Current and Future Applications of

MR-guided Focused Ultrasound 2010

2nd International Symposium

Program & Abstract Book

October 17–20, 2010

Westfields Marriott
Near Dulles International Airport
Washington, D.C., USA

Sponsor Acknowledgements

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Welcome Messages

From the Honorary President

Dear Colleagues,

I welcome you to the 2nd International Symposium on MR-guided Focused Ultrasound. It is an honor to serve as President for this vitally important conference. Like the 1st International Symposium in 2008, this meeting promises to be a landmark event for scientists, clinicians and others involved in the research and development of patient treatments using one of today's most exciting medical innovations, MR-guided focused ultrasound.

A key aim of this year's symposium is to spotlight current and future applications of MR-guided focused ultrasound. Presentations and poster sessions will cover the latest and most significant translational and clinical research, including facet rhizotomy for back and neck pain, functional neurosurgical treatments for neuropathic pain and the emergence of MR-guided focused ultrasound as a platform for targeted drug delivery.

Another important symposium goal is to foster and expand the collaboration between clinicians and scientists, which is a vital aspect of moving a nascent technology like focused ultrasound from laboratory to patient bedside. As a participant, you will have ample opportunity to interact with colleagues from around the world, identify areas of common interest and plan shared pursuits.

By participating in this symposium, you are helping to accelerate the pace at which our field expands and evolves. The knowledge you gain and share and the conversations and collaborations you foster over the next several days will help pave the way for further progress.

Thank you for being part of this important and impactful event.

Sincerely,

Kullervo H. Hynynen, Ph.D.
Sunnybrook Research Institute
University of Toronto
Honorary President:
MR-guided Focused Ultrasound 2010—2nd International Symposium

From the Foundation Chairman

Dear Colleagues,

Welcome to the 2nd International Symposium on MR-guided Focused Ultrasound.

Approximately 130 oral and poster abstracts will be presented this year. Nearly a three-fold increase from the 1st International Symposium on MR-guided Focused Ultrasound in 2008, this volume of work clearly demonstrates the robust growth and increasingly diversified nature of the research and development underway worldwide.

While I am truly excited about the scientific presentations that form the core of this symposium, I realize that its vitality will depend on the interactions among participants. I encourage you to take advantage of every opportunity to communicate, establish and expand collaborations, share ideas and formulate new projects with other symposium attendees.

Thank you for joining us here in Washington, D.C. By participating in the scientific and interpersonal aspects of this symposium, you will help accelerate the development of new, life-saving treatments for millions of patients worldwide.

Sincerely,

Neal F. Kassell, M.D.
Chairman, Focused Ultrasound Surgery Foundation

Symposium Organizer

Focused Ultrasound Surgery Foundation

Today, researchers and manufacturers around the world are developing focused ultrasound therapies for many deadly and debilitating medical conditions. Since its founding in 2006, the Focused Ultrasound Surgery Foundation has been dedicated to accelerating the development and adoption of these new, noninvasive treatments so that they become a standard of care worldwide. Motivating the Foundation's work is the belief that every day without access to focused ultrasound treatments is a day of needless death, disability and suffering for countless patients.

Thanks to the support of philanthropic and corporate donors, the Foundation funds a variety of research and educational initiatives. We also promote collaboration, coordination and communication among researchers, clinicians and others who are pioneering this exciting and rapidly emerging area of medicine.

Our key initiatives include:

- Organizing, coordinating and funding research leading to new applications
- Establishing global collaboration between the research and development initiatives in academia and industry
- Funding training fellowships for clinicians and scientists
- Establishing new Centers of Excellence—luminary sites for research, training and patient care
- Supporting meetings, symposia and workshops
- Facilitating regulatory approval and third-party reimbursement
- Increasing awareness of what has been termed "medicine's best kept secret"

To learn more about focused ultrasound and the Focused Ultrasound Surgery Foundation, visit the Foundation's website: **www.fusfoundation.org**

Committee

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Co-Chairs

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Radiology and Imaging Sciences
National Institutes of Health, Bethesda

Matthew R. Dreher, Ph.D.
Radiology & Imaging Sciences
National Institutes of Health, Bethesda

Map

Main floor

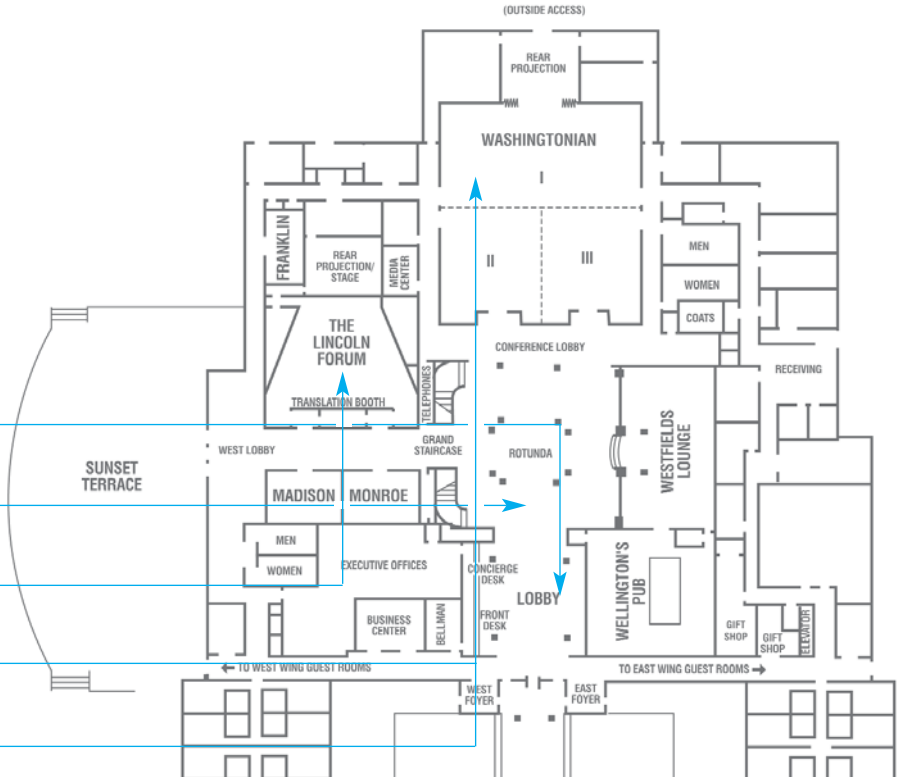
10/17 **Registration**
Lobby

10/17 **Welcome Reception**
Rotunda

10/18–19 **Lunchtime Discussion Groups**
Lincoln Forum

10/18–19 **Exhibits & Posters**
Washingtonian

10/19 **Poster Session & Reception**
Washingtonian



Second floor

10/18–20 **Registration**
Outside Grand Dominion

10/18–20 **Plenary Sessions**
Grand Dominion

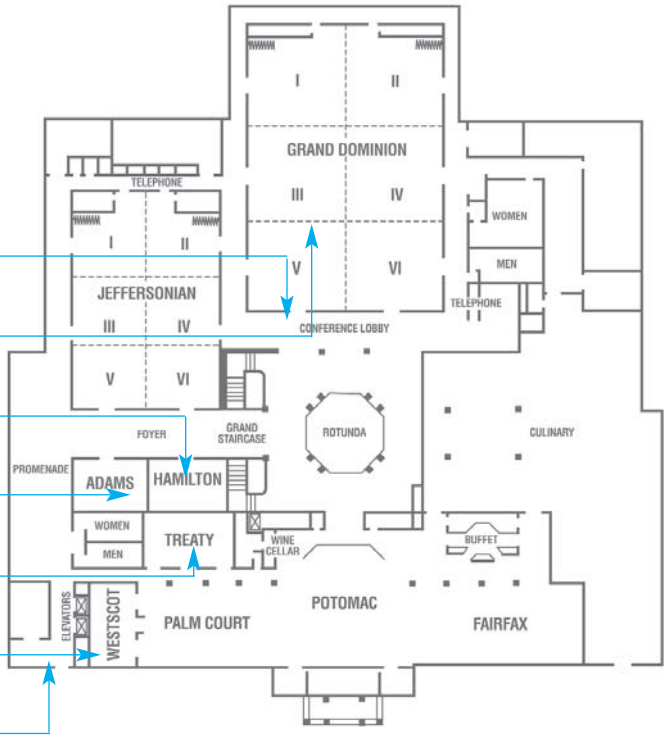
10/18–20 **InSightec Demonstration**
Hamilton

10/18–20 **Philips Demonstration**
Adams

10/18–19 **Lunchtime Discussion Groups**
Treaty

10/18–19 **Lunchtime Discussion Groups**
Westscot

10/20 **Exhibits**
Promenade



General Information

Registration & Information Hours

Sunday	16:00–20:00
Monday	7:00–18:00
Tuesday	7:00–18:30
Wednesday	7:00–13:30

Contact Number: +1 703-818-3603

Special Events

Sunday, October 17

Welcome Reception, Rotunda, 18:00–20:00
Includes drinks and hors d'oeuvres

Tuesday, October 19

Poster Session & Reception, Washingtonian Roomm 18:00 – 20:00
Includes drinks and hors d'oeuvres

Meals

Meals included in symposium registration:

For participants **lodging at the Marriott Westfields**

Monday: Full breakfast and lunch in Fairfax Dining Room, break refreshments
Tuesday: Full breakfast and lunch in Fairfax Dining Room, break refreshments
Wednesday: Full breakfast in Fairfax Dining Room, break refreshments

For participants **not lodging at the Marriott Westfields**

Monday: Light breakfast in Upper Rotunda, lunch in Fairfax Dining Room, break refreshments
Tuesday: Light breakfast in Upper Rotunda, lunch in Fairfax Dining Room, break refreshments
Wednesday: Light breakfast in Upper Rotunda, break refreshments

Dinner options

Symposium registration does not include dinner. Meeting participants are welcome to dine at the Marriott Westfields or at a location of their choosing. Information about nearby restaurants is available from the hotel's Concierge Desk, located in the lobby.

Local Transportation

Information about taxis and other local transportation options is available from the hotel's Concierge Desk, located in the lobby.

Internet Access

Free wireless/wifi internet service is available in hotel lobby only. (The hotel's network is " ibahn")

Guest room internet access is available for $12.95 + tax/day.

Texting

Throughout the symposium, attendees will be asked to silence their mobile phones, but leave them on.

During question and answer periods, symposium attendees will be able to submit their questions via text messages.

Text messages can be sent using a special four-digit number which will be announced during the symposium. Questions will appear on a large screen in the front of the meeting hall.

Attendees without texting capabilities will be able to ask their questions using microphones provided in the meeting hall.

Surveys

Symposium participants will have an opportunity to participate in the following surveys:

Mayo Clinic Uterine Fibroid Treatment Survey
The Center for Uterine Fibroids at the Mayo Clinic will be conducting a two-part, anonymous survey in conjunction with the symposium. Symposium attendees who treat uterine fibroids with MR-guided focused ultrasound will be asked to complete an online survey prior to the Wednesday, October 20 session on Uterine Fibroids and Fertility. Following that session, the same group will be given a hardcopy survey to complete. Esther Bouwsma, M.D., a research fellow at Mayo, says survey responses will increase understanding of factors that currently limit MR-guided focused ultrasound of leiomyomas. Results of a similar study conducted at the 2008 symposium were published in 2009 in Fertility and Sterility, the journal of the American Society for Reproductive Medicine.

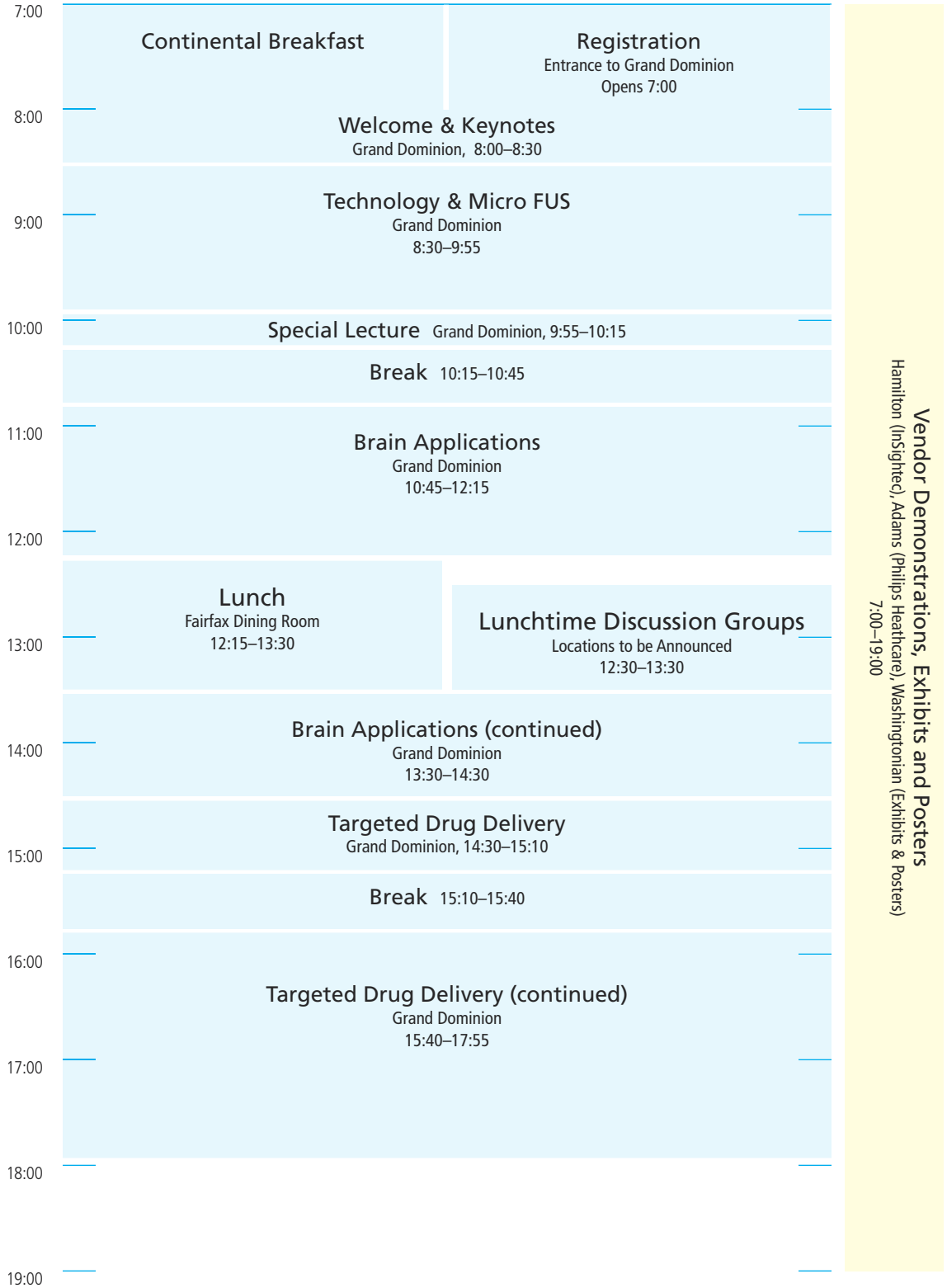
Symposium Feedback Survey
To assist the Focused Ultrasound Surgery Foundation in evaluating the success of the symposium, attendees will be asked to complete a brief, anonymous survey before final adjournment.

Notes

Section Index: Program

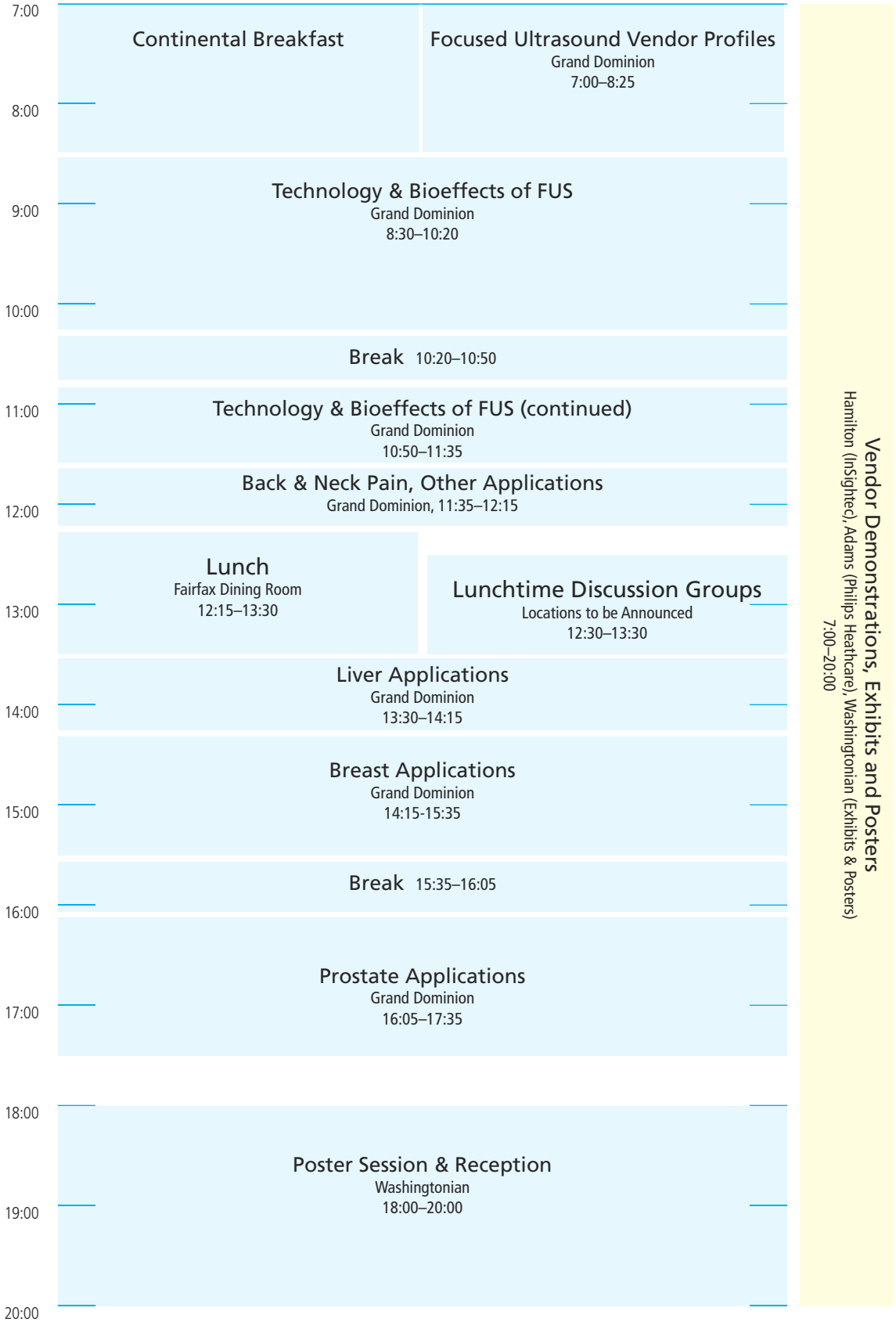
Program at a Glance

Monday, October 18



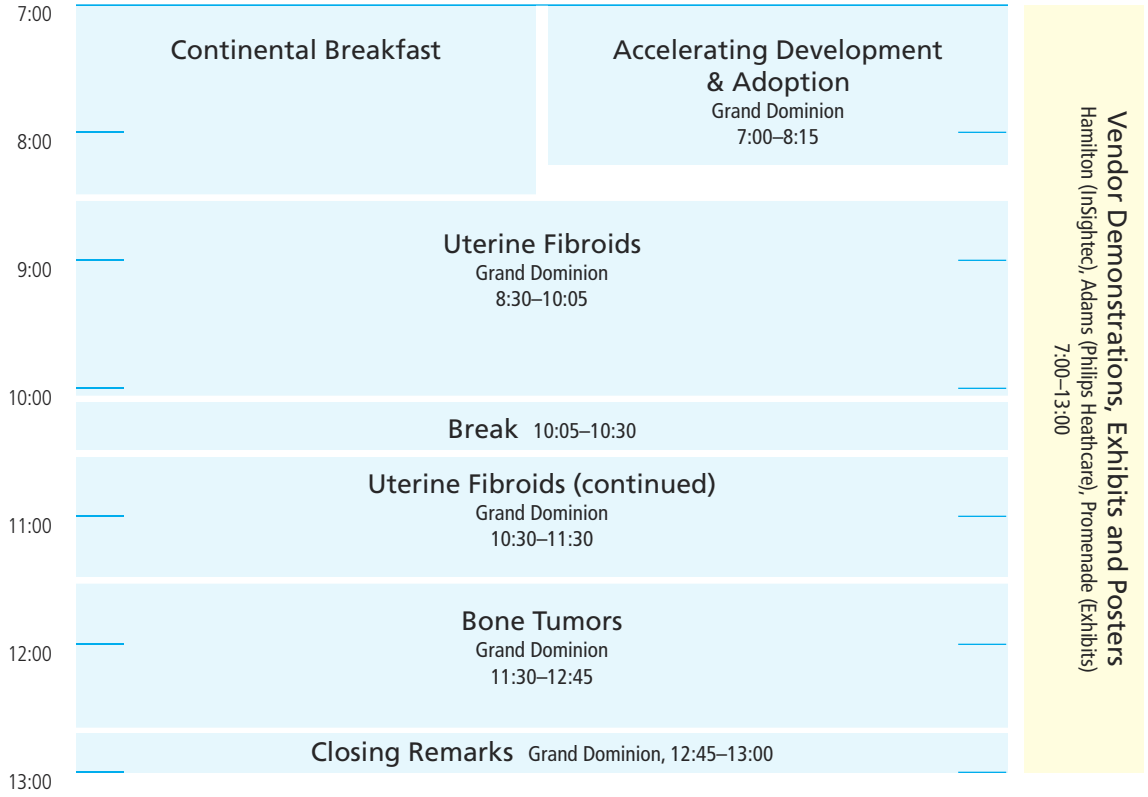
Program at a Glance

Tuesday, October 19



Program at a Glance

Wednesday, October 20



Detailed Program

Monday, October 18

Welcome & Keynotes | 8:00–8:30

Welcome & Opening Remarks…… *N. Kassell*

David & Diane Heller Lecture:
Focused Ultrasound from a Historical Perspective ..…… *K. Hynynen*

Technology & Micro FUS | 8:30–9:55

Moderators: W. Bradley, M. Tanter

IS-2 The Future of Focused Ultrasound Technology …… *M. Fink*

IS-3 The Future of MR Technology …… *E. McVeigh*

T&M-1 Tumor Hyperthermia and Ablation in Small Animals Using a Clinical MR-HIFU System…… *N.Hijnen*

T&M-2 A Small Animals Magnetic Resonance Guided Focused Ultrasound System …….. *E. Zadicario*

T&M-3 Development of an MRI-compatible Focused Ultrasound System for Preclinical Research…… *R. Chopra*

Special Lecture | 9:55–10:15

Brain Applications | 10:45–12:15; 13:30–14:30

Moderators: D. Enzmann, F. Jolesz

IS-4 Focused Ultrasound Surgery Foundation Brain Program Overview…… *N. Kassell*

B-1 Transcranial MR-guided Focused Ultrasound Surgery for Functional Brain Disorders: Neuropathic Pain …….. *E. Martin*

B-2 Transcranial MRI Guided Focused Ultrasound Surgery for Intracerebral Hemorrhage ……..…. *J. Snell*

B-3 Adaptive Focusing of Therapeutic Ultrasonic Beams using MR Acoustic Radiation Force Guidance Clinical Environment …… *M. Tanter*

B-4 Human Cadaver Model for Pre-clinical Evaluation of a 1MHz Ultrasonic Brain Therapy Device …. *J. F. Aubry*

B-5 Cavitation Detection During Blood Brain Barrier Disruption in Primates ……. *C. Arvanitis*

B-6 MR-ARFI Sequences for Focal Spot Localization ..…… *K. Butts Pauly*

B-7 Feasibility of ablating Brain Regions Adjacent to the Optic Nerve While Retaining Nerve Function with Focused Ultrasound Combined with an Ultrasound Contrast Agent ……..…….. *N. McDannold*

B-8 BBB Disruption in Nonhuman Primates Using a Clinical MRgFUS System: Preliminary Results ……*N. McDannold*

B-9 Transcranial Sonothrombolysis In Ischemic Stroke Using HIFU:Introduction of an *In Vivo* Efficacy and Safety Model—First Results …….. *T. Hoelscher*

Targeted Drug Delivery | 14:30–17:55

Moderators: K. Ferrara, K. Li

IS-5 Focused Ultrasound Mediated Targeted Drug Delivery …… *C. Moonen*

IS-6 FUS Mediated Targeted Drug Delivery: FUS Foundation Program Introduction & Overview .… *J. Polefrone*

TDD-1 Mechanisms of Ultrasound-enhanced Drug Delivery ……..…….. *K. Watson*

TDD-2 Temperature Sensitive Liposomes for Ultrasound-induced Drug Delivery Under MRI Guidance: In Vitro and *In Vivo* Results ……..…… *E. Heijman*

TDD-3 Composite Drug-Delivery Agents Comprised of 5FU-Bearing Controlled-Release Nanoparticles Bonded to Microbubbles Inhibit Glioma Growth Upon Activation with Ultrasound ……. *R. Price*

TDD-4 Thermally-mediated Localized Drug Release Using MRI-controlled Focused Ultrasound Hyperthermia ……..……. *R. Staruch*

TDD-5 Ultrasound-enhanced Drug Delivery During Epithelial-Mesenchymal Tumor Transition (EMT)... *K. Watson*

TDD-6 Synthesis and Characterization of MR Image-able Low Temperature Sensitive Liposomes for Use with Magnetic Resonance Guided High Intensity Focused Ultrasound ……..…. *P. Yarmolenko*

TDD-7 MR-guided High Intensity Focused Ultrasound Enhances Targeted Drug Delivery of Low Temperature Sensitive Liposomes in a Rabbit Vx2 Tumor Model ……..……..…… *A. Ranjan*

TDD-8 Improved Treatment in a Rat Breast Cancer Brain Metastases Model by Targeted Delivery of Herceptin Across the Blood-Brain Barrier with MRgFUS ……*E. Y. Park*

TDD-9 Application of Ultrasound to Sonosensitive Liposomal Doxorubicin for Treating Tumors: *In Vivo* Proof of Concept…….. *C. Lafon*

Tuesday, October 19

FUS Vendor Profiles | 7:00–8:25

Moderator: M. Buntaine

Profound Medical, Inc ..... *P. Chipperton*
FUS Instruments, Inc. ..... *R. Chopra*
Image Guided Therapy ..... *E. Dumont*
InSightec, Ltd ..... *K. Vortman*
Philips Healthcare ..... *F. Busse*
Supersonic Imagine..... *J. Souquet*

Technology & Bioeffects of FUS | 8:30–11:35

Moderators: L. Crum, D. Parker

IS-7 Comparison of MRI and Ultrasound Guidance for Focused Ultrasound..... *G. ter Haar*
T&B-1 Boiling and Cavitation During HIFU Exposures ..... *L. Crum*
T&B-2 Targeting Mesenchymal Stem Cells (MSCs) Using Focused Ultrasound Exposures ..... *A. Ziadloo*
T&B-3 Volumetric MRgHIFU Rapid Ablation under Automatic Temperature Control: Experimental Comparison of Different Sonication Patterns ..... *R. Salomir*
T&B-4 A Model of an Equivalent Focused Piston Source to Characterize Nonlinear Ultrasound Fields of 2D HIFU Arrays ..... *V. Khokhlova*
T&B-5 Non-invasive Determination of Patient-specific Tissue Acoustic Properties for MRgFUS ..... *U. Vyas*
T&B-6 High-intensity Focused Ultrasound Ablation Effect on Tumor Growth and the Migration of Endothelial Progenitor Cells ..... *J. Pagan*
T&B-7 Integration of MR Compatible Robotic Arm with MRgFUS ..... *A. Volovyk*
T&B-8 An Enhanced System for MRgFUS Treatment of Uterine Fibroids ..... *Y. Inbar*
T&B-9 Standards for Quality Assurance and Quality Management in Image Guided FUS ..... *D. Schlesinger*

Back & Neck Pain, Other Applications | 11:35–12:15

Moderators: W. Gedroyc, B. Wood

IS-8 Facet Rhizotomy ..... *W. Gedroyc*
O-1 Targeting the Swine Pancreas with MR Guided HIFU ..... *K. Dittmar*

Liver Applications | 13:30–14:15

Moderators: W. Gedroyc, G. ter Haar

IS-9 MR Guided Focused Ultrasound of the Liver ..... *W. Gedroyc*
L-1 Usefulness of 3D Imaging of US, CT and MRI for the Planning and Monitoring of Hepatocellular Carcinoma Treatment Using FUS ..... *H. Fukuda*
L-2 Focused Ultrasound of the Liver During Free Breathing ..... *K. Butts Pauly*
L-13 High-Intensity Focused Ultrasound (HIFU)-Assisted Hepatic Resection in an Animal Model .... *A. Gandini*

Breast Applications | 14:15–15:35

Moderators: D. Brenin, H. Furusawa

IS-10 Breast Cancer—ACRIN Study ..... *M. Schmall*
IS-11 Treatment of Breast Cancer ..... *H. Furusawa*
BC-1 High Resolution and Large Volume Coverage MR Temperature Measurements in Breast..... *N. Todd*
BC-2 Induction of an Immune Response to Breast Cancer with Magnetic Resonance-guided Focused Ultrasound Tumor Ablation in a Mouse Model ..... *P. Eby*
BC-3 Design and Initial Evaluation of a Breast-specific MRgFUS Treatment System..... *A. Payne*

Prostate Applications | 16:05–17:35

Moderators: R. Chopra, C. Tempany

IS-12 MR guided Transurethral Ultrasound Thermal Ablation for Localized Prostate Cancer ..... *L. Klotz*
PC-1 Ablation of Benign static Hyperplasia (BPH) using a Multisectored Transurethral Ultrasound Applicator ..... *G. Sommer*
PC-2 MR Guided Pulsed High Intensity Focused Ultrasound Enhancement of Docetaxel Combined with Radiotherapy for Prostate Cancer Treatment ..... *L. Chen*
PC-3 Initial Experience with MRgFUS for Localized Low-Risk Prostate Cancer in Singapore ..... *C. Cheng*
PC-4 Focal Magnetic Resonance guided Focused Ultrasound Treatment of Low Risk Prostate Cancer ... *S. Kanaev*
PC-5 Full Prostate Gland Coagulation During MRI-guided Transurethral Ultrasound Therapy:Results in Gel Phantoms ..... *W.A. N'Djin*

Wednesday, October 20

Accelerating Development and Adoption | 7:00–8:15

Moderators: Z. Binney, M. Garabrant

Current and Future Landscape for Adoption ..... *Z. Binney, M. Garabrant*

Achieving Regulatory Approval for MR-guided Focused Ultrasound Indications..... *D. Schultz*

Achieving Reimbursement for Image Guided Acoustic Surgery—USA ..... *R. Emerick*

Achieving Reimbursement for MR-guided Focused Ultrasound Indications—International ..... *L. Sweeney*

Collaborative Research Network ..... *H. Huff Simonin*

Uterine Fibroids | 8:30–11:30

Moderators: L. Bradley, H. Brown

IS-13 Fibroid Therapy: What's In Your Tool Box? Hopefully More Than Only Hammers ..... *L. Bradley*

IS-14 MR-guided Focused Ultrasound Surgery of Uterine Fibroids: Into the Mainstream—From Clinical Success to Daily Routine ..... *M. Matzko*

IS-15 Patient Selection for MRgFUS in the Treatment of Uterine Fbroids ..... *S. LeBlang*

UF-1 MRgFUS Treatment for Uterine Myomas: Safety, Effectiveness and Pathogenesis ..... *G. Zelenin*

UF-2 Dynamic Contrast-enhanced Magnetic Resonance Imaging Predicts Immediate Therapeutic Response of MR-guided High-intensity Focused Ultrasound ..... *Y. Kim*

UF-3 Clinical Predictors of Magnetic Resonance-guided Focused Ultrasound Surgery ..... *E. Bouwsma*

UF-4 Analyzing Screen Failures Prior to MRgFUS for Uterine Fibroids: Do African American (AA) Women Have Different Characteristics? ..... *R. Machtinger*

UF-5 Novel Technique for Targeted Vessel Ablation DuringMagnetic Resonance Imaging-guided High Intensity Focused Ultrasound Treatment of Uterine Fibroids ..... *M. Voogt*

UF-6 Magnetic Resonance-guided Focused Ultrasound Treatment of Uterine Fibroids in Patients with Abdominal Scars, Using an Energy-Blocking Scar Patch ..... *S. W. Yoon*

UF-7 Treatment of Adenomyosis by Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS): A One-year Prospective Follow-up Study ..... *J. Rabinovici*

Bone Tumors | 11:30–12:45

Moderators: M. Hurwitz, R. Pfeffer

IS-16 MRgFUS for Treatment of Bone Metastases: Progress and Promise..... *M. Hurwitz*

BT-1 Palliation of Painful Bone Metastases Using High Intensity Focused Ultrasound Therapy with Magnetic Resonance Guidance: Cumulative Sheba Medical Center ..... *R. Pfeffer*

BT-2 Pain Palliation of Bone Metastasis Pain Using High Intensity Focused Ultrasound Therapy with Magnetic Resonance Guidance: Logistical Issues..... *R. Pfeffer*

BT-3 Pain Palliation of Bone Metastasis: Initial Clinical Experience Using High Intensity Focused Ultrasound Therapy with 3T Magnetic Resonance Imaging Guidance ..... *A. Napoli*

BT-4 Overview of Palliative MRgFUS Treatment of Painful Bone Metastases in Spain .... *E. Gomez-Gonzalez*

Closing Remarks | 12:45–13:00

Closing Remarks ..... *N. Kassell*

Poster Session Overview

Brain Applications

Targeted Drug Delivery

Technology & Bioeffects of FUS

Back & Neck Pain, Other Applications

Prostate Applications

Uterine Fibroids

Bone Applications

Young Investigator Awardees Poster Presentations

Invited Speakers & Moderators

Zachary Binney
The Advisory Board Company
Washington, D.C.

Linda Bradley, M.D.
Department of Obstetrics and Gynecology
Cleveland Clinic, Cleveland

William Bradley, M.D., Ph.D.
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University of California, San Diego

David R. Brenin, M.D.
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Haywood Brown, M.D.
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Duke University Medical Center, Durham

Marc R. Buntaine, M.B.A
Still River Systems, Littleton

Falko Busse, Ph.D.
Philips Healthcare, Vantaa

Paul Chipperton, M.B.A.
Profound Medical Inc., Toronto

Rajiv Chopra, Ph.D.
Imaging Research
Sunnybrook Health Sciences Centre, Toronto

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University of Washington, Seattle

Erik Dumont, Ph.D.
Image Guided Therapy, Pessac

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Sunnybrook Health Sciences Centre, Toronto

Suzanne D. LeBlang, M.D.
University MRI, Boca Raton

King C. Li, M.D., M.B.A.
The Methodist Hospital Research Institute
Houston

Matthias Matzko, M.D.
Amper Kliniken AG, Dachau

Elliot R. McVeigh, Ph.D.
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Johns Hopkins University School of Medicine
Baltimore

Chrit Moonen, Ph.D.
Imagerie Moléculaire et Fonctionnelle:
de la Physiologie à la Thérapie
University Victor Segalen, Bordeaux

Dennis L. Parker, Ph.D.
Utah Center for Advanced Imaging Research
Departments of Bioengineering & Radiology
University of Utah, Salt Lake City

Raphael Pfeffer, M.D.
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Chaim Sheba Medical Center, Tel Hashomer

Joy Polefrone, Ph.D.
Focused Ultrasound Surgery Foundation
Charlottesville

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University of Pennsylvania, Philadelphia

Daniel G. Schultz, M.D.
Greenleaf Health LLC, Washington, D.C.

Jacques Souquet, Ph.D.
Supersonic Imagine, Aix-en-Provence

Laurel Sweeney
Office of Medical and Health Affairs
Philips Healthcare, Andover

Mickaël Tanter, Ph.D.
Institut Langevin
Ecole Supérieure de Physique et Chimie
Industrielles, Paris

Clare Tempany, M.D.
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Brigham & Women's Hospital, Boston

Gail ter Haar, Ph.D.
Joint Department of Physics
Institute of Cancer Research:
Royal Marsden Hospital, Sutton

Kobi Vortman, Ph.D.
InSightec, Tirat Carmel

Bradford Wood, M.D.
Center for Interventional Oncology
National Institutes of Health, Bethesda

Notes

Section Index: Abstracts

Diane & David Heller Lecture
IS-1

Focused Ultrasound from a Historical Perspective

Kullervo Hynynen
Sunnybrook Research Institute, Toronto, ON, Canada

Session Topic: Technology & Micro FUS
Presentation Type: Oral
IS-2

The Future of Focused Ultrasound Technology

Mathias Fink
Insitut Langevin, ESPCI, Paris, France

Focusing ultrasonic waves through complex biological tissues is of main importance for ultrasonic-based therapy. We will describe the various techniques available today to get optimal focusing through complex organs. Various techniques proposed both to focus pulsed or sinusoidal waves will be described and compared. They go from phase conjugation to time-reversal approaches. The way to target the tissues that have to be destructed will be emphasized and a discussion on the future of focused ultrasound technology will be conducted.

Session Topic: Technology & Micro FUS
Presentation Type: Oral
IS-3

Future of MR Technology

Elliot McVeigh

Johns Hopkins University School of Medicine, Biomedical Engineering, Baltimore, MD, USA

Session Topic: Technology & Micro FUS
Presentation Type: Oral
T&M-1

Tumor Hyperthermia and Ablation in Small Animals Using a Clinical MR-HIFU System

Nicole Hijnen[1], Edwin Heijman[2], Max Kohler[3], Mika Ylihautala[3], Holger Grüll[1,2]

[1]Eindhoven University of Technology, Biomedical Engineering, Eindhoven, Netherlands,
[2]Philips Research, Bio-molecular Engineering, Eindhoven, Netherlands, [3]Philips Healthcare, Vantaa, Finland

Background/Introduction: Treatment of malignant tumors by either hyperthermia-induced drug delivery or thermal ablation requires complete coverage and precise control of the treatment area and thermal dose. The latter can be achieved by volumetric ultrasonic heating together with MR-based temperature mapping. The clinical translation of these techniques requires thorough preclinical testing in large cohorts. Mice and rat studies are preferred over larger animals as a larger variety of tumor models are available with the additional benefit that therapeutic outcome can be evaluated in combination with standard small animal imaging techniques. Our work aims to develop temperature induced drug delivery and ablation protocols in rats and to subsequently evaluate treatment using (nuclear) imaging methods. Here, we present controlled hyperthermia and thermal ablation of malignant tumors in rats using a clinical MR-HIFU system and a first treatment evaluation using MRI and histology.

Methods: Hyperthermia was performed for 15 min using binary temperature control on lateral gastrocnemius muscle (n=5; 6 W acoustic power) and on subcutaneous inoculated tumors on the hind limb of rats (9L rat glioma; n=5; 8 W acoustic power). For thermal ablation, tumors were partly heated to T = 338 K (n=5, 30 W acoustic power). All animals were positioned in a dedicated small animal 4-channel volume coil that was mounted on the table top of a Philips Sonalleve 3T MR-HIFU system (fig 1). The target area (5.2 x 5.2 x 13 mm^3) was volumetrically heated with continuous wave ultrasound (1.44 MHz). An acoustic absorber prevented whole-body heating. Temperature changes were monitored using proton resonance frequency shift thermometry (FFE-EPI; TR/TE: 52/20 ms; FOV: 250x250 mm^2; matrix: 176x169; slices: 3; slice thickness: 4 mm; NSA: 2; acquisition time: 5.0 s). The treatment effect was monitored with T_2-weighted imaging and dynamic contrast enhanced (DCE-) MRI using Gd-DTPA. From the change in uptake kinetics, the volume of viable tumor tissue was calculated. Excised muscle and tumors were evaluated in histology.

