Original paper

Comparison of apparent diffusion coefficient in diffusion-weighted magnetic resonance imaging and morphological assessment of breast tumors

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The aim of the study was to assess the relationship between the apparent diffusion coefficient in diffusion-weighted magnetic (DWM) resonance imaging (MRI) and selected morphological parameters of the breast lesions. Diffusion-weighted imaging data and the pathology reports of 160 women treated surgically between January 2011 and March 2015 were analyzed. When classified, 107 invasive carcinomas, 13 pre-invasive carcinomas and 40 benign lesions were identified. The mean apparent diffusion coefficient was significantly lower for invasive carcinomas than benign lesions of the breast (0.87 ± 0.02 vs. 1.58 ± 0.04; $p < 0.001$). What is more there was an inverse correlation between value of apparent diffusion coefficient in diffusion-weighted magnetic resonance imaging and the grade of breast carcinomas ($p = 0.04$).

Key words: breast cancer, MRI, diffuse coefficient in DWM, tumor grade.

Introduction

Diffusion-weighted imaging (DWI) represents one of the latest developments in magnetic resonance imaging (MRI). This method is based on the idea that the movement of water molecules in the extracellular fluid may reflect the histological structure of the tissue [1, 2]. Using DWI sequences, the apparent diffusion coefficient (ADC), which is a quantitative measure of the restriction of water molecule movement within a defined area, can be calculated. Several studies have demonstrated that the ADC reflects cell density and can be used to differentiate malignant from benign lesions within a multitude anatomical locations. High cellular proliferation increases the tissue density and may restrict the movement of extracellular fluid due to the formation of additional barriers; subsequently, a decrease in image signal intensity and a lower ADC can be observed [3, 4, 5]. So far, a limited number of independent studies have concluded that ADC evaluation allows for benign tumors to be distinguished from malignant lesions within the breast with high specificity.

Histopathological features of malignant lesions of the breast are among the major determinants of clinical outcomes. Moreover, crucial post-surgery decisions concerning adjuvant therapy, as well as follow-up strategy, are based on the clinicopathological characteristics of the resected lesions. The purposes of our study were to: (1) confirm the efficacy of using DW-MRI-based ADC to differentiate benign from malignant lesions within the breast; and, (2) determine the relationship between ADC and the major histopathological parameters (grading and morphology) in the most common breast carcinomas.

Material and methods

The study was performed at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Cracow Branch, Poland, between January 1, 2011 and March 31, 2015. One hundred and sixty women aged 18-89 years (median: 55.5 years old), who were diagnosed and treated in the hospital during this time, underwent breast MRI with DWI.

All MRI examinations were carried out using the Siemens Magnetom Avanto 1.5-T whole-body scanner with a dedicated phased-array bilateral breast coil. During the MRI, patients were required to lie prone, facing downwards, and a dedicated breast holder was used to eliminate motion artifacts [6]. The imaging protocol included the following resonance sequences: TSE-T1, transverse (for approximately 2 min and 13 s); TSE-T2, transverse (2 min and 37 s); TSE-T2 STIR, transverse (2 min and 33 s); DWI/ADC EP 2D, transverse (diffusion imaging; 5 min and 59 s); and TSE-T1 FL3D, FATSAT, transverse, dynamic (after intravenous contrast infusion; sequences were repeated for 7 min at 1-min intervals). The gadobutrol (Gadovist®) contrast agent was administered intravenously, at a dose of 0.1 mmol/kg, using a dedicated infusion pump with a 2-ml/second flow rate. The analysis was conducted using the BreVis software (Syngo Via VA20B, Siemens, 2013). All patients who were enrolled in the study were previously diagnosed with a suspicious breast lesion, and subsequent decisions concerning surgical approaches and adjuvant strategies were to be made based on the MRI findings. The DWI evaluation was based on a subjective estimation of brightness in the DWI sequence along with the corresponding map distribution in relation to the background. The ADC was calculated afterwards. The measurements were made using the dedicated functionality within the BreVis software, in an area approximately 0.5 cm^2 in the optical center of the pathological lesion.

