Comparison between diffusion-weighted imaging, T₂-weighted, and postcontrast T₁-weighted imaging after MR-guided, high intensity, focused ultrasound treatment of uterine leiomyomata: Preliminary results

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Purpose: To investigate the comparison between diffusion-weighted imaging (DWI), T₂-weighted imaging, (T₂WI) and contrast T₁-weighted imaging (cT₁WI) in uterine leiomyoma following treatment by magnetic resonance imaging-guided, high intensity focused ultrasound surgery (MRg-HIFUS).

Methods: Twenty one patients (45 ± 5 yrs) with clinical symptoms of uterine leiomyoma (fibroids) were treated by MRg-HIFUS using an integrated 1.5T MRI-HIFUS system. MRI parameters consisted of DWI, T₂WI, and T₁-weighted fast spoiled gradient echo before and after contrast. The post-MRg-HIFUS treatment volume in the fibroid was assessed by cT₁WI and DWI. Trace apparent diffusion coefficient maps were constructed for quantitative analysis. The regions of the treated uterine tissue were defined by a semisupervised segmentation method called the “eigenimage filter,” using both cT₁WI and DWI. Signal-to-noise ratios were determined for the T₂WI pretreatment images. Segmented regions were tested by a similarity index for congruence. Descriptive, regression, and Bland–Altman statistics were calculated.

Results: All the patients exhibited heterogeneously increased DWI signal intensity localized in the treated fibroid regions and were colocalized with the cT₁WI defined area. The mean pretreatment T₂WI signal intensity ratios were T₂WI/muscle = 1.8 ± 0.7 and T₂WI/myometrium = 0.7 ± 0.4. The congruence between the regions was significant, with a similarity of 84% and a difference of 8% between the regions. Regression analyses of the cT₁WI and DWI segmented treatment volumes were found to be significantly correlated ($r^2=0.94$, $p<0.05$) with the linear equation, (cT₁WI) = 1.1(DWI) – 0.66. There is good agreement between the regions defined by cT₁WI and DWI in most of the cases as shown from the Bland–Altman plots.

Conclusions: Diffusion-weighted imaging exhibited excellent agreement, congruence, and correlation with the cT₁WI-defined region of treatment in uterine fibroid. Therefore, DWI could be useful as an adjunct for assessing treatment of uterine fibroids by MRg-HIFUS. © 2010 American Association of Physicists in Medicine. [DOI: 10.1118/1.3475940]

Key words: high intensity focused ultrasound surgery, uterine fibroids, leiomyoma, leiomyomata, diffusion-weighted imaging, thermotherapy, ADC map

I. INTRODUCTION

Uterine leiomyomata (commonly called uterine fibroids) are benign tumors of the uterus and affect a high percentage of women with symptoms of pain or dysmenorrhea.^{1–3} The treatment of these tumors include both invasive and noninvasive procedures, such as hysterectomy,^{4,5} myomectomy,^{6,7} uterine artery embolization (UAE),^{8,9} and, more recently,

magnetic resonance-guided, high intensity focused ultrasound surgery (MRg-HIFUS) thermotherapy.^{10–14} Uterine fibroids are the most common indication for hysterectomy.¹⁵ Although hysterectomy is one choice for the treatment of symptomatic fibroid, it can affect the patient’s long-term health. For example, a hysterectomy changes the hormonal status of the patient and eliminates childbearing. These changes can have significant physiological and psychological

effects. Therefore, the use of potentially uterine-preserving strategies has been gaining attention because of the advancements in technology and, thus, the approaches to the management of uterine fibroids. In particular, MRg-HIFUS is now being used for the treatment of these benign lesions.^{10–14} Although the potential uses for high frequency ultrasound¹⁶ and focused ultrasound^{17–19} in biomedicine have been known for a long time, the growing number of applications using focused ultrasound are primarily due to the integration of ultrasound with MRI technology to monitor the ablated tissue with a high degree of accuracy.^{20–23} Moreover, MRg-HIFUS has been approved by the FDA as a noninvasive thermotherapy method for the treatment of uterine fibroids through evaluation in multicenter clinical trials.^{10–12,14,24}