Results & Conclusions: The target temperatures were readily achieved in hyperthermia and ablation treatments while changes in body temperature remained less than 1 K (fig 2). For hyperthermia treatments, no tissue damage was visible by inspection or on MR images. Analysis of the Gd-DTPA uptake kinetics post-ablation indicated an affected area of 550±108 mm^3 (Δ tissue volume with $k_{trans} \geq 0.02$ mL/min). NADH-diaphorase staining showed a sharp demarcation between viable and non-viable cells (fig 3). These results demonstrate that thermal treatment in small animals can be performed on a clinical MR-HIFU system. Future work will be devoted to establish a set of nuclear imaging biomarkers that can be used to evaluate and monitor thermal therapies. The use of a clinical system allows a rapid translation of these protocols into the clinic.

Acknowledgements (Funding): This research was supported by the Center for Translational Molecular Medicine (VOLTA).

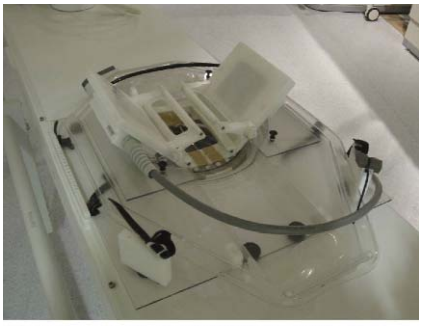

Figure 1. Dedicated small animal HIFU coil.

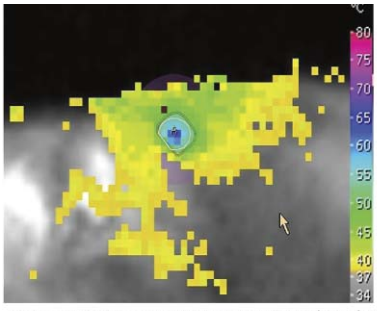

Figure 2. MR temperature mapping. The white contour indicates the 240 EM thermal dose zone, the orange contour the 30 EM zone.

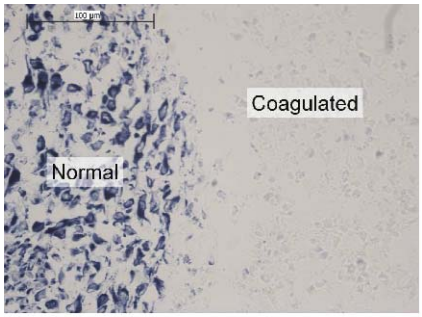

Figure 3. NADH-diaphorase stained tumor tissue post ablation (blue: viable cells, colorless: death cells).

Session Topic: Technology & Micro FUS
Presentation Type: Oral
T&M-2

A Small Animals Magnetic Resonance Guided Focused Ultrasound System

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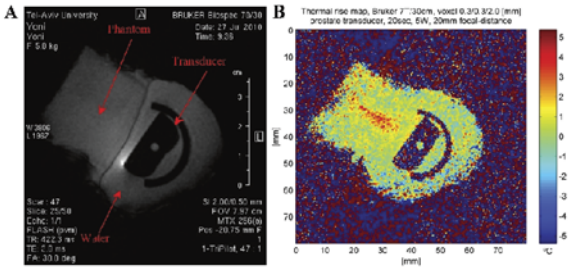
Background/Introduction: Research and clinical applications of magnetic resonance guided focused ultrasound (MRgFUS) are constantly growing where the MRI takes a significant role of imaging the effects induced by FUS. The MRI imaging spatial resolution and gradients capabilities are important in many of FUS experiments, especially in small animals *in vivo* experiments as targeted drug delivery and ultrasound neural stimulation. Here, we report on a high resolution MRgFUS system that integrates Bruker 7T MRI and Insightec planar ultrasound phased array.

Methods: Images were acquired on a 7T Bruker BioSpec 70/30 scanner equipped with 72mm inner diameter volume-coil and BGU20 gradients. Insightec planar phased array FUS transducer, wrapped by a water balloon, was placed inside the MRI bore (Figure 1A) and transmitted acoustic energy (acoustic power of 5W) to a focal distance of 20mm into a tissue mimicking phantom. The phased array FUS transducer is built out of 987 elements with an area of $1mm^2$, arranged over 25x40mm aperture, transmitting ultrasound at central frequency of 2.3MHz. The thermal rise map (Figure 1B) was calculated using the linear dependency of proton resonance frequency (PRF) and temperature, $\Delta T=\Delta\varphi/(C\cdot\gamma\cdot B_0\cdot TE)$, where C=-0.009 is the constant of proportionality, γ is the proton gyromagnetic ratio, B_0 is the magnetic field strength, TE is the echo time and $\Delta\varphi$ is the phase difference between MR phase images measured before and during the heating (TR/TE=422/6ms, FOV=8x8cm, thickness=2mm, in-plane resolution of 0.3x0.3mm).

Results & Conclusions: Bruker 7T MRI and Insightec focused ultrasound systems were successfully integrated. The ultrasound and MRI systems didn't interfere with each other and MR-thermometry was measured during the transmission of ultrasound energy. The combination of high-resolution MRI system and advanced FUS phased array improves the MRgFUS research systems capabilities especially by increasing imaging spatial resolution.



Session Topic: Technology & Micro FUS
Presentation Type: Oral
T&M-3

Development of a MRI-compatible Focused Ultrasound System for Preclinical Research

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Background/Introduction: The development of novel MRI-guided focused ultrasound applications in medicine requires extensive preclinical testing in small animals such as rats and mice due to the widespread use of these species as models of disease. Current clinical FUS systems are not well suited for performing experiments in these small animal models. The goal of this presentation is to describe a commercial research FUS platform based on technology developed at Sunnybrook Health Sciences Centre over the past decade.

Methods: An MRI-compatible, computer-controlled focused ultrasound system comprised of a spherically-focused ultrasound transducer mechanically-scanned over three dimensions has been built and tested. The entire system is non-magnetic and can be operated within a clinical MR imager, or CT scanner. The components of the system are the transducer, 3-axis positioning system, RF electronics (function generator, amplifier, power meter), and computer with custom-written control software.

Results & Conclusions: The range of motion of the system is 10 x 10 x 10 cm with a spatial precision of 0.3 mm. A variety of sonication patterns are possible including single point, multi-point, and scanned exposures. The system has been tested and functions on MR scanners from all major vendors, at both 1.5 and 3 T. In addition, the entire system is portable and can be transported between the laboratory and MRI for in-bore and benchtop experiments. This turnkey research platform is intended to lower the technology barrier that exists for groups to engage in MRI-guided focused ultrasound research.

Session Topic: Technology & Micro FUS
Presentation Type: Poster
P-1

Small Animal Adaptor Setup and Protocols for Magnetic Resonance-guided Focused Ultrasound

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Background/Introduction: Current clinical Magnetic Resonance-guided Focused Ultrasound (MRgFUS) systems are designed solely for human therapies. However, in order to expand the current indications of MRgFUS, it is essential to be able to perform small animal studies. As a result, the positioning, imaging and therapy protocols for small animal studies require substantial modifications. The purpose of this study was to analyze and optimize the technical aspects and setup with a small animal adaptor on a clinical MRgFUS system (Sonalleve 3.0T, Philips Healthcare). Specific protocols as well as techniques for positioning and anesthesia were developed to improve image quality and achieve better treatment outcomes.

Methods: An animal positioning system with an integrated 4-channel small animal MRI coil (Philips Medical Systems, Helsinki, Finland) was designed for rodents. This system was used on the MRgFUS system to hold, image and treat female transgenic tumor bearing mice (inoculated with 10^6 HER-2/neu expressing mammary carcinoma cells subcutaneously in the mammary fat pad). Tumors were allowed to grow to a volume of 1 cc prior to treatment. Degassed water and a gel-pad were used to acoustically couple the animal with the ultrasound transducer. Precise placement of the animal was achieved by using a sliding tray. The animal was positioned on the tray, which was subsequently advanced into the coil. A water circulation system embedded in the positioning system was used to control the animal's body temperature. Animals were anesthetized with 1.5% isoflurane in oxygen (1 liter/min). Imaging was performed using a 3T MR scanner (Achieva 3T, Philips Healthcare) with the small animal coil. Mice were treated by targeting sonications (1.2 MHz, 20W acoustical power, 20s), and the treatment cell size was 2 mm in diameter and 5mm in axial length. Temperature elevations during sonications were monitored using a 2D fast field echo pulse sequence (Coronal image for 1 stack and 15 slices, TE 20 ms, TR 40 ms, temporal repetition time 40 ms) and the proton resonance frequency shift (PRFS) method.

Results & Conclusions: Targeting of the treatment area in implanted tumors in mice model was precise, with 3.2 mm mean offset value of targeted and treated area, resulting in successful ablation of the targeted region of the tumor. As a result, a part of the target tumor was successfully treated in all eight mice. After anesthetization, positioning and treatment, all of the mice survived for subsequent monitoring. This clinical MR-HIFU system combined with a small animal adaptor provides a platform to perform *in vivo* pre-clinical studies of rodents. Small animal setups on clinical system will facilitate translation of new techniques and applications of MRgFUS therapy to humans.

Acknowledgements (Funding): This project is supported by funding from the Focused Ultrasound Surgery Foundation, the Fred Hutchinson Cancer Research Center and equipment and technical support from Philips Medical Systems.

Session Topic: Brain Applications
Presentation Type: Oral
IS-4

Focused Ultrasound Surgery Foundation Brain Program Overview

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Brain disorders represent a highly crucial treatment area for MR-guided FUS. Key reasons are: 1) these conditions are the most devastating and debilitating ailments afflicting humanity and are increasing in prevalence; 2) clinically, the brain is the most difficult organ to treat safely and effectively, and success of MR guided FUS in this segment will be viewed as proof of its ability to treat other organs; 3) from a societal perspective, the brain is a high-profile topic—there is widespread fascination with its workings and fear of its disorders. Successful, new treatments of brain disorders are likely to attract public interest and increase investment in other MR-guided FUS applications.

The Foundation formally organized the Brain Program after receiving a $1 million anonymous donation which enabled the recruitment of two Ph.D. biomedical engineers to work full-time on this initiative.

A robust infrastructure has been established including:

- Brain Advisory Committee
- Data Safety Monitoring Board
- Clinical Trial Steering Committees
- Core Imaging Laboratory
- Core Neuropathology Laboratory
- Research Working Groups for Intracerebral Hemorrhage, Ischemic Stroke, and Neuromodulation

Funding is available on a contract basis for Foundation initiated technical, preclinical and clinical projects.

Session Topic: Brain Applications
Presentation Type: Oral
B-1

Transcranial MR-guided Focused Ultrasound Surgery for Functional Brain Disorders: Neuropathic Pain

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Background/Introduction: Transcranial MR-guided Focused Ultrasound Surgery (TcMRgFUS) implies a novel, non-invasive treatment strategy for a variety of brain diseases. Targets deep inside the brain can be ablated non-invasively with high precision. The aim of this study is to obtain preliminary data on safety, precision, reproducibility and efficacy of tcMRgHIFU interventions in the human brain.

Methods: To date, twelve patients with chronic neuropathic pain were treated after obtaining informed consent. The study was approved by SwissMedic and Ethics Committee. The stereotactic target, i.e. the thalamic central lateral nucleus (CL), is identified using a multiarchitectonic atlas (1). The interventions are carried out on a prototype HIFU system (ExAblate 4000, InSightec) operating at 650kHz with a1024 elements phased array transducer, integrated into a 3T MR-system. Assessment of ablation dynamics, treatment results and patient outcome are done by MRI, MR-thermometry, stereotactic lesion reconstruction, quantitative EEG and clinical/neurological patient follow-up.

Results & Conclusions: Precisely located thermal ablations of 4 to 10mm in diameter were produced according to the treatment plan in unilateral or bilateral CL, in 12 patients. Peak temperatures of 53 to 64°C under continuous visual MR guidance and MR thermometry were achieved. The resulting lesions are clearly visible on follow-up MR imaging. The calculated temperature maps demonstrate precise targeting. In one patient, a hemorrhagic lesion of a few mm^3 next to the target caused a contralateral dysmetria, which subtotally resolved over a three-month period. A comprehensive safety analysis led to changes in the treatment protocol and modifications of the device. Being not limited by trajectory restrictions, individual treatment planning could fully exploit the ability of tcMRgHIFU to shape lesion patterns according to local target anatomy. In addition, data of three months and one year follow-up will be presented in which long-term efficacy and safety has been evaluated. Our preliminary findings demonstrate that tcMRgHIFU can be used successfully for precise, non-invasive functional neurosurgery in the human brain (2).

Acknowledgements (Funding): Acknowledgement: We gratefully thank the Swiss National Research Foundation, The National Center of Competence in Research Co-Me, the University of Zurich, the University Children's Hospital Zurich, Switzerland, the Focused Ultrasound Surgery Foundation, Charlottesville, USA, and InSightec LTD, Carmel-Tirat, Israel, for their support.

Session Topic: Brain Applications
Presentation Type: Oral
B-2

Transcranial MRI Guided Focused Ultrasound Surgery for Intracerebral Hemorrhage

Stephen Monteith[1], Sagi Harnof[2], Max Wintermark[1], Neal Kassell[1,4], John Snell[4], Matthew Eames[4], Eyal Zadicario[3], Jessica Foley[3], Jason Sheehan[1]

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[4]Focused Ultrasound Surgery Foundation, Charlottesville, VA, USA

Background/Introduction: Intracerebral hemorrhage (ICH) is a major cause of death and disability throughout the world. For patients with a large hemorrhage, the clot may be surgically removed from the brain in order to improve survival. Current surgical techniques are complicated by their highly invasive nature and the associated significant disability caused in the process of clot removal. To date, minimally invasive clot-removal techniques have had limited success in addition to raising safety concerns. Preliminary data have shown promise for the feasibility of transcranial MRI guided sonothrombolysis to liquefy the clotted blood in ICH, thereby facilitating minimally invasive evacuation with a small drainage tube.

Methods: Using an in vitro phantom model, our group has demonstrated the feasibility of trans-cranial MRI guided sonothrombolysis. In this model, 40mL of human blood from a healthy volunteer was injected immediately into a latex balloon. After incubation at 37 degrees for between 3 and 24 hours, the clots were weighed and imaged with MRI (T1, T2 and T2*) to confirm adequate clot formation and to allow for clot retraction. Clots were then sonicated using the ExAblate 4000 (InSightec) with both single and multiple sonications under MRI guidance. Clots were extracted at various stages of sonication and correlation between post-sonication MRI images and solid/liquid clot weights and gross appearance were recorded. Using an in-vivo model of ICH in swine, transcranial sonothrombolysis has been performed. Using a well-defined swine model of ICH from the University of Cincinnati (Drs Wagner and Zuccarello), 3-4mL of autologous arterial blood was infused into the frontal region of the pig. MRI was used to confirm the clot. The ICH was then sonicated through the skull of the pig and MRI was utilized to determine treatment effect. Following sonothrombolysis, the liquid clot was aspirated under MRI guidance and the volume of aspirated liquid clot was recorded.

Results & Conclusions: In vitro results with and without interposition of a human calvarium are presented. With optimum parameters, between 55 and 100% of formed solid clot was routinely liquefied both without, and through a human calvarium with CT correction. In the In-vivo model, final post sonication MRI images demonstrated the evacuation of the majority of clot. Histological examination did not reveal additional damage to the surrounding brain as a result of sonication compared to brains with an ICH placement only. Following adequate sonothrombolysis, it is possible to effectively evacuate an ICH in an *in vivo* model. Design modifications to the experimental setup in order to optimize the process of sonothrombolysis are presented.

Acknowledgements (Funding): American Association of Neurological Surgeons (AANS), Neurosurgery Research and Education Foundation (NREF), Focused Ultrasound Surgery Foundation.

Session Topic: Brain Applications
Presentation Type: Oral
B-3

Adaptive Focusing of Therapeutic Ultrasonic Beams Using MR Acoustic Radiation Force Guidance in a Clinical Environment

Laurent Marsac[1,2], Benoit Larrat[1], Mathieu Pernot[1], Benjamin Robert[2], Mathias Fink[1], Jean-François Aubry[1], Mickael Tanter[1]

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[2]Supersonic Imagine, Aix-en-Provence, France

Background/Introduction: In order to focus ultrasound beams through aberrating layers such as fat or bones, adaptive focusing techniques have been proposed to improve the focusing, mostly based on the backscattered echoes. We recently proposed an energy-based technique requiring the sole knowledge of the acoustic intensity at the desired focus. Here, Magnetic Resonance-Acoustic Radiation Force Imaging (MR-ARFI) is used to map the displacement induced by the radiation force of a focused ultrasound beam. As the maximum displacement is obtained with the best corrected beam, such a measurement can lead to aberration correction. Proof of concept experiments were previously shown at 7T using a 64-elements linear phased array operating at 6MHz. Optimal refocusing was then obtained through numerical and physical aberrating layers. This work is extended here in a clinical Philips 1.5T Achieva scanner. The HIFU beam is generated using a 512 elements US phased array (SuperSonic Imagine, France) dedicated to transcranial human experiments and operating at 1MHz.

Methods: Experiments are conducted in phantom gels and *ex vivo* brain tissues through numerical phase aberrators and human *ex vivo* skulls aberrators. A motion-sensitized spin echo sequence (TE=50ms/TR=550ms, spatial resolution is 1.3x1.3x3mm3) is implemented to measure displacements induced by the acoustic radiation force of transmitted beams.

Results & Conclusions: MR-ARFI allowed mapping the distribution of the radiation force at the focus of the array. After the recording of the MR phase signals for different US emissions, the proposed adaptive focusing technique was able to recover the spatial distribution of the phase aberrations. For a random phase aberrator with a maximum 2*pi phase amplitude (one period), the error on the recovered aberration was 0.025 rad. Total acquisition time for 256 ultrasonic emission channels was 2 hours. Those first results in clinical MR at 1.5T show that adaptive focusing of a human transcranial brain HIFU system can be achieved within reasonable time under MR guidance for aberrator layers as strong as human skull. Ongoing work is aiming at accelerating the acquisition in order to reach acceptable durations for *in vivo* protocols.

Acknowledgements (Funding): This work was partly funded by the French National Research Agency (ANR TECSAN).

Session Topic: Brain Applications
Presentation Type: Oral
B-4

Human Cadaver Model for Pre-clinical Evaluation of a 1MHz Ultrasonic Brain Therapy Device

Laurent Marsac[1,2], Dorian Chauvet[3], Benjamin Robert[2], Mathieu Pernot[1], Anne-Laure Boch[3], Najat Salameh[4], Line Souris[4], Luc Darrasse[4], Mathias Fink[1], Jean-Francois Aubry[1], Mickael Tanter[1]

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Background/Introduction: Ultrasonic treatment of the brain has long been hampered by the defocusing effect of the skull. Thanks to adaptive focusing, it was shown in the late nineties that non-invasive transcranial targeting is feasible on desiccated human skulls. The precision of a 1MHz prototype was tested here on fresh human cadaver's heads. The aims of these preliminary experiments were first to validate the feasibility of extracting fresh human heads, and then to perform transcranial adaptive focusing at targeted locations in a clinical environment. The last goal of the present study was to evaluate the precision of a treatment using non-invasive time-reversal focusing based on CT scans of the heads.

Methods: Eight cadavers (full consent donors, all over 70 years old) were carefully decapitated 24 to 72 hours after death. To prevent from an intracranial penetration of air bubbles, the carotid arteries, the internal jugular veins and the cervical dural sac were ligatured during the procedure. A CT scan of the head was performed and used as input in a 3D finite difference time domain simulations in order to compute the propagation of the wave field through the skulls. This step was performed thanks to a simulation-based time-reversal aberration correction. Sonications were performed with an MR-compatible high- power prototype made of 512 transducers, each able to deliver acoustic power up to 20W/cm2 and installed in a 1.5T Philips Achieva scanner. The whole stereotactic procedure is performed with a Leksell frame. Temperature elevations were measured with proton resonance frequency shift MR sequences.

Results & Conclusions: The location of the maximum temperature elevation was found at the targeted location within the MR imaging voxel precision (<1.5mm), corresponding to the full width at half maximum of the therapeutic beam. For 1200W acoustic power during 10 seconds, temperature elevations of 6°C to 10°C were obtained in the brain depending on the specimen. A large discrepancy in the skull bone structure of the specimens was observed, with calcifications leading to a local doubling of the skull thickness in three out of the eight specimens. Nevertheless, this study validated the potential clinical use of this MR-guided brain therapy device operating at 1MHz. Such a system will be particularly suited for targeting brain metastases and the treatment of neurological diseases such as essential tremors.

Acknowledgements (Funding): This work was supported by the French national agency for research (ANR TUCCIRM).

Session Topic: Brain Applications
Presentation Type: Oral
B-5

Cavitation Detection During Blood Brain Barrier Disruption in Primates

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Background/Introduction: Localized and noninvasive transient disruption of the blood brain barrier (BBB) using focused ultrasound after intravenous administration of micro-bubbles (ultrasound contrast agents - UCAs) holds great promise for the pharmacological treatment of cancer, neurodegenerative diseases and other brain disorders. Here we show in a primate model how different types of micro-bubbles oscillations, as they are characterized by their acoustic emissions, can be used to monitor disruption of the BB and provide a real-time safety indicator.

Methods: An MR guided focused ultrasound phased array (ExAblate 4000, InSightec Ltd, Haifa, Israel) with center frequency 220 KHz operated in pulsed mode (pulse repetition frequency 1 Hz; duty cycle 1%; duration 70 sec) was used to disrupt the BBB in a male Rhesus macaques (9-12 Kg) under Ketamine/Xylazine anesthesia. Eleven sonications at different locations using three acoustic power levels (1, 1.5 and 2 W) were tested. At the start of each sonication, 10 ul/Kg of Definity (Lantheus Medical Imaging Inc, MA, USA) was administered intravenously. A passive cavitation detection system placed at the periphery of the primate's head was used to record the acoustic emissions. The cavitation detection system was composed of a custom-made focused PZT transducer and a broadband (0 - 1 MHz) hydrophone (TC 4038, Reson Inc, Slangerup, Denmark). The emissions were captured continuously during the sonications and their power spectrum was used to characterize the bubble oscillations and monitor the treatment in real time. With ultra-harmonic emissions in the absence of broadband noise indicating stable micro-bubble oscillations and broadband emissions indicating micro-bubble collapse. BBB disruption, edema, and extravasation of erythrocytes at the targeted locations were observed using contrast enhanced, T2 and T2* weighted MR images, respectively.

Results & Conclusions: Harmonic emissions were observed at all power levels tested and contrast enhanced MR images showed BBB disruption at all locations. Ultraharmonic emissions were recorded from all five locations that were sonicated at 2 W. The appearance of subharmonic emissions of the order f0/2 and broadband noise (i.e. inertial cavitation) occurred at two locations at the thalamus sonicated with 1.5 and 2 W. At these locations T2 and T2* weighted images indicated the presence of extravasated erythrocytes and edema. In conclusion, this preliminary data suggests that passive cavitation detection during sonication can be used to monitor successful BBB disruption. The correlation of broadband noise with edema indication at T2* weighted images suggests that monitoring of the acoustic emissions may provide a reliable real- time safety indicator. Passive cavitation detection may constitute a major step forward in order to achieve controlled, reproducible and safe delivery of pharmaceuticals in the brain.

Acknowledgements (Funding): Supported by Award Number RC2NS069413 from the NINDAS.

Session Topic: Brain Applications
Presentation Type: Oral
B-6

MR-ARFI Sequences for Focal Spot Localization

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Background/Introduction: MR Imaging of the focused ultrasound focal spot is needed for calibration and fine-tuning of its location. This has traditionally been done with a low-temperature rise and imaged with MR thermometry. However, proximity of the focal spot to vessels or ventricles can alter the location of the subsequent temperature rise. Therefore, it would be desirable to separate the effects of physiological processes at the target tissue from the geometry of the acoustic field. An alternative is to image the focal spot with MR-acoustic radiation force imaging. This method uses a short ultrasound pulse (~20 ms) timed to coincide with a specific gradient, which encodes the radiation force displacement into the phase of the image. The purpose of this work was to demonstrate MR-ARFI capabilities with spin echo and EPI readouts and to optimize the sequences for *in vivo* imaging of the head.

Methods: The MR-ARFI displacement encoding gradients consisted of two pairs of bipolar gradients, "displacement encoding (DE) gradients," which could be modified in duration and amplitude. The DE gradients were related to b-value, where b-value is a metric used in diffusion-weighted imaging to assess diffusion-related signal loss and motion sensitivity. Simulations were performed to calculate the optimal b-value as a function of SNR. Experiments were performed in three *ex vivo* porcine brains with the application of 39 acoustic Watts with the InSightec conformal bone system operating at 0.55 MHz. Spin echo and EPI MR-ARFI images were acquired with TEs varying from 22-60 ms, TR = 1s, and b-values from 0.5 to 200 s/mm^2. To measure realistic noise levels, the same sequences were used to measure the noise in the displacement maps from three volunteers.

Results & Conclusions: With the ultrasound on for less than 3% duty cycle, MR-ARFI images yielded pictures of the ultrasound focus, with a sharp peak at the focus, and displacement dropping off away from the focus. Simulations demonstrate a maximum SNR at a b-value of approximately 100 s/mm^2, but motion-related ghosting in the spin echo images reduced the optimal b-value to 32 s/mm^2. From the combination of *ex vivo* displacement maps and *in vivo* standard deviations, signal-to-noise ratios of 15 were obtained in the spin echo acquisitions. The spin echo images provide superior image quality over the EPI and a factor of 3 improvement in SNR, but the EPI images allowed focal spot localization in seconds, with an SNR efficiency increase over the spin echo of 42.

Acknowledgements (Funding): NIH R21 EB011559

Session Topic: Brain Applications
Presentation Type: Oral
B-7

Feasibility of Ablating Brain Regions Adjacent to the Optic Nerve While Retaining Nerve Function with Focused Ultrasound Combined with an Ultrasound Contrast Agent

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Background/Introduction: This study investigated the feasibility of using focused ultrasound (FUS) to ablate a targeted region adjacent to the optic nerve without causing damage to the nerve itself. We investigated sonication combined with an US contrast agent (Definity), with a hypothesis that it can (1) achieve ablation at reduced exposure levels that avoid bone heating and (2) result in little direct damage to the nerve itself due to its relative paucity of blood vessels.

Methods: Burst sonications (PRF 1 Hz; duty cycle 1%; duration 5 min) were performed in a 4.7T MRI using a 525 kHz transducer (diameter/ROC: 4/3 cm). Lesions were created transcranially in the brains of 22 Sprague Dawley rats. The focal region was targeted on or directly adjacent to the optic nerve, optic tract or optic chiasma. Three exposure levels were tested (0.8, 1, and 1.25 W). Prior to each sonication, Definity (Lantheus Medical Imaging, Inc, MA, USA) of 10µl/kg (10 animals) or 20µl/kg (12 animals) was administered intravenously. Optic nerve damage was monitored by recording visual evoked potentials (VEP) using MRI-compatible electrodes (IVES EEG solutions Inc., Manotick, Ontario, Canada) implanted epidurally into the occipital cortex. Contrast enhanced T1 weighted, T2-weighted and T2*-weighted MR images were used to evaluate the resulting lesions in MRI. Animals were euthanized after 24, 48, 72 hrs, 8 days, or 2 or 3 weeks and brains were removed for histopathological evaluation.

Results & Conclusions: FUS exposure at 0.8 W with 20µl/kg Definity resulted in infracted regions. All cellular elements appeared necrotic, and macrophages infiltration was evident. Three weeks after sonication, the necrotic brain tissue at the targeted location disappeared, and a cyst was evident along with enlarged brain ventricles. Sonication at 1W with 10µ/kg Definity produced smaller size lesion areas. MRI suggested hemorrhagic lesions surrounded by edema and BBB disruption. Despite the fact that the lesions were targeted on or within 1 mm of the optic nerve, tract, or chiasma, visual function as measured by VEP recording did not appear to be severely affected. There was no significant ($P>0.05$) reduction in the amplitudes of the early VEP components (P1-N1 and N1-P2) compared with pre-sonication tests. Although some animals showed slight changes in the amplitude of VEP components, these differences were not significant in 20/22 animals. The latencies of VEP components (P1, N1, and P2) were unaffected or slightly changed; however, the changes were not significant. In conclusion, this preliminary functional and histopathological data suggest that pulsed sonication combined with an ultrasound contrast agent can be used to ablate tissue directly adjacent to the optic nerve while preserving major nerve function. Future work is necessary to evaluate whether more subtle nerve damage results from such exposures.

Acknowledgements (Funding): Supported by a grant from the Focused Ultrasound Surgery Foundation and NIH grant R01EB003268.

Session Topic: Brain Applications
Presentation Type: Oral
B-8

BBB Disruption in Nonhuman Primates Using a Clinical MRgFUS System: Preliminary Results

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Background/Introduction: This work was a safety study of targeted blood-brain barrier disruption (BBBD) via ultrasound bursts combined with a microbubble agent in nonhuman primates. As the BBB prevents the use of most drugs for brain disorders, such a technique could have a major impact. These experiments aimed to address potential safety issues with the technique that cannot be determined using small animals.

Methods: Our Institutional Animal Care and Use Committee approved the experiments. Sonication was performed transcranially in four anesthetized adult male rhesus macaques with the ExAblate 4000 brain transcranial MRgFUS system (InSightec, Haifa, Israel), which uses a 1024-channel phased array (30 cm hemisphere; 220 kHz) integrated with a 3T MRI. Multiple locations in each brain were targeted via electronic beam steering with 70s sonications (10 ms bursts; 1 Hz PRF). In one animal, the beam was steered dynamically during sonication to disrupt a ~1 cm^3 volume. At the start of every sonication, ultrasound contrast agent (Definity, 10 µl/kg) was injected intravenously. BBBD was evaluated in T1-weighted MRI after injection of Gd-DPTA (Magnevist, 0.2 ml/kg). The presence of edema and erythrocyte extravasation was evaluated in T2 and T2*-weighted imaging, respectively. Targets included the thalamus, putamen, cerebellum, cortex, and white matter. In this parametric study, acoustic power ranged from 0.5-10 W. No aberration correction was used. Two animals were tested twice.

Results & Conclusions: BBBD was observed at 27/38 targeted locations. The 11 sonications that did not result in BBBD were at 0.5-1W in one animal; sonication a week later at different targets at 1.5-2W resulted in BBBD. Changes in T2/T2*-weighted imaging, suggesting tissue damage, were evident for sonication at 4W and above (N=6), and for two locations (1.5, 2W) in the thalamus. BBBD without T2/T2*-weighted imaging effects was achieved in 19 locations (1-3W). In 3/6 sessions, BBBD and probable tissue damage also occurred at the location of the geometric focus. These effects were more severe when dynamic beam steering was used. This appears to have been due to voltage transients applied by the FUS system during its operation and will be corrected for our future studies. In one location targeted at 10W, secondary damage was evident between the target and the transducer. In all other locations, the sonication effects appeared to be fully contained to the target location and did not appear to affect any other brain region. Targeting multiple overlapping locations via dynamic steering produced contiguous volumes with BBBD. Overall, these data demonstrate that it is possible to use a clinical MRgFUS system for targeted BBBD in multiple brain structures in a large animal model without producing other MRI-evident effects on surrounding tissues. Future work will evaluate histological and functional effects produced by these exposures and investigate methods to guide the procedure.

Acknowledgements (Funding): NIH grant RC2NS069413. InSightec provided the FUS system.

Session Topic: Brain Applications
Presentation Type: Oral
B-9

Transcranial Sonothrombolysis in Ischemic Stroke Using HIFU: Introduction of an *In Vivo* Efficacy and Safety Model - First Results

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Background/Introduction: To test for transcranial sonothrombolysis using High Intensity Focused Ultrasound (HIFU) *in vivo,* an appropriate animal model is needed. Current *in vivo* sonothrombolysis models for stroke are mainly established in rats and rabbits, using the middle cerebral artery (MCA) as the target vessel. The vast majority of these models aim to accomplish both efficacy and safety testing using the same approach. However, it is questionable whether these models are suitable due to the very different anatomy of the skulls, as well as the intracranial vessel anatomy and vessel sizes compared to humans. We would like to introduce two rabbit models, one being used for efficacy testing (rabbit carotid artery), and one being used for safety testing (rabbit brain).

Methods: *Efficacy Model:* A rabbit carotid artery model has been chosen because of two main reasons: a) the arterial dimensions are comparable to the human intracranial middle cerebral artery in its M1/M2 segments, which are the main targets for sonothrombolysis. B) the model presents feeding arteries and a microcirculation system (brain as the end organ) that can be studied for clot fragmentation, potentially causing downstream strokes. Since the rabbit carotid artery will be positioned inside the cavity of the cadaveric human skull, transcranial HIFU insonation is provided in each case. *Safety Model:* In this model, the rabbit head is positioned inside a human cadaveric skull to mimic transcranial insonation. The right hemisphere of the rabbit's brain is insonated with the same HIFU operating parameters that are used for the efficacy studies. A well-established behavioral test is used to assess neurological deficits in a 10-day observation period after insonation, followed by brain histology.

Results & Conclusions: *Efficacy Model:* To date, the carotid arteries of six animals have been successfully recanalized during 30 seconds of insonation using the following operating parameter combination: acoustic output power (AP): 235W (I_{SPTA}: 244.5W/cm^2), duty cycle (DC): 50%, pulse width (PW): 200ms. In all cases, a thrombotic occlusion of the carotid artery could be achieved. Recanalization was confirmed using high-frequency duplex ultrasound. *Safety Model:* A total of 12 animals have been studied until recently. The right hemispheres of the rabbits have been exposed for 30 seconds to either 235 or 500 Watts acoustic output power, using varying pulse widths and insonation patterns. In all animals, neither abnormal behavior over a time period of 10 days nor pathological findings after histology could be found. In conclusion: 1. The rabbit carotid artery as well as the rabbit brain approach can be used as *in vivo* sonothrombolysis efficacy and safety models; 2. Recanalization of the carotid artery after thrombotic occlusion can be achieved to a high extent using an acoustic output power of 235 Watts; 3. Acoustic powers of either 235 or 500 Watts do not cause short- or long-term damage of non-ischemic brain tissue.

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Session Topic: Brain Applications
Presentation Type: Poster
P-2

Off-focus Heating of Micro-calcifications in HIFU Neurosurgery

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Background/Introduction: The safety of HIFU-based neurosurgical interventions relies on the strict confinement of the ultrasound-induced heating to the planned region of treatment and the avoidance of significant ultrasound-tissue interactions in sensitive off-target tissue structures. Intracranial calcifications exhibit similar acoustic properties as bony structures and thus both scatter and absorb acoustic energy very efficiently, eventually giving rise to unwanted shielding of the ultrasound field and potentially dangerous local heating at sites of calcified tissue distant to the acoustic focus. Macroscopic calcifications with diameters of several mm and high Hounsfield-densities can be readily identified on the pre-treatment CT images used for acoustic modeling of the patient skull and are per standard procedure excluded from the acoustic beam path. Microscopic calcifications, however, might be too small or not dense enough to be detected on CT. The aim of this study was to assess heating characteristics of different types of microcalcifications and to use these data in the safety analysis of a patient treatment session, where an unexpected secondary off-focus hotspot was suspected to be associated with a microcalcification.

Methods: All experiments were conducted on a clinical prototype system for transcranial MR-guided HIFU (ExAblate 4000, InSightec, Tirat Carmel, Israel) integrated into our clinical 3Tesla MR-system (GE, Milwaukee, USA). Agar gels doped with evaporated milk were used as tissue mimicking phantoms and calcium carbonate was added to model calcifications of different sizes and Hounsfield-densities. Numerical simulations of local heating dynamics were done using a commercial FDTD solver (SemCad X, SPEAG, Zurich, Switzerland).

Results & Conclusions: As expected, macroscopic high Hounsfield-density calcium deposits could be easily heated to excessive levels up to 15 mm away from the acoustic focus. Microscopic or low Hounsfield-density calcifications, however, did not absorb enough energy to create significant off-focus heating owing to the field geometry of our half-spherical transducer.

Session Topic: Brain Applications
Presentation Type: Poster
P-3

MR-Guided Focused Ultrasound Surgery for the Treatment of Tremor: A Non-invasive Thalamotomy

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Background/Introduction: Tremor is the most common movement disorder. While tremor is not medically dangerous, it is very disabling and can be very difficult to control with medication. In severe and refractory cases, stereotactic surgery can provide effective relief from tremor. Both stereotactic radiofrequency lesioning and deep brain stimulation targeted to the ventralis intermedius nucleus of the thalamus have proven effective for the treatment of tremors. Both intracranial procedures, however, are invasive, lengthy, and difficult for awake patients to endure. A noninvasive therapy would be welcomed by patients with severe tremor and by those who would rather avoid oral medications. Focused ultrasound lesioning has been of interest to neurosurgeons since the 1950s, but it was never widely adopted due to the difficulty of sonicating through an intact skull. Today, this problem has been overcome with the use of phased array transducers and skull correction algorithms. Thus, ultrasound waves can now be precisely targeted to discrete regions of the human brain without craniotomy using the technological combination of MR guidance and focused ultrasound therapy (MRgFUS). Furthermore, MRI and MR thermography allow for real-time monitoring of the treatment.

Methods: A multicenter pilot trial of patients with medically-refractory Essential Tremor is designed to assess safety and efficacy of MRgFUS Vim thalamotomy. Pre- and post-treatment assessments will be made with the Clinical Rating Scale for Tremor, the Quality of Life in Essential Tremor questionnaire, and MR analysis.

Results & Conclusions: RESULTS: Patients with no prior brain surgery have been safely treated with MRgFUS thalamotomy for neuropathic pain syndromes. MR characteristics of the lesions are reported acutely and at long-term follow-up. CONCLUSION: MRgFUS can be used noninvasively to lesion the brain through an intact skull. Lesioning can be monitored continuously with MRI and MR thermography. The safety and efficacy of MRgFUS lesioning of the Vim thalamus for the treatment of tremor is currently under investigation.

Acknowledgements (Funding): This work is supported by the Focused Ultrasound Surgery Foundation.

Session Topic: Brain Applications
Presentation Type: Poster
P-4

Evaluation of Three-dimensional Temperature Distributions Produced by a Low-frequency Transcranial Focused Ultrasound System within *Ex Vivo* Human Skulls

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Background/Introduction: Transcranial MR-guided Focused Ultrasound (TcMRgFUS) may provide a noninvasive alternative to surgery or other treatments for brain disorders. Use of low-frequency ultrasound provides advantages for TcMRgFUS with respect to skull heating, but is potentially limited by reflection and standing wave effects that may cause secondary hot spots within the skull cavity. This work used three-dimensional MR temperature imaging (MRTI) and *ex vivo* human skulls filled with tissue-mimicking phantom material to search for heating distant from the focal point that may occur during sonication with a TcMRgFUS system as a result of reflections or standing wave effects.

