Original Investigation

Perfusion Parameters in Dynamic Contrast-enhanced MRI and Apparent Diffusion Coefficient Value in Diffusion-weighted MRI: Association with Prognostic Factors in Breast Cancer

Hyun Sil Lee, MD, Sung Hun Kim, MD, Bong Joo Kang, MD, Ji Eun Baek, MD, Byung Joo Song, MD

Rationale and Objectives: To evaluate the association of prognostic factors and subtypes of breast cancer with perfusion parameters in dynamic contrast-enhanced magnetic resonance imaging and apparent diffusion coefficient (ADC) values in diffusion-weighted magnetic resonance imaging.

Materials and Methods: Quantitative perfusion parameters (constant of transfer from plasma to interstitium, constant of transfer from the interstitium to the plasma, extravascular/extracellular volume per unit of volume of tissue [v_e], and initial area under the concentration curve [$_i$AUC]) and ADC values in the entire tumor volume of 52 invasive ductal carcinomas were obtained using histogram analysis. Four measures (25th percentile, mean, median, 75th percentile) were calculated for each parameter and the ADC value. Associations of perfusion parameters and ADC values with prognostic factors and tumor subtypes were analyzed.

Results: Among perfusion parameters, $_i$AUC$_{mean}$ and $_i$AUC$_{median}$ were greater in tumors larger than 2 cm (8.23 ± 2.33, $8.64 \pm 2.67 \times 10^4$) than in those smaller than 2 cm (6.99 ± 1.92, $7.04 \pm 2.15 \times 10^4$; $P = 0.046$, 0.023). $V_{e\ median}$ was higher in tumors with progesterone receptor (PR) positivity (0.54 ± 0.18) than in those with PR negativity (0.44 ± 0.1, $P = 0.041$). There were higher ADC$_{mean}$ and ADC$_{median}$ in tumors with human epidermal growth factor receptor 2 (HER2) positivity (1.306 and 1.278×10^{-3} mm^2/s) than in those with HER2 negativity (1.078 and 1.053×10^{-3} mm^2/s; $P = 0.012$ and 0.020). Higher ADC$_{mean}$ and ADC$_{median}$ were observed in HER2-enriched type (1.404 and 1.378×10^{-3} mm^2/s) than in luminal type (1.096 and 1.073×10^{-3} mm^2/s; $P = 0.030$ and 0.045).

Conclusions: Among perfusion parameters, $_i$AUC was associated with tumor size and $v_{e\ median}$ was associated with PR positivity. Mean and median ADC values showed positive correlation with HER2-positive and HER2-enriched tumors.

Key Words: Breast cancer; magnetic resonance imaging; perfusion; ADC value; prognostic factor.

INTRODUCTION

Biopsy specimens are required for analysis of conventional prognostic factors such as tumor size, axillary lymph node status, histologic grade, and molecular marker expression (1). The availability of magnetic resonance imaging (MRI) has prompted efforts to develop non-invasive MRI-based biomarkers to predict the prognosis of breast cancers using techniques such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI. Various apparent diffusion coefficient (ADC) parameters derived from DWI and perfusion parameters obtained from DCE-MRI have been associated with several prognostic factors (2–4), and recent studies have also reported correlations between pharmacokinetic parameters of breast DCE-MRI and prognostic factors, suggesting poorer prognosis in tumors with higher constant of transfer from plasma to interstitium (K^{trans}) and constant of transfer from the interstitium to the plasma (k_{ep}) values or lower extravascular/extracellular volume per unit of volume of tissue (v_e) values (3,4). However, to our knowledge, there have been no studies so far that have analyzed both

Acad Radiol 2016; ■:■■–■■

From the Department of Radiology, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Banpo-daero 222, Seocho-gu, Seoul 137-701, Republic of Korea (H.S.L., S.H.K., B.J.K., J.E.B.); Department of General Surgery, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea (B.J.S.). Received July 20, 2015; revised December 15, 2015; accepted December 17, 2015. **Address correspondence to:** S.H.K. e-mail: rad-ksh@catholic.ac.kr

http://dx.doi.org/10.1016/j.acra.2015.12.011

perfusion parameters and ADC values in the entire tumor volume for simultaneous correlation of prognostic factors or subtypes. The purpose of our study was to investigate the association of prognostic factors and tumor subtypes in patients diagnosed with breast cancer to both MR perfusion parameters and ADC values. In addition, we compared histogram analysis and region of interest (ROI) analysis for the prediction of prognosis of breast cancer.

