Sucrose acetate isobutyrate-based nanogels as liquid fiducial tissue markers with potential use in image guided radiotherapy

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Background

Within the field of radiotherapy, modern radiation oncology relies on precise imaging techniques such as Computed Tomography (CT), Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) in order to deliver high radiation doses to precisely defined targets [1-3]. Tumors undergoing fractionated radiotherapy rarely display a fixed position during irradiation or within treatment, due to changes in organ filling, breathing motion and tumor size. This usually entails that the planning target volume has to be increased to ensure radiation dose coverage during treatment [4].

Image-guided Radiotherapy (IGRT) is a recently developed technique that has contributed to decreased in planning target volume, as 2D- and 3D images are frequently recorded before and during treatment [1,5]. This protocol has reduced treatment toxicity and improved relapse-free survival [6]. However, a remaining challenge within IGRT is fixation and correlation of the anatomical positions of several tumors to internal fixation points such as the skeleton. Radiopaque fiducial tissue markers (contrast agents) are therefore implanted near or inside the tumor to facilitate precise localization of tumors during therapy and thereby increase radiation accuracy. Solid markers like gold seeds are used routinely as defined targets [1-3]. Tumors undergoing fractionated radiation therapy rarely display a fixed contrast level than the PEGylated AuNP-SAIB gel (as expected due to higher AuNP loading in vivo) [7].

Experimental methods

The AuNPs were synthesized by a three step seeding protocol using chloroauric acid and terpolymerization of 200 μL of SAIB/EtOH/PLA (75:20:5) + 30 mg·mL\(^{-1}\) of biocompatible liquid fiducial injectable markers based upon well-defined coated gold nanoparticles. The AuNPs were synthesized by a three step seeding protocol using chloroauric acid and PNIPAM-coated AuNP-SAIB gel provided high CT contrast and high in vivo stability and was assessed to be a suitable tissue marker for image guided radiotherapy (IGRT).

Results

Stable and uniform PEG- and PNPAM-coated AuNPs were successfully synthesized, confer Figure 2. The dithiolane PEG functionalized AuNPs were discarded due to observed aggregation of the nanoparticles. In vitro stability test of the PEG-AuNP-SAIB gel (Figure 3) showed no burst release of PEGylated AuNPs. This burst release was completely avoided (<1%) with the PNPAM-AuNP-SAIB gel, even with concentrations up to 100 mg·mL\(^{-1}\).

The PEG-AuNP-SAIB gel suffered from PEG-AuNP migration towards the gel-boundaries over time [8]. Figure 4 and 5 show micro-CT scans of mice after injection of the PNPAM-AuNP-SAIB gel. The PNPAM-AuNP-SAIB gel provided high stability in vivo, as well as a higher X-ray contrast level than the PEGylated AuNP-SAIB gel (as expected due to higher AuNP loading being possible with the PNPAM coating).

In vivo contrast and stability of the PEG- and PNPAM-AuNP-SAIB gels were likewise analyzed. The PEG-AuNP-SAIB gel suffered from PEG-AuNP migration towards the gel-boundaries over time [8]. Figure 4 and 5 show micro-CT scans of mice after injection of the PNPAM-AuNP-SAIB gel. The PNPAM-AuNP-SAIB gel provided high stability in vivo, as well as a higher X-ray contrast level than the PEGylated AuNP-SAIB gel (as expected due to higher AuNP loading being possible with the PNPAM coating).

In-vitro stability test of the PEG-AuNP-SAIB gel (Figure 4) showed no burst release of PEGylated AuNPs. This burst release was completely avoided (<1%) with the PNPAM-AuNP-SAIB gel, even with concentrations up to 100 mg·mL\(^{-1}\).

The contrast level and homogeneity of the gels were analyzed manually in each CT scanning slice. First, a bounding box was drawn around each gel, and the gels were segmented by active contour model [9]. The median values of the two gel types were compared using a Wilcoxon rank-sum test [10]. The homogeneity of the gels was then analyzed by first applying a Box-Cox transformation [11] to the two datasets for variance stabilization, followed by a Wilcoxon rank sum test for comparison of variance.

Handling of PNPAM-coated AuNPs was furthermore superior to the PEGylated AuNPs, as they can be lyophilized and stored as a stable powder, that is easily dispersible in EtOH. Based on the presented in vitro and in vivo results, the PNPAM-AuNP-SAIB gel was evaluated to be suitable for in vivo use as a fiducial marker for IGRT.

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