The results of this study suggest that ADCs reflect the cellular proliferative potential, which determines the aggressiveness of carcinomas. ADCs also correlated to the enhancement patterns of breast cancers, which reflect the tumor angiogenesis.
In recent years, it has become possible to select a more appropriate treatment for patients based on the characteristics of the individual cases of breast carcinoma. MRI will contribute greatly to the development of a more accurate treatment strategy by revealing the biological characteristics and the dynamic state of breast carcinomas in vivo.
Personal information

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