RESEARCH ARTICLE

Diffusion weighted MRI and spectroscopy in invasive carcinoma of the breast at 3Tesla. Correlation with dynamic contrast enhancement and pathologic findings.

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Abstract

Background: The most common histological types of invasive breast carcinomas are the invasive ductal carcinoma (IDC) and the invasive lobular carcinoma (ILC). The purpose of our study was to evaluate the role of the diffusion-weighted imaging (DWI) and the in vivo proton magnetic resonance spectroscopy (^{1}H-MRS) at 3 Tesla magnet in invasive breast cancer and correlate them with the dynamic contrast enhancement (DCE) and pathologic findings.

Methods: We retrospectively studied at 3Tesla magnet the apparent diffusion coefficient (ADC) values, the detection of choline in the ^{1}H-MRS and the kinetic analyses obtained after DCE in 181 patients with histologically confirmed invasive breast carcinomas. Among these patients, 160 had IDC and 21 ILC. We used the DWI sequence with a b value of 1,000 mm²/sec for the calculation of the ADC value, the fat-suppressed point-resolved spectroscopy (PRESS) sequence in order to evaluate the existence of a choline peak in the spectrum and the T_1W GRE FAT SAT VIBRANT sequence for the characterization of the kinetic curves. Finally, we correlated the pathologic type of invasive cancer, as well as the type of the kinetic curve with the ADC value and the detectability of choline resonance in the spectrum in each of the 181 patients.

Results: The ADC values in the 158 out of 160 IDC patients, ranged from 0.5×10^{-3} to 1.2×10^{-3} mm²/sec, with 78.1 % having ADC value of 1×10^{-3} mm²/sec. Regarding the ^{1}H-MRS, in 121 out of 160 IDC patients, choline was found in 72.3 %. The ADC values in the 21 ILC patients also ranged from 0.5×10^{-3} to 1.2×10^{-3} mm²/sec with 57.1 % having ADC value of 1×10^{-3} mm²/sec. Regarding the ^{1}H-MRS, in 10 out of 21 ILC patients, detection of choline was positive in 60 % of them.

In the 21 ILC patients, the kinetic analysis after the dynamic administration of contrast medium showed type I (persistent) curve in 4.3 %, type II (plateau) curve in 33.3 % and type III (washout) in 52.4 %. In the 158 IDC patients (missing in two cases) type I curve was obtained in 0.63 %, type II in 19.4 % and type III in 80 %.

From the correlation analysis of the IDC results using Kruskal-Wallis Test and the non-parametric Kendall's tau-b test, the curve type was positively associated (Kendal tau-b: 0.254, p =0.005) with the presence of choline, while the ADC value was negatively associated (Kendal tau-b: -0.224, p =0.011) with the presence of choline.

In the ILC cases, the sample was insufficient for the correlation to become statistically significant. However, the ADC values tended to be lower in IDC patients (78.1 % having ADC value 1×10^{-3} mm²/sec) compared to ILC (57.1 % having ADC value 1×10^{-3} mm²/sec). Choline was more commonly detected in the IDC (72.3 %) than ILC (60 %) patients.

Conclusion: Our results are consistent with previous findings that both ADC values and choline detection in the spectrum play a significant role in establishing the final diagnosis of malignancy, especially when the kinetic pattern of enhancement is misleading. Hippokratia 2016, 20(3): 192-197

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Introduction

Early detection and accurate diagnosis of breast cancer are prerequisites for successful treatment selection. The most common histological types are the invasive ductal carcinoma (IDC) and the invasive lobular carcinoma (ILC), with the ductal type representing 70-90 % according to most series, whereas the lobular type represents 5-15 %[1-3].

The detailed assessment of lesion morphology based on contrast-enhanced magnetic resonance imaging (CE-MRI) remains a subjective task prone to experience related variation and interobserver bias. Thus, kinetic patterns using dynamic protocols as well as molecular information obtained by the in vivo proton magnetic resonance spectroscopy (^{1}H-MRS) and diffusion-weighted imag-

ing (DWI) have been proven helpful in increasing both sensitivity and specificity of diagnosis of invasive breast cancer[4,5].

