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Magnetic Resonance Imaging–guided Volumetric Ablation of Symptomatic Leiomyomata: Correlation of Imaging with Histology

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Abstract

Purpose—To describe the preliminary safety and accuracy of a magnetic resonance (MR) imaging–guided high-intensity–focused ultrasound (HIFU) system employing new technical developments, including ablation control via volumetric thermal feedback, for the treatment of uterine leiomyomata with histopathologic correlation.

Materials and Methods—In this phase I clinical trial, 11 women underwent MR-guided HIFU ablation (Sonalleve 1.5T; Philips Medical Systems, Vantaa, Finland), followed by hysterectomy within 30 days. Adverse events, imaging findings, and pathologic confirmation of ablation were assessed. The relationship between MR imaging findings, thermal dose estimates, and pathology and HIFU spatial accuracy were assessed using Bland-Altman analyses and intraclass correlations.

Results—There were 12 leiomyomata treated. No serious adverse events were observed. Two subjects decided against having hysterectomy and withdrew from the study before surgery. Of 11 women, 9 underwent hysterectomy; all leiomyomata demonstrated treatment in the expected location. A mean ablation volume of $6.92 \text{ cm}^3 \pm 10.7$ was observed at histopathologic examination. No significant differences between MR imaging nonperfused volumes, thermal dose estimates, and histopathology ablation volumes were observed ($P > .05$). Mean misregistration values perpendicular to the ultrasound beam axis were $0.8 \text{ mm} \pm 1.2$ in feet-head direction and $0.1 \text{ mm} \pm 1.0$ in and left-right direction and $-0.7 \text{ mm} \pm 3.1$ along the axis.

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Conclusions—Safe, accurate ablation of uterine leiomyomata was achieved with an MR-guided HIFU system with novel treatment monitoring capabilities, including ablation control via volumetric thermal feedback.

At the present time, the magnetic resonance (MR) imaging-guided high-intensity-focused ultrasound (HIFU) system approved for clinical use in the United States combines an MR-compatible ultrasound transducer delivering therapy via point-by-point sonication with real-time MR imaging that enables treatment planning and temperature monitoring at treatment sites based on proton-resonance frequency shift MR thermometry (ExAblate 2000, Insightec, Ltd, Tirat Carmel, Israel) (1). This system has been used primarily for ablation of symptomatic uterine leiomyomata, as originally described by Tempny et al (1), and has the potential to offer effective, noninvasive treatment. This therapy remains relatively new, however, with recently reported outcomes data describing symptom relief for at least 12 months; as a result, it is not yet broadly reimbursed in the United States (2). In addition to leiomyoma therapy, MR-guided HIFU ablation shows promise for oncology applications, and it is currently under investigation worldwide for noninvasive treatment of liver, bone, and breast tumors in selected patients (3–7).

As clinical experience with MR-guided HIFU ablation has increased, technical limitations of existing MR-guided HIFU platforms have emerged. The small size of individual focal points used in point-by-point sonication result in long treatment times to ablate large leiomyomata because heating and cooling cycles are required at each focal point. This method may also leave untreated viable tissue between adjacent ablation points (8,9). One sonication strategy developed to address this limitation involves electronic steering of the ultrasound focus along predefined trajectories that enable rapid volumetric sonications by taking advantage of heat diffusion. This approach is made possible with phased-array transducers and driving electronics that enable rapid temporal switching of the focal point location within the treated tissue (9–13). Existing MR-guided HIFU platforms may also result in either overtreatment or undertreatment of target tissue. This problem has been attributed to several as yet poorly quantified tissue-specific parameters such as ultrasound attenuation and tissue perfusion that lead to treatment inefficiencies and variability in treatment outcome (8,9,14). Incorporating real-time MR thermometry data into thermal feedback algorithms allows for modification of sonication parameters during therapy, resulting in a spatiotemporally controlled temperature profile that has been demonstrated in phantoms and in vivo (9,15–19). Temperature monitoring in the anatomic near and far field may also enhance safety of MR-guided HIFU. Collectively, these recent technical developments may improve safety and treatment monitoring during MR-guided HIFU therapy (9,13).

A new MR-guided HIFU platform (Sonalleve MR-HIFU fibroid therapy system; Philips Medical Systems, Vantaa, Finland) employs several of these treatment monitoring capabilities, including MR thermometry monitoring of the anatomic target region comprising the near and far field and ablation control via volumetric thermal feedback. More recent studies have provided information concerning the safety and feasibility of this MR-guided HIFU platform for uterine leiomyomata. Voogt et al (20) prospectively evaluated the technical feasibility of this system and compared MR imaging nonperfused volumes with MR-guided HIFU thermal dose estimates. Kim et al (21,22) suggested a relationship between treatment cell size, energy efficiency, and ablation volume with this same platform and correlated dynamic contrast-enhanced MR imaging parameters with MR-guided HIFU thermal dose estimates. These studies do not correlate imaging findings to histopathologic outcome, and they do not describe analyses concerning the spatial accuracy of this system. The purpose of this clinical study was to assess both the preliminary safety and the targeting accuracy of this MR-guided HIFU platform for the treatment of uterine leiomyomata, including imaging-to-histopathologic correlations of ablation outcome.

