Controlled RF hyperthermia using TmDOTA as a MR thermometer

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Introduction

Early experimental and clinical evidences demonstrate a substantial benefit of hyperthermia as adjuvant to radiotherapy and chemotherapy for treatment of some human cancers [1]. In HT therapy, the temperature of a tumor is raised by few degrees above the normal body temperature. Radio-frequency (RF) is used for heating deep-seated tumors since the wavelengths associated with it are considerably longer than the dimensions of parts of human body. As a MR spectrometer is equipped with RF system to excite spins, the spectrometer itself can used as a RF source for HT treatment of tumors. We have developed non-invasive MR thermometers based on the temperature dependence of hyperfine shifted 1H signal of paramagnetic lanthanide complexes of DOTA4- and DOTMA4- [2]. 1H chemical shifts of Tm complexes of DOTA- and DOTMA- are 50-100 times more sensitive to temperature than the water signal and are insensitive to changes in tissue microenvironment such as pH, concentration of other ions and presence of macromolecules. Thus, these paramagnetic complexes provide sensitive and accurate methods for monitoring temperature. In this work, we present a robust MR technique to produce controlled HT using the MR spectrometer as a HT applicator and TmDOTA- to monitor temperature. This technique uses a real-time feedback method for controlling tumor temperature during RF heating. The sample temperature, measured from the 1H frequency shift of TmDOTA-, is used to adjust the RF power to 'lock' the temperature at a desired value.

Methods

The RF HT technique was developed on a 9.4T 89 mm diameter vertical bore magnet interfaced to a Varian console. A 14 mm diameter slotted tube resonator dual tuned to 400 MHz and 100 MHz was used in phantom and animal experiments. 1H spectra from TmDOTA- were acquired using a 1 ms SINC shaped RF to selective excite the H5 signal from the complex at ~230 ppm. RF HT was delivered at 100 MHz. After developing and testing the RF HT technique in phantom experiments, the technique was applied to deliver HT to a sc-implanted RIF-1 tumor in C3H mice. Approx. 2 mmole/kg bodyweight TmDOTA- was injected in the animal through the tail vein and 1H spectra from H5 resonance from TmDOTA- were collected every 20 sec. Heating of tumor was initiated by turning on the decoupler RF at 100 MHz and setting the target temperature to 41oC. The decoupler RF was turned off after 20 min of HT and the tumor temperature was allowed to return to the baseline value spontaneously

Results

Figure 1 shows an example of the application of the RF HT technique to a sc-implanted RIF-1 tumor. A staked plot of some of the 1H spectra showing the H5 signal from TmDOTA- is presented in the top panel. The signal line-width was significantly broad and became broader during the heating because of heterogeneity in temperature. The bottom panel shows changes in tumor temperature and heating RF power levels during the experiment. The initial median temperature of the tumor measured from the chemical shift of H5 signal from TmDOTA- was 34.0oC. Heating was initiated by setting the target temperature to 45.0oC and the heating RF power level to 32 dB. The tumor reached the target 45.0oC temperature within 5 minutes after initiating the RF heating. The feedback mechanism modulated the decoupler RF power during heating such that the tumor temperature remained within 40.3 and 41.2oC. When the heating power was turned off after maintaining the temperature near 41oC for 20 min, the sample temperature returned to the baseline value in an exponential fashion. Half-hour after turning off the heating power, the temperature returned back to 34.0oC.

Conclusions

The presented MR technique provides a robust method for delivering controlled RF HT to sc-implanted tumor models in the magnet. The temperature of the tumor was maintained within 1oC near the target temperature. The major advantage of using a MR spectrometer as a RF HT applicator is that the metabolic and physiologic response to the treatment can be monitored using the same spectrometer. Developments of such methods are in progress.

References

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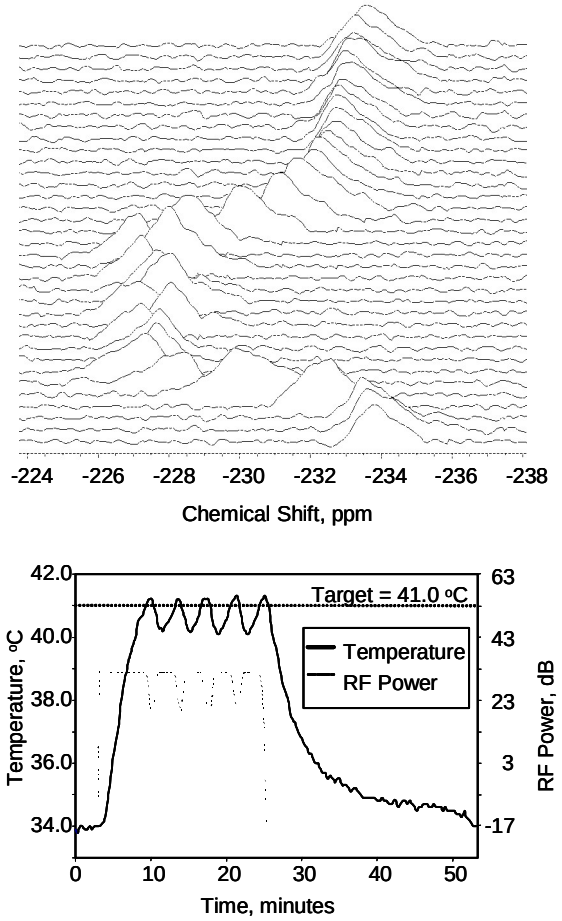

Fig. 1: Representative *in vivo* ^{1}H spectra from H^{5} of $TmDOTA^{-}$ from sc-implanted RIF-1 tumor during controlled RF HT experiment (*top*). Changes in tumor temperature and RF power level when the tumor was heated from 34°C to 41°C (*bottom*).