The histopathology reports of the resected specimens were used as a reference for radiological-pathological comparisons. Highly trained pathologist, in accordance with the most recent classifications, carried out the microscopic examinations. The 2012 World Health Organization classification was used for malignant neoplastic lesions [7]; whereas, for invasive carcinomas, tumors were graded according to the Elston-Ellis modification of the Bloom-Richardson grading system (Bloom-Richardson-Elston grading system) [8]. In the cohort, 107 invasive carcinomas (89% of all carcinomas), 13 pre-invasive carcinomas (carcinomas *in situ*; 11% of all carcinomas), and 40 benign lesions (27 fibroadenomas, five cases of adenosis, four intraductal papillomas, two hematomas, and two other lesions) were identified. Among the invasive lesions, 93 invasive carcinomas not otherwise specified (87% of all malignant lesions), 11 lobular carcinomas (10%), and three cases representing other, less common subtypes were identified. The detailed histopathological characteristics of resected lesions, along with their grading scores (where applicable), are depicted in Table I.

Informed consent was obtained from all individual participants included in the study. Statistical analyses were performed using the Statistica (StatSoft Inc, 2010) ver. 10.0 software package. Student's t-tests and Fisher's exact tests were used, and a p value of less than 0.05 was considered statistically significant.

Results

In total, 160 breast lesions were analyzed. When classified, 120 carcinomas (75.0%) and 40 benign lesions (25.0%) were identified. The average ADC value of all lesions was $1.07 \pm 0.03 \times 10^{-3}$ mm^2/s and was within a range of 0.34 to 2.21×10^{-3} mm^2/s. The mean ADC of malignant lesions (Fig. 1) was lower than that of benign tumors (Fig. 2), and the difference between the two values was highly significant ($0.90 \pm 0.02 \times 10^{-3}$ mm^2/s vs. $1.58 \pm 0.04 \times 10^{-3}$ mm^2/s, respectively; $p < 0.001$). There was a statistically significant difference between the ADC values corresponding to invasive carcinomas compared to that corresponding to non-invasive carcinomas ($p = 0.04$). Detailed data concerning the mean ADC values of all lesions, according to their histopathological characteristics, are presented in Table I.

ROC analysis confirmed the value of the ADC as a classifier to differentiate malignant from benign lesions within the breast. Based on the ROC analysis, the optimal cut-off point was defined as 1.18×10^{-3} mm^2/s (95% CI: $1.14\text{-}1.39 \times 10^{-3}$ mm^2/s), with

Table I. Histopathological characteristics of resected lesions and mean ADC values

	NUMBER	MEAN ± SD $\times 10^{-3}$ MM²/S
Carcinomas (total)	120	0.90 ±0.02
Invasive carcinomas	107	0.88 ±0.02*
Invasive carcinomas (NOS)	93	0.88 ±0.02
Invasive lobular carcinomas	11	0.94 ±0.13
Other carcinomas (apocrine carcinoma, papillary carcinoma)	3	0.90 ±0.04
Pre-invasive carcinomas (DCIS, LCIS)	13	1.04 ±0.07*
Benign lesions	40	1.58 ±0.04

**Student's t-test; p = 0.04 for the difference between invasive vs. pre-invasive carcinomas. NOS – not otherwise specified; DCIS – ductal carcinoma in situ; LCIS – lobular carcinoma in situ*

