Update on Clinical Magnetic Resonance–Guided Focused Ultrasound Applications

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KEYWORDS

• MR imaging • Focused ultrasound • Thermal ablation prostate cancer • Uterine fibroids • Bone metastasis pain management • Breast cancer • Brain disease

KEY POINTS

- Thousands of patients with uterine fibroid have successfully been treated with magnetic resonance (MR)-guided focused ultrasound (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 neurologic disorders.
- MR-guided FUS can be used for more clinical applications (eg, breast and prostate cancer), but clinical trials are needed to prove its potential.

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 absorbs 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 increases as a result of energy absorption by the tissue. At a temperature of approximately 56°C for 1 second, irreversible cell death by coagulative necrosis occurs. Furthermore, blood in small vessels can coagulate and stop the blood perfusion.[1] To reach these temperatures, usually an equal amount of ultrasound energy is applied continuously. Because 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 are compressed and expanded by the ultrasound and can collapse (inertial cavitation), leading to cell damage. Nucleation of such microbubbles can enhance the

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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 target.[2] Thermal ablation is the primary clinical application for FUS.

MAGNETIC RESONANCE GUIDANCE

By performing FUS under image guidance, the target (eg, tumor) can be localized, and the ultrasound focus can be aimed at this target. Two techniques that enable image guidance are ultrasound and MR imaging. The initial FUS treatments were performed under ultrasound guidance, because this technique is inexpensive and has a high temporal resolution. However, the options for treatment planning and monitoring are limited. MR imaging 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, MR imaging 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, because the blood vessels are damaged. In contrast to well-perfused tissue, no increase in signal intensity on postcontrast T1-weighted images is observed in the necrotic tissue. The percentage of nonperfused volume (NPV) of the target volume can be determined, which can be an indication of the success of the treatment. In this review, the current clinical applications of MR-guided FUS are updated.

UTERINE FIBROIDS

Uterine fibroids are common benign tumors in the uterus that can cause abnormal uterine bleeding, pelvic pain, and infertility but are usually symptomless.[3] The ExAblate 2000 (InSightec, Tirat Carmel, Israel) has received both the CE mark (2002) and US Food and Drug Administration (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 multielement phased-array transducers, which are built into a special MR table. They operate at a frequency between 0.95 and 1.35 MHz (ExAblate) and 1.2 and 1.5 MHz (Sonalleve) and can be used in combination with 1.5-T and 3.0-T 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 reintervention rate. For patients with a higher NPV after the treatment, a lower risk of additional treatment was observed within 1 to 5 years after treatment.[5–7] The same holds true for older patients, who have a lower risk for reinterventions.[5,6,8] Based on pretreatment T2-weighted MR imaging, fibroids can be classified into 3 types: (1) fibroids that appear hypointense, (2) fibroids that are isointense, and (3) fibroids that are hyperintense in relation to skeletal muscle.[4–6,9] The NPV of patients with type 3 uterine fibroids was lower than type 1 and 2 fibroids,[4] and these patients required reintervention 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 **Fig. 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 neoadjuvant therapy with gonadotropin-releasing hormone agonist, a therapy that decreases the vascularity of the fibroids,[10] had significantly larger NPV at the same applied energy[11] and a lower risk for additional therapy.[5] In a 5-year follow-up study,[5] an overall reintervention rate of 58.6% was reported. When only patients with an NPV larger than 50% were included, the reintervention 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 seconds[12] 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 decreased.[13] In the new-generation ExAblate system, the transducer can be elevated to minimize the distance from the abdominal wall. This strategy 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 path.[14] In a recent study with 115 patients,[14] these technical improvements, increased experience, and