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Diffusion-Weighted MRI of the Breast in Women with a History of Mantle Radiation: Does Radiation Alter Apparent Diffusion Coefficient?

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Abstract

Objective: Fibrosis from chest irradiation could lower the apparent diffusion coefficient (ADC) of breast tissue. ADC values of normal breast tissue in high-risk women who underwent mantle radiation before age 30 years were compared with a screening control group matched for breast fibroglandular tissue (FGT).
Methods: In this retrospective study, we reviewed 21 women with a history of mantle radiation who underwent breast MRI examinations between 2008 and 2013, and 20 nonirradiated patients (control group) imaged during the same period with matching FGT and similar age. The women were dichotomized into low FGT (10/20, 50%) and high-FGT (10/20, 50%) groups, based on BI-RADS descriptors. All MRI examinations included diffusion-weighted imaging (DWI) (b = 0, 1000); ADC maps were generated and evaluated on PACS workstations by two radiologists in agreement. Region of interest markers were placed on ADC maps in visualized breast tissue in the retroareolar region of each breast. The ADC value was averaged for the right and left breast in each patient included in the study. The Wilcoxon signed-rank test was used to compare the ADC values in the irradiated patients and the matched control patients.
Results: The median breast ADC was lower in the irradiated group (1.32×10^{-3}mm^2/sec) than in the control group (1.62×10^{-3}mm^2/sec; $P = 0.0089$). Low FGT in the irradiated group had a lower median ADC (1.25×10^{-3}mm^2/sec) than it did in the control group (1.53×10^{-3}mm^2/sec). Irradiated high-FGT breasts had a median ADC (1.52×10^{-3}mm^2/sec), as compared with nonirradiated control patients with high FGT (1.82×10^{-3}mm^2/sec).
Conclusion: Previously irradiated breasts have lower ADC values than do nonirradiated breasts.

Key words: diffusion-weighted imaging; breast MRI; mantle radiation; apparent diffusion coefficient; fibroglandular breast tissue.

Introduction

Long-term survivors of Hodgkin lymphoma treated with mantle radiation before the age of 30 years are considered to have a substantially increased risk of developing breast cancer relative to the general population and are currently screened annually with mammography. However, 50%–60% of these previously irradiated women have dense breast tissue, which limits the sensitivity of mammography. Thus, supplemental screening with MRI is also recommended (1, 2).

Diffusion-weighted imaging (DWI) is an MR technique that can be performed as part of a standard breast MRI protocol for breast cancer screening in high-risk patients. DWI is based on the principle of Brownian motion of water molecules, and it reflects both tissue cellularity and cell membrane integrity. DWI results are typically quantified by calculating the apparent diffusion coefficient (ADC), which is directly proportional to the diffusion capability of the water molecules.

Key Messages

- Radiation alters the apparent diffusion coefficient in the breast.
- Previously irradiated breasts have lower apparent diffusion coefficient values than do nonirradiated breasts.

Among long-term survivors of Hodgkin lymphoma, we postulated that in the developing and proliferating breast tissue present in children and young adults with a history of chest irradiation, the fibrosis that could be expected to result from chest irradiation could alter the diffusibility of water molecules across the cell membrane, thereby lowering the ADC in comparison to nonirradiated breast tissue; furthermore, we hypothesized that this change could be permanent.

The purpose of this study was to measure the ADC of normal breast tissue in women with a history of mantle irradiation before the age of 30 years and to compare it with the ADC of normal breast tissue in a control group of nonirradiated women, stratifying for breast fibroglandular tissue (FGT).

Methods

Patients

Our retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by our institutional review board, which waived the need for informed consent.

Based on a review of records of women who underwent breast MRI examinations at our tertiary cancer institution between 2008 and 2013, we identified 21 patients treated with mantle radiation between the age of 11 years and 30 years. All previously irradiated women came for follow-up breast cancer screening eight years or more after treatment and received MRI including dynamic contrast-enhanced MRI and DWI. Breast MRI records of 20 women who underwent screening breast MRI during the same period and had matching breast density levels (as measured by FGT) and age but who had not undergone mantle radiation were identified as controls for comparison. The amount of FGT was evaluated on precontrast T1-weighted fat-suppressed imaging.

MRI Protocol

Breast MRI was performed with the patient prone in a 1.5-Tesla or 3-Tesla commercially available system (Sigma; GE Medical Systems, Milwaukee, WI), using a dedicated 8-channel phased-array breast coil (In Vivo Corporation, Orlando, FL) or a dedicated 16-channel phased-array receiver coil (Sentinelle Vanguard; Sentinelle Medical, Toronto, ON, Canada).

