Correlation between Diffusion-Weighted Imaging and Apparent Diffusion Coefficient with Breast Cancer Histopathological Grading

MONA E. MAREY, M.Sc.*; MAHA HELAL, M.D.*; ASHRAF SELIM, M.D.**; IMAN GOUDA, M.D.***; MOHAMED EL-AZAB, M.D.*; TALAAT HASSAAN, M.D.** and RANIA ZEITOUN, M.D.**
The Department of Diagnostic Radiology, National Cancer Institute* & Faculty of Medicine** and The Department of Pathology, National Cancer Institute***, Cairo University, Egypt

Abstract

Purpose: To correlate the Apparent Diffusion Coefficient (ADC) value using Diffusion Weighted Imaging (DWI) with breast cancer histopathological grading.

Material and Methods: 61 patients with histopathologically proved malignant breast lesions from August 2014 till April 2015 were enrolled in this study which undergoing breast MRI. MRI examination included T1 and T2 W sequences, DWI and DCE-MRI. ADC values are correlated with the histological grades.

Results: Histopathological grade revealed that majority of patients 38/61 (76.56%) were GII whereas 8/61 (13%) were GI and 15/61 (24.6%) were GIII. Mean ADC value of all the examined lesions evaluated was $0.6 \times 10^{-3} \text{mm}^2/\text{s}$ (range 0.1-1.1) which was statistically significant higher than normal parenchyma ($1.59 \pm 0.27 \times 10^{-3} \text{mm}^2/\text{s}$) ($p<0.0001$). The mean ADC values of histopathological grade I, II and III were 0.85, 0.66 and 0.4 $\times 10^{-3} \text{mm}^2/\text{s}$ respectively. ADC value of tumours with high grade (III) was significantly lower than ADC value with lower grade (I & II) ($p=0.00278$). There was significant difference in the mean ADC value of tumours of grade I and III ($p=0.00014$) and grade II and III ($p=0.0039$). However, there was no significant difference between grade I and II ($p=0.137$).

Conclusion: Histopathological grade is one of the important factors used in planning and selection of breast cancer treatment. A significant inverse correlation between ADC value and tumor grading was detected.

Key Words: Malignant breast tumors – Diffusion – Apparent diffusion coefficient values – Histopathological grading.

Introduction

BREAST cancer has a variable biological behaviour varying in clinical presentation, morphology, behavior and response to individualized therapy. The tumor morphological and cytological pattern correlates with the degree of malignancy. Therefore the proper identification of the type of breast cancer can improve the selection of proper treatment and determines the patient's outcome [1].

Traditional classification of breast cancer is based on the clinicopathologic analysis of tumors, the pattern of architectural growth (eg, cribriform, papillary) and the nuclear grade (low, intermediate, or high) [2]. Treatment choices were then selected on the basis of tumor size, local invasion, and lymph node involvement or distant metastases, as defined by the American Joint Committee on Cancer’s TNM staging classification. Survival rates correlate best with tumor size and the presence of axillary metastasis; however breast cancer patients at the same stage of disease can have markedly different clinical courses and clinical outcomes. Although this traditional classification remains relevant in clinical practice, it has been enriched in the past 2 decades by developments in the field of molecular biology [3].

Histopathological grading has widely accepted to be powerful indicator of prognosis and providing an overview of the intrinsic biological characteristics of the tumors. Therefore histopathological grade is one of the important factors used in selection and planning of breast cancer [4]. It refers to the semi-quantitative evaluation of morphological...
Correlation between DWI & ADC with Breast Cancer Histopathological Grading

Characteristics and is a relatively simple and low cost method, requiring only adequately prepared hematoxylin-eosin-stained tumor tissue sections to be assessed by an appropriately trained pathologist using a standard protocol [5].

Histopathological grading of the lesions is performed using Nottingham grading system which is the most widely used histologic grading system of breast cancer. NGS is based on the evaluation of three morphological features: (A) Degree of tubule or gland formation (B) Nuclear pleomorphism. (C) Mitotic count. Multiple studies have shown that Nottingham Grading System has prognostic value that is equivalent to that of LN status and greater than that of tumor size [6].

