Published in final edited form as:

Eur J Radiol. 2016 September ; 85(9): 1651–1658. doi:10.1016/j.ejrad.2016.06.019.

Quantitative Apparent Diffusion Coefficient Measurement Obtained by 3.0 Tesla MRI as a Potential Noninvasive Marker of Tumor Aggressiveness in Breast Cancer

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IRB statement:

This retrospective study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) guidelines and approved by our Institutional Review Board with a waiver of informed consent.

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Abstract

Purpose—To assess the association between apparent diffusion coefficient (ADC), and histological prognostic parameters in malignant breast lesions. The ability of ADC to identify lesions with the presence of Lymphovascular invasion (LVI) in breast carcinoma was also examined.

Materials and Methods—This HIPAA-compliant retrospective study consisted of 212 consecutive patients with known cancers who underwent 3.0T MRI between January 2011 and 2013. In this study, a total of 126 malignant lesions in 114 women, who had undergone DWI (b-values of 0 and 1000 s/mm²) in addition to diagnostic MRI, were included. Patients with less than 0.8 cm lesions, or those who underwent neoadjuvant chemotherapy or suboptimal DW images were excluded. Classical prognostic factors [lesion size, histopathological type and grade, lymph node (LN) status and lymphovascular invasion (LVI)], molecular prognostic markers [estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2(HER2)] were reviewed and recorded. A region of interest (ROI) was drawn within the lesions to measure ADC values. Statistical analyses were performed by the Wilcoxon rank sum test (statistical significance at $P<0.05$). Adjusted p values from multiple comparison analysis were also calculated.

Results—This study demonstrates an inverse correlation between ADC and LVI in malignant lesions and the ability of ADC to identify aggressiveness in lesions with positive LVI. Tumor size, grade, ER, PR, HER2 and lymph node status did not impact tumor ADC value. However, tumors with LVI showed significantly lower ADC values when compared to tumors without LVI, regardless of the enhancement type, histological grade, histological type, and LN status.

Conclusion—Our study shows that ADC could be a potential clinical adjunct in the evaluation of prognostic factors related to malignant lesion aggressiveness such as LVI.

INTRODUCTION

Contrast-Enhanced magnetic resonance imaging (CE-MRI) is currently the most sensitive technique for diagnosing breast cancer, identifying multifocal disease, determining tumor extension before surgery, and assessing the treatment response [1, 2]. Diffusion-weighted MRI (DW-MRI), is a method that does not need a contrast agent and is sensitive to the random motion of the water molecules in tissues. The DW-MRI technique has shown promise as an adjunct to CE-MRI in improving breast cancer diagnosis and monitoring treatment response [3]. Apparent Diffusion Coefficient (ADC), a parameter that is estimated as the rate of exponential diffusion signal attenuation with increasing amount of diffusion weighting, or b-value, is influenced by tissue cellularity and structure [4–6].

Tumor heterogeneity is a major challenge in the era of personalized medicine for better treatment responses and prognosis. Though the exact mechanisms for breast cancer heterogeneity remain unclear, several hypotheses including clonal and cellular diversity have been proposed [7, 8]. Considering the view that several factors in combination, rather than in isolation, would be of greater clinical value in the assessment of breast cancer prognosis, several molecular and gene expression profiles are being studied as general biomarkers to complement the traditional, clinical and pathological prognostic factors [9, 10]. The classical prognostic factors such as tumor size, histologic type/grade and lymph node (LN) status correlate significantly with recurrence-free and overall survival. The presence of molecular prognostic factors such as estrogen (ER) and progesterone receptor (PR) correlates with a good prognosis, while the human epidermal growth factor (HER2) correlates with a poor prognosis. In LN negative patients, the presence of lymphovascular invasion (LVI) has been reported to adversely impact prognosis because patients with positive LVI had a higher rate of distant metastases, increased local recurrence rate after breast conservation therapy and a higher mortality rate [5, 11].

Studies have also reported LVI as a possible independent prognostic factor [12, 13]. However, due to limited sampling, preoperative assessment of LVI status of a tumor by core-biopsy is difficult. The above facts clearly indicate the need for a biomarker that accurately predicts breast cancer prognosis thereby enabling better treatment and patient management.

