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Update on Clinical MR-guided Focused Ultrasound Applications

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SYNOPSIS

Focused ultrasound (FUS) can be used to thermally ablate tissue. The performance of FUS under magnetic resonance (MR) guidance enables aiming the focus at the target, accurate treatment planning, real-time temperature mapping, and evaluation of the treatment. This review updates several clinical applications of MR-guided FUS.

MR-guided FUS has a CE mark and FDA approval for thermal ablation for uterine fibroids and bone metastases related pain management. Thousands of uterine fibroid patients have successfully been treated with minor side effects. Technical improvements, increased experience, and the use of a screening MRI examination should further improve treatment outcome. When used for bone metastases and other bone diseases, thermal ablation leads to pain relief due to denervation, and debulking of the tumor.

The use of a hemi-spherical multi-element transducer and phase corrections have enabled application of FUS through the skull. Transcranial MR-guided FUS has received CE certification for ablation of deep, central locations in the brain such as the thalamus. Thermal ablation of specific parts of the thalamus can result in relief of the symptoms in neurological disorders such as essential tremor, Parkinson's, and neuropathic pain.

No CE mark or FDA approval has been obtained as yet for treatment of prostate cancer or breast cancer, but several approaches have been proposed and clinical trials should show the potential of MR-guided FUS for these and other applications.

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Keywords

Magnetic Resonance Imaging; Focused Ultrasound; Thermal ablation Prostate cancer; Uterine Fibroids; Bone metastasis pain management; Breast cancer; Brain disease

Focused ultrasound

Ultrasound is well known for its application as an imaging modality. To obtain an image, a transducer transmits acoustic waves through the body and receives their reflections at tissue interfaces. Another property of these acoustic waves is that the tissue through which they propagate will absorb their energy. This mechanism is the basis for thermal ablation by focused ultrasound (FUS). By focusing high intensity acoustic waves, the temperature in the focus will increase due to energy absorption by the tissue. At a temperature of approximately 56°C for one second, irreversible cell death by coagulative necrosis will occur. Furthermore, blood in small vessels can coagulate and stop the blood perfusion¹. To reach these temperatures, usually an equal amount of ultrasound energy is applied continuously. As the energy absorption in the ultrasound beam path is lower, the surrounding tissue is spared.

In addition to thermal effects, the tissue can also be damaged through inertial cavitation. Ultrasound waves cause compression and rarefaction of the tissue and during the latter, gas can be drawn out of solution and bubbles can be created. These microbubbles will be compressed and expanded by the ultrasound and can collapse (inertial cavitation), leading to cell damage. Nucleation of such microbubbles can enhance the energy absorption and heating in the focus, a mechanism called enhanced sonication. During an enhanced sonication protocol, short bursts at a very high power are used to form microbubbles in the focus. These microbubbles interact with the acoustic waves, which increases the absorption of energy in the target². To date, thermal ablation is the primary clinical application for FUS.

MR guidance

By performing FUS under image guidance, the target (e.g. tumor) can be localized and the ultrasound focus can be aimed at this target. Two techniques that enable image guidance are ultrasound and magnetic resonance imaging (MRI). The initial FUS treatments were performed under ultrasound-guidance as this technique is relatively inexpensive and has a high temporal resolution. However, the options for treatment planning and monitoring are limited. MRI has excellent soft tissue contrast, allowing for three-dimensional treatment planning. Furthermore, real-time temperature information can be obtained enabling monitoring of thermal damage to ensure coagulative necrosis. After the sonication, MRI can be used to assess treatment response, for example, with contrast-enhanced T1-weighted imaging. The contrast agent, gadolinium, does not reach the necrotic tissue as the blood vessels are damaged. In contrast to well-perfused tissue, no increase in signal intensity on post-contrast T1-weighted images is observed in the necrotic tissue. The percentage of non-perfused volume (NPV) of the target volume can be determined, which can be an indication

of the success of the treatment. In this review, we update the current clinical applications of MR-guided FUS.

