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Comparative study of ADC values and breast cancer subtypes in diffusion-weighted (DM) imaging

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Abstract

Histological subtypes of breast cancer are of great significance in assessing tumor characteristics. Our study intends to assess compare ADC values and histological subtypes of breast cancer in diffusion weighted (DM) imaging. This study retrospectively analyzed breast cancer patients from December 2016 to February 2018. 262 breast cancer patients were examined by DWI (b = 500s / mm^2) and measured for lesions. Spearman correlation analyzed the relationship between ADC value and different degrees of differentiation. ADC value showed significant difference between ductal carcinoma in situ and invasive carcinoma (p <0.05) and also between ductal carcinoma in situ, tubule and sieve cancer (p <0.05). The maximum WDu ADC value of PR-positive tumors was significantly reduced compared to PR-negative tumors (p <0.05) and the maximum WDu of HER-2 positive tumors was significantly elevated compared to HER-2 negative (p <0.05) without difference of Ki-67 status. ADC values showed significant difference in breast cancers with different differentiation (p <0.05) and were correlated with differentiation degrees of lesions (rs = -0.272, P <0.05). ADC value has certain significance for judging the histological type and differentiation degree of breast cancer before surgery. The ADC value of ductal carcinoma in situ and low-differentiated tumor is low and the maximum WTa of HER-2 positive tumor is significantly higher HER-2 negative.

Keywords: DWI, ADC, breast cancer, subtype.

Introduction

Breast MRI is a high-sensitivity imaging tool for detecting breast cancer, which has been widely accepted clinically and is suitable for a variety of clinical indications, including accurate diagnosis of preoperative evaluation of breast cancer. However, it only provides limited specific information, and therefore exposes many patients to unnecessary biopsies, placing unnecessary body burden on patients [1, 2]. In previous studies, the application of diffusion weighted imaging (DWI) in oncology has been increasing. DWI is an advanced MRI technology that can detect the mobility of water molecules diffused in tissues [3, 4]. DWI has several advantages such as short acquisition time (usually 2-3 minutes) and the need to restrict the use of any contrast agents [5, 6]. The diffusion rate of water in the tissue is inversely proportional to tissue cells and the integrity of the cell membrane. The diffusion gradient is usually applied to at least three orthogonal directions to acquire a rotation-invariant action [7]. DWI can detect breast cancer and does not require contrast enhancement materials, so DWI can be used for patients with contraindications to enhanced MRI, such as those with poor renal function and allergies to enhanced MRI materials. DWI is increasingly used in breast imaging applications. Previous studies have confirmed DWI's value in detecting and characterizing breast cancer. Breast cancer is usually associated with water molecular diffusion limitations, currently observed with increased drunk driving signals, and lower apparent diffusion coefficient (ADC) values associated with surrounding normal tissue and benign lesions of the breast. However, there are some exceptions observed with partial benign lesions of the breast having lower ADC values, while ductal carcinoma in situ (DCIS) has higher ADC values than invasive cancers [8]. A meta-analysis of 14 studies showed that the ADC excels at classifying suspicious breast lesions, so into the adc may improve the accuracy

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of assessment of the traditional clinical breast ADCmax and ADCmean performed well in terms of benign and malignancy identification of breast lumps This study of malignant tumor and benign tumor ADCmean are 1.0±0.2 and 1.5±0.2 respectively with the breast lesions of past research results to some extent [9].

In breast cancer, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and proliferation rate (Ki-67) guide treatment decisions and predict tumor response to the adjuvant treatment. The status of immunohistochemical (IHC) tumor receptors and Ki-67 is related to tumor cell number, blood vessels size, and the aggressiveness. In addition, using immunohistochemistry, molecular detection, and other methods, molecular breast cancer subtypes can be identified to guide systemic therapy and early neoadjuvant or adjuvant treatment recommendations. However, so far, information about the status of the receptor and the rate of proliferation must be acquired through invasive tissue sampling. In addition, although breast biopsy and immunohistochemistry of surgical specimens is the gold standard to assess receptors, it has certain limitations. As many as 20% of patients have divergences in the receptor status of biopsy and surgical specimens, and it is not uncommon for pathologists to differ on the assessment of the same specimen [5, 10]. In addition, tumor biology changes after treatment, which can cause changes to receptors. Therefore, it is advisable to study non-invasive methods to assess these prognostic factors. A major advantage of DWI is that ADC is measured in clinic as a quantitative imaging biomarker [11]. DWI and ADC imaging have been proposed as biomarkers to determine tumor prognosis and predictive factors. Although the ADC value of high-proliferative tumors with increased cell numbers is lower than that of low-proliferative tumors, the number of new blood vessels, enhanced vascular permeability, such as tumor ADC values in HER-2 positive patients are higher and tumors with positive hormone receptors are usually less aggressive with fewer new blood vessels, so ADC values are lower [12]. However, the prediction of ADC status as a biomarker for receptor status and the classification of breast cancer subtypes have diverged. This divergence is mainly the judgment of different thresholds, and the main reason for this staging is due to different measurement methods, that is, measuring the entire tumor and the subjectively selected area [13]. Our study intends to assess whether different ADCs measurement methods and indicators could be applied for molecular classification of breast cancer subtypes.

