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Early-stage invasive ductal carcinoma: Association of tumor apparent diffusion coefficient values with axillary lymph node metastasis

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ABSTRACT

Purpose: To evaluate any association between tumor apparent diffusion coefficient (ADC) values and axillary lymph node metastasis (ALNM) in early-stage invasive ductal carcinoma.
Materials and methods: Records of 270 invasive ductal carcinoma patients with stages T1 and T2 disease who underwent breast magnetic resonance imaging, including diffusion-weighted imaging with *b* values of 0 and 1000s/mm^2 were reviewed retrospectively. The tumor ADC values were analyzed for their utility in predicting ALNM using multivariate regression analysis and receiver operating characteristic (ROC) curve analysis.
Results: Of the 270 patients, 58 (21.5%) experienced ALNM. The mean tumor ADC values were significantly lower in patients with ALNM than in those without metastasis (0.880×10^{-3} vs. 0.999×10^{-3} mm^2/s, $P < 0.001$). A ROC curve demonstrated a tumor ADC value of 0.991×10^{-3} mm^2/s to be the optimal cut-off for predicting ALNM. In a multivariate analysis, lower tumor ADC ($\leq 0.991 \times 10^{-3}$ mm^2/s; adjusted odds ratio (OR) = 5.861, $P < 0.001$), large tumor size (>2 cm; adjusted OR = 3.156, $P = 0.002$) and the presence of lymphovascular invasion (adjusted OR = 4.125, $P < 0.001$) were independent variables associated with ALNM. When tumor ADC value was added to known risk factors (i.e., tumor size and lymphovascular invasion), a significant improvement in the accuracy of risk prediction for axillary node metastasis was shown (c-statistic = 0.758 vs. 0.816, $P = 0.026$).
Conclusion: In early-stage invasive ductal carcinoma, lower tumor ADC values are associated with the presence of ALNM.

1. Introduction

The accurate identification of axillary node involvement is essential for staging and management planning in patients with breast cancer, because axillary lymph node status is the most important prognostic factor. Sentinel lymph node biopsy (SLNB) is considered an appropriate alternative to routine axillary lymph node dissection for patients with early-stage breast cancer who are clinically axillary-node-negative [1]. SLNB has been reported to have high accuracy, with a high sensitivity of 91.2%, and a high specificity, approaching 100%, for the detection of axillary nodal metastasis [2]. Although SLNB results in reduction of postoperative morbidity and improvement in quality of life compared with axillary lymph node dissection [3], it is an invasive procedure and carries the inevitable risks of surgical procedures, such as wound infection, lymphedema, seroma, and axillary paresthesia [4]. Additionally, relatively high false-negative rates (8.8–9.8%) of SNLB remain a problem [2,5]. Thus, a non-invasive imaging assessment that provides information on axillary lymph node metastasis before surgery would be beneficial in clinical practice.

Recently, diffusion-weighted (DW) imaging has been incorporated into 'standard' breast magnetic resonance (MR) examinations. It is a functional MR imaging technique that measures the mobility of water molecules in tissues and reflects characteristics of the microscopic cellular environment, such as cell density and membrane integrity [6]. Previous studies have reported that quantitative apparent diffusion coefficient (ADC) values obtained in DW imaging could be used to differentiate between benign and malig-

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nant breast lesions [7,8]. In the study of Kul et al., there was a 13.5% improvement in specificity with the addition of DW imaging to dynamic-contrast enhanced breast MR imaging in the characterization of breast masses [9]. DW imaging may also be helpful for detecting and characterizing ductal carcinoma in situ [10]. In addition, even many mammographically and clinically occult breast cancers can be detected using DW imaging [11].

More recently, some authors have sought to gain information about the heterogeneous tumor biology of breast cancer from DW images and the ADC map and concluded that tumor ADC values are associated with some 'traditional' prognostic factors, such as tumor size, histological grade, and axillary lymph node involvement [12–14]. However, the results have not been consistent across studies [15–17] and the association between tumor ADC values and axillary lymph node metastasis has not been fully determined, especially in early-stage disease. Thus, the purpose of this study was to evaluate the association between tumor ADC values and axillary lymph node metastasis in early-stage invasive ductal carcinoma.

2. Materials and methods

2.1. Patients

Our Institutional Review Board approved this study and waived the need for informed consent. Between May 2013 and November 2014, the medical records of 425 consecutive women diagnosed with invasive ductal carcinoma who underwent preoperative breast MR imaging with DW imaging were evaluated retrospectively. Among them, 341 women who were diagnosed with pathological stages T1 and T2 were included in the present study. Of these women, 29 who had undergone vacuum-assisted biopsies or excisional biopsies for diagnosis before MR imaging, 15 who had no available immunohistochemical data, and 27 who had inadequate DW imaging for the analysis were excluded. In females with multifocal or multicentric breast cancer, the largest tumor was included, and in females with bilateral breast cancer, only one tumor was randomly included. Finally, 270 invasive ductal carcinomas (mean invasive tumor size, 2.2 cm; range, 0.5–5.0 cm) in 270 female patients (mean age, 51.3 years; range, 23–85 years) were included in this analysis.

