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Pelvic applications of MR-guided high intensity focused ultrasound

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Abstract

MR-guided high intensity focused ultrasound (MRg HIFU) is a novel method of tissue ablation that incorporates high energy focused ultrasound for tissue heating and necrosis within an MR scanner that provides simultaneous stereotactic tissue targeting and thermometry. To date, MRg HIFU has been used primarily to treat uterine fibroids, but many additional applications in the pelvis are in development. This article reviews the basic technology of MRg HIFU, and the use of MRg HIFU to treat uterine fibroids, adenomyosis, and prostate cancer.

Key words: MRI—MR guided high intensity focused ultrasound—Uterine leiomyomas—Uterine adenomyosis—Prostate cancer—Tumor ablation

What is MR-guided high intensity focused ultrasound?

MRg HIFU, also known as MR-guided focused ultrasound or MR-guided focused ultrasound surgery (MRg FUS), refers to the use of tightly focused high-energy ultrasound waves to heat and ultimately destroy tissue within an MRI environment. Targeted and sustained energy deposition with a focused ultrasound beam is used to heat the tissue at the focal zone to a threshold temperature of 55–85 °C, resulting in coagulative necrosis. A focal spot temperature of 55 °C is sufficient to cause protein denaturation and coagulative necrosis, but 70–80 °C is an optimal target temperature to insure real tissue necrosis [1]. The use of focused ultrasound for medical therapy is not new. Frontal lobotomy using focused ultrasound through burr holes in animals was first described in 1954 [2]. Extracorporeal shockwave lithotripsy, also a form of therapeutic ultrasound, was approved by the Food and Drug Administration in 1984. The use of focused ultrasound combined with MRI for guidance and monitoring emerged in the 1990s due to advances in imaging, ultrasound technology, and focal therapy. MRI guidance provides three critical advantages during focused ultrasound treatment that can be summarized as the ''three Ts'' of Targeting, Thermometry, and (stereo)Taxis. The excellent soft tissue and multiparametric contrast properties of MRI allows precise delineation and characterization of the target lesion. Real-time MR thermal imaging during the procedure allows for immediate assessment of treatment success and adequacy. The physical linkage of the transducer within the fixed geometry of the MRI scanner provides a stereotactic environment in which the three-dimensional location of the treated lesion is known, so that treatment volume can be accurately planned and the cumulative treatment volume can be mapped and displayed. To date, MR-guided focused ultrasound has been used primarily for the treatment of uterine fibroids, but ongoing

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research and developments promise much wider usage in tumor treatment and tissue ablation.

The two commercially available MRg HIFU systems are Sonalleve (Philips Healthcare, Vantaa, Finland) and ExAblate (InSightec, Haifa, Israel). These two systems are compatible with MRI scanners manufactured by Philips (Philips, Best, The Netherlands) and General Electric (GE Medical Systems, Milwaukee, WI), respectively. It is important to distinguish these two systems, and MRg HIFU in general, from ultrasound-guided HIFU. Available ultrasound-guided systems include Sonoblate 500 (US HIFU, Charlotte, NC), Ablatherm (EDAP TMS, Vaulx-en-Velin, France), and Haifu JC Focused Ultrasound Tumor Therapeutic System (HAIFU^{TM} Technology Company, China). While ultrasound is relatively inexpensive and widely available, it is an inferior method for HIFU guidance because it lacks the precise targeting of MRI, does not allow for thermometry other than the crude detection of cavitation/boiling, and is not stereotactic so that cumulative targeting and tracking of the treated volume becomes problematic. This lack of sophistication likely accounts for the disturbingly high rate of complications seen after ultrasound-"guided" HIFU. In a study of ultrasound-guided HIFU of uterine fibroids, gross hematuria was seen in 19 of 145 patients, presumably due to unintended or unappreciated bladder heating [3]. In a review of whole gland ultrasound-guided HIFU treatment of the prostate, the impotence rate was 20 %–61 %, the incontinence rate was 0.6 %–14.6 %, and the rectourethral fistula rate was 0.7 %–1.2 % [4]. These complication rates appear unacceptably high for a treatment that is intended to be minimally invasive and of low morbidity.

