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Magnetic Resonance Elastography of Uterine Leiomyomas: A Feasibility Study

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Abstract

Objective—To determine the feasibility of performing *in vivo* magnetic resonance elastography (MRE) for uterine leiomyoma.

Design—Pilot study

Setting—Academic Medical Center

Patients—Six subjects planning surgical excision of uterine leiomyomas.

Intervention—MRE prior to planned surgery

Main Outcome Measures—Achieving an appropriate phase signal to noise ratio (PSNR) in the leiomyoma to allow assessment of leiomyoma elasticity in kilo pascals (kPa).

Results—MRE was successful in all subjects for uteri ranging from 100 to over 1000 grams. Subjects had body mass indices (BMIs) ranging from 23.0 to 38.0 kg/m². Appropriate PSNR ranging from 5.45 to 42.28 were achieved for leiomyomas in all subjects. Mean elasticity of uterine leiomyomas ranged from 3.95 to 6.68 kPa.

Conclusion(s)—MRE is a feasible technique for studying the *in vivo* mechanical properties of uterine leiomyomas and demonstrates significant heterogeneity in elasticity between lesions. Further work is necessary to optimize the technique and understand the clinical utility of this technique for women with uterine leiomyomas.

Keywords

leiomyomas; magnetic resonance; elasticity; uterus; feasibility studies; Elasticity imaging techniques/methods; adult; humans; female

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Introduction

Leiomyomas are benign myometrial neoplasms characterized by the presence of excessive extracellular matrix (ECM) that is both structurally and functionally important (1). The ECM in leiomyomas is dynamically regulated throughout the menstrual cycle and serves as a reservoir for growth factors active in leiomyoma biology (2–4). Additionally, the arrangement of ECM proteins also has been shown to be abnormal in leiomyomas and there is evidence that there is altered mechanical homeostasis in leiomyomas leading to activation of solid-state signaling (5,6).

Leiomyomas are typically firmer on palpation than the surrounding myometrium and thus they are typically referred to as fibroids. The mechanical property of soft tissues measured by palpation is elasticity, which compares the ratio of a given stress to the resulting strain. Elasticity of soft tissues varies over several orders of magnitude and produces a wider range of values than captured by other types of imaging such as x-ray absorption or magnetic resonance relaxation times (7). *In vitro* ultrasound strain imaging has demonstrated the elastic variability of uteri containing leiomyomas and endometrial polyps in excised hysterectomy specimens (8).

Magnetic Resonance Elastography (MRE) assesses mechanical properties of *in vivo* tissues in a three step process: First, an external vibrating mechanical driver coupled to the human body transmits shear waves into the relevant tissue. Secondly; a MRE wave imaging sequence is designed to capture images of the propagating shear waves in the tissue. Finally, an MRE algorithm is used to analyze the resulting wave images and calculate stiffness map of the tissue called an elastogram (9).

In vitro and *in vivo* data shows that elastic modulus significantly correlates with pathological findings of diseased tissues. Data from breast specimens have consistently shown shear modulus of various types of carcinoma are much higher than the value of normal adipose-glandular tissue (10–12). *In vivo* hepatic elastographic data shows that fibrotic or cirrhotic livers are much firmer than normal ones(13–19); while benign liver tumors are significantly softer than malignant ones(20).

Our hypothesis is that leiomyomas differ in elasticity. The primary aim of this pilot study was to investigate the feasibility of MRE for uterine leiomyomas and to obtain data regarding the variability of leiomyoma elasticity *in vivo*.

Material and Methods

Patient Population and Data Collection

This *in vivo* MRE study was conducted at the Mayo Clinic, Rochester, MN. MRE has been determined to be a nonsignificant risk procedure by the Mayo Clinic Institutional Review Board, which approved this study. Written consent was obtained from all participants prior to the study. Study procedures were in accordance with ethical standards set forth in the revised Declaration of Helsinki. Women with planned excisional surgery for uterine leiomyomas between April 2008 and March, 2009 were eligible for inclusion.

