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MR MONITORING OF HIFU-MEDIATED LOCAL DRUG DELIVERY WITH TEMPERATURE SENSITIVE LIPOSOMES

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Introduction. Temperature-triggered drug delivery is a promising treatment option in oncology, leading to an improved therapeutic efficacy and reduced toxicity profiles of the drug. Hyperthermia of the tumor can be accomplished using high intensity focused ultrasound (HIFU) under MR image guidance[1], while temperature-sensitive liposomes (TSLs) can serve as drug vehicles that release their payload upon heating. The co-encapsulation of a drug and an MRI contrast agent in the lumen of TSLs provides the ability to monitor the drug delivery process in vivo using MRI[2,3,4]. Here, TSLs incorporating both a chemotherapeutic drug (i.e. doxorubicin) and an MRI contrast agent (i.e. [Gd(HPDO3A)(H2O)]) were evaluated in vitro and in vivo for applications in MRI guided drug delivery.

Methods. TSLs containing doxorubicin and 250 mM [Gd(HPDO3A)(H2O)] were prepared[3]. Release of [Gd(HPDO3A)(H2O)] and doxorubicin from the TSLs during heating was studied in vitro by measuring the T1 and the intensity of fluorescence, respectively. In vivo experiments were performed on rats bearing a subcutaneous 9L tumor on the hind leg. Blood kinetics and biodistribution was studied for liposomes as well as for the liposomal contents ([Gd(HPDO3A)(H2O)] and doxorubicin) after intravenous injection of 111In-labeled TSLs. For MR-HIFU experiments, TSLs were injected intravenously while local hyperthermia in the tumor was induced for 30 minutes, using a 3T clinical MR-HIFU system. The local temperature-triggered release of [Gd(HPDO3A)(H2O)] was monitored with interleaved T1 mapping of the tumor tissue. At t=90 min after TSL injection the rats were sacrificed and tumors were analyzed for doxorubicin and gadolinium concentrations.

Results. In vitro studies showed a rapid and simultaneous release of the drug and the MRI contrast agent from the TSLs at 42 °C, while no leakage was observed over 1 hour at 37 °C. The combination of TSL administration with mild hyperthermia induced significant higher uptake of doxorubicin in the tumor as well as changes in the T1, whereas the T1 values of the surrounding muscle hardly changed. Control experiments with tumor bearing rats that received no HIFU showed only a minor uptake of doxorubicin going along with a subtle decrease in T1 upon injection of the TSLs. For all experiments, a good correlation was found between the ?T1 and the concentrations of doxorubicin and [Gd(HPDO3A)(H2O)] in the dissected tumors[4].

Conclusions. The good correlation between ?T1 and the uptake of doxorubicin in the tumor implies that the in vivo release of doxorubicin from TSLs can be probed in situ with the longitudinal relaxation time of the co-released MRI contrast agents. The combination of MR imaging of drug release from TSLs and pharmacokinetic modeling, may realize a way to quantify and monitor the drug delivery process and serve as a tool in clinical decision making to personalize treatments.

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References: 1) Dromi et al., Clin.Canc.Res. 2007 13 (9) 2722-2727, 2) Salomir et al., JMRI 2005 22 534-540, 3) De Smet et al., J. Control. Release 2010 143 p.120-127, 4) De Smet et al., J. Control. Release 2011 150 p.102-110.