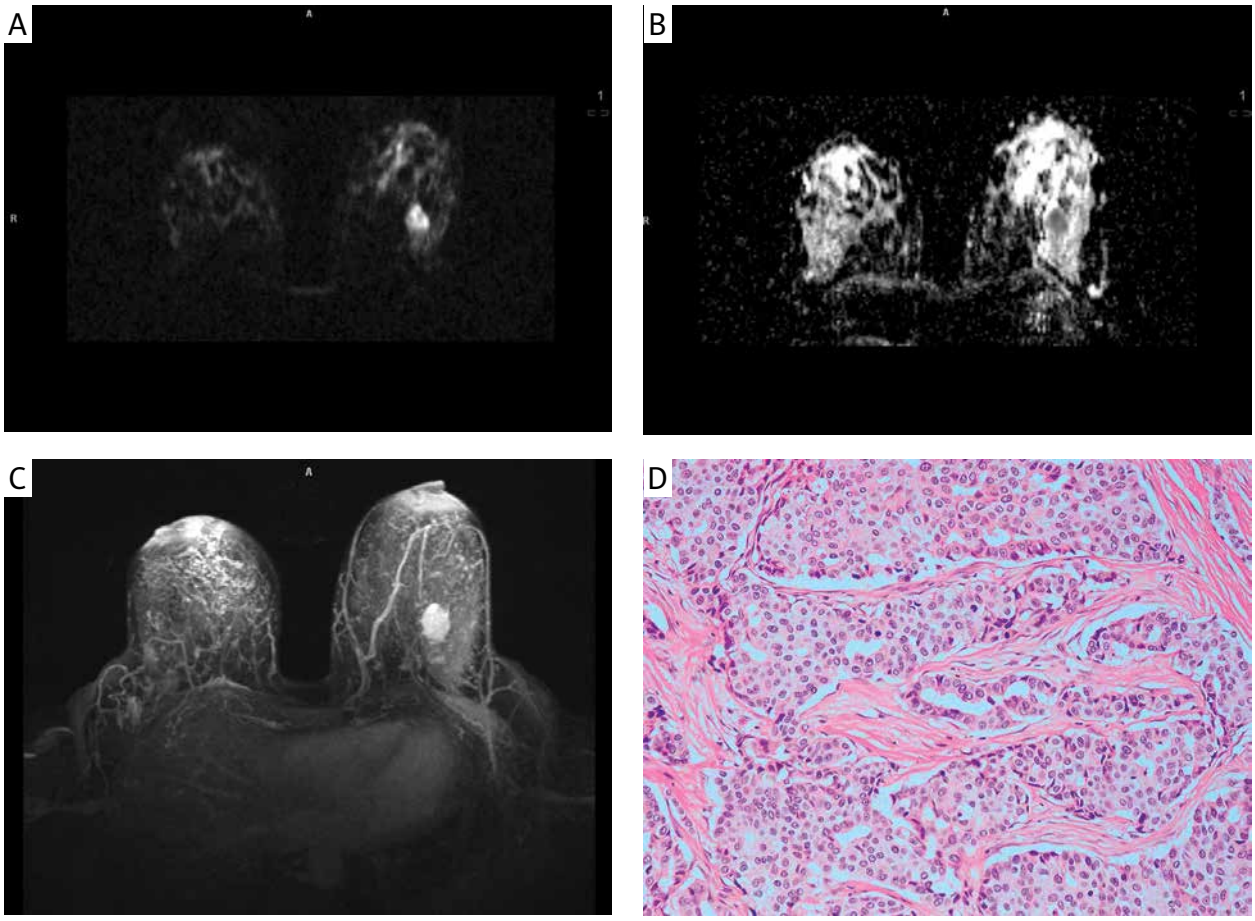

Fig. 1. Comparison of diffusion-weighted images (DWI/ADC) presenting left breast invasive carcinoma (A, B) with MIP reconstruction (C) and histologic texture of the tumour (D)

a sensitivity of 95%, a specificity of 100%, and an accuracy of 96%.

Eighty-nine invasive carcinomas were classified according to the Bloom-Richardson-Elston grading system. Eleven (12%) well differentiated (G1), 48 (54%) moderately differentiated (G2), and 30 (34%) poorly differentiated carcinomas (G3) were identified. The mean ADC values, according to the grading scores of invasive carcinomas, are presented in Table II. The difference between the mean ADC values of the G1 and G3 grading categories proved statistically significant ($p = 0.01$).

Discussion

According to the College of American Pathologists (1999), the prognostic factors in breast carcinoma are divided into three groups: categories I, II and III. The prognostic value of category I (e.g., TNM staging, histological grade, histological type, mitotic figure count, and hormone receptor status) has been proven unequivocally; whereas, categories II and III consist of factors that, although having been studied extensively, still require further validation (category II) or have not been studied sufficiently (category III) [9]. In our study, defined prognostic factors were used for radiological-pathological assessment and comparison. In particular, histological type and histological grade were used (when applicable) due to their close relationship to tissue density and other biophysical features. Increased cellularity of invasive carcinomas, when compared to benign lesions of the breast, resulted in a decreased mean ADC in MRI. This result is in line with previous reports concerning such relationships. According to Luo *et al*., DW-MRI is helpful in differential diagnoses of breast diseases [10].

