4th European symposium on focused ultrasound therapy

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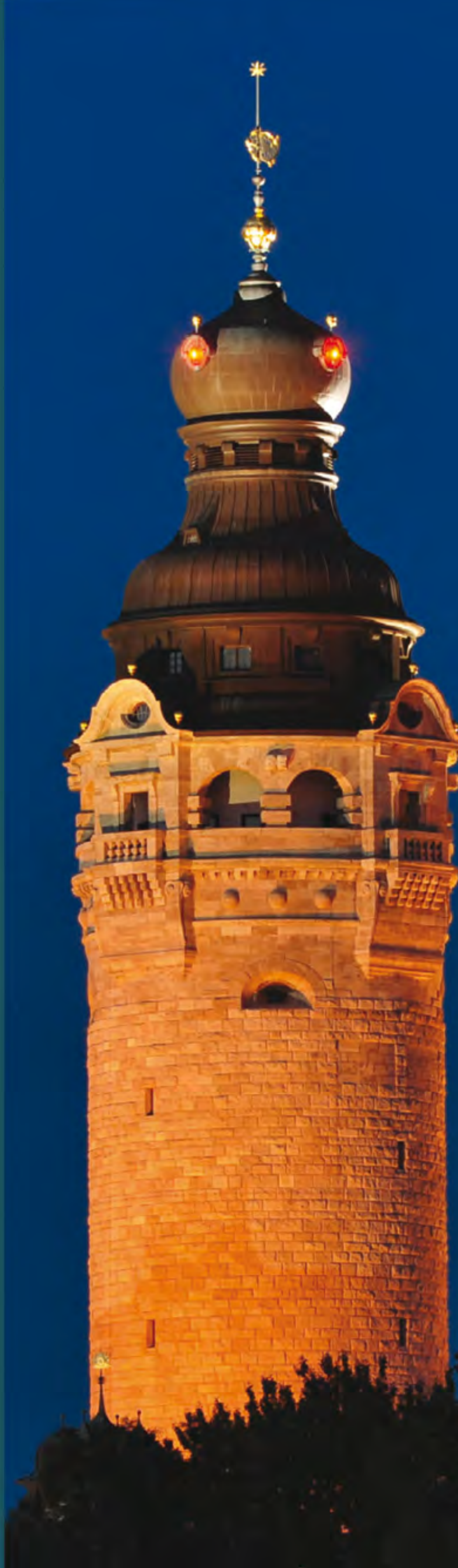
Focused Ultrasound Therapy

4th European Symposium

October 26 – 27, 2017
Leipzig, Germany
Salles de Pologne

Book of Abstracts



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Abstract 1

MR-GUIDED FOCUSED ULTRASOUND ROBOTS FOR PRE-CLINICAL USE

Christakis Damianou and Marinos Giannakou

Introduction
In this paper 3 different MR-guided focused ultrasound pre-clinical robots are presented. In one robot all the moving parts are immersed in water (2 linear axes). In the second one only the transducer is immersed in water(3 linear axes, 2 angular). The third one consist of 3 identical linear stages.

Materials and Methods
The propagation of ultrasound can be inferior-superior, superior-inferior or lateral. The positioning device incorporates only MRI compatible materials such as piezoelectric motors, and plastic (ABS). The robot can host single element spherically focused transducer or phased array transducers.

Results
The system was tested successfully in a phantom which includes agar, Silica and evaporated milk and in animals for various tasks (accuracy, MR compatibility, creation of single lesions, and creation of overlapping lesions). The robots can be used for different applications such as drug delivery, sonothrombolysis, thermal ablation, blood brain barrier opening etc. The accuracy of this robot is 20 μm.

Discussion
Simple, cost effective, portable positioning devices have been developed which can be used in any MRI scanner since they can be placed on the scanner‘s table. The proposed systems have the potential to be marketed as cost effective solutions for performing experiments in small and large animals

Acknowledgement
This work was supported by the Research Promotion Foundation of Cyprus and the European regional development structural funds (project number ΑΝΑΒΑΘΜΙΣΗ/ΠΑΓΙΟ/0308/05 and ΕΠΙΧΕΙΡΗΣΕΙΣ/ΕΦΑΡΜ/0308/01.

Topics: Solution for small animal FUS/HiFU

Abstract 2

Ultrasound Guided High Intensity Focused Ultrasound Ablation of Breast Fibroadenoma: Early Report from the United States Pilot Study

David Brenin, George Stukenborg and Carrie Rochman

Introduction

Fibroadenoma is a common benign breast mass that can cause pain, a palpable lump, and anxiety. Current management includes observation or surgical excision. This study evaluated the safety and feasibility of Ultrasound guided High Intensity Focused Ultrasound (USgHIFU) delivered by the Echopulse device (Theraclion, Paris) for treatment of breast fibroadenomas. Patient safety, cosmetic outcome, tumor response, and patient experience were assessed.

Materials and Methods

Twenty patients with palpable, breast fibroadenomas 1cm or larger were enrolled in a single-arm FDA approved clinical trial (IDE #G130252) and underwent treatment of their tumor utilizing the Echopulse device. Optimal energy per sonication was established for each patient by determining the minimal setting found to produce bubbles within the lesion as observed on real-time B-mode ultrasound. All tumors met the following criteria: Distance from the skin of ≤ 23 mm to the posterior border of the fibroadenoma, ≥ 5 mm from the anterior border of the fibroadenoma, and ≥ 11mm from the focal point of the HIFU treatment. The chest wall was more than 1cm from the posterior margin of the tumor, and tumor volume was between 0.3cc and 10cc. Patient treatment experience, toxicity, cosmesis, and change in tumor size on both physical examination and ultrasound measurement were obtained immediately after treatment and at 3, 6, and 12 months.

Results

Enrollment is complete with 20 of 20 (100%) patients successfully completing therapy. Mean tumor volume was 1.8cc (SD = 1.23, Range 0.57 – 5.7). Mean patient age was 35.2. Forty percent of patients were Caucasian, 40% Latino, and 20% were Black. Fifty percent reported a painful mass prior to treatment. Mean power/sonication = 38.3 watts. Mean number of sites treated/patient = 34.3. All early adverse events were grade 1 or 2, no skin burns, damage to adjacent structures, or other major toxicities were observed at day 0, 7, or 3 months post-treatment. The most common toxicity observed was mild pain, reported by 15/20 (75%) of patients during treatment, and 14/20 (60%) at day 7. Mean pain score during treatment = 16 on a scale from 0 to 100 (100 = worst pain). Mean pain score at day 7 = 12.2. Patient satisfaction from those completing 3 months follow-up was 4.4 on a scale of 1-5 (5 = most satisfied), likelihood of recommending it to a friend or family member was 4.7 (5 = strongly agree).

Discussion

To date, in study IDE #G130252, Ultrasound guided Focused Ultrasound Ablation for treatment of fibroadenoma has been safe, well tolerated, and resulted in minimal toxicity. Based on the above results, a larger multi-center clinical trial is now currently open to accrual in both the United States and Europe.

Acknowledgement

None

Topics: Benign lesions, Breast cancer

Abstract 3

Translation of Research for MR guided Focused Ultrasound Application for Moving Target Tumour Ablation in Abdominal Area: Coil Selection Criteria

Senay Mihcin, Andrew Dennison, Jan Strehlow, Michael Schwanke, Giora Sat, Yoav Levy, Sabrina Haase, Tobias Preusser and Andreas Melzer

Introduction

Objectives: Magnetic resonance imaging (MRI) has been widely utilized in the medical field for imaging, diagnoses and monitoring of treatments. MR guided focused ultrasound applications for tumour ablation heavily rely on MR imaging. MR scans are crucial for planning the treatment, detecting the morphology of the tumour for proper dosimetry. MRI has the superiority over any other imaging modalities by providing thermal data of the sonicated tumour area in real time. However, ablating to a moving target tumour in real time requires real time tracking and real time thermal map of the targeted region. TRANS-FUSIMO project focuses on providing solutions to translate science into clinical applications bringing MRgFUS technology to clinics for liver tumour ablation.

Materials and Methods

1.5T (GE Healthcare Systems, Chicago, USA) and the transducer of ExAblate 2100 CBS system (InSightec Ltd., Tirat Camel, Israel). The software collects images of the transducer for image registrations with MR coordinates then planning imaging, treatment planning and monitoring steps are followed. For liver imaging, 3D FIESTA, in Sagittal and Coronal plane (product PSD) is used. To monitor thermometry during breathing motion, sagittal single-shot, Asset Echo Planar Imaging (EPI) with 100 phases per location (interleaved), TE: 26.4 ms, TR: 100 ms is utilized. To collect data with good temporal resolution and reliable thermal accuracy with maximum signal to noise ratio, a feasibility study is conducted on tissue mimicking phantoms with vascular structure motion to observe the thermometry with different sets of coils such as; cardiac coils (GE Signa, USA), interventional single channel Duoflex coils (MR Instruments, MN, USA), 1.5 T Gem Flex coils (NeoCoil, WI, USA), and torso coils (GE Signa, USA) were evaluated for positioning distance, tracking and realistic thermometry. Motion was provided using INNOMOTION Robotic arm (IBSMM, Prague, Czech Republic) to simulate 1D breathing motion or with an air ventilator mechanism to push and pull the phantom based on the configuration of the coils. Experiment procedure consisted of sonicating for 100 W for 30 seconds for static sonication, static sonication and tracking, and dynamic sonication and tracking algorithms. Results were checked for consistency in these three cases for each coil and across the coil set ups for consistent thermometry data.

Results

Results show that for accurate sonication to a position, registration plays a crucial role. Sonication deviation error was calculated as less than 1 mm in static scenarios. Planning images provided the desired level of detail for planning. Coil evaluation show that cardiac coils 8 channel (GE Signa, USA), interventional single channel Duoflex coils (MR Instruments, MN, USA), 1.5 T Gem Flex coils (NeoCoil, WI, USA) provide consistent thermometry information for static and dynamic cases with tracking. Integration of tracking algorithm caused SNR and efficiency to drop (Figure 1). Torso coils (GE Signa, USA), however. showed severe loss of thermal signal in dynamic cases (Figure1). This is mainly the coil channels are not located close enough to the sonication spot and distance between the channels. Tests with 1.5 T Gem Flex coils showed that distance between the coils is crucial and image quality highly depends on the distance between the coils.

Discussion

For moving target tumour ablation, Trans-Fusimo treatment system provides means to apply focused ultrasound sonication in real time, monitor thermal changes, and track the landmarks in real time. Based on the pre-clinical tests, the distance between the coils play crucial role in image quality and application of the treatment. This might affect the patient selection criteria for reliable application of the system. Currently, we do not recommend use of Torso coils (GE Signa, USA) due to high level loss of thermal signal during monitoring. However, there is a potential for improvement in coil design with more channels to collect high strength signal covering the liver to overcome this weakness to include larger patient population to apply MRgFUS reliably based on the latest state of the art applied technology explained in this study.

Acknowledgement

This work was supported by the European Community's Seventh Framework Programmes [FP7/2007–2017] and [FP7/2014–2019] under grant agreement numbers [270186] (FUSIMO project) and [611889] (TRANS-FUSIMO project)

Topics: Abdomen

Abstract 4

Magnetic Resonance guided High-Intensity Focused Ultrasound ablation of Uterine Fibroids and Adenomyosis: The Impact of Scar-patch on Treatment Outcome

Bilgin Keserci and Nguyen Minh Duc

Introduction

Magnetic resonance (MR)-guided high-intensity focused ultrasound (HIFU) is a hybrid system combining the therapeutic abilities of HIFU and the imaging capabilities of MR imaging. Despite the clinical efficacy of this approach for uterine fibroid and adenomyosis treatments, the presence of extensive abdominal scars in the ultrasound beam path remains a limitation, due to the potential for skin and subcutaneous tissue burns occurring during HIFU treatment.
Our aim in this study was to compare the immediate nonperfused volume (NPV) ratios, the volume reduction ratios, the transformed symptom severity score (tSSS) improvements at 6-months follow-up between the patients with and without abdominal scars for accessing impact of scar-patch in MRgHIFU treatments of both uterine fibroids and adenomyosis.

Materials and Methods

70 uterine fibroid patients (39.1±5.7 years with a range of 22–53 years) and 60 adenomyosis patients (40.5±6.8 years with a range of 30–56 years) who underwent MR-HIFU ablation were divided into 4 groups: (i) no-scar fibroid group (n = 46), (ii) scar fibroid group (n = 24), (iii) no-scar adenomyosis group (n = 38) and (iv) scar adenomyosis group (n = 22).

Results

The mean volume of fibroid was 168.9 ml 140.2 (6.0-637.0 ml) for the no-scar fibroid group and 203.3 ml 197.2 (37-794 ml) for the scar fibroid group, respectively. The mean volume of adenomyosis was 108.9ml 58.2 (17-218.0 ml) for the no-scar adenomyosis group and 122.4 ml 67.2 (32-246 ml) for the scar adenomyosis group, respectively. The NPV ratio was 92.5% 13.4 (32-100 %) in the no-scar fibroid group and 86.6% 15.6 (57.4-100%) in the scar fibroid group (p>0.05). Meanwhile, The NPV ratio was 76.9% 24.6 (10.4-100%) in the no-scar adenomyosis group and 72.5% 27.2 (11.3-100%) in the scar adenomyosis group (p>0.05). The fibroid volume reduction ratio at 6-months was 43.4% 20.9 (20.9-83.6%) for the no-scar fibroid group and 45.5 % 26.1 (3.5-79.8%) for the scar fibroid group (p>0.05). The adenomyosis volume reduction ratio was 21.6% 14.5 (21.9-45.7%) for no-scar adenomyosis group and 22.2% 17.6 (21.9-48.9%) for the scar adenomyosis group (p>0.05). The tSSS improvement at 6-months follow-up was 79.5% 27.9 (-6.7-100%) for the no-scar fibroid group and 70.1% 39.9 (-20-100%) for the scar fibroid group (p>0.05), 59.2% 31.3 (0-100%) for the no-scar adenomyosis group and 60.6% 30.3 (11.1-100%) for the scar adenomyosis group (p>0.05).

Discussion

Our findings revealed that there are not different in treatment outcome in both uterine fibroids and adenomosis between no-scar and scar patient groups. Therefore, we suggest that the scar patch could be used efficiently in the MRgHIFU treatment of uterine fibroids and adenomyosis patients with abdominal scars.

Acknowledgement

All authors have no conflict of interest to declare.

Topics: Abdomen

Abstract 5

Scanning ultrasound as a novel treatment modality for Alzheimer‘s disease

Jürgen Prof Götz, Rebecca M. Dr Nisbet and Gerhard Dr Leinenga

Introduction

Introduction. Alzheimer's disease is characterized by the deposition of amyloid-β as extracellular plaques and hyperphosphorylated tau as intracellular neurofibrillary tangles. Tau pathology characterizes not only Alzheimer's disease, but also many other tauopathies, presenting tau as an attractive therapeutic target. Passive tau immunotherapy has been previously explored; however, because only a small fraction of peripherally delivered antibodies crosses the blood-brain barrier (BBB), enters the brain and engages with tau that forms intracellular aggregates, more efficient ways of antibody delivery and neuronal uptake are warranted.

Here, we investigated the efficacy of a novel 2N tau isoform-specific single chain antibody fragment (scFv), RN2N, delivered by passive immunization in the P301L human tau transgenic pR5 mouse model. We further explored a novel method, scanning ultrasound (SUS) as a tool to transiently open the BBB and facilitate the brain uptake of RN2N.

Materials and Methods

Methods. In the brain, tau exists as multiple isoforms. RN2N is an scFv derived from a 2N tau-specific mouse IgG2a antibody raised against the tau peptide TEIPEGITAEEAGI (aa 84-97 of the longest human tau isoform, tau441). Treatments were performed using P301L tau transgenic pR5 mice generated in the laboratory. Immunization and SUS treatment was done as described. The mice were analyzed by histology and in the elevated plus maze. To assess brain delivery of RN2N, RN2N was conjugated with AlexaFluor®647 (Thermo Fisher) and purified by size exclusion chromatography using a Superdex 200 10/300 column (GE Healthcare) equilibrated in PBS pH 7.4 at 0.5ml/min.

Results

Results. In RN2N-treated mice, the antibody reduces anxiety-like behavior and phosphorylation of tau at distinct pathological sites. When administration of RN2N was combined with focused ultrasound in a scanning mode (scanning ultrasound, SUS), RN2N delivery into the brain and uptake by neurons were markedly increased, and efficacy was significantly enhanced.

Discussion

Discussion. Our study provides evidence that scanning ultrasound is a viable tool to enhance the delivery of biologics across the BBB and improve therapeutic outcomes and further presents single-chain antibodies as an alternative to full-length antibodies. (We will also cover new data on ultrasound as a neuromodulatory tool)

Acknowledgement

This research was supported by the estate of Dr Clem Jones AO, the State Government of Queensland, the Federal Government of Australia (ACT900116), and by grants from The Brain Foundation to R.M.N. and the Australian Research Council (DP13300101932) and the National Health and Medical Research Council of Australia (APP1037746, APP1003150) to J.G. R.M.N. is a recipient of the Alzheimer's Australia Dementia Research Foundation Fellowship and Yulgilbar Alzheimer's Research Program Fellowship.

Topics: Brain panel, Drug delivery, Solution for small animal FUS/HiFU

Abstract 6

T1 Perfusion based Classification in Magnetic Resonance-guided High-Intensity Focused Ultrasound Ablation: Uterine Fibroids and Adenomyosis

Bilgin Keserci and Nguyen Minh Duc

Introduction

Uterine fibroids and adenomyosis are the most common benign gynecological tumors, affecting a high percentage of women. Magnetic resonance (MR)-guided high-intensity focused ultrasound (HIFU) treatment of uterine fibroids and adenomyosis is a promising non-invasive alternative to conventional surgery. Current achievements in HIFU treatment are encouraging and have demonstrated that long-term symptom relief is closely related to the immediate non-perfused volume (NPV) ratio. T2 signal intensity (SI)-based classification is used as the primary MRI classification parameter for determining patient suitability by classifying (i) fibroids into one of three forms as Type I, II and III (ii) adenomyosis in two forms, focal or diffuse type. However, differentiation of type II and III fibroids, and diffuse and focal adenomyosis according to T2 SI-based classification alone exhibits varying treatment results. In principle, based on Pennes's equation, the heat capacity, which reflects tissue temperature, is primarily related to blood perfusion rate and heat conduction coefficient. Therefore, we investigated the role of MR T1 perfusion based time-signal intensity (SI) curves of fibroid and adenomyosis tissue compared to the myometrium in predicting the treatment outcome of HIFU ablation.