MATERIALS AND METHODS

Study Population

This dual-center, single-arm, prospective study (NCT00837161) was approved by the institutional review boards of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, and St. Luke's Episcopal Hospital, Houston, Texas. All patients provided written informed consent. Eligible patients were healthy women (30–59 years old) who were either premenopausal or perimenopausal (follicle-stimulating hormone < 40 mIU/mL). Eligible patients had a fibroid uterus with a uterine size of < 24 weeks of pregnancy. All patients reported severe symptoms attributed to leiomyomata, with leiomyoma size and symptom severity resulting in recommendations for abdominal hysterectomy (23). Symptom severity was assessed by the Uterine Fibroid Symptom Quality-of-Life Questionnaire with a score ≥ 50 necessary for enrollment (24). Targeted leiomyomata were 2–16 cm in diameter and were intramural, nonpedunculated subserosal or submucosal < 5 cm. Hysterectomy was performed 3–30 days after MR-guided HIFU. Pregnant women and women with standard MR imaging contraindications were excluded.

Patients in this study were 39–55 years old (mean, 46 years old), and all patients had completed childbearing (Table 1). Patients had a mean uterine volume of $1,084.7 \text{ cm}^3 \pm 761.9$ (range, 377.5–2,490.5 cm^3) and a mean targeted leiomyoma volume of $246.7 \text{ cm}^3 \pm 356.2$ (range, 2.1–1,140 cm^3). Of the targeted intramural leiomyomata, 10 were located in either the anterior (n = 8) or the posterior (n = 2) body of the uterus; one leiomyoma was submucosal; and one was subserosal, attached to the anterior body of uterus. Three patients had undergone prior myomectomy. Uterine leiomyoma symptoms included excessive bleeding (n = 10 patients), pain (n = 9), bloating (n = 9), frequent urination (n = 7), and constipation (n = 2).

MR-guided HIFU Equipment

Components of this clinical MR-guided HIFU system (Sonalleve MR-HIFU fibroid therapy system) include the MR scanner (Achieva 1.5T, Philips Healthcare, Best, the Netherlands), an integrated three-channel pelvic radiofrequency receiver coil with one anterior and two posterior elements, a 256-element phased-array ultrasound transducer, and an electromechanical transducer positioning system.

MR Imaging

All subjects underwent three MR imaging examinations: MR imaging performed within 6 weeks before MR-guided HIFU, MR imaging performed during MR-guided HIFU, and MR imaging performed 3–5 days after MR-guided HIFU and before hysterectomy. MR images obtained before treatment defined leiomyoma size, volume, location, and presence of enhancement.

All MR imaging examinations were performed with a clinical 1.5T MR system (Achieva 1.5T). MR imaging examinations included three-dimensional T2-weighted planning images and T1-weighted imaging before and after administration of gadopentetate dimeglumine (dose 0.1 mmol/kg body weight; Magnevist, Berlex Laboratories, Wayne, New Jersey) (Appendix 1; available online at www.jvir.org). MR imaging examinations performed before treatment and during MR-guided HIFU were completed with the patient lying in the prone position and using the dedicated pelvic MR coil. Of 11 patients, 2 also underwent MR imaging after treatment in the prone position using this coil. Nine patients underwent MR imaging after treatment in the supine position using a standard 16-channel torso coil with eight anterior and eight posterior elements (SENSE XL Torso Coil; Philips Healthcare).

Ablation Methodology

MR-guided HIFU ablation was performed with a volumetric sonication technique and controlled via thermal feedback. With volumetric ablation, the HIFU transducer applies continuous acoustic energy along concentric circles using treatment cells 4 mm, 8 mm, or 12 mm in diameter (Fig 1a– b), with cooling times between each ablation. The planned treatment volume (PTV) comprises treatment cells within a targeted area (Appendix 2, a– b; available online at www.jvir.org) (13). Volumetric heating may be performed with or without thermal feedback, termed feedback cells and treatment cells. With feedback cells, each volumetric ablation is programmed to achieve ablative temperatures, with duration of sonication determined by the system and adjusted according to the mean cell temperature. For treatment cells, duration of sonication is fixed for each cell size.

Treatment Session

In preparation for treatment, hair from the anterior abdominal wall and pubic region was removed, a Foley catheter was inserted, an intravenous line for administering conscious sedation was placed, and an acoustically transparent gel pad was applied under the pelvic region between the HIFU tabletop and the patient's skin. Of 11 patients, 10 received conscious sedation with midazolam hydrochloride (mean, 3.5 mg; range, 1– 6 mg) and fentanyl (mean, 187.5 μ g; range, 75–325 μ g). In 2 of 11 patients, alprazolam (1 mg each) was administered for anxiolysis before the procedure, at the discretion of the treating physician. No bowel motility agents were used. MR imaging before treatment included a three-dimensional T2-weighted sequence to localize the transducer, uterus, and targeted leiomyoma. The presence of air bubbles at the gel pad–skin interface was assessed by a two-dimensional fast-field echo pulse sequence. If bubbles > 1 mm were detected in the anticipated beam path, the gel pad and patient were repositioned followed by an additional two-dimensional fast-field echo pulse sequence to confirm absence of air bubbles (Appendix 1; available online at www.jvir.org).