Uterine fibroids

Uterine fibroids are common benign tumors in the uterus that can cause abnormal uterine bleeding, pelvic pain, and infertility, but are usually symptomless³. The ExAblate 2000 (InSightec Ltd., Tirat Carmel, Israel) has received both the CE mark (2002) and FDA approval (2004) for the treatment of uterine fibroids. In 2009, Sonalleve (Phillips Healthcare, Vantaa, Finland) received the CE mark. Both FUS systems consist of extracorporeal multi-element phased-array transducers that are built into a special MR-table. They operate at a frequency between 0.95–1.35 MHz (ExAblate) and 1.2–1.5 MHz (Sonalleve) and can be used in combination with 1.5 and 3.0T MR-scanners.

Since the FDA approval in 2004, thousands of patients have been treated, and several follow-up studies have been performed^{4–6}. The success of treatment has been evaluated based on the volume change of the fibroids, improvement of symptoms, and the re-intervention rate. For patients with a higher NPV after the treatment, a lower risk of additional treatment was observed within one to five years post treatment^{5–7}. The same holds true for older patients who have a lower risk for re-interventions^{5,6,8}. Based on pre-treatment T2-weighted MRI, fibroids can be classified into three types: 1) fibroids that appear hypo-intense, 2) fibroids that are iso-intense and 3) fibroids that are hyper-intense in relation to skeletal muscle^{4–6,9}. The NPV of patients with type 3 uterine fibroids was lower than types 1 and 2 fibroids⁴, and these patients required re-intervention significantly more often than types 1 and 2^{5,6}. An example of a successful treatment of a type 1 uterine fibroid is shown in Figure 1. FUS therapy may not be suitable for type 3 fibroids and MR screening can be used to exclude these patients from FUS treatment. Patients who received neo-adjuvant therapy with gonadotropin-releasing hormone agonist (GnRHa), a therapy that decreases the vascularity of the fibroids¹⁰, had significantly larger NPV at the same applied energy¹¹ and a lower risk for additional therapy⁵. In a five-year follow-up study, an overall re-intervention rate of 58.6% was reported⁵. When only patients with a NPV larger than 50% were included, the re-intervention rate decreased to 50%. Insights and experience from the initial treatments have led to adaptation in patient selection and improvements in the FUS-system with the expectation that long-term outcomes should improve accordingly.

In the initial treatments, long cooling periods between sonications were used to prevent thermal build-up along the ultrasound beam path for multiple overlapping sonications. A new strategy to reduce the cooling period to 22 seconds⁶¹ is the “interleave mode” in which the overlap between sonications is minimized by changing the order of the sonications so that the energy absorption in the beam path is decreased¹². In the new generation ExAblate system, the transducer can be elevated to minimize the distance from the abdominal wall. This leads to an increase in the maximum energy in the focus and reduces the energy absorption in the near- and far-field. To limit adverse effects in the beam path, selective transducer elements are automatically disabled if vital structures such as the bowels, bladder, or sciatic nerves are detected in the beam path¹³. In a recent study with 115 patients, these technical improvements, increased experience, and the use of a screening

MRI examination have improved the NPV to an average of 88%¹³, but follow-up data is not yet available. In this study, patients with hyper-intense fibroids on T2-weighted imaging (type 3) were excluded.

An early limitation of MR-guided FUS for fibroids was the long treatment time, often several hours. Both the ExAblate and Sonalleve systems use phased arrays to electronically steer the beam to enlarge the ablated volume during each sonication. The Sonalleve device also has closed-loop feedback, which modulates the power output based on real-time temperature measurements so as to optimize treatment delivery. The technique, along with the “interleave mode” used with the ExAblate system, has increased the treatment rate and reduced treatment times.

In general, the adverse effects after treatment are minor, e.g., transient abdominal pain, mild skin burns, back pain, nausea, and nerve irritation^{5–7,14,15}. In very few cases, serious complications were observed: skin burn requiring repair, fibroid expulsion, persistent neuropathy, and abdominal burn^{5,16}. An area that requires more research is the effect of FUS on fertility. Several studies report successful pregnancies following MR-guided FUS treatment^{17–19}, but there has been no study evaluating the effect on fertility of different treatments for uterine fibroids. A clinical trial will compare the safety and effectiveness of MR-guided FUS and uterine artery embolization (NCT00995878-clinicaltrials.gov). Two additional ongoing clinical trials are (NCT01142791-clinicaltrials.gov), which is investigating the use of enhanced sonication to improve clinical outcome, and a multicenter phase two and three study using the Sonalleve system (NCT01504308-clinicaltrials.gov).