In general, characterization and assessment of uterine fibroids are performed before treatment using both T₁- and T₂-weighted (T₁WI, T₂WI)^{25,26} MR sequences, and after treatment with contrast-enhanced T₁-weighted images (cT₁WI).^{10,11,14,24} Before treatment, cT₁WI is used to determine the viability of the fibroid by the uptake of the contrast agent; if the fibroid enhances after injection, it is determined to be viable. If no enhancement is noted, then the fibroid is nonviable. Similarly, a new method has been developed in which T₂-weighted signal intensity is used as a marker to determine which fibroid will “respond” to MRg-HIFUS. In this method, the signal intensity of the fibroid is compared to myometrium and muscle.²⁶ After thermal MRg-HIFUS treatment, the cT₁WI provides information about the extent of the ablated tissue based on the lack of uptake within the treated region, and thus, the area of treatment appears hypointense. The volume of hypointensity is used to measure treatment effectiveness.

Recent studies have demonstrated that the use of diffusion-weighted imaging (DWI) in identifying and characterizing uterine tissue provides a method to obtain “functional parameter” about both untreated and treated uterine tissues. The term functional parameter describes the ability to image the exchange of water in and out of uterine tissue, which can be measured by the mapping of the apparent diffusion coefficient (ADC) of water parameter from the DWI data and which provides a map of varying degrees of water movement. For example, in regions of low ADC, there is restricted water movement, whereas in regions of high ADC, there is increased water flow. Diffusion-weighted imaging has been used to discriminate between viable and nonviable uterine fibroid tissues in a small set of patients.²⁷ In addition, DWI was used to monitor MRg-HIFUS thermally treated^{12,28} and UAE-treated uterine fibroids.^{29,30} These studies demonstrated the effectiveness of using DWI/ADC mapping in MRg-HIFUS treatment.

Thus, the question is how do the treatment volumes defined by these two different imaging sequences compare? What are the T₂WI imaging characteristics before treatment? The purpose of this manuscript is to investigate the relationship, if any, of the regions defined by cT₁WI and DWI after treatment of uterine fibroids with MRg-HIFUS and the signal characteristics of T₂WI before treatment.

II. MATERIALS AND METHODS

II.A. Clinical subjects

Patients were selected from an *ongoing prospective* study that underwent MRg-HIFUS treatment for uterine fibroids. Treated fibroids were based on the selection criteria that included fibroid size, location, symptom severity, and the beam path restrictions due to the presence of organs, such as bowel, bladder, and nerve bundles in the focused ultrasonic beam path. In this study, 21 patients (mean age = 45 ± 5 yrs) who had clinical symptoms arising from uterine fibroid were selected to participate in this study. Written, informed consent was obtained from all patients and approved by the Institutional Review Board (IRB); the study complied with the Health Insurance Portability and Accountability Act (HIPAA).

II.B. MRI-guided focused ultrasound surgery

The MRI-guided focused ultrasound surgery procedure was performed using a modified HIFUS system (TX Sonics, InSightec, Haifa, Israel), coupled with a standard 1.5 T MRI system (Excite, GE Medical Systems, Waukesha, Wisconsin, USA) and a phased array MRI pelvic coil (USA Instruments, Aurora, Ohio, USA) as previously described.^{10,12,14,28} Briefly, patients were in the prone position for treatment, under conscious sedation, and were continuously monitored by a physician. The sedative agents, midazolam hydrochloride (Versed, Bedford Laboratories, Bedford, Ohio, USA) at a mean dose of 3.0 mg (range of 0.5–6.0 mg), and fentanyl citrate (Fentanyl; Baxter Healthcare, Deerfield, Illinois, USA) at a mean dose of 150 μ g (range of 25–300 μ g), were administered intravenously. The focused ultrasonic energy was delivered to the patients from a 120 mm diameter multielement ultrasonic piezoelectric transducer array immersed in a water tank imbedded in the treatment table inside the MRI system. The procedure consisted of clinical treatment planning: T₂-weighted images (T₂WI) were acquired for calibration of the image space to MRI/HIFUS space. T₁-weighted fast spoiled gradient recalled (FSPGR) echo phase-sensitive images were acquired before and after each sonication period by HIFUS. Each sonication period lasted for approximately 30 s followed by a 30 s cooling period while the temperature was monitored by a gradient echo phase shift imaging sequence. The acoustic power varied in the range of 100–120 W through the MR-guided temperature feedback mechanism to achieve a temperature range of 65–85 °C at the focal point in the fibroid tissue. The total MRg-HIFUS treatment time ranged from 1 to 3 h for all patients. In this study, the patient received only one treatment with no follow-up sessions for treatment as recommended by the Food and Drug Administration (FDA). In addition, we were limited to the total amount (33% and maximum volume treated to 100 mm³) of fibroid that could be ablated. However, current MRg-HIFUS protocols now include the possibility of further treatment and increased volume of treatment.^{14,31}