Preliminary studies have evaluated ADC as a potential prognostic imaging biomarker in breast cancer, correlating with classical and molecular prognostic factors [14–16] as well as with patient outcomes [17]. It has previously been proposed that ADC values may correlate with tumor aggressiveness because ADC values tend to be observed as being lower in invasive tumors than in *in situ* tumors or in other histological subtypes [18–21]. However, these findings are inconclusive due to variability that exists in the strength of correlation between ADC values and the classical (clinical and molecular) prognostic factors.

The aim of this study is to measure the ADC values in malignant lesions at 3.0 T MRI, and compare it with well-known prognostic factors such as histopathological features (size, type, grade, LN status and LVI) and molecular biomarkers (ER, PR and HER2) in order to determine whether ADC values could serve as a potential new biomarker.

MATERIALS AND METHODS

This retrospective study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) guidelines and approved by our Institutional Review Board with a waiver of informed consent.

Patients Selection

In our database and records, we identified 854 consecutive patients who underwent bilateral breast 3.0 T MRI from January 2011 to January 2013. In this group, 212 had known cancers [22], which were diagnosed by needle biopsy prior to MRI examination and subsequently surgically verified. These patients underwent a pre-operative MRI examination to evaluate the extent of disease. Patients who received neoadjuvant chemotherapy (n=37) prior to, or at

the time of imaging, were excluded. Lesions were excluded if the 'in-plane' diameter was < 8 mm (n=11), or if DW-MR images had susceptibility artifacts, poor fat suppression or post-biopsy changes that completely obscured the lesion. A total of 114 patients were included in this study, following these selection criteria (Figure 1).

MRI Methods

MR imaging was performed on a 3.0 T system (Discovery MR750; GE Healthcare, WI) using the body coil as a transmitter and a dedicated 16-channel phased-array receiver coil (Sentinelle Vanguard; Canada). Conventional T1- and T2-weighted images were acquired with and without fat suppression (slice thickness, 3 mm).

Axial DW MR imaging was performed using 2D, DW single-shot, echo-planar imaging (EPI) sequences using the parameters described previously [23] (TR: 6000 ms; TE: 56.4–120.7 ms; flip angle: 90°; number of excitations: 3; acquisition matrix: 98×98 or 128×128; reconstructed matrix: 256×256; field of view, 28–38 cm; slice thickness: 4 or 5 mm; slice gap: 0–1 mm; fat suppression: enhanced; parallel imaging: ASSET; acquisition time: approximately 2 min for 2 b-values). In all the 114 patients, DW-MR imaging was acquired at b-values of 0 and 1000 s/mm². The DCE-MR images were acquired using a previously described protocol [23] with sagittal 3D T1-weighted gradient echo VIBRANT sequences before and at three points at 60-second intervals after an injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Bayer HealthCare, NJ). Subsequently, axial 3D T1-weighted gradient echo VIBRANT delayed CE imaging was performed [23].

Image Review and ADC Analysis

A radiologist with 7 years of experience in breast MRI identified the lesions using T1-weighted CE and the slice location was recorded to match the closest image location on DW images. The ADC analysis was blinded to the pathological type details (including lymph node status and LVI) and prognostic markers, excluding the fact that the lesions were all biopsy-proven cancers.

The MR images were viewed and analyzed on the Advantage Workstation (GE Healthcare, WI) and parametric quantitative ADC maps were generated by READY View software (GE Healthcare, WI). Breast lesions on diffusion images were identified and at least three regions of interest (ROI) were manually positioned over the tumor on DW images to avoid cystic, necrotic or hemorrhagic components and the averaged values were obtained. The ROIs were drawn 'free-hand' within the borders of the lesions and in different adjacent slices for evaluating the lesion heterogeneity. Susceptibility artifacts due to the presence of post-biopsy clips or post-biopsy changes were also avoided in the ROI positioning, in order to rule out any possible influence of prior needle biopsy.

