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Utility of apparent diffusion coefficient as an imaging biomarker for assessing the proliferative potential of invasive ductal breast cancer

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AIM: To determine the clinical utility of apparent diffusion coefficient (ADC) metrics for the non-invasive assessment of tumour proliferation indicated by Ki-67 labelling index (LI) in invasive ductal breast cancer.

MATERIALS AND METHODS: Eighty patients with 80 histopathologically proven invasive ductal breast cancers underwent diffusion-weighted imaging with b-values of 0 and 800 s/mm^2 at a 3-T system. ADC metrics including ADC_{mean}, ADC_{median}, ADC_{min}, ADC_{max}, and ΔADC (ADC_{max}−ADC_{min}) were recorded from the entire tumour volume on ADC maps, and correlated with the Ki-67 LI. Ki-67 staining of ≥14% was considered to indicate high proliferation and <14% was considered to indicate low proliferation.

RESULTS: ADC_{min}, ADC_{max}, and ΔADC showed significant correlations with the Ki-67 LI (for all tumours, r=−0.311, 0.436, and 0.551, respectively; for luminal/human epidermal growth factor receptor 2 (HER2)-negative group, r=−0.437, 0.512, and 0.639, respectively; all $p<0.01$), whereas ADC_{mean} and ADC_{median} showed no significant correlation (both $p>0.05$). Receiver operating characteristic (ROC) curve analysis for the differentiation of high- from low-proliferation groups showed that ΔADC yielded the highest area under the ROC curve for the whole tumour population (0.825; 95% confidence interval [CI]: 0.724, 0.901), as well as for the luminal/HER2-negative group (0.844; 95% CI: 0.692, 0.940).

CONCLUSION: ΔADC may serve as a promising imaging biomarker for the prediction of Ki-67 proliferation status in invasive ductal breast cancer.

Introduction

Breast cancer represents a heterogeneous collection of distinct diseases rather than a single disease. Breast cancer intrinsic subtypes have been established based on analysis of gene expression arrays.[1–3] In clinical settings, surrogate immunohistochemical classification of tumour subtypes is more widely performed than gene sequencing, due to its high feasibility and availability. Using an immunohistochemical examination of molecular markers including oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 labelling index (LI), breast cancers are classified into several subtypes.[1–3] Ki-67 LI, a nuclear marker of cell proliferation, serves as a determining factor in the distinction between luminal A and luminal B/HER2-negative

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carcinomas, which are both hormone receptor positive.[2,3] Luminal B has a higher proliferation index than luminal A as measured by Ki-67. Therefore, luminal B has a worse prognosis and is recommended for chemotherapy in addition to endocrine therapy, compared to luminal A for which endocrine therapy alone is recommended.[1–3] Moreover, besides identifying tumour subtypes, Ki-67 has been reported to play a key role in predicting tumour response to adjuvant therapy and risk of recurrence and death.[4–6]

Recently, there has been increasing interest in preoperative assessment of molecular features in breast cancer using non-invasive imaging tools, of which diffusion-weighted imaging (DWI) appears promising as a contrast-medium-free magnetic resonance imaging (MRI) technique. DWI is sensitive to Brownian motion of water molecules on a length scale (typically micrometres, comparable to cell size) less than the image resolution (typically millimetres) and restriction of water mobility increases the signal intensity on DWI. Thus, DWI is commonly used to infer information about tissue architectural features such as cellularity. Most studies have used the technique via a quantitative measure of apparent diffusion coefficient (ADC) to estimate the degree of restriction to water diffusion in breast cancer.[7–9] Furthermore, ADC has also been investigated with regard to its predictive value of prognostic factors in breast cancer including Ki-67 LI[10–16]; however, inconsistency in results on the correlation between ADC and Ki-67 LI has been reported. Some studies have demonstrated the association between ADC measurements and Ki-67 expression,[10–12] but most studies have shown that there is no correlation between them.[13–16] Even in studies with positive findings, conflicting results have existed; results from the majority have suggested that high-proliferation tumours had lower ADC values,[10,11] whereas a recent study reported the opposite result that high-proliferation tumours had higher ADC values.[12] It was speculated that many factors may account for this inconsistency, such as histological type of breast cancer (tumour heterogeneity) and ADC metric for analysis.

