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High-Resolution Diffusion-Weighted Imaging for Monitoring Breast Cancer Treatment Response

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Abstract

Rationale and Objectives—The aim of this work was to compare a high-resolution diffusion-weighted imaging (HR-DWI) acquisition (voxel size = 4.8 mm^3) to a standard diffusion-weighted imaging (STD-DWI) acquisition (voxel size = 29.3 mm^3) for monitoring neoadjuvant therapy-induced changes in breast tumors.

Materials and Methods—Nine women with locally advanced breast cancer were imaged with both HR-DWI and STD-DWI before and after 3 weeks (early treatment) of neoadjuvant taxane-based treatment. Tumor apparent diffusion coefficient (ADC) metrics (mean and histogram percentiles) from both DWI methods were calculated, and their relationship to tumor volume change after 12 weeks of treatment (posttreatment) measured by dynamic contrast enhanced magnetic resonance imaging was evaluated with a Spearman's rank correlation.

Results—The HR-DWI pretreatment 15th percentile tumor ADC (P = .03) and early treatment 15th, 25th, and 50th percentile tumor ADCs (P = .008, .010, .04, respectively) were significantly lower than the corresponding STD-DWI percentile ADCs. The mean tumor HR-ADC was significantly lower than STD-ADC at the early treatment time point (P = .02), but not at the pretreatment time point (P = .07). A significant early treatment increase in tumor ADC was found with both methods (P < .05). Correlations between HR-DWI tumor ADC and posttreatment tumor volume change were higher than the STD-DWI correlations at both time points and the lower percentile ADCs had the strongest correlations.

Conclusion—These initial results suggest that the HR-DWI technique has potential for improving characterization of low tumor ADC values over STD-DWI and that HR-DWI may be of value in evaluating tumor change with treatment.

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Keywords

Diffusion-weighted magnetic resonance imaging; DWI; breast cancer; treatment response; apparent diffusion coefficient; ADC

Magnetic resonance imaging (MRI) techniques are increasingly used to evaluate tumors in patients with locally advanced breast cancer who are undergoing neoadjuvant (preoperative) chemotherapy. Although change in tumor size is recognized as a surrogate predictor of response to chemotherapy (1,2), tumor morphologic changes tend to occur later in therapy and typically become apparent after biologic effects (3,4). Thus, there is an increasing clinical need to identify early markers for monitoring therapeutic response and improving treatment strategy.

Diffusion-weighted imaging (DWI) has shown promise as a potential imaging biomarker of early treatment response. DWI sequences use diffusion sensitizing gradients to detect differences in water mobility that reflect tissue microenvironment and microstructure. Unlike dynamic contrast-enhanced (DCE) MRI, DWI has the advantage of not requiring the use of a contrast agent.

Previous studies have shown that the apparent diffusion coefficient (ADC) measured from DWI is lower in breast tumors than in benign lesions or normal fibroglandular tissues (5,6) and that ADC has positive predictive value in diagnostic studies of breast cancer (7,8). Moreover, in some studies of patients undergoing neoadjuvant therapy for breast cancer, an increase in tumor ADC has been shown to precede a decrease in tumor size (4) and in a few published reports pre-treatment tumor ADC or early change in ADC predicted tumor volume response or pathologic complete response (6,9–11). However, a number of other studies have not shown DWI tumor metrics to be predictive of response (12–14). Although DWI shows promise for monitoring early treatment changes, the technique suffers from certain technical challenges that may adversely affect its ability to detect such changes.

For example, the in-plane spatial resolution of DWI, typically around 2 mm, is not as high as that of other conventional sequences such as T1-weighted gradient echo imaging used for DCE-MRI. This can result in increased partial volume averaging, which may hinder discrimination between heterogeneous tumor regions or between tumor and normal tissue. Additionally, inadequate fat suppression may also contribute to errors in calculated tumor ADCs (15). Another limitation is that the diffusion weighted single shot echo planar imaging sequences (ss-EPI) typically available on commercial scanners are prone to distortion artifacts because of the relatively long readout durations (16).

One approach to decrease the required readout duration for ss-EPI is to use a reduced field-of-view (rFOV) acquisition which allows for a reduction in the number of k-space lines required to achieve a high-resolution image. An ss-EPI rFOV DWI sequence has recently been developed for the spine using a two-dimensional spatially selective echo-planar radiofrequency excitation pulse and a 180° refocusing pulse to reduce the FOV in the phase-encode direction (17). A high in-plane resolution image can thus be acquired with significantly fewer k-space lines, whereas off-resonance induced artifacts are reduced

because of the shortened readout. Because this method actively excites only the imaging region of interest, it differs from other reduced FOV techniques in that it does not require outer-volume suppression pulses that can result in potentially higher specific absorption rates (18). Unlike inner-volume methods, this sequence has the added benefit of allowing contiguous multislice imaging without the need for a slice skip (19), while simultaneously suppressing the signal from fat, both of which are important considerations in breast imaging.