Methods: Heating during 120 s sonications was monitored within the entire skull volume for 12 different locations in two different skulls. This duration was selected to achieve a sufficient temperature rise while avoiding the cavitation enhancement which is normally used by this system to increase the focal heating at a relatively low time-averaged power level. The system had a 1024-channel hemispheric array operating at 220 kHz (ExAblate 4000, InSightec) and used acoustic simulations based on CT scans to correct skull-induced aberrations. Multiple sonications were delivered at each location while varying the MRTI slice positions in order to provide full coverage of the skull cavity. An automated routine was used to evaluate the MRTI to detect voxels heated by ultrasound and to exclude artifacts. Acoustic power ranged from 110-190W. The mean peak temperature rise at the focus was 8.8±1.0°C and 6.4±0.8°C, respectively, for the first and second skull. No secondary hot spots with a temperature rise of 15% or more of the focal heating were found. Examples of the voxels identified as heating for two locations are shown in the figure. The MRTI noise level (±0.26°C) prevented the identification of possible hot spots with a lower temperature rise.

Results & Conclusions: Analysis of volumetric MRTI that covered failed to find any regions distant from the focus with secondary heating at a level of 15% or more of the peak temperature at the focus. While these experiments do not prove unambiguously that such secondary effects can never occur with this device, they do suggest that they are not common. Future work is needed to evaluate regions close to the focal point and skull surface and to search for hot spots with a lower thermal rise to provide safety margins that are less conservative.

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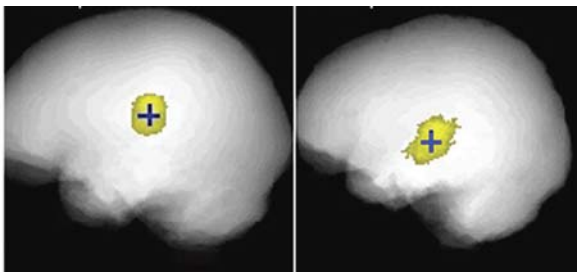

Session Topic: Brain Applications
Presentation Type: Poster
P-5

Optimal Imaging of In Vitro Clot Sonothrombolysis by MR-guided Focused Ultrasound

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Background/Introduction: Patients who develop an intracranial hemorrhage have a poor prognosis with a 35-50% mortality rate in the first 30 days and a morbidity exceeding 80% in survivors. Despite numerous studies, no treatment algorithms have been developed that significantly improve clinical outcomes. Treatment options for intracranial hemorrhage include craniotomy, stereotactic or endoscopic aspiration, and decompressive craniectomy. These treatment modalities are invasive and impose additional risks. Harnof, *et al*, sonicated clots within gel phantoms using MR guidance, demonstrating that they could sonicate 90% of the clot within 10 seconds. Harnof *et al.* and Monteith *et al.* have developed porcine models to evaluate the efficacy of transcranial thrombolysis in the setting of intracranial hemorrhage. While these studies have begun establishing the efficacy of sonothrombolysis, several limitations persist. One of these limitations is the lack of a clear understanding of the MR imaging characteristics of a blood clot as it is being sonicated. This study aims to identify the optimal MR imaging sequence to evaluate sonothrombolysis of intracranial hematomas in real time.

Methods: 12 mL of blood were drawn from healthy volunteers and distributed equally among 3 test tubes. Two test tubes contained no additives, thus allowing clot formation. One was used for sonothrombolysis and the other as a solid control. The third tube contained EDTA to prevent clotting and served as a liquid control. The blood samples were stored for 3, 6, 9, 12, 24, and 48 hours, respectively, in a water bath set at 37°C. At each time point, a set of tubes were imaged using T1, T2 spin-echo, and T2 gradient-echo (GRE) sequences. Immediately afterwards, the first tube was sonicated at 1000 Watts for 30 seconds at 10% duty cycle and 230 kHz using an Insightec ExAblate 4000. The tubes were then reimaged immediately after sonication. Signal of the three MR imaging sequences was measured and normalized to background signal for each time point. Pre- and post-sonication measurements were compared using a mixed model taking into account the paired pre- and post-sonication measurements.

Results & Conclusions: **Prior to sonication, the fully-formed clot demonstrated T1 hyperintensity and T2 hypointensity, while causing blooming artifact on GRE.** The serum surrounding the clot was relatively hypointense on T1 and hyperintense on T2 and GRE. The effects of sonication were most pronounced on T2 weighted images ($p < 0.05$), where immediately following sonication, the treated clot was completely lysed and only the bright T2 serum signal remained. These findings were consistent across all time points up to 48 hours. In conclusion, T2 is the most appropriate sequence for the evaluation of sonothrombolysis of an in vitro clot. These findings remain to be validated *in vivo*.

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Session Topic: Brain Applications
Presentation Type: Poster
P-6

Potential Application of High-Intensity Focused Ultrasound (HIFU) for Vascular Occlusion in Neurosurgery: A Review

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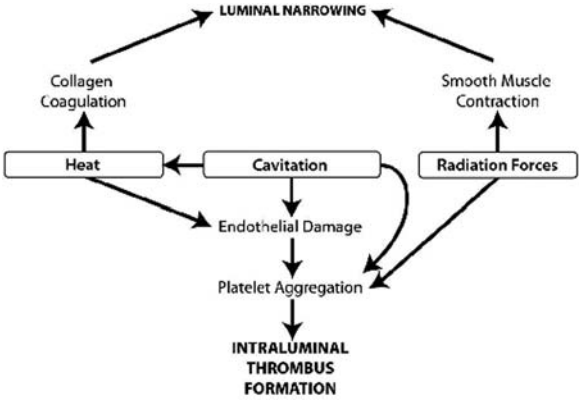
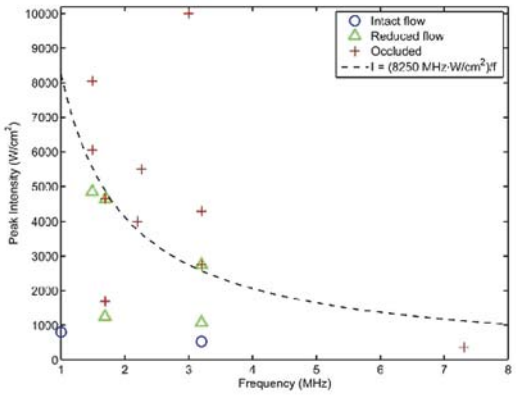
Background/Introduction: Minimally invasive techniques in neurosurgery are continually evolving. The clinical use of high-intensity focused ultrasound (HIFU) has received much attention in treating benign and malignant neoplasms. Additionally, many authors have demonstrated its applicability as a noninvasive method of vascular occlusion. A review of the current literature on the occlusion of intact blood vessels with HIFU is warranted to evaluate this technology's future use in neurosurgery.

Methods: A PubMed search was completed using the terms *focused ultrasound* or *HIFU* linked to *arterial, venous, vessel, vascular, veins, artery,* or, *occlusion*. After review of 177 articles yielded and their references, 14 papers evaluated the effects of HIFU on intact blood vessels.

Results & Conclusions: Magnetic resonance (MR) imaging has proven effective for the guidance of HIFU and will likely be used for intracranial HIFU because of its value in neuroimaging. Additionally, MRA may be effective in assessing vessel occlusion. Although several studies have demonstrated successful immediate occlusion of blood vessels with HIFU, the scarce long-term data available indicates a trend of recanalization and return of treated vessels to pre-treatment diameters. Effective HIFU parameters for extracranial vascular occlusion included intensities ranging from 1690 to 8800 W/cm^2,duration less than 15 seconds, and frequencies ranging from 0.68 to 3.3 MHz. Our analysis of the occlusion results indicates a threshold frequency-intensity product of 8250 MHz×W/cm^2 is needed for vascular occlusion with a sensitivity of 70% and a specificity of 86%. Reported complications include skin burns, hemorrhage, and damage to surrounding structures. Our review of the literature confirms the efficacy of HIFU in its ability to successfully occlude extracranial blood vessels. Although further refinement in this technique and demonstration of intracranial vessel occlusion are needed for neurosurgical applications, HIFU's potential is strong for its future use in cerebrovascular surgery.

Acknowledgements (Funding): Mayfield Educational Research Fund





Session Topic: Brain Applications
Presentation Type: Poster
P-7

Characterization and *Ex Vivo* Testing of a Single-element Interstitial Ultrasound Applicator for the Thermal Ablation of Brain Tumors Under MR Guidance

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Background/Introduction: Conventional treatments for brain tumors involve surgical resection of the lesion in combination with chemotherapy or radiotherapy. In this work, initial design and testing of an alternative, minimally invasive approach based on an interstitial ultrasound probe is presented for performing thermal ablation of brain tumors under MR guidance.

Methods: Initial testing and characterization of a prototype device based on a mono-element design with a 5 MHz element and a 4-mm diameter is presented. Heating experiments were performed in tissue phantoms and in *ex vivo* bovine and sheep brain. Real-time temperature monitoring and lesion characterization was performed using magnetic resonance imaging (MRI) and the obtained temperature rise and lesion volume registered on MRI was compared with numerical modeling.

Results & Conclusions: The results demonstrate that the prototype interstitial probes have good MR compatibility and can be used to thermally ablate a region of brain tissue of up to several centimeters in diameter in several minutes under real-time MR guidance. Interstitial ultrasound applicators, operated under MR guidance, may be a viable, minimally invasive treatment for the thermal ablation of brain tumors.

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Session Topic: Brain Applications
Presentation Type: Poster
P-8

Transcranial Sonothrombolysis in Ischemic Stroke Using HIFU: *In Vitro* Operating Parameter Optimization

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Background/Introduction: **In vitro, it has been shown that transcranial sonothrombolysis using high intensity focused ultrasound (HIFU) can be achieved within seconds and without the further use of lytic drugs, such as tissue Plasminogen Activator (tPA).** It is unknown, however, what operating parameter combination might be favorable to accomplish sonothrombolysis efficaciously and without significant clot fragmentation. Hence, operating parameters, such as duty cycle, pulse width, insonation duration, and power density at the target site, should be tested against each other. Current literature on sonothrombolysis parameter optimization is very limited, especially with regard to HIFU. The aim of this study was to test 4 different duty cycles against 4 different pulse widths while remaining insonation duration and power density were unchanged and to test for efficacy as well as clot fragmentation, using an in vitro flow model.

Methods: An ExAblate 4000 headsystem (InSightec, Inc., Tirat Carmel/Israel) was used. Artificial thrombi (age: 3h) were made from healthy, unmedicated donors and placed into thin-walled PE test tubes. **The latter were placed into the cavity of a human cadaveric calvarium placed upside down into the water-filled hemispheric transducer.** Inlet and outlet of the PE test tube were connected to a peristaltic flow system, maintaining a flow rate of 10ml/min. 4 different duty cycles (5%, 10%, 20%, 50%) were tested against 4 different pulse widths (0.1ms, 1ms, 10ms, 100ms). For all studies the power density was kept at I_{SPTA} 4.89W/cm² (acoustic output power: 235 Watts) and the insonation duration was 30 sec. For quantification, pre/post thrombus weight was measured. Clot fragmentation was assessed using 3 different mesh filter sizes (180µm, 60µm, 11µm).

Results & Conclusions: A total of 400 experiments were performed. Increasing sonothrombolysis efficacy was seen with increasing duty cycle (DC) in combination with increasing pulse widths (PW). Whereas a PW of 0.1ms and a DC of 5% revealed a thrombolysis rate of 6.0%, a PW of 100ms combined with a DC of 50% increased the thrombolysis rate to 64.7%. In comparison of both parameters, increasing DC values alone seem to have a higher effect on clot lysis than increasing PW values alone. Regarding clot fragmentation, no obvious differences to the control mean wet filter weights (difference between dry/wet filters, no sonothrombolysis) could be seen for any of the combinations. In conclusion: 1. Using transcranial HIFU, a maximum clot weight loss of 64.7% could be achieved within 30 seconds in absence of further lytic drugs, such as tPA; 2. Sonothrombolytic efficacy increases with longer duty cycles, longer pulse widths or, preferably, the combination of both; 3. Increasing the duty cycle has a higher impact on thrombolysis efficacy than increasing the pulse width; 4. HIFU-induced transcranial sonothrombolysis, using the parameter combinations presented, does not produce significant clot fragmentation.

Acknowledgements (Funding): This work was sponsored by InSightec, Inc.

Session Topic: Brain Applications
Presentation Type: Poster
P-9

A Safety and Feasibility Study of MR-guided Focused Ultrasound Lesioning in the Setting of Deep Brain Stimulation

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Study Goal: The results of this study will be used to provide preclinical safety data for MRgFUS lesioning of deep brain nuclei that are contralateral to DBS electrodes.

Hypothesis: Magnetic resonance guided focused ultrasound lesioning of deep brain nuclei can be performed safely in the setting of a pre-existing deep brain stimulation system.

Methods: Three experiments are designed to assess the feasibility, accuracy, and safety of MRgFUS lesioning when a neurostimulator has been previously implanted. 1.) Two gel models will be implanted with a DBS electrode and MRgFUS lesions will be delivered to various distances from the electrode tip. MR thermography will be used to monitor for heating of the electrode during the treatment. 2.) Two human cadaver heads will be implanted with a unilateral thalamic DBS electrode, and a contralateral MRgFUS thalamotomy will be planned and performed. The feasibility of targeting around the implanted scalp wires will be determined in addition to temperature monitoring of the intracranial and extracranial electrodes. 3.) Four piglets will undergo stereotactic placement of unilateral thalamic DBS electrode connected to a subcutaneous implanted pulse generator. MRgFUS lesioning of the contralateral thalamus will then be performed. Histological analysis of the brains will be performed immediately (N=2) and at 30 days (N=2) to assess for any tissue damage or heat effect surrounding the electrode. The DBS system will be analyzed for signs of interaction or damage from the MRgFUS treatment.

Preliminary Results: MRgFUS of a target 22mm from a DBS electrode in a gel model with target length and diameter of 5mm using up to 3750 J of acoustic energy (frequency 0.710 MHz) for 15 seconds with a power of 250 Watts and reaching up to 64 degree Celsius did not result in any heating of the electrode.

Session Topic: Brain Applications
Presentation Type: Poster
P-10

Hybrid Referenceless and Multi-baseline Thermometry for MRgFUS Brain Applications

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Introduction: Clinical applications for MR-guided focused ultrasound in the brain have included tumor ablation and neuropathic pain management, and may potentially include the treatment of Parkinson's disease, tremor, and epilepsy. During the FUS ablation accurate temperature measurements are necessary to insure patient safety. Temperature reconstruction is currently performed using single baseline subtraction, which causes errors when motion occurs. To avoid motion the patient's head is fixated in a stereotactic frame during the procedure. However, small motion can occur when the patient moves involuntarily. In addition, pulsation of the brain with the heart beat can be seen. In this study, we investigate if temperature reconstruction methods developed for moving organs can decrease errors in the brain compared to single baseline subtraction.

Methods: Several methods have been developed for temperature reconstruction in moving organs. Here we compare a referenceless, a multibaseline, and a hybrid approach to single baseline subtraction. Eighty consecutive sagittal brain images were acquired from a normal volunteer without heating (GRE, TE/TR = 11.7/23.9 ms, BW = 12.2 kHz). The first 30 images were used as a baseline library and the following 50 images were reconstructed with the different methods. We also used the hybrid method in a sagittal dataset that was acquired during a FUS patient treatment (GRE, TE/TR = 18.6/37.6 ms, BW = 7.36 kHz). Since only a single image was acquired before ablation, the baseline library for the hybrid method contained only this single image.

Results & Conclusions: Single baseline subtraction resulted in temperature errors of 6°C and more in the front of the brain near the cortex and 4°C or more in the center of the brain. There are fluctuations over time possibly caused by pulsation of the brain. Multibaseline subtraction considerably reduces the artifacts to 3°C or less in the front and to ~2°C in the center of the brain. Fluctuations are reduced but still present. Referenceless thermometry alone is not able to determine the temperature accurately, particularly at the base and back of the skull. Overall, the hybrid method achieved the best results. Errors in the front and center of the brain were comparable to the multi-baseline method with 3°C or less and ~2°C, respectively. However, fluctuations over time were much reduced and hardly noticeable.

Temperature maps of the patient undergoing FUS ablation showed a clear depiction of the heating spot with the hybrid method, almost completely removing the severe errors present when using single baseline subtraction.

In summary, these results show that the hybrid method for temperature reconstruction is beneficial to monitor FUS ablation in the brain. When multiple baselines were acquired, the referenceless portion of the hybrid algorithm has less work to do, while when only a single baseline was collected, the referenceless portion of the algorithm contributed significantly.

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
IS-5

Focused Ultrasound Mediated Targeted Drug Delivery

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Objectives: The primary goal is to increase the therapeutic index of potent, often toxic treatments through personalized image-guided treatment, ultimately decreasing adverse effects of drugs by better controlling the pharmacokinetics (PK) and pharmacodynamics (PD) of therapy. This is achieved by locally triggering the deposition or activation of drugs via image-guided ultrasound triggers.

Background/Introduction: Ultrasound can be focused within a region with a diameter of about 1 mm. The bio-effects of ultrasound can lead to local tissue heating, cavitation, and radiation force, which can be used for 1) local drug release from nanocarriers circulating in the blood, 2) increased extravasation of drugs and/or carriers, and 3) enhanced diffusivity of drugs. When using nanocarriers sensitive to mechanical forces and/or sensitive to temperature, the content of the nanocarriers can be released locally. Thermo-sensitive liposomes have been suggested for local drug release in combination with local hyperthermia more than 25 years ago. Microbubbles may be designed specifically to enhance cavitation effects. Real-time imaging methods, such as magnetic resonance, optical and ultrasound imaging have led to novel insights and methods for ultrasound-triggered drug delivery. Image guidance of ultrasound can be used for: 1) target identification and characterization; 2) spatio-temporal guidance of actions to release or activate the drugs and/or permeabilize membranes; 3) evaluation of biodistribution, pharmacokinetics and pharmacodynamics; 4) Physiological read-outs to evaluate the therapeutic efficacy.

Methods: Thermosensitive liposomes have been suggested for local drug release in combination with local hyperthermia more than 25 years ago. Liposomes may carry both hydrophilic and hydrophobic drugs in their aqueous interior and lipid bilayer membrane, respectively. The circulation half-life may be increased by incorporating polyethylene glycol (PEG)-lipids in the bilayer. Nanoparticles may be designed specifically to enhance cavitation effects. Most microbubbles consist of air- or perfluorocarbon-filled microsphere stabilized by an albumin or lipid shell with a size in the range of 1-10 μm. Drugs can be attached to the membrane surrounding the microbubble, they can be imbedded within the membrane itself, they can be bound non-covalently to the surface of the microbubble and can be loaded to the interior of the microbubble, either in an oil or aqueous phase.

Results: Several recent publications have shown that ultrasound triggered delivery is feasible (reviewed by 1,2). Real-time imaging methods, such as Magnetic Resonance, optical and ultrasound imaging may lead to novel insights and methods for ultrasound triggered drug delivery. Image guidance of ultrasound (see e.g. ref 3) can be used for: 1) target identification and characterization; 2) temporo-spatial guidance of actions to release or activate the drugs and/or permeabilize membranes; 3) Evaluation of biodistribution, PK/PD; 4) Physiological read-outs to evaluate the therapeutic efficacy.

Conclusion: The bio-effects of (Focused) Ultrasound can be used for various aspects of local drug delivery and cellular uptake from circulating nanocarriers. MRI guided FUS is particularly useful in case of thermo-sensitive drug nanocarriers. Real-time ultrasound and optical imaging are leading to new insights to increase the therapeutic window with ultrasound

References: 1) Deckers *et al.* JMRI 2008 and JCR 2010 2) Frenkel *et al.* Adv Drug Del Rev 2008 3) www.sonodrugs.eu

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
IS-6

FUS Mediated Targeted Drug Delivery: FUS Foundation Program Introduction & Overview

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Focused Ultrasound-mediated Targeted Drug Delivery (FUS-TDD) has the potential to impact the largest number of patients numerically in an epidemiological sense, yet has considerable challenges to surmount as it sits at the intersection of multiple industries (both device and medical therapies) and stakeholders. The FUS Foundation has an established track-record of engaging various stakeholder groups through its Brain Program and has a unique capacity to aid in the direction and collaboration within FUS-TDD. For this reason the FUS Foundation has initiated a Program in FUS-TDD.

The FUS Foundation strategy includes assuming facilitative and leadership roles in the development of an internally driven research program in FUS-TDD. This is consistent with the Foundations vision and mission and role in bringing together industry, academia, and funding to accelerate the development and adoption of MR-guided Focused Ultrasound. Success will hinge on collaboration among the best and the brightest in the field.

This talk will give an overview of the Program, discuss progress to date and present a framework for future work of the Foundation's FUS-TDD Research Program.

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-1

Mechanisms of Ultrasound-enhanced Drug Delivery

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Background/Introduction: Therapeutic ultrasound can induce mild hyperthermia within a designated region of interest. Advantageous effects of mild hyperthermia include increased blood flow, enhanced microvascular permeability, extravasation of liposome particles, sensitization of tumor cells to radiation and release from temperature-sensitive liposomes. Ultrasound-induced permeability changes in tumor vasculature can promote tumor cell death by enhancing liposomal accumulation and distribution within the tumor. The aim of this study was to determine the physiologic mechanism(s) responsible for liposomal particle accumulation enhancement.

Methods: Animals bilaterally transplanted with mammary adenocarcinoma cells were insonified with a modified SIEMENS Antares ultrasound scanner (MI of 1.9 for 7 minutes resulting in a core tumor temperature of 42°C). Long circulating, ^{64}Cu-labeled liposomes were intravenously injected after insonation. Positron emission tomography (PET) images were acquired at 0, 3, 6, 18, 24, and 48 hours after treatment. The biodistribution of relevant tissues was assayed at 48 hours after injection (% injected dose of radiolabeled liposomes per gram of tissue, %ID/g). Interstitial tumor pressures were monitored using a modified wick-in-needle method. A fluorescence spectrophotometer was used to calculate tumor clearance rate and vascular volume by detecting an intravenously-administered albumin that had extravasated (labeled with Alexa Fluor 647 and administered 30 min prior) compared to an intravascular albumin (labeled with Alexa Fluor 555 and administered 5 minutes prior to euthanasia). Absorption capacity was estimated by placing dissected tumors in isotonic saline for 48 hours. Clearance rate, tumor water content, vascular volume and specific absorption were normalized by the dry weight obtained by desiccating tumors in a 55°C oven for 4 days.

Results & Conclusions: Therapeutic ultrasound treatment resulted in a 2.3-fold increase in accumulated liposomes 48 hours after insonation (10.9 ± 4.7 vs. 4.7 ± 2.4 %ID/g in the contralateral tumor, $p=0.03$). Multiple mechanisms for increased accumulation were detected. Regardless of whether the tumor was insonified prior to or after euthanasia, the interstitial fluid pressure remained stable during heating to 42°C, but fell significantly when the temperature was maintained at 42°C. For tumors treated with ultrasound, the clearance rate of albumin was significantly higher after insonation (91.9 ± 42.5 vs. 72.4 ± 39.7 μl/g for the contralateral tumors, $p<0.01$) with no significant difference observed in vascular volume (41.8 ± 13.8 vs 45.6±16.5 μl/g in control tumors). The water content of tumors (5.6±1.2 vs 5.3±1.2 ml/g) and the relative absorption capacity to isotonic saline (4.8±1.0 vs 4.8±0.8 ml/g) were not significantly changed after insonation during the subsequent 48 hours following US.

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Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-2

Temperature Sensitive Liposomes for Ultrasound-induced Drug Delivery Under MRI Guidance: In Vitro and *In Vivo* Results

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Background/Introduction: Drug release from temperature-sensitive liposomes (TSL) induced by local heating of tissue with high-intensity focused ultrasound (HIFU) is a new promising tool for site-directed cancer therapy. Magnetic Resonance Imaging (MRI) and MR thermometry are used to define the target area and control the local temperature by giving feedback to a therapeutic ultrasound transducer embedded in the MRI patient bed[1]. Loading MRI contrast agents together with the drug into the lumen of the liposomes allows to image and potentially to quantify with MRI the drug release in situ. Here, we present a first study with TSLs loaded with a chemotherapeutic drug, doxorubicin (dox), and an MRI contrast agent (GdHPDO3A) for temperature-induced drug delivery under MR image guidance.

Methods: The release of the encapsulated solutes from the aqueous lumen of the TSLs was studied in vitro as a function of temperature[2] and in gel phantoms using MR-HIFU. As a proof-of-principle, an animal study was performed to correlate the release of dox with GdHPDO3A in tumor-bearing rats at mild hyperthermia (T=42°C). The clinical Sonalleve MR-HIFU system (Philips Healthcare, Finland) was equipped with a binary feedback loop for controlled heating of the tumor between 41°C and 42°C using a 4 mm volumetric treatment-cell (acoustic power: 8W; ultrasound frequency: 1.44 MHz). The rats were positioned inside a small animal system add-on (Philips Healthcare, Finland) designed to enable MR-HIFU treatment of small animals with the clinical Sonalleve MR-HIFU platform. The dedicated small animal system had a HIFU compatible partially submerged 4-channel SENSE animal MR coil situated above the transducer. After preparing and positioning the rat (n=3), the 9L glioma tumor was sonicated two times 15 min at mild hyperthermia. When the temperature of 42°C in the sonication cell was reached (t=0), the TSLs were administrated (5 mg dox/g bodyweight). Interleaved T1-maps were acquired at the specific time points (see Figure 1) using a steady-state inversion recovery Look-Locker MR sequence[3]. A sham group (n=3) was injected with TSLs without applying sonication. T1-maps were acquired continuously until t=70 min. The MR-HIFU system was able to maintain the temperature inside the tumor between 41°C and 42°C during the complete hyperthermia period.

Results & Conclusions: Gel phantom experiments as well as *in vivo* experiments showed a significant change in T1 upon mild hyperthermia with HIFU (Figure 2). In addition, a good correlation between ΔR1 and the amount of dox was found. This proof-of concept study shows the potential for controlled drug delivery under image guidance.

Acknowledgements (Funding): This work was supported through the EU integrated project Sonodrugs (NMP4-LA-2008-213706).

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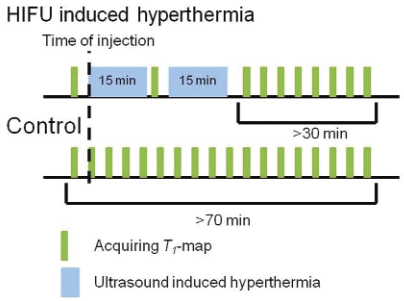
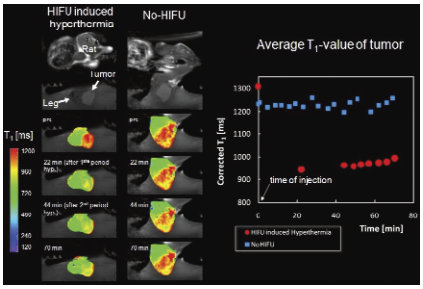


Figure 1: Scheme of the HIFU induced mild hyperthermia drug delivery experiment for the treated and control group.

Figure 2: Right: T1-maps at different time points after TSL injection of a treated and non-treated (control) tumor at HIFU mediated mild hyperthermia. The T1-maps visualize a part of the leg and the tumor region equal to the anatomical images in the first row. The color range corresponds to the color bar on left of the figure. Left: Average T1-value in the tumor as function of time for the treated and non-treated tumor. During the period of HIFU mediated mild hyperthermia T_1-maps could not be acquired.



Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-3

Composite Drug-Delivery Agents Comprised of 5FU-Bearing Controlled-Release Nanoparticles Bonded to Microbubbles Inhibit Glioma Growth upon Activation with Ultrasound

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Background/Introduction: Brain tumors present considerable challenges for therapeutic nanoparticle (NP) delivery. While some NPs diffuse from blood to the tumor core due to leaky microvessels, total NP delivery is still limited by poor convective transport caused by high interstitial tissue pressures. Here, our first goal was to enhance NP delivery to tumors through the use of ultrasound (US)-activated composite agents (MNCAs) comprised of poly(lactic-co-glycolic) acid (PLGA) NPs covalently linked to microbubble (MB) shells. Our second goal was to determine whether delivering 5-fluorouracil (5FU)-bearing controlled-release NPs with MNCAs inhibits tumor growth.

Methods: Rag-1$^{-/-}$ mice received bilateral subcutaneous C6 glioma cell inoculations. Twelve days later, when the tumors were ~80 mm3, MNCAs containing either VivoTag680-conjugated, 5FU-bearing, or BSA-bearing (control) PLGA NPs were injected intravenously. One tumor per mouse was treated with 1 MHz US, while contralateral tumors served as paired "no ultrasound" controls. Co-injections of MBs and NPs at concentrations chosen to match those present in MNCA formulations were also performed. Following treatment, fluorescence mediated tomography (FMT) of VivoTag680 NPs was used to assess NP delivery. In the 5FU studies, tumor growth and cell proliferation (Ki67 staining) were measured.

Results & Conclusions: Activating MNCAs with US resulted in the delivery of 18% of the initial NP dose per gram tissue (ID/g) to the tumor. This NP concentration was ~9-fold greater than for control tumors in which US was not applied (2% ID/g). Co-injections of MBs and NPs also yielded substantially elevated NP delivery upon US-activation; however, NP delivery with the MNCA formulation was still 3-fold greater, indicating that the composite agent strategy confers a significant NP delivery advantage over co-injection. The delivery of 5FU NPs from the MNCA formulation with US resulted in an ~50% reduction in tumor volume at 7 days after treatment when compared to controls in which US was not applied, as well as to controls in which "blank" BSA NPs were delivered, indicating that both US and 5FU confer a therapeutic effect. Interestingly, even at 7 days after treatment, the percentage of tumor cells that were also Ki67^{+} was significantly reduced by 33% when 5FU NPs were delivered via the MNCA formulation. Furthermore, at day 7 after treatment, tumors treated with 5FU NPs via the MNCA formulation were significantly smaller (~33%) than those treated with co-injections of MBs and 5FU NPs. When considered in light of the quantitative FMT data, this final result suggests that the enhanced delivery of controlled release 5FU NPs via MNCAs results in greater tumor growth inhibition than can be achieved with a co-injection strategy.

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Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-4

Thermally-mediated Localized Drug Release Using MRI-controlled Focused Ultrasound Hyperthermia

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Background/Introduction: Thermosensitive liposomes provide a mechanism for triggering the local release of anticancer drugs, but this technology requires precise temperature control in targeted regions with minimal heating of surrounding tissue. The objective of this study was to investigate the use of a preclinical system for MRI-guided focused ultrasound to achieve MRI-controlled hyperthermia and thermally-mediated localized drug delivery *in vivo*.

Methods: Results are reported from ten rabbits, where a focused ultrasound beam was scanned in a circular trajectory to heat 10 mm diameter regions in normal thigh to 43°C for 20-30 minutes. MRI thermometry was used for closed-loop feedback control to achieve temporally and spatially uniform heating. Lyso-thermosensitive liposomal doxorubicin (ThermoDox®, Celsion Corporation, Columbia, MD) was infused intravenously during hyperthermia. Two hours later, unabsorbed liposomes were flushed from the vasculature by saline perfusion, and tissue samples were harvested from heated and unheated thigh regions. The fluorescence intensity of the homogenized samples was used to calculate the concentration of doxorubicin in tissue.

Results & Conclusions: Closed-loop control of FUS heating using MRI thermometry achieved temperature distributions with mean, T90 and T10 of 42.9°C, 41.0°C and 44.8°C within the 10 mm diameter target region, varying temporally by ±0.9°C (SD) over a period of 20 minutes. Doxorubicin concentrations in heated regions were on average 15.3 ± 8.1 (SD) times higher than in the unheated contralateral thigh. The results show the potential of MRI-controlled focused ultrasound hyperthermia for enhanced local drug delivery with temperature-sensitive drug carriers.

Acknowledgements (Funding): Kullervo Hynynen and Rajiv Chopra are founders and have shares in FUS Instruments, a company that is commercializing the preclinical FUS system described in these experiments. Thermosensitive liposomes were provided by the Celsion Corporation. This work is supported by funding through a Terry Fox Foundation New Frontiers Program project grant from the National Cancer Institute of Canada, and by an Ontario Research Fund grant from the Government of Ontario, Canada.

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-5

Ultrasound-enhanced Drug Delivery During Epithelial-Mesenchymal Tumor Transition (EMT)

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Background/Introduction: Epithelial-mesenchymal tumor transition (EMT) is associated with a poor prognostic outcome as tumor cells adopt an irregular, elongated shape with loose cell-cell adhesions and increased migratory capacity. Although ultrasound has been shown to enhance tumor drug accumulation, protocol optimization must account for differences between epithelial, mesenchymal and transitional tumor phenotypes.

Methods: Animals were bilaterally injected with mammary adenocarcinoma cells (MET-1s) in the #4 mammary fat pad; implantation of high-density, confluent MET-1s resulted in epithelial tumors, while low-density plating resulted in a fibrotic phenotype. Tumors were insonified by a modified SIEMENS Antares ultrasound scanner using 1.5 MHz pulses utilizing a low (0.9), medium (1.9) or high (2.9) mechanical index (MI) with or without ultrasound-induced mild hyperthermia (42°C or 37.5°C) delivered over 7, 18 or 35 minutes. A feedback control loop maintained tumor temperature by varying the pulse length. Long-circulating, ^{64}Cu-labeled liposomes were intravenously injected after insonation. The circulation and accumulation of radioactivity were monitored using a positron emission tomography (PET) scanner at 0, 3, 6, 18, 24 and 48 hours after treatment. The biodistribution of relevant tissues was assayed using a gamma counter at 48 hours (% injected dose of radiolabeled liposomes/gram tumor tissue, %ID/g). Resected tumors were fixed in 10% buffered formalin overnight and stored in 70% EtOH until H&E staining was performed.

Results & Conclusions: Well-perfused **epithelial** tumors insonified with an MI of 0.9 resulting in a 5°C rise in core tumor temperature to 42°C for 2 min demonstrated a 2.8-fold increase in accumulation 48 hours post ultrasound (15.4±4.7 versus 5.5±2.3%ID/g in contralateral tumors). For tumors with a **mixed epithelial and mesenchymal** phenotype, an increase in MI and extension of the insonation time to 7 minutes were required to enhance particle accumulation; a 2.3-fold accumulation increase (10.9 ± 4.7 vs. 4.7 ± 2.4 %ID/g in the contralateral tumor, p=0.03) was achieved with an MI of 1.9 and temperature of 42°C for 7 minutes. In **fibrotic** and poorly-perfused tumors, extended insonation time (MI of 1.9, 42°C temperature for 18 min) produced a 3.0-fold increase (10.3±2.6 versus 3.4±1.0%ID/g in contralateral controls p=.001), whereas a lower MI or shorter treatment was unsuccessful. A higher mechanical index without hyperthermia (MI of 2.9, 0.5°C, 35 min) did not increase accumulation even with extended insonation (6.1±2.0 versus 6.0±3.6%ID/g in the contralateral tumor). The results of this study demonstrate ultrasound's ability to enhance chemotherapeutic delivery across a wide range of tumor types; however, treatment planning based on tumor morphology is required.

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Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-6

Synthesis and Characterization of MR Image-able Low Temperature Sensitive Liposomes for Use with Magnetic Resonance Guided High Intensity Focused Ultrasound

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Background/Introduction: Drug delivery to solid tumors currently faces obstacles such as toxicity to healthy organs, insufficient and heterogeneous drug delivery and lack of knowledge of the concentration of the delivered drug. Image-guided targeted drug delivery approaches may improve these shortcomings. Objectives of this study were to: 1) Develop iLTSL - an MR image-able low temperature sensitive liposome co-loaded with an MRI contrast agent (ProHance® [Gd-HP-DO3A]) and doxorubicin, 2) Characterize doxorubicin and Gd-HP-DO3A release from iLTSL and 3) Investigate the ability of magnetic resonance guided high intensity focused ultrasound (MR-HIFU) to induce and monitor iLTSL content release in phantoms and *in vivo*.

Methods: iLTSL was prepared by passively loading Gd-HP-DO3A and actively loading doxorubicin using a pH-gradient method. Release of doxorubicin was quantified by fluorescence and Gd-HP-DO3A release was measured with MR and spectroscopic techniques. Release with MR-HIFU was examined in agar-silica gel tissue-mimicking phantoms containing suspended iLTSL as well as in a Vx2 tumor in a rabbit superficial thigh muscle.

Results & Conclusions: iLTSL demonstrated consistent size and doxorubicin release kinetics after storage at 4°C for 7 days. The magnitude of release was not significantly different between doxorubicin and Gd-HP-DO3A over 10min in HEPES buffer at 37, 40 and 41.3°C ($p>0.05$). Complete release of Gd-HP-DO3A and doxorubicin occurred in ~24s at 41.3°C in HEPES buffer. Faster, but incomplete doxorubicin release (~70%) occurred in human plasma. Relaxivity of iLTSL increased significantly ($p<0.0001$) from 1.95±0.05 to 4.01±0.10mMs^{-1} when heated. Signal increase corresponded spatially and temporally to MR-HIFU-heated locations in phantoms. *In vivo*, injection of iLTSL resulted in stable (>10 min) ~30% signal enhancement in the tumor. A further ~20% increase in signal enhancement relative to pre-injection values was observed in the heated portion of the tumor following four 10-minute heating cycles (target temperature = 40-41°C, measured temperature = 41.1±1.2°C in the 4-mm diameter heated region). These data suggest that MR image intensity may be a surrogate for doxorubicin release. Combining MR-HIFU with iLTSL may enable spatial control and real-time noninvasive monitoring of content release for image-guided targeted drug delivery.

Acknowledgements (Funding): We would like to thank Dr. Melanie Kotys of Philips Healthcare for help with MRI sequence design and Dr. Chrit Moonen and his group for assistance with MR-HIFU. This work is currently supported through the NIH Intramural Research Program, Center for Interventional Oncology, and a CRADA with Philips Healthcare.

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-7

MR-guided High Intensity Focused Ultrasound Enhances Targeted Drug Delivery of Low Temperature Sensitive Liposomes in a Rabbit Vx2 Tumor Model

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Background/Introduction: Low temperature sensitive liposomes (LTSL) have been developed to rapidly release their contents in a tumor at mild hyperthermic temperatures (40-42°C). Targeted drug delivery to solid tumors, while limiting local and systemic toxicity, requires accurate spatial and temporal control of heating. MR-guided high intensity focused ultrasound (MR-HIFU) may be able to provide this precise control of tumor heating. The objective of this study was to investigate the combination of MR-HIFU and TSLs to enhance delivery of doxorubicin in a Vx2 rabbit tumor model.

Methods: Fourteen New Zealand white rabbits, with Vx2 tumors (> 1 cm diameter) grown in the superficial thigh muscle, were randomly assigned into three treatment groups (5 mg/kg intravenous doxorubicin): i) free doxorubicin, ii) LTSL (Thermo-Dox®, Celsion Corp., USA) and iii) LTSL+MR-HIFU. For the LTSL+MR-HIFU group, rabbit tumors were heated with MR-HIFU to 40-41°C for a total of 30 min within 1 hour after LTSL infusion. An integrated MR-HIFU clinical platform (Sonalleve, Philips Healthcare, USA) was used for sonications and MR guidance. The HIFU beam was electronically steered to heat 4 mm diameter regions. Temperature maps including the heating focus were obtained using the proton resonance frequency shift (PRFS) method and a 2D fast field echo pulse sequence (slice thickness=7mm, in-plane resolution=1.39x1.39mm, temporal resolution=2.5s) in coronal and sagittal planes and used to provide real-time temperature feedback control. Four hours after treatment, tumors were harvested. High pressure liquid chromatography (HPLC) analysis of the tumor homogenates was performed to determine tumoral doxorubicin concentration. Treatment groups were compared for differences in mean tumor doxorubicin concentration using analysis of variance (ANOVA) followed by Neuman-Keul's multiple comparison test.

