MR-based dosimetry of ^{166}holmium-loaded microspheres for internal radiation therapy treatment planning

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Introduction- In hepatic arterial radioembolization with β-emitting microspheres, differences in arterial and portal blood supply to liver tumors and normal liver parenchyma are exploited to achieve a high tumor to liver ratio. The large variation in vascularity of tumor and liver tissue observed between patients, as well as possible arteriovenous shunting, necessitates extensive treatment planning using a scout dose, to assure a favorable dose distribution in each individual patient. The currently used Yttrium-90 microspheres (^{90}Y-MS) lack imaging opportunities and do not facilitate high quality biodistribution assessment. An attractive alternative for ^{90}Y-MS, owing to their multimodal imaging possibilities[1] and favorable radiation characteristics[2], constitute Holmium-166 loaded poly(L-lactic acid) microspheres (^{166}Ho-PLLA-MS), which have been proposed and tested for internal radiation therapy of liver malignancies[3, 4]. ^{166}Ho-PLLA-MS have been demonstrated to be a truly multimodal diagnostic and therapeutic agent in the last few years[1]. As opposed to SPECT imaging, MR-guided catheterization and administration of Ho-PLLA-MS was shown to allow direct in vivo visualization of hepatic arterial radioembolization[5]. Furthermore, a fast quantitative MR imaging technique was recently presented to accurately assess and quantify the biodistribution of Ho-PLLA-MS in liver tissue[6]. The aim of this study is to prospectively test the hypothesis that MRI can potentially be used to perform dose calculations of ^{166}Ho-PLLA-MS for treatment planning of transcatheter radioembolization of hepatic malignancies, .

Methods- *Phantom setup* MRI and SPECT experiments were conducted using an anthropomorphic ellipse-shaped perspex phantom (short/long axis = 19/30 cm; height = 7 cm; volume ~ 3 L) containing agarose gel with tumor-simulating gel samples embedded. Tumors were simulated by agarose gel hemispheres (~ 2x3x3 cm). Small amounts of activated ^{166}Ho-PLLA-MS, varying between 0 and 6.2 mg per tumor, were administered to the liquid gel during preparation of the tumors in ice cube containers. The Ho-PLLA-MS contained 17% w/w holmium and were prepared as previously described[2]. The specific activity of ^{166}Ho-PLLA-MS after activation was determined to be 5.83 MBq/mg using a dose calibrator. The activity of the single tumors was determined using the dose calibrator as well (gold standard), exactly providing the amount of activity and indirectly the total mass of Ho-PLLA-MS per tumor. A total amount of 152Mbq in 26 mg of ^{166}Ho-PLLA-MS was distributed over eight tumors with the following amounts: 1.16, 1.16, 2.28, 2.86, 3.52, 3.95, 5.04, and 6.16 mg. As a control, two tumors were made without ^{166}Ho-PLLA-MS.
Imaging:SPECT SPECT images were acquired using a dual-head gamma camera (Vertex MCD, Philips Healthcare, Best, The Netherlands). Imaging settings and attenuation correction were done as previously described[7]. The 360º SPECT study consisted of 120 projections for 30 s/angle. The matrix size was 128x128 with an isotropic pixel size of 4.72 mm. The images were reconstructed on a 128x128x128 matrix with isotropic voxel size of 4.72 mm using 50 iterations, according to a previously described quantitative iterative reconstruction protocol[7]. *MRI* Multiple gradient echo (MGE) sampling of the free induction decay (MGEFID) was performed for T_2^* relaxometry[6] using a clinical 3T MR scanner (Achieva, Philips Healthcare, The Netherlands). Multislice imaging was performed with the following imaging parameters: FOV = 384x312 mm^2; flip angle = 45°; TR/TE1/ΔTE = 400/1.11/0.68 with 16 echoes, isotropic voxel size of 3 mm, 22 slices and total imaging time = 22.8s.
Dose calculations R_2^* maps were determined pixelwise using a weighted linear least squares fitting algorithm (Matlab) on MGEFID data, assuming monoexponential signal decay. Using the relation $[\text{Ho-PLLA-MS}]=(R_2^*-R_2^*(0))/r_2^*$, with R_2^* and $R_2^*(0)$ the local and baseline R_2^* values and r_2^* the relaxivity of Ho-PLLA-MS (180 s^{-1}.mg^{-1}.ml @ 3T), the concentration of Ho-PLLA-MS was determined pixelwise[6]. Multiplication by the voxel volume provided the amount of Ho-PLLA-MS in mg per voxel. These maps were multiplied by the specific activity (MBq/mg) to provide 3D maps of the activity per voxel (Mbq/voxel). The SPECT reconstructions directly provided the activity distribution per voxel (Mbq/voxel). The SPECT reconstructions were up-sampled to an isotropic voxelsize of 3 mm. A 3D ^{166}Holmium dose kernel was calculated using the Monte Carlo code MCNP5 ((vs. 1.20; LANL, Los Alamos, NM), according to the method described in MIRD Pamphlet 17[8]. A point-symmetric dose kernel was generated on a 29x29x29 matrix, utilizing 3 mm isotropic voxels with units [Gy/Mbq]. By convolution of the 3D activity maps with the dose kernel, the absorbed dose maps (in Gy) were obtained for both MRI and SPECT data. Volume of interest (VOI) analysis was performed to determine the total amount of Ho-PLLA-MS present in each tumor. Results were compared qualitatively and quantitatively to reference data obtained with the dose calibrator.

