

Feasibility of MR-guided needle-directed intratumoral HoMS delivery for localized radiation therapy in a large tumor-model

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Introduction

Radioablation by direct intratumoral administration of paramagnetic and radioactive holmium microspheres (¹⁶⁶HoMS; 10-20µm diameter) is a promising treatment option for solid, unresectable tumors, especially in areas where the preservation of surrounding tissue and function is essential (e.g. brain, head and neck region). Intratumoral efficacy of ¹⁶⁶HoMS was previously demonstrated for the treatment of small (4-8 mm) implanted renal carcinoma tumors in mice with a single intratumoral injection [1]. However, in larger tumors the penetration range of the beta particles necessitates a certain volume distribution of radioactive ¹⁶⁶HoMS in the tissue in order to be effective. Therefore multiple well-directed injections may be needed to obtain a more favourable distribution of ¹⁶⁶HoMS inside the tissue [1]. Consequently, precise needle placement and verification of ¹⁶⁶HoMS distribution after intratumoral injection is required. Interestingly, it was recently demonstrated that MRI can be utilized for T₂*-based quantitative assessment of the spatial distribution and dosimetry of ¹⁶⁶HoMS, besides identification of the tumorous and healthy tissue [2]. The goal of the present study is to demonstrate the feasibility of MR-guided needle-directed intratumoral delivery of ¹⁶⁶HoMS in a large tumor model.

Material and Methods

Experimental setup and animal preparation: ¹⁶⁵HoMS were prepared by solvent evaporation, resulting in a size distribution of 10-20 µm and a holmium content of 17 % by weight, as described previously³. Vx2 tumors in the hind limb of New Zealand White rabbits was achieved by subcutaneous injection of viable tumor pieces and the rabbits were treated after the tumor reached a size around 2-4 cm. Prior to scanning, a cylindrical container was placed over the hind limb and filled with agarose, to enable needle MR image-based entry point optimization. **Treatment planning:** The desired injection site within the tumor was determined pretreatment on an anatomical T₂ weighted TSE scan (Fig. 1 a). The needle entry point and preferred trajectory was determined on a 3D gradient echo images, reformatted to the desired orientation (Fig. 1b, c). **Needle positioning and HoMS administration:** ¹⁶⁵HoMS injections were performed using titanium needles (MRI chiba, Somatex, 22G, 0.7mm, 100mm) under MRI-guidance (1.5T whole body MR scanner Achieva; Philips Healthcare, Best, The Netherlands). Needle positioning was facilitated by dynamic 2D dual-plane free induction decay (FID) sampling, which allowed for coRASOR reconstructions to highlight the needles with positive contrast [4] (Fig. 2II). Dynamic visualization of ¹⁶⁵HoMS delivery was facilitated using the same 2D sequences (Fig. 2DI and II). After ¹⁶⁵HoMS administration, spatial distribution was investigated using 3D multi-echo gradient echo sequences, as the presence of paramagnetic HoMS induces signal voids due to dephasing (Fig. 2IIIa, b). **Needle visualization:** Needle visualization with positive contrast was facilitated by coRASOR reconstruction applied to a 2D radial center-out sampling sequence [4]. By introducing a frequency offset, Δf_0 (-2000Hz), to the central reception frequency, f_0 , during reconstruction [5], the titanium needle could be visualised at its exact location with high positive contrast [4,5]. Imaging parameters included: TR/TE = 3.5/ 0.8 ms; scan matrix = 128 x 128, FOV = 192x192 mm²; slice thickness = 6 or 8 mm, flip = 25, dynamic scan time = 0.9s.

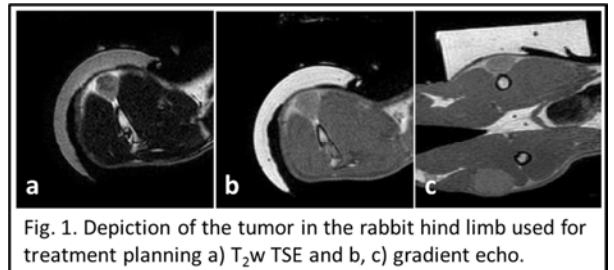


Fig. 1. Depiction of the tumor in the rabbit hind limb used for treatment planning a) T₂w TSE and b, c) gradient echo.