Bone metastases related pain management

The second MR-guided FUS application that received both CE and FDA approval is bone metastases related pain management. For this treatment, the ExAblate and Sonalleve (only CE mark) systems can be used. As cortical bone has high acoustic impedance, a great deal of energy is absorbed by the bone. Therefore, lower energies are applied in comparison to that used in uterine fibroid treatments. Two mechanisms for FUS-mediated pain relief are suggested. The temperature increase in the cortical bone leads to heating of the periosteal surface, which results in thermal damage to the periosteal nerves that are responsible for pain perception²⁰. The second mechanism is tumor debulking due to thermal ablation, which diminishes the pressure on the adjacent tissue. The observed pain relief immediately following sonication advocates for the first mechanism, but there is increasing evidence that tumor debulking also plays a role^{20–22}.

Several hundreds of patients have been treated who have exhausted, declined, or are unsuitable for other pain palliation methods. The success of the treatment can be evaluated based on changes in the pain scores, quality of life scores, and decrease in pain medication usage. A secondary measure is change in tumor size. In two multi-center trials, significant improvements in the pain scores without an increase in the pain medication were observed three months after sonication in 64% of 112²³ and 72% of 25 patients²⁴. In 67% of the patients, the dosage of pain medication was lowered²⁴. In addition to pain relief, necrosis and increase in the bone density were observed three months after FUS treatment^{21,22}.

Figure 2 shows the imaging data of a patient whose treatment led to complete pain relief and reduction in tumor size. There were small areas of NPV seen on post-contrast T1-weighted imaging after the treatment. The use of NPV to evaluate the success of treatment is limited²², and more research in the predictive value of this measure is needed. Generally, no^{20–22,24} or minor adverse events are observed²³. Observed adverse events included skin burns, sonication pain, fractures, neuropathy, post-treatment fatigue, and skin numbness²³.

MR-guided FUS also shows promise for pain relief in other bone diseases. In two studies, osteoid osteoma patients were treated and in 90–100% of the patients symptoms were completely resolved at a 6 to 12-month follow-up^{25,26}. Eighteen patients with facet joint osteoarthritis were successfully treated and a decrease in pain was observed together with an improvement in disability²⁷. Pain relief from osteoarthritis was also observed in six out of eight patients who were treated with MR-guided FUS for medial knee pain²⁸. No adverse events were observed in any of these studies, supporting the use of MR-guided FUS for bone pain management in a range of bone diseases.

Brain disease

Focused ultrasound has great potential for treating brain disease as the technique could be used to ablate targeted tissue without injuring the normal brain. In contrast, during conventional neurosurgery, damage to normal brain tissue is usually inevitable, especially when deep-seated brain structures are involved. The challenge for FUS in the brain is the high acoustical impedance of the skull. The high impedance leads to absorption of a great part of the applied energy, resulting in heating of the skull. This may, in turn, increase the temperature in the brain tissue adjacent to the skull. To minimize skull heating, a hemi-spherical design for the transducer is chosen so that the applied energy is distributed over a larger area²⁹. A lower operating frequency reduces absorption in the bone, at the cost of an increase focal size. It was determined that a frequency of approximately 700 kHz is optimal for transcranial FUS²⁹. Another issue concerning the acoustical impedance of the skull is the large difference between the skull's impedance and that of brain tissue. This difference leads to refraction of the acoustic waves and distortion of the focus. The focus can be restored by using many transducer-elements, each with an optimized phase³⁰. The required phase corrections can be calculated from x-ray computed tomography from which the spatial distribution of the skull thickness and density can be determined. Thermal ablation using FUS in the brain should be performed under MR-guidance as high-resolution anatomical images are a prerequisite for proper treatment planning. The ExAblate Neuro system (InSightec) consists of a hemi-spherical 1024-element phased-array transducer that operates at 650 kHz. This device has received CE mark for targets in the thalamus, sub-thalamus, and pallidum.

