Apparent Diffusion Coefficient in Estrogen Receptor-Positive and Lymph Node-Negative Invasive Breast Cancers at 3.0T DW-MRI: A Potential Predictor for an Oncotype Dx Test Recurrence Score

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Purpose: To measure the apparent diffusion coefficient (ADC) values in estrogen receptor-positive (ER+) and axillary lymph node-negative (LN–) invasive breast cancer and investigate the correlation of ADC with Oncotype Dx test recurrence scores (ODxRS).
Materials and Methods: This was a Health Insurance Portability and Accountability Act (HIPAA)-compliant single-site retrospective study. Patients underwent preoperative 3.0T MRI scans with additional diffusion-weighted imaging sequential scans (b = 0, 600 and b = 0, 1000 s/mm^2) from January 2011 to 2013. The study population included 31 ER+/LN– invasive breast cancers, which underwent ODxRS genomic testing. ADC_{600} and ADC_{1000} parametric maps were generated, and ADC values were calculated from a user-drawn region of interest. ODxRS predicts 10-year recurrence risk in individual patients: low (RS <18), intermediate (RS: 18–30), or high (RS >30). All breast lesions, including subgroups of invasive ductal carcinoma (IDC) lesions and mass-only lesions were dichotomized by RS scores, low-risk versus intermediate/high-risk, and statistical analysis was performed using Mann–Whitney's test (statistical significance at $P < 0.05$) and receiver operating characteristic (ROC) curves. Multivariate analysis was also performed.
Results: Invasive breast cancers, when scored as low-risk by ODxRS, had significantly higher ADC values compared with intermediate/high-risk lesions for both ADC_{600} ($P = 0.007$) and ADC_{1000} ($P = 0.008$) mean values. This was true both when analyzing only mass-lesions ($P = 0.03$ and 0.01) or only IDCs ($P = 0.001$ and 0.009).
Conclusion: Preliminary findings suggest that lesion ADC values correlate with recurrence risk likelihood stratified using ODxRS. Hence, ADC is a potential surrogate biomarker for tumor aggressiveness.
Level of Evidence: 3
Technical Efficacy: Stage 5

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Early detection, diagnosis, and treatment advances have significantly decreased breast cancer recurrence rates.[1] However, tumor heterogeneity, identified on the basis of histologic and molecular characteristics, poses a challenge in accurately determining prognosis and providing effective treatment to an individual patient.[2] In spite of advances in tumor characterization that have resulted in improved treatment of breast cancer, recurrences and treatment failures still occur, raising the need for better treatment modalities and better tumor characterization.[3] On the other hand, breast cancer patients demonstrating a low recurrence risk between 5 to 10 years after diagnosis (early stage with no high

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mortality and good prognostic factors) need to be identified accurately so that they can be spared unnecessary aggressive treatment.[4]

Diffusion-weighted magnetic resonance imaging (DW-MRI) is emerging as a potential clinical adjunct to dynamic contrast-enhanced (DCE) MRI in the evaluation of prognostic factors in breast cancer (mostly by assessing aggressiveness of malignant lesions), and thus DW-MRI may potentially help plan appropriate treatment management.[5,6] The DW-MRI sequence measures in vivo the mobility of water (Brownian motion) and obtains the apparent diffusion coefficient (ADC), which is the directly proportional quantitative measure to water diffusion.[7] The measured ADC will have contributions from more restricted intracellular diffusion, diffusion in the extracellular space, and even diffusion within the intravascular compartment as long as they occur within-voxel incoherent displacement of spins.[8] High cell proliferation increases cell density, creating more barriers to extracellular water diffusion and thereby reducing ADC in tumors. Accordingly, recent studies have reported ADC as a new breast cancer prognostic factor related to tumor aggressiveness.[9,10]

Oncotype Dx (Genomic Health, Redwood City, CA) is a gene-expression profiling assay that incorporates the mRNA expression of 21 genes (16 cancer-related genes and five reference genes) using reverse transcriptase-polymerase chain reaction,[11–13] resulting in a quantitative so-called recurrence score (RS). The principal genes that determine the score are those related to proliferation, ER (estrogen receptor), and human epidermal growth factor receptor (HER2). As a result, a tumor with a higher expression of proliferation will result in a higher score and is likely to show an aggressive behavior in contrast to the tumors with a low score. Since 2007, the American Society of Clinical Oncology recommends the clinical use of Oncotype Dx RS (ODxRS) as a decision-making tool to influence the management of patients with lymph node-negative (LN–), estrogen receptor-positive (ER+) breast cancer.[14] The RS identifies patients most likely to benefit from adjuvant chemotherapy based on their 10-year risk of distant relapse and also those with low risk who are best spared unnecessary treatment.[13,15]

Correlating genomic information with image findings is a new field of research, and the overlap between imaging features and genomic characteristics in breast cancer is not well established. The ability to estimate the likelihood of recurrence on the basis of molecular profile and imaging findings could become an important noninvasive tool for stratifying patients according to prognosis, allowing clinicians to make personalized tailored treatment decisions for an individual patient.[16–18] Our goal was to measure lesion ADC value at 3T and to assess correlation with ODxRS scores.

