

Uterine leiomyomas: correlation between histologic composition and stiffness via magnetic resonance elastography — a Pilot Study

Marzanna Obrzut¹, Bogdan Obrzut², Marcin Zmuda³, Jakub Baran⁴,
 Marian Cholewa¹, Richard L. Ehman⁵, Dorota Darmochwal-Kolarz²

¹Department of Biophysics, Faculty of Mathematics and Natural Sciences, University of Rzeszow, Poland

²Department of Obstetrics and Gynecology, Institute of Medical Sciences, Medical College, University of Rzeszow, Poland

³Department of Clinical Pathomorphology, Provincial Clinical Hospital No 2 Rzeszow, Poland

⁴Institute of Nuclear Physics Polish Academy of Sciences, Cracow, Poland

⁵Department of Radiology, Mayo Clinic, USA

ABSTRACT

Objectives: To evaluate magnetic resonance elastography as a tool for characterizing uterine leiomyomas.

Material and methods: At total of 12 women with symptomatic leiomyomas diagnosed in physical and ultrasound examinations were enrolled in this pilot study. Before surgery, all patients underwent magnetic resonance elastography of the uterus using a 1.5 T MR whole-body scanner (Optima, GE Healthcare, Milwaukee, WI, USA). Surgical specimens were forwarded for histological examination. The findings were allocated into 3 categories depending on the percentage content of connective tissue: below 15%, from 15 to 30% and more than 30%. The median stiffness of leiomyomas for each of the group was calculated. The U-Mann Whitney test was used for statistical analysis.

Results: The stiffness of the leiomyomas ranged between 3.7–6.9 kPa (median value 4.9 kPa). The concentration of extracellular components in the leiomyomas did not exceed 40%. An increasing trend of the stiffness with the growing percentage of extracellular component was observed. Stiffness of the leiomyomas obtained by MRE varies depending on microscopic composition.

Conclusions: The value of stiffness shows a trend of increasing with the percentage of extracellular component of the leiomyoma. Further studies are required to assess the usefulness of MRE in diagnostics of uterine leiomyomas.

Key words: leiomyoma; magnetic resonance elastography; histologic composition

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INTRODUCTION

Uterine leiomyomas (fibroids) are the most common benign gynaecological tumours, which affect up to 70% of women of a reproductive age [1–3]. They develop as a result of the transformation of myometrial smooth muscle, fibroblasts and the formation of a dysfunctional extracellular matrix [4, 5]. The majority of fibroids remain asymptomatic, 20–40% of women with leiomyomas report significant clinical symptoms (e.g. abnormal uterine bleeding, dysmenorrhea, pelvic pain, infertility, and recurrent pregnancy loss) that require effective gynaecological intervention [2, 6, 7].

The management of uterine fibromas varies significantly depending on the patient's age, symptoms, and reproductive plans. For women who wish to preserve their fertility

and avoid surgery, there are numerous medical therapy options available [8]. For symptomatic women after medical treatment failures, surgical procedures are proposed [9]. Strategies for surgical treatment depend on the patient and fibroid characteristics and include myomectomy (in women who want to preserve their uterus or desire future pregnancy) or hysterectomy (for women after a completed childbearing) [9]. Currently, both procedures are mostly performed via laparoscopy with the usage of a power morcellator. Laparoscopic power morcellation is related with a risk of spreading undiagnosed neoplastic tissue within the abdominal cavity, which may significantly worsen the patient's prognosis [10–12]. The true prevalence of uterine sarcomas in presumed fibroids is not exactly known and

Corresponding author:

Jakub Baran

Institute of Nuclear Physics Polish Academy of Sciences, 152 Radzikowskiego St, 31-342 Cracow, Poland

e-mail: jakub.baran@ifj.edu.pl

phone: (+48) 534 065 750

vary from 0.09% to 0.8% depending on the study [13–17]. Also, the medical management of presumed symptomatic leiomyoma, which is found to be sarcoma, may have a negative impact on the outcome due to a delay in appropriate therapy. Despite the fact that some patients' characteristics and abnormal features of uterine tumors on a US or MRI may be suggestive for the presence of leiomyosarcoma, a reliable differential diagnosis is still very difficult [13, 18–20]. Hence, there is an urgent need for finding a new tool that could improve the characterization of uterine masses. In this context, interesting possibilities are offered in recently implemented magnetic resonance elastography (MRE). Malignant transformation often markedly alters the mechanical properties of soft tissue [21, 22], which could be potentially used in the pre-treatment differentiating leiomyosarcoma from the common leiomyoma. On the other hand, elastographic patterns of the leiomyoma, reflecting a relative concentration of cellular and extracellular components, may be helpful in predicting a response to non-excisional therapies such as uterine artery embolization and magnetic resonance-guided focused ultrasound [23]. Both circumstances require knowledge of the typical elastographic features of leiomyomas.

