High-Resolution MRI of SPIO-labeled Yttrium Microsphere Biodistribution in the Rodent Liver at 7T

W. Li[1], Z. Zhang[1], D. Procissi[1], A. Gordon[1], J. Nicolai[1], R. Omary[1], and A. Larson[1]
[1]Department of Radiology, Northwestern University, Chicago, Illinois, United States

INTRODUCTION Hepatocellular carcinoma (HCC), one of the most common cancers with >1 million new cases estimated annually worldwide, constitutes a difficult health challenge because of its poor prognosis and limited treatment options. Radioembolization with Yttrium-90 (^{90}Y) microspheres is a relatively new form of intra-arterial therapy for HCC, in which beta-emitting microspheres measuring 20–30 μm in diameter are delivered directly to tumors (via arterial catheter)[1]. Visualization and quantification of ^{90}Y microsphere biodistribution using conventional radiologic modalities is challenging[2]. Labeling ^{90}Y microspheres with SPIOs offers the potential to use MRI to visualize *in vivo* biodistribution [3]. However, optimization of the amount of SPIO material included within these glass microspheres may be critical. The objective of this study was to investigate the impact of altering glass yttrium microsphere SPIO content; we performed *in vivo* and *in vitro* comparisons of different microsphere SPIO labeling compositions following transcatheter delivery in rodents at 7T.

MATERIALS AND METHODS

SPIO-labeled microspheres: We examined the imaging properties of yttria-alumina-silicate microspheres containing Fe_3O_4 dispersed throughout each glass sphere (added during the manufacturing process) (Mo-Sci Medical, Rolla, MO). Microspheres containing 2, 5, 10, and 20% SPIO (%-by-mass) respectively with diameter distribution from 20 – 40 μm were used in this study.

Rat model: All the experiments are approved by the Institutional Animal Care and Use Committee of the Northwestern University. 4 male Sprague-Dawley rats weighing 200–350 g were used in these experiments. The rats were anaesthetized by inhalation of 2% vaporized isoflurane. Each rat was catheterized through hepatic portal vein with a rat portal vein catheter (Charles River, Wilmington, MA). After catheterization, MR imaging was performed before, during, and after administration of microspheres. The microspheres (5 mg) were administered through two injections and two saline flushes for each injection through the catheter. After MRI, rats were euthanized, and livers were harvested and fixed using 10% buffered formalin for high resolution MRI and histological analysis (hematoxylin and eosin (H&E) staining).

MRI: All studies were performed using a 7.0 T 30 cm bore Bruker ClinScan MRI scanner (Bruker Biospin MRI GmbH, Ettlingen, Germany) with a) Siemens Syngo® clinical user interface and pulse sequences, b) 75mm QuadTransceiver rat coil (Bruker Biospin), c) isoflurane anesthesia system, body temperature control and monitoring system for vital signs (temperature, respiration and ECG), and d) MRI-compatible small animal gating system (SA Instruments, NY) to permit free-breathing acquisitions during intra-procedural and post-procedural MRI measurements. The distribution of SPIO-labeled microspheres was qualitatively characterized with T2 weighted turbo spin echo (T2W TSE), T1 weighted, segmented gradient-echo sequences (TFL) with an inversion recovery preparatory pulse (IR-TFL), and proton density weighted gradient echo (PDW GE) sequences. T2W TSE sequence was applied with following parameters: TR/TE = 2920/29 ms, turbo factor = 12, matrix = 264 × 384, FOV = 61 × 90 mm, number of coronal slices = 32, slice thickness = 0.7 mm, NEX = 1, scan time = 7 min and was synchronized with the respiratory cycle to minimize motion artifacts. PDW GE sequence was performed with TR/TE = 15/3.3 ms, flip angle = 25°, matrix = 256 × 178, FOV = 50 × 35 mm, coronal slices = 32, slice thickness = 0.7 mm, and scan time = 11 minutes. T1 IR-TFL was applied with TR/TE = 1340/1.84 ms, TI = 1200 ms, matrix = 264 × 384, FOV = 61 × 90 mm, number of coronal slices = 32, slice thickness = 0.7 mm, NEX = 1, scan time = 14 min. High resolution *in vitro* T2W images were acquired at a resolution of 0.12×0.12×0.12 mm using a 3D TSE sequence with TR/TE = 2750/46 ms, FOV = 30×30 mm, and NEX = 4.

