

New Generation ExAblate System

**MR guided Focused Ultrasound Surgery
for Uterine Fibroids**

Matthias Matzko



Background

- Amper Klinik AG, Dachau
(450-bed Teaching Hospital of the LMU Munich)

- MR-guided focused ultrasound surgery (MRgFUS):
 - non-invasive treatment approach for symptomatic uterine fibroids
 - high-intensity ultrasound beam
 - MR-guidance
 - Experience since 2008
 - More than 300 treatments with ExAblate 2000 until 11/2010
 - More than 300 treatments with ExAblate 2100/ONE since 11/2010

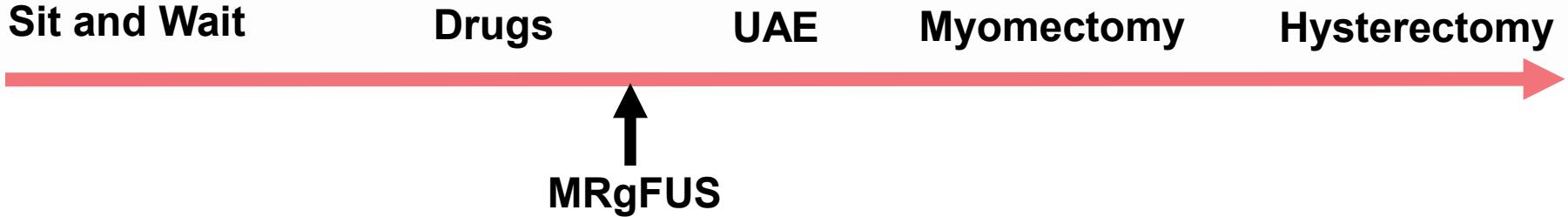


Background

- June 2008 - October 2010: MRgFUS system
 - ExAblate 2000, InSightec, Haifa, Israel
 - 1.5T GE Signa (General Electric Healthcare, Milwaukee, WI, USA)
- November 2010:
 - ExAblate 2100, InSightec, Haifa, Israel
 - 1.5T GE Signa (General Electric Healthcare, Milwaukee, WI, USA)
- Since September 2012:
 - ExAblate O.R., InSightec, Haifa, Israel
 - 1.5T GE Signa (General Electric Healthcare, Milwaukee, WI, USA)



Options for fibroid therapy: Growing invasiveness



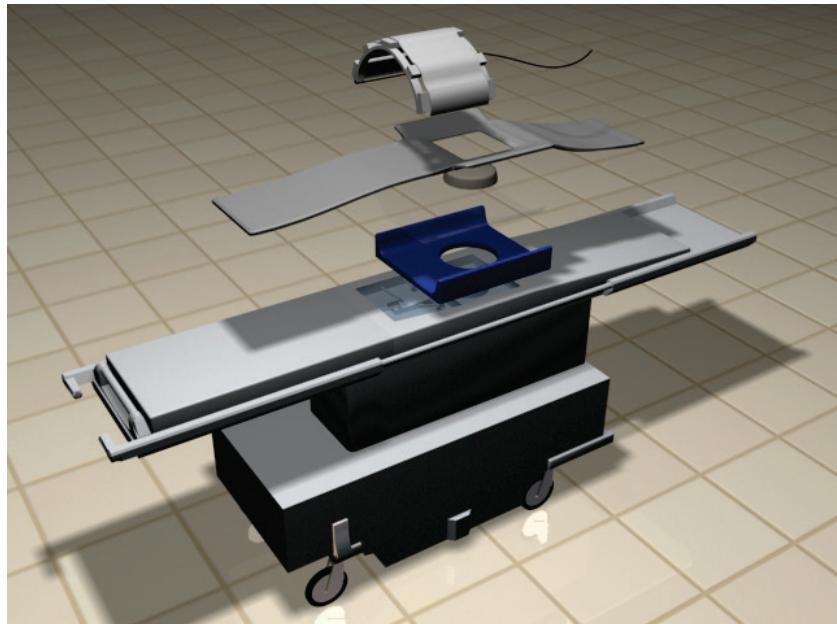
What is MR guided Focused Ultrasound?

Combination of:

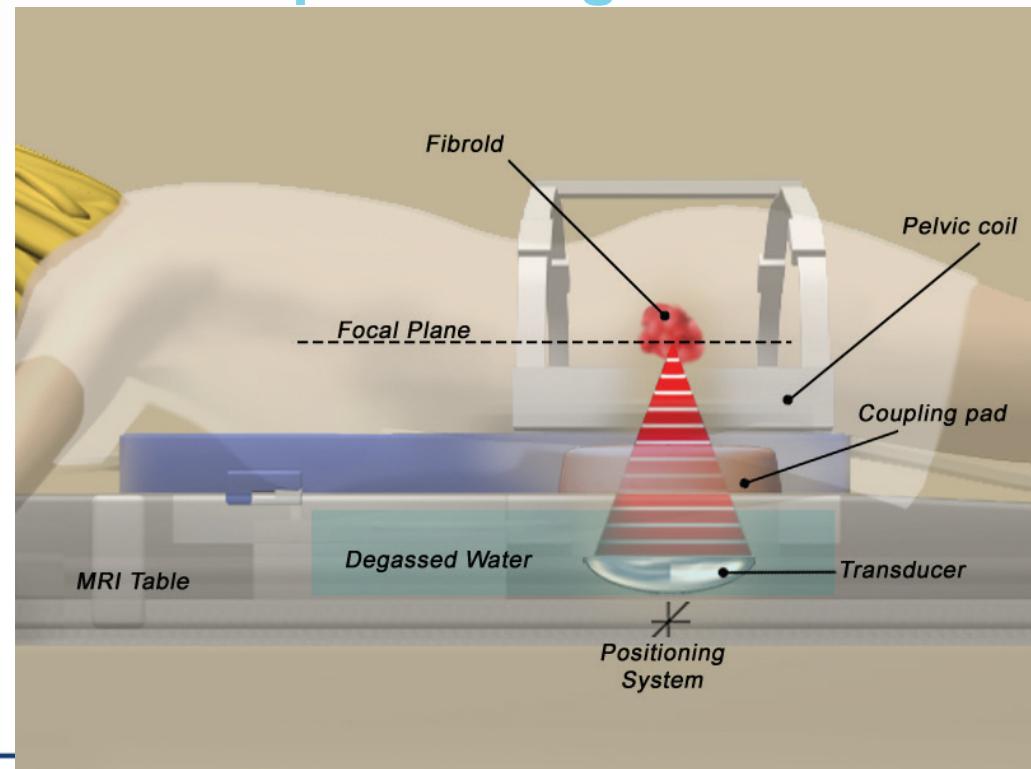
- Focused Ultrasound (Therapeutic, not diagnostic)
- MRI for closed loop guidance and control



Focused Ultrasound has an effect similar to a magnifying glass used to focus the sun's energy on a single point.

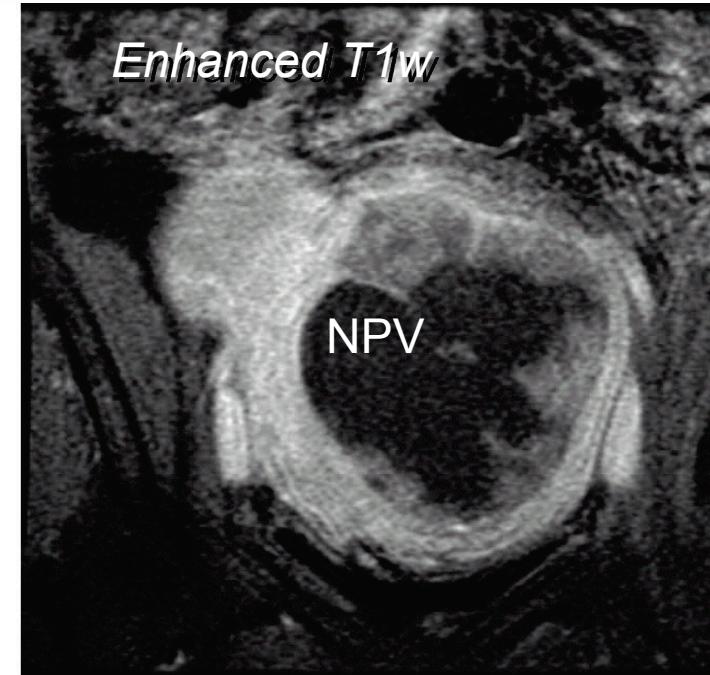


Principle of MRgFUS



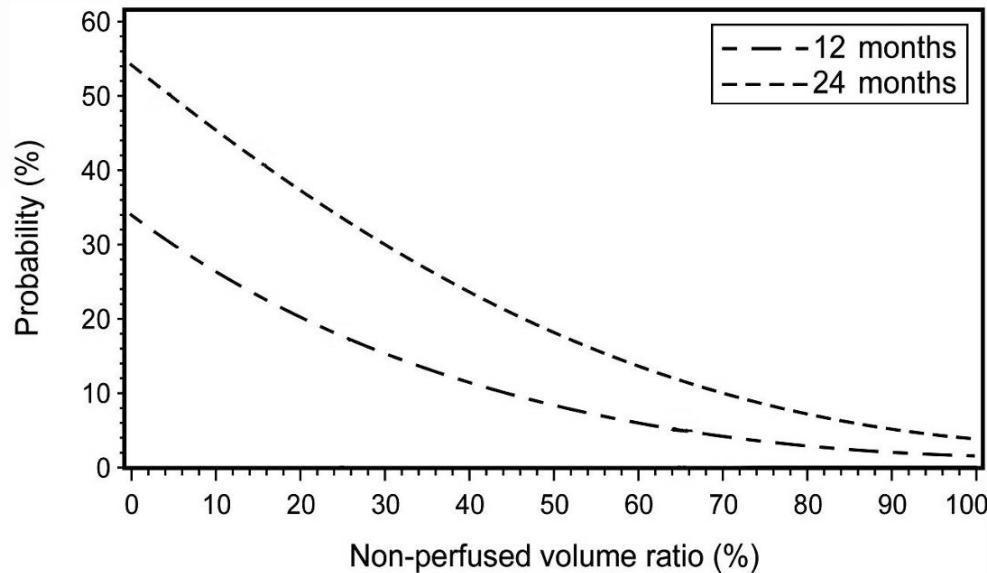
Non Perfused Volume- predictor of success

