MRgHIFU safety issue: Validation of targeting accuracy using an MR compatible ballistic model

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Introduction

Volumetric ablation has been investigated *in vivo* demonstrating that a large and uniform ablation zone can be obtained rapidly (1-2). However, there exists no experimental demonstration to show that such volumetric lesion is indeed centered on a specific predefined target in 3D, i.e. no "gold standard" proof of absence of thermal buildup drift during the sonication (3). The effective spatial control of the induced thermal lesion during fast volumetric ablation should be considered a major safety issue. Therefore before clinical trials, it is highly desirable to evaluate in animal models, the accuracy of the spatial control of ablation for a given volumetric HIFU sonication paradigm. We describe here a method to create a user-defined ballistic target to be used as an absolute reference marker that is both MR-compatible and MR-detectable, while also being a well-established histology staining method.

Material and Methods

A quality assurance method for pre-clinical studies is described here, based on the trapping of a mixture of MR contrast agent (Gadolinium) and histology stain (methylene blue) using localized energy deposition causing cell death and coagulation. As a result, the contrast agent/stain is encapsulated in the intracellular space. The marker fixation paradigm consisted of three steps: 1) RF coagulation (Fig1a): a dedicated RF electrode was designed to operate in monopolar mode using a clinical radio opaque intravenous (i.v.)-dedicated catheter as an active electrical source and a square 6cm^2 copper sheet in contact with the skin (*via* saline serum) as ground contact (RF clinical generator, Celon, Germany)), 2) injection via the needle of 0.2mL mixture of methylene blue (Patent Blue V Sodium 2.5%, Guerbet SA, France) doped with 0.75% gadolinium-DTPA (Dotarem, Guerbet, France), and 3) a second RF coagulation, identical to the first. This ballistic model was used here as a mimicking target for a "virtual" tumor-center to assess the spatial control of HIFU ablation *in vivo* on four New Zealand rabbit thighs (female, weight=3.5±0.5 kg). A high resolution T1w 3D gradient-echo (VIBE) acquisition (0.8x0.8x0.8mm^3, TE/TR/TA/FA/ BW =1.6ms, 4ms, 2.55min, 10°, 650Hz/Px, 50 sec scan time) was used to predefine the position of the ballistic target in the rabbit leg, far from bone/fascia.

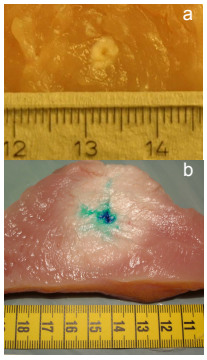

Fig1. (a) Macroscopic RF thermal lesion appearing as a white spheroid area of cooked tissue ex vivo in the pink meat sample background. (b) Macroscopic thermal lesion obtained by MRgHIFU (large white spheroid area of cooked tissue in the pink ex-vivo meat sample) centered on the ballistic target (high density blue spot). Mild blue density resulted from contrast agent dispersion while slicing the meat to cross the central plane of the lesion.

After local aseptic treatment of the skin, the home-built RF-electrode was inserted into the rabbit leg to create the marker (scenario as previously described). MRI was then used interactively to identify the marker and thus the volume of tissue to be targeted, using the same T1 3D gradient-echo (VIBE) sequence. HIFU was used to perform volumetric ablation, prescribed to be centered on the created ballistic target (Fig2.a-c). Heating was produced by MRgHIFU on *in vivo* rabbit thigh, using a randomized 256 element phased array transducer (Imasonic, Besançon, France) with natural focal length and aperture of R = 130 mm and D = 140 mm respectively (f = 1MHz). The HIFU platform uses a programmable 256 channel generator and a 2D positioning mechanism in the XZ plane (Image Guided Therapy, Pessac, France). An in-house written software package was used for on line treatment planning, hardware control and automatic T° control during volumetric sonication. T° elevation was monitored using MR thermometry (MRT) on a 3T whole body MRI scanner (Magnetom Trio, Siemens AG, Germany) using a GRE-EPI sequence with echo train length 9, TE = 8.9 ms , TR=161 ms, FA 15°, BW= 500Hz/pixel, 5 interleaved slices (1sag, 1trans, 3cor). Post-ablation, the animal was awakened and kept under surveillance for 7 days. Postoperative analgesia was administrated (2x0.01 mg/kg/day Buprenorphine) during two postoperative days. On day 7, the achieved spatial control of ablation was evaluated in-vivo post injection of Gadolinium by comparing the pre-defined position of the tumor-mimicking ballistic target and the position of the necrotic and fibrotic areas (i.e. the "gravity center") identified in contrast-enhanced T1w sequences. The animals were euthanized and the sonicated thigh was fixed in 4% formaldehyde and processed for macroscopic analysis and then microscopic histology. With the post-mortem histology the center of the HIFU lesion was compared to the local marker i.e. fixed methylene blue staining (Fig.3).