The ADC value was automatically calculated when the ROI was drawn (mean area: 59.8 mm²; range from 8.4 to 189.6 mm²) for each proven primary malignancy. In multifocal/multicentric disease, the index cancer (represented by the largest malignancy) was analyzed.

The reproducibility of the ADC measurements was assessed by a second reader (a physicist with 10 years' experience in breast MRI), who independently repeated the data analysis on a randomly selected subset of patients (n=25).

Histologic Analysis

A breast pathologist with more than 10 years of experience reviewed the pathology reports for tumor histologic type and histological and nuclear grades. Hematoxylin & Eosin stained slides for the study were obtained from the Surgical Pathology files at our Institution. Tumors were classified using the WHO classification and invasive carcinomas were graded using the modified Bloom-Richardson classification. Axillary lymph node status was determined by pathology on sentinel lymph node biopsy or axillary lymph node dissection. In addition to tumor type and grade, the slides were examined for the presence of lymphovascular invasion (LVI), presence of ductal carcinoma in situ (DCIS) and the status of axillary lymph nodes.

The status of ER (6F11, Ventana, USA), PR (IE2, Ventana, USA) and HER2 (4B5, Ventana, USA) receptors were obtained from the pathology reports for invasive cancers. Tumors were considered ER and PR positive when nuclear staining was present in greater than 1% tumor cells. The HER2 status was determined using the 2013 ASCO/CAP guidelines. Depending on the status of ER, PR and HER2, the cases were classified as: *ER positive*: ER +, PR +/-, HER2 -; *Triple Negative (TN)*: ER -, PR -, HER2 -; *HER2 positive*: ER -, PR -, HER2 + tumors.

Statistical analysis

The ADC values are presented as the mean $\pm$ standard deviation of the mean. Analysis was done for all lesions, and bilateral lesions in the same patient were assumed to be uncorrelated. Reader variability was assessed by the Pearson's correlation coefficient. All ADC values were examined for normality, and non-parametric tests were conducted whenever necessary. The Wilcoxon rank sum test was used for and the significance was established at $p=0.05$. Analyses were conducted in SAS v9.2 and Origin 9.1 software (Origin Lab Corporation, USA). Multiple comparison corrections were implemented using the false discovery rate (FDR) method, with the FDR selected at 0.05.

RESULTS

This study included 114 patients (mean age 48.5 years; range 27–74 years); 103 patients of them (90.4%) had a single lesion, 4 patients (3.5%) had bilateral malignancies [two lesions in bilateral breasts, 2 patients had an invasive ductal carcinoma (IDC) and a ductal carcinoma in situ (DCIS), 1 patient had two IDCs and 1 patient had an IDC and an invasive lobular carcinoma (ILC)]; 6 patients (5.3%) had two different unifocal or independent lesions in the same breast (2 patients with two IDCs, 3 patients had two ILCs and 1 patient had also IDC and DCIS); and 1 (0.9%) had multi-focal lesions (3 IDCs). The total number of malignant lesions was 126 (mean size 2.9 ± 2.1 cm; range 0.8–12 cm) with a mean ADC value of $0.908 \pm 0.156 \times 10^{-3} \text{ mm}^2/\text{s}$.

The data analyses conducted by the two independent readers on the randomly selected subset of patients had a strong correlation, as indicated by a high Pearson's correlation coefficient ($r=0.827$).

ADC values and the correlation with histological and molecular findings

The correlation between ADC values of malignant lesions and their morphological and histological characteristics is reported in Table 1.

Mean ADC values did not differ significantly when tumors were sub-grouped by size. Non-mass lesions had significantly higher ($p<0.001$) mean ADC values as compared to mass lesions. The ADC values according to the types of tumors were significantly different in IDC, ILC and DCIS ($p=0.030$) with low values for IDCs compared to ILC and DCIS lesions. However, when corrections for multiple comparison were applied, the adjusted p-value was not significant. Other comparisons, including those based on the histology and nuclear grading were not significant.