Most important predicting factor for treatment durability is immediate post-treatment non-perfused volume (NPV)



NPV and durability

- The higher the NPV - the greater the symptom improvement
- The greater the NPV- the lower the likelihood of alternative treatments



60% NPV results in alternative treatment rate similar to those of other uterine-sparing treatments

Constraints limiting treatments

Several anatomical and technical system constraints have prevented physicians from obtaining high NPV's:

- Long cooling durations to avoid heating sensitive structures
- Bowel loops, scars and other sensitive organs in beam path
- Patient movement- requiring re-planning of treatment
- Manual physician interventions (planning, editing, checking)

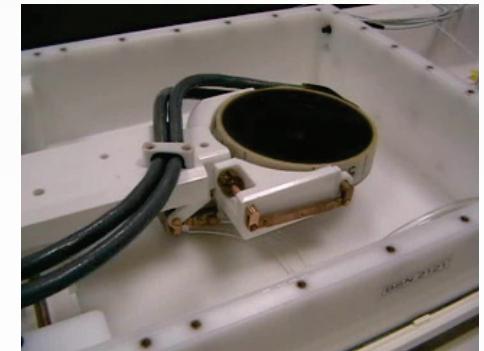
New ExAblate O.R. features to improve NPV, patient suitability

- ❑ Long cooling durations to avoid heating sensitive structures
 - **Transducer elevation and improved focus**
- ❑ Bowel loops, scars and other sensitive organs in beam path
 - **Selective element disabling (beam shaping)**
- ❑ Patient movement- requiring re-planning of treatment
 - **Automatic Movement Detection and re-planning of remaining volume**
- ❑ Manual physician interventions (planning, editing, checking)
 - **Automatic 3D treatment planning**
 - **Optimized treatment modalities, spot sizes and ordering**
 - **Streamlined workflow and fewer stages**

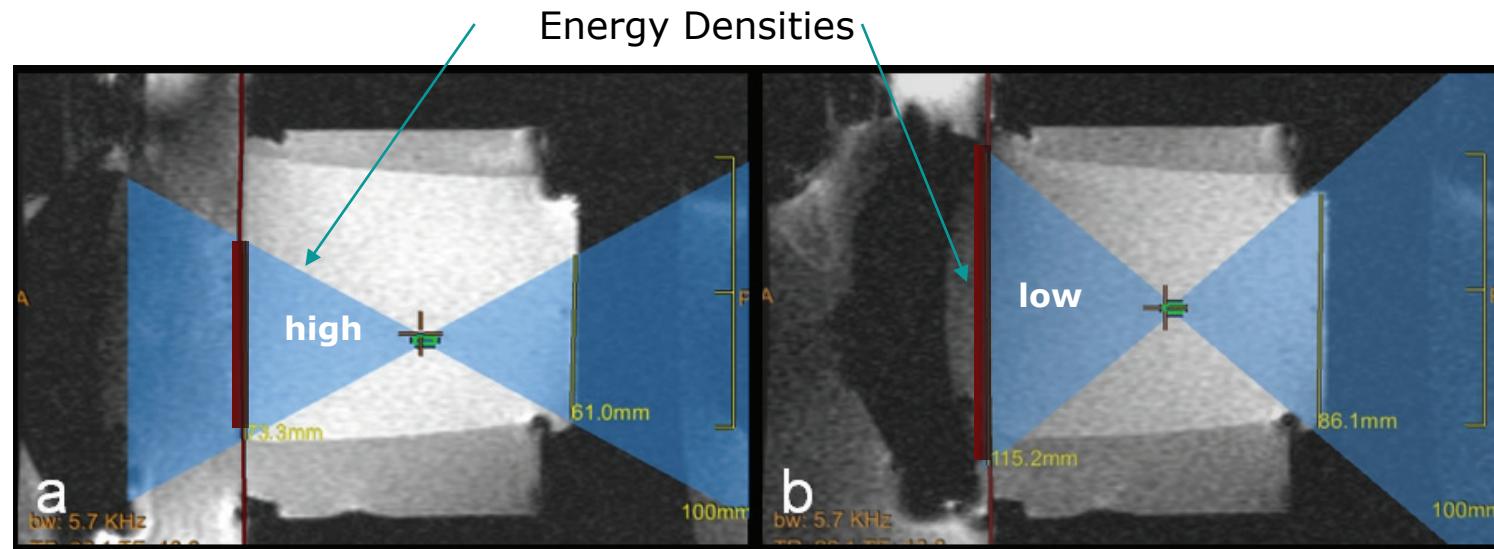


Transducer Elevation

Ability to move transducer up close to skin and within 4 cm of abdominal wall



- **Dramatically reduces the energy density** on skin, near field, far field and sensitive structures
- Improves focus and maximal focal depth
- Reduces need for long cooling durations





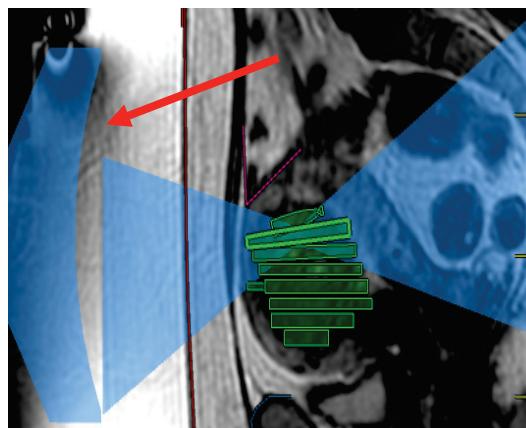
Acoustic Beam Shaping

Anatomic “window” selectively disables elements and stops energy delivery to sensitive areas

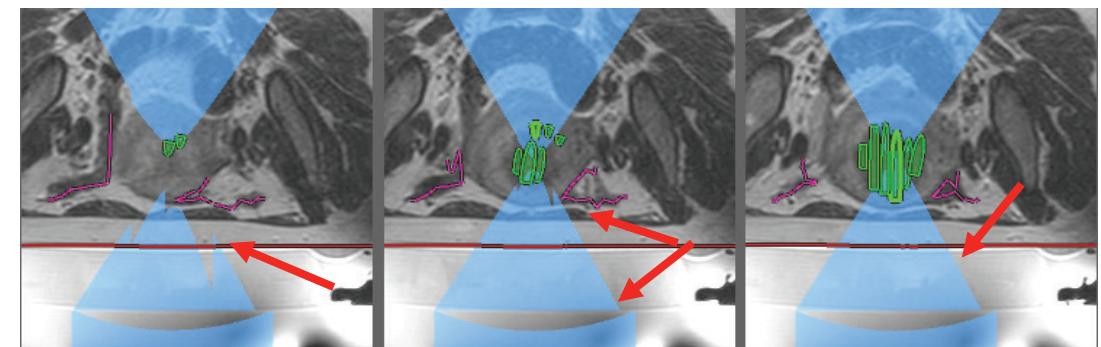
- Shapes the beam to conform to the anatomy
- Avoids sensitive zones with no pass regions (NPR)
- Treats fibroids located behind bowel and/or pubic bone



Increased safety and patient selection



Sagittal view: Energy beam path with elements closed to prevent bowels (NPR)



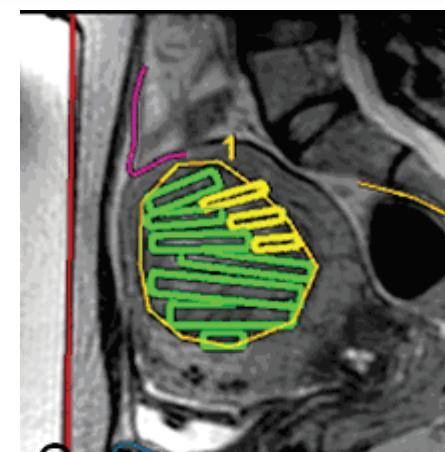
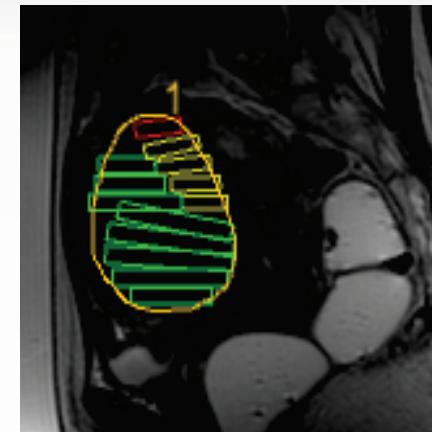
Axial views with elements cut off where bowel, marked by NPR (No pass region)



Automatic 3D Volumetric Treatment Planning

Physician draws the ROT (region of treatment) and the system automatically plans the 3D volumetric treatment

- Variety of spot sizes fill entire targeted volume
- Conformal 3D spot packing maximizes treatment volume
- Spot order optimizes treatment time
- Additional techniques optimize safety and efficacy parameters (LEDR, beam shaping etc)



Automatic treatment planning with various spot sizes and LEDRs. Yellow spots indicate treatment close to sensitive area, red spots not treatable.