A precursor of this system (ExAblate 3000, 512 elements, 670kHz) was used to demonstrate, for the first time, the ability to focus therapeutic ultrasound through the skull into the brain³¹ (Figure 3). In three male glioblastoma patients, with tumors located relatively deep and central in the brain, it was demonstrated that the target tissue can be heated, while significant heating in the tissue close to the skull was prevented. As the researchers were limited by the power of the device (650–800 W), it was estimated that they

did not achieve coagulative necrosis. Extrapolation of their results suggests that this should be possible without overheating the tissue at the brain surface. However, the targetable regions may be limited to deep, central locations in the brain. This makes transcranial MR-guided FUS particularly suitable for treating neurological disorders such as essential tremor, Parkinson's, and neuropathic pain. Ablation of specific parts of the thalamus can result in relief of the symptoms in these diseases.

The feasibility of transcranial MR-guided FUS has been demonstrated for several neurologic disorders. The relief of symptoms and targeting accuracy were used to evaluate the success of the treatments. The lesions were highly visible 24–48 hours after the treatment as a hyper-intense region on T2-weighted imaging. By superimposing the stereotactic atlas of the human thalamus of Morel³² on the T2-weighted images, the accuracy of the treatment can be determined³³. Eleven patients were treated for neuropathic pain by ablating the posterior part of the central lateral thalamic nucleus with MR-guided FUS^{34,35}. The lesions were within a millimeter from the targeted region for all three planes. The pain relief one year after treatment was 56.9% (eight patients in follow-up). In another study, the ventral intermediate nucleus of the thalamus was ablated in 15 patients with severe, medication-refractory essential tremor³⁶. In all patients, this resulted in an improvement of the hand tremor score, the disability scores, and quality of life in a 12-month follow-up. A large, randomized multi-center trial to investigate the use of transcranial MR-guided FUS for the treatment of essential tremor is being undertaken (NCT01304758 - clinicaltrials.gov).

In 13 patients with therapy-resistant Parkinson's disease, the fiber tract between the pallidum to the thalamus was ablated³⁷. In these patients each target had to be heated four or five times to the targeted temperature to have a relief of symptoms. In nine patients, a reduction of 61% in the Unified Parkinson Disease Rating Scale was observed after three months. Although it was sufficient for the targets in the nuclei (grey matter) to reach the targeted temperature once for successful coagulative necrosis^{34,36}, the fiber tracts, consisting of axons protected by myelin sheaths, may need a stronger thermal ablation³⁷.

Compared to other techniques for ablating thalamic nuclei, MR-guided FUS has no risk of intracranial infection and is not limited by trajectory constraints for reaching the target. In general, the adverse events were minor and transient, e.g., paresthesia of the lip, tongue, or finger, ataxia, and an unsteady feeling. In four patients, the paresthesia was still present after 12 months³⁶. In one patient, a bleed with ischemia occurred in the motor thalamus resulting in dysmetria, which gradually decreased over time³⁴. Jeanmonod, et al. recommend the installation of a cavitation detector and the use of sonication temperatures below 60°C to prevent future bleedings³⁴. This detector is now implemented in every treatment.

In addition to symptom relief in Parkinson's disease, essential tremor and neuropathic pain, other applications are conceivable as well, such as epilepsy, trigeminal neuralgia and psychosurgery³⁸. The treatment of glioblastoma may not be the best clinical application due to its infiltrative nature³¹, but tumors with well defined-margins such as metastases might be. However, use for tumor ablation will be limited based on the treatment time and limitations on which brain regions can be targeted for thermal ablation. Currently, only central targets within the brain can be safely sonicated without overheating the skull.