MRg HIFU for uterine fibroids

Background

Uterine leiomyomata or fibroids are benign smooth muscle tumors of variable size and number that affect up to 60 % of women by age 45 years [5, 6]. Depending on size, location, and number of fibroids, common symptoms include pelvic pain and pressure, mass-effect on the bladder or bowel leading to frequent urination and constipation, and excessive menstrual bleeding (menorrhagia), which can lead to anemia. In 10 %–20 % of patients with fibroids, symptoms are severe enough to require treatment. The most common treatment is hysterectomy, and nearly 200,000 hysterectomies are performed for fibroids every year [7]. While hysterectomy provides definitive relief of symptoms, many women want uterine-sparing therapies that allow for more rapid recovery and resumption of usual activities compared with hysterectomy. Women may also wish to preserve their fertility or have concerns that hysterectomy impairs pelvic floor or sexual function [8, 9]. More recently, hysterectomy has been associated with long-term urinary incontinence [10]. Alternative uterine-preserving options include myomectomy, uterine artery embolization, and medical treatment. Myomectomy may be performed hysteroscopically or by laparoscopy or laparotomy, but all these approaches are invasive and have the costs and risks of surgery. Uterine artery embolization is somewhat invasive, involves ionizing radiation, and may cause premature menopause [11]. The latter may be due to unintentional "collateral damage" to the ovaries during the procedure. Medical treatment with hormonal manipulation using gonadotropin-releasing hormone agonists can be used to reduce blood supply and shrink fibroids, but are not recommended for more than 6 months of use. These agents act by inducing menopause but may cause osteoporosis with long-term use and are accompanied by the symptoms of menopause which may often be less tolerable than the symptoms of the fibroids. In addition, fibroids generally resume growth after treatment. Given these considerations, MRg HIFU could be an attractive non-surgical treatment option for many patients with fibroids.

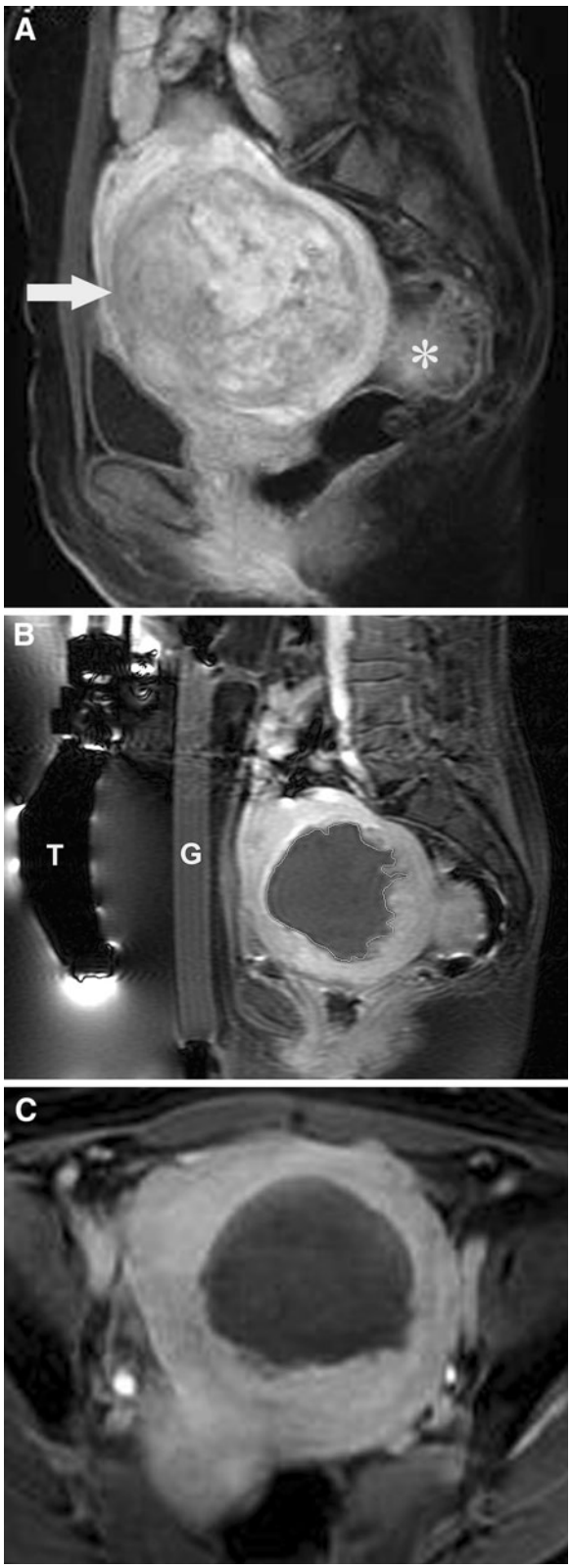
Patient selection

Patients should be carefully evaluated before the performance of MRg HIFU. Clinical and radiological considerations include the following.

Symptom severity. The uterine fibroid symptom and health-related quality of life questionnaire is a validated instrument to quantify bleeding, bulk, and other symptoms due to fibroids. [12]. The questionnaire consists of an 8-item symptom severity scale and 29 health-related quality of life items related to concern, activities, energy/mood, control, self-consciousness, and sexual function. All items are scored on a 5-point scale, so the raw symptom severity score can range from 8 to 40 (i.e., the 29 health-related quality of life items do not contribute to this score). The symptom severity score is usually converted to a 0–100 point scale, using the equation:

$$\text{Transformed score} = (\text{Total raw score} - 8)/32 \times 100$$

This score can be used to evaluate symptom severity and appropriateness for MRg HIFU treatment. For example, a symptom severity score of ≥41 on the UFS-QOL was a requirement for entry into the first major multicenter trial of MRg HIFU for treatment of fibroids [13]. While rigid use of this scoring system may not be appropriate in every case, clinical assessment of symptoms and likely etiology is always required. For example, a solitary 3 cm intramural fibroid is unlikely to be the cause of urinary frequency in a 49 year woman, and treatment with MRg HIFU would not be indicated. It should also be noted that other methods can be used to quantify symptoms