Materials and Methods

89 fibroid patients (39.8 ± 5.4 years with a range of 22–53 years) and 45 adenomyosis patients (40.2 ± 6.1 years with a range of 30–56 years) who underwent MRgHIFU ablation were divided into 2 groups based on dynamic contrast-enhanced (DCE) MR images at screening: group A (Fibroid, n = 60; Adenomyosis, n = 30) if the time-intensity curves of fibroid is lower than that of myometrium and group B (Fibroid, n = 29; Adenomyosis, n = 15) if the time-intensity curves of fibroid is equal or higher than that of myometrium. The immediate post HIFU non-perfused volume (NPV) ratio and fibroid volume reduction ratio at 6-months follow-up were assessed.

Results

The mean volume of fibroids were 197.2 ml 168.0 (6.0-794.0 ml) for group A and 160.5 ml 104.7 (12.0-478.0 ml) for group B. The volume of all adenomyosis were 110.2 ml 59.0 (32-246.0 ml) for group A and 97.3 ml 53.9 (17.0-236.0 ml) for group B. Immediate post HIFU NPV ratio was in fibroid 96.6 % 5.0 (80-100 %) for group A and 47.3% 27.8 (4.2-81.6%) for group B ($p<0.001$) and in adenomyosis 88.6 5.9 (80.1-100 %) for group A and 40.7% 18.0 (11.3-62.7%) for group B ($p<0.001$). The fibroid volume reduction ratio at 6 months was in fibroids 53.1 % 13.5 (21.9-83.6%) for group A and 3.2 % 10.6 (-20.9-19.8%) for group B ($p<0.001$) and in adenomyosis 28.7 % 15.4 (21.9-48.9%) for group A and 6.5 % 8.7 (-10.9-22.6%) for group B ($p<0.001$).

Discussion

Our novel MRI T1 perfusion based classification method could play an important role in classifying not only fibroids but also adenomyosis for predicting the immediate outcomes of HIFU treatment.

Acknowledgement

All authors have no conflict of interest to declare.

Topics: Abdomen

Abstract 7

New Patented FUS Amplitude Modulation Technique for Tissue Ablation by Acoustic Cavitation

Fares Mayia, Mahmoud Yamany, Mushabbab Asiri, Ali Balbaid and Khalid Al Zaid

Introduction

The destructive effect of imploding micro-bubbles (cavities) in an ultrasound field is well known and has many industrial applications such as in ultrasonic cleaning. However, it was not until recently that this effect was harnessed for medical applications: destruction of the tumor mass. Initially, acoustic cavitation is to be avoided when treating tumors by HIFU (high intensity focused ultrasound), which is an extreme form of hyperthermia. This is due to the difficulty in predicting and controlling the cavitation effect.

In recent years, a research group at the Biomedical Engineering Dept., University of Michigan, reported generating controlled micro-cavitation cloud by shock scattering technique with micro second-long pulses applied at 100 – 1000 Hz, [1]. A second competing mechanism (Boiling Histotripsy) was reported by a group from the University of Washington and the Moscow State University, [2]. Boiling Histotripsy (tissue heating by shocks) is achieved by employing milli-second-long pulses at a rate of 0.5 – 1 Hz. Both techniques utilize very high ultrasound power (order of 1000's of W) and < 1% of the wave duty cycle. It is noted that both techniques require high pressure (> 75 MPa) pulsed shockwaves for the generation and implosion of cavities and a minimal pulse rate to maintain the generation of cavities.

The work of other research groups aiming to achieve controlled cavitation using different techniques is summarized below:

Liu HL et al [3]., demonstrated a novel approach for enhancing ultrasound-induced heating by the introduction of acoustic cavitation using simultaneous sonication with low-and high-frequency ultrasound. They used two transducers: a high frequency (1.155 MHz) transducer for thermal effect and a lower frequency (40 KHz) for cavitatation. They reported larger size lesions with the cavitational enhanced thermal effect.

Ikeda et al [4], investigated a method to control the collapse of high intensity focused ultrasound induced cloud cavitation to fragment kidney stones. They examined a novel two frequency wave to generate and control cavitation; 1 to 4 MHz high frequency pulse to generate cloud cavitation followed by 545 KHz low frequency trailing pulse to force the cloud into collapse. Their results showed that the erosion of stones is enhanced by the combined effect of high and low frequency waves over either wave alone. They confirmed that controlled cloud cavitation has potential for the lithotripsy applications.

It is clear from the above literature review that a controlled cloud cavitation can either be generated by low rate pulsing of high frequency ultrasound wave or by multiplying dual high and low frequency ultrasound signals. The high frequency component enables beam focusing and enhances the thermal effect; the low frequency component enables lowering the cavitation threshold. However, in all cases, very high ultrasound intensities are required, and for the dual frequency techniques two transducers instead of one were needed.

The mechanism of generating cavities in an ultrasound field is such that the threshold of cavitation is lower at low frequencies Figure [1].

However, low frequency ultrasound (long wavelength) that can produce a strong cavitation effect is difficult to focus. In contrast, high frequency ultrasound can easily be focused. We have developed a new cavitation generation technique based on modulating the amplitude of the high frequency ultrasound wave. The modulating wave is of lower frequency than the modulated wave. We called this technique “the acoustic amplitude modulation (AAM) technique”. The AAM technique is similar to that used in modulating the Radiofrequency (RF) broadcast signal: high frequency (RF) carrier modulated by lower frequency (audible) signal. Therefore modulating the amplitude of the high frequency ultrasound carrier wave by a lower frequency signal enables generating cavities at lower intensities than when the high frequency ultrasound wave is used alone. The intensity that is required to generate cavities is two orders of magnitude lower when using low frequencies [5]. The AAM technique works in both continuous wave (CW) mode and pulsed wave (PW) mode. CW mode eliminates the need for a minimal pulse rate to maintain cavitation, and it is easier to synchronize with moving body tissue, such as during breathing for example. Furthermore, the percentage of modulation (modulation index) can be varied from 0% (no modulation) to 100% (full modulation). This enables generating a range of sonication effects from thermal (0% modulation) to cavitational (100% modulation), and a combined thermal/cavitational effects between 0 and 100% modulation. Different cavity sizes can be generated by varying the frequency of the modulating signal: lower frequencies generate larger size cavities.

Mechanical tissue fractionation (Histotripsy) has many clinical applications. It can fractionate the tumor mass, fragment solid objects such as kidney stones, and emulsify blood clots. The ability to generate, control, and precisely position these cavities by an ultrasound beam is key to this new therapy. An Amplitude Modulated FUS will enable carrying out non-invasive surgery that can be guided by either B-mode ultrasound imaging or MR imaging. Cavitation only occurs at the focal region and therefore no damaging effects can be expected outside this region.

Materials and Methods

The experimental apparatus consisted of: 1 MHz HIFU Transducer (focal length 75 mm) supplied by Precision Acoustics (Dorchester, UK), Function Generator (Agilent 33521A), RF Amplifier (Electronics & Innovation, RF Power Amplifier A150), Oscilloscope (Agilent DSO-X 3024A Digital Storage Oscilloscope), and Ultrasound Imaging Scanner GE LOGIQe.

A sinusoidal RF amplitude modulated signal is generated by the Function Generator and fed to the RF Amplifier. The output of the RF amplifier is fed directly to the HIFU transducer and the RF signal is displayed on the Oscilloscope. The nominal frequency (1MHz) carrier of the HIFU transducer was modulated by a sinusoidal 10 KHz modulating signal in the amplitude mode. Figure 2 depicts the amplitude modulation process.

All experimental work is performed in a water tank (supplied by Precision Acoustics, Dorchester, UK). Figure 3 shows the experimental set up in the water tank. The tank was filled with deionized/degassed water at room temperature.

To demonstrate the ability of the AAM technique to fractionate tissue and solid material, animal soft tissue samples (bovine liver and chicken breast) and hard material (Calcium Carbonate) chalk samples were placed at the focus of the HIFU transducer (75 mm from the transducer face) and sonicated by the amplitude modulated ultrasound wave. The power of the modulated RF signal is increased to about 100 W (CW mode). At this power, cavitation cloud was observed by Doppler ultrasound and it was confined to the focal region of the HIFU transducer. The effect of cavitation implosion generates micro jetting force at the liquid/material interface resulting in tissue fractionation and solid object fragmentation. A video camera (C in Fig. 3) recorded the fractionating effect on the surface of the material and the ultrasound imaging scanner recorded the effect inside the tissue samples.

Results

The amplitude modulation technique was operated in CW mode to fractionate animal tissue in

vitro. Bovine liver and chicken breast samples were sonicated by 100 W (RF power). Cavitation occurred at the focal volume, 75 mm away from the face of the transducer. Figure 4 (A) shows a hole (Yellow arrow) drilled by the cavitation effect (100% modulation) in Bovine liver sample and a thermal lesion (Red arrow) created by the heating effect only, i.e. 0% modulation. In (B), a longitudinal section of the liver shows the depth of the cavitation hole.
For the experiments involving solid material (chalk), the chalk sample was placed at the focal point of the HIFU transducer and was sonicated by 70 W (RF power) at 100% modulation. The result is shown in figure 5. Fragmentation by cavitational effect has created a hole (red arrow). Further holes were drilled to demonstrate different shapes and sizes.
To demonstrate the ability to generate various hole sizes, the frequency of the modulating signal was varied from 10 to 100 KHz and this has resulted in the various hole sizes in chicken breast, as shown in figure 6. Larger holes created by lower frequency modulating signals.
Figure 7 shows: (A) section of fractionated bovine liver (arrow), and (B) the ultrasound B-mode image of this section. Cavities outlining the fractionated area appear bright in the B-mode image as they are good reflectors. This makes it easy for the operator to demarcate the boundaries of the fractionated tissue. The hole created by the fractionated tissue appears dark as it is filled with water.

Discussion

The rapid growth and collapse of cavities in an ultrasound field in aqueous solution generates micro-jetting that is capable of fragmenting biological soft tissue and some hard material such as chalk. This effect presents a potential method for tissue and hard material mechanical ablation. Data from the literature indicates that the cavitation threshold is lower in low frequency ultrasound fields. The patented Acoustic Amplitude Modulation (AAM) technique presented in this article is a novel method for generating cavitation at fluid/solid interface at low intensities. The method is based on varying the amplitude of a higher frequency ultrasound wave by a lower frequency modulating signal. This results in lowering the cavitation generation threshold. Therefore cavitation can be achieved at intensities lower than those reported in shock wave methods. High intensities shock wave techniques risk tissue thermal injury. In the current AAM technique, the thermal effect can be further controlled by increasing the % of modulation (modulation index). The higher the modulation index the lower the thermal effect, as the energy transfer from the ultrasound wave generates cavities instead of heat.
The new technique operates in both CW and PW modes. CW mode can be synchronized with moving target tissue such as in organs moving during breathing. Further advantage of the new technique is the ability to drill holes of different sizes by varying the frequency of the modulating signal. This gives the operator flexibility when ablating tissue in sensitive sites such as the brain.
Tissue fragmentation by acoustic cavitation has many applications in medical therapy, this includes: destruction of the tumor mass, removal of blood clots, and fragmentation of kidney and other body stones. Cavities appear bright in an ultrasound B-mode image and they can be tracked by Doppler ultrasound. Therefore allowing accurate targeting and easy monitoring of the fractionation process in real time. The new AAM technique combined with FUS has potentials in removing unwanted tissue non-invasively and it is not tissue specific; thus providing a new treatment modality without surgical intervention.

Acknowledgement

The authors wish to thank King Fahad Medical City, Saudi Health Ministry and the Faculty of Medicine for supporting this work by a number of research grants and also for funding the cost of the patent.

Topics: Principles and technology of FUS/HiFU

Abstract 8

A novel monitoring method for HIFU ablation using Physics-based Simulation

Chloé Audigier, Younsu Kim, Emad M. Boctor and Nicholas Ellens

Introduction

High-intensity focused ultrasound (HIFU) has been used to ablate uterine fibroids non-invasively. It is usually performed under MR thermal monitoring, providing reliable real-time thermal information to ensure a complete tumor ablation while preserving as much healthy tissue as possible. Unfortunately, MR-HIFU is expensive and many patients have MR contraindications, which is prohibitive for a widespread use of MR to guide thermal ablation procedures. Therefore, we propose a new monitoring method in which a physics-based HIFU simulation models the changes in acoustic properties with rising temperature and ablation progression to generate thermal maps.

Materials and Methods

The proposed method relies on two sources of information. First, a HIFU simulation based on nonlinear ultrasound (US) propagation using a k-space model coupled with heat propagation in biological tissue using a reaction-diffusion equation. Using the speed of sound (SOS) dependency on temperature, we model the US pressure waves going through the ablation zone and carrying direct time-of-flight (TOF) information. Second, an active US element is fabricated to receive this invaluable intraoperative information. For monitoring, the recorded TOFs are compared to the ones expected from the HIFU simulation. We propose that these two sources of interoperative data be combined in regular intervals to guide treatment, initially in a binary fashion: if the simulated and measured values are similar, the ablation is going as expected and the simulated thermal maps can be used. If the values diverge, the sonication should be stopped. In this way, insufficient ablation in the target region and unexpected off-target heating are both evident.

A phantom with 2% agar and 2% silicon dioxide was built. We first measured its specific temperature to SOS relationship. Then, we performed three consecutive HIFU cycles consisting of a heating phase at 50 W and 1.2 MHz (all elements continuous wave) for 10 s and element-by-element acoustic interrogation (40 cycle pulses from single element) for 24 s using the Sonalleve V2 MR-HIFU system (Philips).

Results

This protocol was modeled. Simulated TOF and thermal maps are compared to the acquisitions for validation. TOF simulated after the first, second and third heating phases are in agreement with the measurements. At the end of the third heating phase, the temperature difference between the simulated and acquired MR thermal images in a ROI was 0.1 ± 1.7˚C on average, with a maximum of 8.8˚C.

Discussion

Those results prove the feasibility of our method for HIFU monitoring.

Acknowledgement

Research reported in this paper was supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under award number R01EB021396.

Topics: Principles and technology of FUS/HiFU

Abstract 9

Pulsed Focused Ultrasound Modulation of Tumor Microenvironments: Implications for Immunotherapy

Omer Aydin, Parwathy Chandran, Scott R. Burks and Joseph A. Frank

Introduction
Immunotherapy is a promising therapeutic modality. One obstacle to successful therapy is the immune suppressive character of the tumor microenvironment which limits treatment efficiency. Recent studies highlight a potential role for non-thermal pulsed focused ultrasound (pFUS) to initiate immune responses against tumors. In this study, we sonicated breast or melanoma flank tumors in mice at different peak negative pressures (PNP) and investigated tumor microenvironmental alterations and changes in immune cell populations of the spleen, lymphoid tissues, and tumors.

Materials and Methods
B16 and 4T1 murine tumor cells were subcutaneously implanted into the bilateral flanks of c57/Black and BALB/c mice, respectively. Once ~5 mm in diameter, ultrasound-image-guided pFUS was administered at 1 MHz (1, 2, 4, 6, 8, or 10 MPa). The entire tumor volume was sonicated with 2-mm spacing between points using a 10% duty cycle and pulse repetition frequency of 10 Hz. At days 1, 3, and 5 post-pFUS, tumors were harvested for histological, cellular, and molecular, analyses.

Results
pFUS increased numbers of mononuclear cells and apoptotic cells within both types tumors. pFUS at 2 or 4 MPa increased intercellular adhesion molecule (ICAM) in both tumor types, but cyclooxygenase (COX)-2 only increased in 4T1 tumors at 4 MPa. Immune cell profiling in B16-tumor-bearing mice revealed increased M1 macrophages in the spleen and lymph tissues tumors was sonicated at 6 MPa comparing to untreated groups. However, all tested sonication pressures increased numbers of primarily M2 macrophages within tumors at 3 days post-sonication. Examining T-cell and natural killer (NK) cell populations, we observed that sonicated tumors increased CD8+ (cytotoxic) and CD4+/CD25- (helper) T-cell numbers in the spleen and lymph nodes. Minimal changes to NK or CD25+ (regulatory) T-cells were observed. Within tumor tissue however, increased numbers of Tcyt cells were absent despite increased numbers of Th cells. Interestingly, Treg cells were increased in tumors following sonication at 6 MPa or greater.

Discussion
pFUS induces molecular responses within tumors and enhances immune cell infiltration. Interestingly, cell infiltration into B16 melanoma tumors was primarily M2 macrophages and Treg cells, which may promote growth and reduce inflammation. Effects on tumor growth and/or metastasis will need to be examined. While still preliminary, the molecular changes observed in 4T1 cells suggest responses to ultrasound may be different across tumor types, reflecting unique pathophysiology, and that ultrasound responses should be determined empirically for each tumor type.

Acknowledgement
NIH

Topics: Breast cancer, Immunotherapy

Abstract 10

Closed-loop Cavitation Control for Safe FUS-mediated Targeted Drug Delivery in Mouse Brain

Beat Werner, Mustafa Cavusoglu, Jia Zhang, Rea Signorell, Alexandros Papachristodoulou, Davide Brambilla, Paola Luciani, Patrick Roth, Michael Weller, Jean-Christophe Leroux and Ernst Martin

Introduction

Localized opening of the blood brain barrier (BBB) using pulsed low-intensity focused ultrasound (LIFU) in combination with systemically injected microbubbles (MB) has been demonstrated to enable targeted delivery of large molecule drugs and antibodies to the brain parenchyma. A crucial parameter of such interventions is the in-situ acoustic pressure that has to drive local MB cavitation sufficiently to trigger BBB opening while remaining bellow inertial cavitation threshold to avoid adverse effects such as bleeding. Here we developed closed-loop cavitation control to dynamically adjust acoustic pressure for driving MB cavitation at safe and effective levels for delivering drug-loaded liposomes into the brain of tumor-bearing mice.

