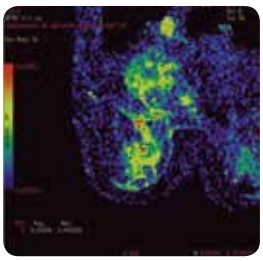

# Analyse Diffusion Sequence in Magnetic Resonance and Apparent Diffusion Coefficient Values in Breast Cancer According to Molecular Subtypes and Histological Parameters of Aggressiveness Between December 2010-December 2016

## Análisis secuencia de difusión en resonancia magnética y coeficiente de difusión aparente en cáncer de mama según subtipos moleculares y parámetros histológicos de agresividad durante periodo 2010-2016

Key words (MeSH)

Breast neoplasms
Diffusion
Magnetic resonance imaging

Palabras clave (DeCS)

Neoplasias de la mama
Difusión
Imagen por resonancia magnética

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## Summary

*Objective*: To analyse diffusion sequence in magnetic resonance (MRI) and apparent diffusion coefficient (ADC) values in breast cancer according to molecular subtypes and histological parameters of aggressiveness in patients who attended the Clinical Center of Stereotaxy (CECLINES), Caracas-Venezuela between December 2010 - December 2016. *Patients and methods*: A retrospective, observational, descriptive and cross-sectional study including 152 patients with an average age of 56 years who met inclusion criteria: female gender, any age group with primary breast cancer diagnosis by percutaneous biopsy, intra-institutional immunohistochemical and anatomical pathology information, MRI results describing diffusion sequence (values b 0 and 1000) and ADC value. *Results*: The diffusion behavior by means of MRI and ADC values did not show significant differences when studying them by histologic grade, molecular subtype or hormone receptor-positivity or negativity. Statistically significant differences were found between ADC values in lesions with Ki-67 ≤14% of 0.808 mm² /s and lesions with Ki-67> 14% of 0.762 mm² /s. The cut-off point for tumor ADC of 0.78 mm² /s showed a statistically significant proportion between groups according to proliferation index in which Ki-67> 14% was more associated with tumor ADC values ≤0.78 mm² /s and Ki -67 ≤14% with tumor ADC values > 0.78 mm² /s. *Conclusions:* ADC values and diffusion behavior do not allow to differentiate lesions on resonance by molecular subtypes, nor to identify histologic tumor grade or hormone receptor status; however, low ADC values correlate adequately with high Ki67 index.

## Resumen

*Objetivo*: Analizar la secuencia de difusión en resonancia magnética (RM) y los valores del coeficiente de difusión aparente (ADC) en cáncer de mama según subtipos moleculares y parámetros histológicos de agresividad en pacientes que acudieron al Centro Clínico de Estereotáxia (CECLINES), Caracas, Venezuela, durante el período diciembre de 2010-diciembre de 2016. *Pacientes y métodos*: Estudio retrospectivo, observacional, descriptivo

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y transversal con muestra de 152 pacientes, edad promedio 56 años, que cumplieron criterios de inclusión: género femenino, cualquier edad con diagnóstico de cáncer de mama primario realizado por biopsia percutánea, información inmunohistoquímica y anatomía patológica intrainstitucional, resultados de RM con descripción de la secuencia de difusión (valores b 0 y 1000) y valor ADC. *Resultados*: El comportamiento de la difusión mediante RM y valores ADC no mostró diferencias significativas al estudiarlos por grado histológico, subtipo molecular ni positividad o negatividad de receptores hormonales. Se observaron diferencias estadísticamente significativas entre valores ADC en lesiones con Ki-67 ≤ 14 % de 0,808 mm²/seg y lesiones con Ki-67 > 14 % de 0,762 mm²/seg. El punto de corte para ADC-tumoral 0,78 mm²/seg mostró una proporción estadísticamente significativa entre los grupos según índice de proliferación, en el que Ki-67 > 14 % se asoció más a valores ADC-tumoral ≤ 0,78 mm²/seg y Ki-67 ≤14 % a valores ADC-tumoral > 0,78 mm²/seg. *Conclusiones*: Valores ADC y comportamiento de difusión no permiten diferenciar lesiones en resonancia por subtipos moleculares, identificar grado histológico tumoral ni estatus de receptores hormonales; sin embargo, bajos valores de ADC se correlacionan adecuadamente con alto índice de Ki-67.