We have optimized this high spatial resolution rFOV DWI sequence (HR-DWI) for imaging the breast. In previous work evaluating the HR-DWI technique in locally advanced breast tumors, image quality and tumor conspicuity were improved compared to the standard commercially available DWI (STD-DWI) sequence, when evaluated by two board-certified radiologists (20). These qualitative improvements were accompanied by statistically significant differences in the tumor ADC distribution. Therefore, we hypothesized that HR-DWI measurements of tumor response to neoadjuvant therapy in patients with locally advanced breast cancer would differ from standard FOV diffusion measurements, and might better correlate with MRI-measured change in tumor volume. We sought to test this hypothesis by 1) comparing the HR-DWI sequence with a STD-DWI sequence for characterizing breast tumor ADCs before treatment and at an early treatment time point and 2) evaluating the relationship between tumor ADC metrics and MRI-measured tumor volume change at the end of treatment.

MATERIALS AND METHODS

Patient Population

MRI was performed on patients with locally advanced breast cancer enrolled in institutional review board–approved studies at our institution. All patients gave informed consent. The study population comprised patients with biopsy-confirmed invasive breast cancer undergoing 12 weekly cycles of taxane-based neoadjuvant therapy who were scanned with DCE-MRI before starting treatment (pretreatment), after 3 weeks of treatment (early treatment) and after completion of 12 weeks of treatment (posttreatment). A subset of these patients was also scanned with both HR-DWI and STD-DWI at the pre- and early treatment time points when time permitted, and only this subset was included in this analysis. Exclusion criteria were patients with missing HR-DWI or STD-DWI at either DWI time point or insufficient DWI data quality for quantitative analysis. Nine women (mean age 48.9 years; age range 24–66 years) met the study inclusion criteria, and all nine had biopsy-confirmed invasive ductal carcinoma. Patients were scanned between April 2010 and June 2011.

MRI Data Acquisition

MRI was performed on a 1.5T GE Signa LX scanner (GE Healthcare, Waukesha, WI) using a bilateral eight-channel phased array breast coil (Hologic [formerly Sentinelle Medical], Toronto, Canada). All imaging was performed in the axial orientation. The diffusion sequences were acquired after DCE-MRI.

Standard DCE-MRI—Fat-suppressed, T1-weighted DCE-MRI data were acquired with a three-dimensional fast gradient echo sequence using the imaging parameters: repetition time (TR)/echo time (TE) = 7 ms/4.2 ms, flip angle = 10° FOV = 280–360 mm × 280–360 mm. Patients received 0.1 mmol/kg body weight of gadopentetate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals, Berlin, Germany) contrast agent.

Diffusion-weighted MRI—STD-DWI data were acquired with a fat-suppressed diffusion-weighted echo planar imaging sequence using the imaging parameters: TR/TE = 6000/ 69.6 ms, b = 0, 600 s/mm^2, FOV = 400 × 400 mm, matrix = 128 × 128, slice thickness = 3 mm, gap = 0, averages = 6, voxel size: = 29.3 mm^3, and acquisition time 4.30 minutes.

HR-DWI data were acquired with the previously described fat-suppressed diffusion-weighted rFOV ss-EPI sequence: TR/ TE = 4000/64.8 ms, b = 0, 600 s/mm^2, FOV = 140 × 70 mm, matrix = 128 × 64, slice thickness = 4 mm, gap = 0, averages = 16, voxel size = 4.8 mm^3, and acquisition time 4.33 minutes.

MRI Data Analysis

ADC maps for the STD-DWI data were calculated using in-house Interactive Data Language (IDL) software (version 7.0,

ITT Visual Information Solutions, Boulder, CO) with an assumption of monoexponential decay and the equation:

$$ADC = -\ln(SD/S0)/\mathbf{\Delta}b(\mathrm{mm}^2/s) \quad (1)$$

where S_0 and S_D are the b = 0 (s/mm^2) and b = 600 (s/mm^2) signals, respectively, and **Δ**b = 600 (s/mm^2). ADC maps for HR-DWI data were constructed automatically from complex averaged images using previously published methods (17).