Materials and Methods

According to approved study protocols isofluorane gas anaesthetized mice were sonicated after tail vein infusion of 50 µl BG8235 MB (Bracco SA, Geneva) at a rate of 1 µL/s on a MR-compatible rodent FUS-system (IGT, Pessac, France) carrying a 6-element 650kHz annular array transducer (Imasonic, Voray-sur-l'Ognon, France) with a centrally inserted passive cavitation detector. Acoustic response was 1.8 MHz high-pass filtered (EF-509, ThorLabs, Newton, USA) to remove dominant 1st and 2nd harmonics, 20 dB pre-amplified (AH-1100, Onda, Sunnyvale, USA), digitized with 12-bit resolution (3204A, Pico Technology, Cambridgeshire, UK) and near real-time processed using MatLab scripts (Mathworks, Natick, USA). Inertial cavitation dose (ICD; Tung, 2010) was calculated by integrating white noise between harmonic frequency bands.

Results

BG8235 being a preformulated, long circulating bubble, ICDs of pulses applied for 200µs at 1Hz repetition rate with a range of acoustic pressures from 0.2 – 0.6MPa could be acquired for several minutes within the same animal without inflicting physiological damage. While ICD/kPa varied largely between animals it consistently displayed a pressure dependent band structure that allowed to separate stable cavitation, onset of inertial cavitation and inertial cavitation regimes which in turn allowed to find an animal/setup dependent ICD dose for safe and effective drug delivery. A closed-loop controller could then by applied to enforce the prescribed ICD by dynamically adjusting acoustic pressure. Typical values for prescribed ICD ranged from 3000 – 7500 (arbitrary units) or 0.3 – 0.6 MPa, respectively.

Discussion

Successful application of a closed-loop cavitation controller in therapeutic drug delivery sessions in mouse models of brain tumors demonstrated the validity of the underlying assumption that in-situ acoustic pressure required to drive desired cavitation regimes varies significantly between individual experiments and during the course of a treatment even when identical brain structures are targeted. Such variances might occur due to differences in skull geometries, transducer angulation, physiological parameters, locally available bubble pool, etc. Dynamic adaptation of acoustic pressure based on the observed MB cavitation dynamics therefore might correct for such variations and could both help to improve reproducibility of experiments and most importantly intervention safety as potentially dangerous inertial cavitation can be detected and subsequently avoided.

Acknowledgement
Financial support from Swiss National Foundation (Sinergia program, CRSII3_147651) is acknowledged.

Topics: Brain panel, Drug delivery, Principles and technology of FUS/HiFU,
Solution for small animal FUS/HiFU

Abstract 11

An experimental demonstration of HIFU self-scanning treatment in moving tissue

Orane Lorton, Nadia Möri, Pauline Guillemin, Sylvain Terraz, Philippe Cattin, Rares Salomir and Laura Gui

Introduction

MRI-controlled tumor treatment by high intensity focused ultrasound (HIFU) is challenging in moving organs. Current motion reduction techniques include gating, apnea, or target tracking. This report focuses on the novel self-scanning approach [1], which overcomes long treatment times (gating, apnea) and focal spot motion overhead (tracking), by keeping the focal spot fixed and letting tissue pass through the focal spot due to its natural motion, generating the heating pattern. Treatment planning consists in computing the optimal acoustic power at each time point to achieve a uniform and time-efficient thermal buildup.

Materials and Methods

Ex-vivo turkey breast tissue samples were subjected to a breathing-like periodic motion, generated by an MR-compatible robot (Innomotion) performing a back and forth straight-line displacement of 20mm, mimicking general anesthesia with controlled breathing. HIFU sonication was achieved with an MR-compatible 256-element phased-array transducer (Imasonic, France, frequency range 974-1049kHz, natural focal length 130mm, aperture 140mm), coupled to the tissue samples through a bath of degassed water and driven by a 256-channel beam former (Image Guided Therapy, France).

Temperature elevation was monitored online with a 3T MRI-scanner (Prisma Fit, Siemens, Germany) in the coronal plane through the focal spot, with a PRFS temperature-sensitive method (resolution 1x1x3 mm3). Temperature elevation maps were computed with the time-referenced multi-baseline 2D PRFS method, corrected for background phase drift using three unheated ROIs for each time frame. Rigid registration of temperature maps allowed displaying thermal history in the tissue reference system. The modulation of applied acoustic power was pre-calculated based on the robot motion pattern according to [2].

Single focal point or two interleaved foci (switching period 0.58s, electronic steering perpendicular to the motion direction, 10mm amplitude) sonication was fractionated in 8 successive breathing cycles. The starting point of each breathing cycle was automatically detected using an in-bore optical camera [3] and used as key point to synchronize the execution of the fractionated sonication. We compared power-modulated and constant power sonications.

Results

Thermometry data was obtained free of measurable interferences potentially due to the simultaneous operation of the HIFU, robot, and optical camera (average SD = 0.45°C). A thermal buildup uniformity score along the self-scanned pattern was defined as the ratio between temperature elevation at the mid-point and the average of temperature elevations at the two extremities. In single focus experiments, constant power sonication yielded a score of 0.40, corresponding to two distinct hot spots, while modulated power sonication a score of 0.92, corresponding to a continuous strip. In double focus experiments, the constant power score was 0.65, while the modulated power score was 0.89.

Discussion

Modulated power sonication allowed a significant improvement in the uniformity of the thermal buildup, proving the feasibility of the self-scanning approach on ex-vivo tissues. Future work involves extending this approach to irregular motion patterns and spatial variation of thermo-acoustic parameters.

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Acknowledgement

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Topics: Principles and technology of FUS/HiFU

Abstract 13

Early Experience of Epilepsy with MRgFUS Treatment

Toshio Yamaguchi, Tomokatsu Hori and Takaomi Taira

Introduction

Transcranial MR guided focused ultrasound treatment (MRgFUS) was performed in two patients with medically refractory epilepsy for the first time in Japan. We describe our early clinical experience for this new field by MRgFUS treatment.

Materials and Methods

Two patients with medically refractory epilepsy were treated with Neuro Exablate (InSightec) on August 2016 and June 2017 at our hospital after the approval of IRB committee.

Results

The first patient is 37 years old female with left temporal lobe epilepsy, who had epileptic episodes (De ja vu type) with aura a few times a month. The target was left hippocampus area, 20mm lateral from the midline and 15 mm above the skull base. Although the maximum energy was applied at 22950 J. (850 W x 27seconds), the temperature did not elevated up above 50 degrees (in fact, 48 degrees). This was probably due to relatively low efficient number of transducers (700) below 25 degrees incident angle (SDR=0.56). During the procedure, she had severe nausea and vertigo, which was well managed by the attending anesthesiologist. MRI on the day did not show any lesioning in the left hippocampus. Although she had several epileptic attack one month after the procedure, she had almost free of her attacks 10 months after FUS treatment.
The second patient was 20 years old with hypothalamic hamartoma with two previous surgeries at the age of 4 and 15. Her target was the border zone between tumor and normal brain tissue on the left side. We got three lesioning sites in different area with the maximum temperature of 54 degrees (12 sonication and maximum 33600 J.). MRI showed lesioning at her left hypothalamic area. Although she tolerated well during the procedure, she had partially loss of visual field probably due to edema in the optic nerve at one week follow-up period. Steroid was administered after the procedure.

Discussion

In our preliminary experience, MRgFUS may be applied for the carefully selected patients with medically refractory epilepsy. Technical issues regarding safety and feasibility should be further evaluated in the future.

Acknowledgement

We acknowledge InSightec FUS team members for the technical support and the FUS members at our hospital for patient care.

Topics: Brain panel

Abstract 14

DEVELOPMENT OF A FAT TISSUE MIMICKING PHANTOM FOR LESION ASSESSMENT IN USgHIFU

Marta Gherardini, Laura Morchi, Andrea Cafarelli, Selene Tognarelli and Arianna Menciassi

Introduction

In the last years, much effort has been devoted to characterize the potentialities of Ultrasound guided High Intensity Focused Ultrasound (USgHIFU) procedures in the clinical domain. Their efficacy in tumors treatment has been widely demonstrated (www.fusfoundation.org), nevertheless a proper acoustic characterization of tissues in the ultrasound propagation path is required in order to improve treatment predictability and properly tune the therapy based on the specific patient's features. In this framework, we present here a fat Tissue Mimicking (TM) phantom aiming at evaluating the effects of US fat absorption on induced HIFU lesions and consequently the required properly tuning actions on HIFU parameters.

Materials and Methods

The fat TM phantoms were produced using agar as bulk material and aluminium oxide (Al2O3) as doping agent [1]. In particular, a concentration composed by 2% w/v of agar and 1 % w/v of Al2O3 powder was selected as the most appropriate for replicating human fat acoustic properties [2]. Speed of Sound (SoS), acoustic impedance (Z) and attenuation (α) were measured using a through transmission technique as described in [3].

Agar sample was prepared by dissolving agarose powder (Sigma-Aldrich, Saint Louis, Missouri, United States) in deionized and degassed water (dd-H2O). Agar solution was kept at high pressure and temperature inside of a traditional autoclave for 15 minutes. Al2O3 powder (Sigma-Aldrich, Saint Louis, Missouri, United States) was then added. The resulting solution was kept at 80°C for 30 minutes under continuous stirring and then cooled down at room temperature to allow material reticulation. The obtained phantom has been used to evaluate the volume of the HIFU lesion induced by a computer-assisted robotic platform for HIFU surgery (i.e., the FUTURA platform developed and assembled during the European FP7 project - FUTURA - www.futuraproject.eu).

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Results

Testing sessions with different HIFU intensities (i.e., I1= 64 W; I2= 96 W; I3= 128 W) were performed on both ex-vivo tissue samples (i.e., control samples) and ex-vivo tissue samples

properly fixed under the fat TM phantom described above (i.e., test samples). The obtained results highlight that the knowledge of thickness and acoustic properties of the over-imposed fat tissue allows predicting the lesion volume induced by a specific HIFU transducer with well-defined US intensity on breast chicken ex-vivo tissues.
Different lesions were produced on ex vivo tissues (breast chicken, fig. 1 of the attached PDF document): i) control sonications - without the TM phantom - performed at three different acoustic powers (i.e., I1= 64 W; I2= 96 W; I3= 128 W) and ii) test sonications performed at the maximum acoustic power (I3= 128 W) but with agar2% + Al_2O_3 1% phantom at two different thicknesses (x1 = 19 mm and x2 = 46 mm) interposed between the transducer and the sample. Due to the acoustic properties of the TM phantom (SoS=1481.6 m/s; Z=1.55 MRayl; α=0.6527 dB/cm @1.2 MHz), we predicted that the US signal should be attenuated ¼ and ½ of the intensity, respectively, thus resulting in a net US dose of 96 W and 64 W (Fig.2, Fig.3 of the attached PDF document).

Discussion
With this work the authors demonstrated that a composite of agar (2% w/v) and Al_2O_3 powder (1% w/v) is a good fat TM phantom for lesion assessment and prediction in HIFU applications. Thus, these results may open new opportunities in the field of personalized medicine as they give indications on how to better tune the therapy parameters based on individual anatomical features. Having knowledge of some specific parameters, i.e., fat tissue attenuation coefficient (α) [2], applied input intensity (Iin) and patient specific fat thickness (x), derived from proper imaging techniques, the effective power on the human tissue can be predicted. Equation 1 (of the attached PDF document) shows the exponential dependency of the attenuated power (Iout/Iin) with respect to fat thickness (x).

Acknowledgement
This work was carried out in the framework of the FUTURA EU project (grant agreement number 611963). The authors would like to thank Prof. Franco Orsi for his precious suggestions and comments.

Topics: Abdomen, other proposal, Principles and technology of FUS/HiFU

Abstract 15

Magnetic Resonance guided High Intensity Focused Ultrasound (MRgHIFU) treatment planning of abdominal neuroblastoma utilizing diagnostic 3D CT images – a retrospective analysis

Stephanie Tung, Aodhnait Fahy, Maria Lamberti-Pasculli, Adam Waspe, Samuel Pichardo and Justin T Gerstle

Introduction

Background: Neuroblastoma is the most common extracranial solid tumour in children. Despite significant advances in multimodal therapies, prognosis for high risk neuroblastoma remains poor. Magnetic Resonance-guided High Intensity Focused Ultrasound (MRgHIFU) offers a potential additional therapy using ultrasound-induced thermal ablation with real-time MR thermal imaging to treat solid tumours. The potential therapeutic impact of this approach is partly dependent on how anatomically targetable individual patient neuroblastoma tumours are to MRgHIFU without risking injury to surrounding structures. MRgHIFU planning to evaluate targetability currently relies predominantly on MR scans which, for the pediatric patient, can involve general anesthesia, longer imaging times, longer wait times and increased cost relative to abdominal CT scans (which are already part of the standard neuroblastoma workup).

Objective: We aimed to retrospectively use diagnostic CT imaging of pediatric patients with abdominal neuroblastoma to evaluate the technical feasibility of planning MRgHIFU therapy and to determine what percentage of neuroblastoma tumours were targetable by MRgHIFU.

Materials and Methods

Methods: Consecutive patients with abdominal neuroblastoma and available CT cross-sectional imaging were studied. CT images were imported into the Philips Sonalleve MR-HIFU treatment planning platform to allow targeting analysis. Prior to image import, a custom Python-based software script modified the image DICOM header file to incorporate data fields required by the Sonalleve software and to numerically recenter and rotate the image field of view on the Sonalleve's intrinisic workspace. Targetability was calculated as the percentage of treatment volume to tumour volume by two independent analysts. Sequential evaluations were done with safety margins of one and two centimetres from bowel and bony structures.

Results

Results: All patients' CT scans were able to be imported into the Philips Sonalleve MRgHIFU system in order to complete treatment planning for MRgHIFU. Tumour size ranged from 7 to 435 cm3. Five patients had tumours that were not targetable due to proximity to bowel, ribs, or spine. Of the three patients with targetable tumours, the percentage of targetable tumour ranged from 25 to 54% when a two-cm safety margin was adopted, and from 39 to 60% with a one-cm safety margin was adopted.

Discussion

Conclusion: This pilot study outlines the feasibility of using patients' CT imaging to evaluate whether a neuroblastoma is targetable by MRgHIFU and if so, what proportion of their tumour is amenable to treatment. This has the potential to allow treatment planning without patients needing undergoing an additional MRI. In this limited dataset, we show that MRgHIFU can partially treat approximately thirty percent of patients with intra-abdominal neuroblastomas. Concern for iatrogenic thermal injury to adjacent bowel was the greatest limiting factor. Further evaluation of a larger dataset of patients is currently underway to determine how targetable neuroblastoma tumors are with MRgHIFU.

Acknowledgement

This paper has not been presented or published elsewhere. The authors have no conflicts of interest to declare. The fellow was funded by the Canadian Institute of Health Research.

Topics: Abdomen, Other indications

Abstract 16

Targetability of osteoid osteoma and bone metastase by MR-Guided High Intensity Focused Ultrasound (MRgHIFU): A feasibility study

Fabrice Bing, Jonathan Vappou, Paolo Cabras, Michel De Mathelin and Afshin Gangi

Introduction

Image-guided percutaneous methods are currently used in clinical practice to treat bone lesions efficiently and durably in terms of pain management. If the treatment is most of the time palliative for metastatic lesions, it must be curative for osteoid osteomas (OOs).
Some clinical studies have reported the efficacy and safety of HIFU in painful bone metastases and OOs treatment. Actually, precautions have to be taken such as the protection of neural structures next to the lesions during ablation or consolidation of the bone after it.
The objective of this study is to evaluate the feasibility of performing HIFU therapy on all the cases treated by percutaneous ablation procedures in our department over the past 2 years, by considering the location, the anatomic environment, the quality of the tumoral bone, the volume of the tumor, but also the necessity to protect neural or articular structures or to consolidate the bone once the ablation has been performed.

Materials and Methods

This monocentric study is based on a retrospective analysis of 112 bone lesions (110 patients) treated between October 2014 and October 2016 using percutaneous ablation procedures for OOs or metastases. Cases were analysed regarding the type, matrix, volume, location, and anatomical environment of the lesions. The necessity to protect neural structures or to consolidate was also considered. Three categories were defined: (1) HIFU may be performed alone; (2) HIFU may be performed with protection of sensitive structures or with consolidation; (3) HIFU is not an optional therapy.

Results

112 lesions (71 were metastases and 41 OO) were considered. Tumors were located in the pelvis (35), upper and lower limbs (35), spine (30), ribs (10) and sternum (2). Concerning OO, 33 (80%) were considered targetable by HIFU alone (46%) or with dissection (34%). Mean volume was 0.7 cm3 and matrix of OO was sclerotic (13), lytic (8) or mixed (12). 51 metastases (72%) were considered to be treatable HIFU, either alone (41%) or with dissection and/or consolidation (31%). Mean volume was 43.7 cm3 and matrix of metastases was sclerotic (9), mixed (20) or lytic (22). The majority of the lesions located in the pelvis (30, 86%) and the peripheral bone (32, 91%) could be treated by HIFU, whereas 20 out of 30 (66%) lesions located in the spine were not considered to be treatable by HIFU.

Discussion

Reviewing OOs and bone metastases treated in our department with invasive ablative techniques, we consider that 80% of OOs and 72% of bone metastases could have been treated using MRgHIFU. However, about it is important to emphasize that about one third of these cases needed invasive protection or consolidation. This result has to be known by the community of interventional radiologists that aim at using HIFU as an ablation therapy, either for OOs or bone metastases.