## Introduction

Breast cancer (BC) is the most common female cancer in the world. Projections indicate that the number of women diagnosed with BC in the Americas will increase by 46 % by 2030 (1). In Venezuela, it represents the leading cause of oncological death (15.6%) among the female population since 2010, with 5,063 cases and 2,067 deaths (2).

BC is a heterogeneous disease, with very diverse biological and clinical behaviour, which evolves and responds differently to treatment (3).

There are a series of parameters determined as prognostic indicators of BC: those based on the histopathological characteristics (size of the tumor, local extension, histological type and grade and lymph nodes), which often do not reflect the evolution of the disease, as a consequence of its molecular characteristics (3). And the immunohistochemical parameters, based on the expression of hormone receptors -estrogenic (ER), progesterone (PR), human epidermal growth factor type 2 (HER2/neu) - and the Ki-67 tumor proliferation rate (reflecting the tumor's proliferative capacity and the significant correlation with high mitotic count); there is a clear association between the BC subtype and the patient's evolution (3-5).

Molecular classification is based on DNA microarray techniques. Due to the complexity of these techniques, there is a tendency to approximate the gene study based on a limited number of immunohistochemical markers (IHQ), so that BC can be classified into subrogate subtypes, equivalent to those based on gene expression profiles (5).

The different molecular subtypes have specific epidemiological risk factors (6), disease progression and response to different treatments that differ among them. This variability implies different clinical management depending on the subtype of BC, which requires parallel diagnostic imaging follow-up (7-9).

Magnetic resonance imaging (MRI) provides additional information in the assessment of the characteristics of BC, due to its ability to evaluate morphological, kinetic and biological aspects thanks to the use of contrast dye, as well as the application of sequences, such as diffusion, which provide new data and allow a better approach to the biological behaviour of tumours (3,4,10-11).

The Diffusion Weighted Image (DWI) technique analyzes the Brownian movement of water molecules that may be restricted in certain pathologic conditions, such as tumors and ischemia; the signal strength in diffusion-weighted images is inversely proportional to the degree of diffusion of water molecules, which will be influenced by the histologic structure; in other words, the signal strength will involve the histologic structure (12).

Diffusion is quantified by the apparent diffusion coefficient (ADC) value, expressed in square millimeters per second, which defines the average area covered by a water molecule per unit of time; this reflects the biological characteristics of the tumor by providing information about the tissues (hypercellularity, increased vascularization, tumor matrix, etc.). The ADC value can be calculated by evaluating the signal attenuation that occurs in diffusion-weighted images made with different values of b (12).

The use of diffusion in breast tumors reveals increased restriction as a function of tissue cellularity and cell membrane integrity, evidencing lower ADC values for breast cancer compared to normal breast tissue or benign tumors (13).

The purpose of this study was to analyze the diffusion sequence (b 0-1000) in MR and apparent diffusion coefficient (ADC) values in primary breast cancer, according to subtypes subrogates and histological parameters of prognostic value, in patients who attended the institution between December 2010 and December 2016.

## Materials and methods

A retrospective, observational, descriptive and cross-sectional study was conducted between December 2010 and December 2016. 450 patients with histological diagnosis of primary BC were given extension MRIs, 7 patients were excluded (no immunohistochemistry and pathological anatomy, no neoadjuvant chemotherapy treatment, diagnosis of ductal carcinoma in situ, recurrent BC or tumor recurrence, no report of MRI, male gender with BC, lesion completely removed by biopsy method).

The study sample is made up of 152 patients (average age 56 years old with standard deviation of 11.16 years, minimum age was 29 and maximum 81 years), after meeting the inclusion criteria: female sex, any age with a diagnosis of primary BC made by percutaneous biopsy without neoadjuvant treatment, histology report -including immunohistochemistry and pathological anatomy-, MRI with diffusion sequence and ADC map.

The carcinomas were classified according to their morphology, with hematoxylin-eosine by conventional optic microscopy, with the Nottingham grading system (Scarff-Bloom-Richardson scale modified by Elston-Ellis) for BC and according to the recommendations of the World Health Organization (14,15); tumor size and axillary status were also evaluated.