Materials and Methods

Subjects

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

A total of 854 consecutive patients with BI-RADS 4, 5, or 6 lesions were included, who underwent preoperative 3.0T MRI with an additional DW-MRI sequence between January 2011 and January 2013. All these studies are done at one site within our network. Patients who received neoadjuvant chemotherapy prior to MRI ($n = 37$) or with suboptimal DW images (artifacts or poor fat suppression) ($n = 29$) were excluded and included only ER + and LN– lesions. In this study population, there were 73 ER + (HER2-negative, PR-positive), axillary LN– tumors. The ODxRS test was performed for treatment planning for 43 of the 73 cases. ODxRS was not performed in 30 cases. In these cases the medical oncologist did not deem testing necessary based either on the size of the invasive carcinoma component (<5 mm or >2 cm as determined microscopically), the grade of the tumor (grade I or grade III), or presence of other comorbidities that precluded chemotherapy. Out of the 43 patients, only 29 had available evaluable DW-MRI data for both b-values (600 and 1000 s/mm^2) for 31 invasive cancers (two bilateral diseases) included. The median age of the subjects was 53.2 years (range 37–74 years)

MR Image Acquisition

MRI was acquired on a 3.0T system (Discovery MR750; GE Healthcare, Milwaukee, WI) using the body coil as a transmitter and a dedicated 8-channel or 16-channel phased-array receiver coil (Sentinelle Vanguard; Canada). Conventional T_1- and T_2-weighted images were acquired with and without fat suppression (slice thickness, 3 mm). Axial DW-MRI was performed using 2D, single-shot echo-planar imaging sequences (TR: 6000 msec; TE: 56.2–94.7 msec; flip angle: 90°; number of excitations: 3; acquisition matrix: 98 × 98 or 128 × 128; reconstructed matrix: 256 × 256; field of view, 30–36 cm; slice thickness: 4 or 5 mm; slice gap: 0–1 mm; fat suppression: enhanced; parallel imaging: ASSET; acquisition time: ~3 min). The DWI images were obtained as part of the patient's clinical MRI examination. Initially, DW-MRI data at b-values of 0, 600 s/mm^2 and 0, 1000 s/mm^2 were collected as sequential scans before the availability of DWI software, which is capable of collecting data within a single MR scan at multiple b-values. The median and range of TE values for a DWI sequence using b600 is 62.1 msec (56.2, 94.7 msec) and b1000 is 62.1 msec (56.2, 94.7 msec) and the maximum difference in TE for a single patient is less than 6.4 msec.

The DCE MR images were acquired using a previously described protocol[19] with sagittal 3D T_1-weighted gradient echo VIBRANT sequences before and at three points of 60-second intervals after an injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Bayer HealthCare, Hanover, NJ). Subsequently, axial 3D T_1-weighted gradient echo VIBRANT delayed CE imaging was performed.

Image Analysis

MR images were analyzed on the Advantage Workstation (GE Healthcare), and parametric quantitative ADC maps were

TABLE 1. Patient, Lesion, and MRI Characteristics

Patient mean age 53.2 years (range 37-74 years)

Lesion characteristics	Value (%)
Number of lesions (total)	***31 (100)***
Lesion mean size 19 ± *10 mm (range 8-44 mm)*	
Size	
≤ 2 cm (T1)	22 (71.0)
> 2-5 cm (T2)	9 (29.0)
Enhancement type	
Mass	23 (74.2)
Nonmass	8 (25.8)
Histopathological type	
Invasive Ductal Carcinoma (IDC)	26 (83.9)
Invasive Lobular Carcinoma (ILC)	4 (12.9)
Invasive Mammary Carcinoma[a]	1 (3.2)
Histological grade	
Low	13 (41.9)
Intermediate	11 (35.5)
High	4 (12.9)
Data not available	3 (9.7)
Lymphovascular invasion	
Not present	19 (61.3)
Present	7 (22.6)
Data not available	5 (16.1)

[a]One invasive carcinoma with mixed ductal and lobular features.

generated by READY View software (GE Healthcare). A radiologist (M.D., with 8 years of experience reading breast MRI) identified the lesions using a T_1 contrast-enhanced weighted image, and the slice location was recorded to match the closest image location on DW images. A region of interest (ROI) was drawn by a radiologist (M.D., with 8 years of experience in breast MRI) within each lesion on DW images on a single axial slice with the largest tumor, while cystic/necrotic portions were avoided. ADC value was automatically calculated when the ROI was drawn for each proven primary malignancy. ADC_{600} and ADC_{1000} were calculated using DW-MRI data collected at b-values of 0, 600 s/mm^2 and 0, 1000 s/mm^2, respectively. ADC map images for the figures were generated by using custom developed image analysis software (Firevoxel; NYU Medical Center, New York, NY). In multifocal/multicentric disease, the index cancer (represented by the largest malignancy) was analyzed. The ADC analysis was blinded to the histopathological type details. The ADC values were measured in units of mm^2/s.