Results

The tumor and surrounding tissue were clearly visualised on the T2w TSE (Fig. 1a) and on the reformatted 3D gradient echo images (Fig. 1b, c) prior to ¹⁶⁵HoMS delivery. Based on these images, an entry point, preferred needle trajectory and slice location was defined, resulting in the slice shown in Fig. 2c. Needle insertion was successfully monitored using the dynamic 2D dual plane sequence. Fig 2a-d presents the conventional (row I) and coRASOR reconstructed (row II) images, clearly demonstrating that coRASOR facilitates high contrast visualization of the needle. Successful HoMS delivery into the tumor was shown in Fig. 2d, which was confirmed post injection in the 3D gradient echo data, showing signal voids in the center of the tumor (Fig. 2IIIa, b). Finally, Fig. 3 demonstrates the added value of consecutive HoMS injections, clearly showing an improved tumor coverage after the second injection as compared to a single injection. Although, five out of six injections were successful, one injection resulted in peritumoral delivery of HoMS.

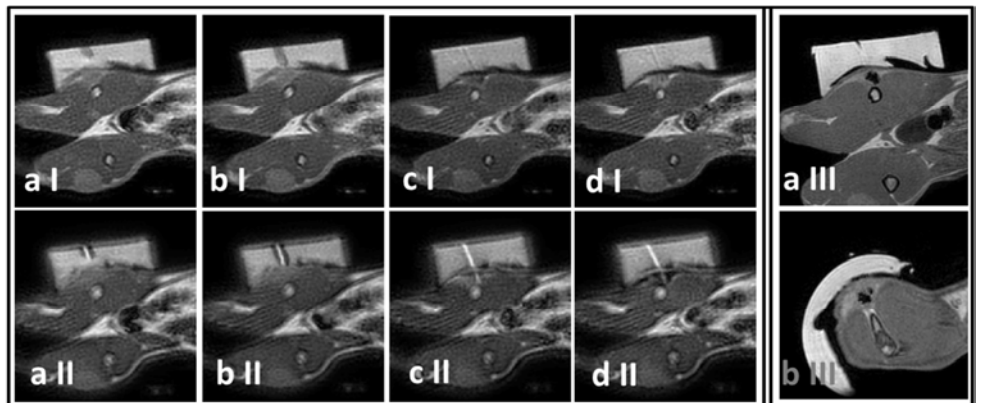


Fig. 2. Dynamic monitoring of the needle positioning and HoMS injection. a, b, c and d show dynamic scans over 30 sec range. Series I and II are conventional 2D and coRASOR images, series III show reformatted gradient echo post HoMS injection.

Discussion & conclusion

In this study, we demonstrated the feasibility of MR-guided needle-directed intratumoral ¹⁶⁵HoMS delivery in a large tumor model. MRI facilitated tumor visualization, entry point determination and needle trajectory planning. The presented approach enabled dynamic monitoring of the needle insertion and needle tip positioning in the tumor, allowing intraprocedural optimization of HoMS delivery. In five out of six attempts, HoMS was successfully delivered in the tumor. As coRASOR reconstruction was demonstrated retrospectively to improve needle visualization by generating positive contrast, causing the titanium needles to be easily identified with high spatial and temporal resolution, its prospective implementation currently has high priority. Future work should also aim at facilitating intraprocedural dosimetry to enable optimization of the number of injection sites and the amount of HoMS to be delivered to eventually provide a favorable dose distribution on the tumor, while sparing the healthy tissue.

References

- [1] Bult et al, PlosOne, 2013;8(1):e52178
- [2] Seevinck et al. Int J Radiat Oncol Biol Phys. 2012 Jul 1;83(3):e437-44.
- [3] Nijsen JFW, EJNM 1999, 26:699-704
- [4] Seevinck PR et al. Magn Reson Med. 2011;65(1):146-56
- [5] de Leeuw H et al. Magn Reson Med. 2013;69(6):1611-22.

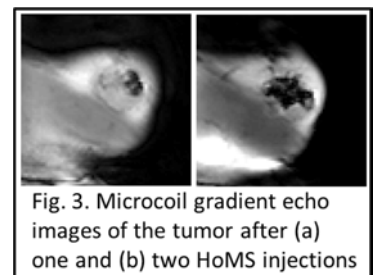


Fig. 3. Microcoil gradient echo images of the tumor after (a) one and (b) two HoMS injections