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# Uterine Myomas: Focused Ultrasound Surgery

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**Uterine fibroids are the most common neoplasm in women. These lesions may be associated with impaired fertility and adverse obstetric outcomes. Medical treatment, myomectomy, hysterectomy and uterine artery embolization have been employed for the management of uterine fibroids. Focused ultrasound surgery (FUS) is a relatively recent technique that relies on mechanical and thermal energy of ultrasound for the ablation of a target tissue under an imaging guidance, that can be either ultrasound (US-guided FUS, USgFUS) or magnetic resonance (MR-guided FUS, MRgFUS). Pre- and peri-menopausal women are potential candidates for treatment; however, individual criteria need to be evaluated in order to establish the eligibility for the procedure. FUS procedure can be performed in an outpatient setting; it is a safe and effective treatment that has demonstrated to reduce symptoms associated with uterine fibroids. The adverse event rate is 8.7% and only 0.2% of patients experiences major complications. Pregnancy is possible after the treatment, and no damage to the endometrium has been observed following FUS procedure.**
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## Introduction

Uterine fibroids (UFs), also known as leiomyomas, are the most common neoplasm in women. They occur in about 70% of female population and may be asymptomatic or cause chronic symptoms, such as heavy menstrual bleeding, noncyclic pain and bladder or bowel disfunction; 25% of patients have symptoms that require treatment. UFs may be also associated with impaired fertility and adverse obstetric outcomes.[1] Hysterectomy has been historically employed as the treatment of choice; however, surgery is associated with a high rate of complications and side effects, as well as with the total deprivation of fertility.[2] Thus, over the last decades, an increasing number of less invasive techniques have been introduced for the control of UFs, including myomectomy (whether laparoscopic or mini-laparotomic), uterine artery embolization (UAE) and focused ultrasound ablation (FUS).

FUS relies on mechanical and thermal effects of ultrasound waves for the focal ablation of target tissues. The procedure is generally performed under an imaging guidance, in order to ensure safety and efficacy.[3]

During the last years, the improvement of the transducer technologies and the advent of real-time diagnostic imaging have encouraged numerous research groups to investigate a variety of therapeutic applications.[4,5]

Focused ultrasounds have demonstrated their efficacy in several conditions and have been approved by FDA for the treatment of UFs, prostate cancer, essential tremor, Parkinson's disease, and painful bone metastases.[4,6] Promising results were achieved in managing various diseases, such as osteoid osteoma and liver, kidney and breast malignancies.[5,7,8]

## Physical principle and biological effects

The therapeutic potential of focused ultrasound has been demonstrated in vivo at first in the 1950s.[4] However, due to the lack of accurate methods for guidance, the clinical applications of FUS has effectively emerged only in the last decade, after the improvement of diagnostic ultrasound imaging system and the advent of magnetic resonance (MR).

Focused ultrasounds are generated outside the body by a transducer made of piezoelectric elements, similar to the one

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used for diagnostic application. Lower frequencies are commonly used for therapeutic applications (220 $Hz^{-1}$ MHz).[9] Ultrasounds can be focused with lens or reflector or, more recently, with phased-array transducers, in which each single element of the transducer is fed by a separate electrical signal, that allow the electrical beam forming and steering.[10]

The incident ultrasound beam is absorbed and converted into heat at the focal point. At a microscopic level, the mechanical energy of ultrasounds causes pressure fluctuations that lead to shearing motion of tissue, resulting in frictional heating. The deposition of acoustic energy in the targeted tissue is called sonication.[11] When the temperature reaches 60°C in the focal point, which is the threshold of protein denaturation, tissue coagulation and necroses begin. Other mechanisms also contribute in determining tissue damage at the focal point, such as stable cavitation, radiation force and torque. Temperature above 96°C can determine tissue boiling and bubble formation, whose effects on surrounding tissues are less predictable, thus 96°C should be the maximum achievable temperature. The dimension of the area of coagulative necrosis depends on the acoustic pressure, time of exposition and tissue composition.[12] The volume of ablation after an individual sonication pulse is small (about 6 mm x 25 mm),[13] thus, to destroy larger structures, more than 1 sonication has to be performed, with an interval between the treatments that protect surrounding tissues from heat accumulation and destruction.[10,12]

## Imaging guidance

Ultrasound guidance (US-guided Focused Ultrasounds, USgFUS) for visualization of target tissue was proposed in the early days of diagnostic ultrasound (in the 1970s) and continued to be the only guidance modality until the 1990s.[14]

MR guidance (MR-guided Focused Ultrasounds, MRgFUS) provides continuous imaging and real-time temperature mapping, to ensure safety and effectiveness of the treatment. The temperature feedback allows to adjust the sonication energy and power in order to obtain complete ablation of the lesions avoiding over-sonication.[15] Several temperature sensitive MR parameters can be used, however proton resonance frequency (PRF) based phase mapping methods are the preferred, due to greater sensitivity in detecting small temperature changes. The PRF-shift methods are based on the difference of the nature of hydrogen bonds between water molecules and consequently the difference of the resonance frequency of water protons at different temperatures.[16]

## Indications and contraindications

Due to the fact that the primary aim of MRgFUS procedure is an improvement of symptoms rather than local tumor control, only symptomatic patients are considered eligible.

Clinical diagnosis needs to be confirmed by MR imaging, also in order to rule out any other potential disease that may present with similar symptoms; in the same circumstance, the "dominant" fibroid needs to be identified: it can be defined as the most likely fibroid to be responsible for symptoms, according to imaging features such as size, signal intensity, vascularization, and other features (Fig. 1).

So, inclusion criteria are generally extended to women whose dominant fibroids have been identified and that are compatible with the clinical presentation; women with seeking uterine preservation; fibroids with MRI features suitable for MRgFUS treatment. However, only a limited portion of selected patients can undergo MRgFUS procedure: relative and absolute contraindications are summarized in Table 1.