◀ **Fig. 1.** **A** Sagittal gadolinium-enhanced T1-weighted MR image in a 44-year-old woman complaining of both bulk symptoms and menorrhagia demonstrates a large enhancing fibroid (*arrow*) that is appropriate for treatment for MRg HIFU. An exophytic fibroid (*asterisk*) is too posterior for HIFU treatment. **B** Sagittal gadolinium-enhanced T1-weighted MR image immediately after MRg HIFU. The large fibroid (outline manually traced to allow calculation of non-perfused volume) demonstrates almost complete non-enhancement, indicating successful treatment. The patient is prone on the MRI table top, and the HIFU transducer (T), which is immersed in an oil bath, is visible. The patient is acoustically coupled to the transducer by a gel pad (G) and a water bath. **C** Axial gadolinium-enhanced T1-weighted MR image 3 months after treatment shows the large fibroid remains non-enhancing and has shrunk in size, reflecting at least intermediate term durability of HIFU treatment response. Symptomatically, the patient reported a significant reduction in both bleeding and bulk symptoms.

due to fibroids. For example menstrual blood loss can be quantified using the alkaline hematin test [14]. This procedure involves treating soiled sanitary towels and tampons with sodium hydroxide solution, which converts hemoglobin to hematin, which is measured. However, the alkaline hematin method is not routinely used in clinical practice because it is cumbersome, labor-intensive, and time-consuming. More commonly, clinical assessment of consistent menorrhagia which results in anemia is used as an indication to proceed with medical or surgical therapy for fibroids.

Menstrual and fertility status. The ExAblate system was approved by the Food and Drug Administration for commercial treatment of uterine fibroids in 2004 [15]. Conditions of use include a requirement that patients should be pre or perimenopausal and that "Patients *must* …have completed child bearing". This later requirements reflects the unknown effect of MRg HIFU on pregnancy and concerns that the procedure might weaken or damage the uterine wall and predispose to uterine rupture during labor or result in other pregnancy complications. In 2009, a premarket approval supplement relaxed this wording slightly to the more ambiguous: "Patients *should* have completed child bearing." [16]. While theoretical, the risk of uterine rupture during labor after previous MRg HIFU seems legitimate, since this complication has been described after myomectomy [17]., and with respect to uterine weakening, it seems reasonable to consider myomectomy and MRg HIFU to be potentially analogous. However, the absolute risk after myomectomy appears low, with only one rupture in a series of 92 deliveries after myomectomy [18]. In addition, a series of 22 pregnancies progressing to delivery after previous MRg HIFU has been described and the results are reassuring—14 patients had uncomplicated vaginal deliveries and 8 had uncomplicated cesarean sections [19]. Arguably, MRg HIFU might be an appropriate alternative for women with non-hysteroscopically resectable uterine fibroids who plan future pregnancy. A clinical trial to recruit such patients with randomization

to myomectomy or MRg HIFU was started in 2008, but was terminated due to poor recruitment [20]. Unfortunately, until adequate data exists, the recommendation to reserve MRg HIFU for those women who have completed childbearing should persist at this time.

MRI safety. Standard MRI contra-indications apply to patients considering MRg HIFU such as ferromagnetic intracranial aneurysm clips, intraocular metallic fragments, or severe claustrophobia. Fibroid enhancement before and after therapy is critical in patient selection and assessment of treatment response (Fig. 1), so MRg HIFU cannot be performed in patients with contraindication to intravenous gadolinium administration such as impaired renal function or prior severe allergic reaction to gadolinium-containing contrast medium. Finally, patient weight must be below the system table limit (250 lbs for ExAblate and 310 lbs for Sonalleve).

Ultrasound safety. MRg HIFU is contraindicated if certain structures (e.g., scar, skin fold or irregularity, bowel, pubic bone, intrauterine device, surgical clips, or any hard implants) will be in the path of the ultrasound beam. In particular, cesarean section scars can be problematic. Scars predispose to burns, probably because of preferential heat deposition in fibrous tissue combined with reduced sensation. Bowel, bone, the umbilicus, and surgical scars cannot be in the beam pathway.