Three treatment modes

3 treatment modes for speedy treatment and maximizing NPV

Single (Interleaved)

Treating one spot at a time, optimizing cooling time

Clustering

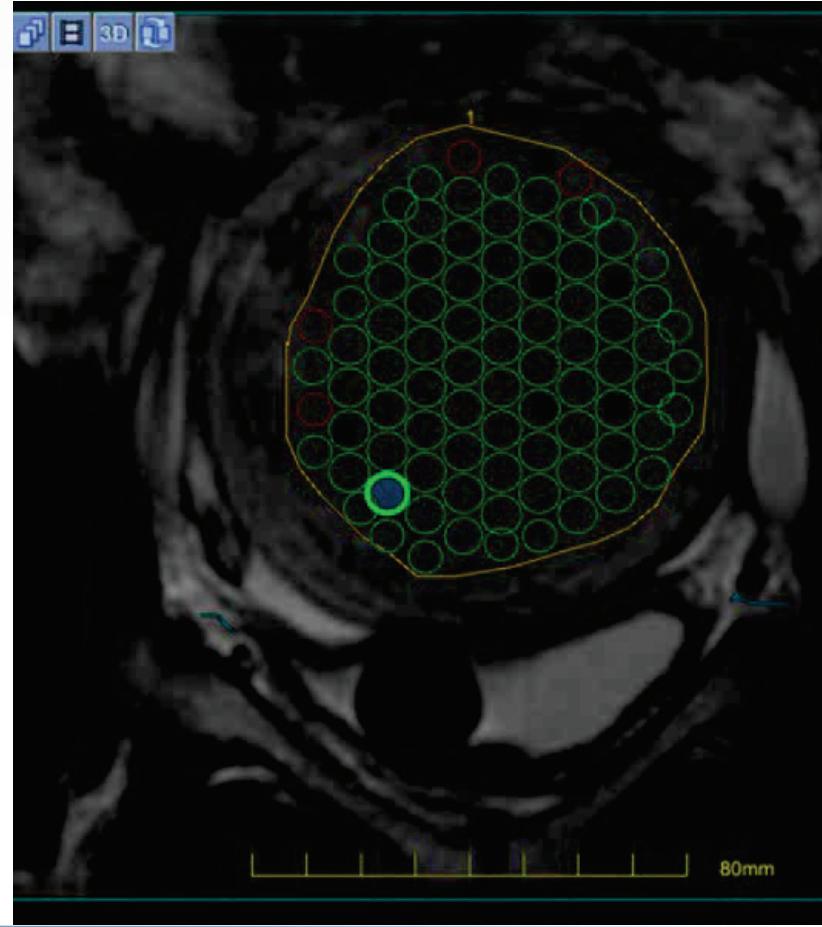
Treating a group of adjacent spots at one time, to enhance the thermal effect and reduce number of iterations between sonifications

Optimal

Combines the two methods: interleaving between

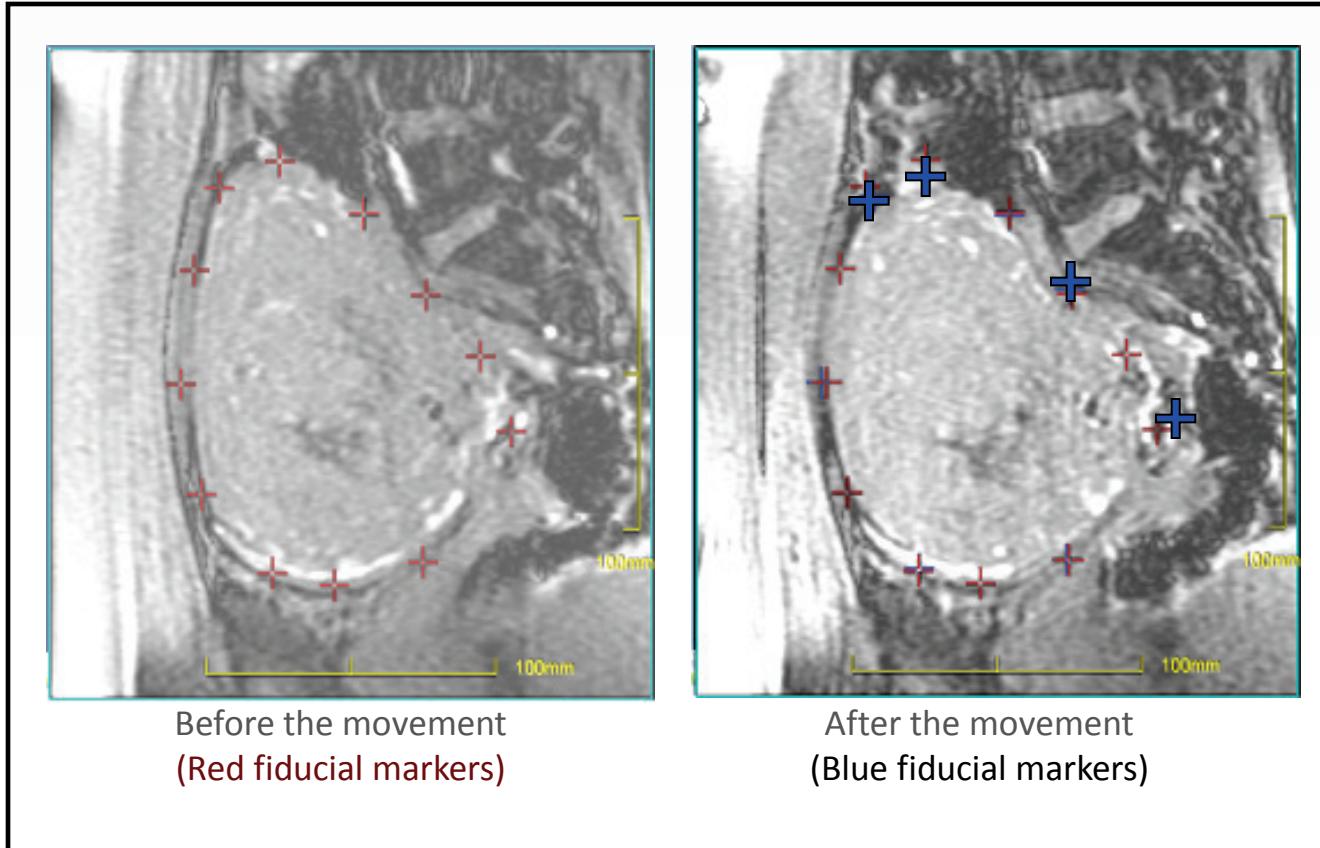
single spots first and then clustering the rest of spots into groups to maximize the treated volume in minimum time

Automatic planner treats the most efficient spots first, interleaving between single spots, and then selects spots to cluster.



Automatic movement detection

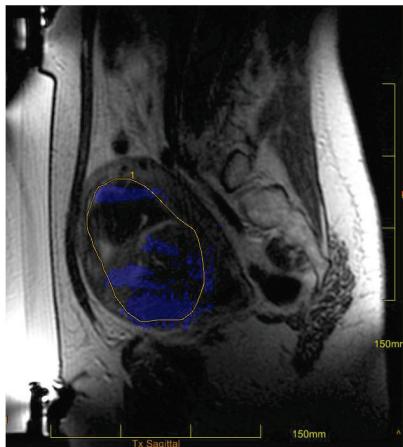
System automatically identifies movement by changing color of fiducials



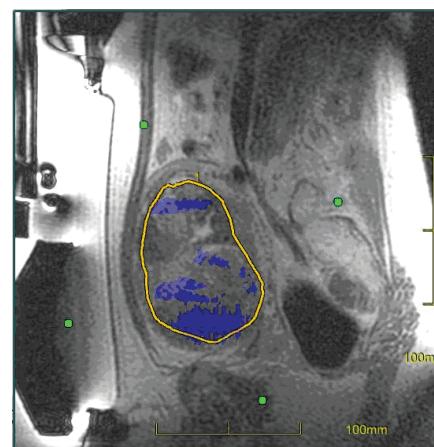


Automatic Replan of Remaining Treatment (50% cases of patient movement)

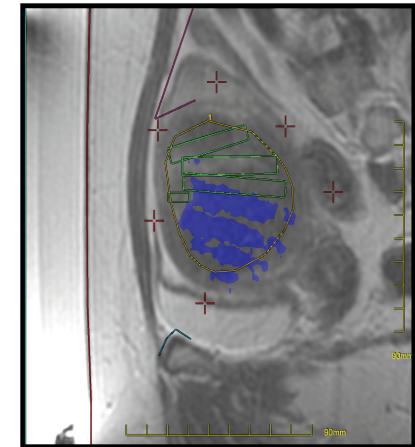
- Automatic detection of patient movement
- Incremental treatment plan automatically generated, based on accumulated thermal dose already treated
- Results in significant time savings no need to replan the entire treatment and no retreating previously treated areas



Before movement



After movement



New incremental plan

Comparison of Results with the two Generations

ExAblate



ExAblate® O.R.