Results & Conclusions: MR-HIFU achieved hyperthermic temperatures of 40-41°C for the duration of treatment. The tumor doxorubicin concentrations were (mean±SEM) 3.35 ± 0.57, 7.8 ±1.12, 39.1 ± 11.9 μg doxorubicin / g tissue for free doxorubicin, LTSL and LTSL+MR-HIFU, respectively. LTSL+MR-HIFU resulted in significantly higher tumor doxorubicin concentration compared to the other treatment groups ($p<0.05$). Combing heating with MR-HIFU with LTSL resulted in approximately 5-fold greater doxorubicin concentration when compared treatment with LTSL alone. Analysis of individual fragments from each tumor demonstrated relatively heterogeneous doxorubicin distribution post MR-HIFU, suggesting that a more conformal hyperthermia treatment may further improve targeted drug delivery to a solid tumor. The combination of LTSL and MR-HIFU clinically relevant hyperthermia significantly improved delivery of doxorubicin to tumor tissue. This image-guided drug delivery technique has potential for clinical translation.

Acknowledgements (Funding): This work is currently supported through the NIH Intramural Research Program, a CRADA with Philips Healthcare, and a CRADA with Celsion Corporation.

Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-8

Improved Treatment in a Rat Breast Cancer Brain Metastases Model by Targeted Delivery of Herceptin Across the Blood-Brain Barrier with MRgFUS

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Background/Introduction: The blood-brain barrier (BBB) has been a major limitation to the clinical applications of chemotherapy to brain tumors because of its low permeability to anti-tumor agents. Animal studies have shown that focused ultrasound (FUS) bursts in the presence of microbubbles is able to temporarily disrupt the BBB, and that a therapeutic dosage of chemotherapy agents can be delivered into the brain and improve outcomes in brain tumor models. Based on previous studies, this study was designed to demonstrate the significance of the Herceptin delivery to a rat breast cancer brain metastases model using this technique. Herceptin has been shown to be an effective treatment in many patients with HER2 overexpressing, node-positive HER2+ breast cancer, but success is limited for patients with brain metastases.

Methods: A total of 43 nude (nu/nu) rats were used in four groups: (1) no treatment (control), (2) treatments with FUS in the presence of microbubbles (FUS only), (3) systemic delivery of Herceptin without FUS treatments (Herceptin only), and (4) FUS treatments with microbubbles and concurrent IV injection of Herceptin. As a metastatic tumor model in the brain, human breast cancer cells (BT474) were directly inoculated into the rat's brain. A single element focused transducer (D = 10 cm, ROC = 8 cm) at 690 kHz was used for the FUS treatments (group 2 and 4). The tumors were exposed to the ultrasound in a burst mode (burst length = 10 ms, pulse repetition time = 1 s, acoustic power = 0.32 W) for 60 s after the injection of ultrasound contrast agent (Definity, 10 μl/kg). For the Herceptin treatments (group 3 and 4), Herceptin was injected at a dose of 2 mg/kg. T1-weighted and T2-weighted images were acquired to guide the targeted area and to evaluate the tumor size. To confirm the BBB opening, contrast enhanced T1-weighted images were acquired after the FUS exposure. Rats were treated weekly for six weeks and follow-up images of the brain were acquired after the weekly treatments for seven more weeks.

Results & Conclusions: Tumor size after the weekly treatments for six weeks were obtained from the MR images of each group. For the US-only and no treatment groups, the tumor sizes were 86 ± 28 mm3 and 85 ± 20 mm3, respectively. The tumor size of rats treated by Herceptin without FUS exposure was 61 ±14 mm3. From the results of rats treated by the MR guided FUS exposure with concurrent injection of Herceptin, the tumor size was 53 ± 19 mm3 and the tumors in three rats out of 10 rats disappeared, and no tumor recurrence was observed. The results of rats treated by US and Herceptin showed the enhancement of the tumor treatment. Due to the temporary opening of BBB induced by FUS with microbubbles, this study suggests that a clinical dosage of Herceptin was effectively delivered to the tumors in a brain and provides supportive results to move this technology to a clinical trial.

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Session Topic: Targeted Drug Delivery
Presentation Type: Oral
TDD-9

Application of Ultrasound to Sonosensitive Liposomal Doxorubicin for Treating Tumors: *In Vivo* Proof of Concept

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Background/Introduction: Drug delivery particles should be stable *en route* to the target tissue and efficiently release the encapsulated drug once at the disease site. The present work shows that these apparently opposing properties may be reconciled by exposing drug-carrying sonosensitive liposomes to ultrasound (US) in the tumor.

Methods: Inertial cavitation (IC) is assumed to be the main mechanism involved in drug release from liposomes. Hence, a spherical transducer, 50 mm diameter and focal length, was used and positionned confocally with a truncated spherical transducer (56 x 34.6 mm^2, focal distance 45 mm) integrating an imaging array. Both transducers operated at 1 MHz. The angle between the acoustical axes was set to 90°. Exposure conditions were set to 256 Hz PRF, 6240 W/cm^2 Isppa and 2.5% DC. *In vitro* tests proved the occurrence and stability of cavitation at the focus and the direct proportionality of ic to exposure duration and liposome release.

Results & Conclusions: *In vivo* experiments were performed on rats implanted with AT2 Dunning tumors. In the phramacokinetic study, 18 rats received an i.v. injection of liposomal doxorubicin (DXR) at 6 mg/kg, 10 days after tumor implantation (D10). The rats were sacrificed sequentially post injection. Blood samples, tumors and different organs were taken for DXR quantification. 20% of injected dose of DXR was still presented in blood two days after injection. Maximal tumor uptake of DXR was observed between D11 and D12. MRI was used to monitor both liposome accumulation and US induced drug release *in vivo* in tumors. For such purposes, similar liposomes containing the MR agents sprodiamide (DyDTPA-BMA) and gadodiamide (GdDTPA-BMA) were used. The gradual accumulation of liposomes in the tumor tissue was visualized on T2* maps (due to the T2* effect of sprodiamide). By mapping R1 (=1/T1), an increase in tumor signal intensity was observed after the application of US to animals injected with liposomes. Next, the efficacy of a combined treatment of liposomal DXR and US on tumor growth was investigated. Twenty-seven rats were divided into 3 groups: US, liposomal DXR at 6 mg/kg and liposomal DXR at 6 mg/kg + US. Injections and US were undertaken at D10 and D12 respectively. Tumors were monitored until D33. US alone did not induce any significant effect on the tumor growth. The group receiving both liposomes and US showed a significantly lower tumor growth compared to controls. In conclusion, the current work demonstrates that sonosensitive drug loaded liposomes exposed to US may be a new mini-invasive therapeutic modality for treating tumors.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-11

Modeling of the Impact of Blood Vessels Flow on the Temperature Distribution During Focused Ultrasound Exposure

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Background/Introduction: There is evidence that focused ultrasound at exposure conditions below the threshold for significant thermal damage can increase drug delivery at targeted areas. Although these results are promising, much more work remains to be done to advance this technology into the clinic. One of the major difficulties is associated with the presence of blood vessels that are an important cause of temperature inhomogeneity, preventing the optimal control of temperature. Toward this purpose, we have been developing finite-element thermal models that take into account the presence of discrete blood vessels for focused ultrasound exposure. The aim is to improve our understanding of the problems associated with heating of tissue by focused ultrasound.

Methods: Blood flow is the main parameter that determines temperature distribution in tissues. In this study, we have employed the bio-heat transfer model developed by Lagendijk that incorporates the influence of discrete blood vessels. Since most of the thermally significant vessels run in counter-flow pair, it is important to consider artery-vein pair systems. In our simulations, we have considered a homogeneous, three-dimensional block of muscle-like tissue with multiple artery-vein pairs.

Results & Conclusions: The thermal treatment is simulated by an ultrasound focus that is stepped through the mid-plane of the computational domain using different delivery methods: (i) the focus is stepped through the mid-plane of the computational domain in a semi-random way to avoid thermal build-up, (ii) the focus is stepped in a sequential manner, or (iii) the focus is stepped through a spiral trajectory. The overall performance of the treatments is evaluated by calculating the thermal dose for the mid-plane of the computational domain. When the power density distribution is kept fixed during the treatments, a huge variation of thermal dose deposition is observed from one insonation to another in all the three cases. Severe under-dosage is observed around the discrete thermally significant vessels and conditions of thermal ablation are observed for location sufficiently far away from the thermally significant vessels. We have also changed the power distribution so that the peak thermal dose remains in a given range for each insonation. In all the three cases, a more uniform thermal dose distribution is observed but under-dosage around the thermally significant vessels still remains. Although these results are only preliminary and they do not take into account the complexity of the real anatomy, they suggest the importance of a treatment planning that takes into account the presence of blood vessels and blood flow. Since it is generally accepted that a more uniform thermal dose distribution produces a better outcome, it is evident that by adjusting the power deposition to take into account the presence of blood flow is an important step toward a better treatment no matter which delivery method is chosen.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-12

Design Principles of Thermosensitive Liposomes for MRI Guided HIFU Triggered Local Delivery of Doxorubicin

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Background/Introduction: The development and commercial availability of MRI combined with high intensity focused ultrasound (HIFU) opens a plethora of possibilities for simultaneous imaging of tumors and localized targeted drug delivery. Accordingly, employing local heating of the target tissue[1] has been used to trigger the release of drugs from thermosensitive liposomal nanoparticles, harboring in addition to the cytotoxic drug also an MRI contrast agent[2]. This approach requires efficient drug and contrast agent capsulation, as well as precise control of the temperature-dependent permeability properties of the liposomes. To this end, the temperature- triggering drug release has to be accurately defined in order to get rapid and effective release of the anti-cancer drug in the tumour.

Methods: The above permeability characteristics of liposomes are controlled by the lipid composition dependent thermal phase behavior of the liposomal membranes. First efforts in this line utilized lysophosphatidylcholine to obtain proper membrane permeability at its melting temperature. However, in order to enhance the anticancer activity, we employed for this utility the anticancer lysophosphatidylcholine analog, edelfosine, and obtained liposomes releasing the encapsulated drug (adriamycin) in a very narrow temperature range of 41 to 43 °C. In addition to the above release profile also the leakage of the drug from liposomes at body temperature should be minimal.

Results & Conclusions: In order to minimize the leakage of liposomes while still retaining the quick release characteristics, we analyzed the thermal phase behavior of a number of lipid compositions by differential scanning calorimetry, with special emphasis in combinations of lipids with complementary effective shapes, so as to avoid the formation of voids and to obtain highly efficient lipid packing at temperatures below the critical release temperature. The above molecular engineering approach proved to be highly efficient, yielding quick drug release and very low leakage. The *in vivo* testing of these liposomes is now in progress. REFERENCES 1. Stewart, E.A. *et al.* Focused ultrasound treatment of uterine fibroid tumors: Safety and feasibility of a noninvasive thermoablative technique. American Journal of Obstetrics and Gynecology 189, 48-54 (2003). 2. de Smet, M., Langereis, S., den Bosch, S.V. & Grüll, H. Temperature-sensitive liposomes for doxorubicin delivery under MRI guidance. Journal of Controlled Release 143, 120-127 (2010).

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-13

Destruction of Circulating Microbubbles in the Vasculature Can Inhibit Tumor Growth: Possible Mechanisms of the Observed Therapeutic Effect

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Background/Introduction: Focused ultrasound is widely investigated as a tumor-therapy tool. Combination of image guidance with ultrasound contrast imaging provides ultrasound delivery information in real time with portable and inexpensive ultrasound imaging systems, using intravenous microbubble contrast. Microbubbles potentiate bioeffects of ultrasound and may reduce the time required for therapy. This study was undertaken with the initial idea to destroy microbubbles by ultrasound in the tumor vasculature and block tumor blood flow.

Methods: Microbubbles were prepared from decafluorobutane gas stabilized with a shell of phosphatidylcholine (PC) and PEG stearate; for leukocyte targeting, microbubbles also contained phosphatidylserine (PS). Mice received MC38 colon adenocarcinoma (J. Schlom, NIH) subcutaneously in the hind leg. Tumor vasculature was evaluated by ultrasound imaging with plain (PC) and leukocyte-targeted (PS) microbubbles. Ultrasound imaging was performed with CL15-7 and 15L8 probes. Therapeutic ultrasound of the tumor or control hindleg muscle was performed under anesthesia by applying TIPS (Philips Research): 1.2 MHz 100,000 cycle ultrasound pulses (5 MPa peak negative acoustic pressure) at 1 s intervals; 3x10 pulses were applied immediately after administration of 50 million PC bubbles. Bloodflow pattern was observed with contrast ultrasound imaging. An hour or next day following treatment, injection of PS-targeted or PC microbubbles was performed, and their retention in the tumor was evaluated. Next day following therapeutic ultrasound treatment, microPET with ^{18}F-FDG was applied. After euthanasia, tissue samples were submitted for histology. For a longer duration therapy study, treatment was repeated twice daily. Animals were euthanized if the tumor reached the protocol-approved size limit, or if an unresponsive skin rupture would occur.

Results & Conclusions: As a result of microbubble destruction by ultrasound, transient reduction of the blood flow in the tumor vasculature was observed; most of the blood flow was restored minutes after treatment. Daily treatments during a two-week treatment study resulted in a significant suppression of tumor growth. In controls, where either microbubble injection or TIPS treatment was not applied, tumor growth was not suppressed. In a long-duration study, median survival time was increased by nearly 3-fold (endpoint by euthanasia performed for humane reasons). Leukocyte accumulation in the vasculature of treated tissues was observed by ultrasound contrast imaging performed with PS microbubbles an hour after therapy. Histology showed leukocyte (neutrophil) accumulation in the treated tissue, which further increased next day following treatment. Histology suggests that the observed FDG accumulation in the treated tissues may be due to the induction of inflammation. Overall, induction of local inflammation in the microbubble+ultrasound-treated tissue may be the mechanism of the suppression of tumor growth.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-14

Feedback Control for Mild Hyperthermia Treatments Using Magnetic Resonance Guided High Intensity Focused Ultrasound

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Background/Introduction: Non-ablative mild hyperthermia (39-45°C) is an effective adjuvant for cancer treatments such as chemotherapy and radiotherapy. Optimal mild hyperthermia treatment would result in accurate and uniform temperature distribution in the target region. Magnetic resonance guided high-intensity focused ultrasound (MR-HIFU) allows for precise temperature control under image guidance, with the ability to noninvasively heat lesions. The objectives of this study were: 1) to develop and implement a clinically relevant mild hyperthermia heating algorithm and 2) to evaluate the ability to monitor and control heating in real-time in a phantom and in an animal model using MR-HIFU.

Methods: An integrated MR-HIFU clinical platform (Sonalleve 1.5T, Philips Healthcare) was used for sonications and MR guidance. Sonications were done in gel phantom and superficial thigh muscles of New Zealand White Rabbits bearing Vx2 tumors. HIFU beam was electronically steered in concentric circular trajectories to heat 4 mm and 12 mm regions in phantom for 30 min, and 4 mm regions in rabbits for up to 10 min. Each rabbit was treated as an independent sample (n=4, total sonications=10). Temperature maps were acquired in coronal and sagittal planes using a 2D fast field echo pulse sequence (TR=54 ms, TE=30 ms, flip angle=19, slice thickness=7 mm, in-plane resolution=1.39 x1.39 mm, temporal resolution=2.5 s) and the proton resonance frequency shift (PRFS) method. An initial low-power sonication was used to correct for spatial mismatch between target and heated regions. An unheated region was monitored to correct for magnetic drift. Real-time feedback control of temperature was achieved by analyzing the mean temperature in the target region within the coronal slice. A binary control algorithm was implemented by sonicating when the mean temperature was <40°C and stopped when the mean temperature was >41°C. Data were analyzed for targeting accuracy (offset), temperature accuracy (mean) and homogeneity of heating (standard deviation (SD), T10 and T90).

Results & Conclusions: Sonications (n=8) in phantom resulted in mean temperatures of 40.6±0.1°C and 41.1±0.1°C, for 4 mm and 12 mm target regions respectively. The average SD, T10 and T90 were 0.7°C, 41.6°C and 39.7°C within the 4 mm target region, and 1.1°C, 42.6°C and 39.8°C within the 12 mm target region in phantom. Sonications in Vx2 tumors in thigh muscle of rabbits resulted in mean temperature of 40.5±0.2°C. Within the target region, the SD was 1.0°C, and T10 and T90 were 41.8°C and 39.2°C, respectively. Mean spatial offset was 1.2 mm. A mild hyperthermia heating algorithm was developed that resulted in accurate (mean= 40.5°C, target 40-41°C) and homogeneous (SD =1.0°C) heating within the targeted region (offset=1.2 mm) in rabbits. This mild hyperthermia algorithm may provide precise and noninvasive monitoring and control of localized thermal dose for chemotherapeutic delivery and radiation sensitization.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-15

Progress Towards Ultrasound-activated Targeted Drug Delivery with Nano-encapsulants and Tumor Cell Poration

Fabian Arditti[1], Bjoern Gerold[2, 3], Dana Gourevich[1, 3], Dun Liu[1, 3], Alexander Volovick[2, 3], Sandy Cochran[3], Jallal Gnaim[1], Paul Prentice[3], Lijun Wang[3], Yoav Medan[2], Eyal Neria[1], Andreas Melzer[3]

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Background/Introduction: Recently, ultrasonic drug release has been a focus of many research groups for stimuli-responsive drug release. It has been demonstrated that focused ultrasound (FUS) can rapidly increase the temperature in tissue in the focal zone. One potential mechanism of drug targeting is to use the induced heat to release or increase penetration of chemotherapy into cancer cells. A potential advantage of this technique over necrotic hyperthermia is that the required temperature increase may be much smaller, significantly reducing the treatment time. Ultrasound-induced cavitation may also be utilized and the efficiency of targeted drug delivery may be further increased by using FUS in conjugation with nano-encapsulated drug carriers.

Methods: The aim of the study reported here is to investigate the effects of ultrasound on the cellular uptake and therapeutic efficiency of an anticancer drug using magnetic resonance imaging guided focused ultrasound (MRgFUS). Human KB cells (CCL-17 cells) were seeded into 96-well plates and heat-treated at 37 - 55 C for 2 - 10 mins. Cell viability was determined using the colorimetric MTT assay. Cells were also subjected to MRgFUS and the degree of cell viability was determined. These experiments were conducted using an ExAblate 2001 system (InSightec Ltd, Tirat Carmel, Israel) and a 1.5 T HDx MRI system (GE Healthcare, Milwaukee, USA, software release 15). Further work has been conducted using bespoke experimental hardware, including a specialized system for laser facilitated ultrasound-induced cavitation.

Results & Conclusions: We have observed a significant decrease in KB cell viability due to heat (temperatures higher than 41 C) in the presence of Doxorubicin (DOX), in comparison with DOX at normal culture temperature (37 C). The synergistic effect of heat with DOX may be explained by several mechanisms. One potential mechanism may be increased penetration of DOX into the cells during heating. In addition, we have confirmed that ultrasound-induced cavitation causes cell necrosis, and we have observed cavitation effects in detail in real time with high speed photomicroscopy. The results to date are promising, but further investigation is needed to optimize the potential of MRg-FUS to enhance cellular uptake of therapeutic agents. A novel delivery nano-encapsulant developed by CapsuTech will be investigated with MRgFUS for its potential as a stimuli-responsive delivery system, including the possibilities of thermal and cavitational response mechanisms.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-16

Initial Experience with a Small Animal System for MRgFUS Targeted Drug Delivery

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Background/Introduction: MRgFUS is increasingly being used in preclinical studies for targeted drug delivery in solid tumors. The use of MR guidance in combination with ultrasound mediation allows for improved visualization, targeting, monitoring, and assessment of the treated region. The small animal models used in many preclinical studies, such as mice or rats, are too small to be conveniently treated with conventional large animal/human treatment systems. To address this issue, a new MRgFUS system (Image Guided Therapy, Bordeaux, France) has been designed specifically for treatment of small animals. This presentation details our initial experience with this system in both *ex vivo* and *in vivo* environments in a Siemens (Siemens Medical Solutions, Erlangen, Germany) TIM Trio 3T MRI scanner.

Methods: The MR compatible system consists of an annular 16-element 3-MHz phased-array ultrasound transducer (3.5 cm radius of curvature, 1 x 3 mm focal spot size) with electronic steering in the z-direction, an actively cooled and degassed water circulation system, piezoelectric motors for 2-D mechanical movement of the transducer and integrated software for designing and executing arbitrary 3-D sonication trajectories. The system is compatible with clinical 3T MRI systems and the 30 cm bore small animal Bruker 7T MRI scanner. *Ex vivo* tissue experiments were performed in our 3T MRI scanner using MRI temperature mapping to evaluate the systems capabilities. *In vivo* experiments were performed on mice with a subcutaneous pancreatic tumor model to evaluate the effects of unloaded and PTX-loaded perfluorocarbon nanoemulsions.

Results & Conclusions: *Ex vivo* tissue results show the accuracy and ease of use of the new system. The reduced water volume, coupled with well-designed local RF receiver coils, results in MR images with very high SNR. Both single- point and continuous scanning results show precise delivery of thermal energy. Temperature measurements reconstructed using a referenceless technique showed no change in the standard deviation of temperatures over a non-heated region during firing or mechanical movement of the transducer. *In vivo* experimental results provide qualitative data that confirm results that have been seen in phantom studies. While motion artifacts due to animal respiration caused artifacts in the MR images, there is a significant increase of heating seen in tumors with both unloaded and PTX-loaded perfluorocarbon nanoemulsions when compared to control tumors when the same ultrasound power and sonication duration are applied. This new system functions very well for the intended application and will enable the further study of ultrasound targeted drug delivery for a variety of applications.

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Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-17

Computational Modeling of Targeted Drug Delivery via HIFU and Low-Temperature Sensitive Liposomes

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Introduction: Studies have shown synergistic effects between hyperthermia and chemotherapy. Clinical trials in image-guided drug delivery combine high-temperature thermal therapy with chemotherapy agents released in the heating zone via low temperature sensitive liposomes (LTSL). LTSL can release their content within seconds upon heating above ~40 °C. Therefore, LTSL combined with locally applied heat can increase drug concentration at the target region, and reduce systemic tissue exposure.

Methods: A spatial and time dependent multi-compartment model was developed to describe the release of DOX from LTSL upon heating, using high intensity focused ultrasound (HIFU) in humans. To reach a larger area of elevated drug concentration, four different focal spots (~16 mm diameter), arranged in a square at 25 mm distance from each were heated sequentially. Three different heating regimens were compared, where each focal spot was heated for 30 s, 1 min, or 2 min with a maximum temperature of 50 °C. Transvascular transport of bioavailable and liposomal DOX, as well as diffusion within the extravascular extracellular space and cell uptake of free DOX were modeled. Additionally DOX concentration was modeled in systemic plasma and normal tissue compartment. Liposomal drug was administered as bolus injection with a dose of 0.7 mg/kg.

Results: Maximum average tumor tissue concentration was calculated in an area of ~50 x 50 mm. For 30 s heating periods, average tumor tissue concentration reached 3.3 ug/g at 1.3 h after HIFU. For 1 min and 2 min heating periods, average tumor tissue concentrations were 3.9 ug/g and 4.7 ug/g, respectively. Peak systemic plasma DOX concentration was in all cases 4.9 ug/g at 29s after bolus administration.

Conclusion: HIFU in combination with LTSL allows localized delivery of drugs with considerably higher local concentrations compared to standard chemotherapy. Computer models may facilitate optimization of drug delivery and heating regimen to maximize local tissue concentration.

Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-18

Thiel Cadaver as a Model for MRgFUS

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Background/Introduction: For centuries, cadavers have been used in medicine for research and educational purposes. The Thiel technique for soft-embalming of cadavers relies on a mixture of salt compounds and very low amounts of volatile formaldehyde to effect fixation of tissue with a number of unique properties. Thiel cadavers are already used in ultrasound-guided regional anesthesia of the cervical region for training purposes. We demonstrate here another promising use of Thiel cadavers in MRgFUS procedures, to study targeting the organs behind the ribcage, for focused ultrasound surgery (FUS) and targeted drug delivery.

Methods: Thiel soft-embalmed human cadavers were used to evaluate the accessibility and efficacy of FUS for various internal organs, such as liver, kidney, pancreas, etc. The experiments were conducted using the ExAblate 2100 system (InSightec, Haifa, Israel) and a 1.5 Tesla HDx MRI (GE, Milwaukee, USA). An ultrasonic phased array transducer with 1024 elements was positioned at the cadaver's right upper abdomen and the ribcage was identified using MRI imaging. Various MRI sequences were used for the imaging of the ribs: LAVA, FIESTA, FSPGR and EPI. A dedicated MATLAB program was written and used for determination of the ultrasonic elements that intersect with the ribcage and blocking its transmission. For every focal location, two sonications were performed for comparison (acoustic power of 25W for 120 sec, one with all elements in the transducer active and the other with elements intersecting with the ribcage inactive.) Fig. 1 depicts the output of the MATLAB program for a certain focal location behind cadaver's ribcage.

Results & Conclusions: The best visualization of ribs was achieved using EPI imaging (TE/TR=30/500 msec, BW=62 kHz). After the application of the MATLAB program, the number of transmitting elements was approximately 600 (~60% of the full array). Without the elements closure, the ribs in the pathway of the ultrasound are heated since the energy propagation to the focus is blocked due to the ribs' acoustic properties. The use of the Thiel embalmed human cadavers as an MRgFUS model is highly promising, due to the anatomical similarity and acoustical properties of Thiel cadavers. This particular embalming process allows using the same cadaver more than once, providing repeatability of experiments (lifetime of the Thiel cadaver is 3 years). Moreover, investigation is underway on perfusion of the vascular system and breathing motion by pressurizing the lungs.

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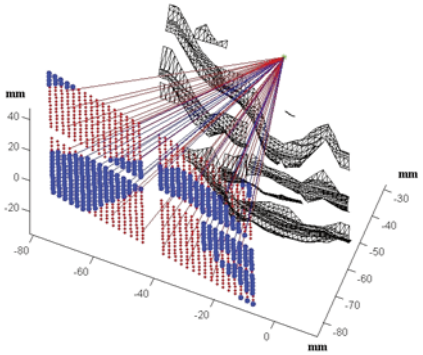

Session Topic: Targeted Drug Delivery
Presentation Type: Poster
P-19

Microbubble Radius and Ultrasound Frequency Effect Microbubble Mediated Drug Delivery Efficacy and Cell Viability

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Background/Introduction: In ultrasound (US) imaging it is well known that microbubble (MB) resonance is dependent on size and can affect contrast imaging. Much less is known about the dependency of drug delivery from microbubbles and of cell viability on MB size and frequency of insonation. As a platform to investigate these parameters we used a model of vascular smooth muscle cell (SMC) proliferation since this is the primary cell type responsible for restenosis following angioplasty. Our goal was to deliver an anti-proliferative drug, rapamycin, to SMCs via ultrasound (US) mediated delivery from MB carriers while minimizing cell death. We hypothesized that larger MBs would increase cell death, but also enhance drug delivery thereby reducing proliferation of SMCs.

Methods: Polydisperse lipid shelled MBs with rapamycin (0.4mg/ml) were formed by ultrasonic agitation, then washed to remove free drug prior to use. MBs were size sorted by centrifugal flotation into small (1.7 ± 0.5 μm) and large bubbles (3.7 ± 1.3 μm). Rat vascular SMCs were cultured in Opticells with serum-containing media and exposed to the large, small, or polydisperse MBs in combination with US (1MHz, 300 kPa, 50 cycle sinusoids at PRF= 100Hz, 8 seconds). Adherence, viability, and proliferation of cells were measured following insonation. Drug dose was kept constant by ensuring a surface area of 30 cm^2 per MB exposure. Destruction of MBs and viability of cells was quantified following insonation at 1, 2.25, 5, and 10 MHz at 500 kPa for 20 pulses each with 20 cycles.

Results & Conclusions: Following insonation, adherence of cells was significantly lower for larger MBs (12%) compared to smaller MBs (23%) or polydisperse MBs (25%). A fluorescent LIVE/DEAD assay differentiated live (green), dead (red), and permeabilized (green & red) cells over the width of the US beam. A significant reduction in live cells was observed between groups treated with large MBs (62% alive) compared to small MBs (78% alive). Conversely, applying small MBs significantly reduced cell death by half compared to large MBs (11% vs. 23%). The effective drug delivery width and region of cell death both decreased with MB radius. The permeable/dead cell ratio was 64% for large MBs and 98% for small MBs. With polydisperse rapamycin MBs we have previously shown that proliferation of SMCs is only reduced significantly when combined with ultrasound. Proliferation rates of cells were reduced further by large MBs compared to small MBs (66% vs. 56%). The size of MBs ruptured was inversely related to the frequency of US. 10 MHz insonation ruptured 47% of small MBs and 11% of large MBs whereas 2.25 MHz insonation ruptured 59% of small MBs and 74% of large MBs. Our results demonstrate the dependence of US mediated drug delivery and viability on MB radius and frequency of US. A better therapeutic ratio is achieved when using small MBs, but a greater reduction in proliferation is achieved with large MBs.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
IS-7

Comparison of MRI and Ultrasound Guidance for Focused Ultrasound

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Successful guidance and monitoring of High Intensity Focused Ultrasound (HIFU) treatments, whether by ultrasound (US), magnetic resonance (MR) or other imaging technique relies on a number of factors, including: i. accurate targeting, for placement of the focus; ii. monitoring of those physical events in tissue that correlate with the required tissue damage (e.g. temperature or bubble activity), and/or of changes in tissue properties that indicate successful cell destruction (e.g., stiffness or changes in attenuation); and iii. monitoring of sensitive tissue regions outside the target volume in order that adverse events may be avoided.

For the purposes of guiding HIFU treatments, US has a number of important advantages. These include its low cost, high spatial and temporal resolution, and its ability to monitor acoustic cavitation, changes in local blood flow and tissue stiffness. Diagnostic ultrasound's inability to penetrate bone and gas may be regarded as a disadvantage for HIFU treatments. However, while it may be a problem that tissue structures lying, for example, behind the ribs cannot readily be visualised, it is also true that a HIFU beam can generally not expose these regions without use of sophisticated delivery techniques such as time reversal. The creation of gas body collections in tissue (for example, from tissue water boiling) is readily visible on a diagnostic ultrasound image. Ultrasound thermometry techniques are still under development and are not as yet in clinical usage.

MR techniques are capable of providing high quality anatomical images, with bone and gas providing no obstacle to visibility. This is an essential pre-requisite for HIFU treatments in the brain. Thermal dose estimation and mapping can be provided in quasi-real time during a HIFU treatment. The size and cost of MR scanners may be a disadvantage to the more widespread use of HIFU. In space limited hospitals, the commitment to a dedicated scanner for HIFU procedures can be a problem, and the pressures of MR radiology provide time constraints on the availability of these systems for lengthy therapeutic treatments.

It seems clear that if HIFU is to find its place in cancer therapy, both US and MR guidance will find their own, complementary, niches in this area.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-1

Boiling and Cavitation During HIFU Exposures

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Background/Introduction: Under the typical acoustic intensities for which HIFU is applied to tissue, both thermal heating and cavitation is expected to occur. When the intensities are sufficient for nonlinear shock formation to occur, boiling can often also be initiated. The formation of bubbles, either from cavitation or boiling, can result in sufficient backscatter so as to modify the shape of the lesion developed to be different from what is expected. We have explored the formation of both boiling and cavitation in HIFU applications and find that they often occur without the user's knowledge. In this presentation, we examine the conditions under which boiling and cavitation can be formed and approaches for detection as well as for differentiation between these two phenomena.

Methods: Experiments have been undertaken in a variety of tissues and tissue phantoms; we particularly prefer transparent tissue mimicking materials that permit high speed photography. HIFU lesions were generated in these materials under acoustic exposures that have been reported in clinical applications. Imaging modalities include MR, ultrasound, and high-speed photography. The use of Passive Cavitation Detectors (PCDs) also provides much useful information on the occurrence of either cavitation or boiling or both.

Results & Conclusions: When ultrasound imaging is used to examine lesion formation, the appearance of hyperechogenicity often occurs. Although this hyperechogenicity has typically been associated with the occurrence of cavitation, we have determined that cavitation seldom generates enough backscatter to be detectable; rather, hyperechogenicity is more often associated with boiling. In particular, we have observed that when the HIFU intensity is sufficiently high that shock formation occurs, boiling can occur in milliseconds. When MR imaging is used, we have observed that boiling can occur even when the MR-generated thermometry registers temperatures on the order of 70 degrees C. Modeling, using weak shock theory, supports this occurrence of boiling. We believe that this apparent misrepresentation of the actual temperature results from spatial averaging over the volume of the MRI voxel.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-2

Targeting Mesenchymal Stem Cells (MSCs) Using Focused Ultrasound Exposures

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Background/Introduction: Stem cell therapy has shown promise in a various diseases; however, the ability of these cells to home to target tissue following intravascular injection has been limited in part due to insufficient release of chemoattractants from existing pathology. Focused ultrasound (FUS) exposures are presently being used for ablating a variety of tumor types in cancer treatment. Continuous FUS primarily generates thermal effects; pulsed FUS exposures can create mechanical effects that enhance tissue permeability for increasing drug and gene delivery. Our recent studies indicate that non-destructive pulsed FUS can generate local release of pro-inflammatory cytokines and chemo-attractants that should increase the homing of bone marrow stromal cells (MSCs) to target tissues. In this study, we investigated the potential of pulsed FUS for enhancing the migration of the superparamagnetic iron oxide nanoparticle (SPION) labeled MSCs in a kidney model, which was evaluated by MRI with histological correlation.

Methods: Human MSCs were obtained from the bone marrow of healthy donors, and expanded. The MSCs were then labeled with ferumoxides (FE), a SPION, and protamine enabling cells to be detected on T2* MRI as hypointense voxels. A custom image-guided FUS system was developed by mechanically coupling a 1 MHz FUS transducer and a portable ultrasound imaging system. In our study, the kidneys in mice (n=18) served as a model tissue, where one kidney was treated with pulsed (p) FUS and the other served as an internal control. For FUS exposures, 100 pulses were given in each of 6 (3x2) contiguous regions (2 mm spacing), using a pulse width of 200 ms, duty cycle of 5% and intensity of 4000 W/cm^2. MSCs were administered systemically 1 hour post treatment. Animals were euthanized on days 1, 3, and 7 post FUS, and kidneys were collected for ex-vivo MRI (7T) and histology. Kidneys were stained with H&E, PAS, and trichrome for morphology; Prussian Blue (PB) staining and anti-human mitochondria (AHM) immunohistochemistry (IHC) were used to detect the presence of MSCs. F4/80 IHC staining was used to detect the presence of macrophages.

Results & Conclusions: Ex-vivo MRI showed hypointense voxels on T2* weighted images in treated kidneys on day 1 and 3 that were not detected in untreated control kidneys. The presence of MSCs in glomeruli and peritubular regions in the pFUS treated kidneys was validated by PB staining and AHM IHC. F4/80+ macrophages were detected in FUS treated kidneys around tubules peaking at day 3; however macrophages were rarely PB + at this time point. Minor mechanical/structural changes were observed in kidneys treated with pFUS. Kidneys appeared to be clear of MSCs by day 7, coinciding with a reduction in macrophages. The study's results indicate that non-destructive pFUS exposures can non-invasively enhance the homing of MSCs to a target tissue. The mechanism for this increased homing is being investigated by molecular assays.

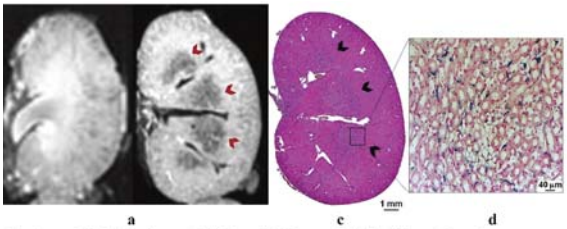

Fig.1: **a** - T2* MRI of control (left) and FUS treated (right) kidney. Hypointense areas (arrows) in treated kidney indicate presence of ferumoxide labeled MSCs; **b** - Prussian blue (PB) staining in section of treated kidney further verifies the presence of MSCs (arrows); **c** - PB positive MSCs visible in medulla of treated kidney.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-3

Volumetric MRgHIFU Rapid Ablation Under Automatic Temperature Control: Experimental Comparison of Different Sonication Patterns

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Background/Introduction: MRgHIFU is a non invasive method for thermal ablation with excellent visualization of the target and for near real time monitoring of temperature. Clinical application of MRgHIFU to localized cancers requires oncologic quality of ablation that may be obtained by volumetric sonication under automatic feedback control of the temperature. The aim of this work was to compare different sonication patterns for volumetric ablation in terms of thermal build up shape, stability and time efficiency.

Methods: In vitro tests were performed on degassed turkey muscle, and an *in vivo* study was conducted on 4 healthy sheep in the thigh muscle. All sonications were produced using a 256-element phased array HIFU transducer operating at 1 MHz (Imasonic, France) positioned by a XZ mechanical system and driven by a multi-channel generator (IGT, France). A clinical whole body MRI scanner (Magnetom Trio a Tim System, Siemens, Germany) was used to perform the study, implementing a GRE-EPI sequence for rapid multi-planar thermometry (TE=8.9ms, TR=161ms, voxel=1x1x5mm3). Heat deposition was monitored in 5 different planes (3 coronal, 1 transversal and 1 sagittal aligned with the HIFU beam axis). A spatio-temporal multi-input, multi-output, non-linear controller of temperature was specifically designed for iterated sonication of a prescribed pattern of foci. Different sonication patterns were experimentally compared: a) line versus circles where the line's length and the circle diameter were set at 4, 8, 12, 16 and 20 mm; b) line versus disk, setting the length of the line equal to the outer circle diameter. For each couple of compared patterns, the sonications were implemented with the same number of foci and performed for the same total duration (duration[s] = 20* pattern_size[mm]). The same target elevation of temperature along the sonication pattern 17.5° C was defined for each experiment.

Results & Conclusions: Line and circular trajectory of the same size have led to similar ablation speed. However, the results in case of the circles and disk patterns clearly showed the tendency of the thermal build-up to drift downwards the HIFU device approx. 30% of the outer circle diameter for both in vitro and *in vivo* tests. For the line sonication, the temperature elevation remains longitudinally symmetrical with respect to the prescribed position of focal plane. The figure below shows the temperature elevation maps measured in 2 orthogonal planes at the end of HIFU in vitro process for a line and a circle (L=D=16mm) under automatic feedback control. Rapid volumetric HIFU ablations under continuous sonication are not recommended by using circles or disk trajectories because of the asymmetric build-up and the significant thermal drift downwards the near field. Combinations of parallel lines trajectories appear to provide the best results for complex treatments.

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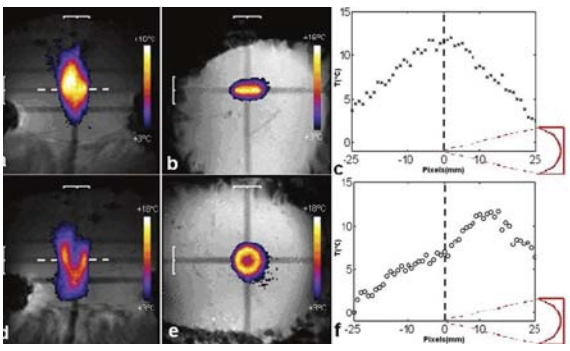

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-4

A Model of an Equivalent Focused Piston Source to Characterize Nonlinear Ultrasound Fields of 2D HIFU Arrays

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Background/Introduction: A current trend in HIFU medical technologies is to use 2D focused phased arrays that enable electronic steering of the focus and formation of patterns of multiple foci. Simultaneously, in many HIFU applications, the acoustic intensity in situ can reach thousands of W/cm2, which causes amplitude-dependent nonlinear propagation effects. Acoustic characterization of array fields, particularly at high intensity, is therefore important for the development of regulatory standards for clinical HIFU devices. However, measuring all the permutations of an array in water is time consuming and difficult to extrapolate to tissue. Numerical modeling works for both water and tissue, but simulating the full 3D nonlinear field of a 2D array is very intensive computationally. In this work, to accelerate calculation, we develop a short-cut to include nonlinear effects in the focal region of an array using a simplified method.