Fibroid and uterine factors. Fibroids must be both appropriate and accessible for MRg HIFU. In general, treatment volume should not exceed 500 cm^3, because the time required for fibroid ablation in a single session is excessive. Larger volumes can be considered by scheduling multiple sessions or by preshrinking the fibroids with GnRH analogs. Peripherally calcified fibroids will reflect the ultrasound beam and are not treatable. Spontaneously infarcted fibroids, as manifested by nonenhancement at MRI, are also not suitable. It has been noted empirically that fibroids of high T2 signal intensity are difficult to heat successfully and should be considered at least a partial contraindication [21]. Interestingly, such high T2 signal intensity fibroids appear to be relatively more responsive to uterine artery embolization [22]. Imaging findings suggesting uterine enlargement is primarily due to adenomyosis and not fibroids or suggesting the presence of gynecologic malignancy are also contraindications to MRg HIFU for uterine fibroid treatment (but as will be discussed below, adenomyosis might be amenable to MRg HIFU). All of these factors require a pretreatment contrast-enhanced pelvic MRI as part of the patient workup. Fibroids that lie too posteriorly in the pelvis (typically 12 cm or more from the skin surface of the anterior abdominal wall) are also typically not treatable by HIFU, because they lie beyond the range at which heating can be successfully achieved.

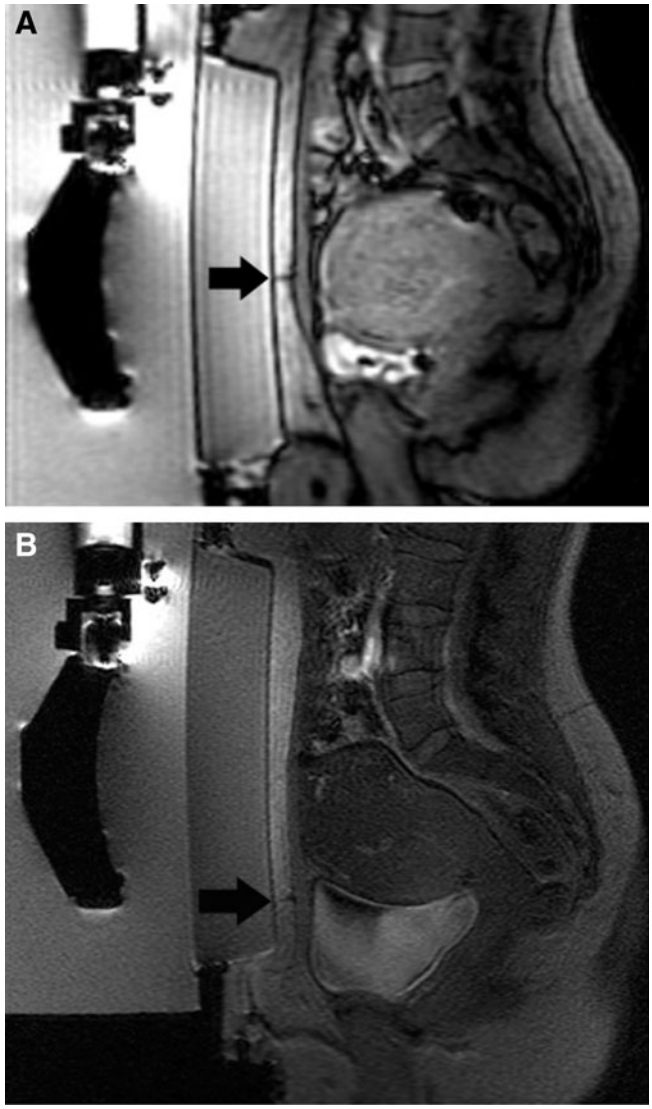


Fig. 2. **A** Sagittal steady-state gradient echo scout MR image in a 46-year-old woman with symptomatic uterine fibroids and a remote history of hysterectomy performed outside the United States. An unusually high location of the scar (*arrow*) is such that HIFU of the fibroid cannot be performed, because the scar would be in the beam path. **B** Sagittal steady-state gradient echo scout MR image after filling of the bladder with 300 cm^3 of water. Bladder filling has elevated the fibroid above the scar (*arrow*) and MRg HIFU is now technically possible. A successful procedure was performed.

Technique

Both commercially available MRg HIFU systems combine a dockable MRI tabletop with a built-in high intensity focused ultrasound transducer. Patients lie prone on a water bath or gel pad over the transducer in the tabletop during imaging and treatment, which can take 3–5 h. The abdomen between the umbilicus and pubic bone should be shaved before the procedure, because tiny bubbles of air trapped by hair can act as a

nidus for heating and burns. Patients generally require moderate sedation to control pain and anxiety during the procedure. A Foley catheter is inserted so the bladder remains empty and the fibroid position remains constant. A preliminary set of images is acquired to localize the uterus. Occasionally, rectal or bladder filling will be required to obtain optimal acoustic access to the target fibroid (Fig. 2). The target volume or volumes are then manually drawn on the T2-weighted images by the operator and an initial set of individual treatment elements are generated by the system. Each element is a narrow cylinder. These can be tailored by the operator, either at the outset or during the procedure. Each focal treatment is known as a sonication and lasts 20–30 s. Required cooling times between sonications account for much of the procedure time. Thermometry during heating of each treatment element insures adequate tissue response, and is also used to track cumulative treatment volume. Typically, a treatment lasts for several hours and involves up to a hundred sonications.