Number of fibroids	3.2 ± 3.0 (1 – 10)	2.2 ± 2.0 (1 – 11)
Total fibroid volume	227 ± 192 mL (8 – 719 mL)	5.4 (Avg) cm (2.0-10.8 cm)
Number of sonications	86 ± 34	60.59 (Avg) (40-105)
Number of fibroids treated	2.2 ± 1.9 (1 – 7)	Single (31%), 2-4 (33%), >5 (36%)
Non-perfused volume NPV	$59.1 \pm 19.0\%$ (34.8 – 100%)	86.7 % (38 – 100%)

ExAblate O.R.: Improved outcomes

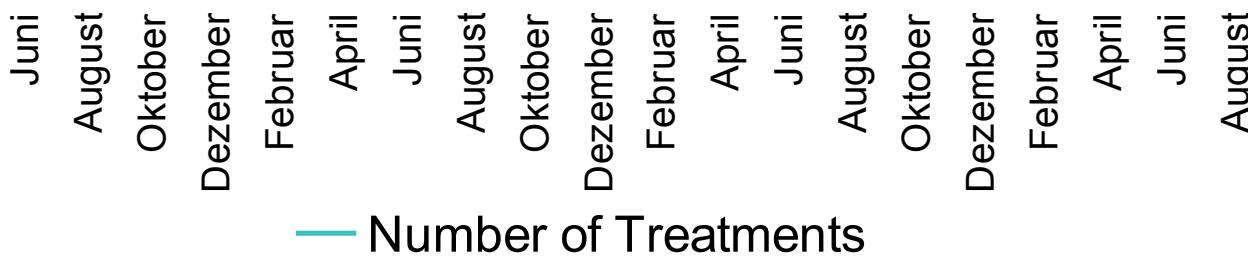


Average NPV
59%

ExAblate® O.R.
2nd Investment



Average NPV
87%



M Matzko, Amper Clinic, Germany

ExAblate durability compared with other uterine preserving treatments

Need for Alternative Treatment	@ 12 mo	@ 24 mo	References
Myomectomy	10.6%	13% - 16.5%	1,2,3,4
UAE (Uterine Artery Embolization)	7% - 10%	12.7% - 23.7%	5,6,7
ExAblate using MRgFUS NPV >60%	6% (NPV=60%) Using former version	13% (NPV=60%) Using former version	8

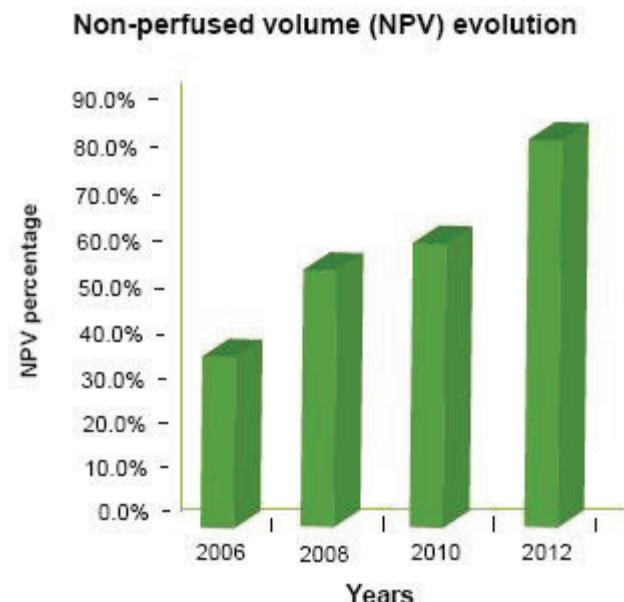
References

1. Subramanian S, Clark MA, Isaacson K. Outcome and resource use associated with myomectomy. *Obs & Gyn.* 2001; 98: 583-587
 2. Nezhat FR, Roemisch M, et al. Recurrence rate after laparoscopic myomectomy. *Am Assoc Gynecol Laparosc.* 1998; 5: 237-240
 3. Rossetti et al. Long term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. *Hum Reprod.* 2001;16:770-774
 4. Doridot et al. Recurrence of leiomyomata after laparoscopic myomectomy. *J Am Assoc Gynecol Laparosc.* 2001;8: 495-500
 5. Spies JB, Bruno J, et al. Long-term outcome of uterine artery embolization of leiomyomata. *Obstet Gynecol.* 2005; 106: 933-939
 6. Goodwin SC, Spies JB, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from FIBROID registry. *Obstet & Gynecol.* 2008; 111: 22-32
 7. Sharp HT. Assessment of new technology in the treatment of idiopathic menorrhagia and uterine leiomyomata. *Obstet Gynecol.* 2006;108: 990-1003
 8. Stewart EA, Gostout B, Rabinovici J, et al. Sustained relief of leiomyoma symptoms by using focused ultrasound surgery. *Obstet & Gynecol.* 2007;110: 279-287
 9. Morita Y, Ito N, Hikida H, Takeuchi S, Nakamura K, Ohashi H. Non-Invasive Magnetic Resonance Imaging Guided Focused Ultrasound Treatment for Uterine Fibroids – Early Experience, *Eur J Obstet Gynecol Reprod. Biol.*, 2008, 139(2):199-203
- 08.12.2012 M. Matzko

Improved NPV over time

Study results show that:

- MRgFUS durability equivalent to other accepted leiomyoma treatments
- Incidence of serious adverse events after MRgFUS is low and appears to decrease with increasing physician experience
- MRgFUS compares favorably with other alternatives to hysterectomy including abdominal and laparoscopic myomectomy and uterine artery embolization (UAE)



* **References:** Elizabeth A. Stewart M.D., et al Focused Ultrasound Surgery of Uterine Leiomyomas Provides Sustained Relief of Leiomyoma Symptoms , *Obstetrics & Gynecology* Aug 1, 2007; 110 (2) ; Okada et al. *Ultrasound in Obstet Gynecol* 2009-Av. NPV ratio 46.6% (N=287) Leblang et al. *AJR* 2010----Av. NPV ratio 55% (N=80). Matzko & Trumm, 2nd MRgFUS Symposium 2010----Av. NPV ratio 59.1% (N=41)

Post-MRgFUS Pregnancies

Total number of pregnancies	109
Mean age	36.1
Age range	27 – 49
Average months to conception	8.8
Total deliveries	54% (59)
- Of them vaginal	63%
Elective pregnancy termination	9% (10)
Spontaneous abortions	20% (22)
Ongoing pregnancies	8% (9)
Unknown	8% (9)
Average baby weight at term delivery	3.27 kg

■ Improved efficacy:

- Ability to increase treatment volume for enhanced clinical results
- To expect: Better long-term results, reduced alternative tx

■ Broader selection of patients

- Improved ability to treat patients with large and vascular fibroids
- Ability to sculpture the beam around obstacles
- CE approval to treat Adenomyosis patients

■ Reduced treatment time

- 3D Automatic treatment planner
- Elongated sonications of up to 70mm

■ Superior ergonomics for patient and physician

- Improved design for better patient comfort
- Streamlined interface



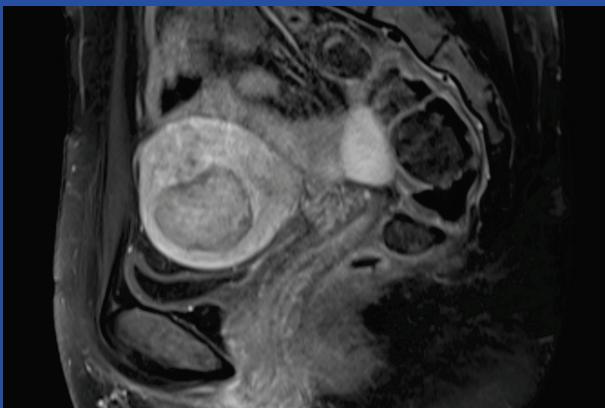
Clinical Case

Patient age: 40 years old

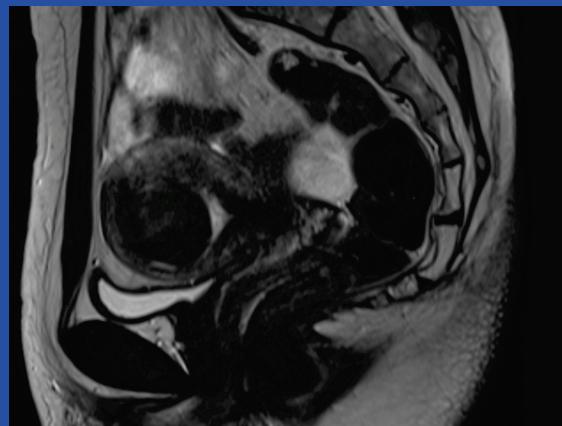
Symptoms: Heavy menstrual bleeding, blood clots and pain.