Histology

The results of histopathological analysis (size, histological type and grade, LN status, presence of lymphovascular invasion status) and the expression of ER, progesterone receptor (PR), and HER2 status were recorded. The ODx test (Genomic Health) was performed using paraffin-embedded tumor tissue blocks for ER + and LN– cases of invasive breast carcinoma after definitive surgery. Based on the gene expression, a quantitative RS (estimated risk of recurrence in 10 years) was determined (RS range: 0–100), with stratification into low (RS <18), intermediate (RS from 18 to 30), or high (RS >30) risk groups.

Statistical Analysis

Statistical analysis was performed on the data using SPSS software (SPSS Statistics for Windows, v. 17.0. Chicago, IL) and using a nonparametric Mann–Whitney's test to test for differences in ADC values (ADC_{600} and ADC_{1000}) by ODxRS score (low vs. intermediate/high) and tumor size based on diameter (T_1: ≤2 cm vs. T_2: 2–5 cm). Additionally, subanalysis were conducted to observe differences in ADC values by dichotomizing into ODxRS score (low vs. intermediate/high) when considering only mass lesions or only invasive ductal carcinomas (IDC). All P values were adjusted for multiple comparisons using the false discovery rate (FDR) method, which controls the expected proportion of null hypotheses that are incorrectly rejected (FDR and statistical significance was established at $P < 0.05$). Both raw and adjusted P values are presented in the tables. Receiver operating characteristic (ROC) curves were also constructed for both ADC_{600} and ADC_{1000} to assess the diagnostic performance of the ADC value in the discrimination between low versus intermediate/high-risk ODxRS.

Results

The mean ± standard deviation (SD) size of the 31 lesions included in the study was 19 ± 10 mm (range 8–44 mm); the histologic type was mostly IDC (26/31; 83.9%), with predominantly low (13/31; 41.9%) or intermediate (11/31; 35.5%) histological grade tumors (Table 1).

The mean ± SD of ADC_{600} value of the 31 ER+/LN– invasive cancers eligible for the analysis was $(1.098 \pm 0.195) \times 10^{-3}$ mm^2/s, and the mean and standard deviation of ADC_{1000} value was $(0.961 \pm 0.176) \times 10^{-3}$ mm^2/s. It should be noted that there was a significant difference between the two ADC values ($P = 0.001$).The median ODxRS was 15 (range: 2–43). Twenty-one of 31 (68%) lesions had a low RS, 9/31 (29%) had an intermediate RS, and 1/31 (3%) had a high-risk RS.

A statistically significant difference was observed when ODxRS was stratified as low-risk versus intermediate or high-risk for both ADC_{600} ($P = 0.007$) and ADC_{1000} ($P = 0.008$) mean values (Table 2) (Figs. (1 and 2)).

Figure 3 shows the scatterplot of ADC_{600} versus ADC_{1000} for all lesions. ADC values at both b factors seem to have a positive correlation coefficient ($R^2 = 0.8171$).

Using univariate analysis and stratifying the lesions according to size, no significant difference ($P > 0.05$) was

TABLE 2. ADC Values Mean and Standard Deviation (SD) of Breast Lesions Stratified Into Low Versus Intermediate/High-Risk Oncotype Dx Recurrence Score (ODxRS) and *P*-values

		ADC_{600} (10^{-3} mm^2/s)			ADC_{1000} (10^{-3} mm^2/s)		
ODxRS	***n* (%)**	**Mean**	**SD**	***P*-value**	**Mean**	**SD**	***P*-value**
Low	21(68)	1.154	0.209	**0.007**	1.004	0.199	**0.008**
Int./High	10(32)	0.981	0.088		0.870	0.029	

observed between ADC mean values of T_1 ($\leq$2 cm) and T_2 lesions (2–5 cm) for low or intermediate/high ODxRS cancers (Table 3).

Table 4 depicts the subanalysis of ODxRS in low versus intermediate/high-risk cancers considering only mass lesions ($n = 23$) or IDCs ($n = 26$). In these subgroups, low-risk cancers had significantly higher ADC values for both b values of 600 and 1000 s/mm^2, even for mass lesions or IDCs, when compared with ADC values from intermediate and high-risk lesions (mass lesions: $P = 0.03$ and 0.01; IDC: $P = 0.001$ and 0.009).