Diffusion-weighted imaging (b = 0, 1000) was performed as a standard sequence during the study period and acquired before administration of contrast medium. Dual shims were applied to optimize B_0 homogeneity. Fat suppression was achieved using spectral spatial pulses. Parallel imaging with array spatial sensitivity encoding technique (ASSET) was applied while acquiring diffusion-weighted images. Diffusion-weighted imaging gradients were applied in three orthogonal planes.

Image Analysis

Apparent diffusion coefficient map acquisitions (b = 0, 1000) were generated by the technologists on a workstation (Advantage Workstation; GE Healthcare) and were analyzed by using commercial software (FuncTool 4.6; GE Healthcare).

Diffusion-weighted images and ADC maps were analyzed using a picture archiving and communication system (PACS) (GE-Centricity Enterprise Web 3.0, GE Healthcare, Barrington, IL). *Normal breast tissue* was defined as the absence of any finding on dynamic contrast-enhanced MRI, as stated on the imaging report reviewed during the selection of cases and controls for the study. The ADC of normal breast tissue was calculated by manual placement of a region of interest (ROI) by a breast imaging radiologist (with seven years' experience in breast imaging) in the retroareolar region, in the middle third depth of each breast studied. The size of the ROI was altered for each exam to encompass the visible normal breast tissue while avoiding partial volume averaging with adjacent fat tissue.

The cases were divided into two broad groups based on the Breast Imaging-Reporting and Data System (BI-RADS) (3): low FGT (including almost entirely fat and scattered fibroglandular tissue) and high FGT (including heterogeneous and extreme fibroglandular tissue). Control patients with matching breast tissue density levels and in similar age range were selected for comparison.

Statistical Analysis

For both the irradiated women and those in the control group, the right and left breast measures of ADC were averaged before statistical analysis. Wilcoxon signed-rank test was used to compare the ADC values of cases and matched controls. The significance level was assessed ($P < 0.05$) for this paired testing. The same analysis was repeated for low-FGT and high-FGT groups.

Results

In total, 41 DWI studies (from 21 irradiated patients and 20 control patients) were reviewed. In the irradiated group, one breast with a benign mass lesion in the retroareolar region was excluded from the study and thus the average ADC of 40 breasts was evaluated. Thirty-two MRI exams were performed on a 3.0-Tesla scanner, and 10 were performed on a 1.5-Tesla scanner. The median age of women in the irradiated group was 46 years (range: 36–68 years), whereas that of the women in the control group was 48 years (range: 39–67 years). The low-FGT subgroup included 10 cases, and the high-FGT subgroup included 10 cases.

The median ADC value in the retroareolar regions of the irradiated breasts was 1.32×10^{-3}mm^2/sec (0.76–2.08) and in the control group of nonirradiated women it was 1.62×10^{-3}mm^2/sec (1.13–2.19). The median ADC value in the low-FGT irradiated group was 1.25×10^{-3}mm^2/sec (0.76–1.78), whereas that in high-FGT irradiated group was 1.52×10^{-3}mm^2/sec (0.83–2.08) (Figure 1).

The median ADC value in the low-FGT subgroup of control patients was 1.53×10^{-3}mm^2/sec (1.13–2.15) (Figure 2), whereas that in the high-FGT subgroup of control patients was 1.82×10^{-3}mm^2/sec (1.31–2.19) (Figure 3).

The median ADC of high FGT in all of the women in study was 1.67×10^{-3}mm^2/sec (0.83 -2.19), and the median ADC of low FGT in all the women was 1.40×10^{-3}mm^2/sec (0.76 -2.15) ($P = 0.0352$) (Table 1).

The Wilcoxon signed-rank test showed statistical difference comparing irradiated women with nonirradiated women ($P = 0.0089$), low-FGT women compared with high-FGT women ($P = 0.0352$), irradiated women with high FGT compared with nonirradiated women with high FGT ($P = 0.0035$), and irradiated