Fibroids Intensity: Hypo/Iso-intense with bright portion on T2w Images

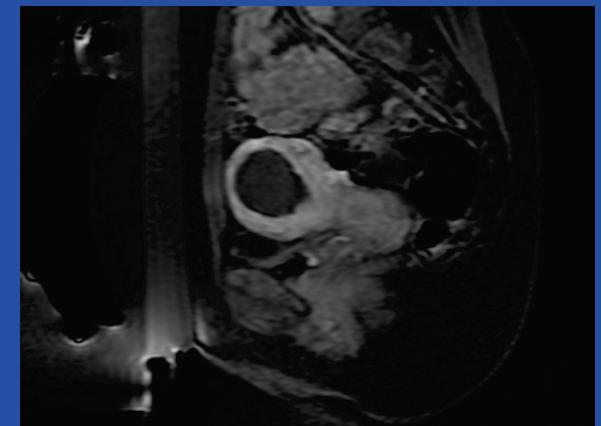
Results: 100 % NPV with no adverse effects



Sagittal T1w+c
Pre-Treatment



Sagittal T2w



Sagittal T1w+c
Post treatment



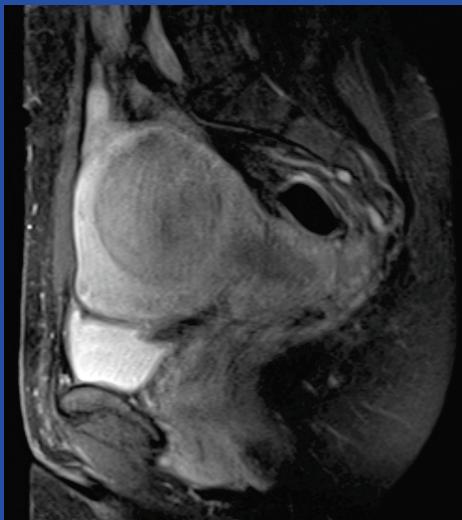
Clinical Case

Patient age: 43 years old

Symptoms: Pressure feeling on bladder
and heavy pain.

Fibroids Intensity: Hypo/Iso-intense with bright portion on T2w Images

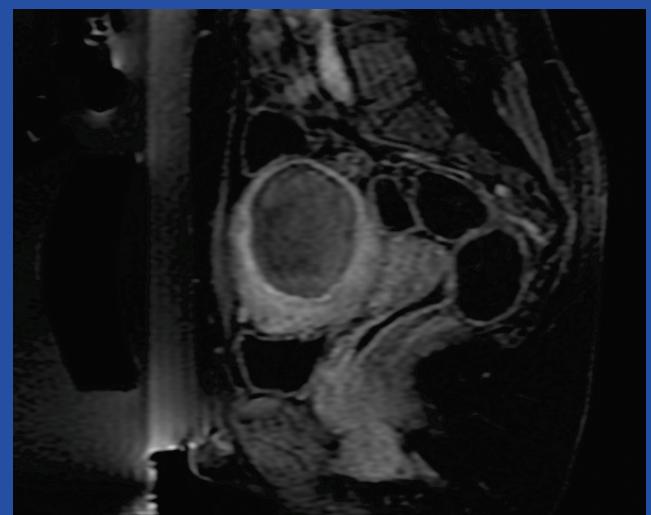
Results: 100 % NPV with no adverse effects



Sagittal T1w+c
Pre-Treatment



Sagittal T2w



Sagittal T1w+c
Post treatment

Clinical Case

Patient age: 45 years old

Fibroids volume: 140cc

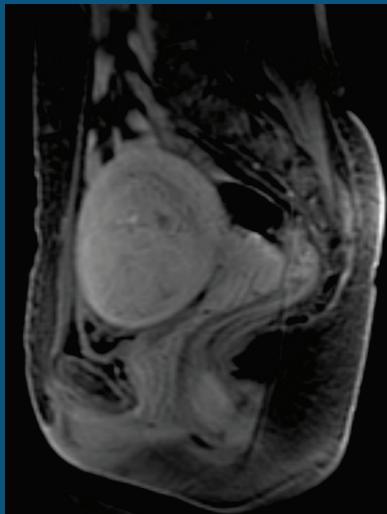
Symptoms: Heavy menstrual bleeding, blood clots and pain.

5 axis motion increased energy density in focus-allowed treatment of *Hyper Intense* areas.

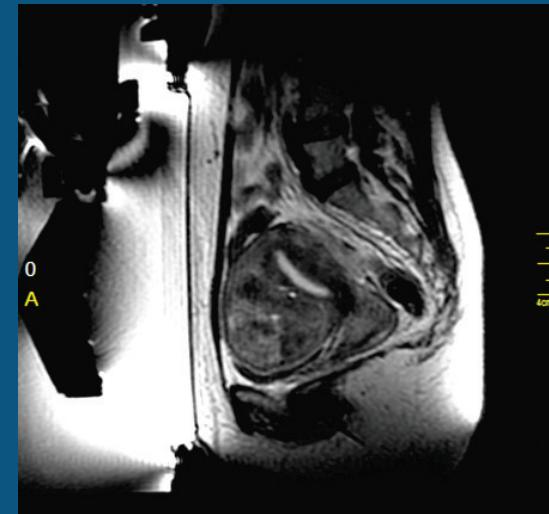
Fibroids Intensity: Iso-intense with bright portion on T2w Images

Sonication time: 180 minutes

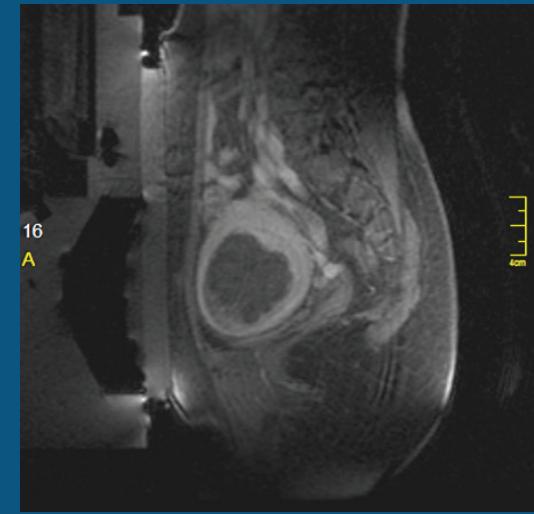
Results: 75% NPV with no adverse effects



Sagittal T1w+c
Pre-Treatment



Sagittal T2w



Sagittal T1w+c
Post treatment

Courtesy of Inbar Y. M.D., Sheba Medical Center, Israel

Clinical Case- Proximity to Bowel and Sacrum

Patient age: 48 years old

Fibroids volume: 240cc

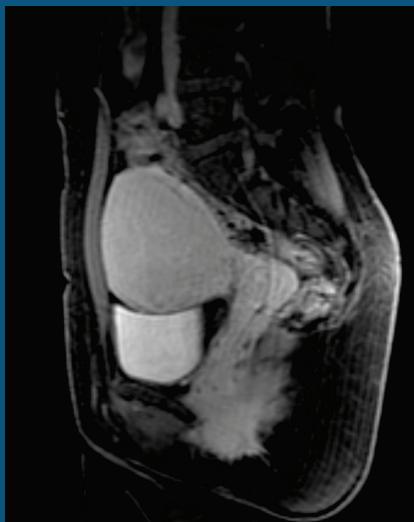
Fibroids Intensity: Iso-intense on T2w Images

Symptoms: Heavy menstrual bleeding and bulging belly.

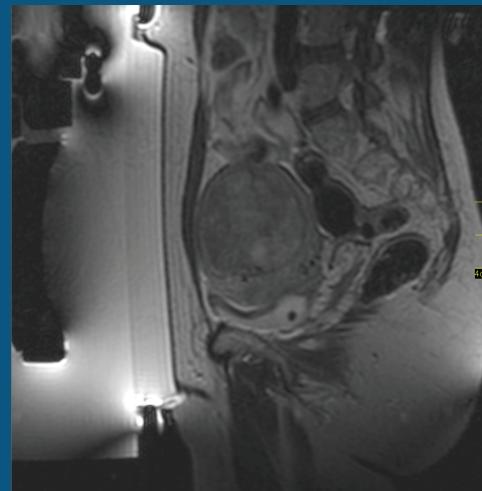
Sonication time: 180min

Results: 91% NPV with no adverse effects

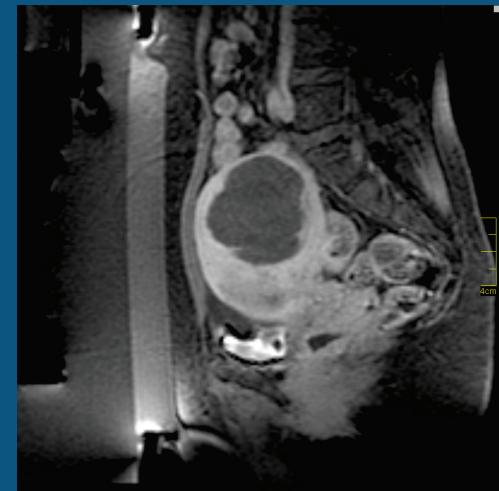
Beam shaping allowed treatment close to sensitive organs and reaching the fibroid's superior portion



Sagittal T1w+contrast
Pre-Treatment



Sagittal T2w



Sagittal T1w+c
Post treatment

Courtesy of Inbar Y. M.D., Sheba Medical Center, Israel

Clinical Case- Hypo-intense Fibroids

Patient age: 45 years old

Fibroids volume: 120cc

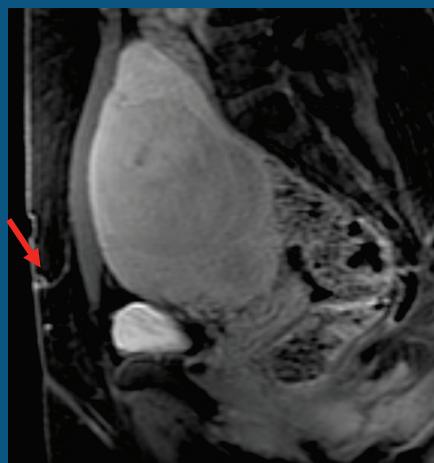
Fibroids Intensity: Hypo-intense on T2w Images