Materials and methods

Patients

The study was conducted with approval of our ethics committee. Informed consent was obtained. The database of our hospital was retrospectively analyzed 262 patients who underwent MRI T2-weighted breast DCE-MRI. Between December 2016 and February 2018, all patients should fulfill the criteria: histopathology confirms breast cancer and availability of receptor status, patients over the age of 18 years, without pregnancy, breastfeeding and treatment. Patients with poor DWI images or invisible lesions, non-luminous enhancement, or multiple masses were excluded. If there is no error after the examination in our hospital in the same period, the patient will be regarded as the influence control.

MRI operating parameters

A 1.5T MRI machine (Philips Medical Co., Ltd.) with a four-channel body phased array coil was used. The half-Fourier single-excitation acoustic echo plane imaging was performed in order to obtain DWI. The specific steps were: lying flat, breathing freely, repetition time (TR), = 5000 milliseconds, echo time (TE) = 70 milliseconds, inversion time (TI) = 180 ms; data acquisition times 5 times; echo sequence length = 41, Slice thickness 5 mm; slice gap 1.5 mm; matrix size, 96x96; reconstruction matrix 256x256, b value, 0 and 1000 s/mm^2, acquisition time is 5 min.

MRI evaluation

After obtaining the imaging MRI images and ADC results, data analysis and MRI evaluation was performed, refer to T2WI and fat suppression T2WI maps, and set the circular or oval ROI on the DWI map and ADC map to select the layer with the largest and most uniform lesion signal intensity to detect ADC value. The region of interest (ROI) obtained includes more than 60% of the maximum diameter of the lesion, and includes the center area of the maximum signal intensity as much as possible, avoiding the edge of the lesion and the necrotic area discernible to the naked eye. ADC values were detected 3 times and the average was calculated as the final measurement value.

Histological evaluation

Histopathological results were reviewed by two pathologists with 12 years of experience in our hospital for tumor histology, histological

classification, and immunohistochemical status (Z.B.). IHC status were assessed using standard Ventana XT equipment (Ventana, Tucson, Roche) according to standard operating procedures including ER, PR, HER2, and Ki67. The staining results were assessed based on the current 2018 ASCO/USCAP guidelines. Tumor molecular subtypes were divided into lumen A (ER- or PR-+ and HER-2-), lumen B (ER- or PR-+ and HER-2+), and lumen B (ER -Or PR-+ and HER-2+), HER-2 positive (ER- and PR-+ and HER-2+), triple negative (ER- and PR- and HER-2-). Ki-67 was a high proliferation index when the positive staining is was to or greater than 20%, and a low proliferation index when the positive staining was less than 20%.

Statistical method

SPSS 19.0 software was adopted for analyzing data. Radiological characteristics (minimum value, mean value, and maximum value of ADC values of WTu (whole tumor) and DpTu (darkest part of tumor)) and histopathology (histology uses direct reading of ADC values), IHC receptor (ER, PR, HER2 use double-blind reading) and the Ki-67 state were assessed by Wilcoxon rank sum and U test. ROC assessed ADC values and CRs as differentiating between different types of breast cancer. ADC values were compared using 2 independent sample non-parametric tests. p <0.05 indicates a difference.

Results

Basic characteristics of patients

We collected 262 breast cancer patients from December 2016 to February 2018 in our hospital. Patients aged 33-82 years with an average age of (53.62 ± 9.35) years. Histological results: 144 cases of ductal carcinoma in situ (38.3%), invasive cancers were divided into 118 cases, of which 43 were small tube carcinomas (37.4%), 27 were sieve cancers (23.5%). There were 13 cases of Paget's with invasive carcinomas and 35 cases of other types (because other subtypes accounted for relatively few, they were combined into other types). The maximum diameter of the lesion ranged from 14 mm to 122 mm, with an average of (32 ± 28) mm. The statistics of each subtype were shown in Table 1.

