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

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Within the field of radiotherapy, modern radiation oncology relies on high precision imaging technologies 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 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 planned 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 planned 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 radiopaque markers due to their excellent radiographic contrast, but the implantation procedure may cause severe complications [7]. Migration of seeds is likewise an issue. As an alternative, liquid fiducial markers are therefore of high interest.

Results

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 PEGA-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 PEGylating 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. In vivo, the PNIPAM-AuNP-SAIB gel was evaluated to be 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.

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