Highly-loaded holmium microspheres for test dose detection and biodistribution prediction in internal radiation therapy of liver malignancies

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Introduction- Transcatheter arterial embolization (TAE) with radioactive microspheres is a promising treatment option for both unresectable liver metastases and hepatocellular carcinoma. This internal radiation therapy is based on the selective lodging of radioactive holmium-166 microspheres (HoMS) in and around the tumor. Activation of HoMS for therapy and nuclear imaging is achieved by neutron activation in a nuclear reactor (γ-rays: 80.6 keV; β-particles: E_{max}=1.8 MeV; $T_{1/2}$=26.8h). In this therapy, the possibility to accurately predict and evaluate the HoMS biodistribution is of major importance[1]. Ideally, one would like to characeterize the exact downstream flow territory after catheterization to predict the area that will be embolized when HoMS is administered and to enable accurate treatment planning and dose calculations. Information about the flow territory can be obtained by MR imaging of the distribution of a test dose (a small amount of HoMS). Once this information is available, a decision can be made whether to go on with the therapy and to administer the therapeutic dose. Since holmium is strongly paramagnetic it can be used as a T_2^* contrast agent as was demonstrated before by the successful qualitative depiction of a therapeutic dose of HoMS in vivo in rabbits and pigs[1,2]. In order to allow biodistribution prediction by MRI using a test dose, we developed highly-loaded HoMS (HoAcAcMS), containing 41% of holmium by weight, to increase the sensitivity on MRI. By increasing the sensitivity of MRI for the test dose, the amount of HoMS used as a test dose can be reduced. The test dose should be as small as possible to prevent a significant change in the flow territory, which would cause differences in microsphere deposition between test dose and therapeutic dose. The aim of this study is to demonstrate the feasibility to use these HoAcAcMS as a test dose predicting the biodistribution of the therapeutic dose. Therefore, we performed MR experiments to investigate the sensitivity of MRI for the HoAcAcMS in vitro in agarose gels. Furthermore, a known amount of HoAcAcMS were administered to the hepatic artery of an excised rabbit liver. Qualitative and quantitative MR imaging were performed after each successive administration to investigate the detectability HoAcAcMS, the predictability of the biodistribution and the accuracy of the HoAcAcMS quantification.

Materials & methods- ***HoMS phantom*** Highly-loaded holmium-acetylacetonate microspheres (HoAcAcMS) were prepared by solvent evaporation, resulting in a size distribution of 15-20 µm and a holmium content of 40.8% by weight. For quantitative imaging three agarose gel (2%) samples were created containing homogeneous suspensions (1mg/ml) of conventional holmium poly-(Llactic acid) microspheres[3] (HoPLLAMS) (17% holmium content w/w), HoAcAcMS or just the agarose gel. ***Biodistribution assessment in ex vivo rabbit liver:*** Up to 50 mg in steps of 10 mg of HoAcAcMS were administered successively into the hepatic artery of an excised rabbit liver. The first dose of 10mg was considered to be the test dose and was used for biodistribution prediction. ***MRI experiments:*** MRI was performed on a 3T whole body scanner (Achieva, Philips Medical Systems, The Netherlands). Phantom experiments: T_2^* relaxometry was performed using multiple gradient echo sampling of FID (MGEFID). Seven echoes were acquired using flyback gradients so as to keep the readout gradient polarity constant. The acquisition parameters included: FOV=128x128x10 mm^3; matrix=128x128x1; $TR/TE_1/\Delta TE/\alpha$ = 500ms/1.58ms/2.7ms/ 50°. Ex vivo rabbit experiments: MGEFID with 15 echoes in gradient flyback mode was applied with a FOV=128x128x40mm^3; matrix=128x128x10; recon. vox. size: 0.5x0.5x4mm; $TR/TE_1/\Delta TE/\alpha$ = 567ms/1.36ms/2.3ms/50°. ***Post-processing:*** R_2^* relaxometry was applied using weighted least squares fitting. Difference images were constructed by subtracting R_2^* images from ex vivo livers prior to HoMS administration from R_2^* images after HoMS administration.

