Pilot Study Correlating Tissue Stiffness and Gross Pathology of MRgFUS Thermal Lesions in Human Liver Cancer Xenoplant Tissue

S. Primak[1], Y. Le[1], J. Lai[1], L. Roberts[1], C. Reynolds[1], P. Rossman[1], J. Felmlee[1]

[1]Radiology, Mayo Foundation, Rochester, MN, United States

Introduction

MR guided focused ultrasound (MRgFUS) thermal therapy represents a new clinical option now available for treatment of uterine fibroids. Research continues to use MRgFUS in many areas of the body including breast, brain, bone, and liver. This study employed animal model xenoplants for FUS applications involving human liver cancer (Hep3B). Unfortunately the MR based thermometry methods most often employed do not always adequately represent the level or spatial extent of tissue ablation. Several authors have shown that tissue stiffness parameters change with tissue heating and may directly reflect tissue damage [1-3]. Our hypothesis is that tissue stiffness parameters, determined using MR elastography, correlate with cellular level thermal damage in liver cancer tissue and reflect tissue ablation. The purpose of these experiments was to evaluate this hypothesis in a pilot study using a nude mouse model with human liver cancer xenoplant.

Materials and methods

Experiments were performed on a 1.5T MR imager (Signa, GE Healthcare, Waukasha WI). Focused ultrasound was provided by a high power single element transducer system designed for operation within the MRI (Mark 0, Insitec Inc, Dallas TX). Stiffness information was acquired using a specialized imaging pulse sequence, where encoding gradients were applied in synchrony with shear waves induced by an external needle driver. The use of the needle had two functions: it is a good marker in lesion targeting and provided shear waves within the target tissue at high frequency. 2D MRE data were collected using shear waves of 130-300 Hz.

Seven nude mice were transfected with Hep3B tumor cells in the flank region. The cells were allowed to grow until the resulting tumor achieved 2-6 cm in diameter. The use of the intra-tumor needle during imaging and animal care concerns resulted in animal sacrifice immediately prior to experiment FUS treatment. Temperature monitoring was conducted during FUS ablation by phase-difference MRI (TE/TR=6/150 msec). 2D MRE data were acquired in the sagittal and coronal planes before and after FUS treatment.

Tumors were removed and bisected along the treatment axis. Each specimen was immersed in 1% solution of 2,3,5 Triphenyl tetrasolium chloride (TTC) at room temperature for about 30 min, at which time the FUS lesions could be clearly identified as white or unstained tissue vs. dark red normal viable tissue. The TTC-stained specimens were then routinely processed for histology.

Results

Histological sections show the FUS lesion to be clearly distinguished from untreated tumor by light microscopy as a stripe shaped region of necrosis. A typical coagulation necrosis exhibits an overall staining with eosin (red pink color) due to increased binding of the eosin to denatured intracytoplasmic proteins. Fig. 1 shows normal viable tissue stained as dark purple (due to Hematoxylin binding) and outlines cylindrically shaped region which represents the spot of maximum power of focused ultrasound. 2D stiffness analysis as shown in Fig. 2 indicates that FUS treated liver tumor increased in stiffness with thermal ablation (from 2-4.5 kPa to 9-15 kPa). The data from all seven animal experiments are shown in Fig. 3, where the average increase in tumor stiffness with FUS was ~3.4 kPa.

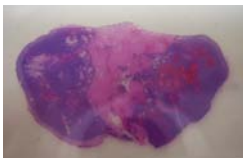

Fig 1. Histological slice

Discussion and Conclusions

This study presents a pilot analysis of tissue stiffness as a means to assess thermal ablation in Human Liver cancer xenoplant tissue. TTC staining improved visualization of ablated tissue immediately after FUS treatment. The data shown in figure 3 indicate that in 5 of 7 experiments, treated liver cancer tissue was shown to significantly increase in stiffness with thermal treatment. In the two experiments where stiffness did not change, the FUS power level was low or the baseline level of necrosis prevented analysis. These data support our hypothesis that tissue stiffness determined using MRE elastography correlates with cellular level thermal damage in liver cancer tissue; and suggest further in vivo experiments with careful control on FUS power level and baseline necrosis in future work

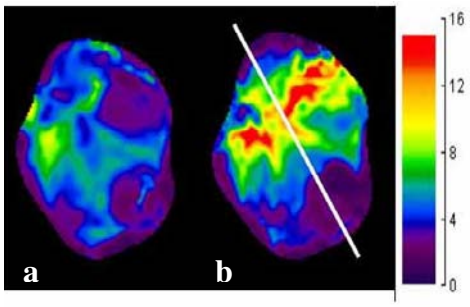

Fig. 2 (a) Coronal 2D stiffness (μ) map before FUS treatment FOV=8 cm;
(b) Coronal 2D stiffness map after FUS treatment, white line shows the sagittal cut for pathology, μcolor bar on the right

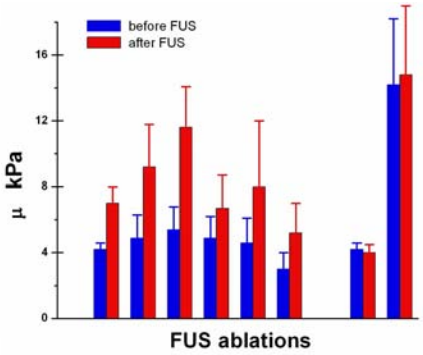

Fig. 3. Represents combined results for all ablation treatments (8 in seven mice) and indicates that stiffness increased as the result of FUS treatment. μdid not change in two cases (on the right) due to low temperature and high level of baseline necrotic tissue (both confirmed by pathology).

References

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3. Le Y, *et al.* MRM 2005, in press.