Recent Magnetic Resonance Imaging (MRI) techniques are based on the estimation of morphological and functional parameters that are influenced by tumor biology. As a consequence, there is a growing interest in their application in a disease like breast cancer, where biological heterogeneity affects prognosis and therapeutic decisions [7].

Diffusion Weighted Imaging (DWI) is a non-invasive technique that detects the random motion of water molecules due to thermal energy (Brownian motion). Apparent Diffusion Coefficient (ADC) values are quantified by measurement of mean diffusivity along three orthogonal directions, which are affected by cellularity of the tissue, fluid viscosity, membrane permeability and blood flow [8].

DWI is sensitive to biophysical characteristics of tissue such as cell density, membrane integrity and microstructure. High cell proliferation in malignant tumours increases cellular density, creating more barriers to the extracellular diffusion, resulting in signal loss and reducing the ADC to be lower than that seen in benign breast lesions or normal tissues. So DWI is a useful tool for tumour detection and characterization as well as for monitoring and predicting treatment [9].

The purpose of our study is to correlate the Apparent Diffusion Coefficient (ADC) value of breast cancer with breast cancer histopathological grading.

Material and Methods

61 patients with pathological proven malignant breast lesions, who were performed from August 2014 till April 2015 at National Cancer Institute Cairo University, were enrolled in this prospective study. In all cases, breast cancer was diagnosed using true-cut biopsy performed under sonographic guidance. Informed consent was taken from all patients.

Exclusion criteria were: Patients who had neoadjuvant chemotherapy before MR examination, those with known allergy to the MR contrast medium or impaired renal functions and patients with metallic implants or pace makers.

MRI technique:

Examinations were done using Philips Achieva XR (1.5T). A dedicated eight-channel breast coil was used. The following series were acquired:

1- DWI axial sequence was performed prior to dynamic images [TR=5150, TE=min, frequency-phase 96 X 96, matrix 96 X 96, thickness=4mm, 0 interval, FOV=32-34cm, NEX=6]. Sensitizing diffusion gradients were applied sequentially in the x-, y-, and z-directions with p-values of 0, 750 and 1000s/mm².

2- The dynamic imaging consisted of 6 individual dynamic series one obtained before and five after rapid bolus intravenous injection of gadopentetate dimeglumine at a dose of 0.1mmol per kilogram of body weight, followed by a 20mL saline solution flush. After the dynamic series, image subtraction was done to suppress the signal from fat, and enhancing lesions were clearly identified on the subtracted images.

3- Axial T₂WI images were obtained with the following parameters: TR, 4845.3ms; TE, 120 ms; NEX, 1; flip angle, 90; FOV: 355.6 X 355.6mm; slice thickness, 4.0mm; and slice interval, 2.0mm (slice overlap, 2.0mm).

MRI interpretation:

Mammographic study was assessed prior to MRI interpretation. Data analysis and interpretation were performed on Philips Extended MR Work Space Explore Release (EWS) workstation. Dynamic thrive were obtained for contrast enhanced images (CE-FS) T₁WI. The parameters were as follows: TR, 7ms; TE, 3.4ms; NEX, 1; flip angle, 10 ; FOV: 340 X 340mm; slice thickness, 2.4mm. We assessed DWI series at b-values 0, 50 and 850 in which findings were either: Restricted diffusion (positive) or facilitated diffusion (negative, or no abnormality detected). To evaluate lesion detectability on DW images, we identified the lesions on images with b-values of 0 and 850sec/mm² by identifying areas of signal intensity higher than that of normal breast parenchyma, and detectability was scored in consensus by using a three-point scale (1=slight, 2=moderate, and 3=excellent) [10].
The visualized lesion in the dynamic scan has to be identified in the corresponding slice of the diffusion weighted images 60 and 850 then a Region of Interest (ROI) is drawn on the lesion (cystic and necrotic areas were avoided). The scanner software provides the mean value within the ROI.

**Histopathological analysis:**

Histopathological grading was analyzed by a pathologist with experience in the breast pathology.