Choline-containing compounds can be detected in most breast cancers[5,6], whereas choline is generally not detected in normal breast tissue. ^{1}H-MRS of the breast provides objective molecular information in a noninvasive manner. On the other hand, since tissue cellularity significantly influences DWI, the estimation of the apparent diffusion coefficient (ADC) value has been reported to be effective for lesion characterization[5].

In the current study, we correlated the histological type of proven invasive breast carcinomas with the ADC values, detection of choline, as well as with the kinetic analysis.

Materials and Methods

During the period 2009-2015 we retrospectively studied 181 patients with histologically confirmed invasive breast carcinomas. This study was approved by the Ethical Committee of Aristotle University of Thessaloniki (No A20535, 11/3/2009). Among these cases, 160 patients had invasive IDC and 21 ILC. Patients presented with clinical or imaging suspicion of breast cancer, positive breast biopsy or were high-risk patients. They underwent magnetic resonance mammography (MRM) with a 3 Tesla (3T) superconductive magnetic system (Signa HDx, General Electric Healthcare, Waukesha, WI, USA) after obtaining written informed consent. A breast-specific 8-channel phased-array surface coil was used. Before gadolinium-based contrast medium administration an axial non-fat-suppressed Gradient Echo (GRE) T1-weighted sequence was performed. Then, axial DWI with spin echo-planar imaging, fat-suppression, b values of 0 and 1,000 sec/mm^2, TR 11,000 ms, TE 68 ms, slice thickness 3 mm, number of excitations (NEX) 4 and matrix 100 x 100 were obtained. DWI assessment included both qualitative interpretation of DWI for lesion detection and quantitative measurement of ADC for lesion characterization. The ADC value was calculated on the ADC map with a manually defined region of interest (ROI) in an area of restricted diffusion with higher signal intensity. In all patients, a bolus of intravenous contrast medium was administered at a dose of 0.2 mmol/kg body weight followed by 10 ml of saline solution. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with fat-suppression (FS) was performed before the injection of contrast medium and six times afterward. The acquisition time was 7 min 10 sec (60 sec per dynamic sequence, one mask image and dynamic images obtained every minute for 7 min). The data obtained by the dynamic procedure were used for kinetic analysis and construction of kinetic curves. After DCE-MRI, sagittal T1 (GRE) FS, axial STIR, and T2 sequences were obtained. Additionally, single-voxel ^{1}H-MRS data was collected from a single rectangular volume of interest that encompassed the lesion using a BREASE (TE-Averaged Point Resolved Spectroscopy - PRESS) sequence. The spectrum was considered positive when a choline peak at a frequency of 3.2 ppm was depicted.

For all statistical analysis, tables and correlation analysis Statistical Package for the Social Sciences program (SPSS) Version 20 (SPSS, Inc. Chicago IL, USA) was used. Kruskal-Wallis is the non-parametric alternative to the ANOVA test and normality and homogeneity of variance were not assumed since the data were non-parametric due to their qualitative nature[7]. In order to confirm the statistically significant differences in the results, it was necessary to examine possible relationships between the factors. Kendall's Tau rank correlation coefficient was used to find statistical associations based on the ranks of the available non-parametric data.

It's a robust test with the ability to handle small sample sizes very well. The Kendall correlation coefficient uses pairs of observations to determine the strength of association based on the pattern of concordance or discordance among the observation pairs. Cohen's standard is used to evaluate the strength of the relationship, where coefficients between 0.10 and 0.29 represent a small association, coefficients between 0.30 and 0.49 represent a moderate association, and coefficients above 0.50 indicate a large association. Ranking was carried out on the variables[7] with the correlation coefficients values between minus one and plus one, signifying that the ranks of both the variables are decreasing or increasing respectively. The dynamic profile and the pathologic type of invasive cancer found postoperatively were correlated with the ADC value and the detectability of choline resonance in the spectrum in each of the 181 cases.

