Theranostics in Radiology: Development of targeted contrast media with treatment capability

AKADEMISK AVHANDLING
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ABSTRACT

Imaging is essential in the diagnostics and medicine of today. The development of new contrast agents is important for obtaining specific information from images and to distinguish disease. Microbubbles (MB) have previously been introduced as a contrast agent for ultrasound. By incorporating super paramagnetic iron oxide nanoparticles (SPION) to the polymer matrix of the MB or between its shell layers we obtain a contrast media for Magnetic Resonance Imaging (MRI); while functionalizing the MB by ligands for labeling with $^{99m}$Tc enables imaging using Single-Photon Emission Tomography (SPECT). The use of hybrid SPECT- and Computed Tomography (CT) or MRI systems enables fusion of the images from the different modalities to obtain SPECT/CT or SPECT/MR images. In the research underlying this thesis we investigated the preclinical characteristics, biodistribution and kinetics of several types of MB in Sprague Dawley rats by injecting single- and multiple layer SPION MB as well as ligand functionalized- and SPION MB labeled with $^{99m}$Tc. The results obtained from imaging was correlated and compared to the histopathology of MB findings in organs. Moreover, mice were injected with Alexa-680 Vivo Tag labeled MB for imaging using a pre-clinical In Vivo Imaging System (IVIS)/µCT.

Sprague Dawley rats (300 ± 50 g) were injected with single layer SPION-, multiple layer SPION-, $^{99m}$Tc-labeled ligand functionalized diethylenetriamine penta-acetic acid (DTPA)-, thiolated poly(methacrylic acid) (PMAA)-, chitosan-, 1,4,7-triazacyclononanone-1,4,7-triacetic acid (NOTA)-, NOTA-SPION- or DTPA-SPION MB intravenously (i.v.) through the tail vein. The rats injected with SPION MB were scanned using MRI, while the rats injected with $^{99m}$Tc-labeled DTPA-, PMAA-, chitosan- or NOTA MB were scanned using SPECT/CT. The rats injected with NOTA-SPION- or DTPA-SPION MB were co-registered using SPECT/CT and MRI. The organs from rats injected with the nuclear medicine marker were removed post mortem and measured for radioactivity. The rats injected with SPION MB were sacrificed and their organs were removed post mortem for histopathology examination using Perls’ Prussian blue staining to show iron content and immunohistochemistry (IHC) to visualize macrophage uptake of MB.

Mice (30 ± 5 g) were injected with multiple layer fluorescence Alexa-680 MB and imaged using IVIS. Their organs were removed post mortem and examined using pathology and the fluorescence of MB was visualized under the microscope.

The uptake of MB was mainly seen in the lungs and liver 1-2 h post-injection, while the main distribution of MB at 24 h post-injection was seen in the liver. In conclusion the MB matrix can be functionalized by ligands, labeled by SPION, $^{99m}$Tc and fluorescence Alexa-680 Vivo Tag to enable its visualization in vivo using multimodal imaging SPECT/CT, SPECT/MRI or IVIS/µCT. Furthermore we have shown that MB can be loaded with cytostatic- or inflammatory drugs for theranostics. Future studies regarding MB should address toxicity and efficiency in drug loading and delivery.

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