Outcomes

Described endpoints are both radiological and clinical. From an imaging perspective, the primary measure of treatment success is the demonstration of non-enhancement in the fibroid on post-gadolinium images obtained immediately after the therapeutic portion of the procedure. Gadolinium is routinely administered at the end of the procedure so this non-perfused volume can be visualized and measured. The non-perfused volume can be expressed as a fraction of the total fibroid volume to quantify the degree of successful ablation. When reviewing scientific descriptions of the non-perfused volume, it is critical to note whether the investigators are reporting the non-perfused volume as a fraction of the individual treated fibroid or the total volume of fibroids in the patients, since both methods have been used in the published literature [1, 13]. Using total fibroid volume as the denominator can make the results of MRg HIFU seem less impressive, but is probably the more honest and clinically meaningful approach. The non-perfused volume ratio is an important endpoint not only because it indicates early technical success but also because it correlates with longer-term and more meaningful endpoints such as symptomatic improvement and fibroid involution [1].

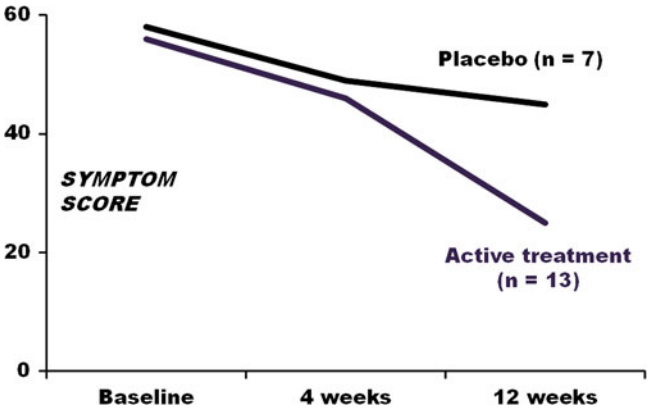


Fig. 3. Results of a placebo controlled trial comparing the change in uterine fibroid symptom severity score at baseline, 4 weeks, and 3 months after randomization of 20 patients to either active treatment with MRg HIFU (n = 13, including one treatment failure). The study showed a non-significant trend toward improved outcome in women undergoing active versus sham treatment (p 0.20). Note that symptoms improved from baseline in the group who underwent a sham procedure, suggesting some of the symptomatic improvement is related to placebo effect.

Published studies indicate that treatment results in significant improvement in both bulk and bleeding symptoms related to fibroids, but are limited because of the lack of placebo control data and industry funding. Existing data is primarily derived from a cohort of 359 premenopausal women with symptomatic fibroids who underwent industry-funded MRg-HIFU in 7 sites worldwide [13, 23]. The potential biases of such industry-funded single-arm trial data have limited community acceptance of this management option by gynecologists and has also limited widespread reimbursement by payers for this modality. In particular, the reported 43 % decrease in fibroid symptom scores seem out of proportion to the more modest 10 %–20 % objective fibroid shrinkage that occurs after MRg HIFU [13, 23], raising the possibility of at least some degree of placebo effect. There is increasing public awareness of the placebo effect in medicine [24], and the need to perform randomized, blinded, studies with a placebo-treated arm. Many physicians and commentators believe the FDA approach to device approval is fundamentally inconsistent with the approach to drug approval; devices can be approved with single-arm data but drugs can only be approved with double-arm controlled trials [25]. The FDA appears to be moving toward a more coherent approval system for both drugs and devices, with a greater emphasis on control data for devices. For example, the FDA required that an ongoing trial of MRgFUS for the palliation of malignant bone pain include a sham arm [26]. Another concern is the increasingly recognized corrosive influence of industry sponsorship on the results of scientific studies [27–29]. Given such concerns, a pilot randomized trial of MRg HIFU was recently completed at UCSF, and confirmed that sham arm studies can be successfully conducted with this procedure. Twenty patients were recruited and randomized to active or sham treatment in a ratio of 2:1. The study also showed a non-significant trend toward improved outcome in women undergoing active versus sham treatment (Fig. 3) [30].

While symptomatic improvement after MRg HIFU is important, broader outcome measures also require consideration, such as cost-effectiveness, durability, and progression to secondary treatment options. For

example, the cumulative 5-year probability of reoperation for recurrent leiomyoma after myomectomy is 6.7 %–9.0 % [31, 32], while the reintervention rate for MRg HIFU after two years of follow up is 17.6 % (12 of 68). [33]. This is comparable to reported reintervention rates of 10 %–20 % at approximately 5 years after uterine artery embolization [34, 35]. The populations, methods, and endpoints of these studies comparing MRg HIFU and myomectomy are different, and while it may be unfair to judge a technology that remains in evolution, the results do suggest MRg HIFU may not be quite as effective or durable as myomectomy. It could be argued that hysterectomy will eliminate all fibroid-related symptoms with certainty and might be considered the gold standard with respect to definitive, rapid, and sustained symptom relief. That said, it is important to note that many women have a pre-existing preference for surgical or non-surgical management, and one size may not fit all comers.