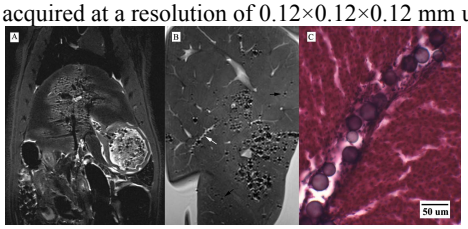

Fig.1. T2W images showing the distribution of 10% SPIO-labeled microspheres *in vivo* (**A**), *in vitro* (**B**) and H&E staining of liver tissue with microspheres (**C**).

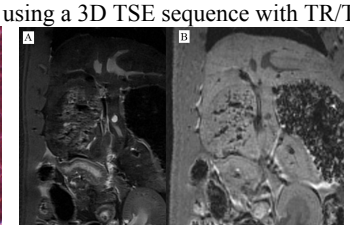

Fig.2. Distribution of 2% SPIO-labeled microspheres in T2 weighted (**A**), T1 weighted images (**B**).

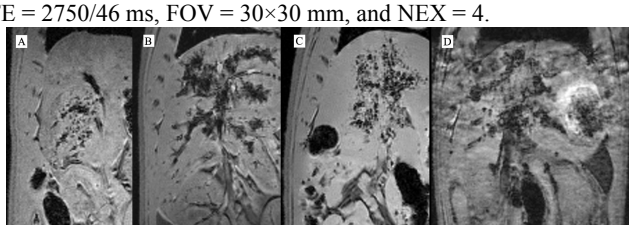

Fig.3. Proton density weighted images for comparison of the distribution of SPIO-labeled microspheres with 2% (**A**), 5% (**B**), 10% (**C**), and 20% (**D**) SPIOs.

RESULTS

SPIO-labeled microspheres were heterogeneously distributed for each of the 4 different SPIO labeling compositions. **Fig.1A** and **B** show representative *in vivo* and *in vitro* T2 weighted images when using microspheres with 10% SPIO content. Histological analysis results (**Fig.1C**) verified microsphere deposits in liver tissue. Ambiguous signal voids and hyperintense regions surrounding blood vessels were found in T2 weighted images (**Fig.1A**). Single SPIO-labeled microspheres and/or small groupings of SPIO-labeled microspheres produced characteristic dipole patterns (black arrows in **Fig.1B**). Strong signal voids were found in T2, T1, and proton density weighted images even with SPIO composition of 2% (**Fig. 2** and **Fig 3A**). As expected greater signal loss was found in tissues infused with microspheres having greater SPIO content, as shown in **Fig. 3**.

DISCUSSION AND CONCLUSIONS

The clinical ability to quantify intrahepatic ^{90}Y microsphere deposition would provide enormous benefits permitting dose optimization to maximize tumor kill while limiting toxic effects on normal liver tissues. SPIO-labeled ^{90}Y microspheres offer the potential to use MRI to detect *in vivo* biodistribution; however, the strong magnetic susceptibility effects of these SPIO-labeled microspheres can rapidly reduce signal below the noise floor complicating rigorous quantification. With the current study we have demonstrated the potential to optimize SPIO content for future studies intended to quantify microsphere concentrations *in vivo*; we found that even with relatively low SPIO content (e.g. 2%) spheres remained readily visible; spheres with lower SPIO contents will be ideal candidates for future study (potentially superior imaging characteristics and allowing greater remaining ^{90}Y payload/sphere).

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