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

Martijn Hoogenboom1, Martijn den Brok2, Erik Dumont1, Gosse Adema1, Arnd Heerschap1, and Jurgen Futere1,4
1Department of Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, 2Department of Tumor Immunology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, 3Image Guided Therapy, Pessac, France, 4MIRA Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, Overijssel, Netherlands

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. 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. Thermal effect is the consequence of absorption of ultrasonic 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. 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 result 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.

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 1ms pulse repetition frequency. 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 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.