DWI ROI Delineation

Tumor ROIs were manually drawn by two MRI scientists with 10 and 5 years' experience in breast MRI, in consultation with a board-certified radiologist specializing in breast imaging. The scientists were blinded to tumor pathology and response to neoadjuvant therapy. One region of interest (ROI) for each tumor was manually defined on the HR-DWI slice estimated to contain the largest tumor area, for each time point (pre- and early treatment) independently. Tumor ROIs were drawn to encompass areas that were hyperintense on HR-DWI (b = 600 combined images) and hypointense on corresponding HR-DWI ADC maps. The boundary of the tumor was chosen to maximize the amount of tumor tissue included, while avoiding surrounding normal appearing tissue. Enhancing areas on DCE-MRI subtraction images (precontrast subtracted from early postcontrast) were also used to verify the location of the lesion. Cysts, clip artifacts, and areas of necrosis were excluded from tumor ROIs based on their appearance in precontrast T2-w and T1-weighted images and nonenhancing tumor areas on postcontrast DCE images.

The tumor ROIs defined on the HR-DWI data were then automatically mapped to the corresponding slice and location on the STD-DWI ADC maps acquired in the same imaging

exam using in-house IDL software. In cases where there was in-plane misregistration between the two acquisitions, the ROI was manually shifted to include only tumor tissue.

DWI Quantitative Analysis

The ADC distribution of the voxels between 0 and 5.0×10^{-3} mm^2/second contained in the ROIs was quantitatively assessed in using the in-house IDL software. Although 5.0×10^{-3} mm^2/second is above the diffusivity of free water at body temperature, it was chosen as the upper limit for initial evaluation of the HR-DWI sequence. Tumor ADC metrics, including the mean, median, standard deviation, and 15th, 25th, 50th, 75th, and 90th percentile ADCs were calculated.

Tumor Volume

Tumor volumes for each imaging visit (pretreatment, early treatment, and posttreatment) were calculated from pre- and postcontrast DCE-MRI data using a previously described semiautomated segmentation method to calculate the volume of all tumor voxels that exceeded an enhancement threshold of 70% at the first postcontrast time point (21). Absolute tumor volume change was defined as (volume posttreatment – volume pretreatment) and percent volume change was defined as (volume posttreatment – volume pretreatment)/ (volume pretreatment) × 100. Additionally, tumors were categorized into responder and nonresponder groups based on the percent change in tumor volume at the posttreatment time point. Responders were tumors with a strong treatment response (>65% tumor volume decrease) and nonresponders were tumors with a weaker response (<65% tumor volume decrease). Sixty-five percent was chosen as a cutoff value based on other published results that expanded on Response Evaluation Criteria In Solid Tumors (RECIST) criteria for evaluating volumetric response of tumors to treatment (22) and evaluated posttreatment MRI tumor volume change as a predictor of recurrence-free survival in breast cancer patients (2).

Statistical Analysis

Differences between tumor ADC values calculated from HR-DWI and STD-DWI sequences were compared using a Wilcoxon signed-rank test. Spearman's rank correlation coefficients were used to assess the relationship between tumor ADC metrics calculated from each DWI method before and at the early treatment time points and change in tumor volume measured by MRI. A nominal statistical significance level of $\alpha = 0.05$ was used to assess statistical significance. Statistical analysis was performed using JMP V9.0.0 (SAS Institute, Cary, NC).

RESULTS

HR-DWI and STD-DWI data were acquired for nine patients with locally advanced breast cancer before and after 3 weeks of taxane-based therapy. All nine patients had invasive ductal carcinoma (six were Scarf-Bloom-Richardson Grade 2 and three were Grade 3). Estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status was available for seven of the nine patients. Of those seven, four were estrogen receptor–positive, two were progesterone receptor–positive, two were HER2

positive, and one was indeterminate for HER2 status. The mean MRI-measured tumor volume was 35.5 cm^3 (SD = ± 29.4 cm^3, range 4.6–82.7 cm^3).

Pretreatment

Examples of pretreatment HR-DWI and STD-DWI images of an invasive breast carcinoma are shown in Figure 1. The mean tumor ADCs of the group before treatment were 1.31 (± 0.30) × 10^{-3} mm^2/second for HR-DWI and 1.37 (± 0.30) × 10^{-3} mm^2/second for STD-DWI. Although HR-DWI mean tumor ADC was estimated to be lower than that for STD-DWI, the difference was not statistically significant (*P* = .07, Wilcoxon). The HR-DWI percentile ADCs were lower than the STD-DWI percentile ADCs; however, the only significant difference was found for the 15th percentile tumor ADC (*P* = .03, Wilcoxon) (Table 1a). Overall these results indicate a pattern of lower tumor ADCs for HR-DWI than STD-DWI that is most pronounced for the lower percentile ADC values.

