European Journal of Radiology 85 (2016) 1004–1011

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

# Characterization of tumor and adjacent peritumoral stroma in patients with breast cancer using high-resolution diffusion-weighted imaging: Correlation with pathologic biomarkers

Hee Jung Shin[a,*], Jin Young Park[a], Ki Chang Shin[b], Hak Hee Kim[a], Joo Hee Cha[a], Eun Young Chae[a], Woo Jung Choi[a]

[a] Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan, College of Medicine, 88 Olympic-ro, 43-gil, Songpa-gu, Seoul 138-736, South Korea
[b] Department of Radiology and Research Institute of Radiology, Medical Imaging Laboratory, Asan Medical Center, University of Ulsan, College of Medicine, 88 Olympic-ro, 43-gil, Songpa-gu, Seoul138-736, South Korea

ARTICLE INFO

*Article history:*
Received 19 August 2015
Received in revised form 14 January 2016
Accepted 17 February 2016

*Keywords:*
Breast neoplasm
Peritumoral stroma
Diffusion-weighted imaging
Apparent diffusion coefficient

ABSTRACT

*Purpose:* To assess whether ADC values of tumor and peritumoral stroma (PS) obtained on high-resolution diffusion-weighted imaging (HR DWI) were different according to pathologic biomarkers in patients with breast cancer.
*Methods:* We retrospectively enrolled 96 patients (age range, 30–75 years; mean, 52 years) with breast cancer who underwent HR DWI at 3T MR scanner. We obtained the apparent diffusion coefficient (ADC) and ADC range of tumor and PS by drawing the region of interest (ROI) of entire tumor. We assessed histopathological features of tumors. ADC values of tumor and PS were compared according to pathologic biomarkers using student *t*-test and Mann-Whitney *U* test.
*Results:* Mean ADC of tumor boundary was significantly higher in ER-negative tumors than in ER-positive tumors (P = 0.005). The ADC ranges of tumor boundary and proximal PS were significantly higher in tumors with high nuclear grade, negative ER, positive HER2, positive Ki67, and lymph node metastasis than those with low nuclear grade, positive ER, negative HER2, negative Ki67, and without lymph node metastasis ($P < 0.05$ for all). ADC range of tumor boundary and proximal PS was significantly lower in low risk tumor than in the others ($P = 0.004$ and 0.002). Mean ADC of whole tumor was significantly higher in low-risk tumor than in non-low-risk tumor (P = 0.030).
*Conclusion:* On HR DWI, ADC ranges of tumor boundary and adjacent proximal PS were significantly lower in low-risk tumor than in non-low-risk tumors.


## 1. Introduction

Invasive breast cancers may harbor abnormalities in adjacent normal-appearing tissue, outside the primary tumor [1] and the microenvironment around the tumor is known to play a role in tumorigenesis [2]. The evolution of breast cancer requires remodeling of the surrounding stromal tissues to facilitate progression and support metabolic demand [3]. The earliest stages of breast cancer is associated with a remodeled stroma, characterized in part by increased angiogenesis and microvessel density [4]. In addition to increased angiogenesis, there are striking changes in the cellular constitutes of the activated cancerous stroma including immune cell infiltrates, remodeling of extracellular matrix and physiologic changes in pH and oxygen tension reflecting increased metabolic demand [3,5,6]. Extracellular mastrix (ECM) remodeling alters stromal properties by altering matrix cross-linking, increasing collagen deposition and reorganizing fibers, leading to an increase in tissue stiffness [7]. Several imaging techniques have been developed to characterize the progressive stiffening of cancer tissue in vivo [8,9]. To translate biologic features of activated stroma that may provide information to enhance individualized patient care, image-based prognostic tools would be helpful to routine clinical practice.

Magnetic resonance imaging (MRI) has increasingly been used to evaluate breast tumor with a high sensitivity, but only a moder-

* Corresponding author.
*E-mail address:* docshin@amc.seoul.kr (H.J. Shin).

http://dx.doi.org/10.1016/j.ejrad.2016.02.017
0720-048X/

ate specificity [10]. Diffusion-weighted imaging (DWI) is a useful unenhanced technique that provides microstructural information at the cellular level and is used to detect changes in the apparent diffusion coefficient (ADC) for tissue water associated with changes in tissue and intracellular structure [11]. Recent studies have demonstrated that it has a potential for the diagnosis and characterization of breast lesions [11,12]. The variations in ADC have been shown to correlate inversely with tissue cellularity, which may be associated with stromal component [13]. However, standard DWI using single-shot echo planar imaging (ss-EPI) method has been limited by low signal-to-noise ratio and image distortion. Recent reports have shown that the high-resolution DWI with reduced field-of-view (HR DWI) has the potential to provide improved spatial resolution and reduced distortion [14,15]. HR DWI showed a higher diagnostic performance for the characterization of breast lesions than ss-EPI [16,17]. There were little studies to evaluate ADC values of tumor and adjacent stroma [18,19]. We hypothesized that ADC values of inner tumor, tumor boundary, and peritumoral stroma may be different and reflect tissue microenvironment or stiffness associated with pathologic biomarker in patients with breast cancer. Therefore, the purpose of our study was to evaluate whether ADC values of tumor and adjacent stromal tissue obtained on HR DWI were different according to the pathologic prognostic biomarkers in patients with breast cancer.