Using a sagittal three-dimensional T2-weighted turbo spin-echo sequence and the system software, the radiologist outlined the PTV of the leiomyoma. The planned HIFU beam path was superpositioned on the patient's anatomic imaging to verify a clear acoustic path. Sonication cells with diameters of 4 mm, 8 mm, or 12 mm were used such that the cells fell within the outlined PTV in all planes (Appendix 2, a– b; available online at www.jvir.org). Safety margins included 4 cm between the PTV and patient's spine or intestine and 1.5 cm to uterine serosa.

A low-power (10 – 40 W) test sonication was performed to verify that heating would occur in the intended location, to correct for any spatial offset from the geometric focus owing to tissue interactions with the HIFU beam, and to determine the power level necessary to achieve therapeutic ablation based on the test sonication power applied and resultant temperature elevation. Low power applied during the test sonication was gradually increased until a mean temperature elevation of 5°C was observed. The treatment cell was exposed to higher power (80 –150 W) therapeutic sonications such that ablative temperatures (> 55°C) and desired thermal dose (> 240 cumulative equivalent minutes at 43°C [CEM43]; see later) were achieved (Fig 2a– d). A 90-second pause, set by system software, allowed tissue cooling between each sonication. Sonications were monitored during therapy, with treatment modified as needed. If women reported symptoms during the procedure, including pain or skin heating, they could press a button to cease treatment. Sonication parameters are presented in Appendix 3 (available online at www.jvir.org).

Real-Time Temperature Display, Thermal Dose Maps, and MR Imaging

The MR-guided HIFU graphic user interface displayed real-time two-dimensional temperature data with a color scale overlaid on gray-scale MR anatomic images (Fig 2a– b). The target and adjacent anatomic near and far fields were monitored with real-time MR thermometry. Thermal dose maps were calculated according to the Sapareto-Dewey equation using a linear interpolation of temperature between dynamic acquisitions with a unit of cumulative equivalent minutes at 43°C (CEM43) (14). Preexisting data suggest that 30 cumulative equivalent minutes at 43°C (30 CEM43) may correspond to the onset of tissue thermal injury, whereas 240 cumulative equivalent minutes at 43°C (240 CEM43) reflects complete necrosis in most tissues (14). Temperature images were acquired for at least 2 minutes after sonication to enable assessment of accumulated thermal dose during cooling. Temperature standard deviation estimates were used for dose compensation and updated according to the signal-to-noise ratio of the acquired image (13). Thermal dose estimates of both 30 CEM43 and 240 CEM43 were displayed during and after each sonication (Fig 2c– d).

Follow-up and Imaging Assessment, Histopathologic Analysis, and Radiologic-Pathologic Correlation

At site 1 (NIH Clinical Center), all patients (n = 9) were admitted overnight. At site 2 (St. Luke's Episcopal Hospital), patients (n = 2) were discharged the same day. Patients were contacted by phone at 24 hours, 48 hours, 1 week, and 2 weeks after therapy to assess symptoms and adverse events before hysterectomy. They returned for a follow-up clinic visit and MR imaging 3–5 days after therapy.

Imaging Assessment

MR imaging scans obtained before and after treatment were analyzed by two independent readers who were informed of the targeted region but were unaware of the PTV (Oulu University Hospital, Oulu, Finland, and Factory CRO, Bilthoven, the Netherlands). MR imaging analysis was performed with either OsiriX imaging software (Pixmeo, Geneva, Switzerland) or ViewForum software (Philips Healthcare). See Appendix 4 (available online at www.jvir.org) for additional details concerning assessment of leiomyoma ablation volumes and HIFU spatial accuracy.

Histopathologic Analysis and Radiologic-Pathologic Correlation

The abdominal cavity and uterine surface were inspected at surgery for unintended thermal damage. Given the large uterine size and other untreated leiomyomata, MR images were examined alongside hysterectomy specimens to facilitate identification of treated leiomyomata (Fig 2e– g).

Hysterectomy specimens were inspected by the pathologist for unintended damage. After gross examination, specimens were bivalved to expose the endometrial cavity and cut at 0.5-cm intervals in the uterine sagittal plane. Cut uterine surfaces were examined grossly for leiomyomata and for pathologic findings representing treatment using hematoxylin and eosin staining (Fig 2g–j). Treated areas were measured for their largest orthogonal dimensions in the planar cut surface with the third dimension estimated by summing the affected 0.5-cm-thick sagittal planes. HIFU ablation volumes were calculated using the prolate ellipsoid volume formula. After all targeted tumors were grossly identified and measured, specimens were fixed in formalin. Representative samples of serosa, myometrium, and endometrium in the treated path and remote from the treated volume were evaluated for histopathologic abnormalities including necrosis, hemorrhage, or fibrosis.

Statistical Analyses

Demographic, study population characteristics, treatment parameters, and adverse events were described using frequency distributions or simple descriptive statistics. Differences between the calculated contour and ellipsoid ablation volumes were assessed using a paired *t*-test, and their agreement was assessed using Bland-Altman analysis. If mean contour and ellipsoid values were not observed to be different, subsequent comparisons were performed between contour values, HIFU thermal dose estimates, and histopathology volumes.