<table>
<thead>
<tr>
<th>Grading breast cancers</th>
<th>Grading breast cancers</th>
<th>Grading breast cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tubule formation:</strong></td>
<td><strong>Mitotic count:</strong></td>
<td><strong>Nuclear pleomorphism:</strong></td>
</tr>
<tr>
<td>- Majority of tumor (&gt;75%) 1</td>
<td>- 0-9 mitoses/10 hpf 1</td>
<td>- Small regular uniform cells 1</td>
</tr>
<tr>
<td>- Moderate degree (10-75%) 2</td>
<td>- 10-19 mitoses/10 hpf 2</td>
<td>- Moderate nuclear size and variation 2</td>
</tr>
<tr>
<td>- Little or none (&lt;10%) 3</td>
<td>- 20 or &gt;mitoses/10 hpf 3</td>
<td>- Marked nuclear variation 3</td>
</tr>
</tbody>
</table>

**Compined histologic grade:**
- Low grade (I) ³ 5
- Intermediate grade (II) 6-7
- High grade (III) 8-9

**Statistical analysis:**

Data were statistically described in terms frequencies (number of cases) and percentages when appropriate. Description of quantitative variables as mean, median and range were used otherwise for qualitative variables number and percentage were used. Our patients were divided into three groups according to the histological grading; grade I, II and III. The mean of the ADC for all lesions and for each histological grade were calculated. One way analysis of variants (ANOVA) and post-Hoc (lsd) analysis were used to test the difference in ADC means between the different histological grades. Comparison between the study groups was done using McNemar test. Agreement was tested using kappa statistic. \(p\)-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) Version 15 for Microsoft Windows.

**Results**

A total of 61 pathologically proven breast cancer patients were initially enrolled and underwent MRI (age range 29-67 years; mean 47 years).

Histopathological analysis revealed most of cases were invasive ductal carcinomas 47/61 (77%), 6 ductal carcinomas in situ (9.8%), 8 invasive lobular carcinomas (13%).

Histopathological grade revealed majority of patients 38/61 (76.56%) were G2 while 8/61 (13%) were G1 and 15/61 (24.6%) were G3.

**DW MRI and ADC assessment:**

1- Visual assessment: ALL malignant lesions (100%) appear as hyperintense signal in DWI (restricted diffusion). Lesion detectability on DW images, we compare signal intensity of lesions on images with \(b\)-values of 0 and 850sec/mm\(^2\) with signal of normal breast parenchyma by using a three-point scale (1=slight, 2=moderate, and 3=excellent) [10]. Of 61 breast cancers, 97.4% were visible as high signal intensity masses on DWI with a score of 2 or more. On DWI, however, detectability was not significantly different among tumour histopathological grading \((p=0.911)\), although the detection score at DWI of grade 3 was higher.

2- Quantitative analysis: Mean ADC value of all the examined lesions evaluated was 0.6 X 10\(^{-3}\) mm\(^2\)/s (range 0.1-1.1).

A statistically significant difference in the mean ADC values of breast cancer (0.6 X 10\(^{-3}\)mm\(^2\)/s) and normal parenchyma (1.59±0.27 X 10\(^{-3}\)mm\(^2\)/s) was detected \((p<0.0001)\).
Correlation between ADC and histopathological grading:

Mean ADC value of IDC (0.62 X 10\(^{-3}\) mm\(^2\)/s) was significantly lower than that of DCIS (0.72 X 10\(^{-3}\) mm\(^2\)/s), \(p=0.00127\). Mean ADC value of IDC (0.62 X 10\(^{-3}\) mm\(^2\)/s) was insignificantly higher than that of ILC (0.58 X 10\(^{-3}\) mm\(^2\)/s), \(p=0.131\).

The mean ADC value of grade I was 0.85 X 10\(^{-3}\) mm\(^2\)/s, of grade II was 0.66 X 10\(^{-3}\) mm\(^2\)/s and of grade III was 0.4 X 10\(^{-3}\) mm\(^2\)/s. ADC value of tumours with high grade (III) was significantly lower than ADC value with lower grade (I & II) \(p=0.00278\). There was significant difference in the mean ADC value of tumours of grade I and III \(p=0.00014\) and grade II and III \(p=0.0039\), however, there was no significant difference between grade I and II \(p=0.137\).