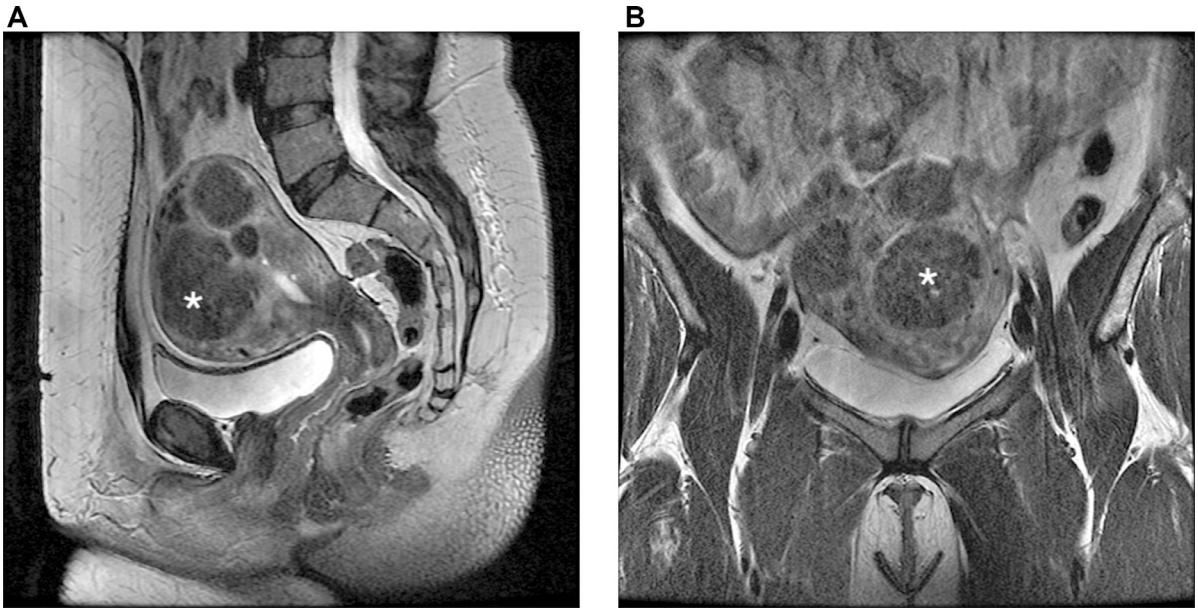


**Figure 1** Sagittal (**A**) and coronal (**B**) T2-weighted MR images of a patient with pain due to multiple UFs. The biggest one is likely responsible for symptoms and thus is considered as the "dominant" fibroid (*white star*).

**Table 1** General Contraindications and MRI Exclusion Criteria in MRgFUS for Uterine Fibroids

| General Exclusion Criteria | MRI Exclusion Criteria |
|---|---|
| MRI contraindications | Fibroid diameter >10 cm |
| Pregnancy | Funaki 3 fibroids |
| Other pelvic diseases | Peduncolated or calcified fibroids |
| **Cutaneous scars** | Not enhancing fibroids |
| | **Bowel interposition** |
| | **Distance from the sacrum < 4 cm** |
| | **Distance skin – midpoint of fibroid > 12 cm** |

Contraindication potentially avoidable with mitigation techniques are displayed in bold.

Absolute exclusion criteria include contraindication to contrast-enhanced MRI, pregnancy and the presence of any other pelvic disease.

A screening MR Imaging (MRI) is mandatory for the assessment of treatment eligibility.[17] MRI is performed with the patient in prone position, which is the treatment position (Fig. 2).

Fibroids with more than 10-12 cm of diameter are usually not treated, in order to avoid prolonged procedure time that may cause discomfort and has been associated with the development of deep vein thrombosis[18] (Fig. 3). However, preliminary treatment with GnRH agonists may allow for fibroid shrinkage, which can result in shortened treatment times.[19,20]

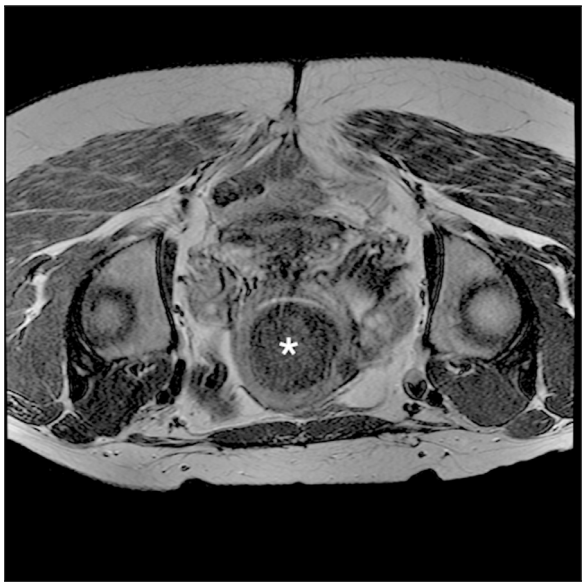

**Figure 2** Pretreatment axial T2-weighted MR image of a 29-year-old patient with a submucosal myoma located in the anterior wall of the uterine body (*white star*). The preoperative MRI is performed with the patient lying in the prone position.

Several other MR-characteristics of the lesions have to be considered in order to assess eligibility: leiomyomas with high T2 signal intensity (Funaki type 3) are usually excluded since they seem to be less responsive to treatment[21]; pedunculated fibroids are not treated since the ablation of the stalk may cause disconnection of the lesion from the uterine wall, requiring surgical treatment to remove free debris into the pelvic cavity; not-enhancing fibroids are excluded, since it indicates already degenerated/infarcted fibroids; the presence of a calcified envelope may determine absorption or reflection of the US energy, with scarce clinical results and unpredictable side effects.

The interposition of bowel between the transducer and the targeted lesion may represents an obstacle to the ultrasound beam path, since the sonication of bowel loops can cause bowel injury and, at worst, perforation. Rectum and bladder filling with ultrasound gel in order to displace the bowel loops or transducer angulation can be used in order to prevent bowel sonication (Fig. 4); however, when these mitigation techniques are not applicable or ineffective, bowel interposition is considered a contraindication to MRgFUS.

If the distance between the mid-point of the lesion and the skin surface is 12 cm or more, an adequate treatment will not be possible, due to the limit of the penetration depth of the ultrasound beam. The proximity of the lesions to sacrum is another contraindication, since heat accumulation in the bone can be transferred to the perineural fat and adjacent nerves, causing nerve injury: the safety distance between target area and the sacrum should be at least 4 cm. Even in these cases mitigation techniques such as bladder and rectum filling can be used (Fig. 5).

The presence of scars is another relative contraindication, since cutaneous scars can absorb ultrasounds, thus causing skin burns. Changing the beam angulation can sometimes prevent this event.[22]

## MRgFUS procedure

MRgFUS can be performed in an outpatient setting, without requiring hospitalization.