The IDC lesions ($n=89$) were predominantly mass ($66/89$, 74.2%), while DCIS ($n=19$) were mostly non-mass lesions ($17/19$, 89.5%); ILC ($n=15$) were $12/15$ (80.0%) mass and $3/15$ (20.0%) non-mass lesions. The mean ADC values also statistically differed ($p=0.01$, adjusted p value = 0.026) between the mass and non-mass IDC lesions ($0.861\pm0.14\times10^{-3}$ mm²/s vs. $0.957\pm0.15\times10^{-3}$ mm²/s respectively). Regarding the molecular subtypes (considering only invasive cancers, $n=107$), ADC values were not significantly different in ER positive, TN and HER-2 positive malignant lesions. Despite this, HER-2 positive cancers showed higher ADC measurements in comparison to other subtypes such as ER positive and TN tumors (Figure 2a). The lymph nodal status was available for 117 cases and lymph node positive cancers showed lower ADC values, however the difference was not statistically significant ($p=0.249$) (Figure 2b). In these cases, it should be noted that ADC values were significantly lower ($p<0.001$, adjusted p value = 0.005) for cancers with LVI compared to those in which LVI was absent (LVI status available for 93 cases) (Figure 2c).

ADC values and Lymphovascular Invasion (LVI) correlation

The correlation between ADC values and lesion characteristics were stratified by the presence or absence of LVI (Table 2) in order to describe the influence of mass enhancement, histological type/grade and lymph nodal status on LVI status. An example of different ADC values in LN positive patients is seen in Figure 3: LN positive patient with (a, b) and without (c, d) LVI. The ADC values were lower (0.972×10^{-3} mm²/s) when LVI is present compared to a lesion without LVI (1.100×10^{-3} mm²/s), as shown in the ADC maps (Figure 3b, d).

Figure 4 represents an example of an LN negative patient with (a, b) and without (c, d) LVI: ADC map shows lower ADC values (0.711×10^{-3} mm²/s) for a lesion with LVI (4b) than for a LVI negative lesion ADC (1.080×10^{-3} mm²/s) (4d).

In lymph node positive cases (Figure 5a and Table 2), the presence of LVI significantly ($p=0.015$, adjusted p value = 0.034) correlated with lower mean ADC values ($0.806\pm0.13\times10^{-3}$ mm²/s) compared to cancers without LVI ($0.974\pm0.15 \times 10^{-3}$ mm²/s).

Even in lymph node negative cases (Figure 5b and Table 2), the presence or absence of LVI appeared to impact the ADC values and we found that node negative-LVI positive cancers had significantly ($p = 0.003$, adjusted p value = 0.011) lower mean ADC values ($0.825 \pm 0.09 \times 10^{-3} \text{ mm}^2/\text{s}$) compared to node negative cancers without LVI ($1.011 \pm 0.17 \times 10^{-3} \text{ mm}^2/\text{s}$). Table 3 summarizes p value and adjusted p values from multiple comparison analysis using the FDR method.

DISCUSSION

The quantitative ADC parameter from DWI is increasingly being used to (i) improve the diagnostic accuracy of CE-MRI in breast cancers [4, 5], (ii) monitor treatment response [2], and (iii) correlate with various prognostic factors [14–16]. Our results are in agreement with studies showing that highly cellular malignant lesions have low ADC values [5].

Studies on tumor size have shown that significant variation in lesion ADC values and tumor size has been documented [15, 18, 24]. However, we did not find a statistically significant difference in ADC values of tumors with different sizes.

Similarly, no statistically significant differences in ADC values were found in tumors with different histological grades, although our results do show that lower grade tumors had higher ADC values than their high-grade counterparts [19, 21]. This finding suggests that histologic grade may represent tumor cellularity.

