Magnetic Resonance Temperature Imaging of Light Activated Nanoshell Thermal Therapy

R. J. Stafford[1], D. P. O'Neal[2], J. D. Hazle[1]

[1]Imaging Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, United States, [2]Nanospectra Biosciences, Inc., Houston, TX, United States

Synopsis

A novel thermal therapy delivery technique using low power near infrared irradiation delivered to a distribution of gold-silica nanoshell particles under MR-guidance has been recently introduced [1]. This research expounds upon the previous research by using MR temperature imaging as a tool to investigate the spatiotemporal temperature distribution associated with an intravenous injection of nanoshells into tumor bearing mice [2]. Tumors were inoculated and grown subcutaneously and injected nanoshells were allowed to accumulate passively in tumors via the enhanced permeability and retention of the tumors. MRI was used in the planning and post-therapy evaluation of treated sites while real-time MR temperature imaging (MRTI) monitored the distribution of temperature within tissue during the procedure. MRTI was demonstrated to be an excellent tool for determining the extent of thermal energy delivered during treatment region and was useful for evaluating the differences in uptake. MR imaging techniques, such as dynamic contrast enhanced imaging, aided in the evaluation of the appropriateness of the tumor models. These preliminary data demonstrate the usefulness of using MR-guidance when evaluating new technologies, such as nanoshells, *in vivo*.

Introduction

Minimally invasive thermal therapy provides a less invasive alternative to local treatment of solid tumors than conventional surgery and is conducive to outpatient treatments. Light activated nanoshell thermal therapy is a novel approach to this set of minimally invasive procedures in that a low power, near infrared (NIR) diode laser can be used to irradiate a volume of tissue using at a sub-lethal level. In regions of tissue containing the nanoshells, preferential absorption of the energy from the laser rapidly heats the tissue. Unlike standard laser induced thermal therapy (LITT) techniques, only tissue with a sufficient concentration of nanoshells is ablated, leading to a highly conformal thermal delivery technique. The unique surface chemistry of the nanoshells give this treatment delivery technique the potential to move beyond the simple systemic application demonstrated here and into the arena of molecularly targeted treatments.

Materials

Gold-silica nanoshells (Nanospectra Biosciences, Inc., Houston, TX) were fabricated to absorb strongly at 808 nm and passivated using polyethylene glycol (PEG) to enhance the circulation time and maximize uptake of the nanoshells in the tumor via the enhanced permeability and retention effect. Tumor cells (CT26.wt) were subcutaneously inoculated onto backs of female Balb/c mice and grown to a tumor burden ≤ 9 mm diameter. Mice anesthetized using 1-4% isofluorane, depilitated at the tumor site and swabbed with 600 MW PEG diacrylate for optical coupling. An intravenous injection of 100-110 µl of PEG passivated nanoshells was delivered 24 hours prior to therapy while control mice received a saline injection. Tumors were irradiated extracorporeally at 4 W/cm^2 from a coherent NIR diode laser (λ=808 nm, 9 mm diameter spot) for 3 minutes. T1-w and T2-w images were used to plan the treatment location and to localize the treatment by verifying the position of the laser fiber prior to irradiation. Imaging was performed using a 3" receive only surface coil and a 1.5 T MR scanner (GEMS, Milwaukee, WI) equipped with high performance gradients (Cardiac Resonance Module). MR temperature imaging employed a complex phase-difference technique [3] using a fast, 2-D RF spoiled gradient-recalled echo sequence (TR/TE = 49.5 ms/10 ms, flip angle = 20°, bandwidth = +/- 16 kHz, FOV = 4 x 2 cm^2, partial Fourier acquisition, matrix = 256 x 64, 2 mm slice thickness) with 6-sec per image. Temperature and dose [4] information were displayed on a remote work station in near real-time using software developed in-house in the MATLAB environment. Mice were sacrificed 24 hours following treatment and tumors were either excised and fixed for histological evaluation (hematoxylin-eosin staining) or harvested and sent for neutron activation analysis to establish their gold content.

Results

The difference in the maximal temperature achieved in the tumor between a nanoshell and a treatment using saline control as measured by MRTI ranged from 15°C -30°C, in excellent agreement with previously published results using an intratumoral delivery paradigm [1]. Temperatures significant for thermal ablation (T>50°C) were achieved in tumors containing nanoshells across the entire tumor while saline controls resulted in superficial heating profiles (Figure 1). The maximal rate of heating was more constant in tumors containing nanoshells compared to saline injected controls at the site of maximal heating (Figure 2), with the rate of heating being roughly the same during the first 50-70 seconds of heating. In general, the nanoshell treated tumors demonstrated elevated temperatures with respect to the control tumors up to the point at which the tumor met the muscle. Figure 3 demonstrates a spatial profile of the maximum temperature achieved between a nanoshell treatment and saline control in which the tumor depth is nearly 4mm. Note how heating in the control continues smoothly across the tissue interface and into the muscle while the nanoshell tumor experiences a sudden drop in maximum temperature across the tumor-muscle boundary, highlighting the effect that the shells have extravasated through the leaky surrounding tumor tissue, but not into the surrounding muscle.

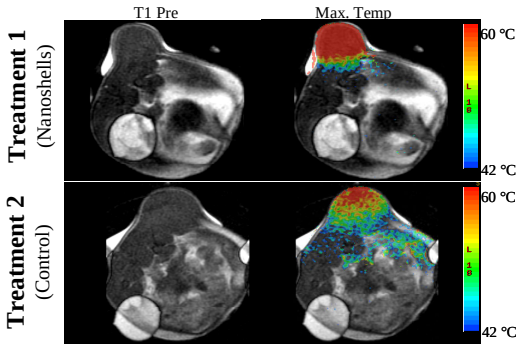

Fig. 1: Comparison of a treatment using systemically administered nanoshells versus a treatment without nanoshells demonstrating the difference in the distribution of maximum temperature.

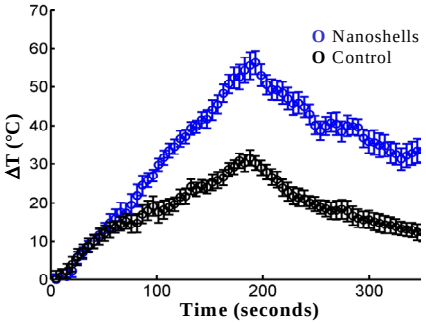

Fig 2: Temperature profile of nanoshell heating vs saline control as a function of time.

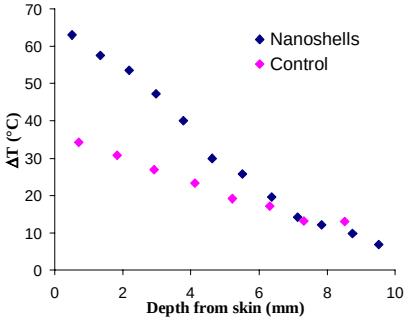

Fig. 3: Spatial profile of maximum temperature change in tumor as a function of distance for nanoshells vs control.

endothelial lining of the tumor microvasculature and into the

Conclusions

The results presented here demonstrate the power of using MR as a tool to aid in the development of light activated nanoshell therapy as it progresses into *in vivo* small animal tumor models by providing a means for assessing the bulk effects on the spatiotemporal heating patterns produced by the shells.

References

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