Methods: Two modeling approaches are compared for a 1.2-MHz, 256-element phased array with 13-cm aperture, 12-cm focal length, and intensity at the elements of up to 10 W/cm^2. Our first model is the full 3D solution of the nonlinear wave equation with a boundary condition defined at the elements of the array. This rigorous model can accurately simulate the entire nonlinear field of the array. Our second model solves the KZK equation and defines a representative boundary condition as a single focused piston source. The effective aperture and initial pressure at the source are set by matching linear simulations of the two models in the focal region of the array following the method proposed for characterization of single-element HIFU transducers [Canney *et al.,* JASA, 124(4), 2008].

Results & Conclusions: Simulations of nonlinear pressure field of the array in water are performed using the two models for low, moderate, and high power source outputs. Axial peak pressure distributions and focal waveforms are compared. It is shown that in the focal region of the array, the simulation results obtained with the simplified model agree well with those obtained with the full diffraction model up to high intensities when shocks are present in the focal waveform. This result implies that even complex array geometries might be approximated by specific conditions on a single focused element. Thus, outputs might be calculated for a range of single element conditions and then used as a look-up table for the output of an array without further calculation. Detailed modeling results have been published recently for a piston focused source with parameters and power range typical for HIFU sources [Bessonova *et al.,* Acoust. Phys., 55(4-5), 2009]. These results can be implemented in practice for users of HIFU arrays to evaluate the importance of nonlinear effects under specific clinical conditions.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-5

Non-invasive Determination of Patient-specific Tissue Acoustic Properties for MRgFUS

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Background/Introduction: Numerical beam simulation techniques used in MR-guided focused ultrasound surgery (MRgFUS) for patient treatment planning rely on accurate tissue properties in order to predict the location and shape of the beam's focus. Due to the large variations in the reported values of acoustic properties (for example, a four-fold variation in the absorption coefficient) and changes in tissue properties during treatment, using table estimates of tissue acoustic properties can only predict an approximation of the beam aberrations caused by tissue inhomogeneities. In this paper we present an inverse parameter estimation technique that non-invasively determines patient-specific tissue acoustic properties (speed of sound and attenuation) using a pre-treatment low-level ultrasound heating pulse and MRI temperature monitoring.

Methods: Our novel hybrid angular spectrum (HAS) beam propagation technique, which extends the traditional angular spectrum technique to inhomogeneous media, is used as the forward model. The use of the fast Fourier transform algorithm and the inverse fast Fourier transform algorithm makes this a rapid technique and ideal for an inverse parameter estimation problem that requires many iterations of the forward problem. We used an iterative parameter estimation technique that minimizes the difference between the experimentally determined specific absorption rate (SAR) distribution (using MRI temperature maps) and the SAR pattern found with the HAS technique (starting with initial values from table estimates of ultrasound tissue properties). The experimental SAR pattern was obtained from the initial rate of temperature increase following a step change in applied power. The estimation technique gave the final ultrasound tissue properties (speed of sound and absorption coefficient) of the media.

Results & Conclusions: The acoustic properties of homogeneous phantoms and ex-vivo meat samples determined by using this iterative parameter estimation technique were compared to independent measurements made using a traditional in-vitro through-transmission substitution technique. The inverse parameter estimation technique resulted in accurate ultrasound property values (within 5 % of those obtained by the through-transmission method). Following these validation experiments, the technique was used to measure tissue acoustic properties in in-vivo experiments and measure changes in tissue acoustic properties after MRgFUS treatment. This technique can be used to non-invasively determine accurate patient-specific acoustic properties for patient treatment planning in MRgFUS.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-6

High-intensity Focused Ultrasound Ablation Effect on Tumor Growth and the Migration of Endothelial Progenitor Cells

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Background/Introduction: To increase the use and effectiveness of HIFU in the treatment of various solid cancers, it is necessary to understand how a tumor remaining viable after ablation responds and repairs. Angiogenesis is critical for tumor recurrence, and therefore, we are studying the migration pattern of endothelial progenitor cells (EPCs), one component of angiogenesis, after local thermal ablation of tumors in mice. Tumor cells sublethally ablated may release a unique set of chemokines in an attempt to attract cells to repair and regrow the tumor. We hypothesize that one target of those chemokines is EPCs in the blood and bone marrow. The location and mechanisms by which these cells are recruited to the tumor may be distinct from other methods of thermal therapy which suggests that specific targets to improve HIFU ablation outcomes may be identified.

Methods: Immunocompromised mice were injected with FSaII tumor cells in the right rear leg. Tumor ablations were performed on 8 mm diameter tumors using a spherically-focused ultrasound applicator specially designed for heating small animals inside the bore of a 7T magnet with dual laser targeting for accurate placement of the lesion. The transducer was run at 40W with a variable duty cycle to control heating. The tumors were ablated at an average peak temperature of 60° C for 1.5 min. One group of mice was immediately injected IV with near infrared emitting indocyanine green (ICG)-labeled EPCs, while the other group was injected with EPCs labeled with a stable in situ dye (PKH). The mice injected with ICG-labeled EPC were optically imaged at various time points up to 72 hours. These images were then compared to those of untreated tumors to observe the migration patterns of EPC in mice that had received HIFU ablation. Tumor and tissue samples were taken from the mice injected with PKH labeled EPC cells 24 hours post ablation and frozen for histological examination of EPC incorporation into tumor and various normal tissues.

Results & Conclusions: The dual-laser targeting of the HIFU transducer allowed for accurate placement of the focus, and therefore accurate and reproducible tumor ablations. We routinely ablated approximately 50% of tumor tissue, leaving the other 50% peripheral tumor tissue viable. We were able to detect an increased amount of ICG signal in the tumor that received HIFU ablation, when compared to controls. Histological examination revealed the presence of EPC cells in the tumor after treatment with HIFU, while the control showed no signs of EPC presence. We are continuing molecular analysis of chemokines and their receptors in tumor and normal tissues post-ablation to further understand the mechanism of action for these results. It appears that HIFU ablation may induce sub-lethally ablated tumor cells to recruit endothelial progenitor cells.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-7

Integration of MR Compatible Robotic Arm with MRgFUS

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Background/Introduction: MR guided Focused Ultrasound Surgery has recently shown to be successful in palliative treatment of bone metastases. ExAblate 2100 Conformal Bone System (InSightec, Israel) is an MRgFUS device with detachable transducer, especially developed for palliative therapy of bone lesions. The manual positioning of the ExAblate 2100 transducer requires a considerable amount of time per treatment location, moreover for some anatomical locations fixation of the transducer in the targeted zone is very challenging. In order to facilitate and speed up the positioning of the transducer, we have combined the ExAblate system with the MR compatible Innomotion robotic arm (Innomotion, Germany). This pneumatically driven robot has been designed for percutaneous interventions, such as biopsies, drainage, and insertion of energetic probes for tumor ablation. The purpose of this project is two-fold: we aim to develop a robotic-assisted positioning of MRgFUS transducer; secondly we intend to integrate the tracking technology with the robotic arm for its automatic alignment with the MR images and vice versa.

Methods: Our experiments are being conducted using ExAblate 2100 Conformal Bone System, attached to the Innomotion robotic arm operating in 1.5T HDx MRI (GE, Milwaukee, USA). The Innomotion robotic arm has been mounted to the ExAblate patient table on specially designed rails, and the conformal transducer has been attached to the robotic arm, using built in-house disk shaped connector, centered at the front end effector of the robot. The MRI tracking technique has been applied with four active micro coil trackers to determine 3D location for different robot positions and automatic alignment with the MRI slice orientation. MR guided positioning and sonication of liver and kidney on two Thiel soft embalmed human cadavers (male and female) have been performed to compare manual and robotic positioning. In addition MR guided core biopsy needle positioning was carried out with the same setup.

Results & Conclusions: Automatic determination of robotic arm location makes MR guided biopsy (or other intervention) procedure more accurate and also speeds up the process. Following the biopsy, robotic arm has demonstrated precise and stable positioning of the ultrasonic transducer in the same session. The acoustic coupling remained intact throughout the entire procedure. There is no change in sonication flow; furthermore, the robotic positioning can save up to 15 minutes for every location, compared to manual positioning. MR guided robotic-assisted positioning of MRgFUS device is feasible and saves considerable time, allowing treatment of more lesions in a single session. The integration of two different technologies—MR-guided biopsy and MR guided ablation raises the potential of a "one stop shop" - diagnosis and therapy.

Acknowledgements (Funding): This work is supported by the EU FBP7 Industrial Academia Partnership Pathway IAPP and the College of Life Sciences at the University of Dundee.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-8

An Enhanced System for MRgFUS Treatment of Uterine Fibroids

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Background/Introduction: Magnetic Resonance guided focused ultrasound (MRgFUS) for the non invasive treatment of uterine fibroids has been used in our hospital in a clinical setting since 2003. Although MRgFUS has proven to be a safe, effective and non invasive alternative for uterine fibroid patients, it still has several drawbacks which can limit the number and type of patients suitable for treatment. In this paper, we present a new and advanced MRgFUS system that seems to overcome many previously encountered obstacles to treatment.

Methods: During this on-going study we use the "advanced ExAblate system" which includes four main new features: an additional degree of freedom for the transducer (elevation in the anterior posterior direction) which can direct the transducer closer to the tumor; the ability to close part of the ultrasound transducer elements in order to shape the beam and thus avoid potentially hazardous areas; the ability to perform elongated sonications with multiple sub-sonications; and an automatic optimal treatment planner which takes into account all degrees of freedom. Treatments are performed in the Sheba Medical Center, Tel Hashomer, Israel, using the advanced ExAblate system (InSightec, Haifa) incorporated on the GE SIGNA 1.5T HDX MRI (Milwaukee). All research treatments are performed under hospital IRB approval and after signed informed consents. Ultimately, the study will include at least ten patients (additional commercial patients will be also included in the presentation).

Results & Conclusions: In this work-in-progress we have already treated 4 patients (5 treatments). Even during these early cases, we have noted that the additional degree of freedom of the transducer enabled the use of higher energy sonications. Further, the ability to close part of the ultrasound elements enabled us to avoid bowel loops, pubic bone and scars, thus allowing treatments that were impossible with the previous system. The automatic planner and large elongated sonications allowed fast and more organized treatments of large fibroids. In addition, the subset of patients with iso or hyper-intense fibroids on T2w images that posed challenges with the previous system were more responsive to the new system. These results can be explained by the fact that the new system uses higher amount of energies per sonication than previously (in average ~4000J/sonication, approximately 1.5 times more than the previous system). We encountered in two cases some sensitivity of the uterus for a few days after treatment. No significant adverse events accompanied the improved treatment outcome that we observed and the increased sonication energy. Conclusions: The new enhanced MRg-FUS system seems to allow better patient selection, increase treatment volumes, enable better treatments of hyperintense fibroids and maintain the known safety of MRgFUS.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Oral
T&B-9

Standards for Quality Assurance and Quality Management in Image Guided FUS

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Background/Introduction: Safely introducing image-guided FUS into the clinic will require significant attention to quality management in terms of the startup and ongoing operation of the equipment, procedures used to deliver therapies, and standards for reporting treatments and outcomes. Because many of the problems and skills required to deliver FUS are directly analogous to those required to deliver radiosurgery and radiation therapy, the experience of the medical physicist may be helpful in guiding the quality management aspects of FUS development.

Methods: This presentation will review the quality management philosophy adopted by the medical physics community for image-guided radiation therapy and radiosurgery, including standards for the acceptance, commissioning, and periodic QA of equipment; patient-specific QA of the image-guidance and treatment delivery process; and formal fault-analysis and continuous process improvement techniques. It will draw parallels and distinctions to the current state of quality management in clinical FUS systems and suggest areas of research that may help standardize FUS QA practices across vendor and institutional boundaries. This would in turn help to demonstrate to the public and to regulatory agencies that FUS can be adequately specified and delivered in a repeatable manner with a high degree of confidence.

Results & Conclusions: Because of the disruptive potential of the technology and because many of the skills required to successfully build and operate a FUS program are skills that traditionally fall under the medical physicist's domain, an emerging technologies task group (TG 193), under the auspices of the American Association of Physicists in Medicine (AAPM), was approved to help to define the role of the medical physicist with respect to this new technology. The presentation will conclude with an overview of the task group charges, current status, and areas of future focus.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-20

Design of Prototype Software for 3D Simulation of Ultrasound Beams in Inhomogeneous Media for Development of MRgFUS Applications

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Background/Introduction: We present a software prototype developed to model the acoustic and thermal fields in MRgFUS applications. It includes quantification of the ultrasound field amplitude, intensity and temperature in focal sonication spots. Comparison between simulation results and real MRgFUS ultrasound fields is the subject of on-going research at our site, the only MRgFUS site in Spain, located at the Scientific & Technological Park Cartuja 93 of Seville. Current available MRgFUS applications include treatment of uterine fibroids and palliative treatment of pain in bone metastases.

Methods: The computer program has been developed using Matlab R2008 (The Mathworks Inc., USA). Integral solutions of the ultrasound fields are programmed using the Rectangular Radiator Method adapted for inhomogeneous media and a 2D phased array transducer model. The thermal dose is obtained following the Pennes Bioheat Model. Object programming is employed. Simulations for evaluation are defined by a simplified user interface. Inhomogeneous media are modeled and defined by boundaries among space regions with different acoustic properties. Available equipment is an ExAblate 2000 system (InSightec Ltd, Israel) in a 1.5T magnetic resonance (GE Healthcare, USA). R&D activities are carried out in the frame of a Laboratory of Non Invasive Technologies for Tumor Treatment, established in collaboration between the author's institutions. Clinical activities are developed at Iberian Medical Institute-Instituto Cartuja and the scientific and technological duties at the Engineering School of the University of Seville.

Results & Conclusions: Developed software has been applied to modeling the ultrasound fields generated by NxN-element piezoelectric transducers (5x5, 10x10, 50x50) and to simulate propagation and focusing of waves. It includes the effects of refraction and diffraction on the propagation in a 3D space with inhomogeneous media. An inverse algorithm has been developed to determine the amplitude and phase required at each individual emitter to obtain a desired "point" focal spot of ellipsoidal shape. It has been applied to evaluate the field amplitude, intensity and temperature at the focal spot at each point of the converging and diverging cones (incident upon and emerging from the focal spot) in a simplified simulation of a medical thermal ablation. This program may be used to evaluate the field amplitude, intensity and temperature in the sonicated volume of MRgFUS, including beam steering and focusing. It defines a potentially useful tool for further development in expanding applications.

Acknowledgements (Funding): This work is partially based on the Dissertation presented by Dr. Rafael Coronado-Santos to the MSc in Biomedical Engineering at Imperial College (London, 2009) supervised by Dr. Robert J. Dickinson and Prof. Dr. Emilio Gómez-González. Work partially funded by a R&D Project by the Spanish National Center for Industrial and Technological Development, (CDTI), Ministry of Innovation and Science, Spain, 2009/10.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-21

Non-invasive Estimation of Tissue Thermal Conductivity from Spatio-temporal Temperature Profiles of Volumetric Sonications Using Magnetic Resonance Imaging Guided High Intensity Focused Ultrasound (MR-HIFU) Therapy: Initial Experience in a Pig Model

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Background/Introduction: MR-HIFU is clinically used for non-invasive ablation of tumor tissue. The local tissue thermal properties determine the temperature distribution during and following sonication. Recently a method for estimating thermal conductivity based on the spatio-temporal temperature distribution was shown [1]. Here we test the feasibility of non-invasive determination of the thermal conductivity *in vivo* in a pig model.

Methods: *Animal Care:* The study was approved by the Institutional Animal Care and Use Committee. The animals were sedated during the procedure, and sacrificed immediately thereafter under Institutional guidelines. *MR-HIFU procedure:* All experiments were done on a Philips 1.5T MR scanner (Achieva) with a 256Ch spherical shell HIFU transducer (freq range 1.2-1.4 MHz), and an integrated receiver coil. The temperature evolution after volumetric sonication (n=10) was recorded in real-time using a multi-shot echo planar imaging technique [3]. Three slices (at xy plane) bisected the focal ellipsoid coronally, and one sagittal (at z plane) slice was positioned to visualize the long axis of the ellipsoid. *Estimation of Thermal Conductivity:* The spatio-temporal temperature evolution following heating is modeled by a Gaussian distribution and thermal conductivity is calculated based on BHT model [2]. In Equations (1) and (2), σ_{0xy} and σ_{0z} represent the standard deviation of the spatio-temporal spread in the coronal and sagittal planes respectively at the end of the sonication. D represents thermal diffusivity, ω_b perfusion rate, T_0 peak temperature, ρ (1060 Kg/m3) tissue density, and c (3600 J/Kg*K) specific heat. Spatial temperature distribution at a given time on the coronal slice was fitted to a 2D Gaussian (Eq.1) to determine $\sigma^2_{xy}(t)$ using MATLAB™. The rate of change of σ^2_{xy} over time yields thermal diffusivity D and thermal conductivity k (Eq.2).

Results & Conclusions: 10 cells with diameter of 4mm, 8mm, 12mm, 16mm were successfully treated at different depths (3.7cm-5.4cm) on the thigh muscle of five pigs (50-65Kg) as described in [3]. Fig.1A depicts the spatial temperature distribution over an (75*75mm^2) area centered at the focus of the 8mm ultrasound cell, right after the heating is stopped (27.72s). The Gaussian surface fit over the temperature in this area is shown in Fig.1B. The time course of the Gaussian variance in coronal plane during the cooling period is shown in Fig. 1C. The thermal conductivity for the pig muscle estimated from the ten sonications (0.54±0.05 W/mK) is consistent with the reported values. Our preliminary results demonstrate the feasibility of non-invasive measurement of thermal conductivity of muscle *in vivo* using MR-HIFU ablations.

Acknowledgements (Funding): This study was partly funded by Ronald MacDonald fund at St. Luke's Episcopal Hospital, and research support from Philips. References: 1. Dragonu I *et al.* NMR in Biomedicine, 22, 843, 2009. 2. Pennes HH J. Appl. Physiol. 1, 93, 1948. 3. Zhang J *et al.* ISMRM, #4131, 2010.

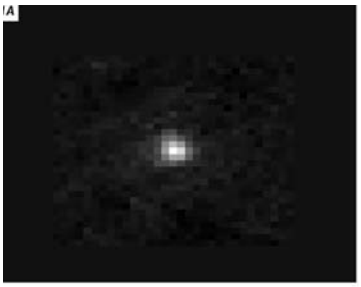

Fig.1A

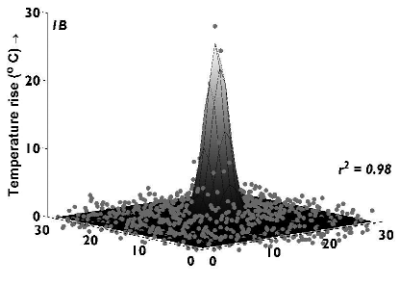

Fig.1B

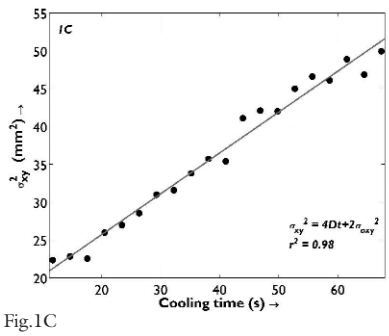

Fig.1C

$$T(\vec{r},t) = T_0 \frac{\sigma_{0xy}^2}{\sigma_{0xy}^2 + 2Dt}\sqrt{\frac{\sigma_{0z}^2}{\sigma_{0z}^2 + 2Dt}}\exp\left[-\frac{x^2+y^2}{2\sigma_{0xy}^2 + 4Dt}\right] \times \exp\left[-\frac{z^2}{2\sigma_{0z}^2 + 4Dt}\right]\exp[-w_b t] \quad (1)$$

$$\frac{\partial(\sigma_{xy}^2)}{\partial t} = \frac{\partial(2\sigma_{0xy}^2 + 4Dt)}{\partial t} = 4D = \frac{4k}{\rho c} \quad (2)$$

Fig.1D

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-22

Acoustic Measurements and Holographic Reconstruction of the Philips MR-guided HIFU Source

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Background/Introduction: Clinical HIFU systems are designed to deliver specified acoustic intensities to desired target sites. Many clinical systems utilize arrays comprising many transducer elements to provide the ability to adjust the focal location relative to the transducer itself. Compared to single-element transducers, arrays involve additional complexity in terms of the hardware and the resulting acoustic field. This complexity can lead to undesirable performance characteristics, including near-field hot spots that cause skin burns and other collateral damage away from the focus. To characterize the performance of a transducer array, a critical first step is to determine how the surfaces of array elements vibrate. Individual elements may behave differently and/or influence one another, while the array structure may also permit non-ideal vibrations such as surface waves. Using pressure measurements on a surface near the transducer, a holographic projection can be used to construct relative vibrations of the transducer surface. Here, this technique is applied to a clinical HIFU array.

Methods: A clinical MR-HIFU system (Sonalleve 3.0T, Philips Healthcare) was programmed to generate triggered pulses at 25 W acoustic power in 'research mode'. The MR-HIFU patient table was located outside the magnet room. A cylindrical test tank (184 mm ID, 300 mm height) was coupled to the table above the transducer array and filled with degassed water. An automated 3D positioning system was placed on the patient table above the water tank. Using this arrangement, hydrophone measurements were acquired in a 2D scan plane approximately perpendicular to the acoustic axis of the array, 40 mm proximal to the array's focus. The scan was executed overnight, using a step size of 0.6 mm and covering a square 86.4 mm × 86.4 mm. Measured pressure waveforms were subsequently analyzed and used to mathematically back-propagate the acoustic field for reconstructing vibration velocities on the surface of the array.

Results & Conclusions: The holographic reconstruction enables identification of individual array elements and reveals their efficiencies. Because the acoustic propagation path included regions of oil (surrounding the transducer) and water (in the test tank), some refraction did occur at the oil/water interface. Accordingly, the reconstruction shows a transducer aperture of about 133 mm, which is somewhat larger than the physical aperture of 127.8 mm. Future reconstructions may be improved by accounting for this refraction and making a more accurate assessment of any misalignment in perpendicularity between the scan plane and the acoustic axis. Holography can be used to estimate a boundary condition for simulating the acoustic output of the array. Thus, hydrophone measurements in water combined with numerical simulations in both water and tissue provide a means to predict and optimize the sound field to which patients are exposed.

Acknowledgements (Funding): This work was supported by grants NSBRI SMST001601 and NIH EB007643.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-23

Proton Resonance Frequency MRI Shows Focal Spot Shifts due to Interfaces During MR-HIFU Treatment

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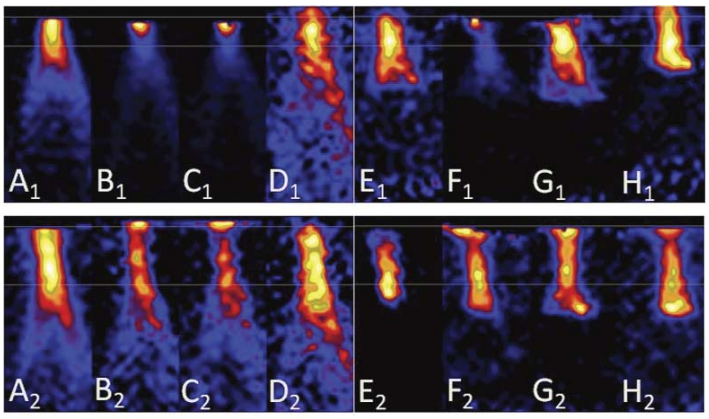
Background/Introduction: MR-guided HIFU is frequently used for ablative procedures where the goal is destruction of a target tissue. Investigating shifts in focal spot, and dose distribution patterns as a result of distal surfaces provides important information for treatment planning. This work considers the impact of reflections from air, acrylic (modeling bone), rubber, and a gel pad when propagated through both a thermal phantom, and excised muscle tissues. The objective of this study was to analyze the effect of different tissue interfaces on the HIFU heating pattern.

Methods: An integrated MR-HIFU platform (Sonavelle 1.5T, Philips Healthcare) was used for sonications and MR guidance. Images were acquired using a 3D T2-w Turbo spin echo sequence (TR/TE = 1000/130 msec, voxel size = 1.2 mm) for treatment planning. Dynamic temperature monitoring based on changes in proton resonance frequency was performed using 2D fast field echo (FFE) EPI (slice thickness 7mm, in plane resolution 1.25mm, temporal resolution 2.9 s). A thermal phantom (vsound = 1536 m/sec, attn coeff = 0.5 dB/cm at 1.2 MHz and 23 degrees C), approximately 8 cm tall, was coupled to the treatment table's mylar membrane using distilled water, and volumetric sonications (4 mm treatment cell diameter) were defined at each of three positions: 4 cm, 2 cm, and 1 cm below the interface. A piece of porcine muscle tissue, approximately 3 cm thick was suspended in a degassed water bath coupled to the treatment table. Volumetric sonications were defined at 1 and 2 cm below the distal surface. Each treatment cell location was sonicated for 20 s (Pac=50W, f=1.195 MHz). Sonications were performed for four interface materials: air, acrylic (to model bone), rubber, and a non-absorbing gel pad used to mimic water for acoustically coupling the patient to the transducer. Data were processed and analyzed using software written in IDL.

Results & Conclusions: The figure shows the results for all materials in the phantom: air, A; acrylic, B; rubber, C; gelpad, D and in the tissue: air, E; acrylic, F; rubber, G; gelpad, H at both a 1 cm depth in the panels labeled with a subscript 1, and at 2 cm depth labeled 2. The center of the focal spot was shifted towards the distal interface in the phantom study for all interface materials at 2 cm, and in some cases heating at the surface was present. The largest shift was seen in the air interface. At a depth of 1 cm heating occurs at the interface. The largest displacement of the focal spot center was observed for the acrylic interface. For the *ex vivo* sample, at 2 cm the focal spots are distorted, but not uniformly shifted towards the interface boundary. Surface heating occurs for all materials except air. At 1 cm below the interface, all focal spots are shifted, with the most extreme shift again occurring in acrylic. Future work will compare experimental data with simulations and investigate the effect of distal surfaces using *in vivo* animal studies.

Acknowledgements (Funding): This work was supported by Philips and R33CA100996-02/CA/NCI.



Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-24

SonoKnife: A Line-Focused Ultrasound System

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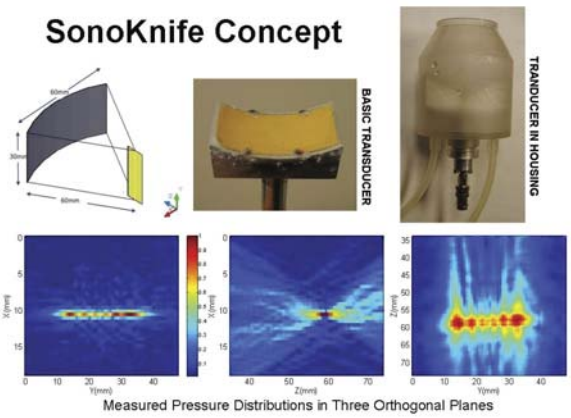
Background/Introduction: The SonoKnife is a new line-focused ultrasound device concept originally motivated for non-invasive thermal ablation of advanced HNSCC and positive lymph nodes. Thermal ablation may reduce the need for surgery while enhancing the therapeutic benefits of conventional chemoradiation. The basic SonoKnife radiator is a cylindrical section ultrasonic transducer (single element or array). Line-focusing may have advantages over the more common point-focusing approach. In particular, a line-focused radiator produces lower peak acoustic intensities compared to an equivalent area/power spherically focused radiator, thus decreasing the likelihood of nonlinear propagation and cavitation. Another potential advantage may be faster ablation of tumors by scanning the acoustic edge. Therefore, a line-focused device may ameliorate one of the main drawbacks of a small focus, namely, a significant reduction in treatment times.

Methods: Numerical simulations were performed to: 1) Characterize the acoustic edge as a function of size, f-number, frequency, depth of line-focus, and thickness of coupling bolus; and 2) Study thermal fields generated by acoustic edge scanning. Pressure fields were computed using open-source FOCUS (Fast Object-oriented C++ Ultrasound Simulator). In addition, the angular spectrum method was used to speed up 3D computations. These acoustic and thermal models are being integrated into an image-based treatment planning system. Prototypes were constructed and laboratory measurements performed. Dimensions were: radius of curvature = 60 mm, chord length = 60 mm and width = 30 mm, and frequency = 3 MHz. Sonication parameters are being determined for animal experimentation.

Results & Conclusions: The acoustic edge was defined as the volume within the 6 dB iso-intensity surface. The shape, dimensions and depth of the acoustic edge as a function of design parameters will be discussed. Both simulations and measurements showed the SonoKnife generates a well-defined and sharp acoustic edge whose dimensions were strongly determined by the transducer's geometry. Assuming 3 W/cm2, temperatures > 60°C were induced in <20 s for a stationary transducer. Field parameters from a SonoKnife were compared to those generated by a spherically focused transducer of equivalent area and power. The SonoKnife's peak pressure and intensity were about 20 times lower than for the point-focus radiator. Simulations showed that scanning the acoustic edge to "carve out" tissue is feasible. Suitable scanning speeds to cover reasonably sized tumors are being investigated. Numerical and laboratory results to date support the feasibility of thermal ablation with a SonoKnife. For a more comprehensive characterization, tissue heterogeneities and nonlinear effects will be taken into account and transient thermal simulation studies will be completed.

Acknowledgements (Funding): Funded by NCI grant RC1 CA147697. We acknowledge general research support by the Central Arkansas Radiation Therapy Institute.



Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-25

Fat Temperature Imaging based upon T1 of Fatty Acid Components using Multiple Flip Angle Multipoint Dixon Acquisitions

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Background/Introduction: Noninvasive and quantitative fat temperature imaging technique is desired for HIFU of the breast. In vitro spectroscopic measurements at 11T demonstrated that the relationship between temperature and T1 of CH2 or CH3 proton is linear and reproducible(1). Since the two components have different temperature coefficients (1), separate observation of these components and quantification of T1 of the component is necessary. In the present study, the fat temperature imaging technique (2) based on a multiple flip angle, multipoint Dixon acquisitions with a least square estimation scheme was examined from a view point of echo time optimization.

Methods: A SPGR-based sequence was designed to evaluate T1 of CH2 and CH3. In the first shot, echoes with different TE's were acquired at a certain flip angle to obtain real and imaginary parts of water, CH2 and CH3 signals using the multipoint Dixon scheme(3). In the following shots, similar echo sets were obtained with different flip angles. The CH2 and CH3 images with different flip angles were then used to derive T1 maps of these components(4). The T1 maps were then converted to temperature maps based on the temperature coefficients obtained previously(1). In order to minimize the component separation error induced by the thermal shift of the water resonance, a set of simulations was performed using a numerical phantom(5). Phantom experiments with two mayonnaise tubes immersed in Gd-doped water were also conducted. One of the mayonnaise tubes was heated up to 55°C, while the other tube was kept at room temperature. The following parameters were used for acquisition; TR, 36 ms, TE, nTE0 with n = 1, 2, · · ·, 16 and TE0 = 1.00, 1.05, · · ·, 1.30 ms; flip angles, 20, 50 and 70 degrees; matrix, 64 × 64; SENSE factor, 2. The acquisitions were repeated in the cooling period of the heated mayonnaise. The error in the separation of the proton components and in the T1 calculation were evaluated.

Results & Conclusions: The numerical simulations demonstrated that the error in the signal estimation can be minimized for a wide range of temperature even with a fixed echo space, TE0, if selected carefully; for temperature around 43°C, TE0 = 1.15 ms yielded smallest error in the CH2 signal estimation. This result was supported also by the experiment. In conclusion, fat temperature imaging would be available based on the proposed multiple Dixon and multiple flip angle technique with an appropriate choice of echo spacing. References (1) Kuroda K *et al.* Magn Reson Med Sci, under review. (2) Kuroda K *et al.* Proc ISMRM-ESMRMB 2010: p. 1818. (3) Reeder SB *et al.* Magn Reson Med 2004;51:35-45. (4) Deichmann R *et al.* J Magn Reson 1992;96:608-612. (5) Lam MK *et al.* Proc ISMRM-ESMRMB 2010: p. 4128.

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Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-26

Initial Results of a Discrete Path Model-Reference Controller for Reducing MRgFUS Treatment Times and Ensuring Treatment Safety

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Background/Introduction: Magnetic Resonance Temperature Imaging (MRTI) makes possible a completely noninvasive treatment modality that can be computer controlled. Previous control strategies have concentrated on MRTI based feedback; however, significant unmet needs exist, especially in realizing fast, practical, safe and effective treatments. To achieve these goals, the controller must adapt based on previous data and anticipate the effects of future heating pulses. A new discrete path model-reference controller (DPMRC) has been implemented which reduces treatment time by optimizing the individual pulse heating and cooling times while guaranteeing treatment safety. The clinician retains full supervisory control while leveraging a computer's ability to rapidly monitor and adjust many parameters simultaneously.

Methods: The controller's overall goal is to minimize the treatment time while guaranteeing delivery of a desired dose to the tumor and the safety of healthy tissue. The clinician subdivides the treatment volume into multiple sites based on MR images during pre-treatment planning, and a trajectory of successive focal zone heating locations is determined. Each treatment site is centered on the focal spot of the US beam and is composed of one or more voxels. The clinician identifies a target dose for each treatment site and either a temperature or a thermal dose limit for the constraint voxels. Low-power heating pulses are used to identify exponential heating and cooling model parameters for each control voxel. This simple and fast model is used to predict when to shut off the beam such that the target thermal dose will be delivered to the treatment site after all cooling has occurred. During treatments, MR temperature measurements are acquired, constraint voxels are monitored for safety, and control voxel predictions are updated.

Results & Conclusions: The DPMRC has been tested experimentally and successfully delivers a target thermal dose to the treatment volume while safeguarding the constraint voxels. The current controller has been implemented and tested with the heating/cooling pulse time optimization feature and anticipates the dose delivered during the period following each individual pulse. The controller runs in real-time and does not require exotic hardware. While seemingly simple, the exponential model has so far proved adequate, and will facilitate many improvements not possible with complicated models. Initial results indicate that this control strategy will be easily deployable in the clinic and will be effective in reducing treatment times while ensuring patient safety. Yet to be implemented controller features include real-time anticipation of dose delivered by future pulses, and the ability to adapt to changing treatment parameters.

Acknowledgements (Funding): This work is supported by the Mark H. Huntsman Endowed chair, NIH grants R01 CA87785 and R01 CA134599, The Margolis Foundation, NSF IGERT Award# 0654414, and the Focused Ultrasound Surgery Foundation.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-27

A Novel Concept of MR-compatible Phased Array HIFU Transducer Dedicated to Abdominal Thermo-ablation

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Background/Introduction: HIFU ablation in abdominal organs requires a large ballistic coverage due to respiratory motion and a high level of delivered energy due to high perfusion. Our aim was to design and implement a randomized, large scale, MR-compliant extra-corporeal phased array HIFU device providing both improved electronic steering capability and robustness against transducer heating. New principles for the elements positioning and for the electronic driving system were investigated in order to maximize the steering range under the constraints of the MR environment. In particular the device is aimed to sonicate a large tumoral volume without mechanical displacement while eliminating any non-sonication delays (usually used for transducer cooling).

Methods: The optimal distribution of elementary transducers was calculated by using in-house developed software for linear acoustic simulation. A polymer-made holding frame was created using 3D printing technique to host individual piezo-ceramic transducers of 5 mm diameter. The device was divided into two families of elements and the individual orientations were defined such as each half-array subset pointed at a different given location. Therefore the steering range could be augmented along one axis in the native focal plane by sequentially activating the sub-arrays. Further, using elementary transducers with different resonance frequencies and exploiting their intrinsic narrow band response, coupled to a parallel electronic driving, we generated MR-compliant spectral multiplexing. Whereas the power generator continuously emitted signals at the maximum available power, each family of transducers could be periodically activated upon the driving frequency. The proof of concept has been made by building and testing two phased-array devices, each one comprising two 64-channels sub-arrays:

Device	Curvature radius [mm]	Aperture diameter [mm]	Sub-array frequencies [kHz]	Inter-foci spacing [mm]
DEV.1	130	150	f1=960 f2=1030	35
DEV.2	80	110	f1=960 f2=1030	16

Results & Conclusions: Acoustic fields, as measured by the hydrophone scanning technique, indicated excellent correlation with numerical prediction over the full steering range (80x40x30mm for the larger array). The devices demonstrated excellent passive and active MR compatibility at 3T. The double subset approach permitted the increase of the steering range by 80% as compared to a single set of elements, also confirmed by high-resolution MR thermometry in ex-vivo tissue. Unlike piezocomposite based solutions, the current approach offers significant advantages: 1) piezoceramics efficiency is higher; 2) 3D printing allows the realization of any shape, regardless of transducer local curvature; 3) Defecting elements can be individually replaced; 4) Production costs are lower. In clinical implementation for treating moving organs, the axis of preferential steering is foreseen to be aligned with the main axis of local tissue motion, to facilitate active motion tracking with HIFU beam. This technology was experimentally demonstrated to be suitable for the implementation of optimized, MR-compatible, phased array HIFU devices providing large electronic steering range.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-28

PET/MRI-guided Focused Ultrasound Hypoxic-tissue Ablations in Solid Tumors

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Background/Introduction: Tumor hypoxia remains a challenge for chemotherapy and for photodynamic and radiation therapy due to poor drug penetration and reduced radiation effect. It would be beneficial to assess tumor oxygenation and treat hypoxic areas so that hypoxic-related therapy resistance may be alleviated. To achieve this goal, we combined ^{18}F-miso PET hypoxia imaging and MRgFUS thermal ablation to attempt to destroy the imaged tumor hypoxic areas. The purpose of this work is to investigate the protocol of PET/MR-guided FUS hypoxic-tissue ablation and evaluate its validity and performance.

Methods: Twelve mice bearing 4T1 mammary carcinoma or FSaII fibrosarcoma tumors were used in this study following the protocol shown in Fig.1. First, we conducted and validated the ^{18}F-miso PET measurement of hypoxia level in tumors. Each mouse was injected with 1mCi of ^{18}F-miso agent through the tail vein. After 1.5-2 h of uptake, the mouse was scanned in a MicroPET (Siemens FOCUS) for 30 min. The intensity of the PET images (i.e., uptake of ^{18}F-miso agent in tumor) was correlated to the absolute pO2 based on the interstitial measurements using an Oxylite oxygen measurement system. Hypoxic areas corresponding to a pO2 level of 7 mmHg or below were delineated and validated by histological analysis. Second, we conducted PET/MRI-guided FUS hypoxic-targeted ablation of implanted tumors. After the ^{18}F-miso PET scan, the animal cradle, in which the mouse, animal sensors, breathing and anesthesia system, and FUS applicator were set up and secured before PET imaging, was transported to the 7T MRI (Bruker) for MRI imaging and MRgFUS ablation, as shown in Fig.2. After registering the PET scans and MRI RARE T2-w images, the obtained hypoxic contours were overlaid on MRI anatomical images and served as the targets for MRgFUS hypoxic-tissue ablation. Hypoxic-tissue ablations were performed using a spherically-focused ultrasound applicator that was specially designed and fabricated for heating small animals inside the bore of a 7T magnet. The online MR temperature imaging was developed to monitor the temperature changes and modulate the sonications. After the ablations, we conducted post-treatment histology assessment to evaluate and validate the effectiveness and accuracy of the hypoxic-tissue ablation.