Early Treatment

When the early treatment tumor ADCs from the HR-DWI and STD-DWI acquisitions were compared, statistically significant differences were found for the mean tumor ADC and the 15th, 25th, and 50th percentile ADCs (*P* = .02, .01, .01, and .04, respectively) (Table 1b). The HR-DWI tumor ADC metrics showed a similar (but stronger) pattern to that for the pretreatment time point (ie, with lower ADC metrics for HDR-DWI than the corresponding STD-DWI ADC) and with the greatest difference found for the lower percentile ADC values.

Difference between Pretreatment and Early Treatment

Within the same DWI technique—Visual assessment of representative pre- and early treatment HR-DW images in Figure 2 shows reduced tumor hyperintensity on the b = 600 s/mm^2 images at early treatment compared with pre-treatment as well as reduced tumor hypointensity on the ADC map at early treatment. The mean tumor ADCs at the early treatment time point increased relative to baseline ADCs for both HR-DWI (1.49 ± 0.37 × 10^{-3} mm^2/s, *P* = .03, +14.1%) and STD-DWI measurements (1.60 ± 0.40 × 10^{-33} mm^2/s, *P* = .01, +16.5%). Statistically significant increases were found in all tumor percentile ADCs measured by both HR- and STD-DWI methods (Table 2).

Between the two DWI techniques—The differences between tumor ADC percentiles measured by HR-DWI and STD-DWI at the pre- and early treatment time points are shown in Figure 3. Comparisons of the median change in ADC from pre- to early treatment are given in the final column of Table 2. Although both HR-DWI and STD-DWI showed increases in tumor ADCs at the early treatment point, the increases in tumor ADCs were not statistically significantly different between the two techniques.

Tumor Volume Change with Treatment

Although six individual tumors had measured decreases in volume between the pre- and early treatment time points, the estimated decrease in mean tumor volume for the group at the early treatment time point was not statistically significant (median = −5 cm^3, 95% CI =

−28, 3 cm^3, Wilcoxon $P = .4$). However, a statistically significant decrease in mean tumor volume was found between the pre- and posttreatment time points (median = −25 cm^3, 95% CI = −41, −7 cm^3, Wilcoxon $P = .004$).

Correlation between Tumor ADC and Tumor Volume Change

Spearman's rank correlation testing revealed statistically significant correlations ($P < .02$) between HR-DWI pretreatment tumor ADC metrics and absolute change in tumor volume at the end of treatment. The correlation was the strongest for the lowest (15th percentile) HR-DWI ADC measured ($\rho = -0.90$, $P = .003$). This correlation and the corresponding STD-DWI 15th percentile ADC correlation are depicted in Figure 4. Statistically significant correlations were also found for pretreatment STD-DWI ADC metrics and change in tumor volume, with similar correlations found for all STD-DWI percentiles (STD-DWI correlation range $\rho = -0.73$ to -0.75, with $P < .05$ in all cases). The Spearman's correlations between all pretreatment ADC metrics and tumor volume change at the end of treatment are plotted for both HR-DWI and STD-DWI in Figure 5.

When the ADC versus tumor volume change correlations for the two sequences were compared for the early treatment time point, the HR-DWI had the strongest correlations with volume change for the lower ADC percentiles (15th, $\rho = -0.86$, $P = .005$; 25th, $\rho = -0.90$, $P = .003$; and 50th $\rho = -0.92$, $P = .002$) and all HR-DWI correlations were stronger than corresponding STD-DWI correlations which ranged from $\rho = -0.75$ to -0.83, with $P < .05$). No statistically significant correlation was found between tumor ADC metrics and percent tumor volume change.

However, there was a clear division between the tumors that had a strong volume response posttreatment (>65% decrease) and those that did not. The responders ($n = 7$) had an average tumor volume decrease of 91 ± 7%; the nonresponders ($n = 2$) had an average tumor volume decrease of 23 ± 8%. Additionally, the mean pretreatment tumor HR-DWI ADC metrics found for the responding group were lower in general than those of the nonresponding group, although the differences were not statistically significant (Table 3a). This trend was not observed for pre-treatment STD-DWI ADCs of the two groups. At the early treatment time point, the responders had higher ADCs than the nonresponders for most ADC metrics as measured by both DWI methods (Table 3b).

DISCUSSION

In this preliminary study, we compared the HR-DWI sequence with a STD-DWI sequence for characterizing breast tumor ADCs before and after 3 weeks of neoadjuvant therapy. We then evaluated the relationship between tumor ADC metrics and MRI-measured tumor volume change at the end of therapy. The results of this study indicate that HR-DWI may be more sensitive for determining low tumor ADC values and show that HR-DWI ADCs, in particular low percentile ADCs, correlate more strongly with posttreatment tumor volume change.