Results

The ADC values in the 158 out of 160 IDC patients (not measured in two patients) ranged from 0.5 x 10^{-3} to 1.2 x 10^{-3} mm^2/sec. In 125 cases (78.1%) the ADC value was 1 x 10^{-3} mm^2/sec, in 29 cases (18.4%) the ADC value ranged from 0.6 to 0.9 x 10^{-3} mm^2/sec and in four cases (2.5%) the ADC value ranged from 1.1 to 1.2 x 10^{-3} mm^2/sec. Regarding the detection of choline with ^{1}H-MRS, in 121 IDC patients it was positive in 72.3%, while in the remaining 39 cases it was not possible to obtain data, either because the lesion was smaller than 1cm in diameter or owing to patient motion (Figure 1; C, D, and E). Using the non-parametric test Kruskal-Wallis (Table 1) we compared choline's presence or absence in IDC lesions with: the margins (sharp or unsharp), the size (in groups), the early enhancement in DCE sequences (split into two groups: 1 to 100, and >100), the type of curve, ADC, grade, multifocality, multicentricity and the presence or absence of lymph nodes. Statistically significant, is the curve type with p =0.005, ADC with p =0.011, and the presence of lymph nodes with p =0.012. All cancers were grade II or III, without the presence of grade I. For this reason, there is no statistical significance in the degree of malignancy with and without choline. From the correlation analysis of the IDC results using the non-parametric Kendall's tau-b test, the curve type was positively associ-

ated (Kendal tau b: 0.254, p =0.005) with the presence of choline, while ADC correlated negatively (Kendal tau b: -0.224, p =0.011) with the presence of choline (Table 2). DCE-MRI perfusion imaging wash-in plateau (grouped as above) correlated with the type of curve (Kendal tau b: 0.157, p =0.047), while the curve type was associated with choline (Kendal tau b of 0.254, p =0.005) and with the presence of lymph nodes (Kendal tau b: 0.244 p =0.002). Importantly, ADC correlated negatively with the presence of choline (Kendal tau b: -0,224, p =0.011) and the presence of lymph nodes (Kendal tau b: -0,165 p =0.03). Choline was also associated with the presence of lymph nodes (Kendal tau b: 0.229, p =0.012). The grade was positively correlated with the presence of lymph nodes (Kendal tau b: 0.302 and p =0.0001). Multifocality was strongly correlated with multicentricity (Kendal tau b: 0.417 and p =0.0001).

