Quantitative MR imaging of the biodistribution of holmium-loaded microspheres used for internal radiation therapy of liver tumors

J-H. Seppenwoolde[1], F. Nijsen[2], L. W. Bartels[1], S. W. Zielhuis[2], F. van het Schip[2], C. J. Bakker[1]

[1]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands, [2]Nuclear Medicine, University Medical Center Utrecht, Utrecht, Netherlands

Introduction - In internal radiation therapy of liver tumors, radioactive embolic microspheres, for example holmium-loaded microspheres (HoMS), are injected in the hepatic artery. Because of the preferential blood flow of the highly oxygenated arterial blood to the fast growing tumors, microspheres that are injected in the hepatic artery will lodge selectively in and around the tumors. If the microspheres contain an activated radionuclide, they will consequently irradiate the tumor region. As described in our previous study [1], the paramagnetic nature of the radionuclide holmium allows the exploitation of MRI, offering some distinct advantages over the conventional nuclear imaging approach. One of these advantages is that MRI allows the depiction of non-radioactive microspheres in a similar way as of radioactive microspheres. If exact quantitative relations between amount of microspheres and MRI signal can be determined, an accurate quantitative description of the biodistribution will result, which can be subsequently used to determine the actual delivered radioactive dose. In this study, we investigated the feasibility of exploitation of MR images to quantify the amount of microspheres present in liver tissue and a validation study was performed in ex vivo rabbit livers and in in vivo animal models.

Materials and Methods - The longitudinal R_1 and transverse R_2 relaxation rates of the HoMS were determined at 1.5 T with a mixed sequence [3] and the transverse relaxivity R_2* was determined with both a multi-echo sampling of the spin-echo (SE) envelope (Fig. 1) or the free induction decay of a gradient echo (GE) sequence. Both employed 15 echoes at an echo spacing of 1.55 msec. The SE acquisition was centered at 30 msec, and the GE acquisition started at 2.38 msec. Relaxation rates were determined by assuming exponential signal decay. Next, in a series of 15 excised ex vivo rabbit livers, multiple well-known and successive amounts of HoMS were administered during perfusion of the liver. In 5 cases the portal vein was connected, in all others the hepatic artery. During each step, multi-echo SE and GE acquisitions were performed, which were subsequently used to reconstruct an R_2* map. Background subtraction, segmentation and application of the determined 'homogeneous calibration curve' resulted in a concentration map of HoMS. After summation, the total calculated amount was compared with the injected amount. Finally, in the 3 tumor-bearing rabbits of the animal models described before [2], the tumor-to-liver ratio was determined using the dual-echo FFE sequence. For both the excised livers of the rabbits and pig models, multi-echo SE and GE acquisitions were performed and the total amount and, where possible, the tumor-to-liver ratio were determined by means of a reconstructed R_2* map.
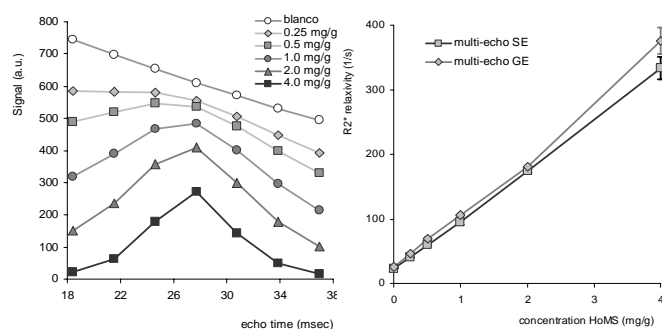

Figure 1: (left) Signal curves of the multi-echo SE acquisition for various concentrations of microspheres in homogenous gels. (right) Transverse relaxivity R_2* versus concentration of HoMS.
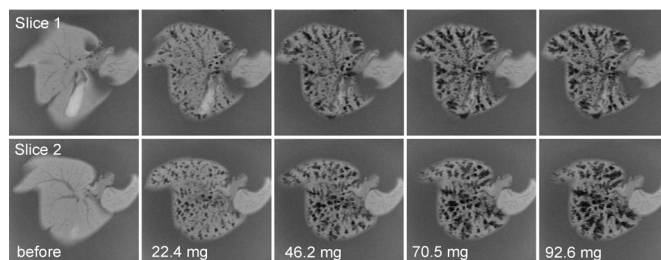
Results - For the homogeneous gels, the concentration dependence of the transverse relaxation rate R_2* was linear and strong (Fig.1) and a weak R_2 effect was observed. Specific relaxation rates were $r_2* = 77.6 \pm 0.7 \times$ [HoMS] s^{-1} and $77.2 \pm 1.6 \times$ [HoMS] s^{-1} for respectively the multi-echo SE and GE acquisition. The r_2 relaxivity was determined to be $1.14 \pm 0.06 \times$ [HoMS] s^{-1}. For all quantifications of the administration of HoMS to ex vivo rabbit livers (example in Fig. 2), an underestimation was found (Fig.3). For administrations in the hepatic artery, the calculated amount was proportional to the injected amount, but underestimated it with a factor of two. For lower doses, the underestimation was less, as was also the case for the 'portal vein' livers. For these livers, it was found that more homogeneous biodistributions demonstrated lower underestimations. For the tumor-bearing rabbits, the in vivo tumor-to-liver ratio determined by MRI was 3.0, 3.1 and 2.1, which is lower than expected from similar experiments [3,4]. The total amount of HoMS present in the excised liver of the treated living pig was determined to be 1070 mg, only a slight underestimation of the injected amount of 1200 mg.

Figure 2: Example of the successive administration of known amounts of HoMS to ex vivo livers, as depicted with a T_2*-w FFE sequence (TE 9.2 ms)

Discussion - The purpose of the study was to validate the quantitative description of the amount of microspheres that are present in a liver and the main finding was that the calculated amount is proportional to the actually injected amount, but underestimates it with a factor of two if the microspheres are administered via the hepatic artery (which is the therapeutic case). However, the underestimation is less if the fraction of microspheres is smaller, or the biodistribution is more homogeneous, as observed for the portal vein livers. It should be noted that the injected amounts are actually higher than one would expect during treatment and for larger subjects the problems of underestimation are expected to be less, also because of a different vascular structure. On the other hand, quantification of a more heterogeneous biodistribution, which can be expected if a tumor is present, could require correction factors that are dependent on the concentration, or actually the heterogeneity, of the biodistribution. Because in this study the total injected amounts of microspheres were the only well known quantities to compare to, a future study will cover an extension of the validation, in which the biodistribution is *locally* compared to, for example, quantitative nuclear images of livers treated with radioactive microspheres.
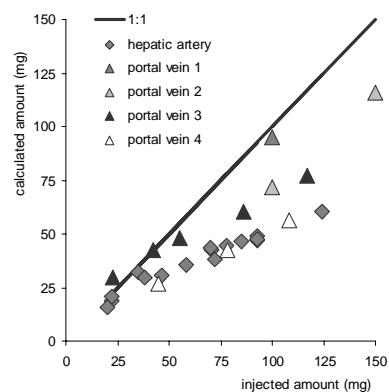

Figure 3: Calculated versus injected amounts of HoMS for ex vivo rabbit experiments in which well-known amounts of HoMS were administered through the hepatic artery or portal vein.

References

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