Differences between the contour MR imaging measurements, 30 CEM43 and 240 CEM43 thermal dose estimates, and histopathology ablation volumes were assessed using paired *t*-tests; pair-wise agreements were assessed using Bland-Altman analyses. Intraclass correlation coefficients were used to assess the overall level of agreement among MR imaging volumes, thermal dose estimates, and histopathology considered together. Data were reported as mean $\pm$ standard deviation and were analyzed using SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina). All *P* values $< .05$ were considered statistically significant.

RESULTS

There were 12 leiomyomata treated in 11 patients. In the 11th patient treated, two leiomyomata were treated during one MR-guided HIFU treatment session. Average treatment session duration, defined as from the time the patient was positioned on the HIFU table until transport to the recovery room, was 3.67 hours $\pm$ 0.7 (range, 2.67–5.55 h). Preplanning time, defined as the time from when the patient was placed on the table to the first survey scan, was 13.2 minutes $\pm$ 5.4 (range, 8–28 min). The planning time, defined as the time from the first survey scan to delivery of the first sonication, was 104.4 minutes $\pm$ 49.2 (range, 48–241 min). The sonication time, defined as the time from the first sonication to the last sonication, was 54.6 minutes $\pm$ 18.0 (range, 23–86 min). The posttreatment duration, defined as the time from performance of the last sonication to transferring the patient off the HIFU table, was 34.2 minutes $\pm$ 12.0 (range, 12–60 min). The duration of time for transfer of the patient to the recovery area, subsequent to removal off the HIFU tabletop, was 13.2 minutes $\pm$ 9.6 (range, 1–16 min).

Of 11 patients, 9 underwent hysterectomy, with a mean time of 9 days between MR-guided HIFU and hysterectomy (range, 3–20 d); 2 patients decided against having hysterectomy citing that the postoperative recovery would interfere with their work schedule and withdrew from the study before surgery. Nontarget thermal injury was not observed on contrast-enhanced MR images obtained after treatment, during surgical inspection at hysterectomy, or at gross pathology assessment. At gross pathology assessment, all leiomyomata showed confluent treatment in the expected location. In eight of nine cases, confluent treatment in the expected location was confirmed at histopathologic assessment with hematoxylin and eosin staining. In one of these eight cases, one patient had an additional 0.8-cm focus of hemorrhagic necrosis within uterine myometrium adjacent to a 2-cm submucosal leiomyoma that moved during treatment. This movement was observed on MR imaging during treatment; concurrently, the patient experienced pain and pressed the emergency button, interrupting treatment after 24.4 seconds of sonication. A ninth patient underwent MR-guided HIFU of a small area within an 11-cm leiomyoma containing extensive myxomatous degeneration. Although identified by needle localization on gross pathology, the area treated by HIFU at histopathology was difficult to identify, being in close proximity to the area of preexisting necrosis. Table 2 delineates ablation volumes determined by MR imaging assessment using the contour method, 30 CEM43 and 240 CEM43 thermal dose estimates, and histopathologic findings for each patient. The histopathologically confirmed mean ablation volume was $6.92 \text{ cm}^3 \pm 10.7$ with a mean targeted leiomyoma volume of 246.7 cm^3 .

± 375.8 . These intentionally small volumes of treatment were in keeping with the study goal, which was to treat enough tissue to allow comparisons between MR imaging findings and pathology.

HIFU Complications

Complications during and after HIFU were described using the Society of Interventional Radiology Classification System for Complications by outcome (25). During and after HIFU, no major complications were reported. Of the minor complications reported, transient abdominal cramping ($n = 9$) or leg pain ($n = 2$) were the most frequently reported. These expected minor adverse events were self-limited, resolving by 72 hours in all cases. Specifically, no skin burns or nerve injuries were observed. One patient with chronic constipation had blood in the stool in the recovery area after HIFU treatment. This adverse event was reported to be a relatively common occurrence for this patient, and was not attributed to HIFU treatment. Another patient who developed transient suprapubic pain and urinary frequency 1 week after HIFU treatment had negative urinalysis and culture; physical assessment did not reveal any findings. The patient was prescribed ibuprofen to relieve the pain symptoms. The beam path was not near the symptomatic area, and these symptoms were attributed to Foley catheterization.

MR-guided HIFU Spatial Accuracy

MR-guided HIFU spatial targeting was assessed by comparing intended and actual treated locations and calculating misregistration values. Test sonications were discarded from misregistration analyses because they were used to calibrate spatial targeting. Mean misregistration perpendicular to the ultrasound beam axis was $0.8 \text{ mm} \pm 1.2$ (range, -2.6 to $+3.7 \text{ mm}$) from the planned location in the feet-head direction and $0.1 \text{ mm} \pm 1.0$ (range, -4.9 to $+1.7 \text{ mm}$) from the planned location in the left-right direction. Misregistration along the beam axis was $-0.7 \text{ mm} \pm 3.1$ from the planned location (range, -8.5 to $+6.2 \text{ mm}$).

Comparison of MR-guided HIFU Treatment Volumes by MR Imaging Assessment, Thermal Dose Estimates, and Histopathology

Mean contour and ellipsoid measured volumes were equivalent and in agreement by Bland-Altman analysis ($P > .05$) enabling subsequent comparisons to be performed using only contour volumes. Mean contour MR imaging ablation volumes were not different from histopathology ablation volumes ($P = .5348$) and were in agreement with histopathology ablation volumes by Bland-Altman analysis ($P = .5345$).