We observed a significant difference, primarily between types of IDC and DCIS. Lower ADC values in IDC lesions might be due to more mass-like lesion types than DCIS. In contrary, Costantini et al [21] reported a significant difference in the mean ADC values between ductal and lobular invasive carcinomas, but no difference in IDC versus DCIS types [21]. Choi et al [25] (at 1.5T) and Bickel et al [26] (at 3.0T) reported significantly lower mean ADC values for IDC compared to DCIS. The difference in the ADC values between IDC and ILC could result from different growth patterns and, lower cellularity of ILC [27]. The molecular subtype categories (TN, ER and HER2) have different behaviors and aggressiveness [28] but without significantly different ADC values. Compared to studies [15, 29] that reported a higher ADC value in TN cancers, we observed a low ADC value (in our series, TN cancers are predominately mass lesions). Our results are similar to the ER positive tumors reported by Costantini et al [28] which had lower ADC values in TN lesions than those observed in the HER2-overexpressing subgroup, although with no statistical significance.

Consistent with other studies, our data show that the lymph nodal status did not correlate with lesion ADC values [20, 25]. However, the mere absence of positive LNs in breast cancer does not automatically imply a good prognosis [30]. In fact, long-term follow-up studies have shown that 30% of node negative patients develop distant metastasis and die of breast cancer [11], reiterating the need for additional biomarkers.

Although node status cancers cannot be differentiated based on ADC values, the presence of LVI consistently correlated with lower ADC values. Our results do not concur with a study done at 1.5T by Kamitani et al [24], where no correlation was observed between breast

cancers and vascular invasion in 81 IDC populations. However, it must be noted that our data is derived from a larger patient population and performed at 3.0T field strength. We therefore propose that ADC measurement can be a useful preoperative, noninvasive tool to support the management of patients with negative lymph nodes.

In a recent study, Mori et al [31] found results that were concordant with our data, showing that ADC values were significantly lower in the LVI-positive group than in the negative one. They also found a significantly larger tumor size and higher axillary lymph node metastasis rate in lesions.

Other studies have shown that the presence of LVI has an adverse impact on breast cancer prognosis. Node negative patients with positive LVI had a higher mortality rate (53%) compared to patients who had lesions with no LVI. This often leads oncologists to treat LVI positive tumors more aggressively [32]. Some reports have suggested that LVI can add prognostic value to the established factors. Song et al. [33] reported that a positive LVI could be a predictor of poor prognosis in LN-positive patients with primary invasive breast cancer. The presence of LVI was also a prognostic factor in patients independent of LN status. Our study showed that although the ADC value did not appear to be a significant tool for the lymph node status, it can be established as an imaging parameter related to the presence of LVI.

Collectively, our results demonstrate that ADC value can be a useful predictor of severity to distinguish node negative cancers with and without LVI. Furthermore, cancers with LVI showed significantly lower ADC values compared to cancers without LVI, independent of histological subtype and grades in the ductal histological type, and in mass lesions. Since we observed that lesions in patients with LVI have a significantly lower ADC value and because LVI is indicative of a potentially aggressive cancer, it follows that lesions with lower ADC values might benefit from a more aggressive treatment than lesions with high ADC.

Our study has some limitations. First, this is a retrospective study with more IDC lesions compared to DCIS and ILC lesions. Second, our population included a specific set of patients with known cancers who underwent MRI for pre-surgical evaluation; we excluded patients who underwent neoadjuvant chemotherapy. Therefore, our sample did not have representative characteristics of the general population in terms of histological types (invasive vs. in situ carcinoma). Furthermore, although we used a 3.0T scanner, we excluded lesions smaller than 8 mm from the analysis to avoid partial volume effects. Future studies may include advancements that allow the inclusion of a larger patient pool and smaller lesions. Finally, in order to reduce inter- or intra-operator variability in ADC measurements, it is preferable to have a standardized DWI acquisition and evaluation method instead of our manually derived ROIs.

In summary, we found that primary tumors with LVI had lower mean ADC values than tumors without LVI, independent of LN status. This suggests that the ADC parameter can be used as a prognostic factor to support the management of patients with negative lymph nodes.

Acknowledgments

We would like to thank Jessica Massler and Girard Gibbons for help with the clinical information database and Seetha Srinivasan for her assistance in editing the manuscript.

This work was supported by Memorial Sloan-Kettering Cancer Center Support Grant/Core Grant (P30 CA008748) and in part by a grant from the Breast Cancer Research Foundation of Memorial Sloan-Kettering Cancer Center.