Complications

Specific complications or side effects of MRg HIFU can be divided into near field, focal zone, and far field effects, in reference to the ultrasound beam path. While this is true across all applications, complications will be primarily discussed for treatment of uterine fibroids, since this application constitutes the vast majority of current clinical experience.

Near field. Skin burns may occur due to targeting of a site too close to the skin surface, or improper coupling due to local scars or skin irregularities. This risk is mitigated by cleaning and shaving the skin before treatment, to optimize acoustic coupling and by excluding patients with scars that prevent acoustic access. In a series of 109 patients, six (5 %) sustained skin burns, at least some of which were ascribed to poor shaving [23].

Focal zone. Patients commonly experience transient heating, pain, or uterine cramping during the sonication. This can be reduced by careful titration of moderate sedation medication. Patients are provided a stop button and can terminate each sonication at any time. Post-treatment discomfort is minimal and patients are usually mobile and ready to be discharged within an hour of finishing the procedure. This is in contrast to the post-procedural pain of uterine artery embolization. In one study, 46 of 62 patients undergoing uterine artery embolization reported severe pain after the procedure and the mean maximal in hospital verbal rating scale (0–10, with 0 being no pain and 10 being the worst pain imaginable) value was 7.7 [36] It is believed that the difference in post-procedural pain after MRg HIFU as against uterine artery embolization is due to the different methods of tissue destruction. Embolization causes painful ischemic necrosis while MRg HIFU causes relatively painless coagulative necrosis. This difference may also explain why fibroid expulsion is also exceptionally rare after MRg HIFU [37], even though it is a well-known complication of uterine artery embolization of submucosal fibroids [38]. The other major risk at the focal zone is improper targeting, with unintended damage to adjacent structures. A case of bowel perforation resulting in a lawsuit settlement of $2.7 million has been reported [39]. Careful attention during the procedure to make sure that the target is within a fibroid and that there has been no confounding movement of the fibroid is critical.

Far field. Nerve stimulation may cause back or leg pain in the far field, presumably due to heat absorption by the pelvic bones with heat conduction and damage to adjacent nerves. Occasionally, this can persist after the procedure. More serious neural injury is rare. In a series of 109 patients treated for fibroids [23], the overall rate of leg pain persisting for more than 10 days was 7 %. One patient with a posterior fibroid developed sciatic nerve palsy. The subject had substantial pain with each sonication, which she did not report during treatment. An EMG and MR-neurography were negative. The neuropathy resolved by 12-months. Review of all treatment images suggested the nerve itself was not directly sonicated but that heat transfer from the pelvic bones led to indirect injury of the nerve.

MRg HIFU for adenomyosis

Background

Adenomyosis refers to the ectopic presence of endometrial glands and stroma in the myometrium, which often results in reactive smooth muscle hypertrophy [40]. The disorder can be clinically problematic because the symptoms of painful or heavy periods may overlap with co-existent endometriosis or fibroids, diagnostic tests may be inaccurate, and there are limited surgical treatment options short of hysterectomy. The reported prevalence of adenomyosis ranges from 1 % to 70 %, depending on population selection and diagnostic criteria, but the mean epidemiological prevalence is likely 20 %–30 % [41].

Patient selection

While the published experience with MRg HIFU for adenomyosis is much more limited than for MRg HIFU for fibroids, similar general, MRI safety, and acoustic considerations apply to patient selection for both applications. For example, in one study, inclusion criteria were MRI confirmed symptomatic adenomyosis measuring between 3 cm and 10 cm in diameter in premenopausal patients over 18 years of age who were willing and able to undergo the procedure. [42].

Technique

The technique of MRg HIFU for adenomyosis is essentially the same as the procedure for MRg HIFU of fibroids, so that the volume of adenomyosis is identified and treated as if it was a fibroid.

Outcomes

Because adenomyosis and fibroids often cause similar symptoms, the UFS-QOL symptom severity score questionnaire is commonly used to quantify therapeutic response. In a study of 39 women undergoing MRg HIFU for symptomatic adenomyosis, the mean symptom severity score decreased significantly from 51.2 before pretreatment to 35.9 at 1 month and then to 24.0 at 24 months. [43]. In another study of 10 patients, a mean, statistically significant improvement of 5.7 points in symptom severity score was seen at 3 months compared to baseline [42]. By way of comparison, a study of 39 patients with long-term (3 years or more) follow up after uterine artery embolization for adenomyosis without fibroids demonstrated a mean reduction in symptom severity (on a scale developed by the authors) of 51 %–53 %. [44]. These results suggest MRg HIFU may be a relatively effective and competitive method for treatment of symptomatic adenomyosis.