Paired comparisons between contour MR imaging ablation volumes and 30 CEM43 thermal dose estimates indicated no significant difference between the mean values of these data ($P = .5510$). Contour MR imaging ablation volumes and 30 CEM43 values showed agreement by Bland-Altman analysis ($P = .5500$), showing small magnitudes of differences within tight thresholds (Appendix 5, a; available online at www.jvir.org). However, contour MR imaging volumes were significantly different from the smaller 240 CEM43 thermal dose estimates ($P = .03$) and did not show agreement with the smaller 240 CEM43 thermal dose estimates ($P = .0328$) (Appendix 5, b; available online at www.jvir.org), suggesting that 30 CEM43 may provide a more accurate description of the treatment volume. Comparisons between histopathology ablation volumes and the 30 CEM43 and 240 CEM43 thermal dose estimates indicated no difference between the mean values of these data ($P = .93$ and $P = .33$). Agreement between histopathology ablation volumes and the 30 CEM43 and 240 CEM43 thermal dose estimates was observed via Bland-Altman analysis ($P > .05$) and could be visually noted by the tight thresholds and small mean differences with minimal data falling outside the thresholds (Appendix 5, c and d; available online at www.jvir.org).

Considered together, the MR imaging, thermal dose, and histopathology measurements showed agreement (intraclass correlation coefficient = 0.6996).

DISCUSSION

We describe the preliminary safety and accuracy of a novel MR imaging– guided HIFU system employing volumetric feedback ablation for the treatment of uterine leiomyomata, with histopathologic correlation. All patients in this study tolerated the MR-guided HIFU procedure well, with no serious adverse events. Confluent zones of treatment were observed in all cases except one for which it was difficult to localize a small ablation zone adjacent to a large, partially necrotic leiomyoma. Agreement was observed between ablation volumes estimated via patients' MR-guided HIFU thermal dose estimates obtained during the procedure and contrast-enhanced MR images and histopathology obtained after treatment, including hysterectomies performed several weeks after HIFU. These findings suggest accurate and predictable thermoablation may be achieved with this MR-guided HIFU system.

Existing MR-guided HIFU platforms have demonstrated safety, feasibility and effectiveness for ablation of leiomyomata, with short-term follow-up. Variation in treatment temperatures, leading to both overtreatment and undertreatment of target tissue, previously limited the accuracy of MR-guided HIFU (9). Controlling ablation by use of real-time thermometry data provided by thermal feedback may prevent tissue overtreatment and undertreatment (9). Representative cases using 8-mm and 12-mm volumetric feedback and treatment cells suggest greater ability to achieve the desired range of ablative temperatures (60°–62°C) and greater temperature control with feedback compared with more traditional treatment cell sonications (Fig 3a– b). Use of volumetric feedback ablation also has the potential for superior energy efficiency compared with point-by-point ablations (13,21). Depending on treatment cell size and power used, the volume ablated per sonication time with the device in this study was 0.12–7.50 cc/min, which would be of interest to assess in future clinical studies.

There are limitations to this study, which was a “proof-of-concept” study with a small number of patients. Similar to Tempny et al (1), by performing a hysterectomy soon after treatment, we were unable to correlate treatment with change in symptoms. Because our study goal was to treat enough tissue to allow comparisons between MR imaging findings and pathology, we did not treat large volumes within each leiomyoma. Several challenges arose because of the small treated leiomyoma volumes. Strategies developed to identify treated areas on gross pathology included review of the MR images by the radiologist, gynecologist, and pathologist and MR imaging– guided needle localization of the HIFU-treated area within the uterine specimen before histopathologic assessment. There are also inherent uncertainties comparing histopathology and MR imaging treatment volumes because of the challenges associated with accurately matching imaging to gross pathology planes, the observed increase in leiomyoma volume when leiomyomata were transected at pathology, and an estimated three-dimensional measurement, orthogonal to the cut surface plane at 5-mm intervals. The modest volumes of ablation achieved with an average treatment session duration of 3.75 hours during this phase I trial are not reflective of future treatment times and achievable ablation volumes. In the next prospective trial with this device, MR-guided HIFU will be used as the primary treatment, with the goal of achieving larger, therapeutic ablation volumes, and patients' symptoms will be followed as a measure of treatment effect.

In conclusion, in this preliminary study, safe and accurate ablation of uterine leiomyomata was achieved using an MR-guided HIFU device employing temperature monitoring of the

target and anatomic near and far fields and volumetric ablation control via thermal feedback, with histopathologic confirmations of treatment outcome. Volumetric MR-guided HIFU ablation with these treatment monitoring capabilities may facilitate predictable, rapid, and confluent thermoablation of benign and malignant neoplasms.

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ABBREVIATIONS

CEM43	cumulative equivalent minutes at 43°C
HIFU	high-intensity–focused ultrasound
MR	magnetic resonance
PTV	planned treatment volume

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APPENDIX 4

Imaging Assessment

Ablation volumes of leiomyomata were measured in two ways:

1. Ellipsoid method: $V = \pi \times (A \times B \times C)/6$, where A , B , and C were diameters measured in orthogonal planes on T2-weighted or contrast images; the volume (V) was assumed to be that of a prolate ellipsoid.
2. Contour method: Each two-dimensional image slice where the ablated zone was observable was manually segmented. The number of voxels contained within the ablated zones was calculated and multiplied by the voxel volume to compute the total volume, with any slice overlap or gap taken into account by the software.