In the 21 ILC patients the ADC values ranged from 0.5×10^{-3} to 1.2×10^{-3} mm²/sec with 57.1 % of the cases having ADC value 1×10^{-3} mm²/sec. In 23.8% of ILC patients, the lesions had "non-mass" appearance, and the ADC values were comparatively higher but always lower than 1.2 mm²/sec. Regarding the ¹H-MRS, in 11 cases it was not possible to obtain data, while in the remaining ten patients, detection of choline was positive in six (60 %) (Figure 2; C, D, and E). In the 21 ILC patients, the kinetic analysis after the administration of contrast medium showed type I (persistent) curve in 4.3 %, type II (plateau) curve in 33.3 % and type III (washout) in 52.4 % (Figure 2; A, B). In the 160 IDC patients, type I curve was obtained in only one case (0.6 %), type II in 31 cases (19.4 %) and type III in 128 cases (80 %) (Figure 1; A, B). Regarding ILC cases, the sample was small and the correlation with any parameter could not be statistically
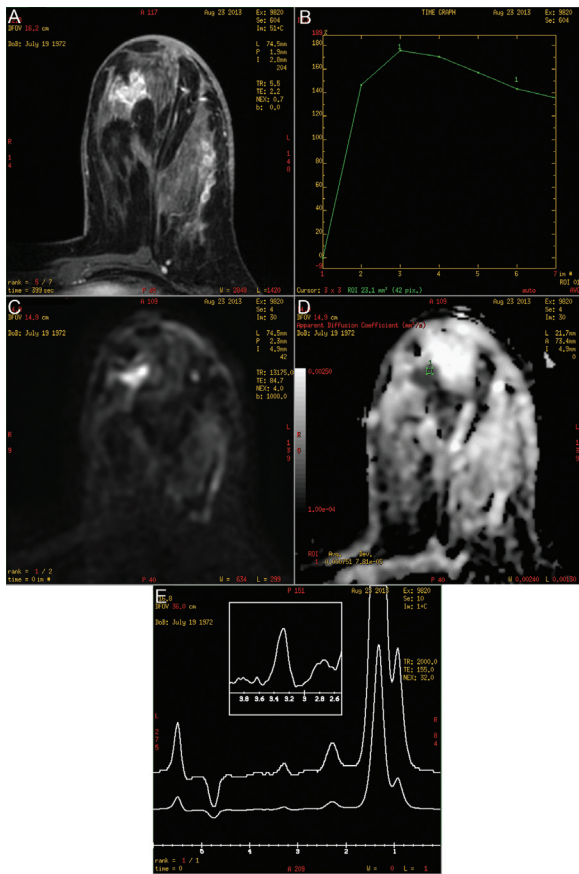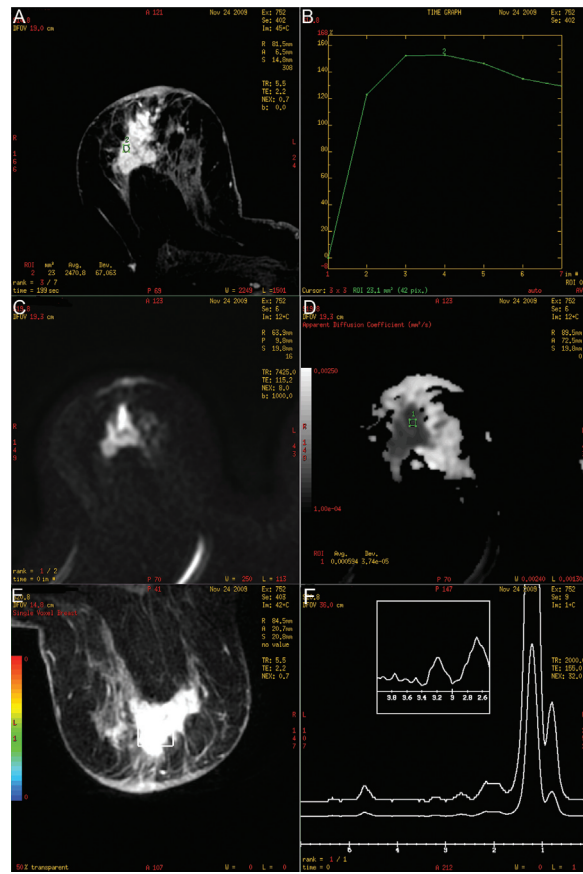

Figure 1: Invasive ductal carcinoma in a 45-year-old woman presenting with a suspicious mass in mammography in the left breast. A) Axial T1W fat-suppressed image post contrast shows an enhancing mass with irregular margins, B) Type III kinetic curve in the mass, C) Axial diffusion-weighted imaging (DWI) image shows a high signal region, D) Apparent diffusion coefficient (ADC) map shows restricted diffusion in the region of interest with an ADC value of 0.9 mm²/sec, E) The in vivo proton magnetic resonance spectroscopy (¹H MR spectrum) shows a choline peak at 3.2 ppm.

Figure 2: Invasive lobular carcinoma in a 52-year-old woman presenting with a palpable mass in the right breast. A) Axial T1W fat-suppressed image post-contrast shows regional non-mass enhancement. B) Type III kinetic curve in the lesion, C) Axial diffusion-weighted imaging (DWI) image shows a high signal region, D) Apparent diffusion coefficient (ADC) map shows restricted diffusion in the region of interest with an ADC value of 0.9mm²/sec, E) Axial T1W fat-suppressed image post-contrast ¹H magnetic resonance spectroscopy demonstrating single-voxel positioning, F) The in vivo proton magnetic resonance spectroscopy (¹H MR spectrum) shows a choline peak at 3.2 ppm.

Table 1: Kruskal-Wallis Test in IDC. Comparison of choline's presence or absence in invasive ductal carcinoma (IDC) lesions with: the margins (sharp or unsharp), the size (in groups), the early enchancement (in two groups: 1 to 100, and >100), the type of curve, ADC, grade, multifocality, multicentricity and the presence or absence of lymph nodes.

	size GROUP	curve type	ADC	grade	lymph nodes
Chi-Square	2.378	**7.741**	**6.503**	1.617	**6.287**
df	1	**1**	**1**	1	**1**
Asymp. Sig.	.123	**.005**	**.011**	.204	**.012**

ADC: apparent diffusion coefficient.