The boxplots (Fig. 4) were also subgrouped based on mass lesions or IDCs and show the statistically different values for ADC_{600} and ADC_{1000} when considering low or intermediate/high-risk ODxRS. All significant findings also showed significance after adjusting for multiple comparisons (Table 5).

Figure 5 shows the ROC curves for both ADC_{600} and ADC_{1000} values, yielding an area under the curve (AUC) values of 0.785 and 0.793 to discriminate low versus intermediate/high-risk ODxRS lesions, respectively.

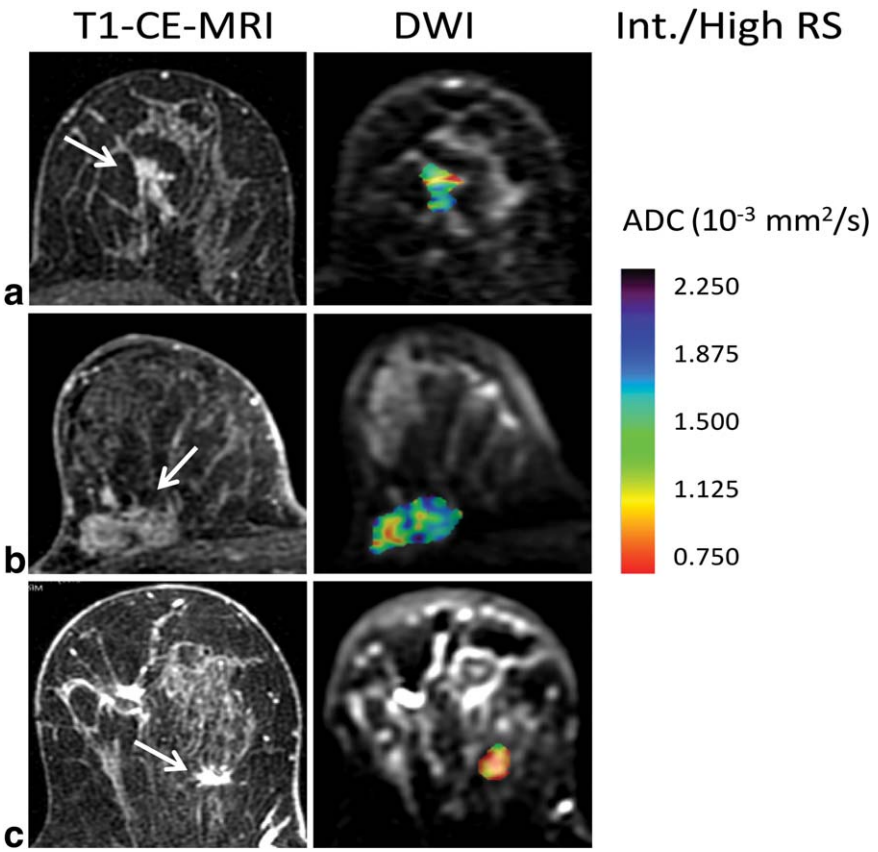

FIGURE 1: Axial T_1-contrast enhanced (CE) MR image (left side shown) and diffusion-weighted (DW) image (DWI) overlaid with the lesion ADC map at b = 600 s/mm^2 (right) are shown for patients with different low-risk Oncotype Dx recurrence scores (RS <18). Scaling of images was arbitrary and ADC color bar was indicated in the units of 10^{-3} mm^2/s. A: A 64 year-old woman with a 2.6 cm heterogeneously enhanced mass, proven invasive ductal carcinoma (IDC) with estrogen receptor-positive (ER+), lymph node-negative (LN–) in the upper inner quadrant of the right breast (RS = 9; $ADC_{600} = 1.26 \times 10^{-3}$ mm^2/s). B: A 65 year-old woman with a 2.7 cm heterogeneously enhanced oval mass, proven IDC ER+, LN– in the left lower outer quadrant (RS = 7; $ADC_{600} = 1.16 \times 10^{-3}$ mm^2/s). C: A 55 year-old woman with a 1.5 cm heterogeneously enhanced mass, proven IDC ER+, LN– in the left upper inner quadrant (RS = 14; $ADC_{600} = 0.941 \times 10^{-3}$ mm^2/s).

