Feasibility of MR guided HIFU on a 7T animal MR scanner, to evaluate pathologic effects of high intensity focused ultrasound in mice

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Target audience: Researchers and clinicians who use high intensity focused ultrasound (HIFU) for tumor treatment.

Purpose: MR image-guided ablations have been developed for local tumor treatment. High intensity focused ultrasound (HIFU) is the only known non-invasive ablation technique available to deliver high energies in a millimeter-sized focus spot[1]. These large amounts of energy result in destruction through cellular disruption and irreversible coagulative necrosis within a few seconds. If correctly targeted, the energy of the ultrasound (US) beam penetrates the tissue without significant absorption or disruption until the beam reaches the focal spot.

The local effects of HIFU in tissue can be separated into thermal and mechanical effects[2]. Thermal effect is the consequence of absorption of ultrasound energy by tissue and conversion into heat. The rapid rise in temperature will induce irreversible damage and local coagulative necrosis. Mechanical damage is due to mechanical forces and acoustic cavitation without high temperature increase[3]. The large pressure differences of the US wave results in shear stress of the tissue, which can result in vascular and cellular damage of the tissue. Cavitation is the interaction between the US waves and microbubbles of gas in tissue, which results in local destruction of tissue without thermal damage.

These different mechanisms results in various ways of tumor destruction and can be created by different HIFU settings. The method of tumor destruction result in different tumor response. However, the best method of tumor destruction with HIFU is uncertain. To get a better understanding about the tumor response to different HIFU settings, animal studies (e.g. mice) are inevitable. For testing different HIFU setting in mice, a millimeter-sized HIFU focus spot should be used and image guidance with good spatial and contrast resolution is necessary to position and visualize the focus spot. Therefore, this study has been set up to examine the feasibility of MR guided HIFU in a 7T animal MR system, to investigate different settings and to evaluate the corresponding tumor outcomes.

Methods: C57Bl/6n wild type mice are subcutaneously injected with B16OVA tumor cells at the right femur. After 10-12 days a tumor size of >8x8mm is reached. A 3MHz, 16 channel phased array HIFU system (Image Guided Therapy -IGT-, Pessac, France) is placed in a 7T wide bore animal MR scanner (ClinScan, Bruker Biospin GmbH, Rheinstetten, Germany). An in-house made gel pad is placed at the membrane of the HIFU system in line with the transducer (figure 1). The mice are carefully positioned in the cavity (approximately 3.5x3.5x1 cm) of the gel pad, which is filled with degassed water for acoustic coupling.

Coronal and axial MR (T1) images are acquired to localize the tumor and transducer. These images are sent to the HIFU trajectory planner software (Thermoguide, IGT) to determine the treatment trajectory. After trajectory planning, the ablation is started. The ablation process is visualized using MR guided thermometry (FLASH sequence, proton resonance frequency shift method with TR/TE=40/4ms, flip angle 25°, 5 slices, 0.3mm inter-slice distance, voxel size 0.78x0.78x1.5 mm^3, 3.8s/dynamic, 0.5 °C temperature accuracy).

To investigate the different pathologic effects of HIFU ablation methods (thermal and mechanical), three different ablation strategies, with an acoustic energy of 43-46W, are applied (three mice per strategy). First method, continuous wave (CW) mode, four second ablation for each millimeter-sized focus spot. Second, pulsed wave (PW) mode, 120 shots of 20ms with a pulse repetition frequency of four. Third, a combination of method two followed by method one. The mice are sacrificed 2 days after ablation. The tumor is removed and used to determine local pathologic responses, using Hematoxylin and eosin-staining (H&E).

Results: With the use of the in-house made gel pad, the mice can easily be positioned inside the MR with good acoustic coupling between the transducer and the mice. No air bubbles are shown at the MR image (T1) within the US path. The temperature increase of each focus spot is visualized inside the tumor with MR thermometry (figure 2). The temperature increase is more than 25°C during CW-mode and less than 12°C during PW-mode. Which correlates to a local temperature of >62°C and respectively <49°C. These temperatures correlate with respectively thermal effects (necrosis) and mechanical effects (cavitation) in these mice. Two out of three mice of the CW-mode group and all three mice of the combined therapy group show large areas of necroses. These areas correlate with the temperature rise shown at the MR thermometry maps. All mice of the PW-mode group show a temperature increase of less than 12 °C. None of these mice show thermal effects, but two of the mice show respectively little and large indications of mechanical effects. Four mice (two, one and one of respectively CW, PW and combined mode group) show collapse of the tumor one or two days after treatment, due to cavitation or thermal heat underneath the skin. At the edge of these cavities there is a clear indication of necroses in the three mice of the CW and combined mode group (Figure 3). The cavity of the mice in the PW-mode group does not show any necroses at the edge or inside the tumor (Figure 4).

Discussion/conclusion: Based on the MR-thermometry it is shown that the focus can accurately be positioned inside the tumor. With the use of MR-guidance the position of HIFU treatment can be controlled and visualized, in both CW and PW mode. The temperature rise, determined with MR-thermometry, correlates with the thermal effects inside the tumor. In both CW and combined mode thermal effects are found. No thermal effects are found using PW-mode, but there are indications of cavitation. Some fine-tuning of the PW-mode is necessary but this study indicates that MR guided HIFU in mice with a 7T animal MR scanner offers potential to investigate different HIFU settings and their pathologic effects.

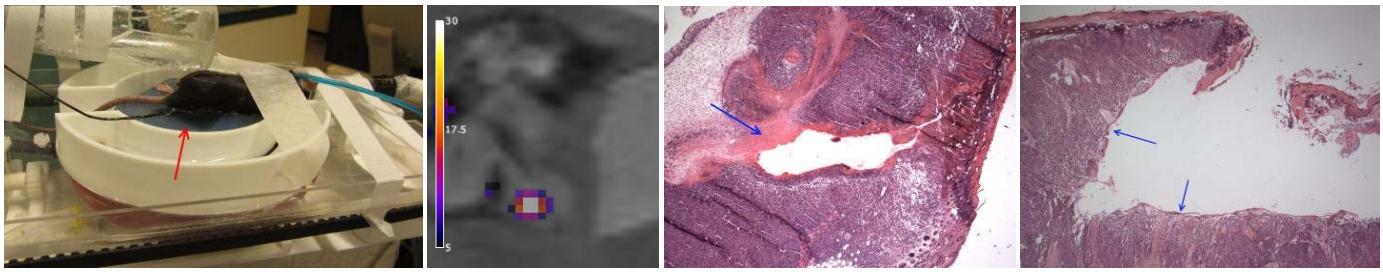

Figure 1: Mice set up at HIFU system with an in-house made gel pad (red arrow). Figure 2: T1 MR image of mice tumor treated with CW-mode with an overlay of the temperature map. Figure 3: H&E-stained sections of CW-mode, cavity with clear indication of necroses at the edge (blue arrow). Figure 4: H&E stained section of PW-mode, cavity without necroses at the edge (blue arrows).

References: 1. Jolesz FA. MRI-guided focused ultrasound surgery. *Annual review of medicine*. 2009;60:417–30. 2. Dubinsky TJ, Cuevas C, Dighe MK, Kolokythas O, Hwang JH. High-intensity focused ultrasound: current potential and oncologic applications. *American journal of roentgenology*. 2008;190(1):191–199. 3. Shehata IA. Treatment with high intensity focused ultrasound: secrets revealed. *European journal of radiology*. 2012;81(3):534–541.