Before treatment, the mean tumor ADC values found for the HR-DWI and STD-DWI data were consistent with other published ADC values for untreated breast tumors acquired with

the same MRI field strength and b values (23). Mean tumor ADC increased significantly as measured by both techniques after 3 weeks of therapy, which is in agreement with other studies of breast cancer patients that have reported significant increases in tumor ADC of a similar magnitude at early treatment time points (24) (6).

Differences between HR-DWI and STD-DWI became apparent when tumor percentile ADCs were evaluated. The pretreatment 15th percentile tumor ADC values (lowest percentile measured) were statistically significantly lower for HR-DWI than for STD-DWI, in agreement with earlier work (20). This pattern was more pronounced for the lower percentile ADCs at the early treatment time point. These findings are consistent with HR-DWI having greater sensitivity to low tumor ADC values. One possible explanation for the difference between the sequences is that the smaller voxel size (4.8 mm^3) of the HR-DWI compared to the STD-DWI (29.3 mm^3) results in decreased partial volume averaging between viable tumor tissue, characterized by high cellularity and low ADC values, and normal fibroglandular tissue that has higher ADC values (6,15). This type of partial volume averaging is likely to be most pronounced where the edges of the tumor meet normal tissue. A study of DWI in invasive breast tumors reported that the tumor periphery was the region of the tumor with the lowest ADC values (25). If this is generally the case, then the partial volume averaging between tumor and adjacent nontumor tissue might disproportionally affect the tumor voxels with the lowest ADCs. Additionally, reduced partial volume averaging may be particularly important for early treatment and posttreatment ADC measurements where tumor size may decrease, potentially making partial volume effects more pronounced as the ratio of tumor inner voxels to tumor edge voxels decreases.

Our results showed that HR-DWI ADC metrics had stronger correlations with posttreatment volume change than STD-DWI for the pre- and early treatment time points, with the strongest correlations found for the lower percentile HR-DWI ADCs. These results support the hypothesis that HR-DWI ADC metrics may be superior to STD-DWI metrics for predicting tumor volume changes.

An additional observation was that pretreatment tumor ADC metrics measured by HR-DWI (but not by STD-DWI) were generally lower for the responders than for the nonresponders. Although the differences between the groups were not statistically significant, they are in agreement with a recent study by Park et al (9). This study showed that for breast cancer patients undergoing neoadjuvant docetaxel/doxorubicin therapy, pretreatment tumor ADC was significantly lower in responders (1.04×10^{-3} mm^2/second), defined as patients with greater than 65% reduction in tumor volume after therapy, than in nonresponders (1.30×10^{-3} mm^2/second). A similar relationship between pretreatment tumor ADC and tumor volume change was also found by Iacconi et al (10). However, other studies have found no correlation between pretreatment tumor ADC and final tumor volume change or pathologic complete response (4,13,24). As has been noted, the discrepancies in findings may be due to differences in DWI acquisition parameters, tumor ROI selection, and how tumor volume is calculated (26). The differences between HR-DWI and STD-DWI with respect to posttreatment tumor volume change are of interest and should be investigated in a larger cohort.

The main limitation of this study is the small sample size. Studies of HR-DWI are ongoing so that future work can assess the relationship between HR-DWI ADC metrics and clinical outcomes in a larger patient population. Another limitation is that the slice thickness for high-resolution diffusion sequence needed to be slightly greater (4 mm) than the standard diffusion sequence routinely scanned at our institution (3 mm) in order to keep the acquisition times constant and ensure a sufficient signal-to-noise ratio for quantitative ADC measurements. Because of their much higher in-plane resolution, the HR-DWI voxels were still six times smaller than the STD-DWI voxels. The use of a single ROI to characterize each tumor is another possible source of uncertainty, because the ADCs in that representative slice may not reflect the full range ADC values throughout the whole tumor. However, this may not be a serious limitation, as recent work found that the diagnostic accuracy of a single tumor ROI was not significantly different from multiple tumor ROIs for evaluating ADCs of breast cancer (27). Additionally, the current study used volumetric response and not pathologic complete response as a surrogate marker of treatment response; however, this approach has been used in other studies (1,9,10) and the relationship between volume change and response has been previously determined (2). A general consideration regarding the application of the HR-DWI technique for breast cancer imaging is that the maximum FOV of the sequence allows for only unilateral breast coverage.

CONCLUSION

This preliminary study suggests that the HR-DWI technique has potential for improving characterization of low tumor ADC values. In addition, HR-DWI may offer improvement over STD-DWI as an early indicator of breast tumor volume change in response to taxane-based therapy. These findings combined with the improved spatial resolution and lesion conspicuity of HR-DWI support further evaluation of HR-DWI for monitoring breast cancer treatment response.