2.2. MR imaging acquisition

Breast MR imaging was performed using a 3-T system (Trio Tim, Siemens Medical Systems, Erlangen, Germany) with a dedicated four[P1] -channel breast array coil (Siemens Medical Systems) with the patients in the prone position. After obtaining a bilateral transverse localizer image, sagittal fat-suppressed T2-weighted turbo spin-echo images were obtained (TR/TE, 7623/91, matrix, 320×246, field of view (FOV), 220×220 mm, slice thickness, 3.0 mm; no gap). Before contrast agent injection, DW imaging was obtained using a single-shot echo-planar imaging technique with fat suppression in the axial plane with the following parameters: TR/TE, 5200/74, matrix, 80×190, FOV, 340×179 mm, slice thickness, 5.0 mm, NEX, 9, acquisition time, 203 s, *b* value of 0 and 1000s/mm^2. Dynamic contrast-enhanced MR images included one pre-contrast and five post-contrast, bilateral sagittal image acquisitions using a fat-suppressed T1-weighted three-dimensional fast low-angle shot sequence (TR/TE, 4.5/1.6, matrix, 352×292, flip angle, 20°, FOV, 220×220 mm, slice thickness, 2.0 mm; no gap). Five post-contrast images were obtained at 90, 170, 250, 330, and 410s after bolus injection of 0.1 mmol/kg gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany) via an indwelling IV catheter.

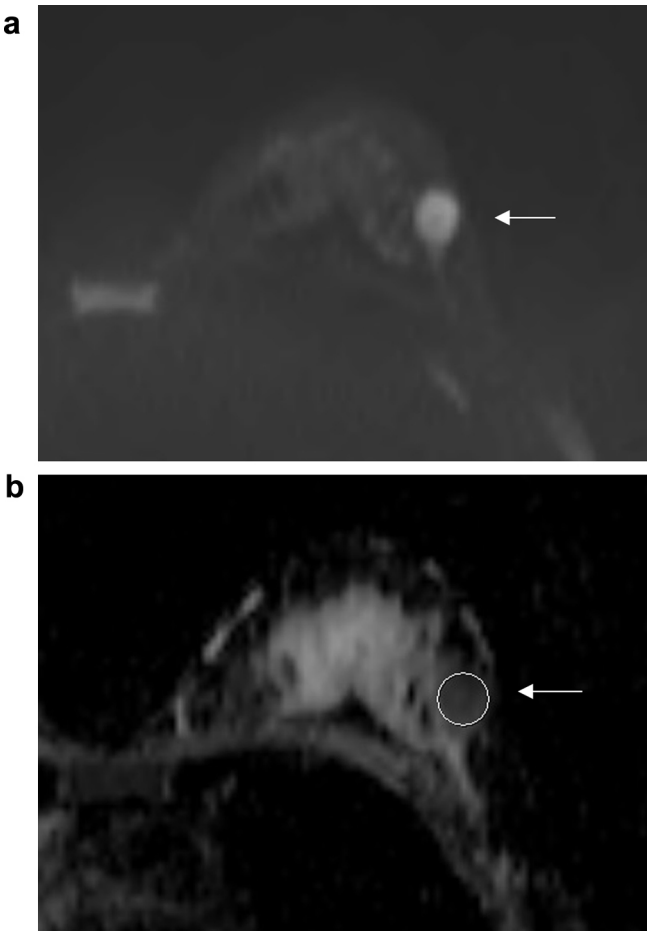

Fig. 1. Invasive ductal carcinoma of the left breast in a 55-year-old woman. a: Axial diffusion-weighted MR image (*b* value of 1000s/mm^2) shows high signal intensity mass (arrow). b: ADC map shows the mass with low signal intensity (arrow). The largest tumor cross section of the tumor was chosen, and the largest oval or round ROI was placed inside the tumor. The mean ADC value within the tumor was 0.816×10^{-3} mm^2/s. Axillary node metastasis was found in two out of 13 resected nodes.

2.3. DW imaging analysis

DW images were independently reviewed by two radiologists (J.Y.K. and H.B.S., with 5 and 2 years of experience in breast MR imaging, respectively); the radiologists were informed that the patients were diagnosed with invasive ductal carcinoma but were blinded to the clinicopathological information of the patients. The independent reviewers identified the lesions with signal intensity higher than that of normal breast parenchyma on DW images with *b* values of 0 and 1000s/mm^2 and then manually drew regions of interest (ROIs) in the corresponding area on the ADC map (Fig. 1). The largest tumor cross section of each tumor was chosen, and the largest oval or round ROIs were placed inside the breast tumor to standardize the image analysis process as much as possible. The placement of ROIs was performed carefully to avoid cystic or necrotic components of the tumor on the basis of combined information from the dynamic contrast-T1-weighted imaging, T2-weighted imaging, and DW imaging. The analysis was performed using the ADC values measured by the radiologist with 5 years of experience.

2.4. Histopathological analysis

All patients underwent surgical resection of breast cancer with SNLB and/or axillary lymph node dissection. SNLB was performed