Illustrated cases:

Case 1:

Fig. (2): 76 years old female patient with left breast lump. (A) Dynamic MRI shows speculated enhancing LIQ breast lesion. (B) DWI \((b=0, 350, 850)\) shows restricted diffusion at LT LIQ lesion, while there are two benign looking lesions seen at outer quadrant showing T2 shin through effect. (C) ADC value of LIQ lesion range from 0.95 X 10\(^{-3}\) mm\(^2\)/s. Histopathology the tumor was proved to be invasive ductal carcinoma grade II.
Case 2:

Fig. (3): 40yrs. old female presented with Lt breast mass. (A) Post contrast dynamic T1 MRI WI shows left breast spiculated heterogeneous enhancing lesion. (B) ADC value of the mass = $1.1 \times 10^{-3}$ mm$^2$/s. Histopathology tumor were invasive ductal carcinoma histological grade I.

Case 3:

Fig. (4): 54 years old female presented with Lt breast lump. (A) CE MRI showed UOQ speculated heterogeneous mass with deep linear extension towards the chest wall. (B) ADC value range 0.72-0.82 X $10^{-3}$ mm$^2$/s. Histopathology of tumour proved to be invasive ductal carcinoma histological grade 3.

Discussion

Breast cancer has a variable biological behaviour moreover the morphological and cytological pattern of the tumour correlates with the degree of malignancy. The proper identification of the type and grading of breast cancer can improve the selection of proper treatment and defines the patient's outcome. The histological type, the tumour stage and breast biomarkers are indices for the degree of malignancy of the breast cancer [6]. DWI can provide information about the tumour biology and physiology therefore differentiates benign from malignant tumours with progressive decrease in ADC value from benign lesions to non-invasive and invasive carcinoma [11]. The ADC is a quantifiable value that provides a measurement of signal attenuation and is affected by microscopic motion, including molecular diffusion of water and blood microcirculation in the capillary network. Water diffusion is greatly influenced by factors such as cellularity, fluid viscosity, intra-and extracellular membrane permeability, active transport, flow and structural directionality [12].

Because of the heterogeneity of breast cancer, we were interested in studying whether the ADC measured by DWI could vary according to histopathological grading. In our study by visual assessment at DWI ALL malignant lesions (100%) appeared as hyperintense signal (restricted).

Lesion detectability on DW images, signal intensity of lesions on images with $b$-values of 0 and 850sec/mm$^2$ had been compared with signal of normal breast parenchyma by using a three-
point scale (1=slight, 2=moderate, and 3=excellent). Lesion detectability was not significantly different among tumour histopathological grading ($p=0.244$).

This result is similar to the findings of Youk et al., 2012 who showed that detectability by means of visual assessment was not significantly different among tumor subtypes ($p=0.911$) [10].

In our study we found mean ADC value of all the examined lesions evaluated was $0.6 \times 10^{-3} \text{mm}^2/\text{s}$ (range 0.1-1.1) which was statistically significant higher than normal parenchyma ($1.59 \pm 0.27 \times 10^{-3} \text{mm}^2/\text{s}$ ($p<0.0001$).

In agreement with the previous studies done by Woodhams et al., 2005, Guo et al., 2002 and Hatakenaka et al., 2008 where the cut off value of ADC for diagnosing breast cancer ranged from $1.13 \times 10^{-3} \text{mm}^2/\text{s}$ to $1.6 \times 10^{-3} \text{mm}^2/\text{s}$, all our ADC values did not exceed the cut off value that differentiates benign and malignant breast lesions in these studies [8,13,14].

In our study; the mean ADC values of histopathological grade I, II and III were 0.85, 0.66 and $0.5 \times 10^{-3} \text{mm}^2/\text{s}$ respectively. ADC value of tumours with high grade (III) was significantly lower than ADC value with lower grade (I & II) ($p=0.00278$).