Complications

While there is less published research on specific treatment of adenomyosis by MRg HIFU, the complications and side effects of MRg HIFU for symptomatic adenomyosis should be considered to be essentially the same as those for MRg HIFU of fibroids.

MRg HIFU for prostate cancer

Background

Prostate cancer is the second most common fatal cancer in American men. Despite this sizeable mortality, many cases of prostate cancer are subclinical, and microscopic foci of incidental prostate cancer can be detected in up to 40 % of men at autopsy [45]. Up to 29 % of patients undergoing radical prostatectomy for screening detected prostate cancer have indolent disease at pathological examination after surgery, based on established characteristics that predict a low risk of progression [46, 47]. That is, many men with prostate cancer have disease that is indolent or incidental and may be better managed by conservative approaches such as active surveillance or focal therapy [48–55], because treatment by the traditional definitive methods of radical prostatectomy or radiation is associated with substantial morbidity (including impotence, incontinence, and anorectal dysfunction) [56]. The widely used modified ''Epstein'' criteria (prostate-specific antigen level ≤10 ng/mL and/or prostate specific antigen density ≤0.15 ng/mL/g, clinical stage T1 or T2A, ≤one-third of biopsy cores positive for cancer, and absence of Gleason pattern 4 or 5 tumor on biopsy) to define patients who may be candidates for more conservative management have been developed [46], and 16.4 % (310 of 1886) of patients being diagnosed under current epidemiological conditions meet these criteria. However, only 9.0 % (28 of 310) of men with such ''very low risk disease'' opt for active surveillance [57], suggesting this is not an appealing option and that many patients would welcome a ''middle way'' using focal therapy that might avoid morbidity associated with more definitive therapy. Recent widely publicized studies suggest that prostate-specific antigen screening for prostate cancer has at most a limited effect on prostate cancer mortality [58, 59] emphasize the importance of providing a therapeutic option that is less nihilistic and more appealing to patients than active surveillance but less morbid than definitive surgery or radiation.

Focused ultrasound for prostatic ablation has a promising early track record. The first commercial focused ultrasound surgery machine (Sonablate 100, Focus Surgery, Inc., Milipitas, CA), which used ultrasound for guidance, was launched in Europe in 1994 to treat benign prostatic hyperplasia. A subsequent multicenter study documented that this was a relatively safe, effective, and durable treatment option [60]. Since then, a second ultrasound-guided focused ultrasound surgery device (Ablatherm, EDAP TMS Inc., France) has become available. Early trials have suggested that ultrasound-guided focused ultrasound surgery can also be successfully used to treat prostate cancer [4, 61–64]. Focused ultrasound surgery is currently an approved treatment for prostate cancer in Europe, Canada, South Korea, Australia, and elsewhere. However, while these early studies using ultrasound-guided focused ultrasound surgery have been encouraging in terms of endpoints reflecting tumor control, the results with respect to treatment morbidity are less promising. Rectourethral fistula has been reported in 0.7 %–1.2 % of patients, impotence in 20 %–61%, and incontinence in 0.6 %–14.6 % [4]. Such distressingly high side effects rates for a treatment that is intended to be minimally invasive almost certainly reflect inadequate and imprecise targeting of focused ultrasound surgery, resulting in unintended damage to the urethra, neurovascular bundles, or rectum. This explanation is supported by the high rate of side effects seen with prostate cryosurgery (another form of focal therapy which uses freezing rather than heating) in which treatment monitoring is also based on ultrasound, with its associated imprecision [65]. There are several reasons to hypothesize that MR-guided focused ultrasound surgery which will achieve equally efficacious focal tumor therapy while reducing these high complication rates. It is difficult to see sensitive structures such

as the urethra and the neurovascular bundles with ultrasound. Due to this poor visualization and imprecise treatment monitoring, these structures could inadvertently be ablated during ultrasound-guided focused ultrasound surgery. MRI provides superior visualization of the neurovascular bundles and the urethra, and provides real time thermometry during a sonication, greatly reducing the risk to these important structures. Ultrasound does not provide the thermal imaging capability of MRI during focused ultrasound surgery. Treatment effects on ultrasound imaging are visualized only as hyperechoic changes in the tissue—mainly a result of ultrasound backscatter and microbubble formation and not necessarily an indication of thermal ablation. Since ultrasound is unable to confirm whether adequate or precisely targeted thermal dose has been achieved during treatment, energy in excess of that needed for ablation is often used. Furthermore, without accurate tumor visualization and thermal dose confirmation, an ultrasound-guided focused ultrasound surgery therapy unnecessarily involves treatment of the whole gland, rather than the focal and precisely targeted therapy offered by MR-guided focused ultrasound surgery. MR thermometry has the ability to provide an accurate pixel-by-pixel temperature reading over time. Accurate MR-thermometry also permits monitoring of any unintended heating of vital structures.