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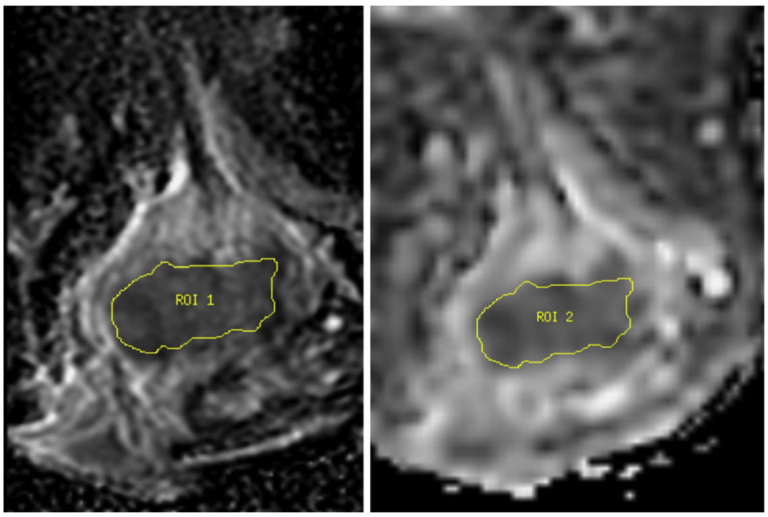

Figure 1.

Representative apparent diffusion coefficient maps of an invasive breast carcinoma acquired with high-resolution diffusion-weighted imaging (DWI; *left*) and standard DWI (*right*). The tumor is visible as a hypointense region in the center of the breast.

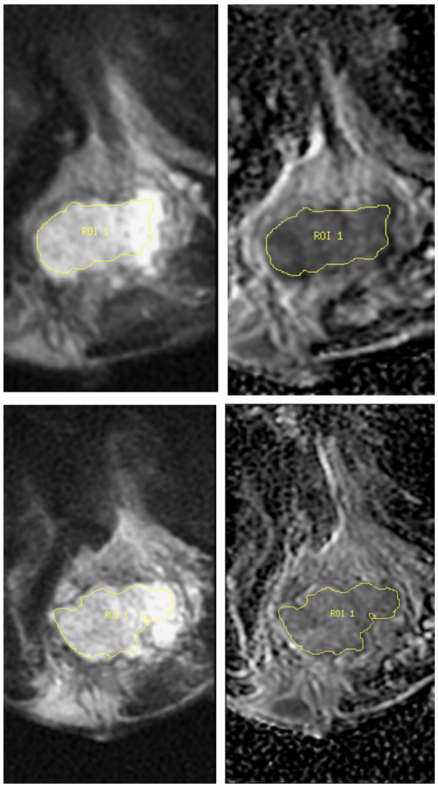

Figure 2.

Pre- (*top row*) and early treatment (*bottom row*) high-resolution diffusion-weighted images of an invasive breast carcinoma. *Left column*: b = 600 images; *right column*: apparent diffusion coefficient (ADC) maps. The tumor is visible as a hypointense region in the center of the breast on the ADC maps. This region appears less hypointense on the early treatment ADC map.

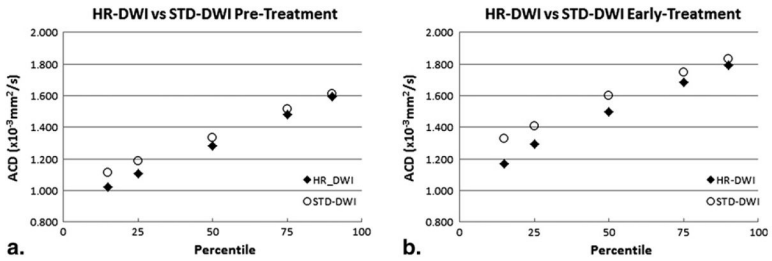

Figure 3.

(a) Pre- and **(b)** early-treatment tumor ADC values were measured at 15th, 25th, 50th, 75th, and 90th percentile. Statistically significant differences between HR-DWI and STD-DWI measurements were found at 15th percentile in pretreatment and at 15th, 25th, and 50th percentiles after early treatment. ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; STD-DWI, standard diffusion-weighted imaging.

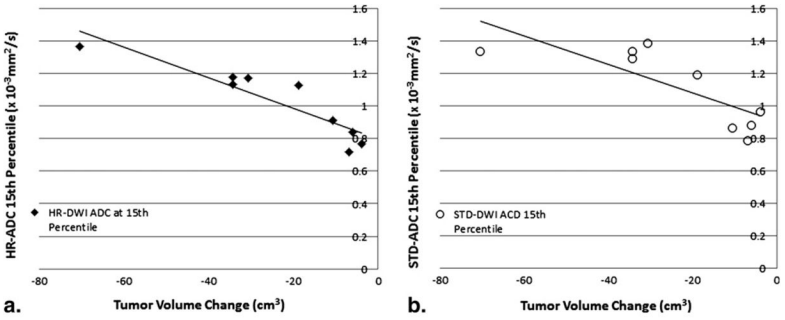

Figure 4.