On the day of the treatment, patients are shaved from the umbilicus to the pubis; an intra-venous access and a Foley urinary catheter are placed.

The procedure is performed with the patient on prone position on a dedicated MR table (Fig. 6), with the abdomen lying in a water bath of deionized degassed water, in contact with an acoustic coupling gel pad located above the ultrasound transducer (Figs. 7 and 8).

In this phase, patients are told what they may feel and that they will have to stop the sonication in case of severe acute pain, neurological symptoms and skin burning sensation A "stop sonication button" is placed in patient's hand and one more button is available on the workstation of the operating physician, for the immediate suspension of energy delivery anytime during the procedure, if necessary.

A moderate strength sedative is administered to help relax the patient, prevent movement, and minimize discomfort during the procedure.

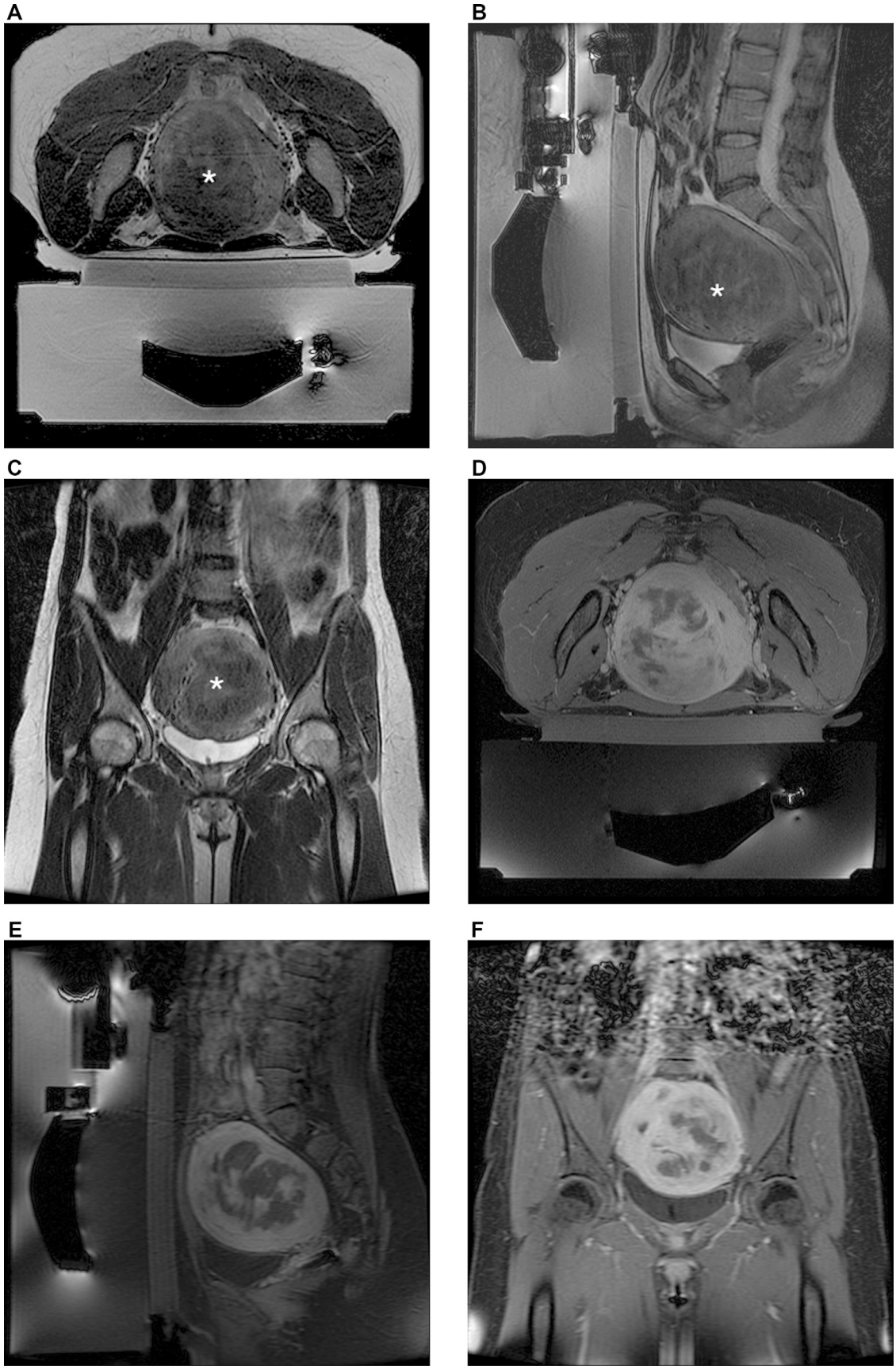


**Figure 3** Axial (**A**), sagittal (**B**) and coronal (**C**) pretreatment T2-weighted images of a big (about 8 cm) intramural fibroid (*white star*). The patient underwent MRgFUS. However the treatment was interrupted, due to the prolonged time required (the procedure lasted about 3 hours) and the proximity to structures such as bowel loops and sacral bone. Axial (**D**), sagittal (**E**) and coronal (**F**) postcontrast T1 fat-sat images acquired immediately after treatment show only a partial devascularization of the lesion.