Objectives

Until now, only two studies have been published on the feasibility of MRE for uterine leiomyomas, without regard to their microscopic composition [23, 24]. The aim of this study was to evaluate the correlation between the elasticity of leiomyomas obtained by MRE and their relative concentration of cellular and extracellular components.

MATERIAL AND METHODS

Patient population

This pilot study included 12 patients with symptomatic leiomyomas, who underwent surgical treatment at the Clinical Department of Obstetrics and Gynaecology of Provincial Clinical Hospital No 2, Rzeszow, Poland between September 2016 and February 2017.

Preoperative diagnosis was based on vaginal speculum examination, bimanual examination and the transvaginal ultrasonography of the uterus. Before surgery, all patients underwent laboratory tests, electrocardiography, anaesthesiology consultation and magnetic resonance elastography of the uterus. Written consent was obtained from each of the patients before the study commenced. The research protocol was approved by the Bioethics Committee of the University of Rzeszow, Poland (Reg. No. 19/04/2016).

Magnetic Resonance Elastography

A 1.5 T MR whole-body scanner (Optima, GE Healthcare, Milwaukee, WI, USA) was used to perform the MRE scans. The

MRE system, includes special acquisition and processing software, as well as hardware consisting of an active and passive driver. The passive driver is a small plastic drum-like device that is placed against the body to transmit mechanical vibrations into tissue. In this study, the passive driver was placed over the uterus in the lower abdomen. The passive driver is connected via flexible tubing to the active driver unit which is located outside the MRI room. The active driver unit generates pressure pulses (at 60 Hz frequency in this study) that are conducted to the passive driver via the flexible tubing.

MRE acquisition was performed using a 16-channel abdominal phase array coil. Shear wave imaging was conducted using a modified 2D gradient-recalled echo-based pulse sequence with the following parameters: matrix size: 256 × 256, slice thickness: 10 mm; TR: 33 ms; TE: 20 ms; flip angle: 30 deg. The resulting wave images were then automatically processed by the scanner using a manufacturer-provided 2D direct inversion algorithm to generate quantitative images depicting tissue stiffness (elastograms) [25–27].

Region of interest (ROI) were drawn manually on the largest leiomyoma, avoiding non-fibroid tissue, using corresponding T2 images as a guide. From the ROI, mean stiffness (kPa) and standard deviation, were reported.

Microscopic evaluation

Surgical specimens were forwarded for histological examination. To visualise the collagenous connective tissue fibers in tissue sections and differentiate them from smooth muscle fibers, Trichrome Stain (Connective Tissue Stain) was applied. In this process staining muscle fibers were dyed red, collagen fibers were stained blue and nuclei stained black/blue (Fig. 1). Due to lack of similar publications and other scientific data, the findings were arbitrarily allocated into 3 categories depending on the percentage content of connective tissue (below 15%, from 15 to 30%, more than 30%).

Statistical analysis

Statistical analysis was performed using Python libraries. The U-Mann Whitney tests were applied. A p value of lower than 0.05 was considered statistically significant.

RESULTS

A greater number of patients were premenopausal than not. Only one patient was postmenopausal. Their age ranged between 26–61 years (median value 40.5 years). The median body mass index (BMI) was 22.45 kg/m². The parity status and type of surgery are presented in Table 1.

In all patients, the preoperative diagnosis leiomyoma was confirmed histologically. The diameter of the largest leiomyoma ranged between 40–109 mm (median diameter 68.5 mm). The median value of leiomyoma stiffness obtained

in our series was 4.9 kPa (range, 3.7–6.9) The concentration of extracellular components in the leiomyomas and their stiffness in specific patients are presented in Table 2.

The biggest subgroup was made up of leiomyomas with contents of fibrous tissue up to 15 percent. The median stiffness in this series was 4.46 kPa. Three patients had leiomyomas with a concentration of extracellular components between 15 and 30% and median stiffness of 5.78 kPa, respectively. More than 30% content of fibrous tissue was found in 2 patients. The median stiffness of those leiomyo-

mas was 6.15 kPa. Example ROI's drawn on elastograms for three patients are shown in Figure 2.