Another approach to treating brain tumors and other brain diseases is the use of transcranial MR-guided FUS to disrupt the blood-brain barrier. This barrier prevents delivery of almost all therapeutic agents to the brain. Low intensity FUS in combination with circulating microbubbles can temporarily (~4 hours) disrupt the blood-brain barrier without apparent damage to the brain. Large molecules, such as antibodies, have been successfully delivered in animal models^{39,40} and a 1024-element ExAblate system operating at 220 kHz has been used successfully in rhesus monkeys to disrupt the blood-brain barrier⁴¹. Another application for transcranial FUS is neuromodulation. In volunteers, a 0.5-MHz transducer was used to stimulate the primary somatosensory cortex. This resulted in significant attenuation of the somatosensory evoked potentials and enhanced performance of sensory discrimination tasks⁴². Future research will show the clinical applicability of MR-guided FUS for neuromodulation, blood-brain barrier disruption, and a variety of brain diseases. Such treatments use lower-intensity sonications and will be able to target a larger portion of the brain.

Prostate cancer

FUS under ultrasound-guidance has been used for many years to treat prostate cancer. However, the ability to visualize the tumor with ultrasound is very limited, and considerable variability in the occurrence of adverse events has been reported⁴³. MRI is the method of choice for depicting prostate lesions and a multi-parametric approach is recommended⁴⁴. There is increasing interest in performing prostate cancer thermal ablation under MR guidance due to the superiority of MR in tumor localization and thermometry. The location of the prostate in the body makes it approachable from two body cavities, leading to a transrectal and a transurethral approach. To date, there is no CE or FDA approval for these methods, but their clinical use is being investigated in several centers.

For the transrectal approach, the Exablate 2100 system can be used with a 990-element rectal transducer. After placement of the transducer in the rectum, the probe is filled with degassed water at 12°C to cool the rectal wall and eliminate air between the rectum and the transducer. In 2012, the first case report described the treatment of a low risk tumor without any adverse events one month after treatment⁴⁵. Napoli et al. treated five patients prior to a radical prostatectomy⁴⁶. They showed good correlation between the region of thermal damage (based on MR thermometry) and the non-perfused region based on contrast-enhanced T1-weighted imaging (Figure 4). Furthermore, on histopathologic sections, extensive coagulative necrosis was observed in the treated region surrounded by a rim of inflamed tissue. However, in all patients, additional tumors (either significant or non-significant) that were not evident on the pretreatment MRI were present outside the treated area.

In-house built^{47,48} and the PAD-105 (Profound Medical Inc., Canada) transducers have been used for the intra-urethral approach. Transurethral ultrasound ablation (TULSA) uses high-intensity unfocused ultrasound. A probe with multiple small transducers is inserted into the urethra and can be rotated 360° at a variable rate to treat the desired region in the prostate. Degassed water runs through the transducer for cooling and coupling, and a cooling device is placed in the rectum. In a feasibility study of eight patients, a 180° angular target around

the urethra was sonicated (at 8 MHz) prior to a radical prostatectomy⁴⁸. A spatial temperature feedback algorithm⁴⁹ was used to ensure that a temperature of 55°C was reached at the boundary of the target. A challenge for MR thermometry in the prostate is not only the movement of the bowels, but also motion of air in the bowels, which can affect the local magnetic susceptibility. Preliminary results from a phase one clinical trial with the PAD-105 in which the entire prostate was sonicated, demonstrated a high correlation between the NPV and spatial temperature maps⁵⁰. No cases of incontinence, fistulas, or rectal injury were reported in these 16 patients after a one-month follow-up. The advantage of treating the entire prostate is that it deals with the heterogeneous and multifocal nature of prostate cancer.

Both the transurethral and transrectal approaches show high correlation between the thermal damage based on MR thermometry and the observed histopathologic effects^{46,48}. These initial results make MR-guided FUS a promising method for a non-invasive treatment of prostate cancer..