According to current ASCO/CAP guidelines, tumours with 1 % or more of marked tumour cells are considered positive and those with less than 1 % of marked tumour cells are considered positive; this procedure was performed within the institution where the research was conducted. Immunohistochemical analysis of the lesions assessed the hormone receptors estrogen (ER) and progesterone (PR) positive and negative; HER2 receptor (positive and negative) and KI67 (greater and lesser than 14); data collected by the group of doctors specialized in breast pathology, with experience between 5 and 30 years (16,17).

The MRI images were taken on a GE Signa Excite HD 1.5 T, Echo Speed Plus Gradient 33/120, using a dedicated HD Breast coil with 8 channels. The sequences used were T1 and STIR axial, T2 with sagittal fat removal and VIBRANT axial. Prior to the intravenous administration of contrast medium, the SE-EPI diffusion sequence was taken, with 10 axial cuts of 5 mm, spacing 0, FOV 36 × 36 cm, matrix 160 × 192, NEX 1, rBW 250 KHz, TR 1800 ms, TE 93.8 ms, fixed for all values of b of 0 and 1000 mm²/s, with a total time of 3 minutes and 52 seconds.

All the images were analyzed by a radiologist, a mastology specialist for over 25 years, on a GE volume share 5 workstation. In the post-processing of the images, the morphological and functional evaluation was carried out using multiplanar maximum signal strength (MIP) reconstructions. The maximum diameters of the tumor in the three planes, the characterization of internal lesion enhancement (heterogeneous/homogeneous) and type of lesion (mass/non-mass) were evaluated. Subsequently, the kinetic curves for signal strength/time ratio acquisition, classification of the curve type I (progressive enhancement), type II (plateau), type III (washing) were analysed. Black/white ADC maps were executed, varying from white (diffusion restriction) to black (no diffusion restriction).

Visual inspection of the signal and calculation of the ADC was performed using Functool(R) for the values of b 0 and 1000 mm²/sec, following the placement of three similar ROIs in the median lesion and one ROI in the glandular parenchyma and fat tissue with a size interval between 20 and 35 mm2. The ADC value of each lesion was correlated with imaging findings and with histopathological and immunohistochemical diagnosis.

## Statistical analysis

Data analysis was performed using the SPSS statistical package version 23, using descriptive statistics with tables, graphs, mean, standard deviation, absolute and relative values; inferential statistics with the homogeneity test of $\chi$ for qualitative variables, and the nonparametric U tests of MannWhitney and Kruskal-Wallis to compare the mean of the apparent diffusion coefficient (ADC); significance was established for statistical tests if $p < 0.005$.

## Results

The most common histologic type of BC was infiltrating ductal carcinoma (IDC) with 74.34%, and infiltrating lobular carcinoma (ILC) with 9.21%.

Of all tumour lesions, histological grade 1 was found at 27.73%, grade 2 at 52.10% and grade 3 at 20.17%.

In immunohistochemical analysis, the frequency of positive NoEs was 69,74 % and negative 30,26 %; positive RPs 65,13 % and negative 34,87 %; positive HER2 receptors 9,87 % and negative 90,13 %.

The tumour proliferation rate (Ki-67) ≤ 14% was found in 30.26% of lesions and >14% in 69.74%. In the classification by molecular subtypes it was observed that the most frequent was luminal B 45.39 %, followed by luminal A 25.00 %, triple negative 22.37 % and HER2+ 7.24 %.

The average ADC of tumor lesions was 0.776 mm²/sec, which is significantly different, with p (0.000), from healthy fat tissue averaging 0.318 mm²/sec and healthy breast tissue averaging 1.340 mm²/sec.

No significant differences were observed in the comparison of MR diffusion behaviour by molecular subtype; however, it is important to note its results in a descriptive manner: for high signal diffusion (restriction) the proportions were 100 % for HER2+, 97,10 % luminal B, 94,12 % triple negative and 86,84 % luminal A; for low signal diffusion (non-restrictive) the proportions by molecular subtype were 13,13 % luminal A, 5,88 % triple negative, 2,90 % luminal B and no cases were observed in HER2+.