Symptoms: Frequent urination
2 yrs post-myomectomy with large scar

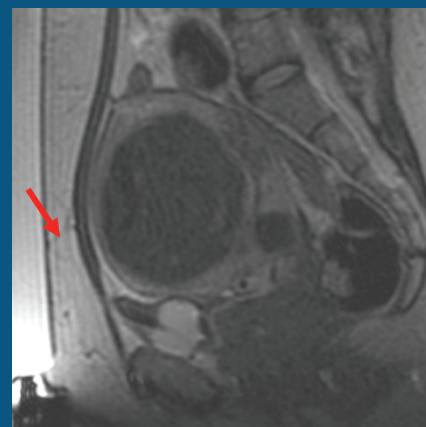
Sonication time: 193 min

Results: 83% NPV with no adverse effects

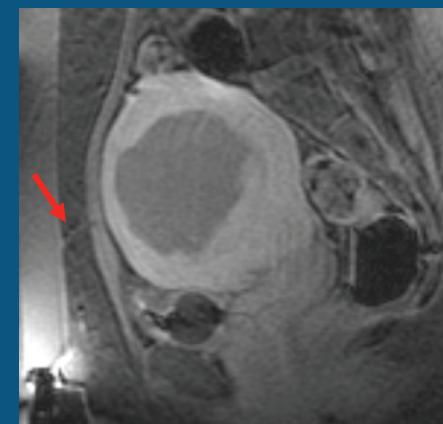
- **No-pass zone LEDR- to avoid sonicating through a transverse large scar- tilting and aperture**
- **Sonications through the scar- with transducer up and without tilt- low energy density on the skin**



Sagittal T1w+c pre tx



Sagittal T2w pre tx



Sagittal T1w+c post tx

Courtesy of Inbar Y. M.D., Sheba Medical Center, Israel

Clinical Case - Scar in Beam Path

Patient age: 43 years old

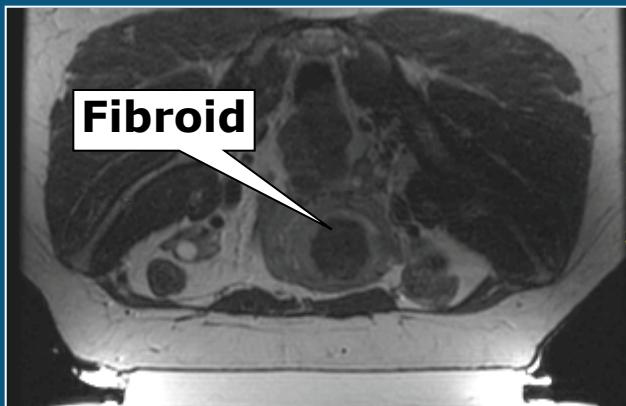
Fibroids volume: 50cc with large scar in beam path

Symptoms: Heavy menstrual bleeding, blood clots and fluctuations in menstrual cycle.

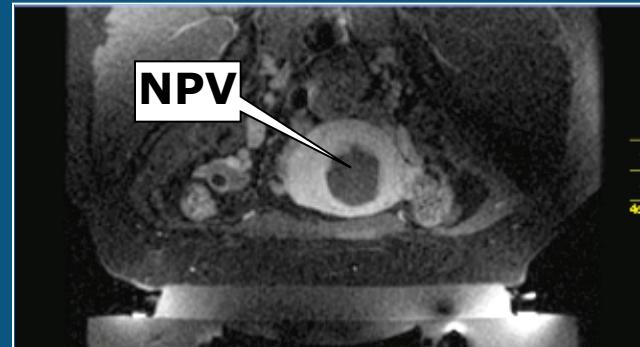
Treatment time: 55 minutes

Results: 90% NPV with no adverse effects

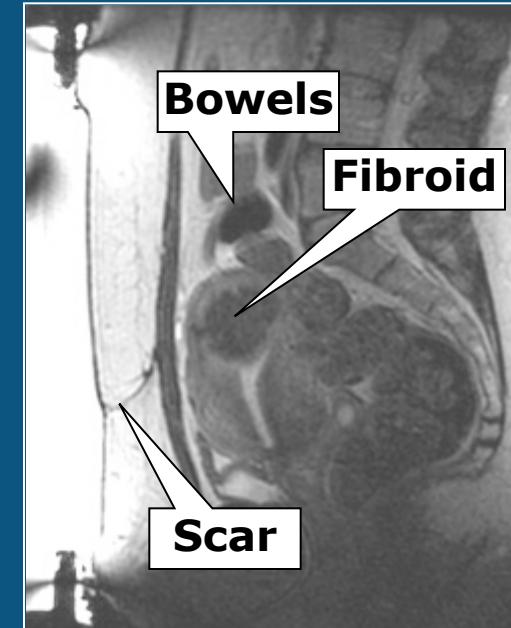
Aperture control and 5 axis motion enabled safe and effective treatment through the scar



Axial T2w
Pre-treatment



Axial T1+contrast
Post treatment



Sagittal T2w
Post treatment

Courtesy of Inbar Y. M.D., Sheba Medical Center, Israel

Clinical Case

Patient age: 28 years old

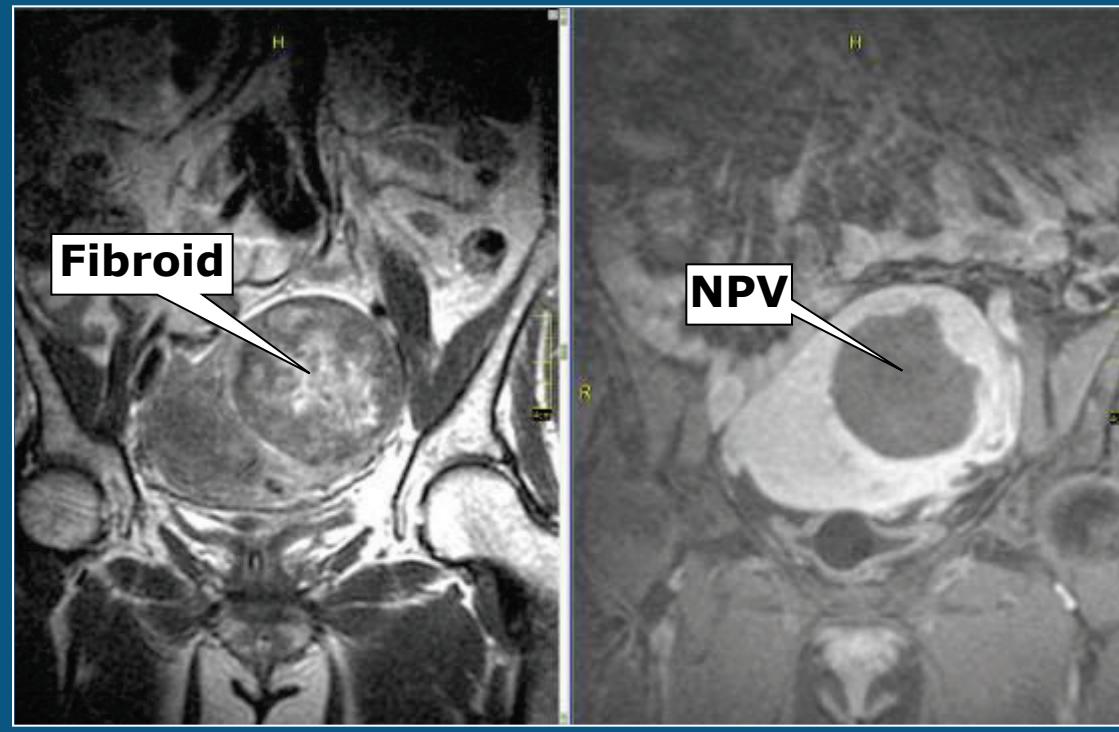
Fibroids volume: 200cc hyper-intense

Symptoms: Heavy menstrual bleeding, blood clots, fluctuations in menstrual cycle, and tight feeling in pelvic area

Treatment time: 3 hours

Results: 80% NPV with no adverse effects

Ability to perform effective treatment for hyper-intense fibroid, due to increased energy density in focus



Coronal T2w

Coronal T1+c Post treatment

Courtesy of COGP, Moscow, Russia

Clinical Case

Patient age: 47 years old

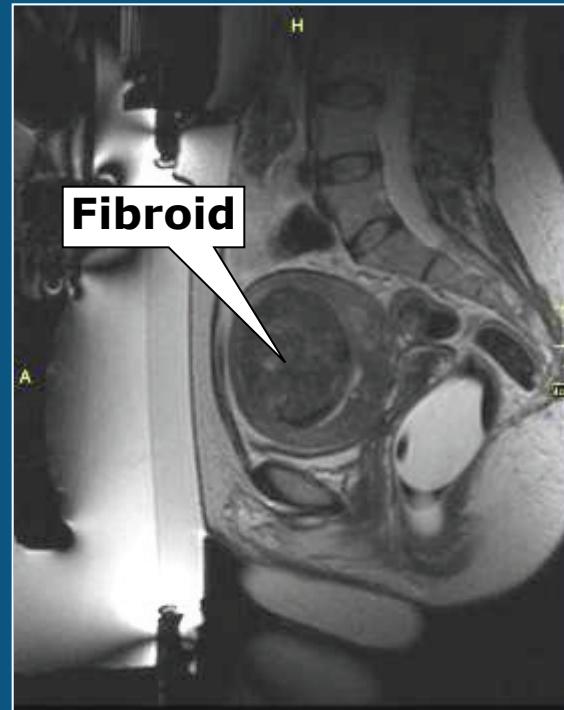
Fibroids volume: 130cc

Symptoms: Heavy menstrual bleeding, blood clots and fluctuations in menstrual cycle.