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HIGHLIGHTS

- Lymphovascular invasion (LVI) positive tumors have lower ADC than LVI negative tumors
- In patients with negative lymph nodes, lower ADC could indicate more aggressive tumors
- ADC could serve as a non-invasive biomarker for LVI

Figure 1.
Flow chart describing patient selection criteria used in our study

Figure 2. Box plots of lesion ADC₁₀₀₀ values according to a) Histopathological subtype (TN= triple negative; ER positive; HER2 positive; $p = 0.365$), b) Lymph node (LN) status ($p = 0.249$), and c) Lymphovascular invasion (LVI) status ($p < 0.001$). Box displays the median and interquartile range (25th and 75th percentiles) for each group.

Figure 3.

Comparison of ADC values when lymphovascular invasion (LVI) is present or absent in patients with negative lymph nodes. (a) DW images (b) and ADC map of a 28 year-old premenopausal woman with family history of breast cancer (BRCA negative); in the right upper inner quadrant breast, a round circumscribed 1.8 cm mass, biopsy-proven invasive ductal carcinoma, with high histological grade, ER positive and LVI present. (c) DW images (d) and ADC map of a 59 year-old post-menopausal woman (BRCA negative): in the right upper inner quadrant breast, a irregular rim enhancing 2.1 cm mass, biopsy-proven invasive ductal carcinoma, with high histological grade, triple negative and LVI absent. LVI positive lesion ADC was lower ($0.711 \times 10^{-3} \text{ mm}^2/\text{s}$) than LVI negative lesion ADC ($1.080 \times 10^{-3} \text{ mm}^2/\text{s}$).

Figure 4.

Comparison of ADC values in the presence or absence of lymph vascular invasion (LVI) in patients with positive lymph nodes (LN). (a) DW image and (b) ADC map of a 30 year-old pre-menopausal woman: in the right lower outer quadrant, multiple enhanced masses (multifocal disease) biopsy-proven invasive lobular carcinoma - ER positive, intermediate histological grade, and LVI present. (c) DW image and (d) ADC map of a 51 year-old woman with dense breast: within the right lower inner quadrant a 2.0×1.8 cm heterogeneously enhanced oval mass, biopsy-proven invasive ductal carcinoma, high histological grade, HER2 positive and LVI negative. Lower ADC value (0.972×10^{-3} mm²/s) was observed in the presence of LVI than in the lesion ADC (1.100×10^{-3} mm²/s) without LVI.

Figure 5.

Box plots of ADC₁₀₀₀ values with or without lymph vascular invasion (LVI) and known lymph node (LN) status. The lesion ADC₁₀₀₀ value was lower when LVI is present than in lesions without LVI, both in node positive ($p = 0.015$) (a) and node negative ($p = 0.003$) (b) patients. Box displays the median and interquartile range (25th and 75th percentiles) for each group.

Table 1

Comparison of ADC values of malignant lesions with morphological and histopathological features

Lesion	n. lesions		ADC	
	n	%	Mean $\pm$ SD	p-value ^{\$}
Size[‡]				
Mean size 2.9 ± 2.1 cm (range 0.8–12 cm)				
	n=126			0.639
Lesions < 2 cm	48	38.1	0.921 ± 0.18	
Lesions 2–5 cm	57	45.2	0.892 ± 0.13	
Lesions > 5 cm	21	18.3	0.910 ± 0.15	
Enhancement type	n=126			<0.001
Mass	83	65.9	0.868 ± 0.14	
Non mass	43	34.1	0.985 ± 0.16	
Histopathological type[*]	n=123			0.030
IDC	89	72.4	0.886 ± 0.15	
ILC	15	12.2	0.968 ± 0.22	
DCIS ^β	19	15.4	0.971 ± 0.11	
Histological grade^{**}	n=99			0.136
Low	22	22.2	0.960 ± 0.20	
Intermediate	43	43.4	0.895 ± 0.16	
High	34	34.3	0.875 ± 0.12	
Nuclear grade^{***}	n=19			0.149
Low	1	5.3	0.965	
Intermediate	10	52.6	0.928 ± 0.13	
High	8	42.1	1.025 ± 0.08	
Histological Subtype[§]	n=107			0.365
Triple Negative	23	21.5	0.853 ± 0.12	
ER positive	64	59.8	0.892 ± 0.18	
HER2 positive	20	18.7	0.954 ± 0.14	
Lymphovascular invasion (LVI)[#]	n=93			<0.001
Present	42	45.2	0.845 ± 0.13	
Not present	51	54.8	0.965 ± 0.16	
Lymph node (LN) status^{##}	n=117			0.249
Node negative	63 ^a	53.8	0.922 ± 0.16	
Node positive	54 ^b	46.2	0.889 ± 0.15	