Breast cancer

Breast tumors are well suited for MR-guided FUS treatment as they are superficial and can be accessed relatively easily through the skin. The tumors are well defined on contrast-enhanced T1-weighted imaging. In 2001, the first MR-guided FUS ablation of breast fibroadenomas⁵¹ and invasive ductal carcinoma⁵² took place. Since then, several hundred patients have been treated. In many of the patients, FUS treatment was followed by surgery^{52–55} and the effect of the treatment could be evaluated based on histopathology. The success of the treatment was variable with complete necrosis of the tumor in 16.7% to 54% of the patients^{53–57}. Best results were obtained when the contrast-enhanced MRI to outline the tumor was acquired immediately before the start of the treatment⁵⁷ instead of during a separate MR exam. Retrospective analysis showed that in some cases of incomplete tumor necrosis, not all recommended treatment margins were treated. This can be prevented by ensuring that the entire tumor is sonicated with an additional 5-mm safety margin⁵⁷. In other patients, the success of the treatment was evaluated by follow-up MRI^{51,58} or biopsy⁵⁹. The treated region is dark and non-enhancing on contrast-enhanced T1-weighted imaging (Figure 5). A high correlation between several parameters from dynamic contrast-enhanced MRI and the percentage of viable tumor was observed⁵³. When contrast-enhanced MRI was used to evaluate the treatment, one should be aware that immediately post-treatment, an enhancing rim around the treated area could be observed (Figure 5). This edema disappeared several days after treatment⁵⁷. In 20 of 21 patients treated with MR-guided FUS, no recurrence was observed on MRI or ultrasound 3 to 26 months after treatment⁵⁸.

Severe and minor adverse events have been reported. These ranged from third degree skin burns, allergic reaction to the plastic material, sonication-related pain and posture-related pain⁵⁷.

For the initial studies, a focused transducer operating at 1.5 or 1.7 MHz was used and moved with a positioning system to treat the tumor^{51,52}. It is expected that in the near future, the Exablate 2000 system can be used with a multi-element phased-array transducer to steer the

focus⁵⁴. A transducer in which the ultrasound beams target the breast from the lateral sides, potentially diminishing heating in critical structures such as the ribs, heart, and lungs, has been developed for the Sonalleve system, but to date, no clinical data have been published⁶⁰. These systems do not yet have FDA or CE approval for treating breast cancer. Clinical trials (e.g. NCT01620359 - clinicaltrials.gov) are expected to demonstrate the clinical value of MR-guided FUS for breast tumors.

Summary

MR-guided FUS has FDA and CE approval for the treatment of uterine fibroids and pain management for bone metastases and the CE mark for transcranial MR-guided FUS for targets in the thalamus, sub thalamus, and pallidum. There is promise for thermal ablation of breast and prostate tumors; however, the excellent soft tissue contrast of MR, the availability of MR-thermometry, and the non-invasiveness of the treatment make MR-guided FUS a potential treatment for many more diseases. Multi-center trials and long follow-up studies have demonstrated the effectiveness and safety of MR-guided FUS to treat uterine fibroids and this has led to improvements in the system, treatments, and patient selection. For other applications, these trials are ongoing or need to be initiated so as to optimize treatments. The clinical value of developments such as targeted drug delivery by blood-brain barrier disruption, enhanced sonication, and neuromodulation needs to be demonstrated.

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Key Points

- Thousands of uterine fibroid patients have successfully been treated with MR-guided FUS, leading to technical improvements and increased experience to further improve clinical outcome.
- MR-guided FUS has been approved to bring thermal damage to the periosteal nerves, which leads to pain relief from bone metastases and other bone diseases.
- Thermal ablation of specific parts of the thalamus with transcranial MR-guided FUS can lead to symptom relief in several neurological disorders.
- MR-guided FUS can be used for more clinical applications, e.g. breast and prostate cancer, but clinical trials are needed to prove its potential.

Figure 1.

A 45-year-old woman with a 418-cm³ fibroid experiencing gradually worsening pelvic pressure and hypermenorrhea. A) Sagittal T2-weighted MR image obtained before treatment shows predominantly hypo-intense fibroid (type 1). B) Sagittal contrast-enhanced fat-suppressed MR image before treatment shows homogeneous enhancement of vital fibroid tissue. C) Sagittal contrast-enhanced fat-suppressed MR image acquired immediately following treatment shows a completely non-perfused fibroid tissue.