Breast lesions may occasionally be difficult to diagnose radiologically, especially in dense fibro-glandular breasts. Over recent years, MRI has been increasingly used in the screening of high-risk individuals, as well as in a routine breast evaluation. Dynamic MRI studies improve the detection and characterization of problematic lesions in the breast; however, the low specificity of MRI remains a limitation [11]. It is therefore no surprise that DWI, based on alterations in the microscopic motion of water molecules, has become widely used in MRI. It is thought that the movement of water molecules in the extracellular fluid reflects the histological or even molecular

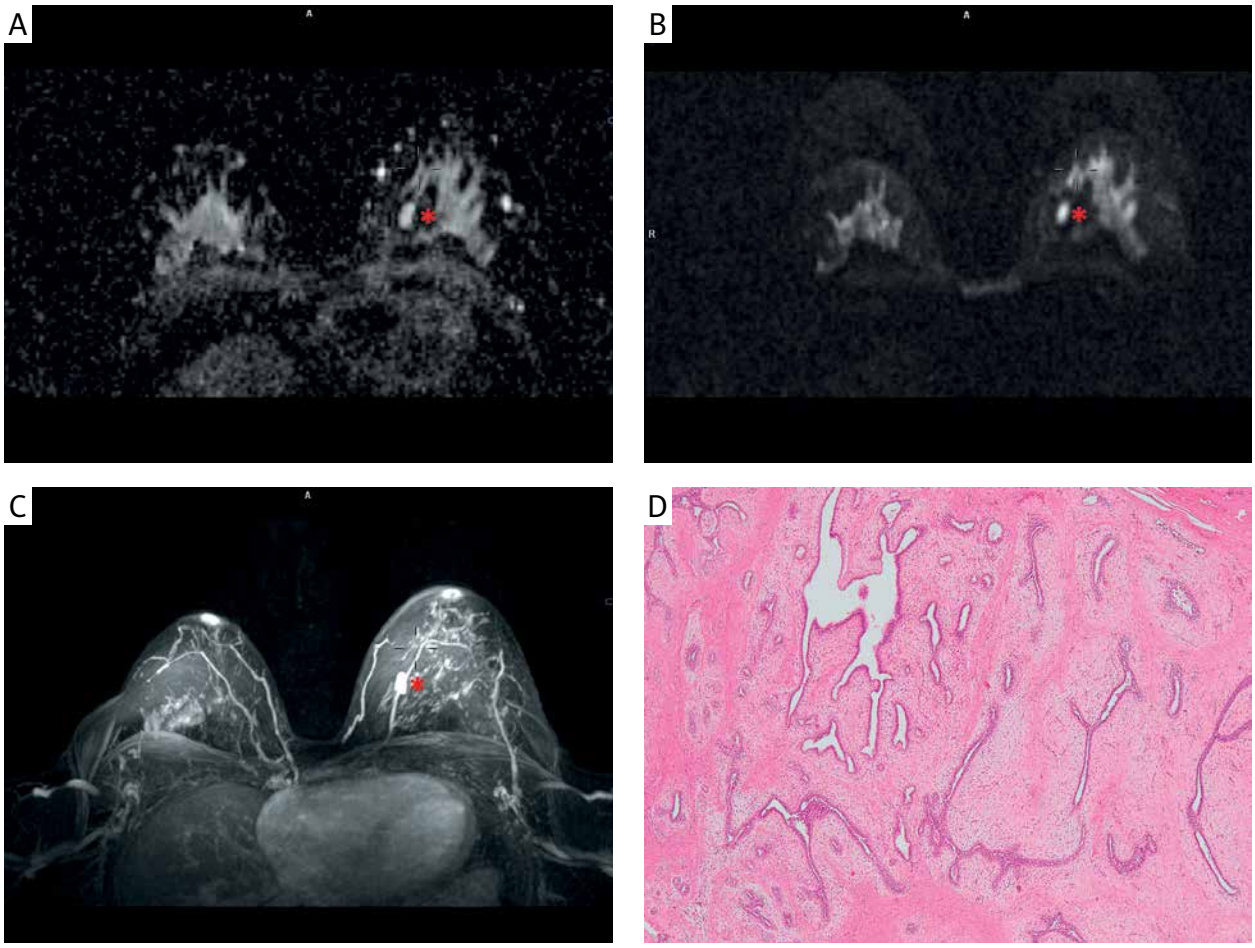

Fig. 2. Comparison of diffusion-weighted images (DWI/ADC) presenting left breast fibroadenoma (A, B) with MIP reconstruction (C) and microscopic picture of the tumour (D)