[‡]Size defined as maximum diameter on DCE-MRI images

ADC: apparent diffusion coefficients calculated from data at $b=[0, 1000]$ s/mm². ADC units are 10–3 mm²/s; Data are presented as mean $\pm$ SD; SD= standard deviation; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma; DCIS= ductal carcinoma in situ; ER: Estrogen Receptor; TN: Triple Negative; HER2: human epidermal growth factor receptor

^{\$}The statistical significance was established at $p = 0.05$

* Not included: 1 invasive mixed ductal and lobular, 1 papillary and 1 metaplastic carcinomas

β_2 DCIS had a microinvasive component

** Only invasive cancers; in 8 cases the pathological review were not possible to assess the grade

*** Only DCIS cases

$\S$ Only for invasive cancers

^a Among 63 node negative lesions, LVI status was available for 44 lesions (10 positive and 34 negative)

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Table 2

Correlation between ADC value and lesion characteristics sub-grouped considering LVI present or absent

	Lesion ADC				
	LVI Negative		LVI Positive		p value
	n. lesions	Mean $\pm$ SD	n. lesions	Mean $\pm$ SD	
Enhancement type					
Mass	33	0.937 $\pm$ 0.16	35	0.814 $\pm$ 0.08	<0.001
Non-mass	18	1.018 $\pm$ 0.16	7	1.000 $\pm$ 0.19	0.535
Histopathological type					
IDC	35	0.946 $\pm$ 0.15	39	0.851 $\pm$ 0.13	0.005
ILC	9	1.020 $\pm$ 0.23	3	0.767 $\pm$ 0.04	0.060
Histological grade					
Low	12	1.014 $\pm$ 0.23	5	0.836 $\pm$ 0.08	0.029
Intermediate	21	0.926 $\pm$ 0.16	19	0.863 $\pm$ 0.16	1.00
High	13	0.954 $\pm$ 0.09	17	0.838 $\pm$ 0.08	0.001
Lymph node status					
Node negative	34	1.011 $\pm$ 0.17	10	0.825 $\pm$ 0.09	0.003
Node positive	15	0.974 $\pm$ 0.15	31	0.806 $\pm$ 0.13	0.015

In 33 lesions the lymphovascular invasion was not mentioned in the pathological report

For 9 lesions, no data available regarding lymph nodal status.

ADC: apparent diffusion coefficients calculated from data at $b=[0, 1000]$ s/mm².

ADC units are 10⁻³ mm²/s; Data are presented as mean $\pm$ SD; SD= standard deviation; LVI= lymphovascular invasion; IDC= invasive ductal carcinoma; ILC= invasive lobular carcinoma

Table 3

Raw and adjusted P values from multiple comparison analysis* when comparing different ADC values. Only p values for significant findings are shown.

Comparison of ADC values	p value	adjusted p value
LVI - Negative vs Positive	0.001	0.0045
<i>Enhancement type - Mass only</i>	0.001	0.0045
<i>Histological grade - High only</i>	0.001	0.0045
<i>Histological type - IDC lesions only</i>	0.005	0.015
<i>Lymph Node Status</i> <i>Negative only</i>	0.003	0.0108
<i>Positive only</i>	0.015	0.0338
Mass vs Non Mass	0.001	0.0045
<i>Histological type - IDC lesions only</i>	0.01	0.0257

*
FDR is assumed to be 0.05