Magnetic Resonance Elastography

Magnetic Resonance Elastography (MRE) scans were performed on a 1.5 T whole-body imager (Signa, GE Healthcare, Milwaukee, WI, USA). Participants were imaged in the supine position with a 19 cm diameter passive driver placed on their abdomen above the uterus together with a custom-built four element phased array MRI imaging coil. Continuous acoustic vibrations at 60 Hz were transmitted from an active driver in the equipment room to

the passive driver through a flexible vinyl tube, which is transmitting shear waves into the uterus. A modified 2-D gradient recalled echo (GRE) based elastography pulse sequence was used to collect wave images with the following parameters: imaging plane=axial or sagittal; FOV=24–42cm; matrix =256×64; fractional phase FOV=0.75–1; flip angle= 30°; NEX=1; Bandwidth =15.63–31.25 kHz; TR=50 msec; TE=24.9–28.5 msec; slice thickness =4–5 mm; slice position = through the uterine fibroid; phase offsets = 4 or 8; MENC = 30.7–31.7 $\mu\text{m}/\pi$ -radian; motion-sensitizing-gradient (MSG) frequency=60Hz; MSG direction= RL (right-Left), AP (anterior-posterior) and SI (superior-inferior); MRE wave images were collected on the respective 3 motion-sensitizing-gradient directions.

Those 3 motion-sensitizing-gradient directional wave images were processed into a quantitative elastogram with units of kilopascal (kPa) using a previously described 2-D local frequency estimation (LFE) MRE inversion algorithm (21,22). Before applying the 2-D LFE algorithm the low spatial frequency background bulk motion and the high spatial frequency noise were removed from the wave data with a broadband Gaussian bandpass filter (16.67–111.11 waves/meter). Two dimensional directional filtering with 8 evenly spaced angles and a 2-D Butterworth bandpass filter with the same bandwidth were also applied to the wave data to improve accuracy of the 2-D LFE algorithm which is limited by the low phase signal-to-noise ratio (PSNR) caused by complex wave interferences. The directional filter separates the complex wave fields into components propagating in different directions and analyzes each of them separately (23). All of the patient data were processed consistently with the same parameters. Regions of interest (ROI) were drawn manually on the elastograms to correspond to the leiomyomas and mean, standard deviation and histograms of the tissue stiffness in the ROI were reported. An appropriate PSNR was used to aid in drawing the ROI and confirms the integrity of the signal. Interpretation of MRE was performed in a blinded fashion without knowledge of clinical information for the participants.

Results

Clinical characteristics of study participants are presented in Table 1. Six women participated in the study with a mean age of 42 ± 10 years (range 34–60). Average time interval from MR Elastography study to surgical intervention was 8 days (range 1–20 days) and the mean BMI of all patients: was $28.9 \pm 6.2 \text{ kg/m}^2$ (range 23.0 – 38.0 kg/m^2)

The first five subjects had clinical MRI studies with gadolinium prior to enrollment in the study allowing assessment of image characteristics. Subject six had a presumed recurrent adenomyoma based on an abnormal ultrasound and her history of resection of a large adenomyoma 8 months prior to the MRE study. However, subsequent hysteroscopic surgery showed only an enlarged uterus and she conceived two months following the MRE and is currently in the third trimester of gestation. Thus, neither pretreatment MR imaging nor uterine histology is available for this subject.

Studied leiomyomas ranged in size from. 4.5 to 22.5 cm in mean diameter and most had MR imaging characteristics of typical leiomyomas (Table 2). MRE was successfully performed in all subjects and uterine leiomyomas were confirmed in all subjects undergoing either myomectomy or hysterectomy (Figure 1). All subjects had appropriate PSNR to allow valid measurements of leiomyomas stiffness (Table 2). Mean elasticity for the studied fibroids ranged from 3.95 to 6.68 kPa and histograms were generated for each subject (Figure 2).

Discussion

Magnetic resonance elastography (MRE) for uterine leiomyomas appears feasible for studying leiomyomas in uteri ranging from 100 to over 1000 grams and leiomyomas ranging from 4.5 to 22.5 cm in mean diameter. Women with variable body habitus were able to be studied and a significant difference in elasticity was demonstrated among leiomyomas. To place these elasticity values in context, the range of elasticities of these myomas exceeds those reported for benign liver tumors (mean 2.7 kPa, range 1.6–3.2) and produced values similar to those seen for fibrotic liver disease (mean 5.9 kPa, range 3.1–12.2) (20).

This is the first report of *in vivo* examination of leiomyoma elasticity. Previous *in vitro* work has utilized ultrasound strain imaging to assess elasticity of extirpated uteri or direct assessment of Young's modulus in small pieces of myometrium and leiomyoma (6,8,24,25). Typically, there are significant differences in elasticity when the same tissues are studied *in vivo* and then *in vitro* (7). However, the increased stiffness of leiomyomas relative to myometrium shown in this study does parallel that seen in studies of surgically excised tissue (6).