Results- Fig. 1 depicts the absorbed energy as a function of the source-to-target-voxel distance, representing a profile of the point-symmetric dose kernel used to determine the absorbed dose. Excellent qualitative agreement was observed between MR- and SPECT-based dose maps, as shown in **figs. 2 a-h**. MR-based dose maps (**Figs. 2a-d**) better delineated the shape of the hemispherical tumor samples as compared to SPECT-based dose maps, which appeared smoothed (**Figs. 2e-h**). However, MR-based dose maps show higher variation in the background where there is no ^{166}Ho-PLLA-MS present, where SPECT-based dose maps showed a homogeneous background dose level. This is quantitatively confirmed in **Figs. 3a and b**. These figures demonstrate the excellent quantitative agreement between MR- and SPECT based dose maps, both providing dose levels between 0 and 70 Gy. VOI analysis on tumor volumes provided a regression coefficient of 1.05 with correlation coefficient R^2 of 0.987 when relating MR-based ^{166}Ho-PLLA-MS dose calculations to the reference data (**Fig. 4**). For SPECT-based ^{166}Ho-PLLA-MS dose calculations a regression coefficient of 1.00 with correlation coefficient R^2 of 0.998 was found.

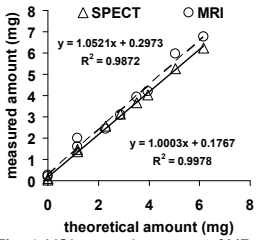

Fig. 4. VOI regression curves of MR- and SPECT-based dose calculations

Discussion & Conclusions- Excellent agreement was found both qualitatively and quantitatively between MR- and SPECT-based dose calculations as well as with the dose calibrator data. The used ^{166}Ho-PLLA-MS amounts were representative for a ^{166}Ho-PLLA-MS scout dose, which in the clinic consists of a total amount of 60 mg used to predict the biodistribution of a treatment dose of roughly 600mg in a liver volume of approximately 1.5L[9]. In conclusion, MR-based dosimetry of ^{166}Ho-PLLA-MS in an anthropomorphic gel phantom was demonstrated to be feasible, indicating the potential of MR-based dosimetry for planning, guidance and evaluation of transcatheter radioembolization treatment of hepatic malignancies with ^{166}Ho-PLLA-MS.

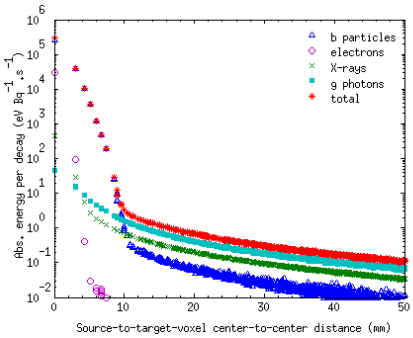

Fig 1. Dose kernel of holmium-166 data.

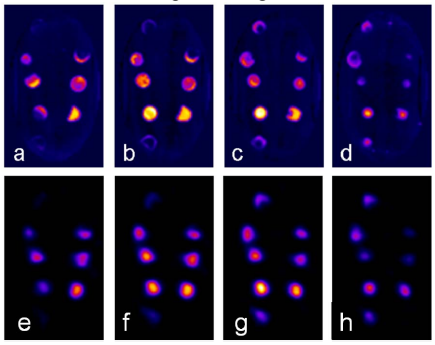

Fig. 2 MR (a-d) and SPECT (e-h) based dose distributions in the agarose phantom

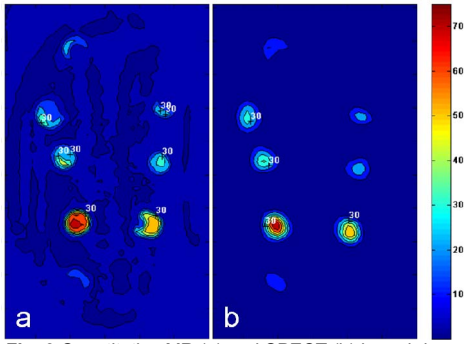

Fig. 3 Quantitative MR (a) and SPECT (b) based dose distribution maps

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