Initial Evaluation of an MR-Hyperthermia Activated Thermosensitive Drug Delivery System

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Purpose: Chemotherapy is an established cancer treatment modality that relies on the administration of a drug. The efficacy of existing systemic chemotherapy is limited by its toxic side effects to healthy tissues. Current innovations in the field of advanced drug delivery are focused on the development of a new generation of responsive systems that can (i) trigger drug release at the tumor site and areas of potential disease spread, (ii) avoid drug deposition in non-target tissues, and (iii) allow for quantitative measurement of the dose of drug delivered to the target tissue. Here we report a pilot evaluation of a novel MR image-guided radiofrequency (RF) hyperthermia-mediated drug delivery platform. In a typical MR-guided RF hyperthermia procedure, image guidance relies on transmit/receive imaging with the body coil [1,2]. We assess the feasibility of MR measurement of heat-induced release and diffusion of a gadolinium chelate Gadoteridol (Gad, Prohance®, Bracco) in a test phantom positioned inside a 6-channel MR dual-function imaging/RF heating prototype [3,4]. The goal of this study is to characterize (i) image SNR in the Agar phantom for both the body-coil and 6-channel receive images, (ii) the diffusion of free Gad through the phantom, and (iii) the diffusion of Gad from a thermosensitive liposome formulation encapsulating Gad at room temperature and at 45°C (hyperthermia temperature).

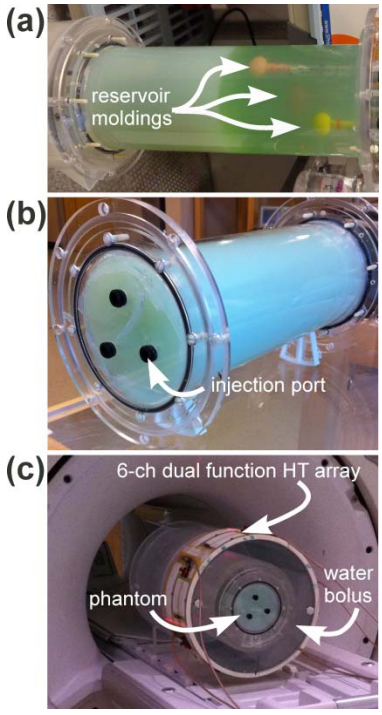

Fig. 1 (a) *Shaping the spherical reservoir moldings in the gel phantom.* ***(b)*** *Front view of the gel phantom showing injection ports for the liposome delivery.* ***(c)*** *Full setup of gel phantom inside the water bolus and 6-channel dual-function array.*

Methods: A thermosensitive nano-sized liposome formulation Gad-HTLC (lipid composition: DPPC / DPPG / MSPC / DSPE-PEG_{2000} in mol% ratios of 57/29/10/4 and diameter of 94.0 ± 1.3 nm) co-encapsulating Gad and cisplatin (CDDP) was developed previously as a novel and imageable targeted drug delivery vehicle [5]. A gel phantom composed of 1.5% Agar (Tm = 89°C) spiked with 0.2% $CuSO_4$ and 0.5% NaCl (to achieve physiologically relevant levels of electric conductivity needed for RF heating), was constructed to determine the effectiveness of heat-induced release of Gad (used as an imageable drug surrogate) from Gad-HTLC. Phantoms contained 3-6 pre-cast spherical reservoirs (**Fig 1a**) and injection ports (**Fig 1b**) where Gad-HTLC and/or Gad were delivered via a suspended needle tip. The phantom + water bolus setup (**Fig 1c**) was positioned inside a previously tested 6-channel MR dual-function imaging/RF heating prototype [3,4]. Blocking circuits on the dual function array were activated, and the setup was imaged with the body coil of a 3T GE MR750 scanner (GE Healthcare, Waukesha, WI). Spherical voids were localized in MR images as shown in **Fig 2a-b**. Gad diffusion through the gel was measured by signal increase along a contour on the edge of the void as depicted in **Fig 2a-b** *(right)*, following a ~200 µl injection of (i) free Gad, and (ii) Gd-HTLC. Experiments were performed both at room temperature (22°C) and at 45°C. After a steady-state temperature was reached, a T_1-weighted spoiled gradient echo (SPGR) sequence at TE = 3.9ms, TR = 18, Flip 90°, FOV 24cm, Matrix 512x512, NEX 3, 3x2 mm slices, was used for imaging/data collection.

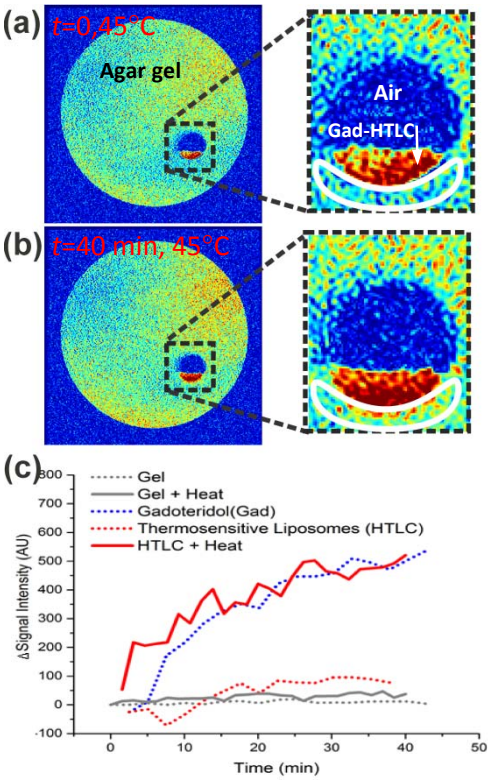

Fig. 2 *MR images showing the differential signal distribution demonstrating confinement of the inactivated Gad-HTLC immediately post-injection* ***(a)*** *and after 40 min of heating at 45°C* ***(b). (c)*** *Plots of the MR signal profiles measured as a function of time relative to baseline signal measured along the white contour shape shown in the left panels in (a). and (b).*

Results: A higher diffusion rate was observed for Gad-HTLC at 45°C compared to Gad-HTLC at 22°C indicating successful heat-induced release of the small molecule Gad from the macromolecular Gad-HTLC. Control tests were carried out with a non-thermosensitive liposome formulation (results not shown here) which showed no diffusion beyond the precast void at both temperatures indicating that no Gad was released at 45°C. The release and diffusion rate of Gad when administered as Gad-HTLC was determined to be statistically different at 45°C compared to 22°C ($p < 0.001$) and similar to that of free Gad ($p = 0.153$) which had a diffusion rate of ~0.19 s^{-1}. **Fig 2c** depicts the change in MR signal over the course of the experiment. Data was acquired for the heated and non-heated cases and fit using an exponential convergence model in Matlab (Mathworks, Natick, MA). **Conclusion:** Overall, results indicate that the body coil provides adequate image quality for monitoring drug release in the current setup, albeit a 3.2-fold decrease in SNR compared to imaging with the 6-channel array. The results also show that the HTLC formulation can achieve the desired payload release characteristics when the temperature rises to the hyperthermia range ~45°C in our experimental setup. Future work will utilize the same physical applicator for both imaging and 3D heat steering for heat-mediated thermosensitive liposome-based drug release.

References: [1] Paulides et al. Phys Med Biol 2010;55:2465-80, [2] Tarasek et al. ISMRM 2014;1333, [3] Tarasek et al. ESHO 2013, [4] Yeo DBT et al. ISMRM 2011;3724, [5] Dou et al. J Control Release 2014; 178: 69-78.