Measurements obtained via each method from each reader were averaged to obtain final measurements of leiomyoma volume and ablation volume for each target.

A custom-made semiautomated measurement tool (Philips Medical Systems, Vantaa, Finland) was developed using software interface description language (IDL version 6.1; ITT Visual Information Solutions, Boulder, Colorado) to assess high-intensity–focused ultrasound (HIFU) spatial targeting accuracy. This measurement tool calculated the center of mass of temperature elevation in the target region and compared the intended sonication location from the HIFU planning software with the actual treatment location indicated as the thermal dose center of mass estimates at the end of the treatment session. Misregistration was defined as the distance between the center of mass and the intended location.

Figure 1.

MR-guided HIFU volumetric ablation. **(a)** Schematic of HIFU transducer and beam, applying focused acoustic energy in concentric circles within a treatment cell. **(b)** Treatment cells 4 mm, 8 mm, or 12 mm in diameter, with a ratio of cell diameter to length of approximately 1:2.5.

Figure 2.

Intraprocedural MR-guided HIFU monitoring and MR imaging and histopathologic findings after leiomyoma ablation with MR-guided HIFU. **(a–d)** Graphic user interface displays multiplanar three-dimensional T2-weighted imaging and overlaid temperature maps **(a–b)** and overlaid thermal dose estimates **(c–d)** during sonication of an anterior intramural leiomyoma within the body of the uterus. Accumulated thermal dose information in the treated volume is displayed at the end of each sonication as a thermal dose estimate. These thermal doses are reported in CEM43, with 30 CEM43 (beige polygon, **c–d**) corresponding to onset of tissue alteration and 240 CEM43 (white polygon, **c–d**) representing predicted territory of complete necrosis. Both 30 CEM43 and 240 CEM43 thermal dose estimates are updated after each sonication. **(e–f)** Sagittal **(e)** and coronal **(f)** contrast-enhanced MR images after HIFU show nonenhancing treated region (black arrows). **(g)** Bivalved gross uterine specimen shows hemorrhagic necrosis in the area of treatment (white arrow). **(h–j)** Low-magnification (4×) histologic images of margin **(h)**, high-magnification (10×) images of margin **(i)**, and high-magnification images of the center of the ablation zone **(j)** confirm necrosis (asterisk) and narrow zone of transition (white arrows) between viable and necrotic HIFU-treated tissue. (Available in color online at www.jvir.org)

Figure 3.

Comparison of mean temperature (T) elevations as a function of time during MR-guided HIFU heating of leiomyomata with 8-mm **(a)** and 12-mm **(b)** treatment cells (gray lines) versus feedback cells (black lines). Feedback cells refer to sonications performed with thermal feedback, for which exposure duration is determined by the system, and sonication duration is adjusted according to measured mean cell temperature. Treatment cells are sonications performed without thermal feedback for which sonication duration is fixed and linked with cell size. **(a)** An 8-mm treatment cell (mean temperature displayed as gray line) is set to deliver energy for a fixed duration of 27 seconds, despite ablative temperatures (60°–62°C) not being achieved at the end of sonication (black arrow). Exposure duration for the 8-mm feedback cell is controlled by an algorithm monitoring mean temperature (black line) and continues heating until ablative temperatures are successfully achieved. **(b)** A 12-mm treatment cell (mean temperature displayed as gray line) delivers energy for a fixed time, exceeding the desired ablative temperature range after cessation of therapy (black arrow), unnecessarily lengthening the treatment time. Exposure duration of the 12-mm feedback cell is adjusted based on the mean temperature achieved (black line) and does not exceed the desired ablative temperature range during the course of therapy.

Appendix 2.

Therapy planning software enables delineation of the planned treatment volume (PTV) and individual sonications during treatment planning. Each sonication cell (either treatment cell or feedback cell) may be assigned its own acoustic power setting, sonication frequency, and cell diameter. **(a)** Individual sonications are delineated, and cumulative volume of individual planned sonications, known as a treatment cluster, is compared with PTV to determine the percentage of target volume to be ablated (in this example, 28%). Regulatory stipulations for this trial permitted ablation of 30% of target fibroid volume. **(b)** Three-dimensional T2-weighted magnetic resonance (MR) imaging allows for multiplanar assessment and treatment planning, with PTV (red ellipse) and planned sonications (green ellipses) superpositioned on anatomic images. After populating PTV with intended sonication cells, the radiologist verifies on all planes to confirm that cells remain within the PTV outline.

Appendix 5.

Bland-Altman analyses assessing pair-wise agreements between magnetic resonance (MR) imaging measurements via the contour method, 30 cumulative equivalent minutes at 43°C (CEM43) (a) and 240 CEM43 (b) thermal dose estimates, and between histopathology volumes and 30 CEM43 (c) and 240 CEM43 (d) thermal dose estimates. Bland-Altman analyses show the mean of the results of the two methods being compared on the x-axis, and their absolute difference on the y-axis. Good agreement between the two methods being compared was defined as (i) a mean difference close to zero (and lack of statistical significance on the *t*-test), (ii) 95% of the data falling within the threshold bars (representing 2 standard deviations of the mean difference, with tighter thresholds indicating more consistency in measurements), and (iii) almost no extreme outliers falling outside 3.5 standard deviations from the mean difference.