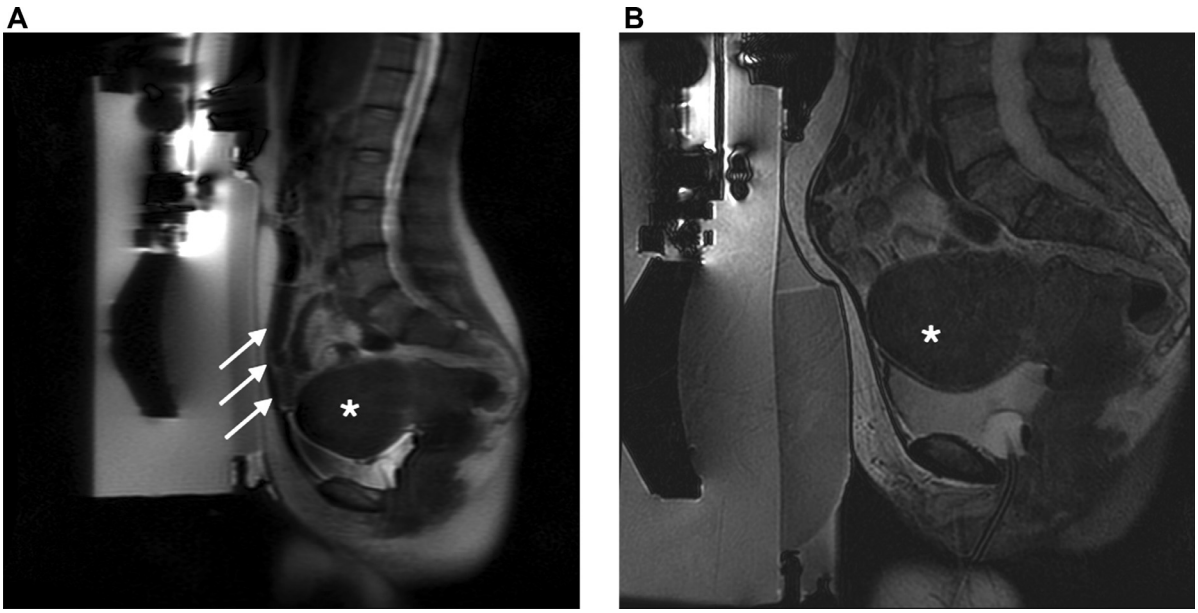


**Figure 4** (**A**) MR images of a patient with a uterine subserosal myoma with a maximum diameter of about 95 cm (*white star in A and B*). The scout sagittal MR image shows the bowel interposition between the transducer and the fibroid (*white arrows*). (**B**) Bladder filling with the US gel shows displacement of the uterus and the bowel loops, as shown in the T2-weighted MR image.

Just before starting a procedure, baseline T2-weighted MRI images in axial, coronal and sagittal planes are obtained for treatment planning and manual segmentation. The region of treatment is defined and drawn with its safety margins by the radiologist in all 3 planes; critical structures are marked using specific low-energy density region and no-pass region markers, in order to prevent the beam path to pass through sensitive organs such as bone, nerves and bowel loops; the operator also establishes fiducial anatomic landmarks to detect and compensate physiologic or accidental motion of the patient during the treatment. At this stage, the bladder and/or the rectum can be filled, if necessary.

Once that the manual segmentation is completed, a dedicated software automatically establishes the optimal

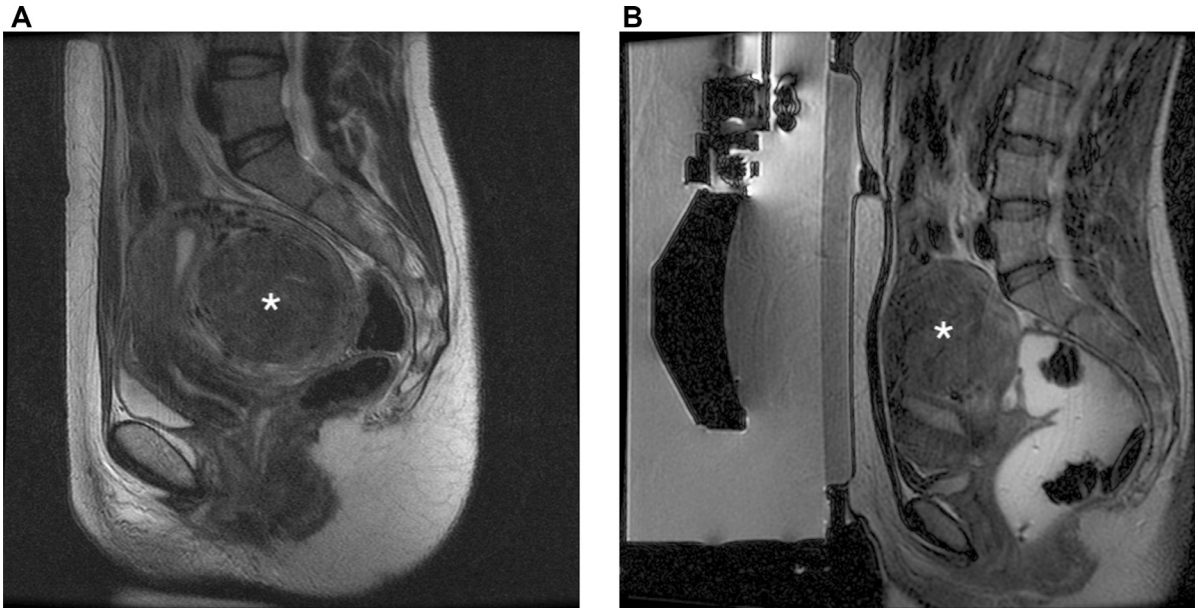


**Figure 5** MR images of a patient with a 6 cm intramural uterine fibroid (*white star in A and B*). Pretreatment sagittal T2-weighted shows the presence of the uterine fibroma in the posterior wall of the uterus which is located close to the sacral bone (**A**). Rectal filling allows uterus to be displaced anteriorly, thus increasing the distance between the uterine wall and the sacral bone, as shown in the T2-weighted sagittal image (**B**).


**Figure 6** Dedicated body system MRgFUS table.

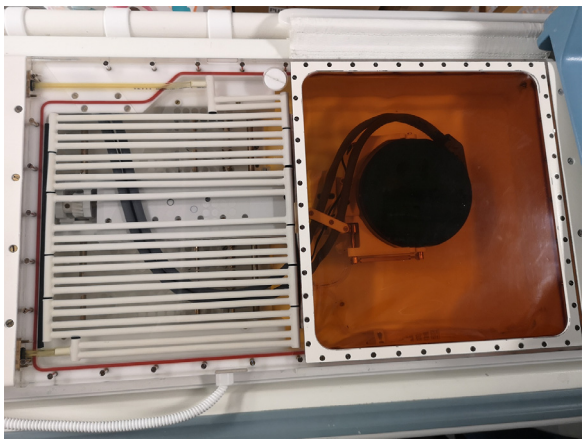

**Figure 7** MRgFUS transducer. The transducer is integrated inside the table within an oil bath and is coupled with a cooling device. The transducer can be moved within the table, allowing the US beam to be directed toward the targeted lesion.

treatment plan calculating the sonication locations, the number of sonications, the energy levels, the sonication duration, the cooling duration, or the spot sizes (Fig. 9). Each of these parameters can be modified by the operator at any moment.

Then a few low energy sonications are performed for final targeting calibration.