[From Trumm CG, Stahl R, Clevert D-A, et al. Magnetic Resonance Imaging–Guided Focused Ultrasound Treatment of Symptomatic Uterine Fibroids: Impact of Technology Advancement on Ablation Volumes in 115 Patients. *Invest Radiol.* 2013;48(6):359–365, with permission.]

Figure 2.

Images of a 64-year-old woman with iliac bone metastasis from breast cancer. A) Axial computed tomography (CT) image shows the presence of a wide lytic lesion located in the right anterior superior iliac spine (arrows) with evidence of focal cortical erosion causing severe pain (pain severity score, 10). B) Axial T1-weighted sequence acquired following contrast agent injection at the end of the MR-guided FUS treatment shows the presence of some small areas of NPV (arrows) inside the lesion and at the periosteal margin. C) At the 2-month follow-up, axial CT identified the presence of some focal areas of de novo

mineralization inside the treated tissue with partial restoration of cortical borders (arrows). D) At 3 months post treatment, the lesion showed further de novo remineralization of the ablated tissue (arrows).

[From Napoli A, Anzidei M, Marincola BC, et al. Primary pain palliation and local tumor control in bone metastases treated with magnetic resonance-guided focused ultrasound. *Invest Radiol.* 2013;48(6):351–358, with permission.]

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Figure 3.

Screenshots from transcranial MR-guided FUS treatment planning workstation. A) Coronal T2-weighted images of the patient in the transcranial MR-guided FUS device. The target of the current sonication is indicated by the blue rectangle. The water filling the space between the patient's shaved head and the transducer can be seen. B) Pretreatment computed tomography (CT) scan data of the cranium is registered to the intra-treatment MRI scans. The cranium is automatically segmented from the CT scan and displayed as a green region on top of the MR images used for treatment planning. Any registration errors can be seen on these images and corrected by the user by using a graphical tool. MR tracking coils integrated into the transducer are used to register the transcranial MR-guided FUS system coordinates with the imaging coordinates. Acoustic models taking into account the patient-specific cranium geometry and density are used to correct for aberrations to the ultrasound beam. C) The beam paths for each phased-array element are superimposed on the images, allowing the user to verify that no beams pass through undesired structures. D and E) Pretreatment contrast-enhanced T1-weighted images, which can be useful for defining tumor margins, acquired the day before treatment can also be registered to the intratreatment images. Axial and sagittal images are also acquired, allowing for treatment planning in three dimensions. F) Sagittal T2-weighted image. [From McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. *Neurosurgery*. 2010;66(2):323–332; discussion, with permission.]

Figure 4.

A) Color-coded MR thermometry acquired during real-time MR-guided FUS treatment shows a definite area of temperature increase corresponding to $>60^{\circ}\text{C}$ (red area). B) A contrast-enhanced MRI scan acquired immediately after treatment shows an area of NPV in the exact location of the delivered sonication. The control MRI also shows the absence of rectal wall injuries or unexpected side effects. C) This macroscopic section after radical prostatectomy demonstrates an extensive coagulative necrosis at the site of sonication. D) This microscopic image (haematoxylin and eosin stained) demonstrates tissue necrosis with a peripheral layer of inflammatory infiltrates.

[From Napoli A, Anzidei M, De Nunzio C, et al. Real-time Magnetic Resonance-guided High-intensity Focused Ultrasound Focal Therapy for Localised Prostate Cancer: Preliminary Experience. *Eur Urol.* 2013;63(2):395–398, with permission.]

Figure 5.

T1-weighted contrast enhanced subtraction image pretreatment (top) and post-treatment (bottom). In the top image, the tumor (arrow) is clearly identified. In the bottom image, the tumor (arrow) is non-enhancing. The hyper-intense areas in the edges of the treated region are hyperemia.

[From Furusawa H, Namba K, Thomsen S, et al. Magnetic Resonance–Guided Focused Ultrasound Surgery of Breast Cancer: Reliability and Effectiveness. *J Am Coll Surg*. 2006;203(1):54–63, with permission.]