ADC value comparison between histology

Because other types were relatively small and had no analytical value, we selected ductal carcinoma in situ, tubal carcinoma, sieve cancer, and Paget's disease with invasive carcinoma for ADC value. Figures 1a-d showed ductal carcinoma in situ, Tubular, sieve, and Paget's disease with invasive cancer. The comparison of ADC values of different histological types was shown in Figure 2. The ADC value of ductal carcinoma in situ was significantly less than invasive carcinoma (p <0.05). Paget's disease of sexual cancer was also statistically different (p <0.05). The ADC values of ductal carcinoma in situ, tubule cancer, and sieve cancer showed differences between two groups (p <0.05 respectively) without difference in ADC value between tubule cancer, sieve cancer and Paget's disease with invasive cancer (p > 0.05).

ADC value comparison between molecular typing

196 (74.8%) tumors were ER positive, and 66 (25.2%) were negative. There were 178 PR positives (67.9%) and 84 negatives (32.1%). HER-2 was positive in 66 cases (25.2%) and negative in 196 cases (74.8%). Based on Ki-67 status, tumor cell proliferation was high in 150 patients (80.6%) and low proliferation in 36 patients (19.4%). Based on the molecular classification of IHC, 173 (66%) patients were diagnosed with lumen A, 32 (12.2%) lumen B, 10 (3.8%) HER-2, 47 (17.9%) Triple negative breast cancer.

Table Ⅱ summarizes the expressions of IHC receptors and the ADC values of Wtu for Ki-67 status stratification. The maximum WTa ADC (p <0.05) and average WTa ADC (p <0.05) of ER+ tumors were significantly reduced compared to ER- tumors. The maximum WDu ADC value of PR+ tumors were significantly lower than that of PR- (P <0.05). Sensitivity, specificity, and area under the curve for predicting ER and PR status were shown in Table Ⅲ. The maximum WTa of HER-2+ tumors were significantly higher than HER-2- (p <0.05). No correlation of different ADC indicators with proliferation rate was found.

ADC value comparison between different degrees of differentiation

There were 55 cases (20.9%) in the highly differentiated breast cancer group, 73 cases (27.8%) in the moderately differentiated group, and 134 cases (51.4%) in the poorly differentiated group. ADC values showed differences in breast cancer with different differentiation (Figure 3) The comparison between the two groups showed a difference in ADC values between poorly differentiated group and highly differentiated group (p <0.05). A correlation of ADC value with the degree of breast cancer differentiation was found (rs = -0.272, p <0.05), as shown in Figure 4.

Discussion

More and more people recognize the potential

value of DWI in breast cancer diagnosis [14]. DWI is particularly attractive because it requires short time and lacks the need for exogenous contrast agents. It is widely available in most commercial magnetic resonance scanners, and diffusion-weighted MRI (DWI) promises to address conventional clinical breast MRI. Some disadvantages are the application of expanded imaging in breast cancer treatment. DWI reflects the microstructure of the tissue and provides information for breast lesions [15]. Potential benefits under study include improving diagnostic accuracy and guiding treatment decisions.

The correct diagnosis of breast cancer is crucial. The gold standard is still a histological diagnosis, but in many patients with locally advanced disease, misdiagnosis and missed diagnosis due to histology out of reach still exist in clinical practice [16]. Studies have shown that the use of DCE-MRI and DWI combined with ADC-mapped multi-parameter MRI could increase diagnostic accuracy of breast cancer. In addition, DWI was a non-invasive diagnostic method to determine prognosis and predictors of breast cancer [17, 18].

DWI has a high clinical application value in distinguishing benign and malignant breast cancer [19]. However, the correlation of ADC value with breast cancer characteristics has important clinical significance. The results of this study show that ductal carcinoma in situ and tubal carcinoma, sieve carcinoma, and Paget's disease with invasive carcinoma are also statistically different (p <0.05). Paget's disease did not show difference in ADC value (p> 0.05). Therefore, ADC seems to be a distinguishing indicator between ductal carcinoma in situ and invasive carcinoma. In terms of histopathology, ductal carcinoma in situ usually differentiates from inexpensive ductal cells to form cancer cells, which are diffuse or sheet-like, with high cell density and small extracellular space [20], and the diffusion of water molecules in tissues is limited. Therefore, the lesion signal increased significantly on DWI, and the ADC value decreased significantly. Studies have also shown significant differences in ADC values between histological subtypes [21].