At this point, the actual clinical treatment can start; the procedure is performed with multiple therapeutic sonications until a sufficient fibroid volume will be covered.[23] Each sonication lasts 20-40 seconds and there is a cooling period between subsequent sonications lasting up to 90 seconds.[13] Real-time MR thermometry will reveal any potentially dangerous heating or unwanted exposure.

After treatment, postcontrast T1-weighted images are acquired to assess the extent of the ablated area; a specific parameter that is helpful in evaluating the percentage of therapeutic necrosis is the nonperfused volume (NPV): it is defined as the nonperfused tissue volume after treatment divided by the whole fibroid volume before treatment (Figs. 10-12).

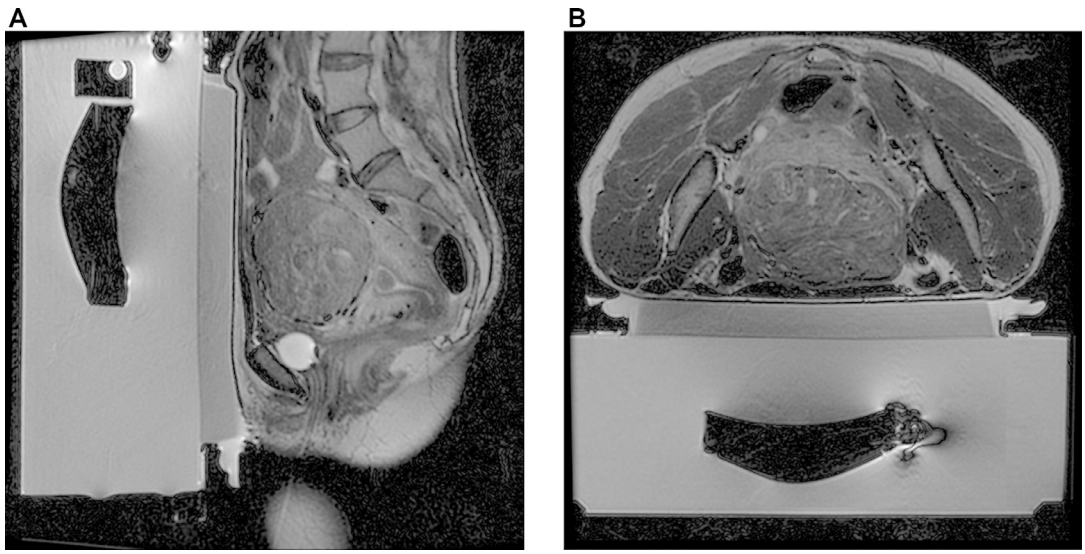


**Figure 8** Sagittal (**A**) and Axial (**B**) T2-weighted MRI images acquired just before a MRgFUS procedure for the ablation of a UF with a diameter of 8cm. The patient is positioned prone on the MRI table, with the abdomen in a water bath of deionized degassed water, in contact with an acoustic coupling gel pad located above the ultrasound transducer; a Foley catheter has been previously positioned. These images are taken at the beginning of the treatment planning, in order to verify the correct patient positioning and the absence of air bubble trapped between the skin plane and the table.