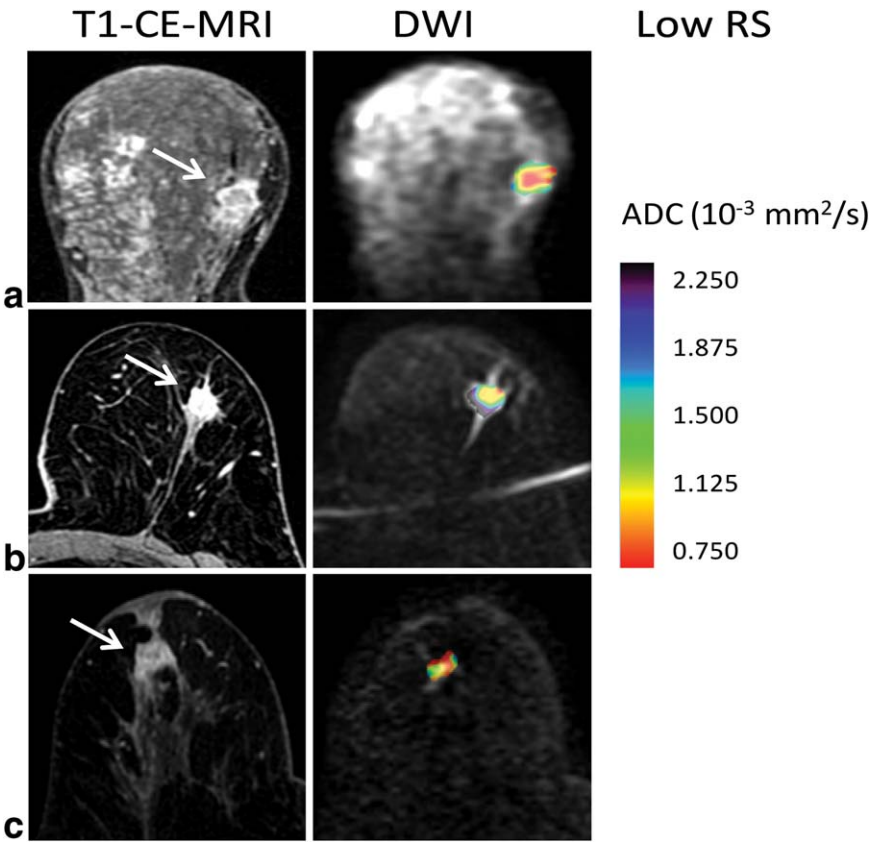

FIGURE 2: Axial T_1-contrast enhanced (CE) MR image (left side shown) and diffusion weighted (DW) image overlaid with the lesion ADC map at b = 600 s/mm^2 (right) are shown for patients with different intermediate/high risk Oncotype Dx recurrence scores (RS ≥18). Scaling of images was arbitrary and ADC color bar was indicated in units of 10^{-3} mm^2/s. A: A 37-year-old woman with a 2.5 cm heterogeneously enhanced mass, proven ductal invasive carcinoma (IDC) estrogen receptor-positive (ER+), lymph node-negative (LN–) in the left upper inner quadrant (RS = 43; $ADC_{600} = 0.974 \times 10^{-3}$ mm^2/s). B: A 55 year-old woman with a 1.6 cm heterogeneously enhanced spiculated mass, proven IDC ER+, LN– in the right upper outer quadrant (RS = 30; $ADC_{600} = 1.09 \times 10^{-3}$ mm^2/s). C: A 55 year-old woman with a 2 cm heterogeneously enhanced oval mass, proven IDC, ER+, LN– in the left central quadrant (RS = 18; $ADC_{600} = 1.06 \times 10^{-3}$ mm^2/s).

Discussion

Our study dichotomized lesions by ODxRS scores and found ADC values to be significantly different based on ODxRS scores. The results demonstrated that the mean ADC value was higher in ODxRS stratified in low-risk than in intermediate or high-risk RS cancers. As noted in the Results, although ADC using either b-value was proved to be significant in stratifying the recurrence score groups, there was also a significant difference observed between ADC_{600} and ADC_{1000} values. There may be some discrepancies or differences in values for the two ADC parameters due to multiple factors, including the effect of pseudoperfusion, the effect of noise on the measurement, and the impact of TE. In the present study, DWI images were obtained as part of the patient's clinical MRI examination with the "optimal TE," option which automatically estimates the shortest TE for the DWI sequence (based on the gradient strength but not on gradient durations) and the delay between diffusion gradient pulses. Note that the TE difference is in the range of 0–6.4 msec between b600 and b1000 scans within a single study, which may cause a minimal effect on the DW signal.