Results & Conclusions: ^{18}F-miso PET scan of mouse tumors with i.v. injection of 1mCi/mouse and 1.5-2 h of uptake can clearly distinguish the hypoxic, necrotic and oxygenated volumes in a solid tumor. The PET measurements of tumor hypoxia were validated by the invasive measurements of tumor pO_2 using an Oxylite system. After registration between PET and MRI (Fig.3), by means of PET hypoxia imaging, on-line MRI temperature imaging and the specialized small FUS applicator, the hypoxic-tissue ablation can be achieved with sufficient accuracy and effectiveness.

Acknowledgements (Funding): Supported by NCI grants CA44114 and RC1 CA147697-01. We acknowledge general research support from the Central Arkansas Radiation Therapy Institute.

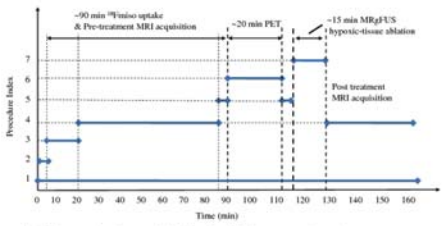

Fig 1. The experimental protocol, including the following seven main procedures: (1). Isoflurane anesthesia, all through the entire experiment; (2).^{18}F miso injection (i.v., ~5 min); (3). Animal handling (~10 min); (4). MRI acquisition such as RARE T2-w imaging, T2, T2*-w imaging and T2* parametric maps, MRI Angiography (~70 min); (5).transport the mouse bed to MicroPET or MRI (~5 min); (6).MicroPET scanning (~20 min); (7).MRgFUS ablation with MR temperature imaging (~ 30 min)

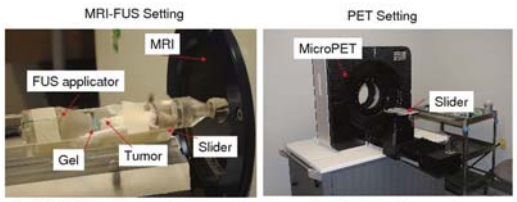

Fig.2. The FUS applicator, animal, sensors, breathing and anesthesia supply were set up and secured in the animal cradle, which can be transported between the MicroPET and 7T MRI magnet without moving animals

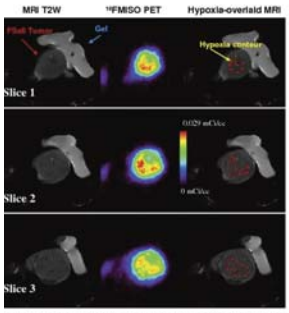

Fig 3. Registration of MRI T2-weighted and ^{18}FMISO PET images over three transverse slices of a FSaII tumor.

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-29

Spatial Accuracy of Volumetric Ablation of Tissue Using Magnetic Resonance Imaging Guided High Intensity Focused Ultrasound (MR-HIFU) with Feedback Control and Multi-slice Thermal Monitoring: Initial Experience in a Pig Model

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[2]St. Luke's Episcopal Hospital, Diagnostic and Interventional Radiology, Houston, TX, USA,
[3]Philips Medical Systems, Clinical Science, Cleveland, OH, USA

Background/Introduction: MR-HIFU is a tool for noninvasive ablation of tumor tissue [1]. It has been shown that volumetric ablation of tissue coupled with real-time monitoring of temperature can improve thermal dose efficiency and save treatment time [2-4]. Here, we report on the spatial accuracy of thermal dose delivery using volumetric ablation in a pig model.

Methods: *Animal Care:* The study was approved by the Institutional Animal Care and Use Committee. The animals were sedated during the procedure, and were sacrificed immediately thereafter under Institutional guidelines. *MR-HIFU procedure:* All experiments were done on a Philips 1.5T MR scanner (Achieva) with a 256Ch spherical shell HIFU transducer (freq range 1.2-1.4 MHz), and an integrated receiver coil. The temperature evolution of volumetric sonication (n=12) was recorded in real-time using a multi-shot echo planar imaging technique [3]. Three slices (at xy plane) bisected the focal ellipsoid coronally, and one sagittal (at z plane) slice was positioned to visualize the long axis of the ellipsoid. *Data Analysis:* Using a custom-built software, the spatial location of the centroid of the thermal dose for each cell was compared against the intended location of the lesion to yield the dose offset.

Results & Conclusions: Feedback and non feedback cells with diameters of 4mm, 8mm, 12mm, 16mm were successfully treated. In two cases, the treatment was automatically discontinued by the safety algorithm once the near field temperature exceeded the predefined safety limit. Thermal dose map of a representative 8 mm cell shown in Figure 1A, reveals an ellipsoidal thermal lesion. White and black pixels represent thermal dose >240 EM, and <30 EM respectively, with gray pixels representing dose in between. Note the sharp boundary between the treated and untreated areas. Thermal dose profile along the x-axis (black) and y-axis (gray) across the pixel with peak temperature is plotted in Figure 1B. The boundary of the intended lesion is also shown (solid vertical lines). The x- and y-offsets for the 10 sonications is shown in Figure 1C. The offset for 7/10 sonications was less than a pixel width, and in all cases the offset did not exceed 2 pixels. The preliminary results suggest that with volumetric ablation it is feasible to: (i) create lesions *in vivo* with accuracies on the order of 1-2 pixels, and (ii) that the transition between treated and untreated regions is sharp resulting little damage to the healthy tissue.

Acknowledgements (Funding): This study was partly funded by Ronald MacDonald fund at St. Luke's Episcopal Hospital and research support from Philips. 1. K. Hynyen *et al.* Radiographics, 16, 185-195, 1996; 2. M. O. Kohler M *et al*, Med. Phys. 36(8): 3521-3535, 2009; 3. J. Zhang *et al*, ISMRM, #4131, 2010; 4. C. Mougenot, *et al.* ISMRM, #526, 2010.

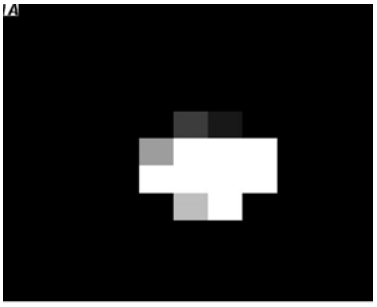

Fig.1A

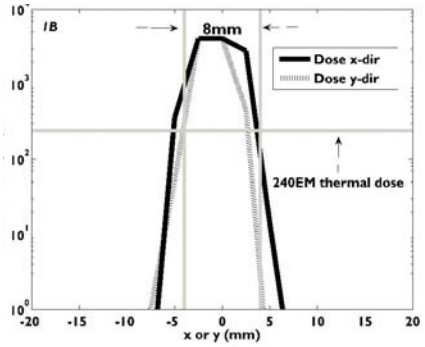

Fig.1B

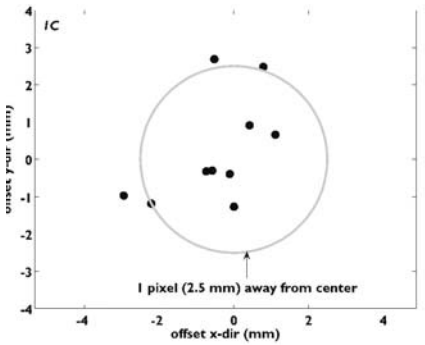

Fig.1C

Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-30

Numerical and Ex-Vivo Characterization of Acoustic Edge of SonoKnife

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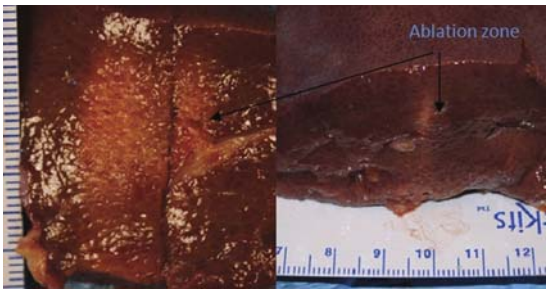
Background/Introduction: Most Head and Neck cancers are treated with radiation therapy, chemotherapy and surgery. Recently, MR-guided focused ultrasound has been researched for tumor treatment as an attractive alternative to surgery due to its noninvasive nature. We propose a new device concept called SonoKnife for treatment of head and neck tumors and malignant neck nodes. A SonoKnife is a scanable, line-focused transducer designed for thermal ablation (55-60oC) of superficial tumors. Here in we report our first set of experimental results using the first SonoKnife prototype to ablate porcine liver *ex vivo*.

Methods: A prototype cylindrical section transducer operating at 3.54 MHz, with a 60 mm radius of curvature, and a height of 30 mm was constructed for laboratory testing. Numerical simulations of the acoustic and temperature fields were conducted previously and reported separately. The acoustic field of the transducer was measured in degassed water using a hydrophone and the contour of the 3dB acoustic pressure was reconstructed. In order to test the feasibility of ablating biological tissue, we compared *ex vivo* data to simulation results to inform treatment planning strategies in the future. *Ex vivo* thermal ablation experiments were carried out using porcine liver. A typical ablation is shown in Figure 1 using 48 W acoustic output power and 52 s radiation time. The acoustic radiation was applied vertically from the top, and left panel in Fig. 1 is a coronal plan of SonoKnife edge, the right panel is a sagittal plane of SonoKnife edge. Serial studies were performed to determine the relationship of ablation size in freshly excised biological tissue with acoustic power and radiation time.

Results & Conclusions: The acoustic field measured in water agreed well with the numerical simulations. The preliminary *ex vivo* experiments using porcine liver showed that the SonoKnife ablated a thin layer of tissue corresponding to the location of the line-focus (acoustic edge). This result supports one of our hypothesis that an acoustic edge can ablate larger volumes in comparison to a point-focus device and thereby addressing one of the main drawbacks of high intensity focus ultrasound, namely, long treatment times. Our current prototype can handle more power so we need more amplifier capacity for faster ablations.

Acknowledgements (Funding): The Research was supported by an NCI grant NO. RC1 CA147697. We acknowledge general research support from the Central Arkansas Radiation Therapy Institute (CARTI).



Session Topic:
Technology & Bioeffects of FUS
Presentation Type: Poster
P-31

Assessment of Focused Ultrasound-Induced Inflammation in Muscle by MRI and Fluorescent Microscopy

Hilary Hancock, Dana Dean, Aneeka Chauhdry, Bobbi Lewis, Melissa Smith, Victor Frenkel, Joseph Frank

National Institutes of Health, Radiology and Imaging Sciences, Bethesda, MD, USA

Background/Introduction: Focused ultrasound (FUS) exposures have traditionally been applied in continuous (c) mode to generate temperature elevations (≥40°C) for ablating solid tumors. Pulsed (p) FUS exposures, with lower rates of energy deposition, typically produce temperature elevations (≤5°C), enabling mechanical effects (i.e., enlarged gaps between cells) that increase tissue permeability for enhancing drug delivery. Although generally thought to be non-damaging, little is known about the effects of pFUS; especially at the cellular level. The objective of this study was to investigate the effects of cFUS and pFUS to evaluate changes in the cytoarchitecture and alterations in the microenvironment by MRI, fluorescent microscopy (FM) and molecular assays in muscle.

Methods: Mice received pFUS or cFUS in the hamstring, where the exposure parameters for each had previously been determined to effectively enhance permeability or ablate tissue, respectively. The contra-lateral thigh served as an internal control. 72 hours prior to treatment mice received tail vein injection of Superparamagnetic iron oxide (SPION)/ Rhodamine nanoparticles (40 nm) to label splenic monocytes. On days 1, 3, and 8 post FUS, animals from each group were imaged at 3T MRI. Cellular MRI was performed with T2W and T2*W axial and oblique sagittal images (image resolution 100x100x500um). Mice were euthanized and both legs were snap frozen for histological and FM confirmation of SPIO labeled macrophages, prussian blue (PB) and immunohistochemistry (IHC) staining. Inflammatory cytokines (e.g. ILIb, MCP1) were analyzed using a standard commercial chemiluminescent protein array.

Results & Conclusions: In mice receiving cFUS, T2W and T2*W MRI showed localized hyperintense signal intensity (SI) and areas of hypointense voxels, indicating edema as well as the presence of SPION labeled macrophages. Smaller areas of high SI were observed in mice in the pFUS group along with hypointense voxels. Fluorescently-labeled and PB positive macrophages were also found in higher numbers in the cFUS mice. The macrophages were initially observed in the periphery and at later time points in the center of the cFUS and pFUS treated muscle. Assays showed that enhanced levels of pro-inflammatory cytokines were present in the FUS treated tissue. Cellular MRI and histological analysis of FUS treated muscle clearly demonstrated the presence of labeled macrophages in response to increased expression of pro-inflammatory cytokines that stimulated homing of these cells compared to control legs. The increased macrophage infiltration was greater in cFUS exposures compared to pFUS. This study demonstrates the need to further evaluate normal tissue response to FUS using noninvasive imaging and molecular biological assays. Characterizing the effects of FUS in tissues should stimulate the investigation of novel applications such as directed targeting of cellular or genetically engineered therapies in the treatment of focal diseases.

Session Topic:
Back & Neck Pain, Other Applications
Presentation Type: Oral
IS-8

Facet Rhizotomy

Wladyslaw Gedroyc

St. Mary's Hospital, Radiology, London, UK

Background/Introduction: Back pain is an extremely common symptom with between 54% and 80% of patients suffering sometime in their life, and it is estimated that facet related pain accounts for up to 50% of these problems. Current therapy for facet disease consists of all pain medication and localized injections all radiofrequency ablation's of facet joints facet rhizotomies.

This study has attempted to explore whether MR guided focused ultrasound, which is noninvasive, can be used to carry out facet joint ablations and therefore improve pain and disability from this condition.

Methods: We have recruited 16 patients from the pain and spinal clinics who have had previous positive successful facet joint interventions and have now presented with recurrent similar pain. Focused ultrasound was applied to the facet joints on both sides at the level of pain and at a level above and level below the site of maximum pain.

Results & Conclusions: The range of motion of the system is 10 x 10 x 10 cm with a spatial precision of 0.3 mm. A variety of sonication patterns are possible including single point, multi-point, and scanned exposures. The system has been tested and functions on MR scanners from all major vendors, at both 1.5 and 3 T. In addition, the entire system is portable and can be transported between the laboratory and MRI for in-bore and benchtop experiments. This turnkey research platform is intended to lower the technology barrier that exists for groups to engage in MRI-guided focused ultrasound research.

Acknowledgements (Funding): Results are provided in terms of pain using visual analog scores and disability using the Oswestry disability index. The mean improvement in pain index was 62.3%, and the mean improvement in the disability index at six months was 56%.

These results show a very promising response to this innovative type of therapy and suggest that further investigation of this technique is warranted to see if this could replace interventional procedures for the treatment of facet associated back pain.

Session Topic:
Back & Neck Pain, Other Applications
Presentation Type: Oral
O-1

Targetting the Swine Pancreas with MR Guided HIFU

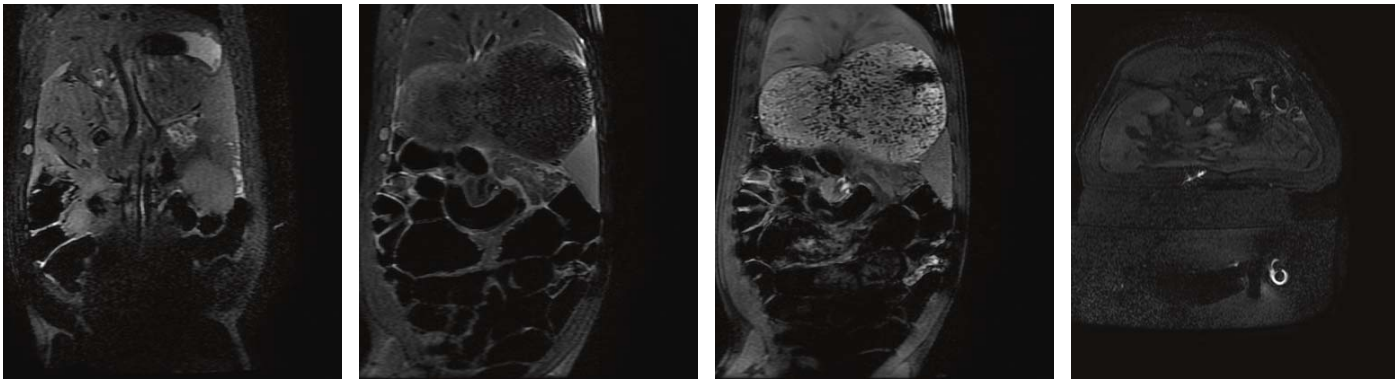
Kristin Dittmar, Blythe Gorman, Ed Hui, Brian O'Neill
The Methodist Hospital, Research Institute, Houston, TX, USA

Background/Introduction: Pancreatic ductal adenocarcinoma is one of the most lethal human cancers. Recent publications in China have demonstrated the ability of HIFU deposited into adenocarcinoma of the pancreas to result in the reduction of pain and improvement in quality of life. Our study uses MRI guided HIFU with real time thermal mapping to quantify the amount of energy deposited. We have treated the pancreas in normal swine with MR guided HIFU to determine the feasibility of this technique.

Methods: Eight swine, with their abdomens shaved and depilated, were laid prone on the table directly over the ultrasound transducer window. The swine were anesthetized, and a blood sample was drawn. A 5 cm thick gel pad and sheet of 1 mil poly separated animal and the mylar film sealing the transducer bath. Degassed water was used as a couplant at each interface. A pre treatment MRI of the abdomen was performed. The pancreas was localized and targeted using the 3 T MR clinical scanner/ ExAblate 2000 (InSightec, Dallas, TX) was used for HIFU treatment. The treatment zone was covered by 'nominal' (10 mm length, 4 mm diameter) spots. Treatment time was 20-30 sec with 60 sec cool down. Varying energy ranged from 1000-6000 J per spot. Peak temperatures in the pancreas recorded between 50 and 65° C. Post treatment, initial images were acquired with post contrast imaging with IV gadolinium. The animals were monitored closely for signs or pain or distress, blood samples of amylase and lipase were drawn and weights were obtained. One week post treatment, a repeat MRI was performed to evaluate for necrosis and complications. Finally, animals were sacrificed and a gastroduodenectomy and pancreatectomy was performed. Any complications were also resected and submitted to Pathology and stained with H&E for microscopic evaluation.

Results & Conclusions: Initial imaging demonstrated early treatment changes of edema and hemorrhage once an energy threshold was reached. Amylase and lipase increases correlated to the imaging changes. Two pigs treated with the highest energy settings demonstrated evidence of pancreatitis. Seven pigs tolerated the procedure well clinically and continued to gain weight without pain medications. One pig had vomiting and needed to receive pain medications. Pathology demonstrated necrosis of the pancreatic parenchyma without damage to the pancreatic vasculature with low energy settings. With higher energy settings the level of pancreatic necrosis ranged from 45% to 65%. Other complications included abdominal wall muscle burns, necrosis of the duodenum and adjacent pancreas, gastric ulcers and reactive follicular hyperplasia in lymph nodes. Targeting of the swine pancreas can be performed with MR guided HIFU. Energy deposited into the pancreas can result in necrosis after a threshold. Complications were noted to occur as the energy deposited increases.

Acknowledgements (Funding): MD Anderson Foundation and Vivian L. Smith Foundation and TMHRI and NIH Grant 5-R01-EB009009-01.



Session Topic:
Back & Neck Pain, Other Applications
Presentation Type: Poster
P-32

Clinical Experience with Magnetic Resonance Guided Focused Ultrasound Surgery for Chronic Low Back Pain Originating in the Facet Joints in Elderly Patients

Motohiro Kawasaki[1], Takahiro Ushida[2], Tomonari Kato[1], Hirofumi Nanba[1], Toshikazu Tani[1]

[1]Kochi Medical School, Orthopaedic Surgery, Nankoku, Japan,
[2]Aichi Medical University, Multidisciplinary Pain Center, Nagakute, Japan

Background/Introduction: Low back pain, a major clinical problem that affects most elderly people, frequently originates in the facet joints. Magnetic resonance (MR) guided focused ultrasound surgery (MRgFUS) is a noninvasive method of treatment that thermally ablates target tissues, focusing multiple ultrasound beams with MR imaging. In recent years, clinical studies have reported that MRgFUS is effective in relieving the pain associated with painful bone metastasis. This therapeutic effect may be attributable to ablation and degeneration of nerve fibers related to pain. The present study was conducted to evaluate whether nerve ablation utilizing MRgFUS can be applied to relief of chronic low back pain originating in the facet joints. Here we report that MRgFUS had therapeutic effects in such patients.

Methods: This study enrolled patients with chronic low back pain originating in the facet joints resistant to other conservative treatments for more than 6 months. Patients who could not obtain analgesia with either medial branch block or facet joint block were excluded. We conducted a single-session treatment for 10 target dorsal facet joints in 6 patients (mean age: 76 years) using the ExAblate 2000 ® system, and assessed most severe low back pain using BPI and limitation in activities of daily living (ADL) before and after the treatment. re.

Results & Conclusions: Low back pain measured by NRS significantly decreased from a mean of 7.5 (6-9) before treatment to a mean of 3.8 (1-6) at the final follow-up visit. Disruption due to pain improved in items including general activities and walking on the ADL scale as well. Treatment time was a mean of 54.0 minutes (46-58 min), the number of sonications a mean of 14.5 (8-18), and ultrasonic energy a mean of 1051.3J （500-1448.1J). There were no adverse effects related to the treatment; however, changes in dorsal facet joint on MR imaging was observed in one patient treated with focused ultrasound beams. We speculate that the favorable effects on low back pain observed in the present study result from ablation of nerve-endings and nociceptors that control the facet joints. It remains unclear what the optimal energy is for MRgFUS for facet joints. It will therefore be necessary to evaluate how much energy should be used and which sites should be targeted in conducting sonication effectively. In addition, degeneration of affected areas in facet joints and spinal alignment, among other factors, need to be assessed as well as long-term analgesic effects. Our findings suggest that MRgFUS could become a novel, less invasive and effective treatment option for chronic low back pain originating in facet joints in elderly patients.

Session Topic:
Back & Neck Pain, Other Applications
Presentation Type: Poster
P-33

Comparison of Dynamic Contrast-enhanced MRI Parameters with 99mTc-sestamibi Uptake Ratios in Benign Thyroid Pathologies

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[2]Trakya university Medical Faculty, Nuclear Medicine, Edirne, Turkey

Background/Introduction: Magnetic resonance imaging has proven to be very accurate in the evaluation of thyroid disease. The aim of this study was to investigate dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) for the noninvasive differential diagnosis of benign thyroid pathologies by correlation with Tc-99m sestamibi uptake.

Methods: The study group included 16 patients (5 males, 11 females; mean age: 44.5) with three types thyroid benign lesions. They all had proven pathologies [adenematous goiter (8), follicular adenoma (4) and nonmicrobial chronic/subacute thyroiditis (4)]. Patients were examined using thyroid Turbo DCE-MRI and Tc99m sestamibi scintigraphy. Hemodynamic parameters obtained by DCE-MRI included peak time enhancement in the first minute ($E_{max/1}$) after contrast administration, second minute ($E_{max/2}$), third minute ($E_{max/3}$), fourth minute ($E_{max/4}$), and fifth minute ($E_{max/5}$), maximum peak enhancement (E_{max}), and the steepest slope. Discriminant analyses were performed to reveal parametric differences of benign and malignant lesions. Early and late 99mTc-sestamibi uptake ratios (EUR and LUR) of thyroid were measured semiquantitatively (maximum lesion-to-nonlesion ratios).

Results & Conclusions: The mean EUR, LUR, $E_{max/1}$, $E_{max/2}$, $E_{max/3}$, $E_{max/4}$, $E_{max/5}$, E_{max} and steepest slope were 2.33+/-2.80, 1.29+/-0.70, 121.9+/-47.8, 106.9+/-45.2, 86.3+/-30.7,77.7+/-26.4, 71.5+/-23.0, 121.9+/47.8, 5.94+/-1.68 for adenematous goiter, and 1.14+/-0.56, 1.11+/-0.38, 118.5+/-52.6, 108.6+/-55.4, 102.6+/-52.6, 96.0+/-51.9, 90.0+/-51.2, 118.5+/52.6, 5.07+/-1.04 for follicular adenomas, and 1.56+/-0.64, 1.46+/-0.60, 104.4+/-15.6, 91.2+/-20.0, 78.4+/-22.5, 74.7+/-25.4, 70.8+/-23.5, 109.7+/17.1, 4.91+/-2.01 for thyroiditis, respectively. Statistically significant correlations were not seen between DCE-MRI parameters and scintigraphic uptake ratios. In order to determine discrimination all of the lesions using DCE-MRI parameters, EUR and LUR, logistic regression was applied to the above mentioned data. When combined these parameters had a 75% of overall accuracy in classifying final pathological diagnosis by the DCE-MRI parameters. Discriminant analysis correctly predicted final pathological diagnosis 56.3% of patients when using scintigraphic uptake ratios. Previous reports indicate that MR-guided interventions and biopsies of thyroid nodules are possible, clinically acceptable and show promising perspectives when thermoablative surgery is investigated. Since there is no report showing the possible role of in MR-guided focused ultrasound in thyroid pathologies, based on results of this and other studies, we suggest that this new technique may be useful in the treatment of benign thyroid diseases and further studies should be performed for assessing its potential.

Session Topic: Liver Applications
Presentation Type: Oral
IS-9

MR Guided Focused Ultrasound of the Liver

Wladyslaw Gedroyc
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Thermal ablation procedures have been used for many years now in the destruction of focal liver tumors with substantial success. The results of these procedures which often use laser or radio-frequency ablation sources placed percutaneously are very similar to the results of open surgical resection in similar cases. Focused ultrasound directed completely noninvasively from an external source should therefore potentially be an effective alternative to these percutaneous procedures. Current problems limiting the use of this modality in the liver are predominantly respiratory movement and shielding from the rib cage, which prevents access to the lesion from bone absorption by the ribs.

This presentation describes early cases that have been carried out using MR guided focused ultrasound where these problems have been surmounted in suitable cases and describes the technological developments which are required to allow this procedure to develop properly so that the majority of patients with hepatic tumors can potentially be treated.

Session Topic: Liver Applications
Presentation Type: Oral
L-1

Usefulness of 3D Imaging of US, CT and MRI for the Planning and Monitoring of Hepatocellular Carcinoma Treatment Using FUS

Hiroyuki Fukuda[1], Kazushi Numata[1], Akito Nozaki[1], Masaaki Kondo[1], Manabu Morimoto[1], Katsuaki Tanaka[1], Masao Ohto[2], Hui Zhu[3], Zhi-Biao Wang[4]

[1]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan,
[2]International HIFU Center, Naruto General Hospital, Naruto, Japan,
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[4]Institute of Ultrasonic Engineering in Medicine, Chongqing University of Medical Sciences, Chongqing, China

Background/Introduction: B-mode conventional sonography is used to monitor the HCC during focused ultrasound surgery (FUS), but tumors located below the diaphragm or deep within the liver are often obscured on conventional monitor sonography. In addition, smaller HCCs cannot be detected clearly on conventional monitor sonography (Fig.1). In this study, we evaluated the safety and usefulness of FUS assisted by three-dimensional imaging of ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) for the treatment of hepatocellular carcinoma (HCC).

Methods: FUS ablation was performed in 13 patients with small HCC (<3 lesions, <3 cm in diameter). The FUS system (Chongqing Haifu Tech) was used under ultrasound guidance. By transferring the sagittal or axial plane of the 3D volume data into the ZioM900, multiplanar reconstruction (MPR) images were displayed in a manner resembling conventional monitor US to assist the FUS treatment.

Results & Conclusions: Overall, 69% (9/13) of the patients in whom good visualization using B-mode sonography could not be obtained because of the influence of multi-reflections, rib shadows, and unclear tumor margins were successfully treated under the guidance of 3D imaging (Fig.2). In 5 of the 13 patients, multi-reflections were responsible for the poor visualization. In 2 cases, the tumor was poorly visualized because of a rib shadow. In one case, the margin of the tumor was too unclear to be detected using ultrasography. The 3D US images obtained as part of the 3D imaging had a high resolution and were useful for examining the area of HCC invasion and for determining the extent of the ablation area. The CT and MRI images, which are not influenced by bone shadows or multi-reflections, were useful for detecting the tumors and for visualizing the presence of the intestines in the sonication zone. FUS treatments were successfully performed in all the patients with the assistance of 3D imaging of US, CT and MRI. In conclusion, 3D imaging of US, CT and MRI are useful for FUS treatment for HCC, compensating for the occasionally poor visualization provided by US monitor.

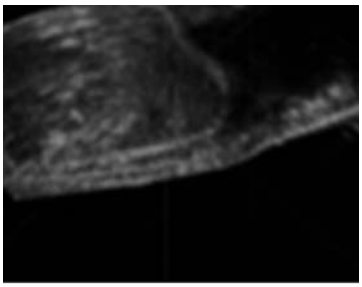

Fig.1 Tumor (arrow) of the monitor ultrasonography was sometimes influenced by multi-reflections, rib shadows and intestinal gas.

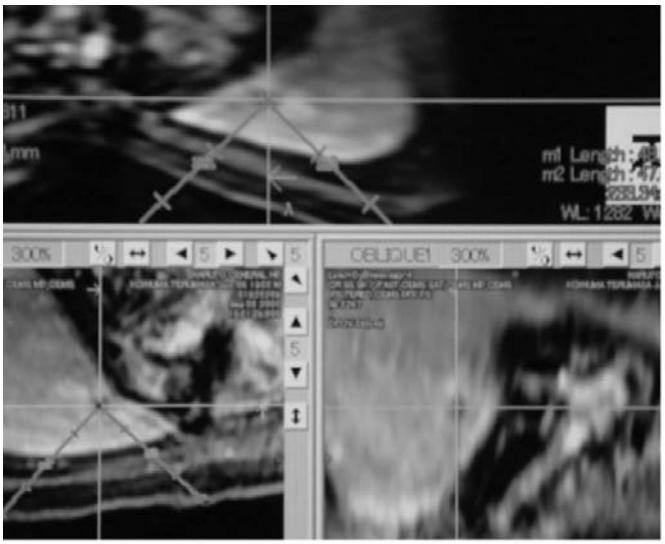

Fig.2. Multiplanar reconstruction (MPR) of 3D MRI using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) in hepatobiliary phase was useful for detecting the small HCC and checking the safety of the procedure by enabling the presence of intestines and lung gas to be identified in the sonication zone (line).

Session Topic: Liver Applications
Presentation Type: Oral
L-2

Focused Ultrasound of the Liver During Free Breathing

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Background/Introduction: Treatment of primary and metastatic liver tumors dramatically improves patient prognosis; however, only 20% of patients at presentation are candidates for surgical resection of these tumors. Focused ultrasound ablation of the liver could be a desirable treatment option for these patients. FUS of the liver can be done by either repeatedly arresting respiration or during free breathing. Here we report on our initial effort to develop and test a system capable of treatment during free breathing.

Methods: The system was designed to include a) real-time imaging and thermometry, b) transducer tracking using MR tracking coils on the transducer, c) real-time liver tracking using vessel registration and respiratory monitoring, and d) slewing of the beam to maintain a constant position of the focal spot in the liver during free breathing. The system also includes a) near-real time MR-ARFI imaging to calibrate the focal spot position, and b) rapid display of reflection data to optimize transducer coupling and to allow turning off elements with poor coupling. Experiments were performed in three porcine livers with the InSightec ExAblate Conformal Bone System operating at 0.55 MHz. The transducer was placed on the upper abdomen of the animal, avoiding the ribs. Gated, dual single shot MR-ARFI acquisitions demonstrated the focus for calibration. Real time MR thermometry used a multishot RS-EPI sequence (TE/TR = 15.9 ms/117 ms and a frame rate of 2.85 frames/s) reconstructed with RTHawk. Temperature processing was done with a hybrid multibaseline and L2 referenceless processing. Ablations performed with arrested respiration and with free breathing were compared. Typical operating transducer power was 150 acoustic W for both ablation and ARFI. Ablation durations were approximately 60 seconds, while for each ARFI image, the ultrasound was on for approximately 20 ms. Livers were examined grossly after necropsy.

Results & Conclusions: Rapid display of the reflection data was critical for positioning the transducer. Rapid MR-ARFI images provided an easy means of calibrating the focal position in seconds across the entire range of respiration, although in general, calibration at one respiratory phase was sufficient. The real-time thermometry provided sufficient frame rate and temporal resolution to image the focal spot. At this point, ablations performed with arrested respiration reached higher temperatures than free-breathing ablations with the same parameters, and there was some residual blurring of the focal spot during free breathing. In conclusion, focused ultrasound ablation of the liver during free breathing is a realistic goal. MR-ARFI plays a key role in the rapid calibration of the system. A reduction in focal spot blurring is desired.

Acknowledgements (Funding): NIH R01 CA12116.

Session Topic: Liver Applications
Presentation Type: Oral
L-3

High-Intensity Focused Ultrasound (HIFU)-Assisted Hepatic Resection in an Animal Model

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Objective: To evaluate the feasibility and safety of High-Intensity Focused Ultrasound (HIFU)-assisted hepatic resection during an open procedure in an animal model.

Summary Background Data: Bleeding is the main cause of postoperative complications of hepatic surgery. To minimize the risk of intraoperative bleeding during hepatectomy, resections are generally carried out under hepatic vascular control despite the risk of liver dysfunction in patients with chronic liver disease.

Methods: Three groups of 12-14-week-old Landrace pigs (n=7/group) were used to evaluate HIFU-assisted liver resection (Group A) vs. liver resection with or without portal triad clamping (Groups B and C, respectively). In each pig, liver resection was performed on the right and left paramedian lobes. The following were evaluated and compared in the three groups: total blood loss, blood loss/cm² of resection area, clip density, procedure duration, and morbidity and mortality.

Results: Median blood loss was 68 mL [28-489.2] in Group A, 194.7 mL [58.5-383.8] in Group B, and 200.05 mL [106.5-523] in Group C. Median blood loss/cm² of resection area was 4.77 mL/cm² [1.66-21.71] in Group A, 11.35 mL/cm² [3.67-17.94] in Group B, and 12.22 mL/cm² [7.81-29.97] in Group C. Median clip density during liver transection was 0.78 clip/cm² [0.35-1.37] in Group A, 1.61 clip/cm² [0.83-2.45] in Group B, and 1.57 clip/cm² [0.80-3.16] in Group C. Median duration of the surgical procedure was 12 minutes (7-30) in Group A, 21 minutes (15-39) in Group B, and 19 minutes (10-27) in Group C. One case of hematic collection was observed (Group B) and one death occured (Group C).

Acknowledgements (Funding): Cancéropôle CLARA Institut de Chirurgie Expérimentale (ICE), Centre Léon Bérard Département de chirurgie. Centre de Lutte contre le Cancer, Lyon). INSERM U556.

Session Topic: Breast Applications
Presentation Type: Oral
IS-10

Breast Cancer - ACRIN Study

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Session Topic: Breast Applications
Presentation Type: Oral
IS-11

Treatment of Breast Cancer

Hidemi Furusawa
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Session Topic: Breast Applications
Presentation Type: Oral
BC-1

High Resolution and Large Volume Coverage MR Temperature Measurements in Breast

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Background/Introduction: Our goal is to develop a robust MR method for measuring temperature changes in breast to be used in our breast-specific MRgHIFU treatment system. The approach will combine undersampled 3-D segmented EPI imaging with temporally constrained reconstruction and one of three susceptibility-induced PRF error correction methods. This work is part of a project funded by a one-year Focused Ultrasound Surgery Foundation research award.

Methods: *MR Sequence:* A 3-D segmented EPI sequence was implemented with the following parameters: 256x72x25 imaging matrix; 1x1x4 mm resolution; 256x72x100 mm FOV; EPI factor 9; TR/TE = 35/10 ms; 2 saturation bands. The phase encoding order was modified such that each of the 25 k-z planes received 9 readout lines (i.e. one EPI shot) before the first k-z plane received its next set of readout lines. In this way, an evenly undersampled k-space data set was acquired every 0.88 seconds and the fully sampled k-space data every 7 seconds. *Temporally Constrained Reconstruction (TCR):* The undersampled k-space data sets were reconstructed using a TCR algorithm that creates an image estimate by iteratively minimizing a cost function that contains a data fidelity term to penalize deviations from the actually acquired data and a temporal gradient term to penalize excessively sharp changes in time. *Susceptibility Error Correction:* Three methods were compared for correcting errors due to respiration: an image atlas-based method, and two reference-less methods based on fitting either a polynomial (Rieke, MRM 2004;51) or near-harmonic function (Salomir, ISMRM 2010; 247) background inside the region of interest of the image phase.

Results & Conclusions: The TCR algorithm was able to successfully reconstruct artifact-free images from the undersampled 3-D k-space for cases of phantom imaging with out-of-FOV motion and breast imaging during free breathing. Each of the three susceptibility correction methods were able to reduce the PRF errors to the noise level for cases of 2-D imaging during phantom heating with out-of-FOV motion and 2-D imaging during free breathing in a mostly aqueous breast. In the more difficult case of imaging in a mostly adipose breast, the atlas-based method performed the best as the two reference-less methods showed larger errors at fat/water interfaces. The initial results are promising for a high resolution, large FOV coverage temperature measurement method that is robust to respiration errors. Ongoing work is being carried out to test the entire approach on multiple female volunteers, improve the reference-less methods in the presence of fat, and extend the method to previously reported techniques for measuring temperature changes in adipose tissue.

Acknowledgements (Funding): This work was directly supported by a Focused Ultrasound Surgery Foundation Research Award and by Siemens Medical Solutions, The Margolis Foundation, the Mark H. Huntsman Endowed Chair, NIH grants R01 CA87785 and R01 CA134599, Dr. Lorena Petrusca and Mr. Thomas Goget.

Session Topic: Breast Applications
Presentation Type: Oral
BC-2

Induction of an Immune Response to Breast Cancer with Magnetic Resonance-guided Focused Ultrasound Tumor Ablation in a Mouse Model

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Background/Introduction: Growing evidence indicates that ablation of cancer *in vivo* can cause immune stimulation and produce a potent anti-tumor response. The purpose of this study is to test the ability of Magnetic Resonance-guided Focused Ultrasound (MRgFUS) to ablate breast adenocarcinoma *in situ* in a mouse model and induce a significant systemic and local anti-tumor immune response. MRgFUS treatment of breast cancer could improve survival by inducing the immune system to seek and kill microscopic metastatic disease.