The aim of the present study was to evaluate the correlations between the ADC value and Ki-67 LI in invasive ductal carcinoma (IDC). To eliminate confounding effects of different histological types on the ADC values, only IDC as confirmed at surgery was included in the present study. Specifically, the subgroups of luminal A and luminal B/HER2-negative IDC tumours were investigated separately. To investigate which ADC metric was optimal, ADC_{mean}, ADC_{median}, ADC_{min}, and ADC_{max} were measured from the whole-lesion region of interest (ROI) on the corresponding ADC maps. In addition, a novel ADC metric, ΔADC, defined as $ADC_{max}-ADC_{min}$, was also analysed.

Materials and methods

Patients

This retrospective study was approved by the Institutional Review Board and informed consent was waived. The radiological and pathological database was searched to identify patients who underwent breast MRI at 3 T before surgery without neoadjuvant therapy, and subsequently, received surgical resection for IDC between September 2015 and February 2016. A total of 98 consecutive patients met these criteria. Among this group, patients were excluded if any of the following criteria applied: (a) no visible lesion detected on DWI (n=5); (b) inadequate DWI quality due to patient motion or artefact (n=4); and (c) lack of immunohistochemical results on breast specimens (n=9). In patients with two or more histopathologically confirmed IDC tumours, the largest was chosen for analysis. Finally, 80 IDC tumours in 80 female patients (mean age, 50.3 years; age range, 26–84 years) were included.

MRI protocol

All of the MRI examinations were performed using a 3-T system (Ingenia, Philips Healthcare, Best, The Netherlands) with a dedicated 16-channel phased-array breast coil. All patients were examined in the prone position. Diffusion-weighted images were acquired bilaterally in the transverse plane with a single-shot echo planar imaging sequence with fat suppression: 5,600 ms repetition time (TR)/65 ms echo time (TE), 90° flip angle, 280×342 mm field of view, 108×129 matrix, 4 mm section thickness, two excitations, b-values of 0 and 800 s/mm^2; 2 minutes 20 seconds acquisition time. Diffusion-sensitising gradients were applied through three orthogonal directions. Following DWI, the dynamic contrast-enhanced MRI was performed by using a three-dimensional T1-weighted high-resolution isotropic volume examination (THRIVE) before and at six consecutive points after an injection of 0.1 mmol/kg of dimeglumine gadopentetate contrast agent (Magnevist, Bayer Healthcare, Berlin, Germany) at a rate of 2 ml/s, followed by a 20-ml saline flush, with the following parameters: 4.2 ms TR, 2.1 ms TE, 10° flip angle, 340×320 mm^2 field of view, 400×320 matrix, 1 mm section thickness.

Image analysis

Images were transferred from the radiological database to an independent personal computer for quantitative DWI analysis by using custom-written Matlab software (Mathworks, Natick, MA, USA). ADC maps were generated on a pixel-by-pixel basis according to the formula:

$$ADC = -(1/b)\ln(S_b/S_0)$$

where b is the diffusion factor (800 s/mm^2), and S_b and S_0 are the signal intensities with diffusion factors b and zero. Image analyses were performed in consensus by two radiologists with more than 7 and 9 years of breast MRI image interpretation; both readers were blinded to the clinical and histopathological information. ROIs were placed manually on each section of the ADC maps to cover as much as possible of the tumour volume, with reference to the dynamic contrast-enhanced images. Whole-lesion volume was automatically calculated by summing all pixels within ROIs. The mean, minimum, and maximum ADC values from

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