MRI Tracking of Iron-labeled Radioembolization TheraSpheres: Phantom and Animal Model Feasibility Studies

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Introduction: Radioembolization is a promising liver-directed therapy for hepatocellular carcinoma (HCC) involving catheter-directed delivery of glass Yttrium-90 beads (TheraSphere®, MDS Nordion) delivering high doses of radiation to HCC while minimizing dose to surrounding tissues. Currently TheraSphere cannot be directly visualized using conventional imaging techniques. *In vivo* visualization would permit a) real-time verification of delivery, b) detection of extra-hepatic shunting, and c) more accurate radiation dosimetry. Previous studies with holmium microspheres exploited the paramagnetic properties of ^{166}Ho to generate T2*-weighted contrast [1]. The success of these studies along with the recent proliferation of iron-labeled stem cell tracking techniques compelled us to investigate the feasibility of labeling TheraSpheres with iron oxide for MRI visualization. In phantom and animal studies we tested the hypothesis that iron-labeled TheraSphere can be visualized using both T2*-weighted negative-contrast (NC) as well as 'white-marker'[2] and Inversion Recovery with On-resonant water suppression (IRON)[3] positive-contrast (PC) MRI.

Materials and Methods: TheraSpheres were modified to include 10%/mass Fe_2O_3 as part of each 20-30μm spheradized glass matrix**.**

NC and PC MRI All studies were performed using a 1.5T clinical scanner (Magnetom Sonata, Siemens Medical Solutions). Imaging parameters common to both NC and PC sequences: 200x125mm FOV, 256 matrix, 5mm slice thickness. T2*-weighted and white-marker specific parameters: spoiled GRE with TR/TE = 85/4 ms, 25° flip-angle, 260Hz/pixel BW, 0% slice-select refocusing for PC. IRON parameters: TSE with TR/TE=3000/12ms, 260Hz/pixel BW, 100Hz saturation BW with 95° flip-angle, turbo-factor 12.

Phantom Studies We constructed an agar phantom containing three wells, each with increasing doses of the iron-labeled TheraSpheres (~2k, 2.5k and 4k spheres respectively). We used both NC and PC MRI to image the agar phantom at a slice orientation parallel to the static magnetic field. For each dose within each phantom image we measured the spatial-extent of contrast (SEC).

Animal Studies We implanted VX2 cells at multiple positions within the left liver lobe of 2 rabbits. After 2 weeks of tumor growth, we positioned a 2F left hepatic artery catheter under DSA guidance to selectively deliver the iron-labeled TheraSpheres (1-2 million spheres/dose). Prior to TheraSphere injection, each rabbit was moved to adjacent MRI scanner for NC and PC imaging. Following *in vivo* imaging, each rabbit was sacrificed and liver harvested for *ex vivo* imaging. Contrast-to-noise ratio (CNR) was measured for corresponding regions (N=15) of TheraSphere accumulation within the NC and PC images. CNR was compared using one-factor ANOVA with α=0.05. Harvested livers were sectioned for histological evaluation of 20μm slices stained using hematoxylin and eosin (H&E) to identify tumor boundaries.

Results: TheraSphere deposits were visible in both phantoms and animal models using each of the three MRI sequences (**Figs. 1-3**). Regions containing TheraSpheres appeared as signal voids in T2*-weighted images or as regions of increased signal intensity within white marker and IRON images. For each sequence, the SEC increased with increasing dose of TheraSpheres (**Fig. 1**). We imaged 4 VX2 liver tumors with both *in vivo* (**Fig. 2**) and *ex vivo* (**Fig. 3**) studies demonstrating preferential uptake of the iron-labeled TheraSpheres by the targeted tumors. **Fig. 3** shows a tumor with peripheral TheraSphere accumulation at the tumor edge clearly visualized with both NC and PC MRI and later confirmed by histology (**Fig. 4**). For our chosen imaging parameters IRON PC MRI provided superior CNR to white-marker PC MRI for visualization of TheraSpheres in the VX2 tumors ($p<0.001$) (**Table 1**).