Figure 3 depicts a box plot with the mean stiffness measurements among groups with different extracellular component. Despite the low number of samples, the increasing trend of the stiffness with the growing percentage of extracellular component is clearly observable. The p value for the stiffness difference between lesions with extracellular component of < 15% and > 30% was $p = 0.05$. Other results were not statistically significant.

DISCUSSION

Magnetic resonance elastography is a versatile MRI-based technique, using propagating shear waves to

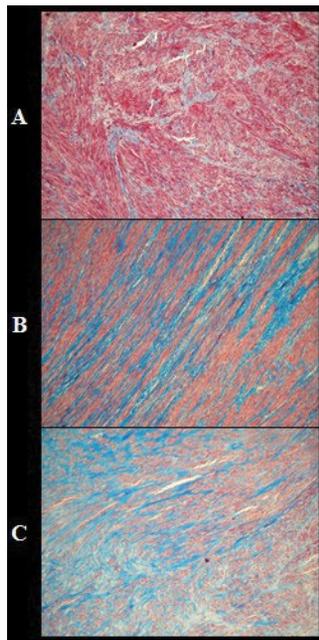


Figure 1. Microscopic pictures of leiomyomas with different histologic composition: fibrous tissue content up to 15% (A), between 15% and 30% (B), and above 30% (C) in trichrome stain

Table 2. Pathology findings and magnetic resonance elastography data of the study group

Patient	Diameter of the leiomyoma [mm]	Extracellular component [%]	Stiffness of the leiomyoma	SD of leiomyomas' stiffness
1	57	< 15	6.18	0.68
2	41	< 15	3.7	1.2
3	109	> 30	6.9	2.8
4	40	< 15	4.5	1.5
5	56	< 15	4.2	1.02
6	62	< 15	4.0	1.2
7	70	< 15	4.9	1.3
8	75	< 15	4.97	1.08
9	67	15–30	4.68	1.06
10	93	> 30	5.39	0.90
11	82	15–30	5.8	2.2
12	80	15–30	5.9	1.6

Table 1. Clinical characteristics of the study group

Patient	Age	Gravidity/Parity	Hormonal status	BMI	Type of surgery
1	49	2/2	premenopausal	20.42	LASH/BS
2	33	0	premenopausal	21.48	laparotomy/myomectomy
3	32	0	premenopausal	24.77	laparotomy/myomectomy
4	28	1/1	premenopausal	19.16	laparoscopy/myomectomy
5	38	3/2	premenopausal	23.42	LASH/BS
6	31	2/2	premenopausal	26.17	LASH/BS
7	43	3/1	premenopausal	20.76	LASH/BS
8	48	2/2	premenopausal	21.09	TLH/BS
9	26	0	premenopausal	27.02	laparotomy/myomectomy
10	46	0	premenopausal	21.05	laparotomy/myomectomy
11	49	2/2	premenopausal	25.10	TLH/BS
12	61	3/1	postmenopausal	27.24	TAH/BSO

LASH — laparoscopic supracervical hysterectomy; TLH — total laparoscopic hysterectomy; TAH — total abdominal hysterectomy; BS — bilateral salpingectomy; BSO — bilateral salpingo-oophorectomy

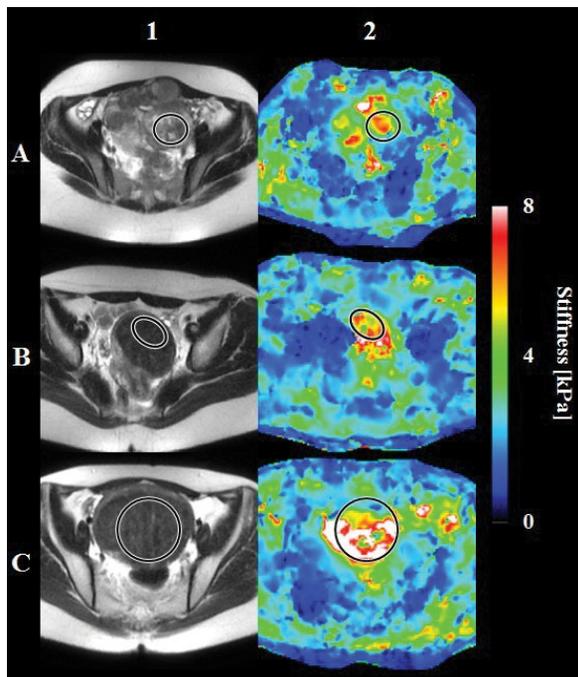


Figure 2. T2w MR images (column 1) and comparison of elastograms (column 2) for patient 6 (row A), 9 (row B) and 3 (row C). The mean stiffness was 3.95 kPa, 4.68 kPa and 6.9 kPa for the above mentioned patients, respectively