The variability of elasticity for uterine lesions may be important in preoperatively differentiating rarer uterine masses from the common leiomyoma. While uterine sarcomas are very rare, they are difficult to differentiate from leiomyomas with conventional imaging modalities (26,27). However uterine sarcomas do tend to be more cellular than leiomyomas and may be able to be distinguished from leiomyomas just as malignant lesions of the liver and breast appear to have different mechanical properties than their benign counterparts (10,12,20). Similarly, there is increasing evidence that cellular leiomyomas may have premalignant potential and thus early identification of these lesions may be beneficial (28–30).

The relative concentration of cellular and extracellular components in leiomyomas also may contribute to their response to non-excisional therapies such as uterine artery embolization (UAE) and magnetic resonance guided focused ultrasound surgery (MRgFUS). Since leiomyomas are not removed in these therapies, their relative cellularity may be influencing their response to treatment and thus having a way to assess this variable may prove useful in predicting response to minimally invasive myoma therapies.

A clear limitation to the current pilot study is the small number of subjects studied to date. Additional studies with a larger sample size and other uterine pathology will clearly be needed to gain statistical power to understand if MRE has clinical utility for imaging uterine disease. Additionally, the current two dimensional MRE process used in this group of patients has the limitation of estimating true mechanical stiffness values especially in small lesions. In the next stage, three dimensional MRE should be employed to overcome this limitation. Finally, new MRE mechanical drivers are in development which can be used to improve the mechanical coupling between the driver and the lower abdomen and to increase the wave penetration to deep leiomyomas regions.

Capsule

In vivo Magnetic Resonance Elastography (MRE) is feasible to perform over a large range of leiomyoma sizes and quantitates variability in the elasticity of uterine leiomyomas.

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Figure 1. shows the MRE study for subject 4. In the top row are coronal, sagittal and axial T2W images from the pretreatment MRI. At the far right the region of interest (ROI) is outlined on the axial image. In the bottom row are MR elastographic wave images with shear waves propagating through the tissue in the X, Y and Z axes and at the far right a composite elastogram with the scale where color represents a change in shear stiffness in kPa.

Figure 2. Plot of mean leiomyoma stiffness for each subject. The histograms representing the distribution of shear stiffness are shown on the top of plot for each subject.

Table 1

Characteristics of the Study Participants (N=6)

Subject	Age	Gravidity/Parity	BMI	Hormonal Status	Race	Indication for Surgery	Surgery
1	34	1/1	24.2	Premenopausal / Secretory Phase	Caucasian	Enlarging Uterus, Menorrhagia	Hysterectomy
2	37	2/0	33.7	Premenopausal	African-American	Enlarging fibroids	Myomectomy
3	40	2/1	23.1	Premenopausal / Proliferative Phase	Asian	Degenerating fibroid and preterm labor	Myomectomy
4	44	0/0	30.7	Premenopausal / Proliferative Phase	Caucasian	Increasing heavy menses and bulk symptoms	Hysterectomy
5	60	3/3	38	Postmenopausal	Caucasian	Enlarging myoma in menopause	Hysterectomy
6	36	1/1	23.7	Premenopausal / Noncycling on OCPs	Asian	Probable recurrent adenomyosis	Diagnostic Hysteroscopy

Table 2

MRI characteristics, pathology findings and MRE data

Subject number	MRI Characteristics			Pathology Findings			MRE Data	
	T1 images	T2 images	Gadolinium enhancement	Histologic Diagnosis	Diameter of largest myoma (cm)	Weight of excised tissue (g)	PSNR	MRE (kPa)
1	Iso	Dark	Heterogeneous	Leiomyoma	22	1640	42.28±15.54	5.18 ± 1.1
2	Iso	Dark	Homogeneous	Leiomyoma	11.8	525	22.63±8.00	5.52 ± 1.07
3	Iso	Heterogeneous	No enhancement	Leiomyoma	22.5	930	7.09±1.24	3.95 ± 0.92
4	Iso	Dark	Homogeneous	Adenomyosis and Leiomyoma	8.5	175	5.45±1.67	6.68 ± 1.04
5	Iso	Dark	Homogeneous	Leiomyoma	4.5	99.6	6.86±0.83	5.19 ± 0.26
6	NA	NA	NA	NA			30.7±11.2	4.04 ± 0.73