Acknowledgement

No acknowledgement

Topics: Benign lesions, Muscular skeletal panel, Other indications

Abstract 17

Prediction-based controller for MR-HIFU mediated hyperthermia

Lukas Sebeke, Xi Luo, Edwin Heijman, Bram de Jager, W.P.M.H. Heemels and Holger Grüll

Introduction

Hyperthermia has been shown in clinical trials to strongly enhance therapeutic efficacy of radio- and chemotherapy. Nonetheless, precise control of the spatial heat distribution is still a challenge and has been identified as one of the reasons for mixed outcomes. MRI-guided HIFU allows to induce heating with millimeter-scale accuracy under near real-time temperature feedback noninvasively and is therefore the ideal technology to address this problem. To fully leverage these capabilities, we have developed a control algorithm which rapidly calculates the most effective heating strategy based on a thermal model and the current temperature in the target region. This control scheme is widely known as model predictive control (MPC) and is the predominant solution to modern advanced process control problems.

Materials and Methods

The control software was developed entirely in Python 2.7. It is designed to function with a commercial Philips Sonalleve V2 System and relies on the Gurobi engine for rapid optimization. Communication with the MRI and HIFU device is made possible by the pyMRI and pyHIFU toolboxes developed by Samuel Pichardo et al.. Based on a mathematical model derived from the Pennes bioheat transfer equation and a cost function which specifies the control objective, the algorithm optimizes the distribution of the available heating power over the target area. The cost function contains terms penalizing temperature deficits, -surpluses and superfluous control actions, driving the controller to calculate heating strategies which minimize the difference between the actual and target temperature distribution. A proof-of-concept study was performed with a tissue-mimicking phantom to demonstrate the feasibility of such a controller. The controller's performance was evaluated using the range of temperatures observed in the target region. This was followed by temperature simulations with a refined controller, exploring controller performance at various degrees of plant-model mismatch. In the simulations, the target tissue was given the thermal properties of pancreas tissue while the controller was fed false information on said properties.

Results

The proof-of-concept study showed a stable temperature distribution in the target region around the target temperature of 41.5 °C with a variance of 0.5 °C. The simulations showed that at a mismatch factor of three in diffusion and power-to-heat conversion parameters, the controller is still capable of stabilizing the temperature distribution between 41 and 43 °C across the full area accessible by electronic beam steering.

Discussion

As opposed to current solutions to MR-guided Hyperthermia, this controller is incorporating a model of the target tissue in its decision-making process. This could yield benefits in terms of control quality, but it also raises concerns regarding computational cost and the reliability of the used model. With our results, we have addressed these concerns, showing that this approach is both feasible and resistant to large plant-model mismatches in heat diffusion and heat production. We believe therefore, that the further development of this approach into a full application is warranted as this will allow the side-by-side comparison with other state-of-the-art hyperthermia controllers.

Acknowledgement

We thank Robert Staruch for his suggestions and helpful discussions. This work is funded by the European Union via the IPaCT Project.

Topics: Principles and technology of FUS/HiFU

Abstract 19

Clinical evaluation of uterine fibroids tissue using multi-parametic MRI sequences

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Introduction

Uterine fibroids are the most common gynaecological benign tumours affecting a high percentage of women[1]. Currently, the Funaki classification is a screening tool for Magnetic Resonance-High Intensity Focused ultrasound (MR-HIFU) therapy[2][3].The Funaki-classification is limited in characterizing uterine fibroids since they can be very heterogeneous[4]. This gives grounds for refinement of the fibroid stratification. Advanced multi-parametric MRI sequences can be used as non-invasive biomarkers.

The purpose of this study is to visualize and gain knowledge about the biological variation and characterization of uterine fibroids. This study will analyse a new multi-parametric MRI protocol for characterization of uterine fibroids and compare them with the traditional MRI-screening parameters and a symptom questionnaire in the classification of uterine fibroids.

Materials and Methods

The study is an ongoing single-centre, explorative research conducted at the Isala Hospital Zwolle, The Netherlands. Clinical symptoms are examined by the uterine fibroid symptom and health related quality of life questionnaire (UFS-QoL). MR scans are performed on a clinical 1.5-T MRI system (Achieva; Philips Healthcare, Best, the Netherlands).

The multi-parametric MRI sequence set contained quantitative T2-mapping and diffusion weighted imaging (DWI) sequences. Data were analysed using a Matlab script. In order to analyse MRI-parameters of the uterine fibroids, Regions-Of-Interest (ROIs) were manually drawn in the T2 weighted images. Correlations determined between the different MRI-parameters, Funaki-classification and the UFS-QoL score. The Spearman's rank correlation was determined for statistical testing the different relationships.

Results

In this study the MRI scans were performed on ten patients. The Funaki type showed a positive correlation with the Scaled Signal Intensity (SSI), see figure 1. The mean quantitative T2 value in the uterine fibroid tissue was 150.6 ms, which is considerably lower than the quantitative T2 value in normal myometrium (224.4 ms), see figure 2.

When using all b-values, mean ADC value of the myometrium ($1410.0 \pm 550.4 * 10^{-6} mm^2/s$) is higher than the ADC value of the uterine fibroid tissue ($1152.9 \pm 393.8 * 10^{-6} mm^2/s$). Low b-values showed myometrium $651.2 \pm 231.1 * 10^{-6} mm^2/s$, fibroids $446.6 \pm 118.1 * 10^{-6} mm^2/s$. A correlation was found between low ADC b-values and the symptom severity score (figure 3).

Discussion

Our study population would include four people for MR-HIFU treatment based on their SSI value, contrary to eight patients when using the Funaki classification. Literature indicates, when using the SSI, a more accurate cut-off value could be identified to have optimal MR-HIFU results. This study showed that even Funaki 3 correlates with SSI.

The different functional imaging parameters showed a difference between normal myometrium tissue and uterine fibroid tissue. Quantitative T2 maps correlated with the currently used Funaki-classification, suggesting uterine fibroid tissue has a lower vascularity than normal myometrium i.e. the uterine fibroid tissue is less hydrated than normal myometrium. The ADC-maps showed less diffusion in the uterine fibroid tissue compared to the myometrium as reported by Ikink et al.[4] An unexpected correlation was found between ADC values, calculated from low b-values, and the symptom severity score. This new finding of this study suggests a relation between an MR readout and clinical symptons. More patients need to be included in this study to statistically confirm this correlation.

Acknowledgement
We would like to thank Maarten Versluis, Jef Gulpers and Servaas van Gompel from Philips Benelux with setting up this MR-HIFU study and delivering support.

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Topics: Fibroid panel

Abstract 20

Factors improving efficiency during HIFU of Uterine Fibroids

Tomasz Łoziński and Justyna Filipowska

Introduction

The aim of this study is to evaluate the efficiency of HIFU therapy of fibroids after using oxytocin during a treatment, and maneuvering of uterine.

Materials and Methods

70 patients with fibroids received oxytocin with NACL or 5% Glucose via a catheter during the whole HIFU procedure. This paper evaluates the time of treatment, side effects, the use of energy, psychological conditions and other related aspects

Results

Although this is still work in progress it can be (tentatively) concluded that the preliminary results are very promising when it comes to the efficiency of treatment. As regards the area of ablation, the follow-up after 3 and 6 months indicates that the size of fibroid decreases in comparison with cases without oxytocin treatment.

Discussion

Utility Oxytocin, and collaboration with gynecologist during treatment are factors influencing for efficiency of HIFU therapy in uterine fibroids.

Acknowledgement

This study was supported by Pro-Familia Hospital , 35-052 Rzeszow,ul. Witolda 6b, Poland

Topics: Fibroid panel

Abstract 21

Efficiency of uterine fibroid treatment with HIFU according to vascularity of fibroid

Tomasz Lozinski and Justyna Filipowska

Introduction
The aim is to evaluate the efficiency of HIFU fibroids therapy according to type of vascularity of fibroid

Materials and Methods
200 patients with uterine fibroids treated with HIFU method between 01.2015-12.2016

Results
The results of observation show that poor vasculated uterine fibroid need less HIFU power and are better treated than good vascuated ones. The NPV rate after trreatment is higher with poor vasculated fibroids comparing with good vasculated ones.

Discussion
HIFU treatment is efficient, safe methode of uterine fibroid treatment. The vascularity of fibroid investigate by dynamic MRI may be important predictor of treatment result.

Acknowledgement
Pro Familia Hospital Rzeszów Poland

Topics: Fibroid panel

Abstract 22

Enhancement of thermal contrast in HIFU treatments by perfluorocarbon microparticles

Orane Lorton, Stéphane Desgranges, Laura Gui Lévy, Jean-Noël Hyacinthe, Zarko Celicanin, Nicolas Taulier, Christine Pépin and Rares Salomir

Introduction
Magnetic Resonance guided High Intensity Focused Ultrasounds (MRgHIFU) is a promising field for the treatment of localized tumors thanks to their ability to perform non-invasive ablation. However, there is a need to search for new methods to enhance the thermal contrast achievable between the focal point and the near or far field areas, in order to protect healthy tissues from the beams. To this aim, we developed a new concept of microparticles to be used as a source of in situ boiling core induction at/around the focal point of the HIFU beam. These microparticles are perfluorocarbon droplets stabilized with specific fluorinated surfactants. We demonstrated the enhancement of HIFU efficiency on tissue heating in presence of these microparticles, using tissue mimicking gel samples.

Materials and Methods
Acoustically absorbent gels were prepared from: water, glycerol (11.2%), antibacterial (0.05%) and silica (5.59%) for tissue mimicking. Non-absorbent gels were prepared from: water, gelatin (3%) and antibacterial (0.05%) to understand the mechanism of the microparticles activation. A small concentration of microparticles (0.5% v/v) was further added to each type of gel in order to quantify the enhancement of local heating induced by identical HIFU sonication.
Each gel was placed in a standardized setup using a resin mold to maintain the samples in a water container for acoustic coupling between the transducer and the gel. Ultrasounds were generated by a hemispherical phased array transducer with 256 elements randomly distributed operating at 1MHz. All gels were sonicated under these conditions: a pattern of 16 points regularly distributed on a 4mm diameter circle, 90ms on 10ms off, repeated 20 times for a total of 33s and 93W acoustic power. The targeting control and temperature monitoring were performed with an O-ring coil in a 3T MRI scanner Prisma Fit (voxel size : 1x1x5mm3, temporal resolution : 1s).

Results
Harmonic ultrasound images at 2.5MHz demonstrated that an increase in the microparticles concentration induces a significant acoustic attenuation. 19F MRI demonstrated in situ an overall uniform distribution of the microparticles corresponding to the prescribed concentration. Experimental data of sonication indicated that the additional temperature elevation between the gels without and with microparticles was 13.1°C and 12.6°C respectively for silica and gelatin gel. A repetition of the sonication at the same location demonstrated a slight attenuation of the heating enhancement by approximately 5% per cycle.

Discussion
The measured effects in the gelatin gel indicate that the microparticles activity is in first order independent of the baseline acoustic absorption in tissue. Repeated exposure of microparticles to HIFU sonication tends to reduce their activity suggesting a possible change of structure. On the other side they are designed to be recirculated in the blood pool, continuously providing fresh agents.

Acknowledgement
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Topics: Principles and technology of FUS/HiFU

Abstract 23

Bisphosphonate could improve skull density ratio of MRgFUS candidates

Hisashi Ito, Kazuaki Yamamoto, Shigeru Fukutake and Tetsumasa Kamei

Introduction

Skull density ratio (SDR) is one of the key factors needed to be taken in consideration in order to succeed in functional neurosurgery for brain diseases using transcranial MR guided focused ultrasound (MRgFUS). According to our treatment protocol, we had to exclude patients whose SDR values were too low (0.30 or less). Here we present 2 Parkinson's disease (PD) patients with low SDR. Their SDR increased after administration of oral alendronate (Aln), a third generation bisphosphonate (BP) and one patient has reached a level enabling her to be eligible for Gpi-pallidotomy using MRgFUS.

Materials and Methods

Patient 1 is a 77-year-old woman with PD (initial symptom: resting tremor in right hand, course: 15 years, H-Y stage: On 3, Off 4). We planned MRgFUS Gpi-pallidotomy because of medication refractory motor fluctuation and dyskinesia. Her first SDR was 0.26. We administered oral Aln 35mg a week to improve the skull condition.

Patient 2 is a 70-year-old woman with PD (initial symptom: clumsiness in bilateral hand, course: 6 years, H-Y stage: On 4, Off 4.5). We planned MRgFUS Gpi-pallidotomy because of medication refractory motor fluctuation and dyskinesia. We started to administer oral Aln 35mg a week because her first SDR was 0.24.

Results

Patient 1 was scheduled Gpi-pallidotomy in August because second SDR elevated to 0.33 after 3 months. For patient 2, we are continuing to administer BP and will re-evaluate third SDR because her second SDR after 3 months was 0.27, which did not reach the acceptable level. There were no adverse events with Aln.

Discussion

The skull is one of the greatest barriers to ultrasonic energy transmission. Skull volume and SDR have been found to have strong relations to the maximal temperature in the target lesion (J Neurosurg. 124: 411, 2016). The percentage of Japanese patients with low SDR is about 20% (unpublished data). Therefore, we have to exclude MRgFUS candidates occasionally because of low SDR value. Aln had been reported to increase the degree and uniformity of bone matrix mineralization and decrease the porosity in cortical bone (Bone 29:185, 2001). BP typified by Aln could be a good option for MRgFUS candidates with low SDR.

Acknowledgement

We gratefully thank Dr. Takaomi Taira (Department of Neurosurgery, Tokyo Women's Medical University) and Dr. Toshio Yamaguchi (Research Institute of Diagnostic Imaging, Shin-yurigaoka General Hospital) for their supports with MRgFUS treatments.

Topics: Neuromodulation

Abstract 24

Comparison of experimental setups for in vitro studies using a clinical HIFU device

Lisa Landgraf, Johann Berger, Michael Unger, Xinrui Zhang, Doudou Xu, Thomas Neumuth and Andreas Melzer

Introduction
High intensity focused ultrasound (HIFU) is a very promising treatment modality for cancer patients. At the moment, it is only approved for ablation of benign or locally restricted tumors (e.g. fibroids, prostate), palliative therapy of bone metastasis and for therapy of essential tremor. The sensible usage of HIFU for combined therapies on different tumor identities depends on efficient characterization of ultrasound effects. Yet there is still a lack of information regarding effects on individual cancer cells. Typical in vitro setups use well plate formats, where plates consist of polystyrene. This standard material possesses high attenuation of ultrasound and therefore leads to excessive heating. Also simple cell monolayers, typically used for pharmacological studies reflect no good properties for comparison of in vitro and in vivo therapeutic ultrasound investigations. These circumstances exacerbate the design of a useful setup. Therefore different experimental approaches shall be examined to overcome named problems.

Materials and Methods
In this study, a clinical MRI Philips Achieva 3 Tesla scanner and Sonalleve system for high intensity focused ultrasound (Philips Healthcare, Best, The Netherlands) were utilized. The target temperature for hyperthermia was set to 43 °C. The system was configured to operate with a power of 60 Watts at 1.1 MHz. MR thermometry was used to monitor the sample temperature. a) In the first setup, a typical 96-well polystyrene plate with 100 µl water in each well was placed in a cut out of a gel pad containing distilled degassed water for coupling. b) In a second setup, 1.5 ml TPX tubes (diagenode, Belgium) were placed in an agar-agar holder to allow sonication of the samples placed inside TPX tubes. c) The samples for sonication in TPX tubes were held in a rack swimming in a water tank with distilled degassed water at 37°C. The ultrasound propagation for each setup was simulated using the MATLAB Toolbox k-Wave (http://www.k-wave.org/).

Results
The preliminary results with the setup using the polystyrene 96-well plate showed excessive heating. Due to the feedback loop from the MR thermometry, the sonication will stop within seconds as a safeguard. In terms of the typically used in vitro procedure, it is not suitable for treatment of cancer cells using the clinical HIFU system. In comparison to the setup b) displayed higher usefulness. The TPX tubes allowed a HIFU therapy for a longer period without undesired heat generation. Due to the air bubbles inside of the agar tube holder, some cavitation events were detected.

Discussion
In conclusion, TPX materials allow the sonication of different samples and would allow sonication of suspension cells. Future in vitro investigations and modification of the setup need to be conducted.

Acknowledgement
The research leading to these results has received funding from Bundesministerium für Bildung and Forschung (BMBF) under grant No.03Z1L511 (SONO-RAY project). We thank Dr. Aswin Hoffmann (OncoRay - National Center for Radiation Research in Oncology, Dresden, Germany) and Dr. Annegret Glasow (Department of Radiation Therapy, Universität Leipzig, Leipzig, Germany) for advices and suggestions.

Topics: Cell culture sonication

Abstract 25

Johann Berger, Lisa Landgraf, Doudou Xu, Xinrui Zhang, Michael Unger, Thomas Neumuth and Andreas Melzer

Introduction

Approaches for a particle based in silico simulation model for combined effects of ultrasound and radiation on tumor cells

Materials and Methods

Since the application of ultrasound is a well-established technique in various fields of the medical treatment of patients, plenty of helpful methods to simulate the effects and propagation of ultrasonic waves in a given tissue have been introduced already. Such simulations provide a very good overview of how given intensities influence a specific medium. Not only the macroscopic, but also the microscopic domain can be examined as well, by looking into the cell behavior under given circumstances and modeling the different proliferation states for example in cellular automata. Yet, the research of combined therapies for ultrasound and radiation is still situated in an early stage of progress. Due to the sparse knowledge of the effects of such a combined treatment on the many different tumor cell types, only few attempts could be made to combine both properties in an in silico model. The goal of this work therefore is to build up a simulation model on the cellular level that accounts for cell properties in specific ultrasound and radiation fields, including absorption characteristics and mechanical effects as well.

