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 high precision imaging techniques like 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 radiation therapy 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 decreasing 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 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 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 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 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 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 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 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 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 during treatment [1,5].

The poster presents the development of a liquid fiducial tissue marker based on sucrose acetate isobutyrate (SAIB) and uniform, coated gold nanoparticles (AuNPs). The 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).

Experimental methods

The AuNPs were synthesized by a three step seeding protocol using chloroaic acid and trisodium citrate (Scheme 1). Three different coating options were tested: 1) Thiol-terminated PEG (SAIB) polymers, 2) thiol-terminated PNIPAM polymers and 3) a dithiolane functionalized SAIB derivative that was synthesized in 4 steps from sucrose.

The AuNPs-SAIB gels were made by dispersing the coated AuNPs in EtOH followed by mixing with SAIB and PLA. In vitro stability studies of AuNP-SAIB gels were conducted in PBS-buffer at 37°C. In vivo contrast and stability of the gels were monitored by micro-CT after injection of 200μL of SAIB/EtOH/PLA (75:20:5) ± 30mg∙mL⁻¹ PNIPAM-AuNPs or 10mg∙mL⁻¹ PEG-AuNPs at the upper left flank of immunocompetent NMR-mice. The X-ray contrast level, gel volume and gel homogeneity were evaluated over time by active contour model.

Results

Stable and uniform PEG - and PNIPAM-coated AuNPs were successfully synthesized, confirFigure 2. The dithiole SAIB functionalized AuNPs were discarded due to observed aggregation of the nanoparticles. In-vit Celestica: test of the PEG-AuNP-SAIB gel (Figure 3) shows the release of PEGylated AuNPs. This burst release was completely avoided (<1%) with the PNIPAM-AuNP-SAIB gel, even with concentrations up to 100mg·mL⁻¹.

Image contrast and stability of the PEG- and PNIPAM-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 PEG-AuNP-SAIB gel. The PNIPAM-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 compared with the PNIPAM coating).

In-vitro, the PNIPAM-AuNP-SAIB gel had a significantly higher median (P-value: 0.0006) as expected due to higher loading of AuNPs. Despite a much better contrast, surprisingly no significant difference was found in the variance of the gels (P-value: 0.0734), thereby indicating the same extent of inhomogeneity in the PNIPAM-AuNP-SAIB gel and the PEG-AuNP-SAIB gel. This is due to the inhomogeneity only being visible at higher intensity levels (Figure 5). Due to the much lesser resolution in clinical imaging systems, the slight inhomogeneity of the PNIPAM-AuNP-SAIB gel will not be visible and will therefore not be an issue in clinical applications.

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

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