Table 1**Subject Demographic Data**

Total No. Patients	11
Patient demographics	
Race	
Caucasian, non-Hispanic	4
Caucasian, Hispanic	1
African-American	4
Asian	2
Age, mean (range)	46 y (39–55 y)
Height, mean (range)	162.0 cm (152–171 cm)
Weight, mean (range)	73.2 kg (56.0–103.4 kg)
Body mass index (range)	27.9 kg/m ² (24.2–35.4 kg/m ²)
Parity, mean (range)	1.5 (0–3)
Uterine volume, mean (range)	1,084.7 cm ³ ± 761.9 (377.5–2,490.5 cm ³)
Targeted leiomyoma volume, mean (range)	246.7 cm ³ ± 356.2 (2.1–1,140.0 cm ³)
Symptom severity	
UFSQOL score, mean (range)	71.1 (50–93.8)

UFSQOL = Uterine Fibroid Symptom Quality-of-Life Questionnaire.

Table 2

Comparison of Ablation Volumes Determined by Magnetic Resonance (MR) Imaging Assessment, Thermal Dose Estimates, and Specific Histopathologic Findings Observed after MR Imaging-guided High-Intensity-focused Ultrasound Therapy

Subject	Contoured Ablation Volume at MR Imaging (cm ³)	30 CEM43	240 CEM43	Ablation Volume at Pathology (cm ³)	Pathologic Findings for Targeted Leiomyoma
1	1.2	5.4	3.0	0.5	Leiomyoma with hemorrhage and fibrosis
2	0.6	1.2	0.4	0.6	Leiomyoma with necrosis and hemorrhage; necrosis and hemorrhage in the endometrium and focally in the myometrium
3	14.2	9.0	3.9	9.3	Coagulative necrosis
4	47.8	20.8	10.2	33.6	Leiomyoma with hemorrhage and necrosis
5	0.2	1.0	0.5	0.2	Targeted leiomyoma without thermal damage adjacent to large fibroid with myxoid degeneration
6	4.8	9.0	4.3	4.9	Focal hemorrhage and coagulative necrosis consistent with HIFU effect
7	23.4	25.0	12.8	NA *	NA *
8	1.5	2.2	1.0	1.9	Leiomyoma with hemorrhage, fibrosis, and focus of pinpoint necrosis in the center of leiomyoma
9	30.0	34.2	15.6	NA *	NA *
10	42.7	37.1	19.4	16.0	Leiomyoma with large area of hemorrhage and fibrosis
11	2.4	2.4	1.1	1.8	Coagulative necrosis
	1.0	0.4	0.1	0.37	Coagulative necrosis

Note.—In subject 11, two leiomyomata were treated during one HIFU ablation treatment session.

CEM43 = cumulative equivalent minutes at 43°C; HIFU = high-intensity-focused ultrasound; NA = not applicable.

* Two subjects decided against having hysterectomy and withdrew from the study before surgery.

Appendix 1

Pelvic Magnetic Resonance (MR) Imaging Parameters for Volumetric MR-guided High-Intensity–focused Ultrasound Treatment Planning