Results

The modeling in this simulation approach can be divided into three stages. Firstly the proliferation cycle for each cell in the special domain that shall be simulated has to be calculated, based on the data obtained from cell experiments conducted beforehand. This can be achieved in a similar way to known procedures from cellular automata simulations. Additionally each cell is supplemented with information on properties depending on ultrasound and radiation intensities respectively. Secondly the computational domain has to be built. A 3D spatiotemporal grid can be used, to define intensities, pressures, etc. at specific positions in space and time. The third stage comprises the particulate simulation of each cell in the given grid over predetermined time steps, that also accounts for cell – cell interactions like adhesion. Visualization and calculations can be implemented using the C++ programming language, OpenGL and the NVIDIA CUDA framework.

Discussion

The presented procedure provides a first approach to combine ultrasound and radiation effects with cell simulations in a particle system, that includes proliferation properties, as well as mechanical and absorption effects.

Acknowledgement

The suggested approach poses questions on the performance feasibility that have to be examined in more detail. Furthermore, there is no sufficient information about up to which scale such a simulation can provide useful results. Nevertheless it may be a good way to show cell behavior in ultrasound and radiation on a semi-large scale, depending on the quality of single cell visualization.
The research receives funding from the Bundesministerium für Bildung und Forschung (BMBF) under grant No.03Z1L511 (SONO-RAY project).

Topics: Cell culture sonication, Principles and technology of FUS/HiFU

Abstract 26

Development of 3D Printed Anthropomorphic Bone Phantoms as Training Aids for MRI guided HIFU (MRgHIFU)

Daniel Butler, Imogen Ptacek, Nick Byrne, Afshin Gangi and Fiammetta Fedele

Introduction
MRgHIFU is emerging as an effective palliative treatment of bone metastasis, but still lacks standardised protocols and treatment planning [1]. The availability of pre-treatment planning tools would facilitate staff training and optimise treatment length [2]. This project investigated the suitability of 3D printed anthropomorphic bone phantoms to help both training of clinical staff.

Materials and Methods
A Philips MRg Sonalleve® system (CE marked for bone metastases) under the MR guidance of a 3T Philips Achieva MRI scanner was used to produce and monitor sonication. 3D printed bone models from anonymised CT datasets were printed using a StrataSys BJet500 3D printer and acrylic based materials ('VeroBlue' & 'VeroWhite'). The bone phantoms were either encased in tissue mimicking material (TMM) [3, 4] or sutured to raw chicken meat samples. Other organs-at-risk (OAR), e.g. bowel, were simulated using an air filled balloons. The phantoms were placed on the HIFU treatment bed atop acoustically transparent gel pads and acoustically coupled by means of degassed water and centrifuged ultrasound gel.

Results
The 3D printed bones demonstrated MRI signal characteristics similar to cortical bone and the TMM generated a bright uniform signal (T1-weighted imaging) akin to fatty tissue. T1-weighted treatment planning images of "bone lesions" (chicken) provided well-defined targets for sonication. Using techniques such as beam shaping and angulation, the clinicians were able to target the lesions whilst avoiding OAR. When the HIFU beam was focused within the 'bone' (distal to the lesion) heating occurred along the pseudo perisosteum and within the lesion instead of at the planned focal point, this is due to reflection of the beam at an interface between two media of differing acoustic impedance; an effect that has been demonstrated clinically [5]. We found that the realism offered by anatomical phantoms aided clinician engagement and understanding of the technique.

Discussion
This work has shown that simple but anatomically relevant phantoms can be created using 3D printed and tissue mimicking materials with characteristics that closely match those seen clinically. The phantoms proved to be a valuable tool for clinicians interacting with MRgHIFU for the first time and highlight the usefulness of training aids for developing treatment planning experience. The use of training phantoms may ultimately help clinicians plan for future procedures and reduce treatment times.
Reference

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Acknowledgement
We would like to thank King's College London radiographer Anita Kingston for her assistance in securing MRI scan time and valuable support during image acquisition.

Topics: Principles and technology of FUS/HiFU

Abstract 27

Establishing an MRI guided HIFU treatment centre: key challenges and strategies for implementation

Imogen Ptacek, Daniel Butler, Fiammetta Fedele and Afshin Gangi

Introduction

Here, we describe our experience of setting up an MRI guided High Intensity Focused Ultrasound (MRgHIFU) service at a London based teaching hospital and review the logistical challenges encountered when establishing this new technique.

Materials and Methods

Our service is located within a university research facility that houses a 3T Philips Achieva MRI. In 2014 the research team was awarded a charity grant to acquire a Philips Sonalleve® MRgHIFU device, which is CE marked for the treatment of bone metastases and uterine fibroids. The system was installed in 2015, but before initiating treatments, the following technical challenges had to be addressed: MRI availability and bore size; lack of anaesthetic facilities; restrictions in patient selection due to beam depth and angulation; establishing and training an MRgHIFU multidisciplinary team (MDT); and achieving healthcare approvals and funding.

Results

HIFU procedures can take up to 4 hours to perform and require substantial MRI access for both treatment and training. We found that the MRI bore size, which is 60cm in diameter, limited our ability to treat patients in a lateral position, which is often required for targeting bone lesions. The construction of an anaesthetic facility, which is essential for bone metastases, incurred significant costs and delays and highlights the advantage of introducing MRgHIFU to a site where anaesthetic support is already established. An MRgHIFU MDT was formed, consisting of interventional radiologists, medical physicists, radiographers and anaesthetists, with little previous experience in the MRgHIFU. We found that simulation training with volunteers and anthropomorphic phantoms was highly effective for engaging the clinical team and preparing them for treatments. Financial reimbursement is only approved for uterine fibroids in the UK and therefore ethical approval and research funding had to be sought for bone metastases treatments.

Discussion

Therapeutic ultrasound offers a diverse range of promising new clinical applications including non-invasive neurosurgery, targeted tumour ablation and drug delivery [1]. Many of these emerging techniques are not yet widely available in a clinical setting. We have demonstrated that it is feasible to establish an MRgHIFU treatment centre and overcome the inherent challenges of introducing this new technique. We encourage other centres to take a systematic approach in planning their MRgHIFU service, taking into account MRI requirements, MDT training, device limitations, and access to anaesthetic facilities.

Reference: Kennedy et al. Br J Radiol 76:590-9 (2003)

Acknowledgement

We would like to thank King‘s College London MR Clinical Research Facilities Manager Louise Shallaby-Boutrus and our colleagues at Transforming Outcomes and Health Economics Through Imaging (TOHETI) for their valuable support in establishing the service

Topics: How to set up a center for FUS/HiFU?

Abstract 28

Focused Ultrasound with Ultrasound Guidance (FUS-HIFU) in Pancreatic Cancer. Survival Results of a Seven-Year Non-Randomized Comparative Controlled Cohort/Follow-up Study.

Joan Vidal-Jove, Angels Jaen, Marta Paraira, Manuela Velat, Antonio Ruiz and Eloi Perich

Introduction
FUS-HIFU is an Interventional Oncology procedure that is usefull at obtaining local disease control with minimal invasive techniques. We describe the experience of the HIFU Surgical Oncology Unit of Hospital University Mutua Terrassa (Barcelona, Spain), the Interventional Oncology Unit of Institute Khuab Barcelona and the Radiology Department of Clinica Santa Elena in Madrid, treating malignant advanced pancreatic tumors. We compare our joint experience of treating patients with FUS-HIFU plus standard chemotherapy regimens versus a cohort of patients treated at the same institution at the same period of time with standard chemotherapy regimens only. This is a seven years non-randomized comparative controlled cohort/follow-up study with a Level 3 of evidence.

Materials and Methods
From February 2008 to May 2016 we have included a total of 57 patients with non resectable pancreatic tumors, stage III and IV. These patients were treated with FUS-HIFU plus standard combinations of chemotherapy mainly with gemcitabine. We only included stage IV patients that responded previously to chemotherapy. As a control group, we have a cohort of 58 patients treated at the same institution at the same time. Those patients underwent systemic chemotherapy with similar standard combinations. We present the results of the 115 group of patients.

Results
The distribution of the 115 cases treated reflects no relevant differences in descriptive data. We specially analyze the 57 patients in the FUS-HIFU plus chemotherapy group. Clinical responses (ablation obtained) were 82% in all cases. We obtained 12 complete responses (21%) at the end of the combined treatment. Major complications included severe pancreatitis (2), skin burning grade III that required plastic surgery (2), duodenal perforation (1). One patient died as a result of a delayed duodenal perforation. Median Survival is 23 months (6 mo – 4.3 year) and Overall Percent Survival is 18 % at 5 years follow up. Survival analysis between the two cohorts of patients shows a statistically significant benefit for the group of patients treated with FUS-HIFU plus chemotherapy ($p=0.0021$).

Discussion
FUS-HIFU is an effective and safe Interventional Oncology ablation of malignant pancreatic tumors. Compared with a similar cohort of patients treated a same hospital, it shows a clear survival advantage in non resectable stage III and IV pancreatic cancer. These results encourage us to engage our efforts towards a Randomized Multicenter Study. Tumor ablation needs to be considered as group of oncological therapies along with Medical, Radiation and Surgical Oncology and re-considered at the light of this experience.

Acknowledgement
I would like to express my gratitude to Pilar Julian, Head of Surgical Operations at Hospital University Mutua Terrassa, Susana Vega and Cristina Torrens for their data management, Dr. Gloria Redondo for her Anesthesiology Support and the staff of Nurses at Hospital University Mutua Terrassa.

Topics: Pancreatic cancer

Abstract 29

Focused Ultrasound with Ultrasound Guidance (FUS-HIFU) in Liver Cancer. Survival Results of a Seven-Year Follow-up Study.

Joan Vidal-Jove, Angels Jaen, Marta Paraira, Manuela Velat, Eloi Perich, Antonio Ruiz and Manuel Alvarez Del Castillo

Introduction
FUS-HIFU is an Interventional Oncology procedure that is usefull at obtaining local disease control with minimal invasive techniques. We describe the experience of the HIFU Surgical Oncology Unit of Hospital University Mutua Terrassa (Barcelona, Spain), the Interventional Oncology Unit of Institute Khuab Barcelona and the Radiology Department of Clinica Santa Elena in Madrid, treating malignant primary and metastatic liver tumors. We underline some considerations about the role of hepatic tumor ablation in the European oncology stage.

Materials and Methods
From February 2008 to May 2016 we have treated 180 malignant cases. Of those, 40 cases of primary and metastatic liver tumors are included in this study. We include patients that were not candidates for surgery or other ablation available, Radiofrequency ablation, Microwave ablation or Embolization. All of the patients were allowed to continue on their systemic chemotherapy treatments after the ablation procedure was performed

Results
The distribution of the 150 cases treated reflects a majority of pancreatic and liver tumors. We specially analyze the 40 liver tumors. Total treatment timings are between 60 and 180 minutes. Difficulties related to pacient positioning, access to segments VII and VIII, and real-time response evaluation prolonged the procedures. Access to deep lesions its feasible (segment I, Inferior Vena Cava). Clinical responses (ablation obtained) were 92 % in all cases. Major complications included skin burning grade III that required plastic surgery (1), and costal osteonecrosis (1). Overall Percent Survival is 28.5 % at 5 years follow up

Discussion
FUS-HIFU is an effective and safe Interventional Oncology ablation of malignant primary and metastatic hepatic tumors. Difficulties related to available devices makes it too cumbersome for accessible lesions at present compared with other ablations available. Access to deep lesions shows an opportunity for this system to increases its possibilities of use.

Acknowledgement
I would like to express my gratitude to Pilar Julian, Head of Surgical Operations at Hospital University Mutua Terrassa, Susana Vega and Cristina Torrens for their data management, Dr. Gloria Redondo for her Anesthesiology Support and the staff of Nurses at Hospital University Mutua Terrassa

Topics: Abdomen

Abstract 30

Tumor Therapy Combining Image-guided Focused Ultrasound and Radiation Therapy -Project

Doudou Xu, Lisa Landgraf, Xinrui Zhang, Michael Unger, Ina Patties, Johann Berger, Shaonan Hu, Damian McLeod, Lydia Koi, Antje Dietrich, Aswin Hoffmann, Mechthild Krause, Marc Fournelle, Steffen Tretbar, Thomas Neumuth and Andreas Melzer

Introduction

The two ZIK-Centers for Innovation Competence, ICCAS in Leipzig and OncoRay in Dresden, have joined forces to start a new multidisciplinary 6.3 million Euro research project: SONO-RAY - Tumor therapy combining image-guided (PET-MR and MR) focused ultrasound (FUS) and radiation therapy (RT). The hypothesis underlying this approach is that the combination of two tissue-destroying energies is more effective in cancer treatment than the effect of employing one of the above two energy forms alone.

Materials and Methods

In vitro FUS and RT: A high throughput in vitro sonicator with 1.14 MHz single transducer made by piezoelectric ceramic material was employed and allows individual sonication for wells in a 96-well plate. A 150 kV X-ray machine (DARPAC 150-MC) was employed for irradiation at doses of 0 – 20 Gy. The analysis was conducted by using three different cell lines for prostate cancer (PC-3, Vcap, LNcap), glioblastoma (LN405, U87MG, T98G) and head/neck tumor (FaDu, UT-SCC 5, UT-SCC 8). Effects at the cellular level on metabolism (WST-1), proliferation (BrdU), membrane integrity (LDH release) and apoptosis (Annexin V) were detected after treatment.

In vivo: PET-MR and MR guided FUS system allows precise sonication treatment for small animals bearing tumors, under real-time MR-thermometry. Small animal PET-MR system (nanoScan, Mediso) will be integrated with a FUS transducer (11×11 matrix array) which allows the function of beam forming to achieve hyperthermia treatment. Local tumor irradiations under normal blood flow conditions will be given with 200 kV X-rays (0.5 mm copper -filter) and 20 mA at a dose rate of ~ 1.1 Gy/min (X-ray machine type Yxlon Y.TU 320-D03).

Robot installed in PET-MR: An MR-compatible robotic arm system (INNOMOTIONTM, Innomedic)was installed with Biograph mMR MR-PET (Siemens Healthineers) in the Department of Nuclear Medicine of the University Medical Center Leipzig to investigate the effects of a combination of FUS and RT. The robotic arm will reposition the ultrasound transducer during the sonication treatment. It is possible to detect residual tumor tissue after the treatment by using PET-MR imaging to provide an optimal treatment outcome.

MR guided FUS-Sonalleve: The Philips Sonalleve MR-FUS system was installed in Leipzig University Hospital at the beginning of 2017, introduced a new approach for uterine fibroids and bone metastasis. The Sonalleve system also offers solutions of hyperthermia platform in combination with radiation and chemotherapy in cancer treatment.

MR guided FUS-prostate system: The TULSA-PRO System (Profound Medical) is a transurethral MR guided FUS system for whole gland ablation of the prostate. A test system was installed at the university hospital Dresden to perform the world's first compatibility tests on a Philips Ingenuity TF PET-MR scanner. The system comprises a transurethral ultrasound applicator with 10 FUS elements working at 4 or 14 MHz to heat the rim of the prostate up to 55 deg Celcius. The power and frequency of the 10 ultrasound transducers are individually steered by real-time MR-thermometry.

Results
Experimental facilities from in vitro to in vivo until clinical stage have been installed and tested. Preliminary in vitro study of FUS and RT exposure alone and the combination treatment for T98G glioblastoma cells, FaDu head and neck cells is undergoing.

Discussion
In conclusion, in vitro investigations of effects of FUS hyperthermia and RT combined therapy on different tumor cell lines will be performed to determine optimal FUS parameters and time interval between FUS and RT treatment.

Acknowledgement
The research leading to these results has received funding from Bundesministerium für Bildung und Forschung (BMBF) under grant No.03Z1L511 (SONO-RAY project).

Topics: Cell culture sonication, Radiation therapy

Abstract 31

Focusing precision and lesion size in cerebello-thalamo-tractotomy by MR Imaging-Guided High Intensity Focused Ultrasound (MRgFUS)

Ronald Bauer, Ernst Martin, Stefan Haegele-Link, Georg Kaegi, Nikolas Arne Wegener, Sebastian Schreglmann, Andras Jakab and Beat Werner

Introduction
Focusing precision in tcMRgFUS tractotomy depends on the ability of the treatment system to compensate for acoustic field distorsions induced by the patient skull.

Materials and Methods
The cerebello-thalamic tract (CTT) is our target of choice for the treatment of essential or dystonic tremor. The orientation of the CTT in the target volume based on anatomical studies (Ref.: Morel: stereotactic atlas of human thalamus) in the sagittal projection is about 60 to 65° relative to ACPC line and in coronal projection about 40 to 45° relative to axial intersection of ACPC line. We report our preliminary experience in 10 CTT tractotomies. The final thermal lesion at the focal point has a shape of an ellipsoid. The angle of the main axis of lesion was measured in relation to the ACPC line (sagittal view) and to axial intersection of ACPC line (coronal view) using BrainLAB software and compared with direction of CTT. Focusing precision was evaluated on MRI 48 hours po. by comparing the coordinates of focal point to the 3 dimentional coordinates of thermal lesion. The lesion size and orientation was the compared in two groups of 5 patients each. In group 1, the desired therapeutic response could be achieved while keeping the acoustic focus at the original target position during the whole treatment; in group 2, the acoustic focus had to be electronically steered away from the original target position for inadequate therapeutic response.

Results
MRgFUS intervention resulted in a prompt suppression of the Tremor in the extremity contralateral to the site of intervention in all 10 patients at the end of procedure. Group 1: lesions are 175 mm3 in average and show a good alignment of their main axis with orientation of CTT. Group 2: average lesion size was 303 mm3 and there is a clear misalignment between main lesion axis and CTT. Correlation between lesion volume and sagittal angle: Pearson 0.8; p=0.0056 The focal point is excentric to the centre of lesion. There is a predominant thermal spread in superior and anterior direction.

Discussion
We observed qualitatively a correlation between the alignment of the effected lesion with the targeted neuronal tract and the lesion size required to achieve the desired therapeutic effect. Future work will aim at better understanding and predicting the lesion orientation to adapt planning procedures accordingly.