Example correlations for the pretreatment tumor 15th percentile ADCs and absolute tumor volume change between visit 1 and visit 3 for **(a)** HR-DWI (r^2 = 0.83, P = .0007) and **(b)** STD-DWI (r^2 = 0.62, P = .01). ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; STD-DWI, standard diffusion-weighted imaging.

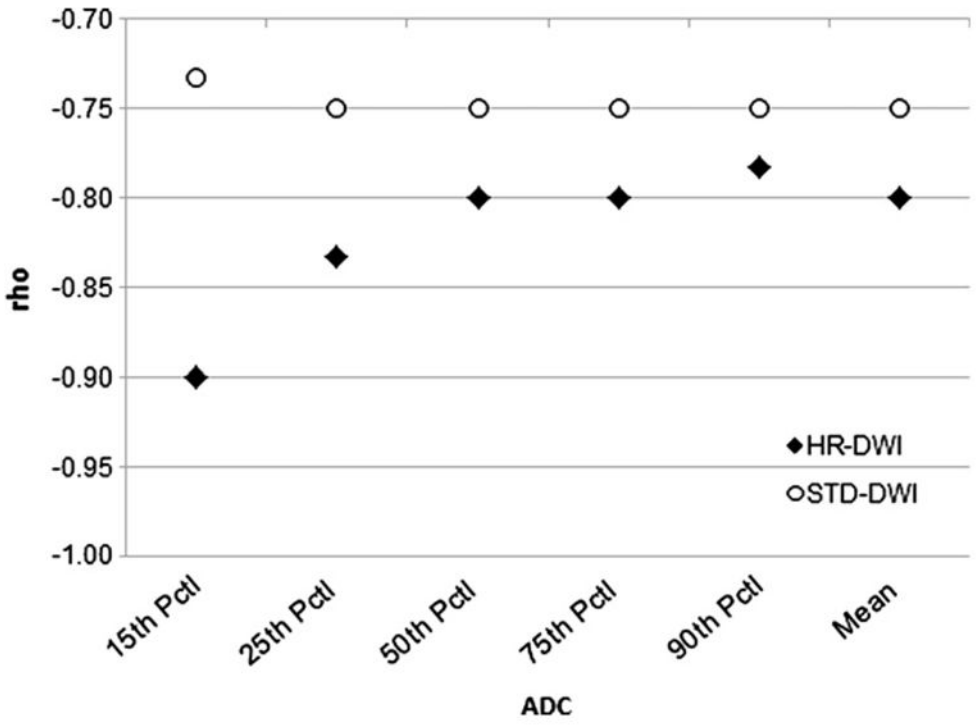

Figure 5.

Plots of estimated pretreatment Spearman's correlations for HR-DWI and STD-DWI tumor ADC metrics. Spearman's correlations were calculated to assess the relationship between tumor ADC metrics (mean and percentile ADCs) and tumor volume change at the end of treatment. The strongest correlation with tumor volume change was found for HR-DWI 15th percentile ADC. ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; STD-DWI, standard diffusion-weighted imaging.

TABLE 1A

Pretreatment Tumor ADC Metrics Measured with Both HR-DWI and STD-DWI

Tumor ADC Variable ($\times 10^{-3}$ mm^2/second)	Mean HR-DWI (SD)	Pretreatment Mean STD-DWI (SD)	Median Difference (95% CI)	Wilcoxon P Value
Mean ADC	1.31 (0.30)	1.37 (0.30)	0.062 (−0.021, 0.152)	.07
15th percentile	1.02 (0.22)	1.11 (0.24)	0.095 (0.006, 0.184)	.03
25th percentile	1.11 (0.25)	1.18 (0.25)	0.082 (−0.005, 0.159)	.07
50th percentile	1.28 (0.32)	1.34 (0.31)	0.047 (−0.033, 0.140)	.20
75th percentile	1.48 (0.39)	1.52 (0.35)	0.037 (−0.058, 0.133)	.36
90th percentile	1.59 (0.42)	1.61 (0.38)	0.022 (−0.068, 0.115)	.50

TABLE 1B

Early Treatment Tumor ADC Metrics for the Same Group of Tumors Measured with Both HR-DWI and STD-DWI