MATERIALS AND METHODS

Patients

Institutional review board approval was obtained for this retrospective study, and informed consent was waived. Between February 2012 and March 2013, 81 consecutive breast cancer patients diagnosed by percutaneous biopsy underwent DCE-MRI and DWI on a 3T MRI system for preoperative evaluation. Among them, a total of 29 patients were excluded because they had received preoperative neoadjuvant chemotherapy ($n = 12$), had histologic types other than invasive ductal carcinoma (IDC) ($n = 11$), or due to processing software failure ($n = 6$). Finally, a total of 52 masses from 52 patients (mean age 54.8 years, range 36–72 years) were included in the analysis of perfusion parameters and ADC values.

MRI Acquisition

All breast MR examinations were performed using a Siemens MAGNETOM Verio 3.0T MRI system (Siemens Healthcare, Erlangen, Germany). The images were obtained using the following sequences: (1) an axial turbo spin-echo T2-weighted imaging sequence with a repetition time (TR)/ echo time (TE) of 4530/93 ms, a flip angle of 80°, an field-of-view (FOV) of 320 × 320 mm, a matrix size of 576 × 403, a slice thickness of 4 mm, and an acquisition time of 2 min 28 s; (2) a DWI sequence (readout segmented echo planar imaging (EPI)) with two different b values (0 and 750 s/mm^2), a TR/TE of 5600/55 ms, an FOV of 360 × 180 mm, a matrix size of 192 × 82, a slice thickness of 4 mm, and an acquisition time of 2 min 31 s; (3) precontrast T1-weighted three-dimensional volumetric interpolated breath-hold examinations with a TR/TE of 2.7/0.8 ms, an FOV of 320 × 320 mm, a matrix size of 256 × 192, and a slice thickness of 2 mm with different flip angles (2°, 15°); (4) DCE axial T1-weighted imaging (T1WI) with fat suppression with TR/TE of 2.5/0.8 ms, a flip angle of 10°, a slice thickness of 2.0 mm, and an acquisition time of 4 min 30 s (temporal resolution 6 s) after an intravenous bolus injection of 0.1 mmol/kg gadobutrol (Gadovist, Schering, Berlin, Germany) as recommended by the manufacturer; and (5) delayed, high-spatial resolution, contrast-enhanced axial T1WI with fat suppression, a slice thickness of 1.0 mm, and an acquisition time of 2 min 30 s.

Imaging Analysis

MRI data were retrospectively reviewed and evaluated in consensus by two independent radiologists, with 10 and 4 years of experience in breast MRI, who analyzed the perfusion parameters and ADC values. The radiologists knew that the patients had histopathologically confirmed IDC, but they were blinded to other clinical information such as the molecular markers or subtypes of the index tumors.

Perfusion Parameters

Perfusion parameters were quantitatively analyzed using dedicated DCE-MRI software (Olea Sphere 2.3, Olea Medical, La Ciotat, France) based on extended Tofts mathematical model. Native T1 maps were generated using two different flip angles (2°, 15°). The arterial input function was obtained from the aorta or axillary artery by automatic arterial input function selection algorithm. Four perfusion parameters were used to assess tissue and vascular permeability characteristics: K^{trans} (min^{-1}), k_{ep} (min^{-1}), v_e (mL/100 mL of tissue, %), and $_i$AUC (no unit, initial area under the concentration curve in 120 s) (5,6). For the estimation of the perfusion parameters, we semiautomatically drew a volume of interest covering the whole tumor area (Fig 1a) and manually drew a ROI at the highest K^{trans} value in the automatically analyzed K^{trans}-based perfusion map. The histogram analysis was performed for the entire tumor volume. Various histogram values were calculated, including 25th percentile, mean, 50th percentile (median), and 75th percentile. Only the mean value was included in ROI analysis.

ADC Values

ADC values were calculated using Siemens MR OncoTreat software (Siemens Healthcare). We manually drew three ROIs on representative axial, sagittal, and coronal images of the index tumor on contrast-enhanced T1WI image (Fig 1b) and then applied the same ROIs to DWI and ADC maps of the index tumor. The software generated an entire tumor volume reconstruction, voxel-based ADC values, and a histogram of the ADC data including calculations for the 25th percentile, mean, 50th percentile (median), and 75th percentile ADC values. A ROI was manually drawn at the lowest ADC value of the index tumor on the ADC map and the mean value was evaluated.

Histopathologic Analysis

Histopathologic information was obtained from pathology reports. Tumor size was regarded as the maximum diameter of the tumor on the surgical specimen. Tumors were graded according to the modified criteria of Bloom and Richardson. Estrogen receptor (ER) or progesterone receptor (PR) positivity was indicated by stained nuclei in >10% of cancer cells on 10 high-power fields. Positive Ki-67 expression was defined by a rate of Ki-67 positivity in >14% of the cancer cell nuclei (7,8). The intensity of HER2 expression was semiquantitatively scored as 0, 1+, 2+, or 3+. Tumors with