Experimental characterization of relaxation properties of Ho, Dy, Gd, and Y-loaded microspheres for internal radiation therapy of liver tumors

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Synopsis
In internal radiation therapy for treatment of unresectable liver tumors, radioactive therapeutic microspheres are injected in the hepatic artery. Because several radionuclides are also highly paramagnetic, they can be directly visualized with MRI. In this study, microspheres were loaded with Holmium, Gadolinium, Dysprosium and Yttrium. Relaxometry was performed under variation of particle size and field strength, showing a strong and linear relationship between concentration of the microspheres and observed R2* relaxivity for Ho, Gd and Dy. The calibration curves as determined in this study can be used to obtain quantitative and dosimetric maps for internal radiation therapy under MRI.

Introduction
In internal radiation therapy for treatment of unresectable liver tumors and metastases, radioactive microspheres are injected into the hepatic artery. The microspheres accumulate in the small vessels and irradiate the surrounding tissue. Currently used microspheres are made of glass and contain the radioactive isotope Yttrium [1]. To overcome drawbacks of the Yttrium therapy, e.g. high density of the microspheres and a lack of γ-emission, Holmium-loaded poly lactic acid microspheres (HoMS) have been developed [2]. Due to the paramagnetic nature of Holmium, HoMS can be directly visualized with MRI. To determine quantitative relations to allow dosimetry, imaging properties of Holmium have to be determined for various conditions. Since Holmium is not the only radionuclide with a high magnetic susceptibility value, it would be interesting to characterize the relaxation properties of other candidates for the internal radiation therapy, e.g. Dysprosium and Yttrium [3]. Because Yttrium is currently used in internal radiation therapy, it was also examined. In this study, microspheres were loaded with selected radionuclides and relaxometry was performed under variation of particle size and field strength.

Materials & Methods
The microspheres were prepared by solvent evaporation of respectively holmium/gadolinium/dysprosium/yttrium-acetylacetonate in poly (l-lactic acid) [4]. Sieving of dried microspheres resulted in fractions of 20-50 µm for Gadolinium-loaded microspheres (GdMS), Dysprosium-loaded MS (DyMS) and Yttrium-loaded MS (YMS). For HoMS, different series were sieved: <10 µm, <20 µm, 20-38 µm and 38-50 µm. As a result of different preparation procedures, the loading percentages of the microspheres varied, as given in Table 1. The microspheres were suspended in 2% Agar. Concentrations of the microspheres ranged from 0 to 4 mg/ml and the series were prepared in duplicate. To mimic relaxation conditions in liver tissue (T1 = 500 ms, T2 = 50 ms), 30 mg/l MnCl2 was added. During cooling, the suspensions were sonicated to remove air bubbles. All experiments were performed on both 1.5T and 0.5 T clinical scanners. Due to the weak paramagnetic nature of yttrium, YMS gels were only investigated on 1.5 T.

To determine R1 and R2 relaxation rates, a mixed sequence [5] was used, combining a multi-echo spin-echo (echo spacing 20 ms) with an inversion recovery. R1 and R2 were calculated by least square fits of the obtained signals. The transversal relaxation R2* was determined by exponential fits of data obtained by multiple GE sequences with an echo time increase with steps of 2.5 ms. Individual images were normalized using the standard deviation of the background noise. All obtained duplicated relaxation rates were averaged and concentration dependencies were determined using least square linear fitting.

Results
For all microspheres, the observed R1 rate was hardly dependent on the concentration of the microspheres. Depending on the size of the microspheres, the R2 dependence was weak, but increased for smaller particles (Table 1). The observed R2* rate was largest for Gadolinium, followed by Holmium and Dysprosium. Relaxation rates at 1.5 T were approximately three times the rates at 0.5 T (Figure 1). All R2* curves showed a strong linear dependence on the concentration. Due to the weak paramagnetism of Yttrium, it hardly showed any relaxation effects, even for high concentrations. The R2* relaxation for HoMS decreased for small particles (< 10 µm) but also for larger particles, whereas an increased R2 relaxation rate was observed for the small particles.

Discussion
The relaxation properties of some candidates for internal radiation therapy were characterized. Microspheres loaded with Holmium, Gadolinium and Dysprosium show a strong and nearly pure R2* effect. For smaller Holmium-loaded microspheres (<10, 20 µm) this pure R2* effect is weakened due to the role of diffusion effects, because the size of the microspheres approaches the typical diffusion length of protons, resulting in a transition of the static dephasing regime to the diffusion narrowing regime [6]. The reason why R2* effects decrease for larger microspheres (38-50 µm) remains unclear. Perhaps an inhomogeneous loading pattern of the microspheres can cause this effect. The results also showed that observed relative relaxation rates are not exclusively determined by the theoretical χc of the uncoupled ions of the elements. Due to the coupling of the ions in the acetylacetone complex, their effective susceptibility value apparently changes, as determined in this study. Future studies will apply these experimentally determined calibration curves to obtain quantitative and dosimetric maps of paramagnetic radionuclides using MR imaging.

References