II.C. MRI protocols

The imaging protocol consisted of a series of T_2 -weighted fast spin echo (FSE), T_1 -weighted fast spoiled gradient recalled echo, spin phase shift gradient echo, and diffusion-weighted echo planar imaging (DW-EPI) sequences, which were acquired before, during, and after the treatment. The multiplane T_2 WI FSE images [TR/TE, 5000/100 ms; echo train length(ETL)=12; slice thickness(ST)=4.0 mm; matrix size=256×128; field of view(FOV)=36×36 cm] were acquired for calibration and treatment planning. For treatment monitoring, axial T_1 FSGR images (TR/TE=26/13 ms; flip angle, 30; matrix size=256×128; FOV=28×28 cm; ST=5.0 mm) were acquired during the focused ultrasound treatment to monitor the temperature through NMR thermometry using phase maps. The pre- and postcontrast axial and sagittal T_1 -weighted FSPGR images (TR/TE=185/1.5 ms; matrix size=256×128; FOV=28×28 cm; ST=6.0 mm) were acquired to define the amount of ablated tissue using gadopentetate dimeglumine (Magnevist, Berlex Laboratories, Wayne, New Jersey, USA) at a dose of 0.001 mmol/kg, administered through the antecubital vein using a power injection device (Medrad, Pittsburgh, Pennsylvania, USA), 5 s after the start of image acquisition. The contrast agent bolus injection was followed by an injection of a 20 ml saline solution to flush the contrast agent. After the treatment, but before cT1WI, multislice axial DW-EPI (TR/TE=5000/90 ms, b=0,500–1000; matrix size=128×128; FOV=28×28 cm; ST=6.0 mm) was acquired for correlation with the axial cT1WI of the ablated tissue.

The acquisition of different b-values allows for the creation of trace apparent ADC maps on a pixel-by-pixel basis for quantitative analysis according to the equation

$$\text{ADC} = - \sum_{i=1}^n \frac{\ln(S_i/S_0)}{b_i}, \quad (1)$$

where b_i =the diffusion gradient values; $b=\gamma^2 G^2 \delta^2 (\Delta - \delta/3)$, γ =gyromagnetic ratio, G =gradient strength, δ =diffusion gradient duration, Δ =time between diffusion gradient pulses, S_0 =1st image ($b=0$), and S_i =ith image.

II.D. Image data analysis

All the images from the patients acquired before and after treatment were analyzed using a workstation (Sun Fire T2000 server, Sun Microsystems, Mountain View, California, USA) and a comprehensive image analysis software package (Eigentool, Image Analysis Laboratory, Henry Ford Hospital, Detroit, Michigan, USA). The volumes of treated uterine tissue were obtained by using a semisupervised segmentation method called Eigenimage (EI) filter.^{32–34}

II.D.1. T_2 Image characteristics

Tissue characteristics of uterine fibroids were determined from the axial T_2 images with regard to signal intensity of the fibroid, visible muscle (piriformis, rectus abdominis, or iliatus), and myometrium before treatment. Regions of interests (ROIs) were drawn using at least 5×5 pixel within fi-

FIG. 1. Eigenimage filter (EI) images generated using T_1 -weighted sequences (T_1 WI) after MR-gHIFUS. (a) Precontrast and postcontrast T_1 WI, with corresponding treated and untreated tissue signature vectors indicated on the serial T_1 WI by arrows running through two sets of pixels. (b) The segmented EI demonstrates the excellent delineation between treated and untreated fibroid tissues. (c) Histogram analysis of number of pixels vs relative gray scale intensity for the T_1 WI, demonstrating the separation of the segmented tissue.

broid, myometrium, and visible muscle were selected. Ratios of fibroid to muscle and fibroid to myometrium were determined.