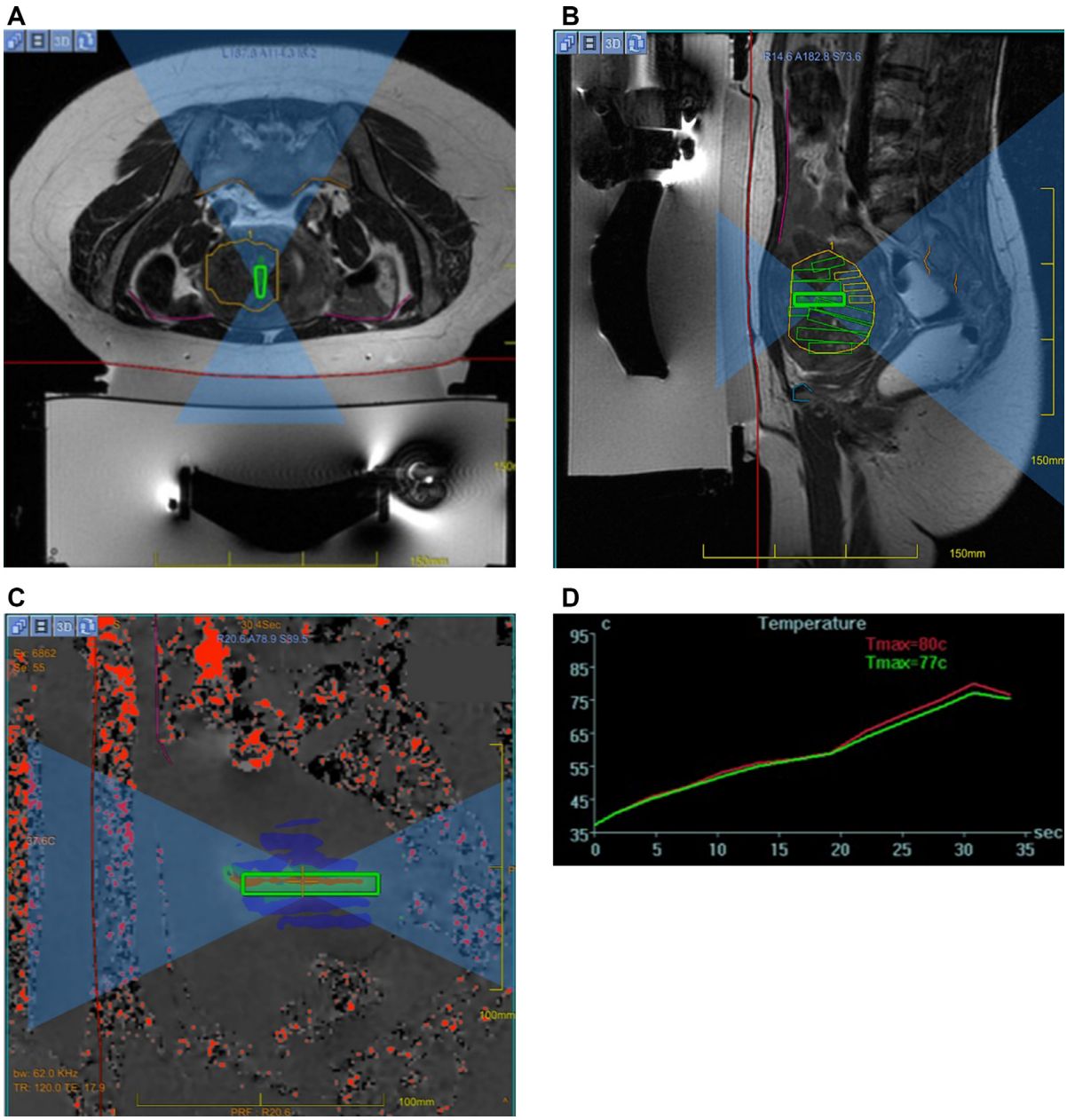


**Figure 9** Axial (**A**) and Sagittal (**B**) MRI images acquired during the planning phase at the beginning of MRgFUS procedure. US beam representation is shown in light blue; the red line indicates the skin-gel pad interface; the orange line indicates the nonpass region marker along the surface of the sacrum, in order to avoid any potential neural injury to sacral nerves; the pink line indicates the nonpass region marker of bowel loops; the region of treatment is bordered by a yellow line. Once that all these regions are manually marked, the software automatically splits the region of treatment into many discrete sonications (green boxes): the operator can change automatic parameters in any time during the procedure. (**C**) Real-time thermometric map obtained at the end of a single sonication during the procedure using proton resonance frequency sequences; the red area within the sonication volume represents the site where the critical threshold for necrosis has been reached. (**D**) Temperature trend in treated area during the sonication time, measured in real-time. (Color version of figure is available online.)

Patients are asked to mention any symptoms and are examined for any evidence of skin burning. Most patients can usually return to work a few days after the treatment, with significantly less intense postprocedure pain and impairment compared to UAE or surgery.[23]

Clinical conditions are also monitored after treatment and during established follow-up; fibroid-related pain and symptoms can be assessed with a wide range of parameters including Visual Analogue Scale (VAS) or the Symptom Severity Score (SSS): their change during time can

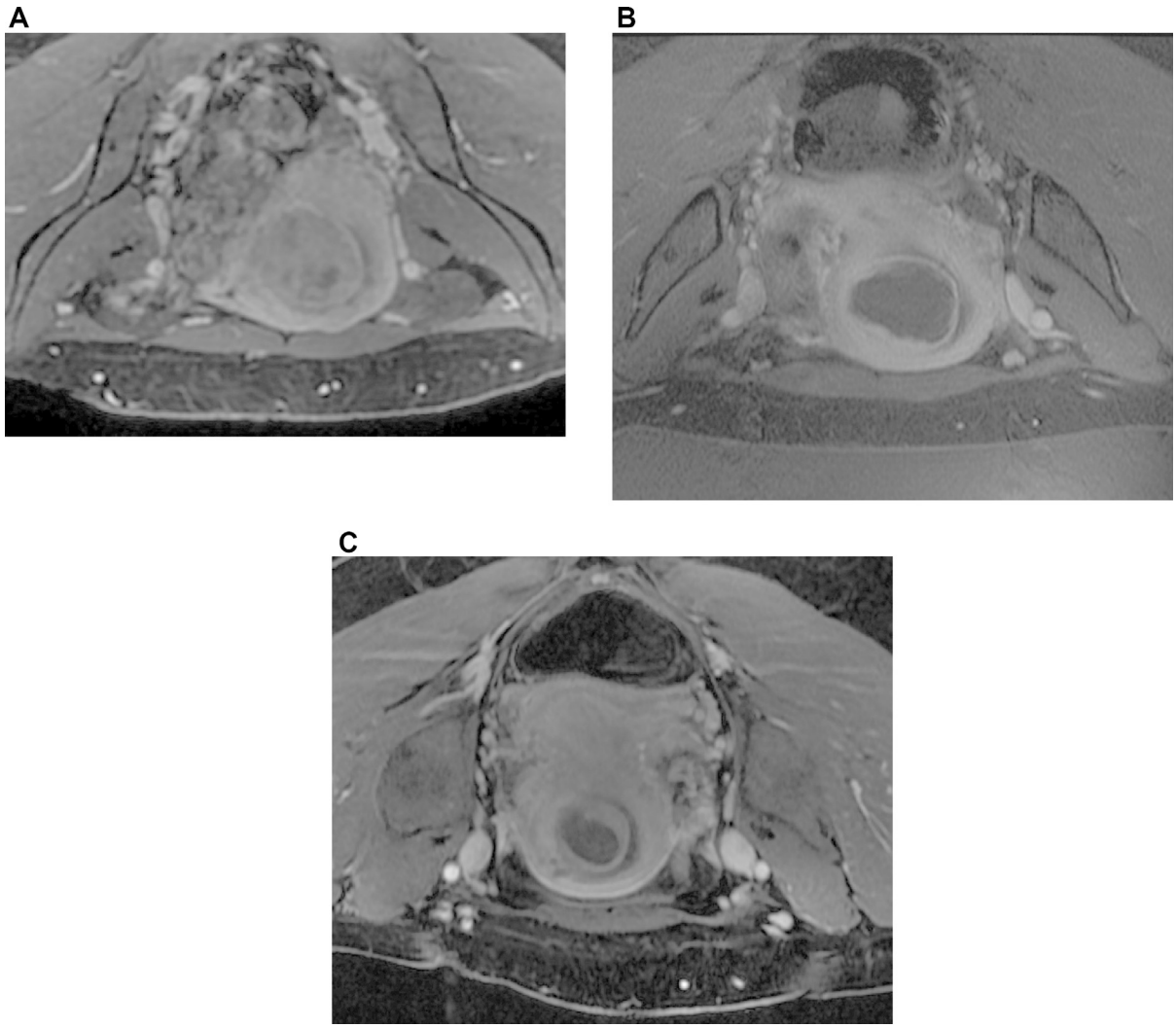


**Figure 10** Pre- and post-treatment contrast-enhanced axial Magnetic Resonance images of a patient who underwent MRgFUS treatment for UF. (**A**) Preprocedural scan demonstrates the presence of an enhancing lesion with diameter of 4cm (**B**). Postprocedural image shows the necrotic area within the lesion, defined as the NPV (about the 80% of initial volume). (**C**) Three months after the treatment the volume of the whole lesion decreased, with maximum diameter of 3cm; the nonperfused area is still present within the fibroid.

indicate a potential improvement of symptoms as a consequence of treatment.