## 2. Methods

### 2.1. Study population

This retrospective study was approved by the institutional review board in our institution and the requirement for informed patient consent was waived. From November 2013 to July 2014, we retrospectively identified 651 patients who underwent high-resolution DWI with reduced field-of-view (HR DWI) at 3T MR scanner. Among them, we retrospectively included only patients with a biopsy-proven breast cancer who underwent preoperative breast MRI. We excluded the following patients; who had noninvasive breast cancer; who underwent neoadjuvant chemotherapy; and who did not undergo surgery after breast MRI. Finally, we included 96 patients with biopsy-proven malignant masses (age range, 30–75 years; mean age, 52 years), who were reported in our previous study [20]. We obtained the data about age and pathologic reports from electronic medical records. Fibroglandular tissue (FGT) amount was visually assessed by using a combination of T1- and T2-weighted imaging and was graded, on the basis of BIRADS (Breast Imaging Reporting and Data System) criteria, as fatty (<25% of breast comprised glandular tissue), scattered (25%–50% of breast comprised glandular tissue), heterogeneously dense (51%–75% of breast comprised glandular tissue), and dense (>75% of breast comprised glandular tissue).

### 2.2. MRI acquisition

Dynamic contrast-enhanced MRI (DCE-MRI) was performed using a 3T MR scanner (Skyra, Siemens Medical Solutions, Erlangen, Germany) with a dedicated eighteen-channel phased-array breast coil (Siemens Medical Solutions, Erlangen, Germany). Bilateral breast imaging was performed with the following protocol: an axial T2-weighted sequence (TR/TE, 1100/131 ms; flip angle, 125°; 1.5-mm thickness without an interslice gap; field of view (FOV), $340 \times 210\,mm^2$; matrix size, $256 \times 416$; acquisition time, 134 s) and a 3D T1-weighted FLASH dynamic gradient-echo sequence (TR/TE, 5.6/2.5 ms; flip angle, 12°; matrix size, $384 \times 384$; FOV, $360 \times 360$; 0.9-mm thickness without an interslice gap; and one unenhanced and five contrast-enhanced acquisitions with a temporal resolution of 59 s). An intravenous bolus injection of 0.1 mmoL/kg gadoterate meglumine (Dotarem, Guerbet) was administered at a flow rate of 2 mL/sec using an MR compatible power injector (Spectris; Medrad, Pittsburgh, PA, USA) followed by a 20-ml saline flush.

HR DWI was acquired using an EPI sequence with reduced FOV and acquisition parameters were as follows; TR/TE, 8800/100 ms; flip angle, 90°; FOV, $103 \times 150\,mm^2$; matrix, $176 \times 256$; slice thickness, 3 mm; and acquisition time, 4 min 14 s. Spatial resolution of HR-DWI was $0.59 \times 0.59 \times 3$ mm. Diffusion-weighted gradients were applied in three orthogonal directions and two *b*-values (0 and $1000\,s/mm^2$) were used. An ADC value was calculated using Image J (open-source software supported by the NIH). One radiologist with an experience of 10 years in breast MRI had manually drawn the regions of interest (ROIs) at all slices of the tumor, as reflected in the DCE-MRI. Apparent necrotic or cystic components were avoided by referring to T2-weighted images.

### 2.3. Quantitative analysis of high-resolution DWI

ADC maps were calculated on a pixel-by-pixel basis, according to the equation: ADC = −ln [S1/S0]/(b1-b0), where S0 and S1 are the signals intensities in the ROI obtained by two gradient factors, b1 and b0 (b0 = 0 s/mm2 and b1 = 1000 s/mm2, respectively). The ADC images were manually segmented into inner tumor, tumor boundary, and peritumoral stromal tissue, according to the manually drawn tumor ROIs in all slices including regions that were assigned as partial volume averaged tumor based on the DCE-MRI and HR DWI. The tumor showed generally hyperintense on DWI and hypointense on ADC map. The tumor ROIs were manually drawn to the margin of the entire tumor with high signal intensity on DWI and then copied to the ADC map. Fibroglandular tissue was segmented on the b = 0 image of the DWI, excluding the fat from the skin. A fuzzy C-means clustering procedure was performed to select all fibroglandular tissue visible on the DWI at b = 0 using Image J.

Inner tumor, tumor boundary, and peritumoral stromal tissue were segmented according to a similar method as described in the previous study [18]. In our study, the spatial resolution of HR DWI was $0.59 \times 0.59$ mm, and we calculated ADC values every two-pixels in all slices (0.59 mm x 2 pixel = 1.18 mm). We defined five regions of tumor and peritumoral stroma as follows; inner section of tumor as an area inside 2-pixel apart from the manually drawn ROI ($-\infty$ to − 2 pixel; $-\infty$ to −1.18 mm); tumor boundary as a band-like area inside and outside from ROI (−2 to + 2 pixel; −1.18 to +1.18 mm); whole tumor as an area within the ROI ($-\infty$ to 0); proximal stromal shell as an area just outside the tumor (+2 to +6 pixel, +1.18 to +3.54 mm); middle stromal shell (+14 to 18 pixel; to +8.26 to +10.26 mm); and distal stromal shell (+26 to +30 pixel; +15.34 to +17.7 mm). The mean, minimum, and maximum ADCs of all voxels within these five regions were calculated. Minimum-to-maximum ADC difference (ADC range) of each voxel was also calculated and labeled as $ADC_{range}$.

### 2.4. Histopathologic assessment

Surgical pathology was obtained from definitive surgery in all patients. Histopathologic information, including nuclear grade, histologic grade, estrogen receptor (ER) status, progesterone receptor (PR) status, HER-2, Ki-67, extensive intraductal component (EIC), and axillary nodal status, were obtained from pathologic reports. All pathologic parameters were divided as binary manner. Estrogen (ER) or progesterone receptor (PR) positivity was scored using an Allred score [21], which is a semiquantitative system considering the proportion of positive cells (scored on a 0–5 scale) and staining intensity (scored on a 0–3 scale). The proportion and intensity scores are then summed to produce total scores of 0 or 2 through 8. The tumor was considered positive for ER or PR if