Tumor ADC Variable ($\times 10^{-3}$ mm^2/second)	Mean HR-DWI (SD)	Early Treatment Mean STD-DWI (SD)	Median Difference (95% CI)	Wilcoxon P Value
Mean ADC	1.50 (0.37)	1.57 (0.40)	0.117 (0.008, 0.224)	.02
15th percentile	1.17 (0.31)	1.33 (0.38)	0.170 (0.077, 0.247)	.01
25th percentile	1.29 (0.33)	1.41 (0.39)	0.117 (0.036, 0.192)	.01
50th percentile	1.50 (0.39)	1.60 (0.40)	0.117 (0.001, 0.231)	.04
75th percentile	1.69 (0.43)	1.75 (0.43)	0.053 (−0.059, 0.183)	.50
90th percentile	1.79 (0.44)	1.83 (0.44)	0.050 (−0.099, 0.193)	.55

ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; SD, standard deviation; STD-DWI, standard diffusion-weighted imaging.

Mean tumor ADC as well as the mean ADC values for the 15th, 25th, 50th, 75th, and 90th percentiles for HR and STD-DWI were compared using a Wilcoxon signed-rank test.

TABLE 2

Comparison of HR-DWI and STD-DWI Tumor ADC Change: Pretreatment to Early Treatment

Tumor ADC Variable ($\times 10^{-3}$ mm^2/second)	HR-DWI Median (95% CI), P Value	STD-DWI Median (95% CI), P Value	STD/HR Difference Median (95% CI), P Value
Mean ADC	0.16 (0.021, 0.36) 0.02	0.23 (0.059, 0.40) 0.02	0.045 (−0.045, 0.13) 0.4
15th percentile	0.13 (0.020, 0.29) 0.02	0.23 (0.058, 0.37) 0.03	0.087 (−0.044, 0.16) 0.2
25th percentile	0.17 (0.032, 0.33) 0.01	0.24 (0.078, 0.38) 0.02	0.040 (−0.065, 0.12) 0.3
50th percentile	0.20 (0.029, 0.42) 0.02	0.26 (0.084, 0.48) 0.02	0.045 (−0.047, 0.16) 0.3
75th percentile	0.14 (0.014, 0.40) 0.02	0.21 (0.025, 0.45) 0.02	0.022 (−0.062, 0.13) 0.6
90th percentile	0.11 (0.004, 0.40) 0.04	0.22 (0.025, 0.45) 0.03	0.041 (−0.058, 0.26) 0.5

ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; STD-DWI, standard diffusion-weighted imaging. Changes in tumor ADC metrics from pre- to early treatment measured with HR-DWI (column 2) and STD-DWI (column 3), and the difference between HR-DWI and STD-DWI (last column). Changes in mean ADC as well as changes in the 15th, 25th, 50th, 70th, and 90th percentiles for HR-DWI and STD-DWI were compared using a Wilcoxon signed-rank test.

TABLE 3A

Pretreatment HR-DWI and STD-DWI Tumor ADC Metrics for the Group with >65% Tumor Volume Reduction and the Group with <65% Tumor Volume Reduction at the end of Treatment

	Pretreatment			
Tumor ADC Variable ($\times 10^{-3}$ mm^2/s)	**HR-DWI >65% volume change Mean**	**HR-DWI <65% volume change mean**	**STD-DWI Mean > 65% volume change**	**STD-DWI mean < 65% volume change**
Mean ADC	1.30	1.34	1.38	1.32
15th percentile	1.02	1.02	1.14	1.03
25th percentile	1.11	1.11	1.21	1.11
50th percentile	1.28	1.40	1.35	1.27
75th percentile	1.46	1.55	1.52	1.49
90th percentile	1.56	1.70	1.60	1.63

TABLE 3B

Early Treatment HR-DWI and STD-DWI Tumor ADC Metrics for the Group with >65% Tumor Volume Reduction and the Group with <65% Tumor Volume Reduction at the End of Treatment

	Early-Treatment			
Tumor ADC Variable ($\times 10^{-3}$ mm^2/s)	**HR-DWI >65% volume change Mean**	**HR-DWI <65% volume change mean**	**STD-DWI Mean > 65% volume change**	**STD-DWI mean < 65% volume change**
Mean ADC	1.50	1.46	1.64	1.44
15th percentile	1.19	1.11	1.37	1.19
25th percentile	1.31	1.23	1.45	1.27
50th percentile	1.51	1.45	1.65	1.43
75th percentile	1.69	1.69	1.79	1.60
90th percentile	1.79	1.81	1.87	1.69

ADC, apparent diffusion coefficient; HR-DWI, high-resolution diffusion-weighted imaging; STD-DWI, standard diffusion-weighted imaging.