

Detection and quantification of Holmium-166 loaded microspheres in patients with liver metastases: initial experience within the framework of a phase I study

G. H. van de Maat¹, M. Elschof², P. R. Seevinck¹, H. de Leeuw¹, H. de Jong², M. Smits², M. van den Bosch², M. Lam², B. Zonnenberg², A. D. van het Schip², J. F. Nijsen², and C. J. Bakker¹

¹Image Sciences Institute, University Medical Center, Utrecht, Netherlands, ²Department of Radiology and Nuclear Medicine, University Medical Center, Utrecht, Netherlands

Introduction: Internal radiation therapy using radioactive Holmium-166 loaded microspheres (HoMS) has shown to be a promising technique for treatment of liver metastases [1]. Unlike Yttrium-90 microspheres, which lack imaging capabilities, HoMS can be detected by Single Photon Emission Computed Tomography (SPECT) using the Holmium-166 photopeak and by MRI using the paramagnetic properties of Holmium. Due to their paramagnetic character, the microspheres induce local field inhomogeneities which cause MR signal dephasing and therefore additional T_2^* decay [2]. The T_2^* relaxation time or its inverse, the R_2^* relaxation rate, can be used to quantify the amount of HoMS [3, 4]. In this paper we report the first results of the detection and quantification of HoMS in patients with liver metastases included in a phase I clinical study [5]. We will demonstrate a) that accurate HoMS concentration maps can be estimated from T_2^* weighted data, b) that the resulting concentrations maps show good correspondence to activity maps acquired with SPECT and c) that the total amount of HoMS determined using the MR-based concentration maps agrees well with the total amount of HoMS that was delivered.

Materials and methods Data acquisition: MRI and SPECT data was obtained from a patient that was included in a phase I study [5] that was started this year at the University Medical Center Utrecht (UMCU, The Netherlands). The study was approved by the Independent Ethics Committee. MRI: MRI multi gradient echo (MGE) data of the Free Induction Decay (FID), which has been shown to be superior to sampling of the spin echo in previous work [4], were acquired using a 1.5T whole body scanner (Philips Healthcare, Best, The Netherlands). Imaging was done 1 week before and 1 week after hepatic arterial radio embolization with ¹⁶⁶HoMS. 16 echoes were acquired during breath-hold using a multi-slice MGE sequence with an in plane resolution of 2x2mm² and a slice thickness of 6mm. Further scan parameters included: FOV: 288x384mm², nr. of slices: 45, TR/TE1/ΔTE: 440ms/1.33ms/1.15ms, flip angle: 50°, scan time: 3 x 19s breath-hold. Furthermore, T_2 -weighted spin echo images were acquired with the same FOV and voxel size for anatomical information and segmentation purposes. Scan parameters included: TR/TE = 830ms/80ms, scan time: 2 x 19s breath-hold. In addition T_1 -weighted gradient echo images were acquired for localization of tumor tissue.

SPECT: SPECT images of the ¹⁶⁶Ho photo peak were acquired one day after administration of HoMS using a FORTETM dual-headed gamma camera (Philips Healthcare, Best, The Netherlands) equipped with medium energy general purpose collimators. Energy windows were set to 80.6 keV (15%) for the photopeak and 118 keV (12%) for scatter correction. Data was reconstructed to a 128³ matrix size with an isotropic voxel size of 4.7mm³ using an ordered subsets expectation maximization algorithm including a hybrid scatter correction method [6].

Image analyses: R_2^* values were estimated voxel wise by fitting signal intensities from the MGE data to a mono-exponential function: $S(TE) = S(0) \cdot \exp[-R_2^* TE]$ where TE is the corresponding echo time [4]. Only signal intensities with a signal to noise ratio (SNR) larger than 3 were included in the fitting procedure to avoid influence of Rician noise. After manual segmentation of the liver, a baseline R_2^* value determined from the dataset acquired prior to administration of HoMS, was subtracted from the estimated R_2^* values to determine the relative R_2^* increase. To exclude voxels that were affected by air-tissue boundaries (for instance near the lungs and stomach) only values between 0 and 50s⁻¹ were included in determining the baseline R_2^* value. After subtraction, R_2^* values were divided by the relaxivity of HoMS ($r_2^* = 100 \text{ s}^{-1} \text{ ml}^{-1} \text{ mg}$ at 1.5T for a Holmium content of 18.7% (w/w) [4]) to calculate the concentration HoMS per voxel. From these concentrations, the amount of HoMS per voxel and the total amount in the liver were calculated using the voxel size.