Purpose	Site	Sequence	Parameters
T2 planning images *	Site 1	3D sagittal turbo SE	TR/TE 1650/120 (repetition time ms/echo time ms), 90° flip angle, FOV 220 mm, matrix size 192 × 192, in-plane spatial resolution 1.15 × 1.15 mm, slice thickness 2.0 mm, intersection gap –1.0 mm, bandwidth 583.6 Hz, echo train length 73, number of signal averages 1, direction of phase encoding AP, direction of frequency encoding FH, 160 sagittal slices, SENSE 2.0, scan time 292 s
	Site 2	3D sagittal turbo SE	TR/TE 2000/180, 90° flip angle, FOV 250 mm, matrix size 144 × 144, in-plane spatial resolution 1.74 × 1.74 mm, slice thickness 2.5 mm, intersection gap –1.25 mm, bandwidth 715.9 Hz, echo train length 90, number of signal averages 2, direction of phase encoding AP, direction of frequency encoding FH, 110 sagittal slices, SENSE 1.8, scan time 302 s
Intraprocedural bubble detection	Both	2D fast field echo	TR/TE 411/15, 60° flip angle, FOV 250 mm, matrix size 224 × 224, in-plane spatial resolution 1.12 × 1.12 mm, slice thickness 2.5 mm, intersection gap 0 mm, bandwidth 41.3 Hz, echo train length 1, number of signal averages 2, direction of phase encoding RL, direction of frequency encoding FH, 11 coronal slices, SENSE 1.6, scan time 117 s
Intraprocedural temperature mapping	Both	2D fast field echo with echo planar imaging	TR/TE 54/20, 19° flip angle, FOV 400 mm, matrix size 160 × 160, in-plane spatial resolution 2.5 × 2.5 mm, slice thickness 7 mm, intersection gap 0 mm, number of signal averages 1, echo planar imaging factor 11, 6 slices, temporal resolution 2.9 s/dynamic
Precontrast imaging	Site 1	T1-weighted 3D turbo field echo with spectral selection attenuated IR	TR/TE 8.2/4.0, 10° flip angle, FOV 260 mm, matrix size 288 × 288, in-plane spatial resolution 0.9 × 0.9 mm, slice thickness 3 mm, intersection gap –2 mm, number of signal averages 1, bandwidth 173.0 Hz, echo train length 40, direction of phase encoding AP, direction of frequency encoding FH, IR delay 90, 58–93 sagittal slices, SENSE 1.5, scan time 258–358 s
Precontrast imaging	Site 2	T1-weighted 3D turbo field echo with spectral selection attenuated IR	TR/TE 4.2/2.0, 10° flip angle, FOV 250 mm, matrix 160 × 160, in-plane spatial resolution 1.56 × 1.56 mm, slice thickness 3 mm, intersection gap –1.5 mm, number of signal averages 2, bandwidth 434.5 Hz, echo train length 40, direction of phase encoding AP, direction of frequency encoding FH, IR delay 90, 92 sagittal slices, SENSE 1.5, scan time 295 s
Postcontrast imaging	Site 1	T1-weighted 3D turbo field echo with spectral selection attenuated IR	TR/TE 8.2/4.0, 10° flip angle, FOV 260 mm, matrix size 288 × 288, in-plane spatial resolution 0.9 × 0.9 mm, slice thickness 4 mm, intersection gap –2 mm, number of signal averages 1, bandwidth 173.0 Hz, echo train length 40, direction of phase encoding AP, direction of frequency encoding FH, IR delay 90, 58–93 sagittal slices, SENSE 1.5, scan time 258–358 s
Postcontrast imaging	Site 2	T1-weighted 3D turbo field echo with spectral selection attenuated IR	TR/TE 4.0/1.9, 10° flip angle, FOV 340 mm, matrix 160 × 160, in-plane spatial resolution 2.1 × 2.1 mm, slice thickness 4 mm, intersection gap –2.0 mm, number of signal averages 2, bandwidth 434.5 Hz, echo train length 40, direction of phase encoding AP, direction of frequency encoding FH, IR delay 90, 110 sagittal slices, SENSE 1.5, scan time 305 s
T2 planning images †	Site 1	3D sagittal turbo SE	TR/TE 970/130, 90° flip angle, FOV 220 mm, matrix size 192 × 148, in-plane spatial resolution 1.15 × 1.49 mm, slice thickness 2.0 mm, intersection gap –1.0 mm, bandwidth 882.8 Hz, echo train length 96, number of signal averages 1, direction of phase encoding AP, direction of frequency encoding FH, 120 sagittal slices, scan time 209 s
Precontrast and postcontrast imaging ‡	Site 2	T1-weighted 3D turbo field echo with spectral selection attenuated IR	TR/TE 4.8/2.4, 10° flip angle, FOV 250 mm, matrix 288 × 288, in-plane spatial resolution 0.87 × 0.87 mm, slice thickness 2.5 mm, intersection gap –1.25 mm, number of signal averages 2, bandwidth 434.5 Hz, echo train length 40, direction of phase encoding AP, direction of frequency encoding FH, IR delay 90, 110 sagittal slices, SENSE 1.5, scan time 362 s

AP = anteroposterior direction; FH = feet-head direction; FOV = field of view; IR = inversion recovery; RL = right-left direction; SE = spin echo; SENSE = sensitivity encoding factor; 3D = three-dimensional; 2D = two-dimensional; TE = echo time; TR = repetition time.

* For each patient, a single sagittal 3D T2-weighted turbo SE sequence was obtained for treatment planning. If additional anatomic information was required for target localization, additional 2D T2-weighted turbo SE images were obtained in either the axial or the coronal plane. Then either T1-weighted SE MR images or 3D T1-weighted gradient echo images were obtained. For contrast-enhanced images, fat-suppressed T1 SE or 3D T1-weighted gradient echo images were obtained. Pelvic MR images were obtained before and after treatment according to the same protocol.

† MR imaging protocol parameter variations for treatment planning images for each of the first patients treated at site 1 and site 2. MR imaging protocol parameters for these patients on treatment day and after MR-guided high-intensity-focused ultrasound treatment and for all other patients were as otherwise listed in this table.

Appendix 3

Treatment Parameters for Sonications Delivered during Magnetic Resonance Imaging– guided High-Intensity–focused Ultrasound Therapy

Total no. sonications performed	99
Test sonications	26
Therapeutic sonications	73
Total number of sonications completed	82
No. sonications aborted prematurely	17
Aborted by software	14
Aborted by patient [*]	3
Average power of test sonications (W) (n = 25)	25 ± 15
Average power of therapeutic sonications (W) (n = 76)	108 ± 19
Average single sonication duration (s)	28 ± 13
Average cumulative sonication time per patient (s)	252 ± 117
Average maximum temperature for therapeutic sonications (n = 71 [†])	62.5°C ± 4.7

^{*} Three therapeutic sonications were aborted by a patient who experienced transient pain during treatment of a submucosal fibroid that moved during treatment (see Results).

[†] Two therapeutic sonications were removed from temperature analysis because of obviously faulty temperature readings > 100°C caused by patient motion and poor signal-to-noise ratio.