In study of Gouhar et al., 2011 done on 31 patients, they reported that the mean ADC value of the malignant lesions was $0.85 \pm 0.12 \times 10^{-3} \text{mm}^2/\text{s}$ (range 0.51-1.11 $\times 10^{-3} \text{mm}^2/\text{s}$). The mean ADC value of grade I was $0.96 \pm 0.12 \times 10^{-3} \text{mm}^2/\text{s}$, of grade II was $0.87 \pm 0.07 \times 10^{-3} \text{mm}^2/\text{s}$ and of grade III was $0.75 \pm 0.12 \times 10^{-3} \text{mm}^2/\text{s}$ [6].

There was significant difference in the mean ADC value of tumours of grade I and III ($p=0.00014$) and grade II and III ($p=0.039$). However, there was no significant difference between grade I and II ($p=0.137$).

This is consistent with Gouhar et al., 2011 who reported that tumours with higher grade showed significantly lower ADC value ($p=0.0001$) compared with lower grade. There was significant difference in the ADC value of tumours of grade I and III ($p=0.0001$) and grade II and III ($p=0.003$) but there was no significant difference between grade I and II ($p=0.054$) [6].

This is also in agreement with Abdel Razek et al., 2010 who reported that there was a significant difference between grade I and III and grade II and III and insignificant difference between grade I and II. There was an inverse correlation between ADC value and histological grade ($p$-value=0.0001) in this study [15].

However Uematsu et al., 2011 reported mean apparent diffusion coefficient value was $1.067 \times 10^{-3} \text{mm}^2/\text{s}$ for grade I cancers, $1.021 \times 10^{-3} \text{mm}^2/\text{s}$ for grade II cancers and $1.041 \times 10^{-3} \text{mm}^2/\text{s}$ for grade III cancers. Although the apparent diffusion coefficient value was lower for grade II than for grade I tumors, the differences were not statistically significant [16]. Also Yoshikawa et al., 2008 and Choi et al., 2011 found that the mean ADC of breast cancer did not significantly correlate with histological grade [2,17].

**Limitations:**

1- Variable histological types which may influence the significance of the results.

2- It was difficult to exactly match a histologic specimen with the ROIs selected on DWI.

3- Tiny areas of necrosis which not apparent by DCE MR Images may interfere with the ADC value.

**Conclusion:**

DWI represented by mean ADC values exhibited significant correlation with the histological grade of the breast cancer which plays an important role in the treatment selection and patient outcome.

**Conflict of interest:**
The authors declare that there is no conflict of interest.

**References**


6- GOUHAR G.K., EL-HARIRI A.M.A. and LOTFY W.: Malignant breast tumours: Correlation of apparent diffusion coefficient values using diffusion-weighted images
العلاقة بين الرنين المغناطيسي بقياس خاصية الإنتشار مع تصنيف الأنسجة لسرطان الثدي

سرطان الثدي هو أكثر أنواع السرطان شيوعا لدى النساء وهو السبب الثاني الأكثر شيوعا لوفاة من السرطان بين النساء، معظم الحالات تكون قابلة للشفاء وهذا يعتمد بصورة كبيرة على الإكتشاف المبكر. تستند التقنيات الحديثة في التصوير بالرنين المغناطيسي (MRI) إلى تقييم الخصائص البيولوجية والوظيفية للورم. ونتيجة لذلك، هناك إهتمام متزايد في تطبيقها في مرض مثل سرطان الثدي، حيث يؤثر على التصنيف البيولوجي على التشخيص وبالتالي على قرارات العلاج.

وكان الهدف من هذا العمل أن ندج الرابط بين الرنين المغناطيسي بخصائص الإنتشار مع الخصائص وتقييم الأنسجة سرطان الثدي. تستخدم في اختيار قرارات العلاج تتم الدراسة بمعهد الأورام، جامعة القاهرة. السحب 11 مريضة. تصنيف الأنسجة سرطان الثدي (ADC) يقسم إلى ثلاثة درجات. وجدت علاقة عكسية بين قيم معدل الإنتشار (ADC) وتصنيف الأنسجة لسرطان الثدي.