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 correlation of the anatomical positions of several tumors to internal fixation points such as increased to ensure radiation dose coverage during treatment [4].

Experimental methods

The AuNPs were synthesized by a three-step seeding protocol using chloroauric acid and Sodium Citrate [7]. Three different coating options were tested: 1) Thiol-terminated PEG-sodium polyacrylate (SAIB) 2) thiol-terminated PNIPAM-sodium polyacrylate and 3) a dithiolane-SAIB coating. The thiol-terminated PEG-sodium polyacrylate (SAIB) coatings are known to prevent aggregation of the nanoparticles. In vitro stability and was assessed to be a suitable tissue marker for image guided radiotherapy (IGRT).

Results

Stable and uniform PEG- and PNIPAM-coated AuNPs were successfully synthesized, confer Figure 2. The dithiolane SAIB functionalized AuNPs were discarded due to observed aggregation of the nanoparticles. In vitro stability test of the PEG-AuNP-SAIB gel (Figure 3) showed a burst 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.

In vivo 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 being possible with the PNIPAM coating).

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.

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 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 can be lyophilized and stored as a stable powder, that is easily dispersible in EO/TH. Based on the presented in vitro and in vivo results, the PNIPAM-AuNP-SAIB gel was evaluated to be suitable for use as a fiducial marker for IGRT.

References

[10] F. Wilcoxon, Biometrics 2.6, 80

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