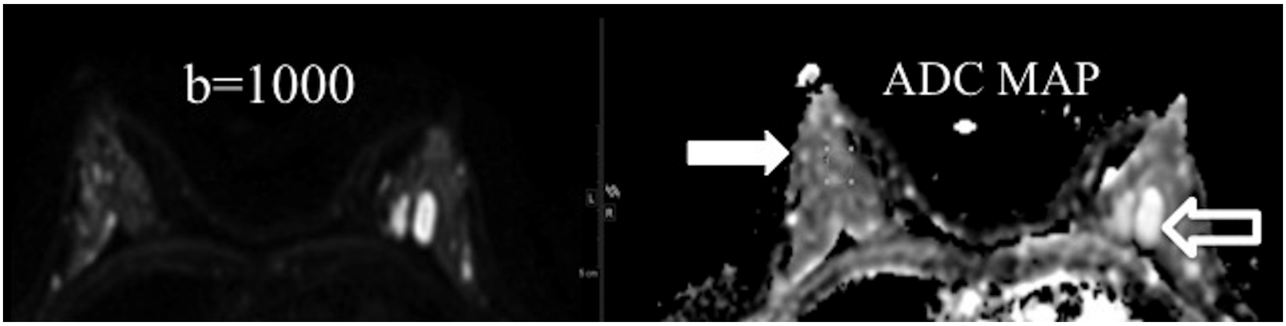

Figure 1. An example of an irradiated woman (case) with high breast fibroglandular tissue. The region of interest marker was manually placed in the retroareolar area of the right breast (arrow). The left breast was excluded because of the presence of a benign lesion (open arrow). Apparent diffusion coefficient = 1.35×10^{-3}mm^2/sec.

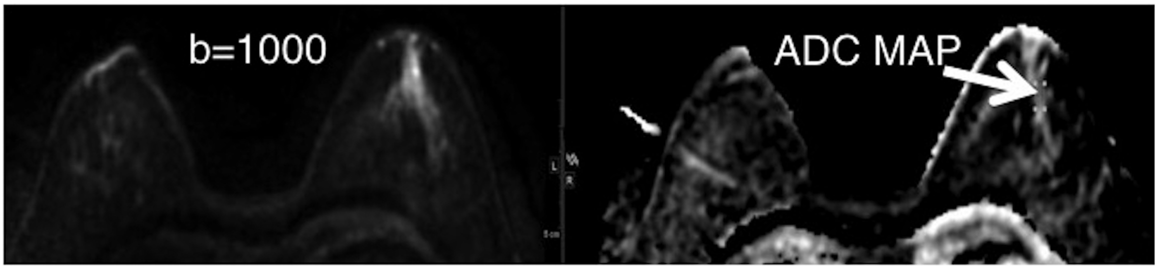

Figure 2. The control group with low breast fibroglandular tissue. The region of interest marker was placed in the retroareolar tissue of the left breast (arrow). Apparent diffusion coefficient = 1.20×10^{-3}mm^2/sec.

women with low FGT compared with nonirradiated with low FGT (P = 0.0026).

Discussion

Women who received mantle radiation between the ages of 10 and 30 years are at high risk for developing a second malignancy. Breast cancer is the most common solid tumor in women in this cohort, with an estimated actuarial incidence of approximately 35%. The cumulative risk is even higher in women who received radiation between the ages of 10 and 16 years, and it is related to the radiation dose and radiation field volume (4). Some 13%–20% of women treated for childhood Hodgkin lymphoma will be diagnosed with breast cancer by the ages of 40–45 years (5); in contrast, the cumulative incidence of invasive breast cancer in the general population is only 1% by age 45 years. For women with a history of mantle radiation, the lifetime risk of developing breast cancer is greater than 20%, which is similar to that of patients with high-risk gene mutations; furthermore, breast cancers in these women are more likely to be bilateral than are those found in other women, and the majority of them will develop within the radiated field (6).

For women who have undergone mantle radiation between the ages of 10 and 30 years, the American College of Radiology (ACR) recommends annual mammography screening starting at or after 8 years after radiation therapy but not before the age of 25 years (7). However, approximately half of the women treated with supradiaphragmatic radiation for Hodgkin lymphoma between the ages of 10 and 30 years have extremely dense or moderately dense breasts, which limits early cancer detection by mammography (1, 8).

Thus, recommendations from scientific societies (1, 2, 9) state that for women with a 20% or greater lifetime risk for developing breast cancer such as these, screening should include contrast-enhanced MRI in addition to two-view mammography. The inclusion of MRI in screening for this group increases the cancer yield (10, 11).

A recent study found that MRI and mammography had comparable sensitivity and specificity in screening survivors of Hodgkin lymphoma (12). Diffusion-weighted imaging has been shown to have the potential to increase the positive predictive value of MRI for lesions of varied sizes and types (13). Diffusion-weighted imaging reflects the biological characteristics of tissue, particularly the cellularity and the integrity of the cell membrane, which alter the diffusion of water protons.

