MR Guided Focused Ultrasound Thermal Therapy in a Canine Tumor Model

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Introduction: Magnetic resonance imaging guided focused ultrasound (MRgFUS) therapy is a rapidly evolving technology for the non-invasive treatment of soft-tissue masses, including tumors [1]. In order to evaluate this technology in vivo, small animal tumor models (VX2 carcinoma in rabbits) have been employed [2]. However, the rabbit is not of adequate physical scale to simulate the conditions faced in human tumors (diameter, depth, etc).

The canine transmissible venereal tumor (TVT) has been shown to be a robust large animal tumor model [3]. The tumor can be implanted in many organs and grows to centimeter dimensions in a few weeks. This model system was chosen to evaluate MRgFUS of tumors that grew to centimeter dimensions in a few weeks. This technology in vivo, small animal tumor models (VX2 carcinoma in rabbits) have been employed [2]. However, the rabbit is not of adequate physical scale to simulate the conditions faced in human tumors (diameter, depth, etc).

The canine transmissible venereal tumor (TVT) has been shown to be a robust large animal tumor model [3]. The tumor can be implanted in many organs and grows to centimeter dimensions in a few weeks. This model system was chosen to evaluate MRgFUS of tumors that were of the same general scale (1-2 cm diameter) and depths (2-4 cm) typical of breast tumors in humans that are to be treated in a pending clinical study.

MR temperature imaging using the phase-difference technique was performed during sonication. Post-therapy assessment included T2, T1+C, and diffusion weighted imaging. MR image data were correlated with detailed histopathology of the resulting thermal injury.

Methods: Mongrel dogs were acquired from the UT Health Science Center-Houston. The dogs ranged in weight from about 45-50 lbs. A combination of meditomidine (0.5 mg/kg, intramuscular) and ketamine (25mg/kg, intramuscular) or isoflurane will be used to induce general anesthesia. The meditomidine and ketamine or isoflurane will be used to induce general anesthesia. Daily oral Cyclosporin-A (10mg/kg) was administered to mildly immunosuppress the animals, allowing for improved tumor development, growth, and metastasis. Oral Cyclosporin-A is administered BID for 2 weeks followed by SID maintenance. Cyclosporin is administered 1 week prior to tumor inoculation and continued until tumor treatment or harvest 30-40 days following inoculation. 0.5 cc of tumor fragment are injected into multiple sites at different depths in the paraspinal muscle masses. Tumors were allowed to grow 2-4 weeks to achieve mean diameters of 1-2.5 cm.

Studies were performed using a prototype MR compatible focused ultrasound therapy system (TxSonics, Haifa) interfaced to a whole-body MR scanner (General Electric Signa, Milwaukee, WI). Pre- and post-therapy images were acquired to assess the thermal damage. T2-weighted (FSE, TE/TR = 85/4000 ms, ETL = 12), T1-weighted (FSE, TE/TR = 20/400 ms, ETL = 4, with and without Gd contrast), and diffusion weighted images (b = 250, 500, and 750) were acquired.

Temperature sensitive MR images are acquired using a fast, spoiled gradient-echo (fGRE) sequence. Acquisition parameters are TE/TR = 8.6/18.4 ms, BW = 9 kHz, flip angle = 25°, slice thickness = 4 mm, and 256 x 160 acquisition matrix. The acquisition time is 3 s per image. Two images are acquired prior to sonication for baseline phase information, 4 are acquired during sonication, and 4 are acquired during the cooling period.

The FUS system uses a spherical, air-backed transducer with a focal length of 10 cm. The transducer is mounted on a three-dimensional positioning platform under computer control. Coordinates for focal ablations to cover the entire target volume are determined algorithmically. These locations are sonicated sequentially, with 60 second cooling delays, to cover the entire target volume ( usually tumor plus 5 mm margin). Sonication time is 12 seconds with input power of 70-90 W depending on tumor depth.

Results: A total of 8 tumors in 4 dogs were treated using MRgFUS. The tumors ranged in size from 1.0 to 2.5 cm in maximum diameter. Depth from the proximal tumor surface to the skin ranged from 1.0 to 2.5 cm, mean tumor depths ranged from 2.0 to 3.5 cm. A T2-weighted planning image is shown at the left in Fig. 1. The corresponding post-therapy T1-weighted+Gd image is shown in the right. The planned and MR post-therapy image volumes correlated well in all cases.

For seven days after therapy the animals were sacrificed and detailed histopathologic assessment of the tumor and surrounding tissue was performed. In general, agreement between planned, imaged, and pathologically proven ablation volumes was within 3 mm.

Discussion: MRgFUS is shown to be capable of treating tumors up to 2.5 cm in diameter at depths of up to 4.0 cm in a large animal model. Treatments were accomplished in a total of approximately 2 hours. This makes MRgFUS clinically viable technology for ablation of tumors in a substantial fraction of breast cancer patients.

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References:

Figure 1  On the left is a pre-therapy T2-weighted planning image. On the right is the corresponding post-therapy T1-weighted+Gd image immediately following MRgFUS therapy.