II.D.2. Eigenimage filter

The Eigenimage (EI) Filter is a linear filter that maximizes the projection of a desired tissue (treated uterine tissue) while minimizing or suppressing the projection of undesired tissue (untreated uterine tissue) onto a composite image called an Eigenimage using the Gram–Schmidt orthogonalization.³² The EI algorithm requires the definition of tissue signature vectors that represent the tissue type of interest. A tissue signature vector is calculated from the mean value of gray level intensities under a selected ROI from a tissue type in each image of the entire data sequence, as shown in Fig. 1. For example, a tissue signature vector defining treated uterine tissue (desired) would be created from cT1WI images by placing a ROI in the area of hypointensity or in the area of untreated tissue. Similarly, a tissue signature vector would be created for nontreated tissue (undesired) would be created on the cT1WI images. Similar methods would be used on the DWI. One tissue signature vector would be created for each tissue type per image set (desired or undesired). The tissue signature vector is a mathematical descriptor for a tissue class. For this study, one tissue signature vector, treated tissue, was selected as desired tissue; $\vec{d} = [d_1 d_2 \cdots d_n]^T$, where n is the n th image in the series, was chosen from uterine tissue (areas of ablation) and a second tissue signature vector was selected for undesired tissue, $\vec{u}$ (similarly defined as $\vec{d}$) for the untreated uterine tissue. Tissue signature vectors were selected from the cT1WI and DWI for desired and undesired tissue. Then, these tissue signature vectors were utilized for the creation of a filter vector, $\vec{e} = [e_1 e_2 \cdots e_n]^T$, where $\vec{e}$ =filter vector and T is the transpose.

FIG. 2. Representative examples of T1-weighted and diffusion-weighted Eigenimages from a 47-year-old patient undergoing MR-gHIFUS. (a) Pre- and postcontrast T₁WI (cT₁WI) after treatment. (b) Eigenimages of the untreated and treated segmented tissues. There is excellent delineation of the different tissue types. (c) Diffusion-weighted images (b=0 and 1000). (d) Eigenimages of the untreated and treated segmented tissues.

The filter vector (e) is used in a Gram–Schmidt orthogonalization procedure by a linear combination of original images to create the composite EI.^{32–36}

The enhancement or suppression of segmented tissues in the EI filter technique is based on the contrast criteria for the selected tissue signature vectors (Fig. 1). When using the EI filter technique, the goal is to determine an optimizing criterion that maximizes a projection of the desired tissue, characterized by the desired tissue signature vector $\vec{d}$, while minimizing (suppressing) the projection of one or more undesired tissues, characterized by the tissue signature vector $\vec{u}$ onto the composite image (see Appendix).

The EI algorithm provides selective enhancement or suppression of different tissues by each tissue signature vector and allows for excellent segmentation of each different tissue type, for example, treated and untreated uterine tissue [Figs. 2(b) and 2(d)]. The total treated area defined by the EI was determined using a 95% confidence interval above the peak (treated tissue) identified on the histogram (Fig. 1). This method of determining the lesion area in brain has been shown to have intra- and interobserver reproducibility errors of 7%–10%.³⁷ The above volume segmentation process was performed for each fibroid, using both cT₁WI and DWI data set for desired (treated) and undesired (nontreated) tissue (Fig. 2).