## Results in literature

MRgFUS has shown to be an effective approach in the management of UFs. The SSS significantly decreases after MRgFUS treatment and is about −30.5 at 12 months which is comparable to the results after UAE and slightly lower when compared to myomectomy (−37.6) The re-intervention percentage is about 13%-14% at 12 months.[24]

Reported adverse event rate is 8.7%, most of which is due to minor side effects. Skin burn is the most frequent and can be often prevented ensuring the absence of air trapped between the transducer and the patient's skin. Other reported adverse events are vaginal bleeding or abnormal discharge, cystitis, urinary retention, constitutional symptoms, nerve damage or transient pain. Major adverse events occur in 0.2% of patients: deep vein thrombosis, high degree skin burn, bowel perforation and sciatic nerve injury have been reported[24,25] These data support the overall safety of MRgFUS treatment when compared to UAE and myomectomy, in which the adverse event rate rises to 19% and 25% respectively, with a 2.9% of major complications after UAE.[26,27] Moreover, the improvement of FUS technologies and operator learning curves have determined a further reduction of the adverse events compared to early reports, as suggested in more recent works.[24]

To date, there is lack of randomized research in the preservation of fertility after MRgFUS in comparison to the other uterus-preserving interventions for UFs. Surgical myomectomy exposes patients to a high risk of obstetric complication in case of a future pregnancy[28] and is associated to classical surgical complications such as pelvic adhesions that may decrease the reproductive potentials[29]; experts agree that

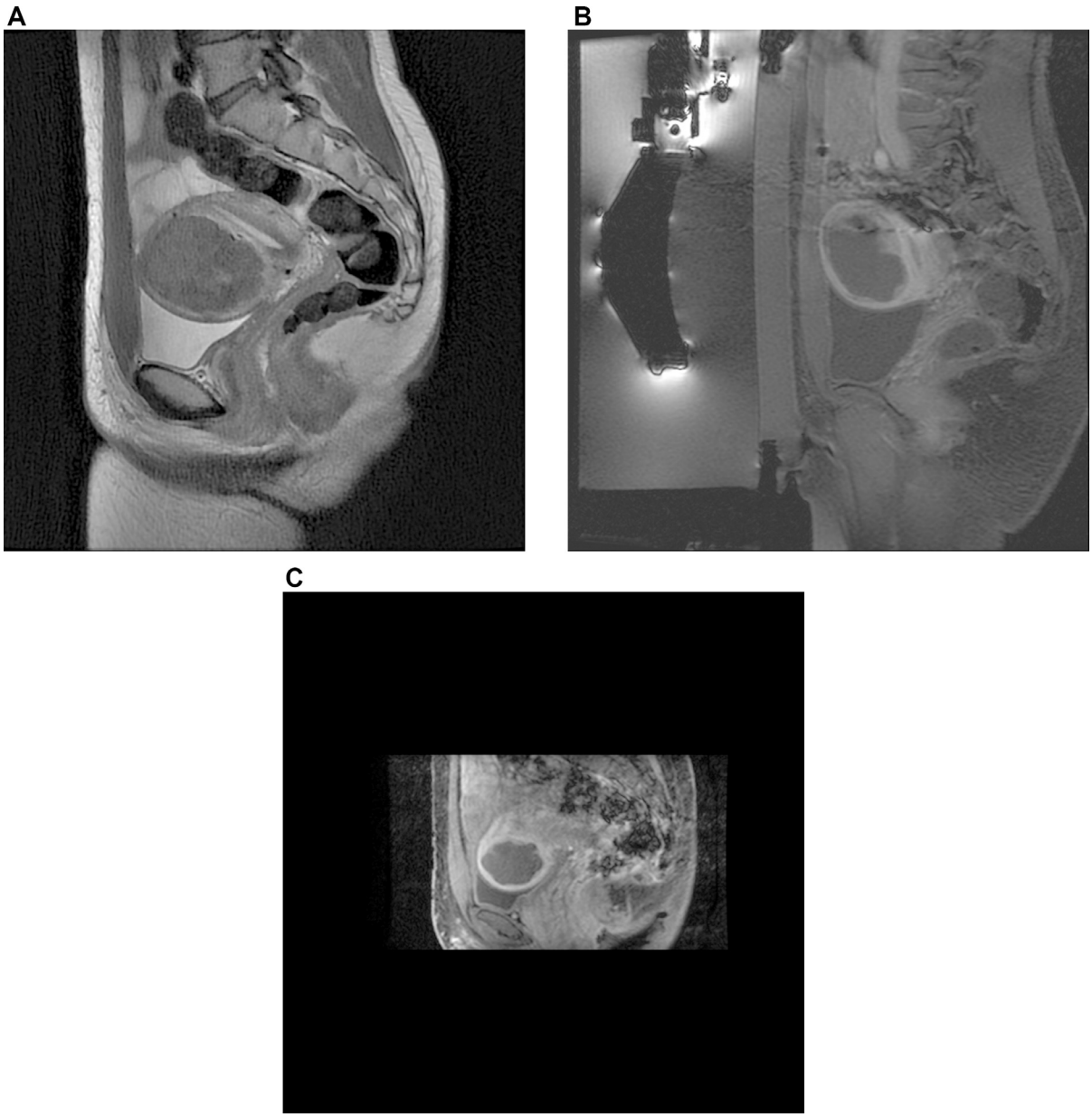


**Figure 11** Pre- and post-treatment contrast-enhanced Magnetic Resonance sagittal images of a patient who underwent MRgFUS treatment for UF. (**A**) Preprocedural scan demonstrates the presence of the fibroid on the anterior aspect of the uterus, with diameter of 5.5cm and with reduced enhancement compared to normal myometrium. (**B**) Immediate postprocedural image shows the necrotic area within the lesion, defined as the NPV (about the 80% of initial volume). (**C**) At long-term follow-up (24 months), the nonperfused area can be still easily recognized within the fibroid.