Table 2: Correlations using the non-parametric Kendall's tau-b test, invasive ductal carcinoma (IDC) lesions with: the margins (sharp or unsharp), the size (in groups), the early enchancement (in two groups: 1 to 100, and >100), the type of curve, ADC, grade, multifocality, multicentricity and the presence or absence of lymph nodes.

		curve type	ADC	choline	grade	lymph nodes
curve type	ρ		-.094	.254**	.058	.244**
	Sig. (2-tailed)		.219	.005	.447	.002
ADC	ρ	-.094		-.224*	-.059	-.165*
	Sig. (2-tailed)	.219		.011	.416	.030
choline	ρ	.254**	-.224*		.112	.229*
	Sig. (2-tailed)	.005	.011		.204	.012
grade	ρ	.058	-.059	.112		.302**
	Sig. (2-tailed)	.447	.416	.204		.000
lymph nodes	ρ	.244**	-.165*	.229*	.302**	
	Sig. (2-tailed)	.002	.030	.012	.000	

ADC: apparent diffusion coefficient, *: Correlation is significant at the 0.05 level (2-tailed), **: Correlation is significant at the 0.01 level (2-tailed), ρ: Kendall's tau-b.

significant. However, the ADC values tended to be lower in IDC compared to ILC patients and choline detection was more common in IDC than in ILC patients.

Discussion

This work presents research based on clinical experience at the 3 Tesla MR scanner installed at our institution. Due to increased signal to noise ratio in 3T scanners compared to 1.5T, DWI could be obtained with a higher spatial resolution without sacrificing the signal intensity. At the same time, 3Tesla provides increased chemical shift between water, fat, and choline which increases the confidence in the qualitative choline peak detection. Similarly, the increased chemical shift between water and fat enables better suppression of the fat signal and thus better visualization of the lesion margins[8].

The detection of lesions in MRM is based mainly on their differential enhancement behavior after the administration of intravenous contrast medium compared either to normal fibroglandular and fatty tissue or benign lesions[9]. Angiogenetic factors such as the Vascular Endothelial Growth Factor (VEGF), released by the malignant tumoral cells induce sprouting of preexisting capillaries and de novo formation of new leaky vessels[10,11]. Also, the existence of arteriovenous shunts within the tumor leads to an accelerated extravasation of contrast medium and perfusion shortcuts[12]. Immunohistochemical studies have also shown that angiogenesis in ILC is probably influenced by a number of different factors since the expression of VEGF is quantitatively lower compared to IDC[13]. Furthermore, the diffuse and frequently slower growth of ILC is not accompanied by extensive angiogenesis, and this results in reduced enhancement in MRM, thus making its detection more difficult to accomplish[1].

The type III kinetic curve in 80 % of the 160 IDC patients in our study is in agreement with other studies: on dynamic scanning, a typical malignant tumor shows an initial rapid and strong increase of the signal intensity followed by a rapid decrease. This phenomenon reflects the washout of the contrast agent[14,15]. Type III kinetic curve in our study is much more frequent in IDC compared to ILC patients, the latter showing 52.4 % incidence. This is in accordance with the study of Dietzel et al[16], while earlier studies reported that washout is seen only in a minority of cases[3]. Mann et al[17] also observed that only a minority of ILC cases exhibit type III kinetic curve, while most of ILC exhibit type I curve. It should be noted that in our study the ILC cohort of patients was small, while in the studies of Dietzel et al[16] and Mann et al[3,17] the samples were larger and consequently the results more valid.