structure of the tissue. DWI can help to characterize malignant lesions of the breast with impressive specificity [12]. According to Min *et al.*, DW-MRI is an accurate diagnostic tool for the differentiation of benign and malignant breast lesions. Using a threshold ADC value of 1.23×10^{-3} mm^2/s, DW-MRI achieved a sensitivity of 82.8% and specificity of 90.0%, as well as a positive-predictive value of 92.3% and a positive-likelihood ratio of 8.3 [13]. In the present study, the optimal cut-off point was 1.18×10^{-3} mm^2/s (95% CI: $1.14\text{-}1.39 \times 10^{-3}$ mm^2/s), with a sensitivity of 95%, a specificity of 100%, and an accuracy of 96%.

In the present study, 160 women with breast lesions initially detected using routine methods (e.g., mammography and/or ultrasound assessment) received DWI. In the case of pre-menopausal women, the procedure was performed between the 4th and 12th days of the menstrual cycle, to avoid potential differences in uptake of the contrast agent in the glandular tissue of the breast [14, 15]. MRI brings a number of benefits to breast imaging, and presently the list of indications includes: screening of high risk individuals (e.g., women with a family history of breast carcinoma; particularly, *BRCA1* mutation carriers), searching for the primary tumor in metastatic cancers of unknown origin, postoperative imaging of the implant (to evaluate implant integrity and post-implantation complications), assessing multiple foci, postoperative control (especially after breast-conserving operations), as well as the detection of early recurrence [16, 17, 18, 19].

A comparison of the mean ADC values of invasive carcinomas versus benign lesions led to the discovery of a statistically significant difference between the

Table II. Mean ADC values according to the Bloom–Richardson–Elston grading score of invasive carcinomas

	NUMBER	MEAN ± SD ($\times 10^{-3}$ MM^2/S)
Total	89	0.88 ±0.02
G1 (well differentiated)	11	0.98 ±0.04*
G2 (moderately differentiated)	48	0.88 ±0.04
G3 (poorly differentiated)	30	0.84 ±0.03*

** Fisher's exact variance test, p = 0.01 for the difference between G1 vs. G3 categories*

two. Low ADC values were demonstrated in both ductal (invasive carcinomas not otherwise specified) and lobular carcinomas. The mean ADC values of malignant tumors are much lower than those of benign lesions of the breast. Moreover, for preinvasive carcinomas (both ductal and lobular) the mean ADC values fell somewhere in-between, suggesting a linear relationship between this parameter and the biological exponents of malignancy. Interestingly, with the growing grading score, the decrease of the mean ADC value could be observed. This finding should be interpreted with caution due to the limited number of well differentiated (G1) carcinoma cases in our study; however, it is in line with previous reports by Woodhams *et al*. and Mayrhofer *et al*. [20, 21]. In light of the meta analysis by Tsushima et al., it can be concluded that ADC evaluation is useful for the differentiation of malignant and non-malignant breast tumors, given the pooled sensitivity and specificity of 0.89 (95% confidence interval [CI]: 0.85-0.91) and 0.77 (95% CI: 0.69-0.84), respectively [22]. Despite this confidence, the localization of benign lesions of the breast on ADC maps may remain challenging due to poor contrast with surrounding glandular tissue.

To summarize, ADC is a useful parameter to differentiate benign and malignant lesions of the breast. Over recent years, the obstacles that previously impeded the transfer of this technique into clinical practice have been overcome, and significant progress has been made, particularly in terms of guidelines, procedural standardization, and MRI-guided interventions [23, 24]. Given the ease with which the technique could be introduced, and the fact that it would take relatively little additional time, ADC combined with dynamic studies may improve the efficacy of MRI studies in the characterization of problematic breast lesions.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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The authors declare no conflict of interest.

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