Some people have found that HER-2+ cancer has a higher ADC average, but ER and PR status is not related to ADC average. Some studies have observed that the average ADC of ER-positive tumors is low without correlation of ADC with hormone receptor or HER2 status [22]. We found that observed mean ADC values were related to ER status and not to PR, HER2, or Ki-67 proliferation rates. Our study differs from previous studies and we selected histological samples from retrospective samples, and the loss of antigen may be the cause that is different from other studies [23]. The ADC average is the average of the selected ROI. The method of using ROI to cover the entire lesion may show the true ADC value of the heterogeneous lesion more effectively. We found that the maximum WTU was the most useful ADC indicator for predicting and prognosticating QIB. However, further study is required to verify these ADC indicators before they can be used in patient treatment decisions. This study found significant differences of ADC values between highly and poorly differentiated breast cancers. ADC value of poorly differentiated breast cancer is significantly reduced compared to highly and moderately differentiated cancer [24]. Our study selected histological samples from retrospective sources, and the loss of antigen may be the reason why it is different from other studies. In the results of this study, although ADC values did not show difference between the high-, medium-, and low-differentiation groups, as the degree of differentiation decreased, the ADC value tended to gradually decrease, and highly differentiated tumor cells were mitotic. The ADCmean differentiate benign and malignant lesions of the best effect, was at 1.98 / SEC is the best threshold and sensitivity of 84.1%, specificity of 90.2%, positive predictive value was 86.7%, negative predictive value was 88.2% while the current study did not compare the DCE and DWI for breast cancer detection accuracy, can the previous meta-analysis DCE- comprehensive sensitivity and specificity of MRI were 93.2 and 71.1% respectively [25]. Some scholars have shown that ADC might be a differential diagnosis marker for adenosquamous carcinoma in lung cancer. At the same time, it also has certain significance as a factor affecting staging [26]. Based on the results of this study, we will propose a prospective study design to further clarify our research conclusions.

Disclosure of conflict of interest

None.

Conclusion

Our research further expands DWI's ability to be used as an imaging biomarker. ADC values have certain significance in judging the histological type and differentiation degree of breast cancer before surgery, and have obvious advantages in molecular subtypes.

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Table and Figure legends

Table 1. **Basic patient characteristics**

	Ductal carcinoma in situ	Tubular carcinoma	Sieve carcinoma	Paget's disease with invasive carcinoma	Other types	P
Number（n）	144	43	27	13	35	
Age	56.4±16.3	53.8±16.9	54.8±14.3	51.8±15.7	56.6±12.3	>0.05
Tumor diameter (mm)	35.2±23.1	37.5±18.3	34.7±17.5	32.4±15.9	36.9±17.9	>0.05
lymph node metastasis (Yes/No)	87/57	29/14	19/8	9/4	23/12	>0.05
Distant metastasis (Yes/No)	45/99	22/21	12/15	6/7	15/20	>0.05

Table 2. **ADC values between IHC receptors and Ki-67 status stratification.**

ADC s/mm2	ER（+） n=196	ER（-） n=66	p	PR（+） n=178	PR（-） n=84	p	HER-2（+） n=66	HER-2（-） n=196	p	Ki-67(low) n=36	Ki-67(high) n=150	p
DpTu（Max）	2.11 (1.93, 2.32)	2.34 (2.15, 2.60)	<0.05	2.12 (1.93, 2.33)	2.26 (2.08, 2.48)	<0.05	2.33 (2.14, 2.40)	2.13 (1.93, 2.34)	<0.05	2.05 (1.85, 2.15)	2.14 (1.96, 2.38)	＞0.05
DpTu（Min）	0.01 (0.00, 0.32)	0.02 (0.00, 0.41)	＞0.05	0.02 (0.00, 0.33)	0.01 (0.00, 0.36)	＞0.05	0.26 (0, 0.51)	0.00 (0.00, 0.30)	＞0.05	0.11 (0.00, 0.43)	0.00 (0.00, 0.40)	＞0.05
DpTu（Average）	1.03 (0.92, 1.15)	1.13 (0.97, 1.37)	P<0.05	1.03 (0.92, 1.16)	1.10 (0.96, 1.23)	＞0.05	1.11 (1.03, 1.19)	1.04 (0.93, 1.16)	＞0.05	1.08 (0.98, 1.19)	1.05 (0.93, 1.17)	＞0.05