UAE is associated with lower pregnancy rates, higher miscarriage rates and more adverse pregnancy outcomes in comparison with myomectomies.[30] On the other hand, recently reported results demonstrated no impairment of the ovarian function[31] and the possibility to conceive after the FUS therapy for UFs[32-39]: pregnancy is possible after the treatment, with no increased rate of spontaneous abortions or pregnancy complications.[38] In 2015, FDA approved MRgFUS with next-generation ExAblate system for the treatment of symptomatic UFs and changed the labeling to allow consideration for women who desire to maintain fertility. However, guidelines are still controversial about this topic: in accordance to the recent Radiological-Gynecological Expert Meeting, a recommendation on the use of FUS prior to a planned pregnancy cannot be made and if a patient wants to become pregnant after MRgFUS/HIFU therapy and a minimum 6-month interval between MrgFUS treatment and conception is recommended.[40] In our direct experience over 10 years of UF treatments with MRgFUS and more than 350 women treated, the concern regarding possible fertility has not been raised; 24 patients delivered vaginally, 6 required cesarean section (planned); we record 5 abortion with no direct relation to the prior MRgFUS. Our data are in line with other centers reported in literature.

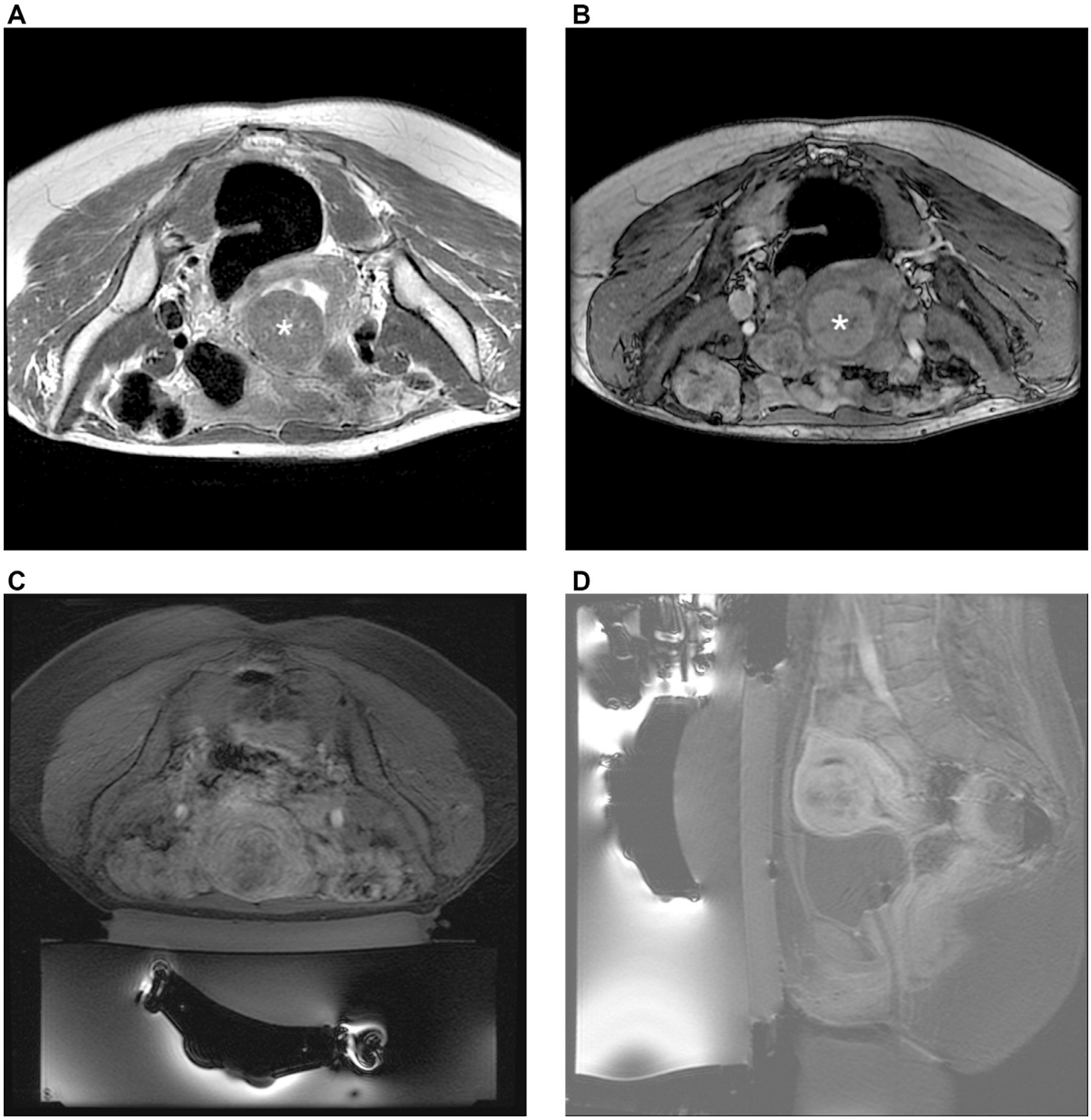


**Figure 12** Pre and post-treatment images of a UF in a 40-year-old woman. Pretreatment axial T2-weighted (**A**) and postcontrast T1-weighted (**B**) images show a high vascularized intramural myoma located in the anterior wall of the uterus (*white star*). Post-treatment axial (**C**) and sagittal (**D**) postcontrast T1-weighted images show the nonperfused area. The procedure was interrupted by the patient before its conclusion because of pain due to a mild skin burn. Calculated NPV was about 20%.

Concerns have been raised also about the costs of this MR-guided procedure, however 1-year all-cause costs for MRgFUS seems to be comparable to the one of myomectomy and UAE.[41]

## Conclusion

Noninvasive MRgFUS ablation represents an effective procedure in relieving symptoms related to UFs, with a low rate of adverse events in comparison to other uterus-sparing therapies; it is repeatable and does not seem to impair the possibility to conceive and the obstetrical outcome in case of pregnancy. These encouraging results indicate this technique as a suitable and desirable approach that could benefit from a wider application, especially women with a desire for future pregnancies or for a conservative uterus-sparing management. In fact, MRgFUS is always proposed as first therapeutic option in our institute, if the patient fulfills all the eligibility criteria and does not show any contraindications; if patients cannot undergo or refuse MRgFUS treatment, they are directed towards medical therapy (in case of women in perimenopausal age) or surgery.

However, in clinical practice, the choice of the most appropriate approach for the management of UFs needs to be individualized depending on factors such as age, symptoms, size and location of fibroids, desire for future pregnancy or preservation of the uterus, the physician experience, and patient preference[7]; a multidisciplinary approach is thus necessary, involving specialists from different areas of interest, such as the gynecologist and the interventional radiologist.

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