II.D.3. DWI/ADC characteristics

Diffusion/ADC map tissue characteristics of uterine fibroids were determined using ROIs drawn to encompass most of the identified fibroid with care taken to stay from the edges of the fibroid to reduce any partial volume effects. First, ROIs were drawn on the baseline (within the fibroid) on the cT₁WI for colocalization with the ADC map values (see Figs. 3 and 4). After treatment, ROIs were created from the EI results described above and overlaid onto the ADC map for quantitative measurements from the largest treated

FIG. 3. Representative examples of axial postcontrast T1-weighted, diffusion-weighted, and T2-weighted images (cT₁WI, DWI, and T₂WI, respectively) from a 47-year-old patient undergoing MR-gHIFUS. (a) Pretreatment, axial postcontrast T₁WI (cT₁WI) exhibited increased signal intensity in the fibroid, with no increased signal on the axial DWI (b=1000). The apparent diffusion coefficient of water (ADC) map shows no signal changes. The fibroid is “dark” on the axial T₂WI image compared to the myometrium. (b) After MR-gHIFUS treatment, the cT₁WI image demonstrates decreased contrast uptake within the treated region, and the DWI shows increased signal intensity in the same regions, with a corresponding decreased signal within the ADC map. There is also increased signal intensity on the T₂WI, indicative of vasogenic edema. (c) EI segmented tissue demonstrates close correspondence between the cT₁WI and DWI.

area, if two or fibroids were treated in the same session. Ratios of the ADC (ADC_r) values were calculated by dividing regions of treated tissue by nontreated tissue for each time point.

II.D.4. Similarity index

To measure the “congruence” or overlap of the segmented regions, a binary image was made of each segmented region

FIG. 4. Representative examples of axial postcontrast T₁-weighted, diffusion-weighted, and T₂-weighted images (T₁WI, DWI, and T₂WI, respectively) from a 50-year-old patient undergoing MR-gHIFUS. (a) Axial cT₁WI image demonstrates decreased contrast uptake within the treated region, and the DWI shows increased signal intensity in the same regions, with a corresponding decreased signal within the ADC map. There is little or no increased signal on the T₂WI, indicating that vasogenic edema has not occurred. (b) Eigenimages of the treated and untreated tissues from the cT₁WI and DWI demonstrate close correspondence between the regions.

TABLE I. Demographic patient data, fibroid volume, and quantitative T₁WI, DWI, T₂WI, and ADC data for all patients. DWI=diffusion weighted imaging, ADC=Apparent diffusion coefficient, TX=treatment, myo=myometrium

	Age (yr)	cT ₁ WI (mm ³)	DWI (mm ³)	ADC 10 ⁻³ mm ² /s	ADC (TX) 10 ⁻³ mm ² /s	ADCr ratio	Fibroid	T2 muscle	Myometrium	Ratio (fibroid/muscle)	Ratio (fibroid/myo)
Mean	45	9.6	10.0	1.8	1.2	0.3	33	24.9	65.6	1.8	0.7
SD	5	9.7	9.2	0.5	0.3	0.2	32	35.1	83.0	0.7	0.4
Max	53	45.1	39.8	2.6	1.8		130	151.3	367.7	3.1	1.6
Min	37	0.6	0.7	1.0	0.7		4	3.7	11.4	0.8	0.2

defined by the EI filter using the axial cT₁WI and DWI. The images were coregistered to the same location and verified using anatomical landmarks within the uterine cavity.³⁴ To measure the regions in common for both the T₁WI and DWI, a logical AND between the two regions was obtained. Then, a logical XOR was performed for the difference between regions. Pixel counts of each of these regions were acquired and multiplied by the pixel size and slice thickness to convert to volumes. The similarity of two segmented regions is defined as twice the common area of the sum of the individual areas,

$$S = 2 \frac{n\{A_1 \cap A_2\}}{n\{A_1\} + n\{A_2\}}, \quad (2)$$

where A₁ is the cT₁WI and A₂ is the DWI segmented areas if A₁ and A₂ have the same shape and size and also are in the same position, A₁*A₂=1. A representative case is shown in Fig. 3.

II.E. Statistical analysis

Quantitative statistics (mean, standard deviation, volume) were obtained in the cT₁WI, T₂WI, and DWI data. Regression analysis was performed between the different MR parameters for assessment of the treatment in the uterine fibroids. A similarity index was used to compare the overlap between treatment regions. The Bland–Altman technique was used to assess the measurement error and identify any systematic differences or biases by plotting the differences versus the means for both methods.^{38–40} Significance was set at $p < 0.05$.