Patient selection

Despite many conceptual advantages, there are two major hurdles to implementing a focal therapy program for prostate cancer. First, the correct subset of patients must be identified so that patients with indolent or subclinical disease may be offered the management option of active surveillance while patients with aggressive disease receive the appropriate radical treatment. This is a biologic question, and accurate risk stratification of patients with prostate cancer is a non-trivial challenge [66]. Second, assuming appropriate candidates can be clinically selected, the cancer must be correctly identified and precisely ablated during the focal therapy [67]. This is primarily a radiological problem. MR-guided focused ultrasound surgery seems best suited to patients with a visible dominant tumor at MRI, so that treatment is delivered to a tumor depicted by the same modality being used to guide therapy. This avoids the potential inaccuracies in "blindly" treating a designated portion of the prostate-based purely on positive biopsies. Previous studies have demonstrated that endorectal multiparametric MRI may improve tumor localization, staging, and volume estimation to allow non-invasive identification of prostate cancer [68–70], but it is unknown whether and how these techniques can be used to select patients eligible for focal therapy by detecting the dominant intraprostatic tumor focus. Ideally, MR targets would be identified with high sensitivity and specificity. At a minimum, it seems reasonable to require that dominant tumor sites should be identified with high certainty when selecting patients for MR-guided focused ultrasound surgery. The rationale for this statement is that focally treating a false positive tumor with an investigational device rather than conventional treatment is problematic since the true site of dominant disease would presumably be untreated. Conversely, not offering investigational therapy to patients with uncertain dominant tumor foci seems reasonable, since they are still candidates for any established treatment regimen and have not been denied any standard treatment. A recent study of 88 patients who underwent endorectal multiparametric MRI before radical prostatectomy showed all visible tumor foci seen by either of two readers ($n = 42$ and 48, respectively) on T2-weighted images associated with at least 0.54 cm^3 of concordant spectroscopic imaging abnormality were correctly identified dominant treatable intraprostatic tumor foci [71]. In a subsequent study using this criterion in 20 patients, all 9 tumor foci independently identified by both readers as treatable did correspond to histopathological tumor foci but 5 lesions identified by only one reader, but not both, were all false positives [72]. This suggests that identification of treatable tumor foci before MRg HIFU for prostate cancer should require both multiparametric AND independent multi-reader confirmation.

Technique

The two MRg HIFU systems currently available have taken different approaches with respect to treatment of prostate cancer. The Insightec system uses an endorectal probe which combines a phased-array ultrasound transducer for precisely targeted treatment, an imaging coil, and a cooling system to prevent rectal damage. The Philips system uses a urethral device [73, 74]. Arguments can be made for and against both approaches. The rectal approaches may provide greater geometric flexibility and shaping of the target volume. The urethral approach may be faster and less likely to injure the rectum, but may not be as flexible with respect to working around the neurovascular bundles. It may be that both approaches should be available, with the final choice of a rectal or urethral approach being made depending on the location and shape of the tumor target in each individual patient. Irrespective of approach, another important factor is determining the correct margin when planning treatment based on an MR-defined tumor volume. In a study of 20 patients with prostate cancer who underwent endorectal multiparametric MRI before radical prostatectomy, there was no error in defining the capsular border of the dominant tumor while on the non-capsular border, expanding the contour by 5 mm included 95 % of tumor volume initially excluded by the non-capsular MR

contour. [72]. This suggests adequate tumor coverage is achieved by expanding the treatment contour at the non-capsular margin by 5 mm.

Outcome

To date, most data on patient outcome after HIFU of prostate cancer is derived from populations treated with ultrasound-guided HIFU, with reported five-year biochemical control rates of 45 %–84 %. [75]. Longer-term studies looking at hard endpoints (development of metastatic disease and mortality) will be required to determine the true effectiveness of this approach, either as monotherapy for localized low risk disease or as combination therapy in conjunction with radiotherapy for higher risk disease. The potential role of "preheating" the prostate with HIFU before radiation is investigational, but has strong theoretical support. Hyperthemia is known to provide clinically meaningful supplementary benefit when combined with radiation [76], either because heating acts as a radiosensitizer or because of heat-related immune stimulation [77].

Complications

No published data exist on complication rates after MRg HIFU of prostate cancer, but based on experience with US-guided HIFU, potential complications could include bladder neck/urethral stricture, urinary tract infection, urinary incontinence, urinary retention, impotence, rectal burn, or rectourethral fistula [75].

Conclusion

MRg HIFU is an exciting new method of precisely targeted and controlled tissue ablation that offers a minimally invasive therapeutic option for several pelvic conditions, including fibroids, adenomyosis, and prostate cancer. The technology is potentially disruptive of current clinical practice patterns, and so wider adaptation will require multidisciplinary and multicenter investigations resulting in data demonstrating long-term efficacy and cost-effectiveness, in order to convince referring providers and third party payers that the approach should be added to our routine clinical armamentarium.

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