assess the mechanical properties of tissue [28]. The most established and documented clinical application of MRE is the evaluation of chronic liver disease [29–33]. In recent years, MRE has also been evaluated in characterization of focal liver lesions [22, 34], and for assessing the spleen, pancreas, kidneys and prostate [35–39]. Experiences with MRE in the field of gynaecology are quite limited. There are only a few publications dealing with the stiffness of a normal uterus [40] and leiomyomas [23, 24]. None of the research groups investigated the stiffness of leiomyomas in correlation with their histologic composition. In this context, our research provides data to fill this gap.

The present study confirms the findings of Stewart et al. [23], that magnetic resonance elastography is a feasible technique for the assessment of mechanical properties of uterine leiomyomas. The median value of leiomyoma stiffness obtained in our series (4.9 kPa) was comparable to that of above cited study.

The stiffness of the leiomyoma is markedly higher than the stiffness of both the normal corpus and cervix uteri, which were evaluated by Jiang et al. using 3D MRE technique [40]. Compared to other pathologic lesions, the elasticity of leiomyomas exceeds those of benign liver tumors (mean 2.7 kPa, range 1.6–3.2 kPa), but it is similar to the elasticity of fibrotic liver disease (mean 5.9 kPa, range 3.1–12.2 kPa) [22].

The content of the extracellular component in leiomyomas from our series did not exceed 40%. The concentration

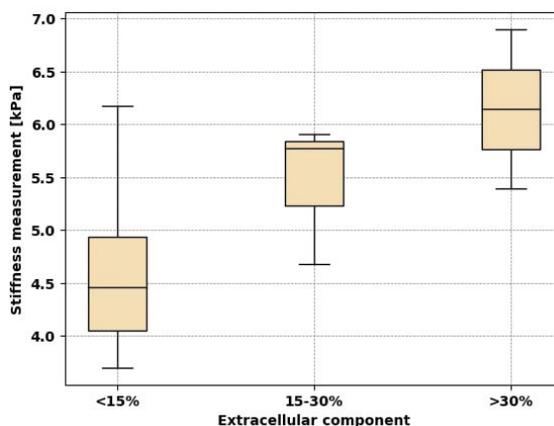


Figure 3. Box plot depicting variance in shear stiffness measurements for all groups of patients

of collagen fibres correlated with the value of stiffness of the leiomyoma (Fig. 3). Leiomyoma stiffness, as an increasing trend, is observable with the increased extracellular component; however, statistical analysis only approached demonstrating a significant difference between the groups with the highest and lowest collagen concentration. The relatively large scatter of stiffness values in the group of lowest extracellular component is probably due to the inhomogeneity of leiomyomas.

To the best of our knowledge, this is the first study investigating the correlation between the elasticity of leiomyomas obtained by MRE and their relative concentration of cellular and extracellular components. The presented observations can be potentially helpful in preoperative differentiating common leiomyomas from their malignant counterparts. Because uterine sarcomas tend to be more cellular, they may be able to be distinguished from the leiomyomas based on the altered mechanical properties. This expectation is also related to the need for preoperative distinguishing between common leiomyoma and cellular leiomyoma, as they may have premalignant potential [41, 42]. Our series included neither leiomyosarcomas, nor cellular leiomyoma, so this hypothesis is purely theoretical. However, it seems to be justified based on similar observations regarding breast and liver tumors [21, 22, 34].

The limitation of the presented paper is the small size of the study group, and its one-institutional character. Multi-centre research with a larger patient series will be required to gain appropriate statistical power to objectively assess the usefulness of MRE in evaluating the microscopic composition of leiomyomas. Besides, in our study two-dimensional MRE have been used, which is limited in estimating the true mechanical property of tissue, especially in small lesions. It was the reason for our patient selection and qualifying only those with middle-size and larger leiomyoma. In the follow-

ing investigations a 3D-MRE should be used to overcome this limitation.

CONCLUSIONS

In conclusion, this study demonstrates that stiffness of the leiomyomas obtained by MRE varies depending on their histologic composition. The value of stiffness shows a trend of increasing with growing percentage of extracellular component of the leiomyoma. Further investigations with a larger patient group and 3D-MRE are needed to assess the usefulness of MRE in evaluating leiomyomas and defining its possible clinical application.

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