III. RESULTS

Patient demographics, treated volumes, ADC values, T₂WI ratios, and congruence results are summarized in Table I. The mean pretreatment T₂WI signal intensity ratios were T₂WI/(fibroid/muscle)=1.8±0.7 and T₂WI/(fibroid/myometrium)=0.7±0.4. After treatment, all patients exhibited decreased signal intensity in the cT₁WI, concurrent with heterogeneously increased DWI signal intensity localized in the treated fibroid regions after ablation, with areas of decreased signal intensity and heterogeneity on the ADC maps.

In general, the cT₁WI volumes (mean:9.6±9.7 mm³; range:0.6–45 mm³) were similar to the DWI volumes (mean:10±9.2 mm³; range:0.7–39.8 mm³). However, there were a small subset of cases (n=5;23%, $p=0.89$), where the DWI volume was slightly larger (7%) but not sig-

nificantly larger than the cT₁WI volume. There was a significant congruence between the Eigenimage-defined cT₁WI and DWI regions. The mean difference between the cT₁WI and DWI region was 8%, with a similarity index of 84% between the regions. Moreover, there is good agreement between the regions defined by T₁ and DWI in most of the cases as shown from the Bland–Altman plots in Fig. 5, where the two parameters did not exhibit a large bias with only two outliers and mean of -0.4 (8%) difference between the treatment areas. Finally, regression analysis of the data for cT₁WI and DWI segmented treatment volumes was found to be significantly correlated ($R^2=0.94$, $p<0.05$) with the linear equation, (cT₁WI)=1.1(DWI)-0.65, as shown in Fig. 6, indicating that these two parameters were highly correlated after MRg-HIFUS.

Figure 3 demonstrates the high correlation and overlap between the DWI and cT₁WI regions after MR-gFUS treatment, as defined by the EI segmentation. On pretreatment MR images, there was contrast enhancement on the T₁ images, with no increased signal intensity noted on the DWI (b=1000) or T₂-weighted image indicative of a viable fibroid [Fig. 3(a)]. However, after treatment, there was a marked decrease of contrast uptake on the cT₁WI, with increased signal intensity on the DWI and corresponding decreased signal intensity within the ADC map. Moreover, the increased signal on the T₂WI indicates the formation of va-

FIG. 5. Bland–Altman plot of difference between cT₁WI and DWI measured volumes using a 95% confidence interval. The data show that the two parameters do not have a large bias with only two outliers and a mean of -0.4 mm³ between treatment areas. This mean difference accounts for an 8% difference between the two measurements indicating a good agreement using these different MR parameters to mark the area of MRg-HIFUS treatment.

FIG. 6. Scatter plot of cT1WI and DWI volumes with 95% confidence intervals. The data show that the two parameters are significantly ($p < 0.05$) correlated with regard to treatment area definition. Moreover, the congruence data suggest that these are complementary parameters.

sogenic edema [Fig. 3(b)]. Finally, the comparison of the regions shows an excellent overlap between the cT₁WI and DWI-defined EI segmented areas. Similar results described above are shown in Fig. 4 with the exception of the lack of vasogenic edema on the T₂WI.

IV. DISCUSSION

We have demonstrated that treatment regions defined by DWI and cT₁WI after MRg-HIFUS in uterine fibroids exhibit a high similarity index and good correlation between the volumes of treated tissue. These data indicate that these imaging sequences are indicative of the treatment extent and that the combination of DWI and cT₁WI is effective for use in the assessment of treated and adjacent tissue after MRg-HIFUS. Moreover, there was excellent overlap between DWI and cT₁WI-defined areas based on an unbiased segmentation algorithm and the Bland–Altman analysis demonstrated good agreement. Thus, by combining DWI and cT₁WI information, a more complete picture of the efficacy of treatment in uterine tissue can be realized.