Methods: The overall approach employs MRgFUS to elicit a measurable immune response following treatment of breast carcinoma in mice of a single genetic background. To establish tumors, female transgenic mice endogenously expressing rat HER2-neu from a tissue-specific retroviral promoter (FVB/N parental strain) were inoculated with 10^6 HER-2/neu expressing mammary carcinoma cells subcutaneously in the mammary fat pad. Animals were assigned to experimental and control groups. Animals in the experimental group were subject to a single partial MRgFUS treatment of the tumor after it grew to a volume of 1 cc. Animals were anesthetized with 1.5% isoflurane in oxygen (1 liter/min) and imaged using a 3T Achieva Philips scanner and small animal coil. A single localized MRgFUS treatment of the tumor was performed with an MRI-compatible high intensity focused ultrasound (HIFU) transducer (Philips Research). Animals were recovered after treatment and returned to cages to allow development of an immune response. Mice were sacrificed 7 days after treatment and peripheral blood, spleen and tumor were collected. Red blood cells were lysed and the remaining nucleated cells were primed for 6 hours with rat HER-2/neu peptides. Cells were positively sorted over magnetic columns for CD3 (T cells). Using a combination of extracellular staining (CD4 or CD8) and cytokine secretion capture, precursor frequency for different T cell subsets after peptide stimulation were determined using multi-color flow cytometry. Tumor was sectioned and stained to confirm partial ablation.

Results & Conclusions: We have successfully implanted the tumor cells, grown the tumor in the animal model, imaged the tumor, accurately treated part of the tumor with MRgFUS and recovered the animal. Complete treatment of the experimental cohort and results of immunologic testing are pending. The anticipated results of immune interrogation are that animals bearing HER-2/neu-tumors treated with MRgFUS compared to untreated animals will demonstrate an increase in primed circulating Her-2/neu antigen specific effectors and have low circulating antigen specific toleragenic cells. We will present our progress on this multi-disciplinary translational project to use MRgFUS to induce an immune response in mice with breast carcinoma.

Acknowledgements (Funding): This project is supported by funding from the Focused Ultrasound Surgery Foundation, the Fred Hutchinson Cancer Research Center and equipment and technical support from Philips Research.

Session Topic: Breast Applications
Presentation Type: Oral
BC-3

Design and Initial Evaluation of a Breast-specific MRgFUS Treatment System

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Background/Introduction: A new exposure system has been designed specifically for magnetic resonance-guided focused ultrasound (MRgFUS) breast tumor thermal therapy that addresses the unique challenges of MRgFUS of the breast.

Methods: A laterally firing breast-specific HIFU transducer was designed and evaluated using innovative ultrasound beam modeling software. Custom RF receiver coils were designed by implementing the Biot-Savart law in Matlab simulations. SolidWorks was used to design a flexible breast-specific transducer positioner, suspension tank, and patient table.

Results & Conclusions: In this system, the breast is not compressed against a membrane but is suspended with tension on the nipple in a cylindrical tank that is water-coupled to the transducer, providing approximately 270° of access around the treated breast while minimizing the volume of coupling fluid. Acoustic and thermal simulations were performed with real patient breast data to optimize the design of the transducer for the specific anatomy of the breast. Transducer parameters--including aperture size and shape, frequency, radius of curvature and element location and size were varied and their effects on grating-lobe clutter, focal zone size, steering limits, total power and SAR deposited in the tumor were evaluated. A laterally shooting transducer that takes advantage of the large lateral acoustic window of the breast was designed with 256-randomly placed elements operating at 1-MHz, a 10 cm radius of curvature and an 8 x 10 cm aperture size. To obtain the best signal coverage and SNR, several coil designs were evaluated. It was found that a 13-channel MRI receiver coil array that mounts directly on the cylindrical tank improved the SNR 2.7 times compared to a single loop placed at the chest wall. This increase in SNR allows for higher-resolution images to reveal the details of the breast anatomy as well as more accurate MR temperature maps resulting in improved thermal dose calculations and more efficacious treatment outcomes. Finally, the patient table has been ergonomically designed for improved comfort. The patient lies prone with the affected breast suspended in the cylindrical tank with the non-treated breast compressed. Unique advantages of this improved designed include a larger acoustic window than that of axially shooting transducers yielding access to a wider population of breast tumors, increased SNR to enable faster imaging and more accurate temperature monitoring, and improved patient comfort.

Acknowledgements (Funding): This work is supported by NIH grant R01 CA134599, the Ben B. and Iris M. Margolis Foundation, the Mark H. Huntsman chair, and the Focused Ultrasound Surgery Foundation.

Session Topic: Prostate Applications
Presentation Type: Oral
IS-12

MR guided Transurethral Ultrasound Thermal Ablation for Localized Prostate Cancer

Laurence Klotz[1], Michael Bronskill[2], Masoom Haider[3], Linda Sugar[4], and Rajiv Chopra[2]

Health Sciences Centre, Divisions of [1]Urology, [2]Imaging Research, [3]Radiology, and [4]Pathology, University of Toronto, Toronto, ON, Canada

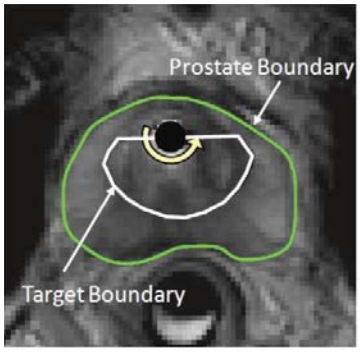

Figure 1: Target boundary selected for treatment

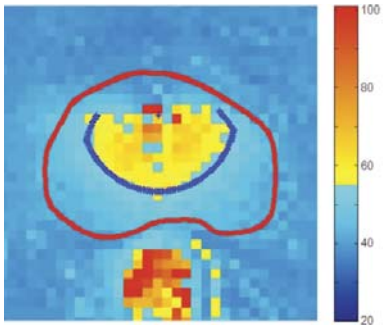

Figure 2: Maximum temperature distribution measured during treatment

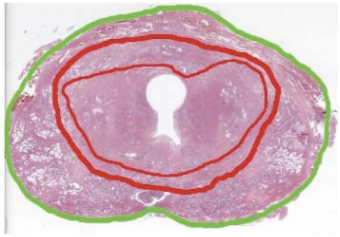
Figure 3: H&E stained section showing inner and outer boundary of thermal damage

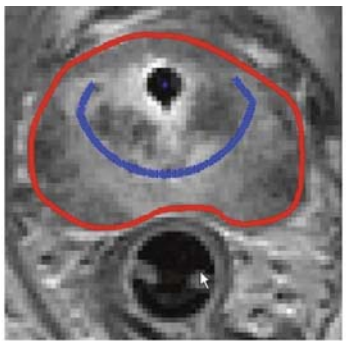
Figure 4: Contrast enhanced image obtained after treatment

Introduction: MRI-guided transurethral ultrasound therapy i has been under development within our group for a number of years, and has been evaluated successfully in simulations [2], gel phantoms [3], and a preclinical canine model [4]. This study reports on the initial experience using this technology.

Methods: Eight men diagnosed with low- to intermediate- risk prostate cancer (T1/T2A, PSA<15 ng/ml, Gleason < 7 (3+4)) and scheduled for radical prostatectomy were enrolled into this study. Prior to surgery, subjects underwent treatment of a subvolume within the prostate gland with MRI-guided transurethral ultrasound therapy. Imaging was performed in a closed-bore 1.5T MR imager (Signa, GE Healthcare, USA) using an 8-channel cardiac phased array coil for imaging. Under spinal anesthetic, a transurethral device was inserted into the prostate gland and attached to an MRI-compatible positioning system which included a rotational motor. Subjects were then transported into the MRI. Oblique-axial T2-weighted images were acquired transverse to the device to select a region within the gland for treatment. Once selected, high-intensity ultrasound energy was delivered to the prostate, while MR images were acquired continuously (FSPGR, FOV=26cm, 128x128, slice=10mm, TE=9ms, TR=40ms). The spatial temperature distribution was calculated by phase subtraction using the PRF-shift method. Temperature maps were analyzed during treatment. The rate of rotation and output power of the ultrasound applicator were adjusted to elevate the temperature along the boundary of the target to 55°C. Ultrasound was delivered from a planar transducer (10 mm x 3.5 mm) at 8MHz, with an acoustic intensity of 10W/cm2. Following treatment, contrast-enhanced images were acquired (3D FGRE, TE=min full, flip=13°, slice=2mm, 256x256, FOV=26cm). Subjects were then transported immediately to the OR for radical prostatectomy.The pattern of thermal damage observed on H&E stained whole-mount sections was compared with imaging measurements obtained during treatment.

Results: Treatment lasted two hours, with ~10 min. of ultrasound delivery. MR temperature measurements within the prostate gland were stable, with a measured uncertainty of ~1.5°C. A semicircular target boundary (Figure 1), with radii of 10-18mm was defined by prostate geometry and an ultrasound frequency-specific treatment algorithm. Maximum temperature distribution (Figure 2) shows a continuous region of heating within the target boundary, and accurate heating of the outer boundary to the desired 55°C. Mean targeting error was >2 mm (~1 pixel). The histological section was consistent with temperature measurement data (Figure 3).

Conclusion: Initial results confirm the feasibility of generating precise spatial heating patterns in the prostate gland using transurethral ultrasound therapy and MR thermometry. These results motivate continued development of this technology for the treatment of localized prostate cancer.

References: 1. Chopra *et al*, Med Phys, 2008. 2. Burtnyk *et al*, Int J Hyperthermia, 2009. 3. Tang *et al*, Phys Med Biol, 2007. 4. Chopra *et al*, Phys Med Biol, 2009. 5. Boyes *et al*, J Urol, 2007.

Session Topic: Prostate Applications
Presentation Type: Oral
PC-1

Ablation of Benign Prostatic Hyperplasia (BPH) Using a Multisectored Transurethral Ultrasound Applicator

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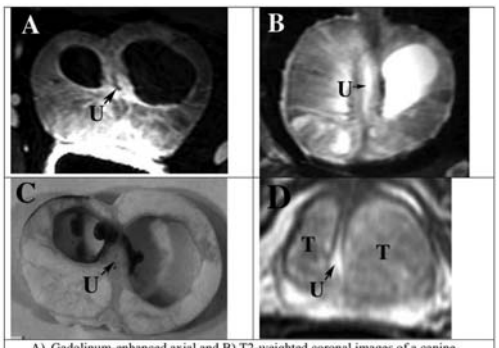
Background/Introduction: Benign Prostatic Hyperplasia (BPH) contributes to an extremely common symptom complex termed LUTS (Lower Urinary Tract Symptoms), which includes diminished urinary flow rates. While medical therapy for BPH has become increasingly utilized, surgical options including TURP (TransUrethral Resection of the Prostate) are still very commonly used to treat BPH. The volume of surgeries in the US for BPH is 3 to 4 times that of radical prostatectomies for prostate cancer. New minimally invasive techniques have been popularized and developed in the hope that they will have fewer complications than TURP, less requirement for anesthesia, a shorter hospital stay, and fewer undesired side-effects. Unfortunately the durability of such treatments has proved limited. There is thus a very large clinical need for an effective and durable minimally invasive treatment. We studied a novel intraurethral ultrasound technique to ablate the BPH,"transition" zone of the dog prostate.

Methods: Transurethral ultrasound applicators, consisting of multi-sectored tubular transducer arrays (7 MHz, 10 mm long x 3.5 mm OD, dual 120° sectors with 30° anterior inactive zone), were devised to sonicate and ablate the anterior-lateral portions of the prostate gland between the bladder neck and verumontanum. The array is positioned on the distal end of a flexible catheter within an expandable cooling balloon within the urethra ensures uniform contact and affords thermal protection of the urethral mucosa. A 5 cc bladder balloon on the distal end can be inflated to firmly position the applicator within the prostate, with the in-active zone rotated to aim toward the anterior gland, The applicator remains stationary during the 5-15 min procedure, and multisectored power levels are controlled based upon closed loop boundary control with MRTI. Zones of ablation were created on either side of the urethra in the regions of the canine "transition" zone of BPH in three dogs, and animals were re-scanned and sacrificed five weeks later. Histologic analysis of resected prostates was performed.

Results & Conclusions: Images obtained at MR imaging and pathology one month post-ablation are shown below, for one study of a canine prostate affected by BPH. There was complete resorption of ablated regions at this time, with preservation of the prostatic urethra. Transurethral applicators of the general design proposed are ideally suited for ablation of the enlarged transition lobes, representing BPH on either side of the urethra, while sparing damage to the prostatic urethra. The technique would appear very promising for minimally-invasive treatment of BPH in patients.

Acknowledgements (Funding): Supported by NIH grants R01 CA111982, R01 CA121163 and R21 CA137472.



A) Gadolinum-enhanced axial and B) T2-weighted coronal images of a canine prostate with 2 regions of ablation on either side of the urethra (U) and C) corresponding axial pathologic specimen. D) T2-weighted axial MRI of human prostate involved with BPH, evident as bilateral enlarged transition-zone (T) lobes.

Session Topic: Prostate Applications
Presentation Type: Oral
PC-2

MR Guided Pulsed High Intensity Focused Ultrasound Enhancement of Docetaxel Combined with Radiotherapy for Prostate Cancer Treatment

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Background/Introduction: Our previous studies have showed increased ^{3}H-docetaxel concentration in prostate tumor in MR guided focused ultrasound (MRgFUS) treated animals vs. those without MRgFUS treatment *in vivo* using a nude mouse model. The purpose of this study is to determine if MRgFUS improves the efficacy of enhanced docetaxel delivery combined with RT in inhibiting prostate tumor growth.

Methods: LNCaP cells (10^{6}) were injected into the prostates of male nude mice. When tumors reached the volume of 47 ± 2.8 mm^{3} on MRI, treatment started using an InSightec ExAblate 2000 system with a 1.5 T GE MR scanner. The animals were randomly divided into 7 groups (n=5 per group). The 7 groups are: Group 1 – Docetaxel + HIFU + Radiotherapy (RT); Group 2 – Docetaxel + RT; Group 3 – FUS treatment + docetaxel; Group 4 – docetaxel only; Group 5 – FUS treatment only; Group 6 – RT only; and, Group 7 – control. Animals involved with FUS treatment were treated with pulsed ultrasound using 1 MHz; 5 W acoustic power and the 81 mode setting (5 Hz frequency with 0.1s power on, 0.1s power off) for 60 seconds for one sonication. The FUS treatment parameters were determined based on our previous phantom studies. Multiple sonications were used to cover the whole tumor volume depending on the tumor sizes. Animals involved with docetaxel treatment received docetaxel in 5 mg/kg (animal body weight) by tail vein injection immediately before or after the MRgFUS treatment. For animals treated with RT, the anesthetized mice were immobilized in the supine position with surgical tape in a jig to deliver radiation to the prostate while shielding the lungs, abdomen, and legs. Animals received a single dose of 2 Gy. The RT dose was chosen based on typical patient daily fractional dose. All animals were allowed to survive for four weeks after final treatment. The tumor growth was monitored on a 7T MR scanner at one week and four weeks before euthanasia. A t-test was used for statistical analysis.

Results & Conclusions: The relative tumor volume for the MRgFUS + docetaxel + RT treated group is 1.0 ± 0.3 and 1.9 ± 1.0 at one week and four weeks after treatment, respectively; For the docetaxel +RT group it is 1.4 ± 1.0 and 2.6 ± 2.6, respectively; for the FUS + docetacxel group it is 1.5 ± 0.4 and 3.1 ± 2.3, respectively; for the docetaxel group the relative tumor volume is 1.1 ± 0.5 and 2.7 ± 1.6, respectively; for the FUS group it is 2.1 ± 0.8 and 5.4 ± 2.7 respectively; for RT only it is 1.3 ± 0.4 and 4.2 ± 2.5, respectively and for the control group it is 2.6 ± 0.68 and 6.7 ± 2.5, respectively. These preliminary results demonstrate that pulsed MRgFUS may have great potential to improve the efficacy of docetaxel delivery in inhibiting prostate cancer growth especially combined with RT. More experiments are needed for more reliable statistical analysis and optimal treatment conditions. .

Acknowledgements (Funding): This work was partially supported by Focused Ultrasound Surgery Foundation, DOD PC073127 and Varian Medical Systems.

Session Topic: Prostate Applications
Presentation Type: Oral
PC-3

Initial Experience with MRgFUS For Localized Low-Risk Prostate Cancer In Singapore

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Background/Introduction: Active surveillance is an accepted option for patients with low-risk prostate cancer. The drop out rate, however, is substantial mainly due to the fear of under-staging and missed opportunity for cure while under surveillance. There is a need for an effective treatment with low morbidity commensurate with the low risk of the condition. This is a report of the initial experience of Focal therapy of the prostate using Magnetic Resonance Imaging Guided Focus Ultrasound (MRgFUS).

Methods: Patients with untreated low risk prostate cancers were selected. The inclusion criteria included those with PSA <10 ng/dl; Gleason score = 6; no more than two lesions <10mm each on transperineal mapping biopsy. Three patients underwent mapping biopsy, CT/MR imaging and were selected for the trial. Under anesthesia, the transrectal probe was inserted and the MR localization of targets performed. Background thermometry was followed by detail planning of the treatment area. The critical areas of the rectum, urethra, sphincter, bladder base and neurovascular bundles were excluded and protected from the beam path. The target areas were sequentially sonicated under real time thermometry monitoring. A final contrast enhanced MR was performed to outline the non-perfused area. All three patients were observed in the hospital for 24-48 hours. No complications were observed. They will undergo repeat MR imaging and repeat biopsy subsequently

Results & Conclusions: All three patients experienced minimal discomfort during and after the treatment. Patient 1 and 2 had no urinary dysfunction after treatment and were able to void after removal of their indwelling urethral catheter the next day. Patient 3 had an anterior located lesion which necessitated a suprapubic catheter insertion prior to treatment. The beam path crosses the urethra and he was counseled regarding the possibility of voiding dysfunction after treatment and necessity to use the suprapubic temporarily. He was able to void normally a week after the treatment. The suprapublic catheter was left capped as a safety catheter until two weeks post-treatment. The immediate contrast enhanced MR demonstrated the desired non-perfused areas corresponding to the plan. So far the safety of the treatment is demonstrated with all three patients experiencing minimal morbidity. Initial efficacy demonstrated by the non-perfusion on contrast enhanced MR will be further confirmed by biopsy.

Acknowledgements (Funding): National Cancer Centre, Singapore; Singapore General Hospital and InSightec.

Session Topic: Prostate Applications
Presentation Type: Oral
PC-4

Focal Magnetic Resonance Guided Focused Ultrasound Treatment of Low Risk Prostate Cancer

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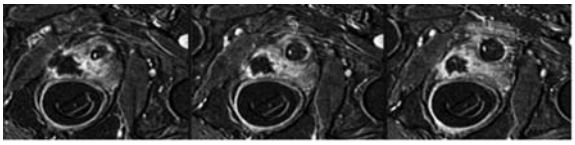
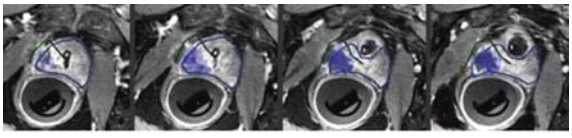
Background/Introduction: The role for focal therapy in the treatment of prostate cancer may be most applicable to patients with prostate cancer tumors that pose little risk of progression, as long as the treatment has minimal effect on quality of life and does not adversely impact survival. Focal ablation of the index cancer, or of the sector of the prostate that harbours that cancer, could be very attractive for patients with low-risk cancers who are uncomfortable with the risks stress and inconvenience associated with active surveillance and with the significant quality of life impairing side effects associated with all kinds of radical therapy.

Methods: ExAblate-2100 (InSightec Ltd.) is a device for MR Guided Focused Ultrasound Surgery (MRgFUS). It is a non-invasive thermal ablation device that is integrated with a GE MR Imaging system to allow real time controlled ablation of tissue. To date, four patients with mapping biopsy proven low risk prostate cancer were treated using MRgFUS at Petrov Research Institute of Oncology, St. Petersburg, Russia. Treatments were completed without any adverse events. According to the protocol, treated patients are being followed up to six months post treatment, for safety and initial efficacy. Follow-up visits are scheduled at one week, and at one, three, and six months. During each visit, treatment safety is evaluated by recording the incidence and assessment of the severity of any device or procedure related adverse event. Initial efficacy is measured by PSA levels and patient completion of treatment related quality of life questionnaires referring to urinary symptoms, sexual function, bowel function as well as overall health. At the six month follow-up, patients are expected to undergo repeated MR Imaging and prostate biopsy.

Results & Conclusions: Results: No device or procedure related adverse events occurred. The Foley catheter was removed at the end of the procedure from three patients. (In the first patient, the catheter was retained for 12 hours for cautionary reasons. No adverse events related to the use of a urinary catheter and related to anaesthesia were observed. No rectal wall injury or sexual function impairment due to potential neurovascular damage have been reported; one patient reported impotence prior to treatment. Pic.1 MR & dose image after procedure. Pic.2 MR image with contrast after procedure.

Conclusions: These initial results clearly show that focal MRgFUS treatment has the potential of treating localized prostate tumors (instead of the entire prostate), while preventing or reducing the risk of incontinence and impotency. The MRI is used for Magnetic Resonance thermometry which allows closed-loop real-time treatment monitoring and control, with patient-customized energy adjustment. Furthermore the high quality imaging enables accurate anatomical identification of the treatment area, especially the neurovascular bundles, which cannot be clearly identified by US guidance and in some patients, the low-risk prostate tumors can also be identified by the MRI.





Session Topic: Prostate Applications
Presentation Type: Oral
PC-5

Full Prostate Gland Coagulation During MRI-guided Transurethral Ultrasound Therapy: Results in Gel Phantoms

W. Apoutou N`Djin, Mathieu Burtnyk, Ilya Kobelevskiy, Stefan Hadjis, Lauren Persaud, Michael Bronskill, Rajiv Chopra

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Background/Introduction: MRI-guided transurethral ultrasound therapy has recently been evaluated for safety and feasibilty in human volunteers by treating a small subvolume of prostate tissue immediately prior to radical prostatectomy. In order to transfer this treatment technology to clinical use, the next challenging step is to use this technology for coagulating the volume of tissue equivalent to the prostate gland. This preclinical study evaluates in vitro the feasibility of treating the whole prostate gland and compares various treatment strategies with respect to treatment time, accuracy, and safety.

Methods: An 8-channel, MRI-compatible ultrasound therapy system was evaluated in tissue-equivalent gel phantoms using five human prostate models (average volume: 33.5 cm3). 3D prostate profiles were segmented from MR clinical images performed on subjects after insertion of a transurethral heating applicator into the prostate gland. Multislice real-time MR thermometry feedback from the entire prostate was performed in a 3T MR scanner, which enabled the acquisition every 7s of up to nine 5-mm slices covering a total volume of 200x200x45 mm3, with a spatial resolution of 1.5x1.5x5 mm3. During ultrasound exposures, decisions on acoustic power, frequency, and device rotation rate were made for each ultrasound element independently, based on temperature maps and prostate target radii. Low and high power treatment approaches using maximum acoustic powers of 10 or 20 W.cm-2 were tested as well as single and dual-frequency strategies (8, 4.5, 4.5/14.5 MHz). The dual-frequency strategy used the fundamental frequency or the 3rd harmonic component, depending on the prostate radius.

Results & Conclusions: 8 MHz single frequency 10 W.cm-2 exposures used in previous studies were incapable of treating the largest radii during full gland coagulation. Decreasing frequency to 4.5 MHz, however, enabled treating 97% of the gland. In addition, increasing the power from 10 to 20 W.cm-2 reduced treatment times by approximately 50%. On average, full prostate coagulations were performed in 25.6 ± 3.2 min at a rate of 1.8 ± 0.4 cm3.min-1. Finally, a 20 W.cm-2 dual-frequency 4.5/14.5 MHz treatment was shown to be the most efficient configuration in achieving full human prostate treatments while maintaining good treatment accuracy for small radii. The dual-frequency strategy particularly enhanced treatment safety by reducing overshoot close to the prostate base and apex, confirming our previous treatment simulations. The principles of prostate thermal therapy using an MR-thermometry-guided transurethral ultrasound technique have been shown to be suitable for full gland treatment in human prostate geometries. Dual-frequency ultrasound exposures offer a promising configuration for further clinical investigations of full prostate treatments.

Acknowledgements (Funding): Financial support was received from the Terry Fox Foundation, the Ontario Institute of Cancer Research, the Ontario Research Foundation, the Health Technology Exchange and Profound Medical Inc.

Session Topic: Prostate Applications
Presentation Type: Poster
P-34

Improved MR Thermometry in the Prostate

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Background/Introduction: MRgFUS treatment of prostate cancer is promising. However, there is a need for accurate thermal imaging to ensure effective treatment in the targeted region, while minimizing damage to the rectum, urethra, and neurovascular bundles. In the traditional phase difference proton resonance frequency (PRF) shift thermometry technique [Ishihara *et al.* MRM, 1995], motion induced phase disturbances can result in inaccurate temperature estimation. Previously, we demonstrated a fat-referenced thermometry technique in the breast that reduced measurement error caused by respiratory and cardiac motion [Hofstetter *et al.* ISMRM, 2010]. This technique uses the signal from fat to compute a phase disturbance correction map for all pixels, even those that don't contain fat. This capability is vital to extending the method to the prostate, a fat-free organ.

Methods: Equation 1 shows the fat-referenced temperature change calculation, where γ is the gyromagnetic ratio, α is the PRF change coefficient, Bo is the main magnetic field, TE is the echo time, $\Delta\varphi w$ is the difference between baseline and measurement water phase images, and $\Delta\varphi b$ is the phase disturbance correction map. The phase disturbance correction map is estimated by fitting a second order spatially-varying polynomial to the phase difference of corresponding fat images. After obtaining written informed consent, imaging without heating was performed on a healthy male volunteer. Single slice prostate images were acquired on a 3T GE MR750 scanner. For each of two measurements, three spoiled gradient echo (SPGR) images with echo times TE = {11.71ms, 12.50ms, 13.29ms} were acquired using the scan parameters: TR = 20ms, flip angle = 10°, FOV = 40cm, matrix 128×256, axial 8mm slice, bandwidth 62.5kHz. Three-echo IDEAL [Reeder *et al.* MRM, 2004] processing was used to reconstruct complex fat and water images. Temperature change maps were computed using fat-referenced and conventional baseline PRF shift methods.

Results & Conclusions: Reconstructed water and fat magnitude images are shown in Fig. 1a and Fig. 1b, respectively. The distribution of fat surrounding the gland (Fig. 1b) can be used to estimate background phase change. Absolute value of the measurement error for both the fat-referenced and conventional PRF shift technique is shown in Fig. 2. In the 393-pixel prostate gland region, the root mean square (RMS) measurement errors are 2.5° C and 4.1° C for the fat-referenced and baseline PRF shift techniques, respectively. We have tested the fat-referenced thermometry technique in unheated volunteer imaging of the prostate. Results from this work suggest that there exists sufficient fat in the proximity of the prostate gland to employ such fat-referenced techniques. The phase disturbance related measurement RMS error in the gland was reduced by nearly a factor of 2 when compared with the baseline PRF shift measurement.

Acknowledgements (Funding): We thank Dr. Yoav Medan at InSightec for many helpful discussions.

$$\Delta T(x,y) = \frac{\Delta\varphi_w(x,y) - \Delta\varphi_b(x,y)}{\gamma\alpha B_o TE} \qquad (1)$$

Equation 1

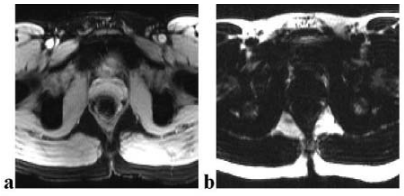

Fig 1. Axial prostate images, with (a) water magnitude image, and, (b) fat magnitude image.

Fig. 1a & 1b

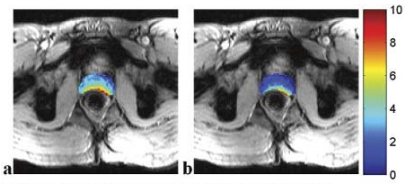

Fig 2. Absolute value of measurement error (°C) in the prostate gland.

Fig. 2

Session Topic: Prostate Applications
Presentation Type: Poster
P-35

MRgFUS for Cancer Therapy: Non-Thermal Effect

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Background/Introduction: MR-guided focused ultrasound (MRgFUS) thermal ablation has been applied for cancer surgery and bone palliation clinically worldwide and at Fox Chase Cancer Center. The aim of this work is to explore the non-thermal effect and the feasibility of MRgFUS for prostate cancer therapy.

Methods: We have used an InSightec ExAblate 2000 system together with a 1.5T GE MR scanner for this study. Suitable ultrasound parameters were investigated to perform non-thermal sonications, keeping the temperature below 42°C as measured in real time by MR thermometry. LNCaP and PC3 cells were placed in thin plastic vessels and inserted in an ultrasound gel phantom with the ultrasound beam focused on the tumor cells. Cells were exposed to pulsed ultrasound (1MHz; 6W and 10 W acoustic power; 5Hz frequency; 0.5duty cycle: 0.1s power on, 0.1s power off) for 60 seconds. Cell viability was assessed by trypan blue dye exclusion and clonogenic assay. The percentage of dead cells were measured by trypan blue dye exclusion at 24h after HIFU. Immediately after HIFU, cells were counted, and known numbers of cells were plated into 100-mm dishes. The plates were incubated for 14 days and stained with 0.25% methylene blue. The colonies were counted. LNCaP cells (106) were injected into the prostate of male mice (n=8). When tumors reached the volume of 49±3mm3 on MRI, the tumor-bearing mice were treated with MRgFUS once a week for two consecutive weeks. Animals were treated with pulsed ultrasound for 60 seconds in each sonication. A total of 4-6 sonications were used to cover the entire tumor volume. The animals were allowed to survive for four weeks after the last treatment. The tumor growth was monitored on MRI and compared with the control group.

Results & Conclusions: Non-thermal cell damage by HIFU exposure was observed for both LNCaP and PC3 cells. At 6 W acoustic power, the cell-death rate was 23.3+1.7% and at 10 W it was 46.3+1.9% for the LNCaP cells. The control group has a 12.7+0.3% death rate. For PC3 cells, the cell-death rate was 18.7+0.7% for the treated group and 9.0+0.6% for the control cells at 6W and 60 seconds. The clonogenic assay results were consistent with the trypan blue dye analysis. Significant tumor growth delay was observed in the mice treated with MRgFUS. The mean tumor volume for the MRgFUS treated mice was about 30% smaller than that of the control mice one week after the MRgFUS treatment, and it was about 50% smaller four weeks after the MRgFUS treatment. Our in vitro and *in vivo* experimental results have confirmed the non-thermal effect of HIFU. Further experiments are needed to derive optimal ultrasound parameters and fractionation schemes to maximize the therapeutic effect.

Acknowledgements (Funding): This work is supported in part by Focused Ultrasound Surgery Foundation, DOD PC073127 and Varian Medical Systems. Technical support from InSightec is acknowledged.

Session Topic: Prostate Applications
Presentation Type: Poster
P-36

LOFU-HIFU Combination Presents a New Paradigm of Using Focused Ultrasound for In Situ Tumor Vaccination

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Background/Introduction: Unfolded protein response (UPR) determines the fate of tumor cells between survival and cell death. UPR induces the expression of molecular chaperones, such as heat-shock proteins (HSP) that try to correct protein misfolding. If unfolded protein persists, they are targeted for degradation by the proteosomes into peptides bound to HSPs. We hypothesized that low energy focused ultrasound (LOFU) would increase protein misfolding in tumors, thereby inducing UPR and breakdown of misfolded proteins with subsequent release of tumor-derived peptide-HSP complexes in the blood, which serves as potential in situ tumor vaccine.

Methods: The LOFU regimen was optimized based on immunomodulatory and cytotoxic changes in three murine tumor cell lines, Panc-2 , RM-1 , and E.G7 using the Phillips TIPS system, operated at 1 MHz, 100% duty cycle and 0-4 watts for 1.5s. Cells were harvested (6, 24, 48h and day 7) for detection of cell surface expression of MHC-I, Calreticulin, FAS and HSP70 by flow cytometry and HSP70 ELISA of cell lysates. Phagocytosis assay was performed by coculturing marrow-derived DCs or JAWS-II cells with CellTracker-labeled LOFU-treated tumor cells, followed by flow cytometric detection of engulfed tumor cells. DC activation was analyzed by CD80, CD86, MHC-II and CD40 flow cytometry. T-cell activation was analyzed by coculturing OVA-specific splenocytes with LOFU-treated OVA+ E.G7 cells, followed by measurement of IFN-γ secretion in culture supernatant by ELISA. Finally, C57BL/6 mice bearing palpable RM-1 tumors were treated with LOFU (weekly for 3wks) and sacrificed at 4th wk and tumor specific T cell response was assessed by IFN-γ ELISPOT.

Results & Conclusions: LOFU induced: a) the expression of intracellular HSP70 (13.4±5.8 fold), b) translocation of cytoplasmic calreticulin on the cell surface (50-79.5%), c) increased cell surface expression of Fas, d) decreased activation of STAT3, and e) produced marginal cell killing (15.6±4.4%), 24 h post-LOFU treatment. Immature DCs phagocytosed LOFU-treated tumor cells (10-16.3%), followed by induction of cell surface CD80, CD86 and MHC-II expression (2-3 fold induction) indicating increased DC activation. A strong tumor-specific immune response was generated by weekly cycles of LOFU+HIFU treatment over 3 weeks (0.17±0.03% IFN-γ+ tumor specific T cells). This was in contrast to the tumor-specific antibodies predominantly generated after a high HIFU treatment (antibody titer: 1/800). Control mice with untreated tumors had no detectable tumor-specific T cells. The combination of the LOFU+HIFU treatment was the most effective in reducing tumor growth over other treatment cohorts ($P<0.01$). In conclusion, LOFU+HIFU treatment induced a strong T cell-mediated tumor-specific immune response which supports additional investigations tailored to augment tumor-specific immune responses to control recurrent and metastatic cancer, using a focused ultrasound-based autologous in situ tumor vaccination approach.

Session Topic: Prostate Applications
Presentation Type: Poster
P-37

Simulation Validation and In-Vitro Demonstration of 3D MRI-controlled Transurethral Ultrasound Prostate Therapy

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Background/Introduction: MRI-controlled transurethral ultrasound therapy uses a linear array of transducer elements and active temperature feedback to create volumes of thermal coagulation shaped to predefined prostate geometries in 3D. The specific aims of this work were to demonstrate the accuracy and repeatability of producing large volumes of thermal coagulation (> 10 cc) that conform to 3D human prostate shapes in a tissue-mimicking gel phantom, and to evaluate quantitatively the accuracy with which numerical simulations predict these 3D heating volumes under carefully controlled conditions.

Methods: Eleven conformal 3D experiments were performed in a tissue-mimicking phantom within a 1.5T MR imager to obtain non-invasive temperature measurements during heating. Temperature feedback was used to control the rotation rate and ultrasound power of transurethral devices with up to five 3.5 x 5 mm active transducer elements. Heating patterns shaped to human prostate geometries were generated using devices operating at 4.7 or 8.0 MHz with surface acoustic intensities of up to 10 W/cm^2. Simulations were informed by transducer surface velocity measurements acquired with a scanning laser vibrometer enabling improved calculations of the acoustic pressure distribution in a gel phantom. Temperature dynamics were determined according to a FDTD solution to Pennes' BHTE.

Results & Conclusions: The 3D heating patterns produced in vitro were shaped very accurately to the prostate target volumes, within the spatial resolution of the MRI thermometry images. The volume of the treatment difference falling outside ± 1 mm of the target boundary was, on average, 0.21 cc or 1.5% of the prostate volume. The numerical simulations predicted the extent and shape of the coagulation boundary produced in gel to within (mean ± stdev [min, max]): 0.5 ± 0.4 [-1.0, 2.1] and -0.05 ± 0.4 [-1.2, 1.4] mm for the treatments at 4.7 and 8.0 MHz, respectively. The temperatures across all MRI thermometry images were predicted within -0.3 ± 1.6 °C and 0.1 ± 0.6 °C, inside and outside the prostate respectively, and the treatment time to within 6.8 min. The simulations also showed excellent agreement in regions of sharp temperature gradients near the transurethral and endorectal cooling devices. Conformal 3D volumes of thermal coagulation can be precisely matched to prostate shapes with transurethral ultrasound devices and active MRI temperature feedback. The accuracy of numerical simulations for MRI-controlled transurethral ultrasound prostate therapy was validated experimentally, reinforcing their utility as an effective treatment planning tool.

Acknowledgements (Funding): This research was supported by Ontario Graduate Scholarships in Science and Technology, the Natural Sciences and Engineering Research Council of Canada, the Terry Fox Foundation, the Canadian Institutes of Health Research, the Ontario Research Foundation and the Health Technology Exchange.

Session Topic: Prostate Applications
Presentation Type: Poster
P-38

Combination of HIFU, Immunotherapy and Surgery for the Treatment of Prostate Cancer

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Background/Introduction: Although high-intensity focused ultrasound (HIFU) has been demonstrated as a promising treatment modality for early stage prostate cancers (CaP), its broad impact on the overall management of CaP patients have not yet been explored. In this study, we assess the effect of combination of HIFU, immunotherapy and surgery on CaP with emphasis on tumor recurrence and host survival.

Methods: To establish a murine CaP model, 8x10^4 RM-9 cells were injected subcutaneously in C57BL/6J mice. The tumor was grown for about a week to reach 5-7 mm in diameter before treated by mechanical HIFU. Four days after the HIFU treatment, the primary tumor was removed surgically. In some groups, CPA-7 at 0.75 mg/kg was injected via tail vein one day prior to HIFU treatment, followed by additional seven injections every three days thereafter to downregulate phosphor-STAT3 (pSTAT3), a key molecule in the activation of Treg cells and immunosuppressive response. After surgery, the animals were monitored for up to 40 days or until the humane endpoints.

Results & Conclusions: Compared to surgical resection of the primary tumor, HIFU treatment prior to surgery significantly reduced tumor recurrence while improving the survival of the mice in two weeks (44% in HIFU + surgery group vs. 11% in surgery only group). The percentage of CD4+ T cells in spleen and tumor draining lymph nodes (TDLN) was increased by 21%, however, (CD4+ FOXP3+)Treg cells were increased by 10% while the expression of pSTAT3 was slightly down-regulated after HIFU treatment. With CPA-7 treatment, pSTAT3 was inhibited by more than 50% both in RM-9 cells treated in vitro and in inoculated tumors *in vivo*. In addition, the number of CD4+ T cells was increased by 60% with a concomitant decrease in Treg cells by more than 5% both in spleen and TDLN. Moreover, CPA-7 + surgery increased the number of dendritic cells (DCs) by 39% and matured DCs by 22%, compared to surgery alone. In 40 days after surgery, tumor recurrence was reduced by 50% while survival rate increased by 50% in the CPA-7 treated groups. Altogether, our results suggest that a rational combination of HIFU, immunotherapy, and surgery may improve the overall treatment outcome for prostate cancer.

Acknowledgements (Funding): This work was supported in part by NIH through grant number 1R21-CA135221 and a Prostate Cancer Pre-SCORE grant from Duke Comprehensive Cancer Center.

Session Topic: Prostate Applications
Presentation Type: Poster
P-39

Tissue Morphological Response in Prostate Cancer Patients After Treatment with a Prototype MRI Guided Ultrasound Ablation Technique

Aaron Boyes[1], Ilya Kobelevskiy[1], Stephen McCormick[1], Mathieu Burtnyk[1], Alexandra Colquhoun[3], Linda Sugar[2], Rajiv Chopra[1], Michael Bronskill[1], Laurence Klotz[3]

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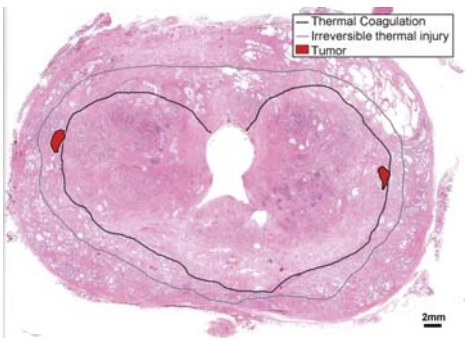
Background/Introduction: Diseases of the prostate are an attractive target for minimally invasive image-guided therapies, because this organ is relatively free of motion, and easily accessible either transrectally or transurethrally. Our group has developed a transurethral device designed for MRI-guided thermal intervention in the prostate, which has been tested extensively in gel and canine models. These experiments have been useful in validating theoretical simulations which defined the parameters used for control, and in refining the treatment system in practical terms. After many such refinements, we have recently completed a feasibility trial in patients, in which a prostate sub-volume was targeted for treatment. Here we will describe the pathological response in prostate tissue, following this novel thermal therapy.