Results- Relaxation rates determined for the agarose samples were 28.8s^{-1}, 109.8s^{-1} and 216.4s^{-1} for native gel, HoPLLAMS and HoAcAcMS, respectively, as shown in Fig. 1. The HoAcAcMS, in which the holmium content was increased by a factor of 40.8/16.9=2.4 compared to the conventional HoMS, induced a relative increase in R_2^* relaxation rate by a factor of (216.4-28.8)/(109.8-28.8)=2.3. The HoMS test dose (10mg) was well detectable on the T_2^* weighted FFE images of ex vivo rabbit liver (Fig.2). R_2^* subtraction images allowed the selective visualization of the HoMS biodistribution (Fig.2). The images acquired after administration of the test dose (Fig.2b) showed a HoMS distribution that provided a good indication for the distribution of the subsequent administrations (Fig. 2b-e).

Discussion & conclusions- HoAcAcMS allowed test dose detection when administered to an ex vivo rabbit liver. Furthermore, the test dose provided a fairly good prediction for the biodistribution of the subsequent HoMS administrations. In the liver areas in which HoAcAcMS were detected after the test dose, accumulation of HoAcAcMS was observed after successive administrations (Fig.2). In one liver lobe no HoAcAcMS were detected after successive administrations (bottom of Fig.2), which was correctly predicted by the test dose. However, in the upper left area of the liver no HoAcAcMS were detected after administration of the test dose, whereas HoAcAcMS were detected after successive administrations. This discrepancy might be attributed to the fact that this experiment involved an ex vivo rabbit liver that was not perfused, which may alter the flow territory and consequently microsphere lodging, when compared to the in vivo situation. Recently, a high correlation was shown between microsphere deposition and flow territories in vivo[4], although limitations have been identified as well[5]. In conclusion, highly-loaded HoAcAcMS have been designed exhibiting a high sensitivity on MRI. These microspheres can be used to predict the biodistribution within the liver. Further research is necessary to relate ex vivo results to in vivo findings and to determine the potential of HoAcAcMS in detecting extra-hepatic shunting as well. Technical and methodological developments in MRI and therapeutic agent design as presented in this work, open the way to perform fully MR guided transcatheter hepatic arterial embolization radiation therapy with holmium-166 microspheres in the near future[2,6].

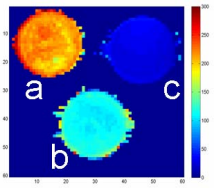
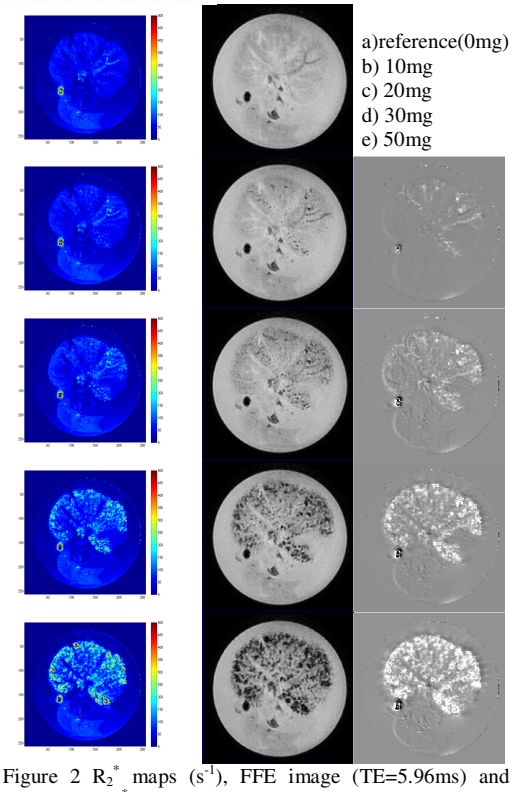


Figure 1. R_2^* map of agarose gel samples with
a) HoAcAcMS ,
b) HoPLLAMS and
c) native gel.



a)reference(0mg)
b) 10mg
c) 20mg
d) 30mg
e) 50mg

Figure 2 R_2^* maps (s^{-1}), FFE image (TE=5.96ms) and difference R_2^* images (HoMS-reference) of rabbit liver with HoMS administered.

References

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