Evaluation of nanoshell mediated tumor ablation with real time multiplanar MR temperature imaging in a canine brain tumor model

A. Shetty[1], R. Price[2], J. Schwartz[3], R. Uthamanthil[1], J. Wang[3], A. Elliott[1], J. D. Hazle[1], and R. J. Stafford[1]

[1]The University of Texas M.D.Anderson Cancer Center, Houston, Texas, United States, [2]Baylor College of Medicine, [3]Nanospectra Biosciences, Inc.

Introduction: 30-40% of patients with head and neck cancers have recurrent loco-regional disease after completion of definitive treatment, including surgery, radiation therapy and chemotherapy [1] These approaches also cause serious functional impairment, and treatment of a recurrent tumor is a previously irradiated or post-surgical fibrosed field is a difficult problem [2]. A controlled minimally invasive alternative is the proposed treatment of nanoshell mediated heating with intratumoral fiber placement. The nanoshells consist of a spherical silica core, an outer shell of gold, and a coating of PEG to inhibit opsonization by the immune system. These particles are configured to preferentially absorb near-infrared (NIR) light and to emit heat through the process of surface plasmon resonance [3] and concentrate in the tumor by extended permeability and retention (EPR) effect. To overcome the light penetration limitation of surface illumination, delivery is achieved by MR guided placement of laser fibers into the tumor.

Material and Methods: Under anesthesia, burr holes were created in the right and left parietal bone of adult hound dogs n=6 (about 3 cm posterior to bregma and 1 cm lateral to midline), which were then fitted with skull bolts. Then, a 14-gauge catheter with trocar for support was introduced ~ 1.5 cm into the brain. Freshly excised TVT xenografts, grown in SCID mice, were minced into small pieces and inoculated into the brain via an 18 gauge spinal tap cannula and trocar on one side. A sham inoculation was done on the contralateral side. Handling of animals was in accordance to an Institutional Animal Care and Use Committee approved protocol. All imaging was performed on a 1.5T whole body MR scanner (EXCITE HD, GE Healthcare, Waukesha, WI) using an 8-channel, receive-only phased-array head coil (MRI Devices Corp, Gainesville, FL). After imaging confirmation of tumor size ~ 1cm size, nanoshells (AuroShell^{TM} particles, provided by Nanospectra Biosciences Inc., Houston TX) were infused at a rate of 5ml/min for a dose of 5.2ml/kg. 50µl blood was collected for evaluating the nanoshell t (1/2) in circulation by dynamic light scattering method (DLS)[3]. 24 hrs later, under imaging guidance, a 1-cm diffusing tip laser fiber (808 nm wavelength) within an actively cooled sheath (Visualase Inc, Houston, TX) was introduced intratumorally and delivered laser irradiation. Real-time monitoring of the temperature changes was accomplished using a temperature sensitive echo-planar imaging sequence [4] to obtain 5 planes of temperature images every 6 seconds(TE: 925ms,TR: 544ms,FOV: 20cm by 20cm,BW: ± 250kHz). Laser treatment of 3.5-4.2 W/cm2 with power times of 180 seconds was delivered. This created lesion sizes in the range of 1-1.5cm. Post-ablation MR assessment of tumor ablation included T1-weighted post-contrast imaging (TE: 9.2ms,TR: 800ms,FOV: 20cm by 20cm,BW: ± 25Khz) and T2-weighted imaging (TE: 100ms,TR: 4000ms,FOV: 20cm by 20cm,BW: ± 19.2 kHz). 48 hr follow up MR imaging was done, before necropsy by exsanguination. The prostate was sectioned in a plane, congruent to the MR imaging planes and digitally photographed. Tisssue samples were collected for Nuclear Activation Analysis (NAA) [5] (for tissue gold quantification). Tissue measurements were made by observers on the vendor supplied workstation (Advantage Windows version 4.1, GE Healthcare Technologies, Milwaukee, WI). MATLAB (Mathworks Inc, Natick, MA) software was used for processing temperature data and to estimate Arrhenius damage.

Results: Preferential damage was seen on the tumor side, with minimal damage in the contralateral normal brain. MR temperature monitoring showed that the tumor temperature was ~ 18˚C higher than the control side (fig 1a&b). Based on the temperature history, the Arrhenius damage estimation was 82 sq. mm and it matched well with the 48 hr imaging measurements. Damage on post DCE T1 was 89.1sq.mm (fig 1d) ,on T2 was 90.9 sq.mm(fig 1e) and 86.3 sq.mm on pathology slice(fig 1c). Small pockets of residual tumor was observed on the post-dynamic images and confirmed on histology. The DLS ratio at 15 minutes was in the range of 3.7 to 7.2 with t(1/2) range 360-405 minutes.

Conclusion: These preliminary results prove the efficacy of these nanoshells to deliver lethal damage to the tumor in a minimally invasive manner. The tumor heated up to a higher lethal temperature (~18˚C), compared to the contralateral control side. The damage was confirmed on pathology, with localized necrosis in the tumor and no damage in the normal brain. The survival of the tumor at the periphery could be due to the higher blood supply from the tumor capsule and the surrounding normal tissue. A longer follow-up imaging study could give an insight of treatment success and subsequent tumor regression. One of its biggest advantages is lack of cumulative toxicity. Although repeated use of radiation therapy and chemotherapy is very limited, nanoshell mediated heating can be applied many times at the recurrent site. It does not compromise subsequent treatments, and could be developed as a promising adjuvant to surgery, radiotherapy and chemotherapy.

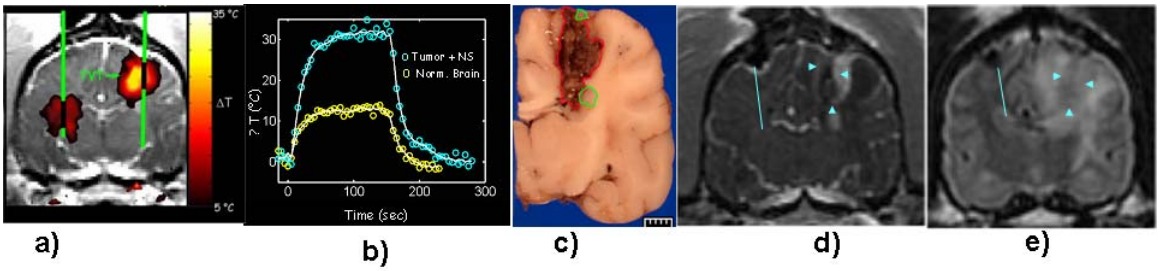

Figure 1: a)Maximum temperature image(overlay on post-DCE T1) and b) the temperature rise plot in the tumor and normal brain, c) Red outline shows the damage on gross pathology, green outline – viable tumor d) &e) shows the damage on post-DCE T1 and T2 images(arrow heads) and fiber track (line) in contralateral normal with no visible damage.

References:[1]Jager RF,AJNR,**26**:1193-1200(2005) [2] Gluckman JL,Laryngoscope,**93**:71-74(1983) [3] Elliott AM, Med Phy , **34**:3102-08(2007) [4] Xie H, Nanomedicine,**3**:89-94(2007) [5] Stafford RJ, et al, JMRI **20**:706-14 (2004) [6] James WD, J Rad Nuc Chem , **271**:451-55(2007)