Indeed, recent reports have shown the utility of the DWI and ADC mapping in the differentiation of untreated fibroids. In particular, Shimada *et al.* compared a contrast enhancement index, defined by the T₁WI, to ADC map values and DWI. There was a significant correlation between the cT₁WI and ADC mapping, and the ADC map values could distinguish completely hyalinized and nonhyalinized uterine fibroids in patients.²⁷ In addition, it has been shown that DWI and ADC mapping are useful for monitoring uterine tissue after UFE treatment and MRg-HIFUS.^{12,28–31} However, these studies did not attempt to correlate the overlap and investigate systematic bias of the volumes of treatment defined by cT₁WI with DWI and ADC mapping.

Pilatou *et al.* compared the cT₁WI and DWI signal intensity changes with the MRg-HIFUS treated and found that the

two areas generally agreed. However, there was a subset of patients (10/46) that exhibited no discernable DWI changes.³¹ The lack of agreement between cT₁WI and DWI in 10/46 case may be due to several factors. The authors used a different DWI sequence than the present study, e.g., line scan diffusion imaging (LSDI) which employs multiple diffusion-weighted SE column excitations to create a two-dimensional image and reduces the sensitivity to motion. They limited the DWI interrogation of the treated tissue to only one slice and used a manual segmentation method to define the regions. In addition, the use of only DWI signal intensity can be problematic due the possibility of “T2 shine through” phenomena.^{41–43} Finally, the temporal evolution of the DWI/ADC mapping is well known to be “biphasic” and renormalizes as the tissue progresses toward necrosis, which could explain the lack DWI hyperintensity in the patients at the time of observation.^{44–47} The current study extends the use of DWI and ADC mapping in the treatment of uterine fibroids and suggests that a multiparametric approach (cT₁WI, DWI, and T₂WI) is useful for monitoring uterine tissue after MRg-HIFUS treatment.

For instance, from the two cases presented in the figures, we can discern different degrees of water movement within and around the treated uterine tissue. In Fig. 3 on the T₂WI, there is clear hyperintensity within the treated area, which indicates that vasogenic edema has occurred. Vasogenic edema is defined as the “bulk flow of water” and is usually noted as increased signal intensity on a T₂WI due to the increase in water in the tissue.^{48,49} Thus, coupled with the signal intensity changes seen on DWI, which at acute times, reflect cytotoxic or cellular edema, may indicate that further tissue “destruction” may occur after treatment. In Fig. 4, within the area of treated tissue, there appears to be no signal hyperintensity on the T₂WI, which indicates that vasogenic edema or bulk water movement had not occurred and further tissue destruction maybe be forthcoming. Furthermore, it has been reported that T₂WI imaging characteristics may be able to potentially select or grade fibroids for treatment based on the signal intensity.²⁶ In particular, a fibroid with T₂WI low signal intensity (compared to surrounding tissue) is a type 1 fibroid, intermediate signal intensity indicates a type 2, and high signal intensity indicates a type 3. Types 1 and 2 are thought to be better responsive to MRg-HIFU treatment than type 3 and our findings are in accord with this.²⁶

Physiologically, DWI provides important information about the movement of water in tissue and can demonstrate differences between the flow of water in normal tissue and pathological environments. These changes in the microdiffusion of water within the intra- and intercellular environments are depicted on the DWI and ADC map.⁵⁰ For example, with an alteration, such as restricted movement, in the flow of water within a tissue, cytotoxic edema will develop and be visualized as an increased signal intensity on the DWI. These signal changes may be attributable to many factors, such as shifts of water from the extracellular space to the intracellular space, increased tortuosity of the diffusion pathways, restriction of the cellular membrane permeability, cellular density, and disruption of cellular membrane depolariza-

tion.^{44,45,49,51} Heat will also change the motion of water and disrupt the bound and unbound proteins within the tissue and the release of these proteins maybe the reason for the decreased in water movement after MRg-HIFUS treatment. This amount of change in water movement is related to the tissue type and blood flow pattern to the treated area.

