Focused Ultrasound – A paradigm shift to non-invasive surgery

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Introduction

Focused ultrasound is an early-stage, non-invasive therapeutic technology with the potential to treat a wide range of serious medical disorders. Stemming from more than 18 distinct bioeffects of focused ultrasound in tissue, it is now approved or under investigation to treat over 100 conditions ranging from neurological disorders to cancers, pain and cardiovascular disease. Over the past several years, the field has experienced unparalleled progress, and recent research advances have brought us to the tipping point for the technology to transform from research to widespread clinical use.

Methods

In Focused Ultrasound ultrasound is focused through the intact skin into a target area in the body. Depending on the physical parameters (power, peak pressure, continuous, pulsed, duty cycle), the energy deposition in the focal area lead to various tissue effects, including thermal ablation, mechanical disruption of cell structures (histotripsy) and neuro modulation. Other effects like mild hyperthermia or the temporal opening of the blood-brain barrier are utilized for a targeted delivery of drugs. Image guidance is used for treatment planning, monitoring tissue changes (US) or temperature (MRI) during the procedure and validating technical success.

Results

Regulatory approvals for non-invasive treatment of multiple medical conditions around the world have validated the technology and have given patients new treatment options. With clinical results recognized by health insurance companies in multiple countries, these treatment options are becoming available to a broader patient population.

Conclusion

This presentation will give an overview of the available technology, current clinical indications and summarize the ongoing work on new indications in the field, address the key challenges in adoption and research opportunities, and share the Foundation's strategy for advancing this field including funding, awareness building, workshops and other opportunities for collaboration.

Magnetic resonance imaging-guided thermal Therapy with Focused Ultrasound in Preclinical MRI

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Introduction

Non- or minimally invasive thermal therapy using e.g. focused ultrasound as a local treatment of benign and malignant cancer diseases has received increasing interest in recent years. Focused ultrasound is an intervention which allows precise and non-invasive tumor treatment without skin penetration based on Magnetic resonance imaging (MRgFUS). Tumor heating at moderate temperatures (41-46°C) using MRgFUS has the potential to achieve sensitization before radiation therapy. The purpose of this study was the implementation of a new preclinical FUS system and MRI based targeting and temperature control in tumor bearing mice.

Methods

A novel MRI conditional FUS phased-array transducer (11x11 elements, copper shielding, aperture 1.0cm^2, frequency 2.0MHz) was developed and installed at 7T MRI (Bruker). The MR-compatibility of the transducer was tested with an agar-$CuSO_4$ phantom prior to intervention. For *in vivo* MRgFUS, a mouse was anesthetized with 2% isoflurane in air and oxygen. The sonication was started manually for 55s at 4.8W/cm^2 followed by MR-thermometry [FLASH: TE=4.5ms, TR=80ms, FOV=8x5cm^2, slices=6 (2mm), matrix=64^2; acquisition time=17s]. The sonication power was adjusted to hold the temperature at 45°C for 30min. Real-time temperature monitoring at the skin was performed with fiber optics (Luxtron). MR-thermometry was visualized offline in MATLAB.

Result

MR-images of the phantom showed 2.4-fold reduction of the signal-to-noise (SNR) from 161 to 67 in presence of the transducer. FLASH-images of the mouse showed SNR of 11. FUS heating *in vivo* was achieved and target temperature was reached after 2min. The target temperature (45°C) varied ±1°C. Thermometry calculations showed maximum temperature discrepancy of ≤1.4°C between the temperatures measured by fiber optics (44.3°C) and thermometry (42.9°C).

Conclusion

This study showed the feasibility of targeted non-invasive FUS interventions and MRI based temperature control preclinically. The measured SNR ensures minimum background noise for MR-thermometry calculations.

Radiosensitization of human cancer cells with *in vitro* focused ultrasound

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OBJECTIVES

Due to non-invasiveness and quantitative temperature control with magnetic resonance imaging (MRI), focused ultrasound (FUS) could be a potential sensitizer to support oncological radiation therapy (RT) in future. Here, the impact of thermal and mechanical effects of FUS combined with RT on human cancer cells was investigated *in vitro*.

METHODS

Human glioblastoma (T98G) and prostate cancer (PC-3) cells were seeded in ultrasound-penetrable 96-well plates (Greiner Bio-One). An *in vitro* FUS-system was developed (IMSaT, Dundee) and modified, comprising a programmable motor system (VELMEX Inc.) and customized 1.47MHz transducer. Moderate FUS heating was induced at 225W/cm^2 (45°C, 30min) and cavitation at 1204W/cm^2 for 40s. Cavitation was measured with fiber-optic hydrophone (Precision Acoustics) and validated chemically with terephthalic acid (TA, Sigma). Temperature was monitored by thermal camera (Optris) during sonication. Single RT at 10Gy was applied using X-Rays (Gulmay; 0.76Gy/min) 60min after FUS. Effects on metabolic activity (WST-1, Roche), DNA double-strand breaks (γH2A.X, Cell signalling) and cell migration (Transwell-Matrigel assay, Corning) were evaluated.

RESULTS

Combination of FUS heating and RT leads to significant ($p \leq 0.05$) reduction in metabolic activity in T98G to 79% and in PC-3 to 41%, compared to RT alone with 96% and 54% metabolic activity, respectively. The number of residual DNA double-strand breaks was significantly enhanced after FUS+RT (T98G: 18; PC-3: 9 foci/nucleus) compared to RT alone (T98G: 12; PC-3: 4 foci/nucleus). Interestingly, application of short FUS-cavitation and RT lead to reduction in metabolic activity (48%) and reduced the potential of PC-3 to migrate from 54% (RT) and 77% (FUS-cavitation) to 33% (FUS-cavitation+RT).

CONCLUSIONS

Our results demonstrated that FUS induced thermal and mechanical effect has great potential to radiosensitize cancer cells non-invasively. In addition, short FUS-cavitation treatment combined with RT seems to be more effective compared to the moderate heating for longer time.