Acknowledgement
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Topics: Brain panel

<u>**Abstract 32**</u>

Volume reduction after circumferential High Intensity Focused Ultrasound of breast fibroadenomata

Mirjam Peek, Rose Baker and Michael Douek

Introduction

Breast fibroadenomata are the most common benign breast lesions in women and are generally treated conservatively. In the HIFU-F trial, patients with breast fibroadenomata were successfully treated with circumferential High Intensity Focused Ultrasound (HIFU) treatment in order to reduce the treatment time and the fibroadenomata volume. We developed a model to help select the optimal size and volume of fibroadenoma for HIFU treatment.

Materials and Methods

In the HIFU-F trial, 50 consecutive patients ≥18 years of age with symptomatic fibroadenomata, visible on ultrasound, were recruited prospectively. All patients underwent ultrasound assessment before, three, six and 12 months post-HIFU treatment and both volume and maximum diameter of fibroadenomata, were assessed. We used orthogonal regression analysis (MINITAB statistics package) to compute the ratio of final to initial tumour volume, against initial tumour volume with a 95% confidence interval (CI). The fibroadenoma volume required to obtain a 30%, 40% and 50% reduction were calculated at three, six and 12 months follow-up.

Results

HIFU treatment was performed in 51 patients (53 treatments) with a mean diameter of 2.6 cm (SD 1.4 cm). At three months follow-up, a fibroadenoma of 4.39 cm3 (CI 1.99 – 9.70 cm3) or smaller will obtain a 30% reduction, 2.56 cm3 (CI 1.20 – 5.49 cm3) a 40% reduction and 1.36 cm3 (CI 0.46 – 4.01 cm3) a 50% reduction; at six months follow-up a volume of 8.76 cm3 (CI 3.33 – 23.03 cm3) or smaller will obtain a 30% reduction, 6.58 cm3 (CI 2.95 – 14.69 cm3) a 40% reduction and 4.70 cm3 (CI 2.44 – 9.04 cm3) a 50% reduction; at 12 months follow-up a volume of 9.59 cm3 (CI 3.11 – 29.57 cm3) or smaller will obtain a 30% reduction, 6.62 cm3 (CI 2.66 – 16.48 cm3) a 40% reduction and 4.28 cm3 (CI 2.05 – 8.90 cm3) a 50% reduction. For a spherical fibroadenoma, up to a fibroadenoma volume of 0.27 cm3, circumferential is equivalent to whole lesion ablation.

Discussion

Circumferential HIFU treatment of fibroadenomata is effective at achieving reduction in volume. Optimal fibroadenoma volume for HIFU treatment can be estimated using orthogonal regression and this should also be compared to whole lesion ablation.

Acknowledgement

Funding: Unrestricted educational grant for HIFU-F-trial from Theraclion Ltd (Malakoff, France). Acknowledgements: We would like to thank King‘s College London and Guy‘s and St. Thomas’ NHS Foundation Trust.

Topics: Benign lesions, Breast cancer

Abstract 33

Concept for integrating a MR-compatible robotic arm into the clinical infrastructure

Michael Unger, Johann Berger, Lisa Landgraf, Xinrui Zhang, Doudou Xu, Thomas Neumuth and Andreas Melzer

Introduction

Focussed ultrasound (FUS) as a non-invasive therapy for treating tumor diseases is becoming more and more relevant. Although, only the ablation of benign and locally restricted tumors is approved, a combined therapy of FUS and radiation therapy (RT) is promising to improve the outcome while lowering the radiation dosage. Due to the integration in the patient table, currently available HIFU systems only allow the treatment in very specific regions. Hence, a robotic arm positioning the FUS system according to the treatment planning is more versatile. For further studies on combined FUS-RT treatment, the robotic arm system needs to be integrated into the existing clinical infrastructure.

Materials and Methods

The MR-compatible robotic arm system (InnoMotion by InnoMedic GmbH) was not compatible with the Biograph mMR MR-PET system (Siemens Healthineers) in the Department of Nuclear Medicine of the University Medical Center Leipzig. Therefore, the C-arm holding the robotic arm was modified to fit onto the patient table. A 3D-printer (Makerbot Z18) was used to manufacture the necessary parts.

To integrate the system into the clinical infrastructure, the software of the robotic arm system needs to acquire images from the MR system during the planning and treatment phase. The MR system acts as a DICOM server which provides the imaging data to the robotic arm system. To enable operation alongside the common diagnostic use, the robotic arm system should be attached to the secondary network interface of the Biograph mMR MR-PET system.

Results

The robotic arm system was successfully modified to fit the Biograph mMR MR-PET system in the Department of Nuclear Medicine of the University Medical Center Leipzig. A concept for integrating the robotic arm system into the clinical IT infrastructure was provided.

Discussion

Using MR-PET imaging technique improves the evaluation of the effectiveness of combined FUS-RT treatment. Due to the early stage of these combined therapies, MR-capable robotic systems are hardly available. Therefore, these systems lack standard for clinical integration. After getting approval by the clinical IT department, further evaluation and validation studies will be conducted.

Acknowledgement

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Topics: Principles and technology of FUS/HiFU, Radiation therapy

Abstract 34

An in vitro study of ultrasound-induced hyperthermia combined with radiation therapy for glioblastoma cells

Xinrui Zhang, Doudou Xu, Lisa Landgraf, Shaonan Hu, Ina Patties, Michael Unger, Johann Berger, Annegret Glasow, Marc Foumelle, Steffen Tretbar, Thomas Neumuth and Andreas Melzer

Introduction

Focused ultrasound (FUS) is a precise way to generate mild hyperthermia (40-45°C) in tumor tissue. Many literatures reported that synergistic effect of combined hyperthermia and radiation therapy (RT) enhances radio sensitivity of tumor cells. However, few data showed the impact of acoustic waves on cancer cells. Glioblastoma multiforme is a highly proliferative and invasive tumor the most common subtype of high grade glioma. T98G glioblastoma cells were employed in this investigation. The aim of SONO-RAY project is to develop the proof-of-concept and workflow by using FUS and RT combination therapy for cancer treatment. In this study, a new developed in vitro ultrasound sonicator was applied to investigate the synergetic effect of US and RT on T98G glioblastoma cells.

Materials and Methods

To determine radiation dose curves of RT alone on T98G cells, a 150kV X-ray device (DARPAC 150-MC) was employed at doses of 0-20 Gy. For investigations a sonicator with 96 transducer elements working with homogenous wave was used to sonicate cells in a 96-well microplate at 1 MHz frequency. An infrared thermal camera (PI450 by Optris GmbH) with imaging software (PI connect version 2.10) was used to monitor real-time temperature in the wells during sonication. T98G cells were exposed to acoustic intensity (0.05 W/cm2) induced hyperthermia (40- 47 °C). As control a thermal block induced hyperthermia (43 °C) at a duration of 30 min, respectively. For combination, irradiation was conducted at a dose of 10 Gy for T98G cells 30 min post thermal block hyperthermia and 4 h post US hyperthermia treatment. Effects at the cellular metabolism (WST-1), proliferation (BrdU) and membrane integrity (LDH release) were detected after treatment.

Results

The RT dose curve results demonstrated a dose-dependent loss on cellular NAD(P)H levels of 60 % for T98G cells at 20 Gy. Cell membrane damage was reflected by LDH release from 4 % (0 Gy) to 17 % (20 Gy). The highest impact of RT was detected during analysis of DNA synthesis (BrdU) which nearly stopped at dosages above 5 Gy. Preliminary results indicated that cells treated by combined US hyperthermia with irradiation showed a lower cell viability of 18 % (WST-1 assay) in comparison to all single treatment groups and thermal block hyperthermia-RT combination group (47 % viable cells).

Discussion

US-induced hyperthermia showed a higher efficiency than thermal block hyperthermia in single treatment and combination groups. We provided first evidence that US effects are not limited to induce hyperthermia, but has biomechanical effects on cell too. The reliability and the mechanisms behind this beneficial combined treatment needs to be investigated in detail and on other tumor cells in future studies.

Acknowledgement

The research receives funding from the Bundesministerium für Bildung und Forschung (BMBF) under grant No.03Z1L511 (SONO-RAY project).

Topics: Cell culture sonication

Abstract 35

Statistical shape model based targeting for MR-guided focused ultrasound neurosurgery

Andras Jakab, Zoé Goey, Ruth Tuura, Ronald Bauer, Lennart Stieglitz, Gabor Szekely, Ernst Martin and Beat Werner

Introduction

The current standard for targeting subcortical structures during functional neurosurgical interventions relies on transferring stereotactic 3D coordinates from an anatomical atlas onto the patient's brain MR or CT images. This approach faces the following shortcomings: (1) the source of such atlases is often one histologically processed brain, which may not incorporate information on inter-individual anatomical variability; (2) the rigid transfer of target coordinates does not allow precise alignment with the patient`s subcortical anatomy. Our project aims to utilize statistical shape models (SSM) to overcome these limitations, and utilizes the 3D digitized version of the Morel atlas of the thalamus and basal ganglia.

Materials and Methods

In our talk, we demonstrate the use of a prototype targeting pipeline through five exemplary MRgFUS interventions that have been performed between January 2016 and June 2017 at the University Children's Hospital in Zurich. The method uses the pre- or intraoperatively acquired 3DT1 and T2 MR images of the patients, on which the visible outlines of the thalamus are delineated manually. Based on the anatomical correspondence between the visible thalamus outlines and the individual thalamic nuclei stored within the SSM, individualized targets maps and confidence interval maps are generated.

Results

The outlines of the thalamus could be delineated on the patient's intraoperative MRI, and the predicted volumes of the ventrolateralis-posteroventralis (VLpv or Vim) nucleus and the cerebello-thalamic tracts were in close proximity to the actual imaging targets. By fusing the resulting target and confidence interval maps with the patient's MRI, a feasible visual guidance was provided for the operating neurosurgeon.

Discussion

The efficiency and safety of functional neurosurgical interventions, such as high intensity focused ultrasound ablation, depend on the accuracy by which the target structures are reached. Using patient-specific, imaging based markers of the individual thalamic anatomy has the potential to improve accuracy. Our further efforts include the development of a software prototype – NeuroSHAPE – which will offer a user-friendly interface to apply the SSM-based targeting approach to MRgFUS treatments.

Acknowledgement

A. J. and Z. G. are supported by the Hasler Foundation. A. J. is supported by the FZK-Foundation, OPO-Foundation and the Stiftung für Wissenschaftliche Forschung, University of Zurich.

Topics: Brain panel

Abstract 36

Low intensity ultrasound increases the lifespan of mesenchymal stromal cell transplants in skeletal muscle

Scott Burks, Matthew Nagle, Saejeong Kim and Joseph Frank

Introduction

Mesenchymal stromal cells (MSC) are currently the most clinically applicable stem cell type for transplantation. Transplanted MSCs act as "paracrine-factories" by continually releasing cytokines, chemokines, and trophic factors (CCTF) that reduce host inflammation and stimulate endogenous regeneration mechanisms. MSCs have shown promise for a wide range of diseases from ischemia to graft-versus-host disease. While MSCs are considered immune privileged and can evade immune surveillance, they typically do not engraft into host tissue and usually die within 3-10days post-transplantation. Efforts to extend the lifespan of MSCs previously have involved chemical or genetic manipulation of MSCs prior to transplantation, but these approaches are not readily translatable. We have found that pulsed focused ultrasound (pFUS) interacts with host tissues to upregulate a variety of anti-apoptotic, pro-mitotic factors that could increase the lifespan of transplanted MSCs. In this study, we tested the hypothesis that daily unfocused therapeutic ultrasound (TUS) exposures following implantation of luciferase-transfected human MSC (LMSC) into murine hamstrings would prolong survival of transplanted MSC. Furthermore, we examined the proteomic profile of the hamstring microenvironment to investigate relevant molecular changes following TUS.

Materials and Methods

10^6 human LMSCs were intramuscularly transplanted into each hamstring of C3H mice. LMSCs were transfected with renilla luciferase using lentoviral vectors and expressed under the EF1 promoter. Beginning on the day of implantation (D1), mice received daily TUS sonication to one hamstring (1 MHz US, 2 W/cm2, 10% duty cycle, 10 min total exposure time). After TUS, mice were bioluminescence imaged for 10s after receiving an intraperitoneal injection of D-luciferin (150 mg/kg). Mice were euthanized on D6. Temperature measurements were obtained in different group of mice using an implanted thermocouple. Other mice that did not receive LMSC were given a single application of TUS and then muscle was harvested at various times for molecular analysis. Dynamic proteomic profiling following TUS was performed with a Milliplex multiplex cytokine assay (EMD Millipore) and single-plex enzyme-linked immunosorbent assays (ELISA).

Results

TUS exposures result in a combination of mechanical and thermal effects. TUS raised hamstring temperature from 36 to 41 during the 10 min exposure. Total bioluminescence in treated and control legs decayed each successive day, but decay was slower in the TUS-treated hamstrings. Accordingly, by D6, bioluminescence was nearly undetectable in untreated legs, while still light was being emitted from TUS-treated legs. The number of MSCs that remained in treated legs was approximately 10 times greater than in contralateral muscle. Molecular changes for 20 hr post-sonication were predominately anti-inflammatory. Notably, statistically significant ($p < 0.05$; ANOVA) elevations were detected for interleukins
(IL)-1a, 4, 6, and 10, tumor necrosis factor-a (TNFa), nuclear factor kB (NFkB), cyclooxygenase-2 (COX2), and hypoxia-inducible factor-1a (HIF-1a), vascular endothelial growth

factor (VEGF), intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM).

Discussion

TUS to skeletal muscle containing transplanted MSCs extends the resident time of live MSCs in tissue by slowing MSC death/clearance rates. Molecular profiling revealed elevations in several factors that are consistent with hypoxia and transient ischemia, that are known to prolong MSC survival. Low intensity TUS is benign. Further mechanistic investigations into TUS exposures are necessary to expression of NFkB or HIF-1a via other pathways. These results have profound implications for a wide range of MSC therapies because TUS is noninvasive, safe, and inexpensive. Therefore, extending a clinically approved routine and straight forward treatment strategy to extend the survival of transplanted MSCs could, increase longevity and function of transplanted cells, reduce the number of transplantations/injections required to treat disease and ultimately contribute to improvements in cellular therapy.

Acknowledgement

This study was funded by the Intramural Research Program and the National Institutes of Health Clinical Center.

Topics: Muscular skeletal panel

Abstract 37

Multiple courses of BBB opening with pulsed Focused Ultrasound and Microbubbles promotes phosphorylated Tau production

Zsofia Kovacs, Maggie Sundby, Bobbi Lewis and Joseph Frank

Introduction

Blood-brain barrier (BBB) opening with pulsed Focused Ultrasound and Microbubbles (pFUS+MB) has been proposed as a novel strategy for Alzheimer's disease therapeutics either by reducing the number of plaques with anti-Aß antibody or by microglia activation [1-5]. Pathologies and dementias of the nervous system such as Alzheimer's disease and Parkinson's disease are associated with Tau proteins that no longer stabilize microtubules properly, and is associated with Tau hyperphosphorylation. The goal of this study was to investigate the impact of multiple courses of BBB opening with pFUS+MB on potential phosphorylated Tau (pTau) production.

Materials and Methods

Female rats (n=6) received 6 weekly pFUS+MB OptisonTM (GE Healthcare, Little Chalfont, Buckinghamshire, UK) in the striatum and the contralateral hippocampus. 100 µl OptisonTM was infused over 1 minute starting 30 sec before pFUS while rats inhaled 100% O2. 3 daily doses of 300 mg/kg BrdU (Sigma Aldrich, St. Louis, MO) was administered intraperitoneally before sonication to label proliferating cells in vivo. Peak negative pressures of 0.3-0.5 MPa was applied in 10 ms burst length and 1% duty cycle (9 focal points, 120 sec/9 focal points – cortex (C), 120 sec/4 focal points – hippocampus (H)) using a single-element spherical FUS transducer (center frequency: 548.00 kHz; focal number: 0.8; aperture: 7.5 cm; FUS Instruments). T2, T2* and Gd-enhanced T1-weighted images were obtained by 3.0T MRI. Animals were euthanized one week after the sixth pFUS treatment. Histological evaluation for microglia and astrocytes, neurogenesis, micro hemorrhage and pTau was performed. Statistical analysis was performed comparing sonicated to contralateral brain.

Results

After each sonication GdT1 MRI demonstrated BBB disruption in the C and the H. T2* MRI showed hypointensities indicative of metallophagocytic cells and ferritin accumulation in both treated regions associated with brain atrophy. Histological evaluation showed astrocyte and microglia activation, and the increase in BrdU+ cells consistent with neurogenesis. In addition to the cellular activation, hyperphosphorylated Tau positive neurons occurred in the C and H evidence of neuronal injury following multiple weekly courses of pFUS+MB.

Discussion

Various multiple pFUS+MB treatment protocols have been used in both normal and experimental models with demonstrating limited damage by MRI or by histological examination [6]. However, this study demonstrates that weekly pFUS+MB exposures in rats resulted in morphological and pathological changes on MRI and histology that demonstrated evidence of vascular damage with persistent BBB disruption, microhemorrhages by MRI, and astrocytic and microglial activation, neuronal loss and damage with significant increase in pTau present both cortical and hippocampal neurons. Moreover, increased evidence of neurogenesis based on BrdU+ neurons were observed in areas of brain atrophy. These results demonstrate the pFUS+MB induced sterile inflammation [7] resulted in cumulative parenchymal damage and pTau production that was detected by MRI and on histology underlying the importance of long term monitoring of the brain following multiple sonications before its clinical translation. In particular, the presence of hyperphosphorylated Tau in neurons needs further investigation.

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Acknowledgement
This project was funded by the Intramural Research Program of the National Institutes of Health.