Most important, DWI provides a quantitative biophysical parameter, called the ADC of water map. The ADC map is an indicator of the movement of water within the tissue and gives an average value of the flow and distance a water molecule can move.⁵⁰ For example, a “decreased” ADC is interpreted as “reduced” flow of water and appears “hypointense” on the image, whereas, an “increased” ADC indicates no restricted water flow and appears hyperintense on the ADC map. The ADC has been related to the state of tissue during the evolution of cerebral ischemia,^{45,46,51} fibroid progression,^{12,28} and tumor changes.^{52–57} Since DWI/ADC mapping can detect changes within the water tissue at the earliest time points, this may provide a method of early indication of treated uterine fibroids using MRg-HIFUS.

Currently, most, if not all, centers use gadolinium, T₁-weighted contrast imaging to define the extent of treated tissue after MRg-HIFUS treatment. This is because viable fibroids before treatment have an increased uptake of contrast after injection of gadolinium due to increased vascular supply, whereas degenerated fibroids do not. Moreover, due to disruption of tissue vascularity in the area of MRg-HIFUS treatment, the area of tissue will appear hypointense and the treatment volume can be measured from contrast agents. Postcontrast T₁WI provides no information about the cellular environment or surrounding tissue other than a signal void within the image. The data shown in this report demonstrate that treated volumes defined by cT₁WI and DWI are highly correlated with little bias. This combination of radiological parameters will provide an anatomical-functional map of the tissue, which may be useful for defining treatment success. However, further studies involving a much larger patient population are needed to further validate these findings and correlate the treatment volumes with histological data assessed by cT₁WI and DWI in uterine fibroids treated by MRg-HIFUS. In conclusion, we have demonstrated that regions defined by postcontrast T1 and DWI are highly correlated, with excellent congruence, after treatment of uterine fibroids using MRg-HIFUS.

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APPENDIX: EIGENIMAGE FILTER METHOD

The contrast criteria can be expressed as

$$\text{MAX} \left[PRJ = \frac{(\vec{e} \cdot \vec{d})}{\sqrt{(\vec{e} \cdot \vec{e})}} \right], \quad (\text{A1})$$

where $\vec{e}$ is not a null vector, subject to the constraint $\vec{e} \cdot \vec{u} = 0$ for all undesired tissue signature vectors. In the case of one undesired tissue type (which is the case for the studies presented in this manuscript), the filter vector for segmenting $\vec{d}$ from $\vec{u}$ is given by

$$\vec{e} = \vec{d} - \frac{\vec{d} \cdot \vec{u}}{\vec{u} \cdot \vec{u}} \cdot \vec{u}. \quad (\text{A2})$$

From Eq. (A2), it can be seen that the projection of the desired tissue onto the EI is

$$\vec{e} \cdot \vec{d} = \vec{d} \cdot \vec{d} - \frac{(\vec{d} \cdot \vec{u})^2}{\vec{u} \cdot \vec{u}} = \|\vec{d}\|^2 - \|\vec{d}\|^2 \cos^2(\theta) = \|\vec{d}\|^2 \sin^2(\theta) > 0, \quad (\text{A3})$$

where θ is the angle between $\vec{d}$ and $\vec{u}$. The projection is nonzero and positive, as long as $\vec{d}$ is not parallel to $\vec{u}$. The projection of the undesired tissue onto the EI is

$$\vec{e} \cdot \vec{u} = \vec{d} \cdot \vec{u} - \frac{(\vec{d} \cdot \vec{u})(\vec{u} \cdot \vec{u})}{\vec{u} \cdot \vec{u}} = 0. \quad (\text{A4})$$

From Eq. (A4), it can be seen that the undesired tissue signature is suppressed in the EI and should be mapped to zero. The composite image generated is a weighted sum of the images in the MRI sequence and given as

$$\text{EI}_{ij} = \sum e_k P_{ijk} = \vec{e} \cdot \vec{P}_{ij}, \quad (\text{A5})$$

where EI_{ij} is the gray level of the ij th pixel in the composite image and P_{ijk} is the k th element of the ij th pixel vector $\vec{P}_{ij} = [P_{ij1} P_{ij2} \cdots P_{ijk}]^T$, i.e., the gray level of the ij th pixel in the k th image in the image sequence.

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