The diffusion behavior and ADC showed no significant difference when compared by tumor histologic grade; however, ADC averages were 0.788 mm²/sec for grade 1; 0.771 mm²/sec grade 2 and 0.766 mm²/sec grade 3 (Table 1).

**Table 1. MRI Comparison of CDA by Histologic Grade in Breast Cancer Patients**

| Histological grade | ADC-Tumour (mm²/sec) | *p* |
|---|---|---|
| | Average (DE) | |
| 1 | 0,788 (0,153) | 0,702 |
| 2 | 0,771 (0,149) | |
| 3 | 0,766 (0,135) | |

Note: Based on the Kruskal-Wallis Test. Tumor ADC values do not vary significantly when compared between different histologic grades.
Source: Prepared by the authors.

When comparing ADC by molecular subtype and hormone receptors, no significant differences were observed (Tables 2 and 3).

**Table 2. Comparison of ADC using MRI by molecular subtype in breast cancer patients**

| Molecular subtype | ADC-Tumour (mm²/sec) | p |
|---|---|---|
| | Average (DE) | |
| Luminal A | 0,784 (0,148) | 0,617 |
| Luminal B | 0,782 (0,125) | |
| Triple negative | 0,749 (0,173) | |
| HER2+ | 0,794 (0,132) | |

Nota: Basada en la Prueba de Kruskal-Wallis. Al comparar el ADC por subtipo molecular no se observaron diferencias significativas.
Fuente: Elaboración propia.

**Table 3. Comparison of ADC by MRI according to hormone receptors in breast cancer patients**

| Receptors | ADC-Tumour (mm²/sec) | p |
|---|---|---|
| | Average (DE) | |
| *Estrogens* | | |
| Positive | 0,783 (0,133) | 0,266 |
| Negative | 0,759 (0,162) | |
| *Progesterone* | | |
| Positive | 0,778 (0,134) | 0,700 |
| Negative | 0,772 (0,158) | |
| *HER2* | | |
| Positive | 0,794 (0,117) | 0,820 |
| Negative | 0,774 (0,145) | |

Note: Based on the Mann-Whitney Test. When comparing ADC in estrogen receptors, progesterone and HER2, no significant differences were observed.
Source: Prepared by the authors.

When comparing the ADC of the tumoral lesion between the groups of patients with Ki-67 ≤ 14% and > 14% were observed significant differences with p (0.027): the patients with Ki-67 ≤ 14% had an average of 0.808 mm²/sec, higher than that found in the patients with Ki-67 > 14% of 0.762 mm²/sec (Table 4).

**Table 4. Comparison of ADC by MRI according to Ki-67 in breast cancer patients**

| Ki-67 | ADC-Tumour (mm²/sec) | U de Mann-Whitney | p |
|---|---|---|---|
| | Average (DE) | | |
| ≤ 14 % | 0,808 (0,140) | 1.744,50 | 0,027* |
| > 14 % | 0,762 (0,142) | | |

Note: Based on the Mann-Whitney Test; *significant differences in mean p<0.05. When comparing the ADC of the tumor lesion between the groups of patients with Ki-67 ≤% and >14%, statistically significant differences were observed, demonstrating an inverse proportional relationship: the lower the rate of cell proliferation, the higher the ADC value.
Source: Prepared by the authors.

The previous result allowed to find a cut-off point for the tumor ADC with the median at 0.78 mm²/sec, and then to compare the proportions of this cut-off point between the tumor groups with Ki-67 ≤ 14 % and > 14 %. The results obtained showed significant differences with p (0.016) in the proportion of the tumoral ADC when compared to the Ki-67 groups, in which the tumoral ADC ≤ 0.78 mm²/sec were found proportions of 38.64 % for the Ki67 group ≤ 14 % and 60.19 % for the Ki-67 group > 14 %; for the tumoral ADC > 0.78 mm²/sec the proportions were 61.37 % for Ki-67 ≤ 14 % and 39.81 % for Ki-67 > 14 % (Table 5).