Conclusion: Iron-labeled TheraSpheres can be visualized using both NC and PC MRI. These visualization/tracking strategies are well suited for the recently introduced MR-IR suite offering the potential for real-time confirmation of TheraSphere delivery and improved dosimetry calculations at the time of therapy. Future studies will optimize iron-labeled TheraSphere composition and evaluate which MR imaging strategies provide optimal sensitivity and specificity for TheraSphere localization in both animal models and patients.

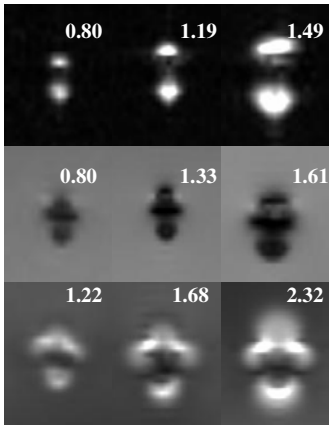

Fig.1 Iron-labeled TheraSphere phantom with dosage increasing from left to right (~2k, 2.5k, and 4k spheres). Top row: white-marker PC images. Middle row: T2*-weighted NC images. Bottom row: IRON PC images. Notice the demonstrable increase in SEC (cm, listed @ upper right) with increasing TheraSphere dose.

Table.1 Relative CNR for NC and PC MRI of Iron-labeled TheraSpheres in VX2 Rabbits

T2*weighted	54.30 ±12.84
White marker	17.52 ± 5.71
IRON	83.20 ± 24.47

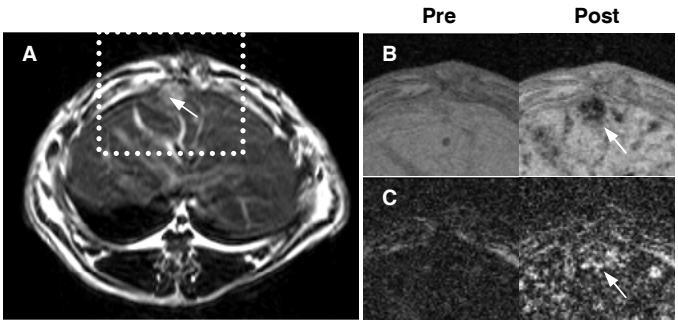

Fig.2 *In vivo* VX2 rabbit images with tumor (arrows) at center of dashed ROI box within anatomic TSE image (**A**). Pre- and post-injection T2*-weighted NC images (**B**) and white-marker PC images (**C**) clearly depict selective accumulation of iron-labeled Theraspheres within the tumor.

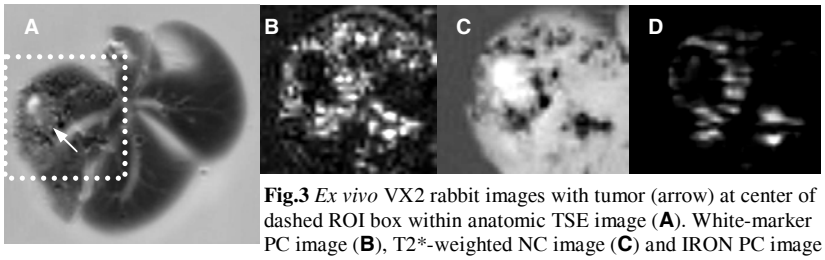

Fig.3 *Ex vivo* VX2 rabbit images with tumor (arrow) at center of dashed ROI box within anatomic TSE image (**A**). White-marker PC image (**B**), T2*-weighted NC image (**C**) and IRON PC image (**D**) clearly depict selective accumulation of iron-labeled Theraspheres at the periphery of the VX2 liver tumor.

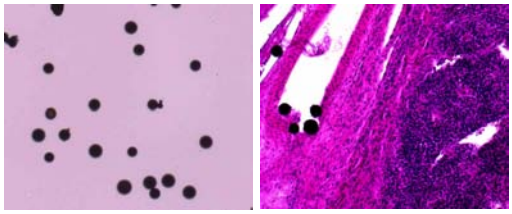

Fig.4 Light microscope images (10x magnification) of the 20-40 μm iron-labeled TheraSpheres (left) and H&E histology (right) depicting TheraSphere deposits at the periphery of the VX2 tumor from Fig. 3.

References:

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3) Stuber *et al*, Proc Intl. Soc. Mag. Reson. Med. 13(2006).