In our study, breasts with fatty tissue density in both irradiated and nonirradiated women had lower ADC values than did dense breasts. This result is concurrent with the results reported by Partridge et al and Iacconi et al (14, 15), and it confirms that there are differences between the ADC values of normal breast tissue in breasts of different densities. Furthermore, in this study, ADC values were lower in irradiated breasts than in nonirradiated breasts. This finding is likely a result of tissue fibrosis caused by radiation injury, and it could alter the detection and characterization of breast lesions with DWI. Based on the knowledge of the biochemical cascade of radiation induced cell injury where cell inflammation ultimately evolves into fibrosis and causes alterations in cell membrane permeability, this finding is likely a result of tissue fibrosis caused by radiation injury. Fibrotic tissue alters the dynamics of the motion of water molecules across the cell membrane by increasing the cellular density and reducing the extracellular matrix water fraction. Biopsy of breast tissue of the irradiated women to confirm fibrosis, however, was not undertaken, and this is an important limitation of our retrospective study.

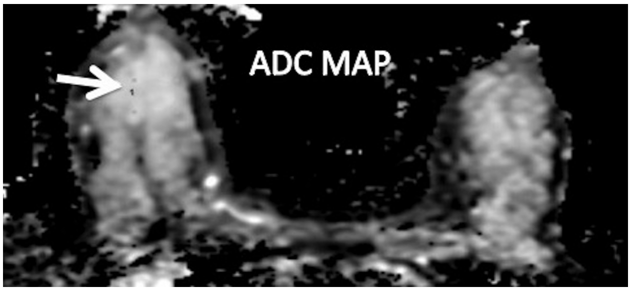

Figure 3. The control group with high- breast fibroglandular tissue. The region of interest marker was manually placed in the retroareolar area of the right breast (arrow). Apparent diffusion coefficient = 2.10 × 10^{-3}mm^2/sec.

Table 1. Comparison between Patients with Irradiated Breasts and Control Patients and Subgroups of Density

	Patients with Irradiated Breasts	Control Patients	Wilcoxon Signed-Rank Test ($P < 0.05$)
ADC mm^2/sec (range)	1.32 (0.76–2.08)	1.62 (1.13–2.19)	0.0089
Median age (years) (range)	46 (36–68)	48 (39–67)	
	High FGT	**High FGT**	
ADC mm^2/sec (range)	1.52 (0.83–2.08)	1.82 (1.31–2.19)	0.0035
	Low FGT	**Low FGT**	
ADC mm^2/sec (range)	1.25 (0.76–1.78)	1.53 (1.13–2.15)	0.0026
	All women (cases + controls)		
	High FGT	**Low FGT**	
ADC mm^2/sec (range)	1.67	1.40	0.0352

Abbreviations: ADC, apparent diffusion coefficient; FGT, breast fibroglandular tissue.

Our findings differ from those of a study by O' Flynn et al (16), in which women at high risk of developing breast cancer showed higher ADC values than did women at normal risk of developing breast cancer. However, the studied population included nonirradiated BRCA 1 and BRCA 2 gene carriers in addition to mantle irradiated women, and results were not stratified for the two groups. In our opinion, DWI has the potentiality to detect changes in tissue structure, which are also probably different for the mantle irradiated and the gene carrier groups.

A possible further explanation of these different results is the influence of ROI placement on the ADC value that could significantly affect the quantitative measurement especially if no mass is identified (17), whereas minor differences in ADC measurements can occur using different workstations and postprocessing systems. According to recent publications, in fact, even using different software, ADC measurement is generally reliable (18, 19).

One limitation of our study was its small sample size. However, given the evolution of radiation therapy options for pediatric Hodgkin lymphoma, it was expected that we would find only a small number of women who had undergone mantle radiation. This small sample size also hindered the analysis of further subgroups based on different field strengths at which MR examinations were performed.

Furthermore, prepubescent girls whose breasts developed after treatment and mature women with breasts irradiated at the time of treatment could have different ADC results, but, unfortunately, this information was not available in hospital records, and it should be considered as a limit of the current analysis.

The principal aim of this preliminary study was to observe if there are quantitative ADC changes in irradiated patients.

Possible practical consequences of the reduced ADC values of breast tissue in irradiated women could be differences in quantitative DWI measurements of malignant lesions not conforming to those currently reported in literature. However, validation in a larger sample group is needed.

Another limitation was that information regarding the dose of radiation and the volume of the radiation field were unavailable. Both of these parameters may affect the degree of fibrosis that is expected to develop and, hence, influence ADC values. Our assumption that radiation injury induces fibrosis in the breast was also an important limitation of this retrospective study.

Conclusion

The breasts of women with a history of mantle radiation have lower ADC values than do the breasts of nonirradiated women. The difference in ADC values may be attributable to postradiation fibrosis, which alters the dynamics of water diffusion in tissues. It remains to be determined whether detection of malignant lesions in DWI is altered and if the ADC values of invasive cancers in previously irradiated women are lower than those of cancers that develop in nonirradiated women.

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Conflict of interest statement

None declared.

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