However, overall, it seems as though cellularity is a dominant component that allows for both ADC values to

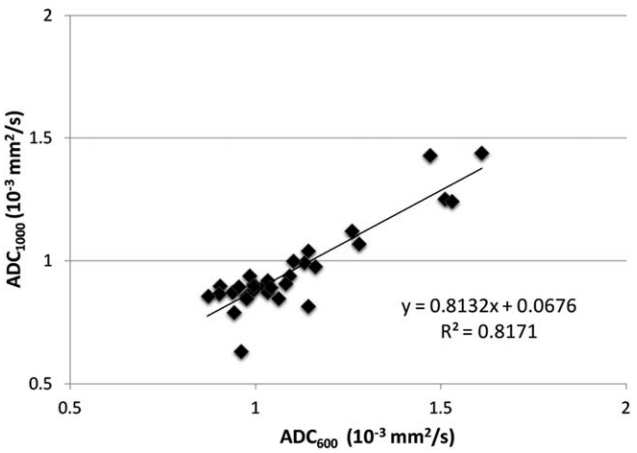

FIGURE 3: Scatterplot of ADC_{600} versus ADC_{1000} for all lesions: ADC values at both b factors have positive correlation coefficient ($R^2 = 0.8171$).

TABLE 3. ADC Mean and Standard Deviation (SD) Values in T1 (≤2 cm) and T2 (2-5 cm) Lesions Correlated With the Recurrence Risk Score According to Oncotype Dx (ODxRS)

	ADC_{600} (10^{-3} mm^2/s)					ADC_{1000} (10^{-3} mm^2/s)				
	T1 (≤ 2 cm)		T2 (>2-5 cm)			T1 (≤ 2 cm)		T2 (>2-5 cm)		
ODxRS	*n*	Mean ± SD	*n*	Mean ± SD	*P*-value	*n*	Mean ± SD	*n*	Mean ± SD	*P*-value
Low	14	1.132 ± 0.208	7	1.199 ± 0.217	0.40	14	0.978 ± 0.206	7	1.057 ± 0.189	0.26
Int./High	8	0.985 ± 0.085	2	0.965 ± 0.134	0.71	8	0.875 ± 0.031	2	0.852 ± 0.085	0.27

significantly differentiate between low and intermediate/high ODxRS scored cancers. The same trend was demonstrated when the lesions were subgrouped only as mass lesions, or IDCs, to exclude the possible influence in the ADC values on account of lesion features (mass versus nonmass or different histological subtypes) because it is well known that mass lesions and IDC show significantly lower ADC values than nonmass lesion[10] and other histological subtypes,[20] respectively.

Several studies[9,10,20–27] have evaluated ADC as a potential prognostic factor by analyzing its relationship with traditional and molecular prognostic factors, although the impact of ADC on prognosis still needs to be validated. Recently, Rabasco et al[28] investigated the correlation between ADC in breast cancer and the presence of distant metastases at 3 years, suggesting that ADC values may represent a significant prognostic factor.

Our results are interesting considering recent related studies[9,21,23–27] that correlate ADC values with other prognostic markers such as histopathological features (size, histopathological type, grade, lymph nodal status) and molecular biomarkers (ER, PR, and HER2 status). These report, in general terms, that ADC is lower in more aggressive lesions.

The current study shows that, independent of the tumor size for ER+/LN– lesions, a lower ADC value correlates with an increasing ODxRS and consequently an incremental estimate recurrence risk of cancer. This finding could allow for the use of ADC to identify patients who are at low risk for recurrence and provide an alternate prognostic marker in determining patients who are ER+/LN–, who require adjuvant chemotherapy.

To our knowledge, only a few studies have investigated the correlation between imaging findings (MR and conventional imaging) with ODxRS. Initially, Daye et al[29] evaluated the tumor features on contrast-enhanced breast MRI as a prognostic marker for breast cancer compared to ODxRS. They retrospectively analyzed 61 women diagnosed with ER+/LN– invasive breast cancer and evaluated seven tumor-specific features, including lesion size and shape, margin morphology, enhancement morphology and amount, presence of multifocal disease, and associated nonmass enhancement. Tumor multifocality and lesion size were the most important in predicting the recurrence risk categories, with the best performance in distinguishing the low- from high-risk groups, suggesting that MRI tumor features can predict the RS category as determined by the ODxRS assay.

Yepes et al[16] investigated whether mammographic or sonographic features could predict the ODxRS in patients with T_1 or T_2 tumors, hormone receptor-positive, HER2-negative, and LN– breast cancers. Of all the findings, only pleomorphic microcalcifications within a mass on mammograms and posterior acoustic enhancement on ultrasound reached statistical significance on multivariate logistic regression, resulting in association with intermediate or high-risk RS lesions. However, as reported, there was a markedly low interobserver agreement and a wide variability in predicting the RS, based on the imaging characteristics alone (regardless of years of experience as breast imagers), suggesting that

TABLE 4. ADC Mean With Standard Deviation (SD) Subgrouped in Mass Lesions and Invasive Ductal Carcinoma (IDC) for Low and Intermediate/High-Risk Oncotype Dx Recurrence Score (ODxRS)

	Mass lesions ($n = 23$)		IDC ($n = 26$)	
ODxRS	ADC_{600} ($P = 0.03$)[a]	ADC_{1000} ($P = 0.01$)[a]	ADC_{600} ($P = 0.001$)[a]	ADC_{1000} ($P = 0.009$)[a]
Low	1.140 ± 0.184	0.988 ± 0.19	1.152 ± 0.202	1.005 ± 0.203
Int. / High	0.989 ± 0.088	0.867 ± 0.029	0.949 ± 0.061	0.872 ± 0.022

[a]Significant value. ADC values are represented in the units of 10^{-3} mm^2/s.