Topics: Brain panel

Abstract 38

Peak Negative Pressure (PNP)-dependent molecular and pathologic responses of rat myocardium by pulsed focused ultrasound

Kee Jang, Tsang-Wei Tu, Bobbi Lewis, Scott Burks and Joseph Frank

Introduction
Image-guided high intensity focused ultrasound (HIFU) has been used for cardiac resynchronization therapy (CRT) (Quesson et al., Scientific Reports 6, 2016) because the technique is noninvasive; however, the molecular changes associated with sonicating the myocardium are mostly unknown. The purpose of this study was to investigate the molecular and pathologic responses in the rat myocardium following pulsed focused ultrasound (pFUS) exposures.

Materials and Methods
Eight to ten week old female Sprague Dawley rats were imaged on a 3T MR scanner and T2-weighted MR images were acquired with 8.9ms repetition time (TR), 4.5ms echo time (TE) in 1mm slice thickness through the chest wall in sagittal plane. The MR images were used for pFUS targeting to the left ventricular (LV) myocardium (center frequency 1.1MHz; peak negative pressure (PNP) 3 or 6 MPa; 10ms bursts; 1Hz PRF; 100 sonications/point, 20 (6MPa) or 40 (3MPa) focal spots (RK-100, FUS Instrument). Following pFUS treatment, molecular analysis was performed of myocardial lysate (n=5/timepoint) over the time period up to 48hr along with cardiac injury markers using ELISAs. Immunohistochemical analyses were performed to examine the pathologic changes following sonication. Statistical analysis was performed using ANOVA with multiple comparisons to sham control with $p<0.05$.

Results
pFUS treatment to the LV induced significant microenvironmental molecular changes with a clear different pattern of transient molecular/pathologic immunomodulation dependent on PNP. Immediate proteomic responses were observed with pFUS at 6MPa that lasted up to post 12hr of sonication without cardiac injury marker elevation. In comparison, there was a delayed molecular response observed with pFUS at 3MPa and the cytokines, chemokines and trophic factors and cardiac injury marker expression peaking between 12 to 24 hr post pFUS. Histological differences were also dependent on PNP with that significant edematous development as well as immune cell infiltration was observed at 6MPa and limited histological changes were observed at 3MPa. Pulmonary damage following pFUS was dependent on PNPs with significant pulmonary hemorrhage observed at 6MPa in comparison to 3MPa and sham control.

Discussion
We demonstrated that there was a PNP influenced the timing and amount of induced molecular and pathologic changes of LV myocardium following pFUS. At 6MPa sonication resulted in changes associated with blunt chest trauma whereas at 3MPa the findings were consistent with stunned myocardium. Further evaluation of physiological/functional roles of pFUS-induced molecular change in myocardium would be necessary to better understand the effects of CRT in the heart.

Acknowledgement
This work was supported by the Intramural Research Programs of the Clinical Center and the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health.

Topics: Principles and technology of FUS/HiFU, Solution for small animal FUS/HiFU

Abstract 39

How to setup a FUS/HIFU-Center (Leipzig)

Leonard Leifels, Maximiliam Beimler, Juliana Melasch, Tim Ole Petersen, Patrick Stumpp, Thomas Kahn and Andreas Melzer

Introduction
For decades surgery has been the only cure for various solid tumors. But more recent advances in image-guided minimally invasive techniques have increased their popularity. They have become a growing field in the treatment of solid tumors, pain and certain neurological disorders. Among the thermal ablation therapies, high-intensity focused ultrasound (HIFU) represents a completely non-invasive, promising approach due to a gently and effective local treatment.
In the Department of Radiology at Leipzig University Hospital the Philips Sonalleve is in process to be put into operation. During the last two decades the Department already has collected first-hand experiences in the field of interventional MR imaging.
Our aims are to establish a MR-HIFU service in the part of Eastern Germany primarily to provide a clinical therapy option for cancer treatment and contribute to the growing body of evidence in the clinical as well as the research community. Aim of this study is providing an overview of first steps, pitfalls and promblems in setting up a FUS/HiFU-center.

Materials and Methods
To setup a center for FUS/HiFU is associated with a lot of considerations. Amongst others installation of the system including an inpatient ward, enough space for preparation and post-interventional treatment, organizing a responsible team with interventional radiologists, registered nurses, medical technical radiologic assistant, medical physicians and secretaries. Also it is important to acquire Patients for FUS/HiFU-therapy. It’s important to inform our clinical colleagues about our MR-HiFU principles that aim to expand, rather than to compete with coexisting hospital resources and services. To avoid satisfying results a strict indication and patient selection is crucial. That demands a high number of primary screenings to pick the most suitable patients. To realize that diverse marketing strategies were implemented to gather further possible patients. In addition to that involved physicians from Leipzig visited different centers to gain experience in treatment and learn about pitfalls and difficulties of the starting phase.

Results
To setup a center for FUS/HiFU is associated with a lot of considerations, including the choice of the FUS/HiFU-system, installation of the system, building up the working environment, marketing, building up a network between assigning physicians, sreening for patients and learning how to perform the procedure. Here we give an overview about our experiences building up an FUS/HiFU-Center.

Discussion
To setup a center for FUS/HiFU is associated with a lot of considerations, including the choice of the FUS/HiFU-system, installation of the system, building up the working environment, marketing, building up a network between assigning physicians, sreening for patients and learning how to perform the procedure. Here we give an overview about our experiences building up an FUS/HiFU-Center.

Acknowledgement
No Acknowledgement.

Topics: How to set up a center for FUS/HiFU?

Abstract 40

IGT-FUS Reusable Tissue Mimicking Material Phantom

Andrew Dennison, Joyce Joy and Andreas Melzer

Introduction
This work reports preliminary testing of a reusable focused ultrasound (FUS) tissue mimicking material (TMM) phantom for image guided therapy (IGT) applications such as system calibration, validation and quality assurance. Several TMM's suitable for testing FUS systems and transducers have been published to date, with examples including polyacrylamide (PAA) doped with egg-white or albumin proteins or thermal responsive colour changing ink. These are single-use relying on dissection after FUS treatment to perform optical lesion cross validation. Commercial quality assurance phantoms can also be purchased which are expensive and have proprietary recipes. These are reusable for IGT-FUS, but lack the capability for lesion cross validation assessment. Until now, this has resulted in need of both single and reusable phantoms for IGT-FUS system validation.

Materials and Methods
In this work N-Isopropylacrylamide (NIPAM) material with a cloud point of 52°C was fabricated which had comparable properties (density, elasticity, water content) to soft tissues and other PAA based TMM phantoms. This material is optically transparent at temperatures below its cloud point. Above the cloud point, the material becomes opaque, allowing an IGT-FUS system to perform thermal and optical lesioning of the phantom. Upon cooling the material becomes transparent again making it reusable for thermal studies.
For 1litre of NIPAM phantom material the following ingredients were added stepwise; 990ml of de-ionised water, 1.3g of ammonium persulfate (APS), 2.9 ml of acrylic acid, 60 g of NIPAM and 2.5 g of N,N'Methylenebisacrylamide. The solution was mixed and vacuum degassed for 30 minutes at -1Bar. This was poured into a casting die and 2.7 ml of Tetramethylethylenediamine (TEMED) added to initiate curing at room temperature for 24hours.

Results
The prepared NIPAM phantom material was tested using Exablate 2100 MRgFUS system (Insightec, Israel) and a 1.2MHz confocal HIFU system (IGT, France) for a range of FUS power (20-100W) and duration (30,45,60s). Lesion assessment was cross validated by MRI PRF shift thermometry and optical image assessment. The NIPAM phantom produced thermal and optically visible lesions using both FUS systems successfully. At low power values (<50W), with a thermal rise below the cloud point of the NIPAM material, a clear steady temperature signal was observed. At higher temperatures, beyond the cloud point threshold, there was significantly decreased signal to noise.

Discussion
Here we present a N-Isopropylacrylamide (NIPAM) TMM phantom, with a chemically tuneable temperature threshold or cloud point, that offers reusability and optical cross validation without the need for destructive dissection. This material allows lesion visualisation during treatment using MRI, Ultrasound, Thermal and Optical imaging, creating a single phantom for validation, benchmarking and calibration applications of IGT-FUS.

Acknowledgement
MRI Group IMSaT led by Prof. Andreas Melzer: Andrew Dennison, Joyce Joy, Lukasz Priba, Helen Mcleod, Baljit Jagpal

Topics: Phantoms and tumor cell treatment

Abstract 41

Mechanical focused ultrasound forces directly activate TRPC1 cation channels in murine kidney and skeletal muscle to enhance stem cell homing.

Matthew Nagle, Michele Bresler, Saejeong Kim, Joseph Frank and Scott Burks

Introduction

Pulsed focused ultrasound (pFUS) induces microenvironmental changes in tissues that enhance homing and efficacy of intravenously-infused mesenchymal stromal cells (MSC). How pFUS interacts with tissue to cause these changes are unclear. MSC homing depends upon nuclear factor k-B (NFkB) activation of cyclooxygenase-2 (COX2) transcription, which require cytosolic Ca2+ transients. To explore how pFUS activates these Ca2+-dependent processes in vivo, mouse muscle and kidneys were sonicated while cavitation and tissue displacement were measured. Mice were also given different drugs to disrupt Ca2+ channel function and then COX2 expression and MSC homing to kidneys and muscle were assayed. TRPC1, which functions as a mechanically-sensitive cation channel or a calcium release-activated channel (CRAC) was investigated using TRPC1-knockout mice.

Materials and Methods

C3H or TRPC-ko mice received hamstring or kidney pFUS at 1 MHz, 5 Hz pulse repetition frequency, 5% duty cycle, and 4 MPa peak rarefaction pressure. Passive cavitation was detected by hydrophone and tissue displacement was determined from radiofrequency data acquired during ultrasound imaging. Mice were euthanized 4hr post-pFUS and COX2 expression was measured by ELISA. For MSC homing studies, 106 human MSC were intravenously-infused 4hr post-pFUS and mice were euthanized 24hr later. MSC were quantified histologically after immunostaining for human mitochondrial markers. GdCl3 (0.04mmoles/kg), ruthenium red (RR) (0.01mmoles/kg), or verapamil (25mg/kg) were given before pFUS. Interactions between channel components were measured histologically and with co-immunoprecipitation. One-way ANOVAs with p-values <0.05 were considered significant.

Results

Statistically significant increases in COX2 and increased homing of MSC were measured in muscle and kidney with mean tissue displacement of ~60 um for muscle and ~70 um for kidney. Half-harmonic emissions were essentially undetected in both tissues. Indiscriminate blocking of Ca2+ channels by GdCl3 prevented COX2 upregulation and MSC homing to both tissues. Likewise, specifically inhibiting mechanically-sensitive Ca2+ channels with RR or voltage-gated L-type Ca2+ channels with verapamil abrogated COX2 upregulation and MSC homing. Lastly, COX2 was not upregulated and MSC did not home to muscle or kidneys following pFUS in TRPC1-ko mice. Immunostaining and co-immunoprecipitation revealed that L-type Ca2+ channels were complexed with TRPC1 channels, but not ORAI1/TRPC1 complexes, which function as a CRAC.

Discussion

Mechanical pFUS forces mechanically activate TRPC1 to drive molecular changes that enable MSC homing. Tissue displacement without detectable cavitation suggests tissue is influenced by acoustic radiation forces. Activation of TRPC1 and voltage-gated Ca2+ channels are critical, but their functional relationship is ambiguous. TRPC1 is a mechanically-sensitive channel, but when complexed with ORAI1, a CRAC. Therefore, activation could occur when 1) mechanically-activated TRPC1 currents locally depolarize voltage-gated Ca2+ channels to amplify Ca2+ influx or 2) pFUS activates voltage-gated Ca2+ channels though capacitive currents (ref), which activate TRPC1-containing CRAC to amplify Ca2+ influx. Voltage-gated Ca2+ channels colocalizing with TRPC1, but not ORAI1/TRPC1 CRAC complexes suggests against the notion that TRPC1 functions as a CRAC in this pathway. Rather, it is mechanically activated by pFUS and those currents subsequently activates voltage-gated Ca2+ channels by local depolarization to generate sufficient Ca2+ influx to drive NFkB and COX2 signaling.

Acknowledgement

This work was funded by Intramural Research Program at the NIH Clinical Center

Topics: Stem cells

Abstract 42

IN VIVO MEASUREMENTS OF MBN DEPTH FOR FOCUSED ULTRASOUND ABLATION OF PATIENTS WITH FACET RELATED BACK PAIN: PREDICTORS FOR PATIENT CANDIDACY

Suzanne Leblang, Hannah Zwiebel, Daniel Baldor, Arik Hananel and Ron Aginsky

Introduction

To evaluate candidacy for direct focused ultrasound ablation of the medial nerve branch in patients with facet related back pain.

Materials and Methods

100 patient (54 female and 46 male) lumbar noncontrast CAT scans were retrospectively evaluated and the depth from the skin to the medial branch nerve (MBN - residing at the junction of the transverse process and articular facet) from L2-L5 was recorded bilaterally. Other measurements included the smallest width of the pedicle and the 3 dimensions of the transverse process bilaterally at each level. Body Mass Index (BMI) was also calculated. A step-wise linear regression model was built to identify the strongest predictors of MBN depth with independent variables including age, gender, vertebral level, BMI, and pedicle side (right or left).

Results

The average distance of skin-to-MBN increased as the lumbar level increased measuring 64.4mm at L2, 72.0mm at L3, 79.2mm at L4, and 79.1mm at L5. The minimum distance was 36.2mm and the maximum was 129.9mm. The linear regression model returned BMI, vertebral level, and gender as significant predictors of MBN depth. All were independently significant to $p< 0.001$, and the regression equation fit the data well ($p < 0.001$ and $r2= .61$). Analysis also demonstrated that MBN depth increases more rapidly in men than in women as BMI increases.
MBN Depth (mm) = 2.2*BMI + 4.9*lumbar vertebral level + 3.6 (if female) – 5.4
The average thickness of the pedicles also increased as the lumbar level increased measuring 92 mm at L2 and 16.1 mm at L5. There was no significant trend in the dimensions of the transverse process as the lumbar level changed.

Discussion

The average distance from the skin to the MBN combining both men and women is less than 79.1mm. To date, no clinical studies have published the in vivo distance from the skin to the MBN in patients with low back pain to determine if the MBN resides within an area that can be targeted with current FUS technology as the depth of the focal spot is limited. AS BMI is associated with increasing probability of low back pain being due to facet joint pain across all ages, this may be a modifiable risk factor to then allow such patients to benefit from FUS therapy. This is also the first clinical study reporting the pedicular thickness which allows for comparison with animal models previously showing a certain thickness of bone likely protects the far field neural structures.

Acknowledgement

The authors wish to acknowledge the help of Lucas Gardian for his assistance.

Topics: Musculo Skelettal

Abstract 43

Artifact from Myomectomy scars on MRI images-What does this mean for MRgFUS candidacy for Uterine Fibroids?

Suzanne Leblang

Introduction

To evaluate whether artifacts along the myomectomy incisions in the subcutaneous tissues and the uterus affect MRgFUS treatment.

Materials and Methods

20 patients that were treated with MRgFUS for recurrent uterine fibroids s/p myomectomy were retrospectively evaluated. MRI scans pre and post MRgFUS treatment were reviewed and the length and thickness of the subcutaneous scar, the location of T2* and T1 post contrast fat saturation artifacts along the beam path, and the post treatment nonperfused volume were recorded. The clinical chart was reviewed for the myomectomy surgery reports, the time interval between the myomectomy and the MRgFUS treatment. Adverse events were documented.

Results

Despite artifacts from surgery in the subcutaneous tissues and along the uterine wall, the MRgFUS beam was able to penetrate thru the artifact and result in successful ablation of the uterine fibroids with most cases resulting in NPV>70%. The older subcutaneous portions of the scars were less prominent on MRI scans compared to newer scars. Surgical reports stated that resorbable sutures were used in all cases. The artifact did not block the ability to monitor the heating on the thermal map images. There were no cases of skin burns.

Discussion

Artifact from prior myomectomies should not preclude treatment with MRgFUS. These artifacts manifest as areas of blooming on T2 * and T1 post contrast fat saturation sequences yet do not represent metal artifact as these surgeries were performed with resorbable suture material. It is possible that the artifact stems from hemosiderin deposits along the incisions or dye from the sutures has leaked into the tissues.

Acknowledgement

The author wishes to acknowledge Lisa McKenzie and Lana Amiel for their help with this project.

Topics: Other indications. What can go wrong? How to avoid complications

Abstract 44

In-silico First-stage Evaluation of a Focused Ultrasound Treatment System for Moving Targets

Michael Schwenke, Jan Strehlow, Daniel Demedts, Sabrina Haase, Diego Barrios Romero, Sven Rothlübbers, Caroline von Dresky, Stephan Zidowitz, Joachim Georgii, Senay Mihcin, Mario Bezzi, Christine Tanner, Giora Sat, Yoav Levy, Jürgen Jenne, Matthias Günther, Andreas Melzer and Tobias Preusser

Introduction
Focused ultrasound (FUS) increasingly enters clinical routine as a treatment option. Currently, no clinically available FUS treatment system features automated respiratory motion compensation. Quality assurance of such a complicated system is challenging and involves great efforts for manual experimentation. We here aim at reducing these efforts by utilizing numerical FUS simulations for automatic system testing.

Materials and Methods
A novel FUS treatment system with motion compensation is described, developed with the goal of clinical use. The system consists of a clinically available MR device and FUS transducer system. The controller is very generic and could use any suitable MR or FUS device. MR image sequences (echo planar imaging) are acquired for combined motion observation and thermometry. Image-based tracking of anatomical features is performed and motion predictions are estimated to compensate for processing delays. FUS control parameters are computed repeatedly and sent to the hardware to steer the focus to the (estimated) target position.
To allow for extensive testing of the motion compensation over wide ranges of parameters and algorithmic choices, we replace the actual MR and FUS devices by a virtual system equipped with a numerical FUS model to predict the outcome of the treatment during respiratory motion. All calculations of individual components of the motion compensation produce individually known errors with however unknown impact on the overall therapy outcome. To analyze the overall impact, we define an intuitive quality measure that compares the achieved temperature to the static scenario, resulting in an overall efficiency with respect to temperature rise.