Results: R_2^* maps of 3 typical image slices prior to HoMS administration are shown in the first column of figure 1. In the second column, R_2^* maps of similar slices after administration of HoMS are shown. It is clearly visible from the high intense areas in the second column, that the presence of HoMS leads to an increase of R_2^* values. The third column shows concentration maps, calculated from the R_2^* maps, superimposed on corresponding spin echo images. The concentration maps show that, after subtraction of the baseline R_2^* value of the liver, R_2^* values apparently only increased at certain locations, indicating local accumulations of HoMS. The presence of these local accumulations is confirmed by the SPECT images (fourth column), which show high activity at similar locations. Since the data from column 1, 2 and 4 were acquired at separate time points, patient position differed between scans and therefore image slices and anatomical structures are not exactly aligned. The total amount of HoMS in the liver, as determined from the concentration maps, was 546mg, compared to an administered amount of 524mg. In the last column of figure 1, T_1 -weighted images acquired prior to administration of HoMS are shown. On these images, tumorous tissue is clearly visible (dark areas). Tumor locations correspond well to locations with high HoMS concentrations.

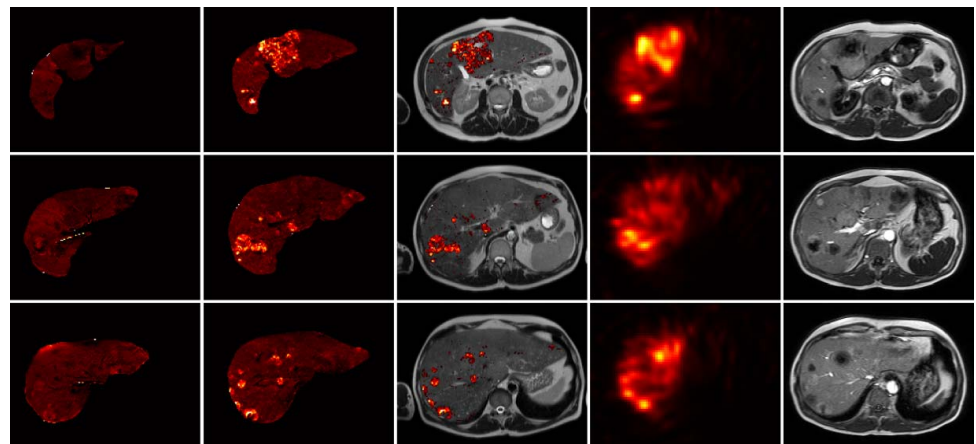


Figure 1) R_2^* maps prior to (first column) and after (second column) administration of HoMS, concentration maps superimposed on Spin echo images (third column), SPECT images (fourth column) and T_1 -weighted images (fifth column) of 3 typical images slices. Since data was acquired at separate time points, slices are not exactly aligned

Discussion and conclusion: First results obtained within the framework of a phase I study on patients treated with Holmium-166 loaded microspheres, showed that it is possible to detect and quantify the microspheres by using a MGE sequence. R_2^* maps determined from the MGE data showed high intensities at several locations indicating the presence of HoMS. By using the relaxivity of HoMS, concentrations of HoMS per voxel were determined. The total amount of HoMS in the liver determined from these concentrations appeared to be in good agreement with the total amount that was administered. The presence of HoMS as determined by MRI was globally confirmed by SPECT images, despite the fact that the in-plane resolution of SPECT was much lower. Comparison of the MR-based concentration maps and SPECT data to T_1 -weighted images showed that the microspheres mainly accumulate at the tumor site. To allow more accurate comparison between MR images (prior to and after administration of HoMS) and SPECT images, registration tools have to be developed. Registration would also allow for voxel wise normalization of R_2^* values resulting in more accurate estimation of local concentrations.

We clearly demonstrated the potential of MRI-based detection and quantification of HoMS in patients, providing information on the biodistribution with high spatial resolution within a short measurement time. This opens the way for image-guided (near) real-time interventional procedures and offers the possibility to investigate the relationship between the HoMS bio-distribution and therapeutic outcome after hepatic arterial radioembolization.

References: [1] RJ Mumper et al. J Nucl Med 1991; 32: 2139 [2] JF Nijsen et. al. Radiology 2004; 231: 491 [3] JH Seppenwoolde et al. Mag Res Med 2005; 53: 76 [4] PR Seevinck et al. MRM 2008; 60: 1466 [5] ML Smits et al., J Exp Clin Canc Research 2010, 29:70 [6] de Wit et al. Phys Med Biol 2006; 51: 4773