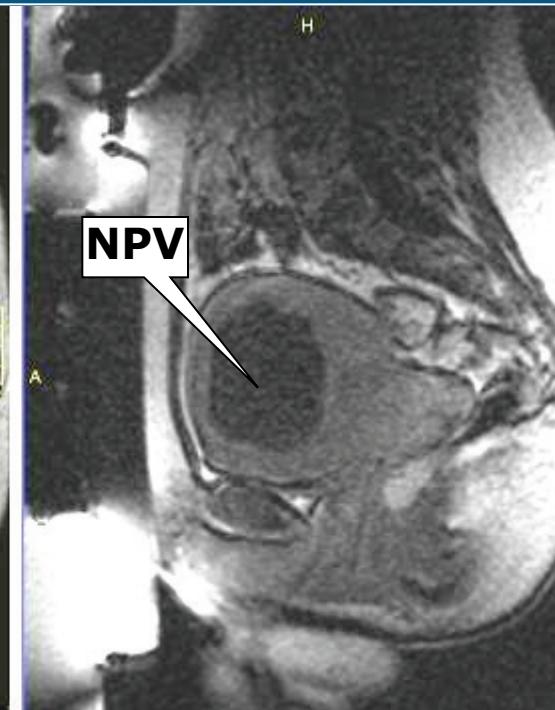
Treatment time: 1 hour ,
40 minutes

Results: 90% NPV with no adverse effects

Ability to perform fast and effective treatment with complete ablation of fibroid in 1.4 hours



Sagittal T2w



Sagittal T1+c Post treatment

Courtesy of COGP, Moscow, Russia

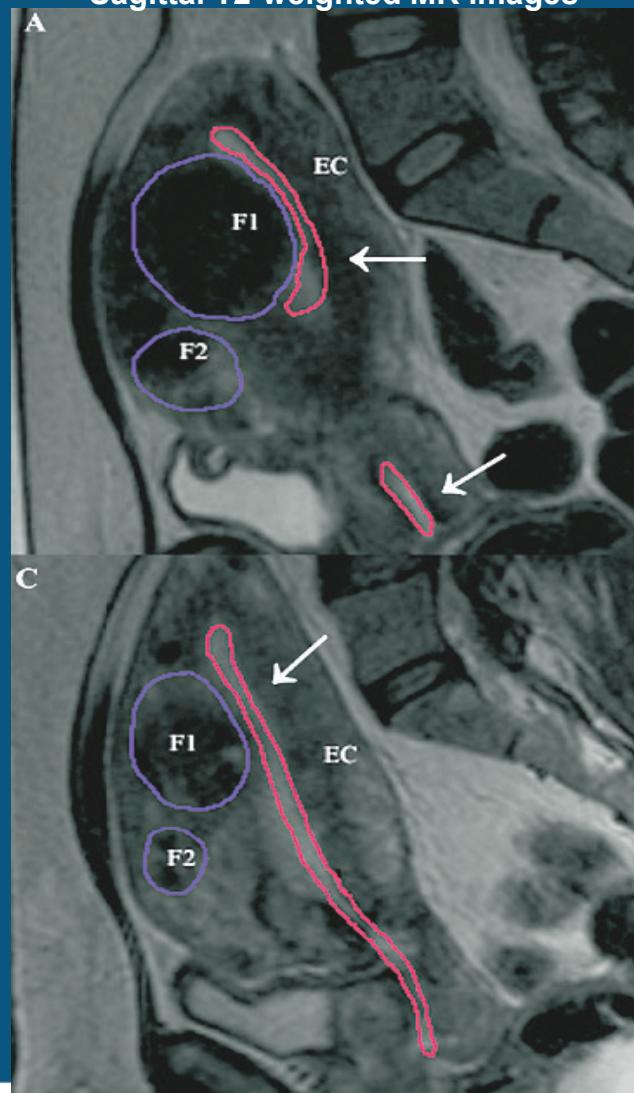
Clinical Case - Post MRgFUS pregnancy

(A) Before treatment shows two major fibroids (F1 and F2) which caused an S-shaped configuration of the endometrial cavity (EC)

(C) One year after treatment with MRgFUS both F1 and F2 have decreased in size, although F1 decreased more.

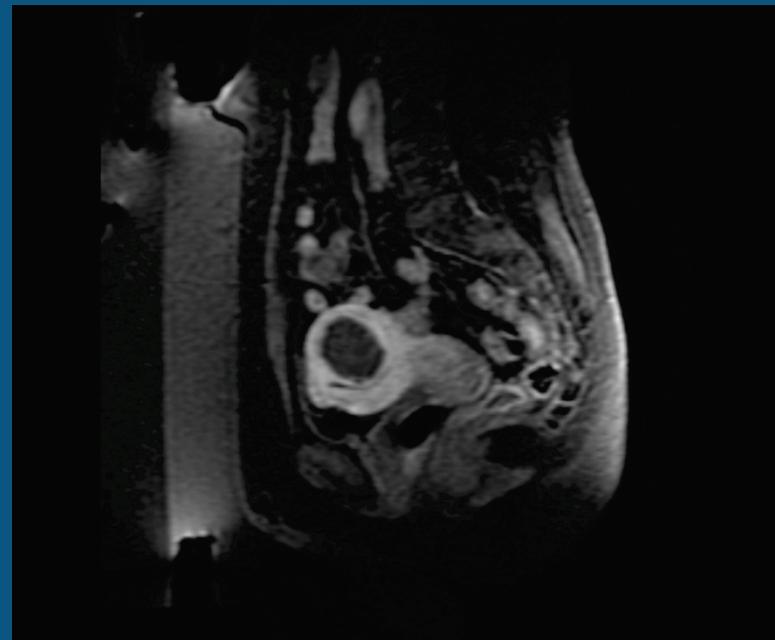
NOTE: the repositioning of the endometrial cavity, due to F1 shrinkage. The endometrial cavity can now be visualized in its entirety in the same plane.

Sagittal T2-weighted MR images



Courtesy of COGP, Moscow, Russia

Pregnancy after MRgFUS



39 yo. Nulligravida. **2 years of infertility**

Treated July 2008:

Intramural 16 cc- 40 sonic.- **NPV: 95%**

Subserosal 8cc- 8 sonic.- **NPV: 40%**

1st pregnancy: 4 months after treatment. CS at 41 weeks due to previous myoma.

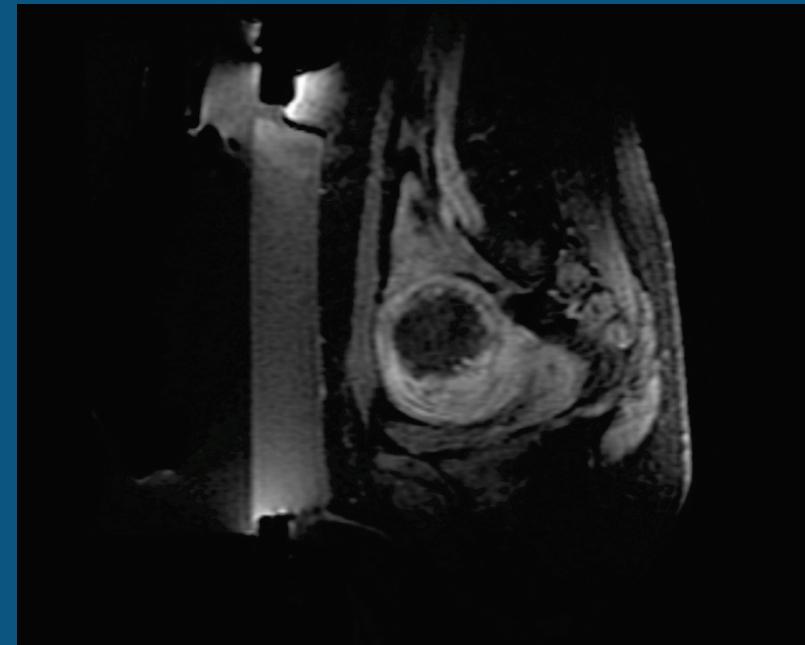
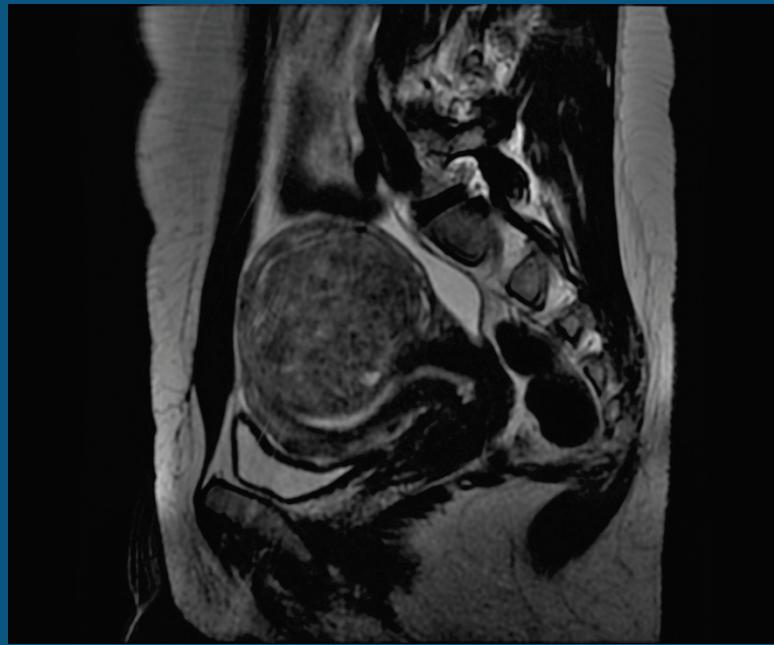
Baby weight: 3800 g.