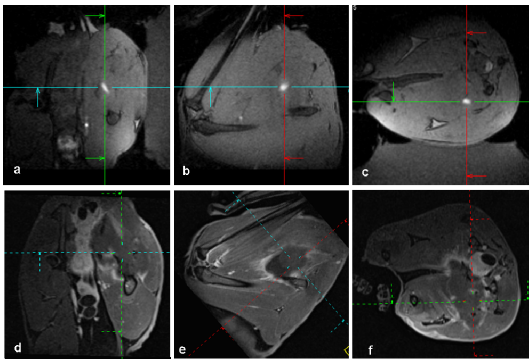

Fig2. in vivo T1 weighted images pre(a-c)- and 7-day post (d-f)- HIFU therapy. The ballistic target is clearly seen before the treatment in each section through the 3D reconstruction (a-c). The apoptotic and necrotic area formed 7days after treatment is visible as a hypo signal zone surrounded by a hyper intense rim (d-f) and corresponds to the planned HIFU ablation.

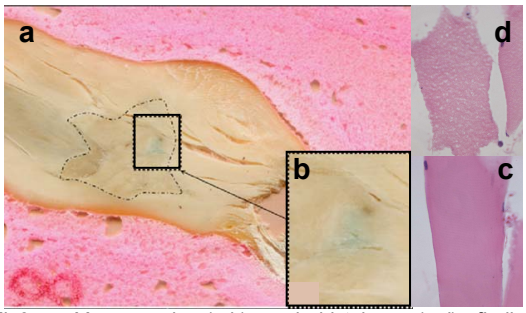

Fig3. Macroscopic (a-b) and histology (c-d) findings corresponding to the rabbit in vivo images shown in fig2. The HIFU ablated area (surrounded by dashed contours and corresponding to the large hypo-intense area in fig2:d-f) appears here off-centered compared to the ballistic methylene blue target, due to HIFU-induced muscle contraction during the treatment, resulting in off-centered ablation. Normal muscle cells showed clear striation by hematoxilin-eosin staining, as well as peripheral nuclei while necrotic and fibrotic areas appeared with lighter staining and showed a complete loss of striation & slightly smaller size of the cells.

Results: The Gadolinium-doped marker was easily detectable with MR imaging and therefore this method provided a minimally invasive and robust ballistic target, which mimicked a "virtual" tumor. We demonstrated that methylene blue was trapped by immediate coagulation of tissue using localized RF energy deposition, and any un-trapped staining was cleared by the tissue perfusion *in-vivo*. Staining was also detectable after 8 months of formalin fixation, i.e. highly stable histology marker(Fig.3:a-b). *Ex-vivo* coagulative lesions are easy to center on the ballistic marker, but such results may be difficult to obtain in-vivo e.g HIFU- induced muscle contraction during the treatment(motion detected on-line by MRT). In Fig.3a, during control (7days), the HIFU-ablated volume seems to extend asymmetrically around the initial target. Histology, that reveals a clear difference between the area treated by HIFU and the normal muscle (Fig.3:c-d), demonstrates that the HIFU-ablated volume is indeed off-centered due to the muscle contraction (fig3.a). No methylene blue was detected outside the RF ablated tissue indicating normal clearing of the un-trapped staining.

Discussion: In our model, the created target did not modify the local acoustic properties (as demonstrated by harmonic US imaging), had small size (e.g. comparable to the wavelength of HIFU) and no side effects (in term of biocompatibility) were noticed. Moreover, the RF coagulated small volume of tissue (2-3 mm) and the trapped tracers induced no local magnetic perturbation in the phase maps acquired with the PRFS T°-sensitive GRE-EPI sequence. Other applications of our fixated marker may concern the tissue "tattooing" as landmarks for diseased tissue/tumour or healthy structure at risk to be delineated for surgery. The coagulating energy applied here was radio-frequency-like (RFA), but laser ablation device (LITT) may also be used with an appropriate design of the delivering tool. **References:** (1) Salomir R. et al. JMRI2000. (2) Palussiere et al. MRM 2003. (3) Petrusca L. et al ISMRM 2010.