Results
With a clinically available monitoring image rate of 6.67 Hz and 20 FUS control updates per second, normal respiratory motion is estimated to be compensable with an estimated efficiency of 80%. This reduces to about 70% for motion scaled by 1.5. Extensive testing over wide parameter ranges involving 6347 simulated sonications shows that the most influential component is the temporal motion prediction. Utilizing a history-based motion prediction method has advantages over a linear extrapolator for normal respiratory motion.

Discussion
The estimated efficiency of the new treatment system is already suited for clinical applications. The simulation-based in-silico testing as a first-stage validation reduces the efforts of real-world testing. Due to the extensible modular design of the system in combination with automatic testing, the described approach might lead to faster translations from research to clinical practice.

Acknowledgement
The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreements no. 270186 (www.fusimo.eu) and no. 611889 (www.trans-fusimo.eu).

Topics: Abdomen, Principles and technology of FUS/HiFU

Abstract 45

3D ultrasound based motion tracking with MR-thermometry

Pierre Bour, Valéry Ozenne, Baudouin Denis de Senneville, Erik Dumont and Bruno Quesson

Introduction

MRI-guided High Intensity Focused Ultrasound (MR-HIFU) treatment of mobile organs (heart, liver, kidney) remain challenging since it requires compensation of motion on MRI thermometry and real-time update of HIFU beam position to track the targeted region. As of now, motion corrections in MRI have been proposed using a MRI echo navigator, image registration or using external sensors. However, the aforementioned methods either slave the motion correction on MR-acquisition or lack in 3D correction. To overcome these limitations, we proposed to use a full 3D ultrasound based motion correction using the HIFU probe in transmit-receive mode. This method does not require any additional device inside the magnet and do not require compromises on MR-thermometry. A validation was performed on agar gel under controlled motion and a proof of feasibility was carried out, in vivo, on pig liver.

Materials and Methods

Motion tracking was implemented using ultrasonic speckle-tracking on four sub-apertures of the HIFU transducer. Estimation of the displacement was performed at 10 Hz update rate, based on the cross-correlation of backscattered signals between consecutive HIFU shots (2 ms) followed by a triangulation algorithm. The computed displacement was exploited in real-time to steer the HIFU beam for target tracking between consecutive position measurements. MR-temperature imaging (proton resonance frequency shift method) was preformed simultaneously using a fast echo planar imaging sequence as previously published. Three coronal slices were acquired around the HIFU focal spot with an echo navigator (used as a gold standard for displacement estimation) positioned in head-feet orientation. The method was evaluated on an Agar gel positioned on a mobile platform allowing translation in the head-feet direction oscillating with a controlled amplitude and frequency. Then, the method was evaluated in vivo in the liver of a pig.

Results

On an Agar gel, displacement estimations on y axis were in agreement with a 1D navigator echo, positioned in the head-feet direction (amplitude error < 1%). The maximum displacement and velocity measured were 14 mm and 1.1 mm.s-1, respectively. Ablation was performed with a sonication duty cycle of 63 % during 60s at 100 W acoustic power. The maximum temperature increase was 18.1°C and 26.6°C without and with focus correction, respectively. On the same slice, the peak width at half maximum of the temperature distribution at the end of the sonication in [x , y] was [1.3 , 2] cm and [1.6 , 1.6] cm without and with correction, respectively. Displacement estimations in vivo on y axis, were in good agreement with the echo navigator signal positioned at the liver-lung interface. The maximum temperature increase was 16.2°C and 23.5°C without and with focus correction, respectively.

Discussion
Motion correction and online HIFU beam steering were successfully performed in vitro and in vivo. In vitro, efficient target locking was confirmed by temperature evolution and displayed a complete compensation on the motion artifact observed when motion correction was disabled. In vivo feasibility study was promising for further validations during ablations in mobile organs.

Acknowledgement
This work received financial support from the French National Investments for the Future Programs ANR-10-IAHU-04 (IHU Liryc) and Laboratory of Excellence ANR-10-LABX-57 (TRAIL).

Topics: Abdomen

Abstract 46

Uterine fibroids: apparent diffusion coefficient as a biomarker for monitoring the success of high-intensity focused ultrasound therapy

Teija Sainio, Jani Saunavaara and Roberto Blanco Sequeiros

Introduction

High-intensity focused ultrasound (HIFU) therapy is a noninvasive treatment method that can be used to treat a variety of tumors. At the moment HIFU therapy is most commonly used to treat uterine fibroids. One drawback of HIFU therapy is that the treated tissue cannot be identified during the treatment. This may increase the risk of not achieving optimal treatment result. The purpose of this study is to determine the feasibility of using the apparent diffusion coefficient (ADC) as a biomarker that could be monitored during the treatment and evaluate the volume of the treated tissue.

Materials and Methods

Twenty patients who underwent the diffusion-weighted imaging (DWI) before and after the HIFU treatment were enrolled in this study, and 14 of 20 have underwent the MR examination with DWI at 3-month follow-up. Treatment was performed with MR image-guided focused surgical system (Sonalleve) coupled with 3-T MR system. The DW images were measured with different b-values: 0, 100, 400, 600, and 800 s/mm2. The ADC maps were reconstructed from the DW images with different combinations of b-values with Philips software for quantitative analysis. Regions of interest localized to areas of hyperintensity on ADC maps were drawn on posttreatment maps. Quantitative ADC values were obtained from treated and nontreated uterine tissue before and after the treatment and from 3-month follow-up ADC maps. The treated tissue was assessed from the contrast enhanced 3D T1-weighted images.

Results

The uterine fibroids selected for the study had no hypointense or hyperintense changes on the ADC maps before the treatment. However considerably increased ADC value changes were localized to treated tissue on posttreatment ADC maps. Thus ADC values for treated fibroid tissue were decreased at 3-month ADC maps compared to posttreatment ADC values.

Discussion

The uterine fibroids selected for the study had no hypointense or hyperintense changes on the ADC maps before the treatment. However considerably increased ADC value changes were localized to treated tissue on posttreatment ADC maps.

ADC values for treated fibroid tissue were further increased at 3-month ADC maps compared to posttreatment ADC values.

Acknowledgement

This work was supported in part by The Education and Research Foundation of Turku University Hospital and Medical Imaging Centre of Southwest Finland, Turku University Hospital.

Topics: Abdomen

Abstract 47

Therapeutic Effects of Ultrasound-guided Radiofrequency Ablation on Adenomyosis

Wen Luo, Guangbin He and Xiaodong Zhou

Introduction

Adenomyosis is one of the most common benign disorders for women in reproductive age. Ultrasound-guided RFA has been used to necrotize the local tissues, which is accepted as one technique showing excellent local control and acceptable morbidity. In the current study, we employed CE US for evaluation of therapeutic effects of ultrasound-guided RFA on 210 patients with adenomyosis in our hospital.

Materials and Methods

210 patients with adenomyosis were ablated via ultrasound-guided RFA. CE US was performed before ablation and 1, 3, 6, 12 months after ablation. Vascular perfusion of lesions was evaluated as follows: homogeneous, heterogeneous, no perfusion, surrounding vessels on CEUS before and after ablation. Serum antigen CA125 and hemoglobin was observed.

Results

The size of adenomyosis lesions was 3.1±1.2cm. Before ablation, 68% lesions presented homogeneous enhancement, while the others were detected as heterogeneous enhancement. One month after ablation, 89% lesions showed no perfusion which indicated the total necrosis of the lesions, The necrosis of ablated areas was identified in pathological results. 11% lesions presented surrounding vessels but no central perfusion. Three months after ablation, 6% lesions had lower enhancedment than the surrounding tissues, which may indicated the residuals. Six months after ablation, clinical symptoms of all the patients were improved and uterine volume were decreased. The level of CA125 was decreased and hemoglobin achieved normal gradually.

Discussion

CEUS has an important role in evaluation of the foci and the therapeutic effects.

Acknowledgement

None

Topics: Fibroid panel

Abstract 48

Effects of High intensity focused ultrasound plus radiofrequency on large uterus fibroid

Liwen Liu, Xiaodong Zhou and Wen Luo

Introduction
In the past years, HIFU was used for treatment of Uterine fibroids. However, more and more literature discovered residual tissue and blood flow after HIFU, which is a hot point in HIFU field. Recently, RF ablation was also reported to be used for treating fibroids with a better ratio of complete necrosis but higher complications. In this study, we try to combine HIFU and RF ablation for treatment of fibroids and investigated the effects of those treatments in order to provide evidence for ttreatment of uterine fibroids.

Materials and Methods
Patients with fibroids (>3cm in diameter) randomly divided into two groups and ablated by using HIFU or HIFU plus RF ablation accordingly. The effects of ablation was evaluated by contrast-enhanced ultrasound.

Results
102 fibroids with diameter of 3.0 cm to 8.2 cm were included in this study. CEUS showed the complete ablation rates were 72% in HIFU group, 96% in HIFU plus RF group ($P<0.05$). Complication rate in HIFU group was 10% and 2% in HIFU plus RF group ($P<0.05$).

Discussion
For the treatment of large fibroids, HIFU plus RF ablation could be more valuable to achieve higher complete ablation and less complications than single HIFU.

Acknowledgement
None

Topics: Fibroid panel

Abstract 49

Comparison of effects of radiofrequency ablation vs high intensity focused ultraound on uterous fibroid

Xiaodong Zhou, Guangbin He and Wen Luo

Introduction

Uterine fibroids are common benign tumors in females. Although hysterectomy has been the traditional method for treating uterine fibroids in the past, recently organ retention has been the physiological and psychological requirement for some patients. Currently, ultrasound-guided ablation therapy was developed quickly, such as HIFU and RF ablation. We investigated the effects of those treatments in order to provide some evidence for the clinical selection of a suitable, minimally invasive method for treatment of uterine fibroids.

Materials and Methods

Patients randomly divided into two groups and ablated by using HIFU or RF ablation accordingly. Each group were divided again into subgroups A, B, and C based on size and subgroups E, F, and G based on fibroid blood supply grades. The fibroid diameters in subgroups A, B, and C were 2.0 cm <or= D < 4.0 cm, 4.0 cm <or= D<6.0 cm and 6.0 cm <or= D<8.0 cm, respectively, and fibroid blood supplies were classified into three grades corresponding to subgroups E, F, and G, respectively. The effects of ablation was evaluated by contrast-enhanced ultrasound.

Results

122 fibroids with diameter of 2.1cm to 6.5cmwere included in this study. The complete ablation rates were 89% in HIFU group, 95% in RF group ($P<0.05$). The comparison between the treatments in subgroup A and subgroup E showed that the effects of HIFU was similar to those of RF group ($p > 0.05$). In other subgroups, the complete ablation rates of RF ablation were higher than those of HIFU ($p < 0.05$).

Discussion

HIFU could be the preferred method for the treatment of small, hypovascular fibroids. RF ablation could be helpful for the large and hypervascular fibroids.

Acknowledgement

None

Topics: Fibroid panel

Abstract 50

Cavitation threshold in murine model of pancretic cancer

Lorenzo Francesco Giuliani and Matteo Primavera

Introduction

HIFU is a promising and expanding field of modern medicine. Pancreatic cancer is high mortality tumor due to its aggressiveness, retroperitoneal location and in most cases late diagnosis. The use of HIFU ,in the treatment of pancreatic cancer, is of greatly value thanks to its non invasive nature and ability to hit target areas without compromising nearby structures. One of the major obstacles in this scenario is to find the ideal treatment window in order to avoid other viscera and great vessel, this can be a challenging task due to physiological body movements and the location of the pancreas.

Materials and Methods

The aim of our study was to establish the cavitation threshold during HIFU treatment using a murine model of pancreatic cancer. For each mouse, we considered the tumor dimensions and location and decided to perform an ex vivo or in vivo treatment. The tumors were induced by injection of TH4 pancreatic tumor cell lineage subcutaneously or orthotopically during a laparoscopy procedure. Some of the mice received doxorubicin hydrochloride during treatment using a syringe pump.
Before the treatment, the mice were imaged using US to localize the tumor, adjacent structures and the treatment window.
Regarding the ex vivo mice treatments, we removed and embedded the tumors in a gel matrix made with 100ml of PBS water mixture and 1.5 gr of Agarose; then we proceeded to perform the treatment.

Results

The experiment confirmed our previous theoretical threshold power need for cavitation to occur in the target tumor. The cavitation was shown with the measurements and analysis of the oscilloscope recorded data and also in the histological analysis. Histologically there was a clear difference in the target areas treated by different powers in the same tumor and they were reproducible in the other mice as well.

Discussion

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Acknowledgement

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Topics: Pancreatic cancer

Abstract 53

Efficacy of Magnetic Resonance-guided Focused Ultrasound Surgery in the treatment of uterine adenomyosis

Yang Feng and Xiaoming Gong

Introduction

To evaluate the treatment efficacy of uterine adenomyosis using Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS)

Material and Methods

Sixteen symptomatic uterine adenomyosis patients were included in this study from January 2016 to May 2017. Uterine volume were measured before and 3 months after treatment using MRI images. Painful VAS score, amount of menstruation, hemoglobin were evaluated before and 3 months after treatment.

Results

All patients have dysmenorrhea. Nine of them have Menorrhagia. Before the MRgFUS treatment, Uterine volume was 378.20±155.17cm3before the treatment and and 300.40±133.36 cm3 after treatment, with a reduction rate of 20.0±17.3% (P>0.05). VAS scroe was 8.3±1.7 before the treatment and 5.5±3.8 after 3 months of the treatment (P<0.05) .7 of 9 patients with menorrhagia have reduction of menstruation, two patients remain menorrhagia . One patient did hysterectomy 3 months after treatment as sever pain persist. One patient got pregnancy one year after treatment with IVF and GnRH-a treatment.

Discussion and conclusion

MRgFUS is an e Effective treatment for adenomyosis in a short term follow-up. Long term follow-up is needed.

Acknowledgement

not yet

Topics: Fibroid panel

Abstract 54

Comparison of static and dynamic motion models for MRI guided focused ultrasound liver treatment

Joyce Joy, Andrew Dennison, Jan Strehlaw, Andreas Melzer

Author Keywords: Focused Ultrasound, Dynamic Motion, static, thermometry

Introduction
Focused ultrasound treatment has been approved by the FDA and CE marking for several indications, such as treatment of prostate cancer, bone metastases, and uterine myoma. To treat organs that move when patients breathe, current methods can only be applied with patients required to hold their breath or under anaesthesia so partial control of the patient's breathing is given. The TRANS-FUSIMO (Clinical Translation of Patient-Specific Planning and Conducting of FUS treatment in Moving Organs) EU project aims to use MRI guidance to refocus the therapeutic ultrasound beam target position to adapt for the movement of the liver, to reach the tumour site effectively while sparing the surrounding healthy tissue. The fundamental controlling technology needed for the method is being developed by the Fraunhofer Institute for Medical Image Computing, Bremen named as the Trans-FUSIMO treatment system (TTS). This work reports experiments conducted at Institute of Medical Science & Technology, Dundee, UK for testing the TTS for both static and dynamic motion models.

Materials and methods
A motion model with trackable channels was developed for testing. This contained a daily quality assurance (DQA) focused ultrasound phantom with a tracking ring collar placed around it. This 3D printed tracking ring collar was made using PLA (Poly lactic acid) and had 8mm tracking channels filled with degassed water embedded to approximate large liver vessel structures. Focused ultrasound was delivered using the Exablate 2100 MRgFUS system (Insightec, Israel). TTS controlled this MRgFUS system and an Echo Planar Imaging (EPI) MRI scan sequence (TR=142ms, TE=69.9ms, Slice thickness =5, flip angle = 40) was used for image guidance, tracking and thermal monitoring. FUS (Power: 75W, Duration: 30s) were applied and repeated 15 times under both the static and dynamic scenarios. A motion range similar to breathing motion (20mm) was produced by moving the DQA-collar assembly in a custom linear motion water tank filled with 15l of degassed water for FUS coupling with the Exablate transducer. Motion was actuated using an Innomotion MRI Robot (Innomedic, Germany) at a speed of 8 mm/s.

Results
Peak temperatures during sonications were recorded for all static and dynamic scenarios. The results indicated a mean peak temperature of 12.60 ± 1.07 deg.cel for static and 11.3 ± 0.8 deg. cel for dynamic experiments. The isotropy of the sonicated lesions was also measured as a metric to show system tracking performance as the ratio of the length of the lesion diameter on both x and y axes (y/x) produced in the TTS thermal mapping for MRI monitored coronal scans. For static FUS the isotropy was 0.94 ± 0.03 and for dynamic FUS, 1.32 ± 0.16.

Discussion and conclusion

Here we report preliminary results for the TTS software/hardware system under project development for static and dynamic MRgFUS preclinical validation scenarios. Test conditions and models were constructed to validate linear motion reproducibly to simulate a respiratory induced liver motion range on a FUS reusable tissue mimicking phantom target. Results show that combined monitoring, tracking and thermometry can be achieved using a single EPI MRI scan sequence with appropriate parameterisation. The temperature monitoring results of static vs. dynamic sonication fall within 1% deviation. The isotropy measurements indicated a slightly elongated lesion on the y axis for dynamic FUS compared to the static. This lesion elongation was marginal and within acceptable target values for preclinical testing. Future optimisation of the tracking component of TTS is expected to improve this further to satisfy pre-clinical trials. The expected impact of this method if fully successful would be to enable the possibility to use MRgFUS to treat moving abdominal organs under respiratory motion such as kidney, pancreas or even lungs.

Acknowledgement

MRI group IMSaT led by Prof. Andreas Melzer: Joyce Joy, Andrew Dennison, Lukasz Priba, Baljit Jagpal, Helen McLeod

Fraunhofer Institute for Medical Image Computing, Bremen led by Prof Tobias Preusser:
Jan Strehlow, Sabrina Hasse.

Topics: Other proposal

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