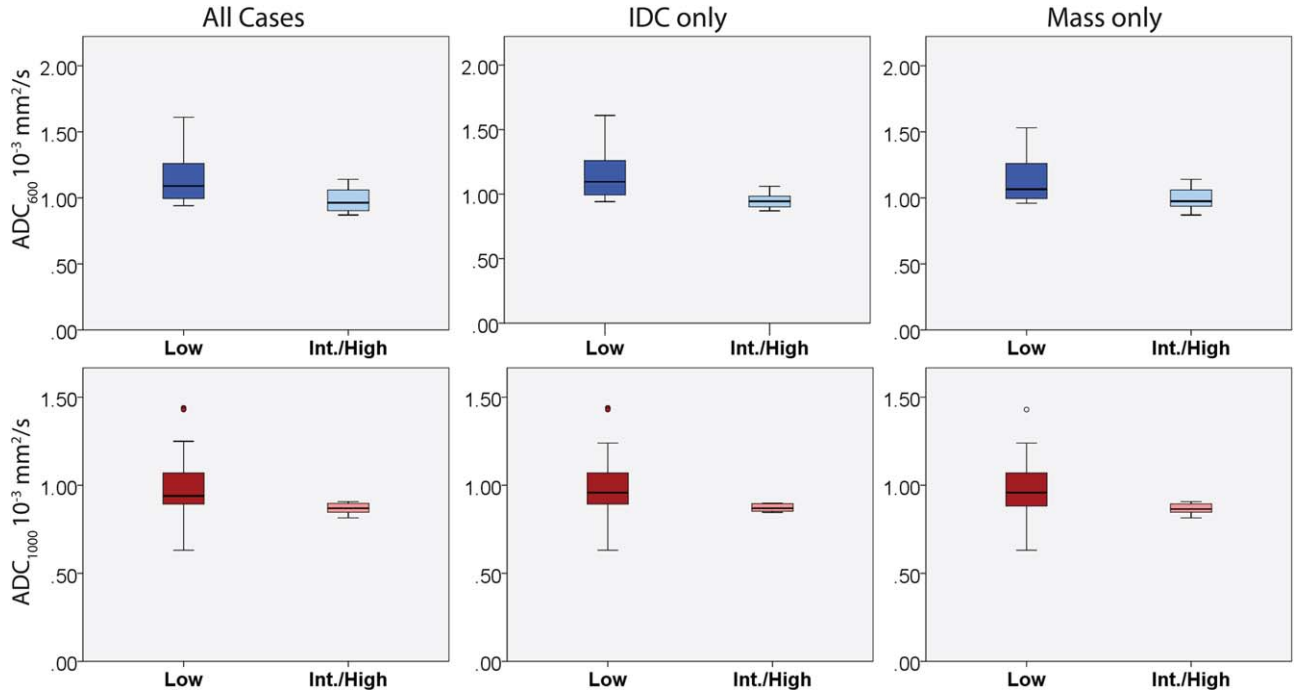

FIGURE 4: Boxplots show median and interquartile range (25th and 75th percentiles) of ADC_{600} and ADC_{1000} values for all lesions, masses, and IDC lesions for low or intermediate/high-risk ODxRS.

imaging findings alone cannot consistently predict the risk of recurrence or whether chemotherapy is needed. More recently, Dialani et al[17] reported that oval shape on mammograms, the presence of vascularity and posterior acoustics on ultrasound images, and lobulated shape on MR images, in combination with low ER positivity, PR negativity, and HER2 positivity, were associated with high recurrence scores.