The statistical analysis in our study showed a positive correlation of type III curves with lower ADC values

in the IDC cases. This reflects the increased cellularity of the malignant lesions without the need for the administration of contrast medium. According to Partridge and McDonald[18], DWI shows strong potential as an adjunct technique to reduce breast biopsies, demonstrating overall better specificity than DCE-MRI. Furthermore, some investigators suggest that ADC may correlate with prognostic pathologic markers such as cancer grade or biomarkers, including hormone and growth receptor status[19]. Kim et al[20] reported an association of lower ADC values with pathological prognostic factors, including higher histological grade, larger tumor size, and the presence of axillary lymph nodes. Axillary lymph node metastatic tumors had much lower ADC values than the tumors without axillary lymph node metastasis, while the axillary lymph node status was found to be independently associated with ADC paving the way for a preoperative detection method of axillary lymph node metastasis. DWI is a technique that is worth further investigating as its additional role in improving the detection rates of axillary lymph node metastasis could be very valuable. It has been previously shown that the grade of breast cancers is not associated with the ADC value in any significant way[21], in agreement with our results. Cipolla et al[22] have managed to show an association between low ADC values and high grade invasive breast cancer. Tumor size is an important prognostic factor, associated with long-term survival in breast cancer patients. Larger tumors have more positive lymph nodes and are associated with a poorer prognosis[23]. Razek et al[21] and Park et al[24] reported that the tumor size was significantly associated with the ADC value, while Choi et al[25] found no significant association between the tumor size and mean ADC: the mean ADC value of the larger tumors was lower than that of the smaller tumors. In our study tumor size and grading showed no statistically significant correlation with ADC value while lymph node status was significantly correlated with ADC. Multiple studies have evaluated optimal ADC thresholds for the reduction of false positive findings. Recommended threshold ADC cutoffs may vary from 0.9 to 1.76 x 10^{-3} mm^2/sec[18], while the authors of a meta-analysis of 12 articles recommended a threshold for malignancy of 1.23 x 10^{-3} mm2/sec at b =1,000 sec/mm^2 [19]. In our study employing a 3T magnet, the ADC values in 160 IDC and 21 ILC patients ranged from 0.5 to 1.2 x 10^{-3} mm^2/sec at b =1,000 mm^2/sec; these findings agree with the threshold of the studies mentioned above.

Since ADC is inversely correlated with cellular density[26,27], non-mass lesions could exhibit higher ADC due to more interspersed normal fibroglandular tissue[18]. This was confirmed by our study in which the non-mass ILC lesions exhibited higher ADC values compared to IDC lesions. However, in all cases, ADC was lower than 1.2 mm^2/sec. For the IDC cases, the correlation between the type of the kinetic curve and the ADC value was statistically significant (p =0.04). This reflects the increased neovascularity which results in rapid washout of the contrast medium and is associated with higher cellularity and reduced ADC value. Based on the correlations shown in Table 2, there is a strong correlation of the ADC with the presence of positive axillary lymph nodes.

According to ^{1}H-MRS in our 3T magnet study, detection of choline in the spectrum was found in 72.3 % of IDC and 60% of ILC patients. This molecular information reflects the increased cellular turnover of the invasive lesions[28]. Recent studies report that ^{1}H-MRS can potentially improve the accuracy of an MRI scan, increasing its specificity to 85 %[29]. Our somewhat lower detection rate could be due to several reasons. Small size and non-mass appearance of some lesions resulting in inaccurate voxel position. In some cases, there was central necrosis or adjacent hemorrhage resulting in inhomogeneity of the magnetic field. Finally, movement of the patient owing to the length of the examinations as ^{1}H-MRS was performed at the end of the scan. We believe that if we hadn't included the cases in which a previous interventional procedure had taken place, our results would have been more consistent with the current ^{1}H-MRS studies. The combined assessment of morphological patterns on CE-MRI and the kinetic data together with ^{1}H-MRS allowed us to successfully characterize the breast lesions. A larger sample size would have allowed for stronger correlations, but it was not feasible.

Conclusion

DWI is safe, highly sensitive and when used in conjunction with DCE increases the accuracy of cancer detection. ^{1}H-MRS offers additional information in evaluating breast lesions. The results from the current study provide positive evidence to support DWI and ^{1}H-MRS as useful adjuncts to standard breast MRI protocols in assisting with the diagnosis of breast cancer. The ADC value of a lesion can also be used as a prognostic factor to assess its aggressiveness. Also, correlations of ADC values with prognostic markers may provide information about the prognosis of the disease and help develop a more effective treatment plan.

Conflict of Interest

The authors report no conflict of interest.

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