**Table 5. Relationship of the ADC cut-off point using MRI and Ki-67 in breast cancer patients**

| Tumour ADC (mm²/seg) | Ki-67 | | p |
|---|---|---|---|
| | ≤ 14 % | > 14 % | |
| | *n* ( %) | *n* ( %) | |
| ≤ 0,78 | 17 (38,64 %) | 62 (60,19 %) | 0,016* |
| > 0,78 | 27 (61,37 %) | 41 (39,81 %) | |

Note: Based on the statistical homogeneity test χ, Fisher's exact statistic; *significant differences in the ratio p < 0.05. After defining a cut-off point for tumour ADC of 0.78 mm²/sec, lesions with Ki-67 ≤ 14% were more frequently located above this cut-off point, with a statistically significant difference when compared to the group of lesions Ki-67 > 14%.
Source: Prepared by the authors.

## Discussion

Significant differences were found between ADC values of tumoral, fatty and healthy parenchyma tissue; this data reflects the usefulness of this value to differentiate benign from malignant lesions, similar to what is presented in the literature (3,18).

The behaviour of diffusion lesions and the ADC values shown between the different histological types of BC and molecular subtypes showed no statistically significant differences, not in accordance with what was published by Bo Bae Cho et al, who showed lower ADC values in the histological type ILC when compared with the rest (18-21).

No significant differences were obtained between ADC and tumor histologic grade in correlation to that expressed by Prieto Sánchez et al., but contrary to that demonstrated by Razek et al (3,22).

When analyzing ADC values among the different tumor receptors, no significant differences were found; however, as in other publications, when detailing them individually, it was evident that the positive HER2 type was discreetly larger than the rest. Unlike other authors: the ADC value in triple negative was the lowest of all (18,23-25).

When ERs, PRs and HERs2 were positive, ADC values were discreetly higher than when they were negative; however, this difference was not statistically significant, as demonstrated by Martincich et al and Choy et al, who showed a low ADC value in ERs and PRs positive by a significant margin (23,25).

The ADC value was significantly higher when the Ki-67 was ≤ 14% (Figure 1); and lower in tumors that presented a Ki-67 > 14% (Figure 2), as published by Choi et al. and Choi and Choi et al. (19,25); although the values of the tumour proliferation index in these publications were different from those used in this analysis.

This result allowed to find a cut-off point for the tumour ADC (0.78

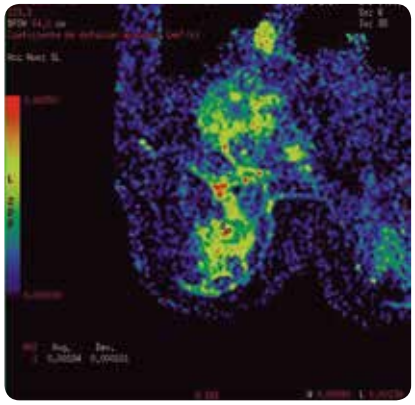

Figure 1. 59 year old IDC patient with 4 % Ki67 and ADC 1.8 mm2/sec.

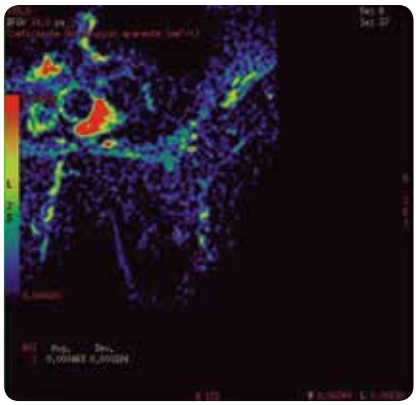

Figure 2. 55 year old IDC patient with 80% Ki-67 and ADC 0.463 mm2/sec.

× 10-3 mm²/sec); demonstrating with a statistically significant difference, that for a tumour ADC ≤ 0.78 more than 60 % of the tumours had a Ki-67 index > 14 % and for tumour ADC > 0.78 mm²/sec the highest proportion was for Ki-67 ≤ 14 %. Data not found in the literature reviewed.

Thus, it is concluded that the low ADC value can be correlated with high Ki-67 levels; however, no values of this coefficient were found that could by themselves provide MRI with the ability to classify tumor lesions by molecular subtype, histologic grade, hormone receptors, or HER2 positivity.

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