Moreover, Ashraf et al[30] evaluated the correlation between intrinsic imaging phenotypes in 56 breast cancer lesions (including both ductal and lobular carcinomas) with ODxRS. Based on kinetic findings, number of pixels, and tumor area, a moderate correlation between DCE-MRI features and RS were seen and four distinct imaging phenotypes were assessed. Phenotypes 1 and 2 consisted entirely of tumors that had an RS lower than 31 and included only low- and medium-risk tumors, whereas phenotypes 3 and 4 consisted of a mix of all the recurrence risk categories. Overall, tumors with a high risk of recurrence gene expression profile tend to show predominantly rapid contrast material

TABLE 5. Raw and Adjusted *P* Values From Multiple Comparison Analysis

			P-value	
			Raw	**Adjusted**
ODxRS Low vs. Int./High		ADC_{600}	0.007[a]	0.020[a]
		ADC_{1000}	0.008[a]	0.020[a]
Size T1 vs. T2	*ODxRS Low only*	ADC_{600}	0.400	0.556
		ADC_{1000}	0.260	0.286
	ODxRS Int./High only	ADC_{600}	0.710	0.700
		ADC_{1000}	0.270	0.375
Mass only ODxRS – Low vs. Int./High		ADC_{600}	0.030[a]	0.050
		ADC_{1000}	0.010[a]	0.020[a]
IDC only ODxRS – Low vs. Int./High		ADC_{600}	0.001[a]	0.010[a]
		ADC_{1000}	0.009[a]	0.020[a]

[a]Significant value.

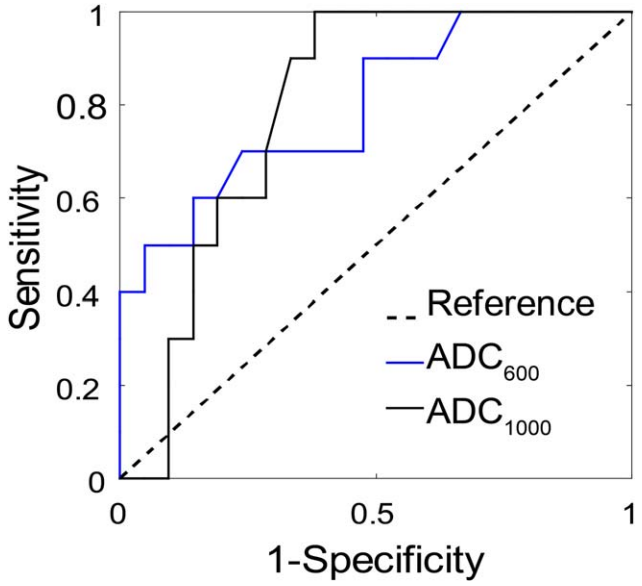

FIGURE 5: Receiver operating characteristic (ROC) curve demonstrating AUC (area under the curve) for ADC values at both b factors (600 s/mm^2 and 1000 s/mm^2) to discriminate low versus intermediate/high-risk Oncotype Dx Recurrence Score. AUC values were calculated as 0.785 and 0.793 using ADC_{600} and ADC_{1000}, respectively.

uptake. Similarly, Sutton et al[18] investigated a broad range of morphological and textured-based image features on DCE-MRI of early stage Luminal A-like (ER+, PR+, HER2–) IDC and its correlation with ODxRS. Two computer-extracted histogram-based kurtosis image features on the first and third postcontrast images were significantly associated with ODxRS, and an increased kurtosis was found to be a significant factor, implying a higher risk. Besides, Li et al[31] demonstrated that regression models of MR computer-extracted image phenotypes (MRI radiomics) were significantly associated with breast cancer risk of recurrence as predicted with research-based multigene assays, including ODx.

There are limitations to our study. First, it was a retrospective study with a small sample size. There were more patients with a low-risk ODxRS and only one patient who had an RS above 30. As a result, this high-risk ODxRS case was combined with the remaining intermediate-risk patients into one group. Although high-risk patients receive additional chemotherapy treatment, among intermediate-risk patients the oncologist generally decides which patients receive chemotherapy based on the individual patient's clinical history, whereas low-risk patients do not receive any additional treatment. Furthermore, it is noted that the ROI drawn for obtaining ADC measurements may not completely reflect the whole tumor characteristics and may disregard other important features because it came from a single representative slice and not full 3D volumetric analyses. Additionally, more detailed analysis of the MRI data could reveal more features of the tumor microenvironment. Finally, the association between ADC values and disease-free survival, or overall survival, could not be evaluated due to limited follow-up of the population.

In the present work, we focused only on the imaging-based ADC measurement, but we advocate, accordingly with other works studying image-based features correlated with ODxRS, that the combination of the multiple parameters, including standard markers, quantitative image-based features, and diffusion imaging may create an integrated customized prognostic tool that can better support clinical decision-making and prognostic assessment for breast cancer treatment.

In summary, ADC is a potential surrogate biomarker for malignant lesion aggressiveness in ER+/LN– invasive breast cancers and may reflect the expectance of recurrence, or an advantage with chemotherapy, based on ODxRS. However, at the moment pathologic and genetic markers remain far more reliable in indicating prognosis and the need for adjuvant treatment compared with imaging biomarkers. Further studies with larger cohorts would be needed to validate these findings prospectively in association with recurrence outcome, based on patient follow-up to confirm our preliminary data.

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