Table 3. **ER, PR sensitivity, specificity, and area under the curve.**

WTu ADC（Max）	Sensitivity	Specificity	AUC
ER	90%	48%	0.73
PR	57%	72%	0.67
WTu ADC （Average）	Sensitivity	Specificity	AUC

ER	93%	25%	0.66

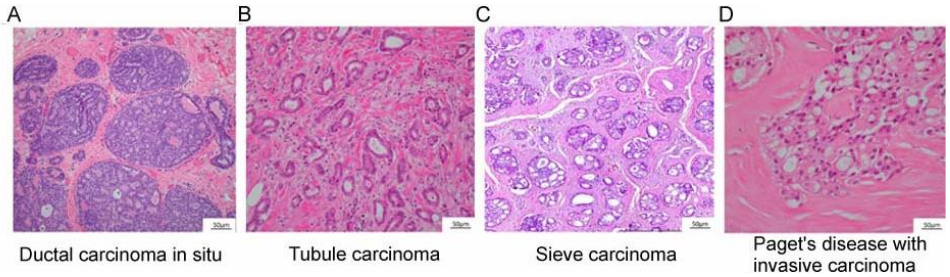


Figure 1. **Different histological types of breast cancer**

Figure a show the morphological results of ductal carcinoma in situ; Figure b shows the morphological results of tubulocarcinoma; Figure c shows the morphological results of sieve carcinoma; Figure d shows the morphological results of Paget's disease with invasive carcinoma.

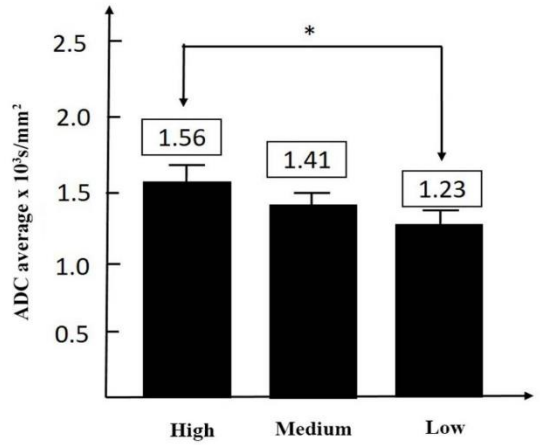


Figure 2. **ADC values for different histological types. The difference in ADC values between ductal carcinoma in situ, tubule carcinoma, and sieve carcinoma was statistically significant (* indicates p <0.05).**

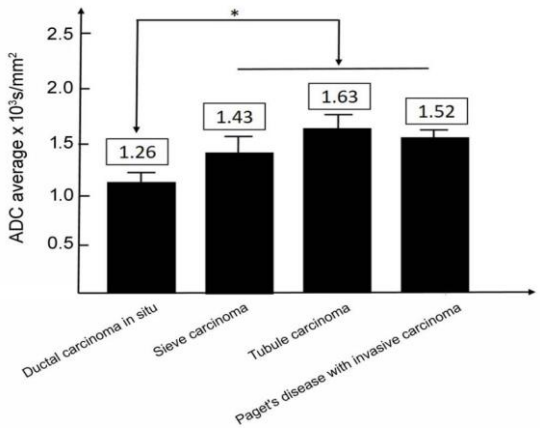
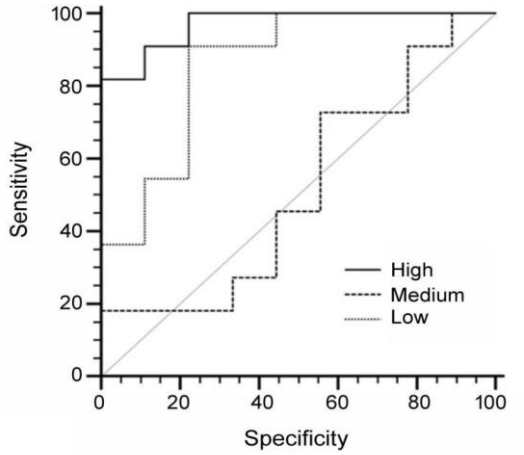


Figure 3. **The difference in ADC values between**



the poorly differentiated and highly differentiated groups was statistically significant (p <0.05).

Figure 4. **Correlation between ADC value and degree of breast cancer differentiation.**