2nd pregnancy: 2.5 years after treatment. CS at 39 weeks due to face presentation.

Baby weight 3430 g.

Courtesy of H. Millan, MD, Instituto Cartuja, Seville, Spain

Pregnancy after MRgFUS



41 yo. Nulligravida. **3 previous IVFs** (the last one with oocytes from donor)

Previous myomectomy

Treated September 2010:

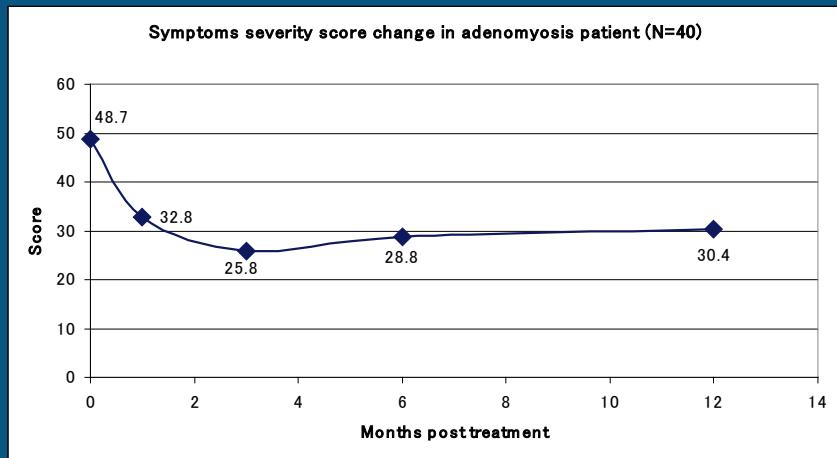
Intramural 130 cc-70 sonic.-**NPV 80%**

Pregnancy: 7 months after treatment (frozen embryo transference)

Courtesy of H. Millan, MD, Instituto Cartuja, Seville, Spain

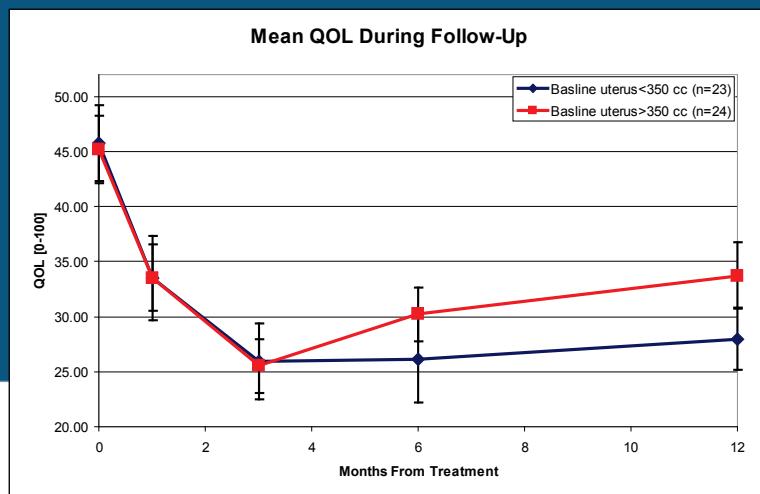
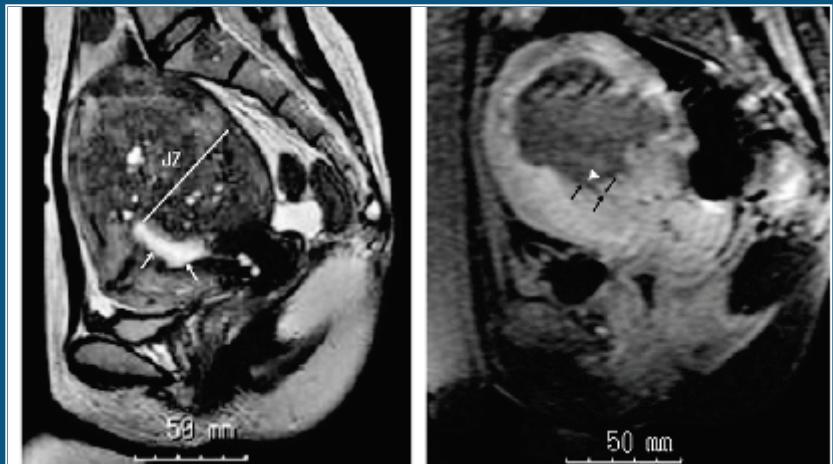
Adenomyosis

- 40 patients reached 12 months follow up with significant symptoms improvement which is consistent after the treatment and during the follow up ($P<0.01$).
- High safety profile, and no serious adverse events.



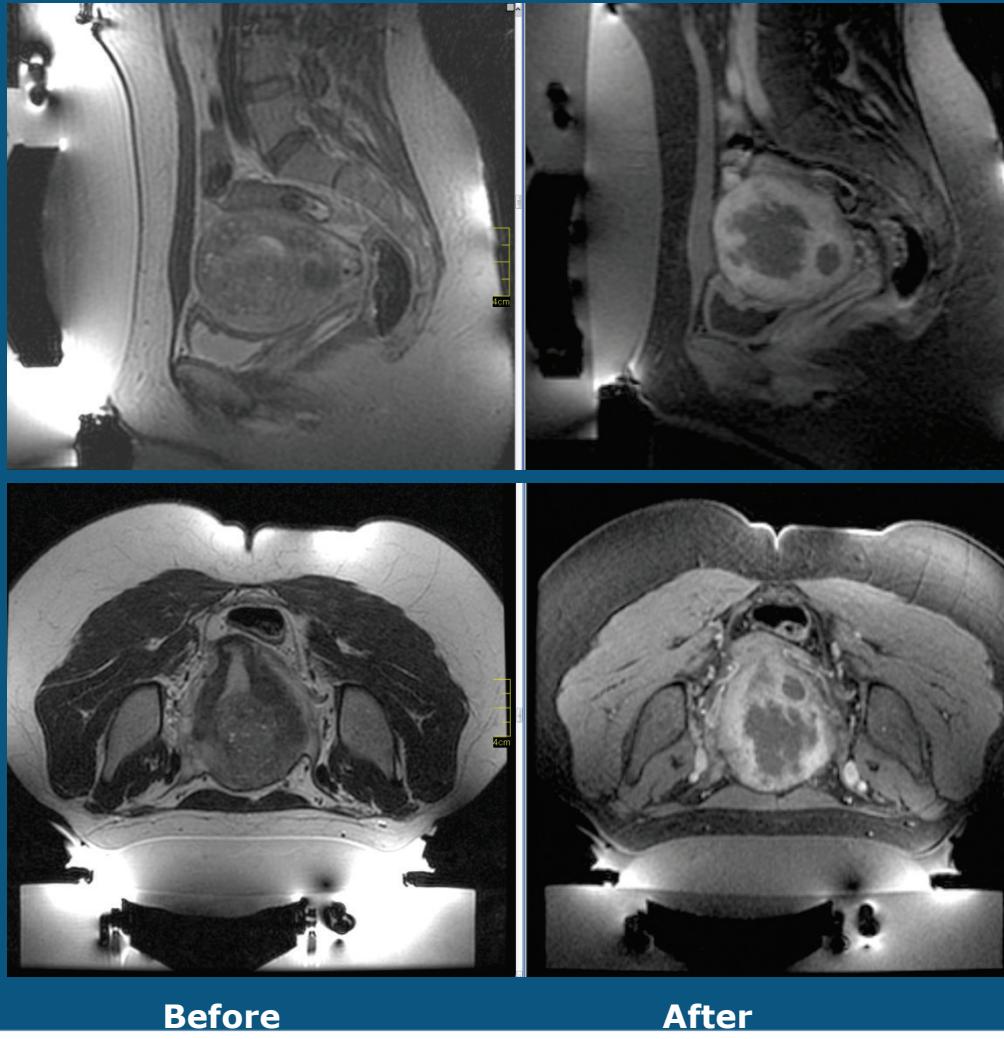
Graph shows Symptom Severity Score data of 40 treated patients at 12 months follow-up

Published paper: Fukunishi H, Funaki K, Sawada K, Yamaguchi K, Maeda T, Kaji Y. Early Results of Magnetic Resonance Imaging-guided Focused Ultrasound Surgery of Adenomyosis : Analysis of 20 Cases, JMIG, 2008.



Clinical Case: Adenomyosis

Patient age: 39 years old
Adenomyosis and tiny fibroid
Symptoms- menometrorrhagia
Sonication time: 160min
Results:
FocalAD NPV 79%
Tiny fibroid NPV 100%.



Courtesy of Inbar Y. M.D., Sheba Medical Center, Israel