Methods: Ethics approval was granted for investigational device testing at our institution. Patient volunteers (N=8) scheduled for radical prostatectomy, were selected from a population with low to medium grade prostate cancer, confirmed by biopsy. A few hours before prostate removal, each patient was given a spinal block anesthetic and positioned in a 1.5T MRI, with the treatment device positioned within the prostate. Using a planar ultrasound transducer operating at 8MHz, prostate sub-volumes (up to 30% of prostate tissue) were coagulated by a carefully controlled rotation of the device. MRI thermometry provided the required information for control of the device's power and rotation rate. After prostatectomy, an extensive histological procedure was followed to define a region of acute thermal damage in the prostate. Whole mount H&E stained tissue sections, carefully positioned perpendicular to the urethra, were made at 1mm separation throughout the gland. This procedure provided 30-40 slides, enabling accurate correlation between histology, MRI, and the position of the transducer during the treatment.

Results & Conclusions: A continuous region of coagulative necrosis was defined based on a marked lack of organization in the epithelium, and loss of internal nuclear detail. These characteristics encompassed a region up to 16mm from the device centre, and were well correlated with the spatial temperature distribution during each treatment. Outside this clearly defined area, there was a gradual reduction in thermal effects with normal appearing tissue visible at ≤3mm from the boundary of thermal coagulation. Additional secondary effects of thermal therapy were also noted, including dilation of glands, hemorrhagic effects and thermal fixation. Incidental findings of overlap between the heating pattern and prostate carcinoma occurred, suggesting a similar sensitivity to thermal therapy in tumor. Histological confirmation shows that this therapeutic method delivers accurate treatment of volumes defined in the prostate.

Acknowledgements (Funding): We gratefully acknowledge financial support from the Ontario Institute for Cancer Research, the National Cancer Institute of Canada, and the Terry Fox Foundation.



Session Topic:
Accelerating Development & Adoption

Overview

New technologies face numerous obstacles to rapid development and adoption, a reality which can limit patient access to life saving treatments decades after their initial introduction. This session will discuss some of the key barriers to the adoption of focused ultrasound, with particular emphasis on the displacement of older technologies, regulatory hurdles, and reimbursement challenges.

Presentations will highlight the issues most relevant to symposium attendees, and discuss ways in which researchers, clinicians and industry can collaborate to accelerate both development and adoption.

Moderators Zach Binney and Matthew Garabrant are analysts at The Advisory Board, a healthcare best practices research firm serving over 2,800 hospitals and health systems across the country. Matt and Zach work for the company's Technology Insights program, which specializes in providing customized clinical technology investment guidance for technology acquisition decision makers in hospitals and related organizations. They will discuss the competitive environment for focused ultrasound and the likely evolution of this landscape where competing technologies are emerging and declining.

Daniel Shultz, M.D. will describe the regulatory requirements in the US and EU for new applications for focused ultrasound, and discuss ways in which this audience can contribute to the process. Dr. Shultz previously held positions at the FDA and currently provides consultancy on regulatory strategy.

Descriptions of coding and reimbursement aspects with global and regional considerations will be given by Laurel Sweeney and Rebecca Emerick, from Philips and InSightec respectively.

After attending the session, delegates will have an understanding of the environment for focused ultrasound across current and future applications, will understand the key obstacles to adoption that exist, and be familiar with practical ways in which obstacles can be addressed.

Session Topic: Uterine Fibroids
Presentation Type: Oral
IS-13

Fibroid Therapy: What's In Your Tool Box? Hopefully More Than Only Hammers

Linda D. Bradley

Cleveland Clinic, Department of Obstetrics and Gynecology, Cleveland, OH, USA

While hysterectomy remains the most effective option for women seeking permanent relief of fibroid related symptoms, the one hammer and nail surgical philosophy is no longer practical for our diverse patient population. Likewise, the uterus isn't solely owned by the gynecologist any longer. A collaborative practice between the interventional radiologist and gynecologist is paramount to offering novel and effective therapies. Additionally, a surgeon's surgical repertoire and philosophy, socioeconomic, geography, reimbursement of services, and scope of options available in a medical community impact practice patterns.

A slow decline in hysterectomies this past decade is perhaps because there are myriad options now available for the treatment. Patient desire for uterine preservation and patient demand for alternatives to hysterectomy have channeled fervent discussion between the patient and her physician; which have prompted gynecologists to embrace novel technology. Physicians, who continue to only recommend the one hammer (hysterectomy) option, may find fewer nails in their practice. Gynecologists must possess many tools in their toolbox in order to remain up to date in their specialty.

Uterine health is more than the sum of its individual parts. Approximately, 50% of women with uterine fibroids are asymptomatic. For those women, reassurance is all that the doctor should order! Bury the word "tumor." State what you mean. Use clear language such as, "your uterus is enlarged and it is (or is not) causing any problem." Follow the patient annually, unless new symptoms occur. Our goal should focus on establishing patient-centered outcomes that meet the patient's needs. Tenets important to the patient may include her concerns about sexuality, sense of "intactness," avoidance of general anesthesia, prolonged recovery, surgical scars, or need for blood transfusion. These critical conversations are an essential part of the patient/physician dialogue.

We now have many more hammers to treat the nail. Alternatives to hysterectomy include: hormonal, anti-fibrinolytic therapy, non-steroidals, levonorgestrel-releasing intrauterine system, myomectomy, uterine fibroid embolization (UFE), MRI-guided focused ultrasound (MRgFUS), and endometrial ablation. Many of these options provide excellent outcomes for the ideal candidate. Each fibroid is unique and one of a kind. It's our role to utilize the patient history and most cost-effective technology to evaluate the patient chief complaint. When possible, a minimally invasive surgical route is recommended.

Choosing alternatives to hysterectomy requires that the physician understand the inclusion and exclusion criteria, outcomes, complications, and patient preference. Most importantly, size and location of fibroids does matter as it relates to options offered. A litany of all the alternative options should not be given to the patient, because there will be reasons why one option is not suitable for the patient. Critical conversations and critical evaluation directs appropriate therapy.

Matching the right patient with the right procedure requires the right doctor to explain the options and offer the most minimally invasive surgical option or medical option. It might also include the right team of interventional radiologists to perform UFE or MRgFUS. When hysterectomy is indicated, a minimally invasive approach should be recommended.

Clearly more research and federal dollars are needed to understand uterine fibroids. We need more randomized control trials, long-term registries and outcome based-research. Until then, individualize the care of your patient. Make sure that you have more than one hammer to treat the nail.

Session Topic: Uterine Fibroids
Presentation Type: Oral
IS-14

MR-guided Focused Ultrasound Surgery of Uterine Fibroids: Into the Mainstream – From Clinical Success to Daily Routine

Matthias F. Matzko[1], Christoph G. Trumm[2]

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Purpose: To present technical outcome and clinical response of magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS) of symptomatic uterine fibroids and to share operating experience of more than two years of ablation experience.

Methods: Between 06/2008 and 04/2009, MRgFUS (ExAblate 2000, InSightec, Haifa, Israel) ablation was performed in 41 women (42±6 y; range 26-55 y) with symptomatic uterine fibroids under conscious sedation. MR images obtained before (T2w FSE) and immediately after the treatment (T1w FSE fs with i.v. gadolinium) were used to calculate the number and total volume of uterine fibroids, and the non-perfused volume (NPV) of the treated fibroids, using a standard sum of the slices method. The NPV ratio (%) was calculated as the ratio of the sum of NPV of all treated fibroids divided by the total volume of all uterine fibroids. Clinical response was assessed with the symptom severity scale (SSS) of the Uterine Fibroid Symptoms Quality-of-Life Questionnaire obtained at baseline and 3 months after treatment. Mean change of the SSS was analyzed using a paired t-test.

Beyond that and in terms of our experience with two years FUS-based ablation of uterine fibroids with more than 230 treatments we want to show and discuss interesting cases.

Results & Conclusions: MRgFUS treatment was well tolerated by all women. No major complications occurred. Average (MV±SD) number and total volume of fibroids visualized on pre-treatment MR images were 3.2±3.0 (range, 1-10) and 227±192 mL (range, 8-719 mL), respectively. A mean of 2.2±1.9 (range, 1-7) fibroids were treated per patient. Mean NPV was 59.1±19.0% (range, 34.8-100%). Transformed SSS decreased significantly ($p<.001$) from 62.7±12.7 at baseline to 35.5±10.8 after 3 months. Conclusion: Our results show that MRgFUS for selected and suitable patients is a safe and effective treatment alternative for symptomatic uterine fibroids, resulting in early and significant symptom relief. Efforts in the further development of the technology are necessary to extend the range of patients that are suitable for therapy and to overcome obstacles regarding the executions of daily routine therapy.

Session Topic: Uterine Fibroids
Presentation Type: Oral
IS-15

Patient Selection for MRgFUS in the Treatment of Uterine Fibroids

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Appropriate patient selection is critical for ensuring the success of MRgFUS in patients with uterine fibroids. Despite recent advances in this technology, patient candidacy is still based on the ability to effectively heat the fibroid tissue and complete the treatment in 1-2 sessions. We know from recent publications that shrinkage rates of fibroids are between 20-50% depending on the non perfused volume (NPV) after treatment and this must be taken into consideration when determining candidacy and overall fibroid load.

Of the 342 patients screened with MRI pelvis with and without contrast 67% were candidates based on the original screening criteria. Of these, 127 patients have been treated with MRgFUS, 102 patients were candidates but have elected not to proceed with MRgFUS (mostly due to reimbursement issues), and 113 patient (33%) were NOT candidates due to a variety of other pelvic pathologies (not suspected on physical examination or ultrasounds) and technical factors that would preclude the beam from entering the fibroid (below).

Too many fibroids (>5): 39
Adenomyosis: 19
Nonenhancing (hemorrhagic or necrotic): 13
Intracavitary lesions (fibroids or polyps): 13
Too deep or pedunculated: 9
High signal on T2 images: 9
Findings suspicious for cancer: 8
Too large (>10 cm without Lupron): 7
Too small (<2cm): 6
Clips/metal in beam path: 3
History of liposuction: 1

The 33% that were not candidates still benefited from the MR screening exam. Most patients were excluded due to the presence of too many fibroids and adenomyosis. There were 13 patients that fit into 2 exclusion criteria categories.

Too many and intracavitary lesions: 4
Too many and nonenhancing: 3
Too many and too deep/pedunculated : 2
Too deep/peculated and high signal on T2 images : 1
Intracavitary and high signal on T2 images: 1
Adenomyosis and too small: 1
Adenomyosis and Too deep /pedunculate:1

Of the 8 patients with MRI findings suspicious for cancer, 6/8 had pathology proven sarcomas (2), endometrial cancer (1), or benign findings (3). 2 patients have not had surgical confirmation of their suspected pelvic abnormalities. The most common radiographic findings in patients with cancer was a heterogeneously enhancing mass where the necrosis was not centrally located and concurrent blood products in the endometrium. Although 8 patients had suspected cancer on MRI scans, 3/8 had proven malignancies and thus 3/342 patients screened with MRI had cancer. This % is higher than the reported incidence of both endometrial cancer and uterine sarcomas although the patients that were screened in this study are a subset of patients that are more symptomatic than the general population.

This data shows that 67% of patients with symptoms and ultrasound findings consistent with fibroids are potential candidates for MRgFUS based on MRI findings. Proper evaluation of images ensures that the procedure could technically be performed to ensure a successful outcome. The 33% of patients that are not candidates still benefit from characterizing their pelvic pathologies which allows for more directed therapies and importantly can suggest the presence of an underlying malignancy not otherwise suspected clinically.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-1

MRgFUS Treatment for Uterine Myomas: Safety, Effectiveness and Pathogenesis

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Background/Introduction: Uterine myomas are common benign tumors in women of reproductive age. They are treated with hysterectomy, myomectomy, drug therapy, uterine artery embolization (UAE), and Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS). Patients prefer non-invasive treatment to preserve fertility and avoid surgery. In 2004, the U.S. Food and Drug Administration approved the ExAblate 2000® MRgFUS system for uterine myoma therapy. The success of MRgFUS depends on the pathogenic characteristics of the myomas before treatment, such as cellular composition, mitotic activity and edema. The current study examined the safety and efficacy of MRgFUS treatment for different pathogenic characteristics of myomas.

Methods: A total of 611 patients, aged 20-55 years, with symptomatic uterine myomas underwent MRgFUS treatment between 2006 and 2009, and were followed for 36 months. Prior to the treatment, patients underwent general physical and gynecological examinations, MR imaging, trepan biopsy of the myoma, and ultrasound imaging. Safety was determined by tracking adverse events. Efficacy was assessed by measurement of the non-perfused volume (NPV). Ultrasound, MR imaging with contrast enhancement, symptom scores, and treatments durability were also used as efficacy measures.

Results & Conclusions: There was a very low rate of post treatment complications (0.8% or 5 cases out of 645 procedures). MRgFUS resulted in volume reduction, symptomatic improvement, an increase in the Quality of Life (QoL) score, reduction in the vascularity of the treated myomas, and long-term durability (2.5-3 years). An NPV value of at least 20% results improvement in clinical symptoms. A durability of symptoms improvement for 1-1.5 years correlated with an NPV between 50-80% and 2.5-5 years correlated with an NPV exceeding 80%. MRgFUS was more effective for patients with less than 3 myomas unobstructed, myomas characterized by MR-hypo-intensity, a diameter of 2 to 6-8 cm, and an intramural component greater than 30%. Hypo-intense myomas are optimal candidates because the abundant connective tissue absorbs the FUS energy. Mitotically active and edematous myomas are not ideal due to limited connective tissue and the absence of a substratum for FUS absorption, respectively. In conclusion, MRgFUS is a safe treatment for uterine fibroids; and effective in prevention of the clinical symptoms of uterine myomas, preparation for transcervical myomectomy, and delay of surgery.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-2

Dynamic Contrast-enhanced Magnetic Resonance Imaging Predicts Immediate Therapeutic Response of MR-guided High-intensity Focused Ultrasound Ablation of Symptomatic Uterine Fibroids

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Background/Introduction: Up to now, high signal intensity of uterine fibroids on T2-weighted MR image has been known as the most important poor prognostic factor of MR-HIFU therapy. However, assessment of tissue perfusion as a predictor of HIFU therapy has not been tried yet. Therefore, the purpose of our study was to evaluate DCE (dynamic contrast-enhanced)-MR parameters in predicting ablation efficacy of MR-HIFU (MR-guided high-intensity focused ultrasound) therapy in the treatment of symptomatic uterine fibroids.

Methods: Ten symptomatic uterine fibroids (diameter: mean 8.9cm, range 4.7-12cm) in ten women (mean age 42.2) were treated with MR-HIFU therapy using volumetric ablation technique. DCE-MR and conventional contrast-enhanced MR were obtained as a baseline and an immediate follow-up study, respectively. After regions of interest of each treatment cell were properly registered to both MR studies, DCE-MR parameters (K^{trans}, v_e, v_p) and operator-controllable therapy parameters (power, frequency, treatment cell size) were investigated on a cell-by-cell basis in order to reflect tissue inhomogeneity. Then, two types of ablation efficacy index (240 EM ratio = volume of 240 equivalent minutes at 43°C / NPV ratio = treatment cell volume, non-perfused volume/treatment cell volume) were correlated with those parameters using multiple linear regression analysis to know which factors were significant predictors for ablation efficacy.

Results & Conclusions: Number of treatment cells used was 293 (4mm, n=12; 8mm, n=115; 12mm, n=149; 16mm, n=17) in total, and all of them were analyzable. 240EM and NPV ratios were 1.06±0.58 and 0.67±0.39, respectively. K^{trans} (240 EM ratio, B=-10.167, p<0.001; NPV ratio, B=-8.028, p<0.001) among DCE-MR parameters and acoustic power (240 EM ratio, B=0.005, p=0.010; NPV ratio, B=0.006, p< 0.001) and frequency (240 EM ratio, B=1.137, p=0.001; NPV ratio, B=1.409, p<0.001) among therapy parameters were revealed to be independently-significant predictors for both types of ablation efficacy. Conclusion: Ktrans of baseline DCE-MR, acoustic power and ultrasound frequency were revealed to be independently significant determinants for the immediate therapeutic response of volumetric MR-HIFU ablation of symptomatic uterine fibroids. High Ktrans value is deemed to be a significant predictor of poor treatment results. Therefore, in such cases, the choice of higher acoustic power and/or higher ultrasound frequency would enhance the ablation efficacy.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-3

Clinical Predictors of Magnetic Resonance-guided Focused Ultrasound Surgery

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Background/Introduction: There is accumulating evidence for the efficacy and safety of MRgFUS treatment in women with uterine leiomyoma. However, it is still not clear which patients benefit most from this minimally-invasive technique and which patients need additional treatment because of lack of symptom relief or recurrence of symptoms. Our objective is to identify baseline patient characteristics that predict successful MRgFUS treatment.

Methods: Our cohort consists of one hundred thirty women consecutively treated with MRgFUS at Mayo Clinic between March 2003 and December 2009 under commercial treatment guidelines. Following treatment, the patients were followed through phone interviews conducted at 3-, 6-, and 12-month intervals to assess self-reported symptom relief and additional procedures. A retrospective cohort analysis was conducted utilizing medical charts to assess demographic, medical and gynecological histories and presenting symptomatology. The Kaplan-Meier method was used to estimate the cumulative incidence of additional treatment, and Cox proportional hazards models were fit to evaluate factors associated with the need for a subsequent procedure.

Results & Conclusions: Our study group was comprised of largely Caucasian (87.5%), premenopausal (92.4%) women with an average age of 45.1 ± 5.5 years (range: 31–58). Almost half of the patients were overweight (45.3%) and a little more than half of the patients were nulliparous (54.3%). At baseline, women reported heavy menstrual bleeding (61.5%), bulk symptoms (67.7%) and pain (15%). The mean duration of the dominant symptom was 20.6 ± 15.7 months (range: 3-86). The majority of the patients (61.5%) had multiple fibroids and the volume of the total fibroid load was 305 ± 292 cc3 (range: 18-1845). Seventy-one patients were treated in a single session and 59 women underwent two sessions on consecutive days. The mean duration of follow-up was 18.3 ± 10.8 months (range: 1 day–49.6 months). Twenty-seven women underwent a subsequent fibroid treatment within a mean of 15.8 ± 8.8 months (range: 6.2–25.3). The cumulative incidence of additional fibroid treatment was found to be 9.7% and 24.8%, 12 months and 24 months after treatment respectively. Younger age at treatment (p=0.016) and having a single fibroid (p=0.029) were associated with the need of additional treatment. Other variables such as weight, smoking status, parity, age at fibroid diagnosis, presenting symptoms, baseline symptom severity score (SSS), total fibroid volume, concomitant diagnosis of adenomyosis or endometriosis, prior use of oral contraceptives or past medical history were not found to be associated with the treatment outcome. Research focusing on identifying baseline predictors of successful MRgFUS will help clinicians in their daily decision-making to choose the most optimal fibroid treatment for their patients.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-4

Analyzing Screen Failures Prior to MRgFUS for Uterine Fibroids: Do African American (AA) Women Have Different Characteristics?

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Background/Introduction: Symptomatic uterine fibroids can be treated by MRgFUS technology. In order to optimize the likelihood of a successful outcome, understanding selection criteria is important. Previous studies have suggested that African American (AA) women have more severe fibroid disease than women of other racial and ethnic groups. The aim of our study was to compare the rate and the reasons for women excluded from treatment due to "screen failure" between AA women and other women with symptomatic uterine fibroids who sought MRgFUS treatment as a part of clinical trial protocols.

Methods: A retrospective analysis of the medical charts of subjects was performed. This was of two groups of women who had self-selected this treatment option—namely an AA and a non AA group (Caucasian and Asian). All were evaluated at our hospital from 4/2004 to 2/2006. Our screening protocol included a history, physical and a pelvic MRI to exclude anatomic issues precluding a safe and effective treatment. All women completed the UFS- SSS-QOL questionnaire, which focuses on the woman's quality of life and fibroid symptoms (range from 0: no symptoms to 100: severe symptoms). The typical symptom severity score (SSS) for a normal menstruating woman is 37.5-53.1 according to the UFS-QOL questionnaire. As this treatment focuses on symptomatic fibroids, patients with UFS-SSS-QOL <42 or those where fibroids could not be safely or completely treated as assessed by pelvic MRI were defined as "screen failures" and were not treated. Only patients that were classified as screen failures were included in this analysis.

Results & Conclusions: A total of 94 subjects provided informed consent for MRgFUS studies—40 AA and 54 non AA. Thirty-nine women (41.4%) failed to meet one or more enrollment criteria and were deemed screen failures. AA women were more likely to be screen failures (52.5% vs. 33.3%, p=0.06). The reason for screen failure also differed significantly between groups. AA were more likely to fail screening due to MRI findings (76.2% vs. 38.9%, p<0.05), while non AA women failed screening due to a UFS-QOL SSS <42 (44.4% vs. 9.5%, p<0.05). AA subjects had a higher mean number of fibroids at screening MRI (11.7+11.8 vs. 4.4+3.5, p<0.04) and their fibroids' mean diameter was smaller (2. 7+0.9cm vs. 5.9+cm, p<0.01) compared with non AA, although the uterine sizes were similar in both groups. AA patients seeking MRgFUS treatment for uterine fibroids presented with a significantly larger number of fibroids which are significantly smaller compared with non AA, and they were found to have significantly more technical problems which would interfere with safe delivery of treatment. The main reason for screen failures among non AA was inadequate fibroid' associated symptoms compared the AA population. These findings are consistent with prior studies which suggest AA women may have more severe disease than non AA women.

Acknowledgements (Funding): Dr. Machtinger is funded for a part time fellowship by the Focused Ultrasound Surgery Foundation.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-5

Novel Technique for Targeted Vessel Ablation During Magnetic Resonance Imaging-guided High Intensity Focused Ultrasound Treatment of Uterine Fibroids

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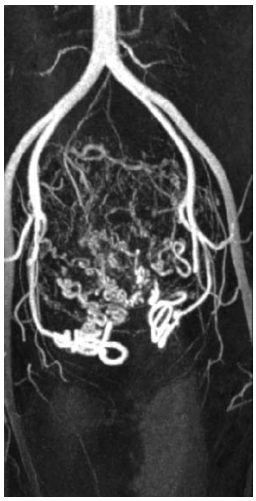
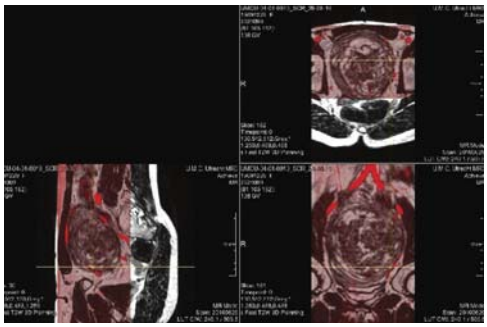
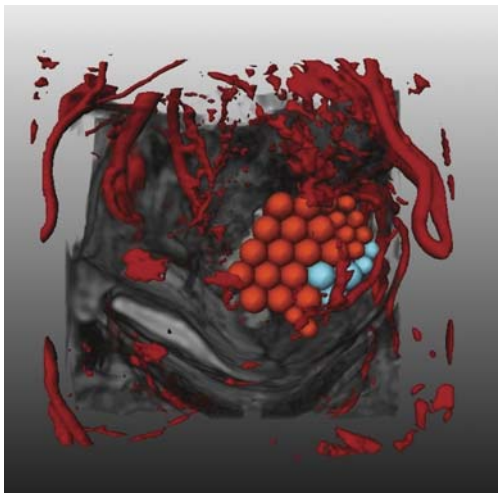
Background/Introduction: Magnetic Resonance Imaging-guided High Intensity Focused Ultrasound (MR-HIFU) is a non-invasive treatment modality for uterine fibroids. Limiting factor is the long treatment time, which can exceed four hours. Methods to increase efficacy should therefore be explored. We observed that ablation of a small target area within the fibroid sometimes resulted in almost complete fibroid necrosis. The most likely explanation is ablation of vessels supplying the fibroid, resulting in downstream necrosis. We present a method for targeted vessel ablation, which potentially can be used to achieve fast, complete fibroid ablation during MR-HIFU.

Methods: Magnetic Resonance Imaging-guided High Intensity Focused Ultrasound (MR-HIFU) is a non-invasive treatment modality for uterine fibroids. Limiting factor is the long treatment time, which can exceed four hours. Methods to increase efficacy should therefore be explored. We observed that ablation of a small target area within the fibroid sometimes resulted in almost complete fibroid necrosis. The most likely explanation is ablation of vessels supplying the fibroid, resulting in downstream necrosis. We present a method for targeted vessel ablation, which potentially can be used to achieve fast, complete fibroid ablation during MR-HIFU.

Results & Conclusions: We used this method in two patients. Targeted vessel ablation resulted in almost total fibroid devascularisation (84 respectively 90%) of treated fibroids in these patients. The truly ablated volume in patients 1 and 2 was 50 ml and 122 ml, respectively, while the non-perfused volume determined immediately post-treatment was 211 ml and 282 ml, respectively, which is 4.2 and 2.3 times higher than expected based on the thermal dose distribution. The possible mechanism is that the thermal stimulus causes vessel constriction, resulting in decreased cooling by blood; and thus, an increased temperature inducing thermal coagulation of the vessel wall. Areas containing supplying vessels to the fibroid were sometimes more difficult to heat compared with other areas (figure 3, blue treatment cells), demonstrated by longer ablation time needed and lower end temperature in that region (about 50° Celsius, versus 60-70° Celsius in 'normal' fibroid tissue). This is probably due to the heat sink effect of local blood flow. One patient complained of pain during heating of these areas. In our opinion, targeted vessel ablation may be a promising technique for obtaining larger non-perfused volumes in less treatment time. Careful visualization of the supplying vessels by use of an MRA technique is needed for proper treatment planning.







Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-6

C=Magnetic Resonance-guided Focused Ultrasound Treatment of Uterine Fibroids in Patients with Abdominal Scars, Using an Energy-Blocking Scar Patch

Sang-Wook Yoon

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Background/Introduction: Previously, abdominal scars were considered a contraindication to Magnetic Resonance-guided Focused Ultrasound (MRgFUS) treatment of uterine fibroids, if they were in the energy beam path. The purpose of this study was to assess the clinical potential of an energy-blocking scar patch for MRgFUS treatment of uterine fibroids in patients with abdominal scars.

Methods: The current study is a HIRA compliant, prospective, nonrandomized, single arm study, which was approved by an institutional review board. After providing informed consent, patients with symptomatic leiomyomas and abdominal scars were enrolled and treated with MRgFUS using an isolating patch covering the scar. Scar patches composed of ultrasound blocking material were placed on patients' skin in order to cover the scar prior to treatment. Adverse events were recorded during the procedure, and throughout a follow up period of 3 months. Immediately following each treatment, contrast enhanced T1-weighted MR images were acquired, and the non-perfused volume (NPV) ratio was measured to determine the technical success of the treatment.

Results & Conclusions: Twenty patients with a mean age of 44 years were treated for their symptomatic uterine fibroids. The average size of the scar was 3.2 X 104.6 mm. All treatments were completed with no technical problems. No serious adverse events were reported. The average NPV ratio was 53.5%±21%. The scar patch provides an effective treatment option for patients with uterine fibroids and scars in the beam path, who were previously excluded from MRgFUS treatment due to an increased risk of skin burn.

Session Topic: Uterine Fibroids
Presentation Type: Oral
UF-7

Treatment of Adenomyosis by Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS): A one-year Prospective Follow-up Study

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Background/Introduction: To date, there is no accepted conservative uterus-preserving interventional therapy for uterine adenomyosis. The aim of this study was to evaluate the efficacy and safety of magnetic resonance-guided focused ultrasound surgery (MRgFUS) for symptomatic adenomyosis after a one year follow-up.

Methods: Fifty-two patients with symptomatic adenomyosis diagnosed by MRI were treated by MRgFUS at five hospitals in Japan, Singapore and Israel in a prospective, nonrandomized, multi-center study. Patients were followed-up clinically for 12 months to evaluate changes in their symptoms and possible side-effects. Changes in the Symptoms Severity Score (SSS) based on the Uterine Fibroids Symptoms Quality of Life (UFS-QOL) questionnaire, and a grade of bodily pain, adverse event report using the SIR classification system served as outcome measures.

Results & Conclusions: Of the 52 patients, 47 reached the one-year follow-up without the need for alternative treatments. In these 47 patients, we observed a significant reduction in mean SSS from 47.1±16.1 at pre-treatment to 30.9±14.3 at 12 months post-treatment ($P < 0.001$). This reduction correlated negatively with uterine size (correlation =-0.35; $P=0.012$) . There was a significant reduction in the mean score of general bodily pain from of 3.3±1.3 pre-treatment, to 2.5±1.2 at 12 months post-treatment ($P < 0.001$). Only five transient minor adverse events were recorded during the one-year follow-up. The results of this study indicate that MRgFUS can be an effective and safe non-invasive treatment option for uterine adenomyosis.

Acknowledgements (Funding): We wish to acknowledge the staff of the five centers that participated in this study and enabled us to recruit and treat the participants in such a successful manner. The study was supported and funded by InSightec.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-40

Uterine Fibroid Treatment Patterns After Introduction of an Interdisciplinary Fibroid Program

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Background/Introduction: The management of uterine leiomyomas is typically carried out by a single specialist, the gynecologist. We sought to investigate the effect on pattern of practice after the introduction of a novel multidisciplinary fibroid program that includes both the gynecologist and the interventional radiologist.

Methods: We designed the first interdisciplinary fibroid program at UCLA, which commenced on August 2008 and has continued to the present. Patients referred to UCLA for evaluation of management of leiomyomas are seen by both a radiologist and a gynecologist in an outpatient setting. All treatment options including magnetic resonance guided focused ultrasound (MRgFUS), uterine artery embolization, myomectomy, hysterectomy and watchful waiting are discussed with patients at time of consultation. Evaluation by our radiologist was among the inclusion criteria for patients in the study. In this IRB-appoved study, the charts of all patients who underwent evaluation at our fibroid treatment program were reviewed and subsequent treatment patterns were determined.

Results & Conclusions: There were 334 patient inquires, and 145 (43%) patients received formal consultation by our radiologist (Table 1). Sixty-four (44%) patients underwent treatment; of those, 27 (19%) patients underwent MRgFUS and 9 (6%) patients are pending MRgFUS treatment, for a total of 36 patients (25%) who received or will be receiving MRgFUS. Ten patients (7%) received UAE, 13 (9%) patients received myomectomy, 3 (2%) underwent hysterectomy, and 2 (1%) are pending treatment pending completion of hormone therapy. Eighty-one (56%) patients did not undergo treatment: 29 (20%) are candidates for MRgFUS but are pending decision; 32 (22%) did not meet MRgFUS qualification criteria; 16 (11%) desired MRgFUS but treatment was denied by their insurance provider, 2 (1%) were pending further evaluation, and 2 (1%) opted for watchful waiting. A total of 36% of patients who were evaluated by our radiologist desired MRgFUS; of those, 70% patients have received treatment and the remaining 30% were denied coverage by their insurance company. Conclusions:
An interdisciplinary unbiased approach to fibroid treatment is effective and at our institution. Approximately one-third of our patients desire MRgFUS.

Table 1: Treatment patterns of patients evaluated at UCLA Fibroid Program

TREATMENT GROUP (n = 64)	No. pts (%)
HIFU	27 (19)
HIFU pending	9(6)
UAE	10(7)
Myomectomy	13(9)
Hysterectomy	3(2)
HIFU/myomectomy pending hormone treatment completion	2(1)
NON-TREATMENT GROUP (n= 81)	
Not Candidates	32(22)
Candidates pending decision	29(20)
Further evaluation pending by gynecologist	2(1)
Pts interested in MRgFUS but denied by insurance	16(11)
Opted for no treatment	2(1)

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-41

Short-term Results of Magnetic Resonance Imaging-guided Focused Ultrasound Surgery for Adenomyosis Patients Indicate Symptomatic Relief and Pain Reduction

Sang-Wook Yoon

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Background/Introduction: To evaluate the degree of symptomatic relief obtained following treatment with Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) in patients with adenomyosis.

Methods: 35 consecutive patients, who were diagnosed as suffering from symptomatic adenomyosis, were treated with MRgFUS. Treatment efficacy was measured by tracking the level of menstrual pain as well as the symptom severity score (SSS) from the Uterine Fibroids Symptoms Quality of Life (UFS-QOL) questionnaire over the period of 6 months.

Results & Conclusions: The degree of menstrual pain, as reported by the treated patients, was reduced from a mean of 8.5 ± 2.4, at baseline, to 4.5 ± 2.4 by the 6 months follow-up ($P<0.001$). In addition, the level of symptoms (bleeding and pressure) as measured by the SSS has also decreased from a mean baseline score of 54 ± 15 to 32 ± 14 over those 6 months ($P<0.001$). No serious complications were recorded during the treatments or the follow-up period. Short-term clinical improvement (as measured by the decrease of symptoms) for symptomatic adenomyosis treated with MRgFUS has been shown in this study. The treatment modality allows safe treatments. Longer follow-up is required in order to verify the sustainability of this treatment option.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-42

The Effects of Single Dose of GnRH Agonist Prior to Magnetic Resonance Guided Focused Ultrasound Surgery of Uterine Fibroids

Sang-Wook Yoon

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Background/Introduction: MR guided focused ultrasound surgery (MRgFUS) is a non-invasive treatment for symptomatic uterine fibroids. GnRH agonists are generally used in a continuous fashion for decreasing fibroid volume and vascularity prior surgery and were also found as effective prior to MRgFUS. Usually, multiple doses of GnRH agonist involve postmenopausal side effects. The purpose of this study is to assess the initial safety and efficacy of a single dose of GnRH agonist prior to MRgFUS, by reducing fibroids vascularity and size.

Methods: Fifteen premenopausal Asian patients received a single dose of GnRH agonist. Thirty days later, the patients were treated with the MRgFUS. Mean patients age was 37.3±5.3 years. Nineteen fibroids were treated with mean fibroid volume prior the GnRH agonist injection of 192.1cc±111cc. The fibroid vascularity was measured before the injection and in treatment day by standardizing its mean pixel intensity to a 0-100 scale, using reference intensities of muscle and fat in the images, respectively.

Results & Conclusions: No adverse events were reported during follow-up. None of the patients expressed postmenopausal discomfort. Mean fibroid shrinkage between screening and treatment day was 12%±11%. The mean fibroid vascularity reduction was 38%±85%. The reduction in intensity was higher in cases with hyper-intense baseline fibroids. The post treatment non perfused volume ratio was 62%±22%. The mean treatment duration in minutes was 153±26. One dose of GnRH agonist prior to MRgFUS treatment has the potential to improve treatment efficacy by reducing fibroids vascularity and size, while avoiding the side effects of multiple doses of GnRH agonists.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-43

Diffusion Weighted Imaging of MR-guided High Intensity Focused Ultrasound Ablation of Uterine Fibroids: Influence of Different B-values

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Background/Introduction: The purpose of this study was to assess the feasibility of using diffusion weighted MR imaging (DWI) and apparent diffusion coefficient (ADC) mapping with different b-value combinations to evaluate treatment results after volumetric magnetic resonance imaging-guided high intensity focused ultrasound (MR-HIFU) ablation of uterine fibroids.

Methods: Imaging data from thirteen patients from two different treatment centers with a total of sixteen symptomatic uterine fibroids treated with volumetric MR-HIFU ablation were analyzed. Pre-treatment (n=16 fibroids), directly post-treatment (n=15) and 1 month follow-up (n=14) images were obtained by using T1-weighted contrast-enhanced (CE) imaging and DWI using b-values 0, 200, 400, 600 and 800 s/mm², on a 1.5-T MR-HIFU system. ADC maps were constructed for quantitative analysis of ablation results. Regions of interest localized to non-perfused areas on post-treatment CE images were drawn to identify treated regions inside the fibroids. Quantitative statistics were obtained from treated and non-treated uterine fibroid tissue. Four different combinations of b-values were used to calculate the ADC: 1) using all b-values; 2) using the lowest two b-values emphasizing perfusion effects (0, 200 s/mm²); 3) using the highest b-values emphasizing mainly diffusion effects (400, 600 and 800 s/mm²); and 4) using lowest and highest b-values which is the most commonly used method in literature (0, 800 s/mm²).

Results & Conclusions: The mean ADC in non-perfused tissue decreased immediately post-treatment compared with perfused fibroid tissue, and increased one month post-treatment (Figure 1). Calculating the ADC with only the lowest b-values (0 and 200 s/mm2) was found to reflect decreased ADC values in treated fibroid tissue compared with non-treated tissue best (Figure 2A). One month after treatment ADC values increased, best recognizable when high b-values were used (Figure 2B). We conclude that DWI and ADC mapping are promising for evaluation of treatment results after volumetric MR-HIFU of uterine fibroids. On average, the ADC of treated tissue decreases immediately post-treatment, followed by an increase one month post-treatment.

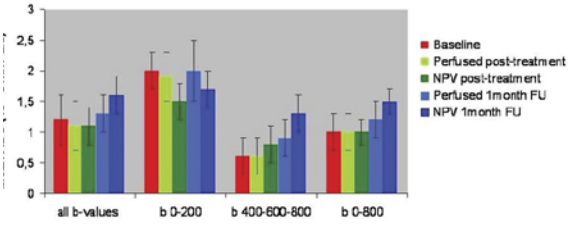

Figure 1

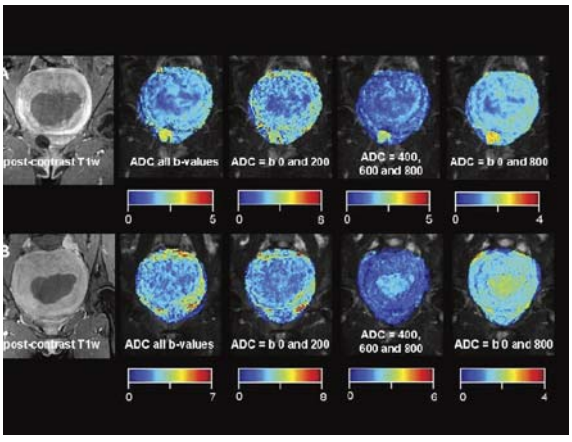

Figure 2A

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-44

Initial Results of Fertility Preservation After MRgFUS Treatment of Uterine Fibroids in Spain

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Background/Introduction: Our site is the only MRgFUS site in Spain, located at the Scientific & Technological Park Cartuja 93 of Seville. We present the initial results of fertility preservation after MRgFUS treatment of uterine fibroids in our patient series.

Methods: Equipment: ExAblate 2000 (InSightec Ltd, Israel) in a 1.5T MR (GE Healthcare, USA). R&D is carried out in the frame of a Laboratory of Non Invasive Technologies for Tumor Treatment, established in collaboration between the author's institutions. Clinical activities are developed at Iberian Medical Research Institute—Instituto Cartuja and the scientific and technological activities at the Engineering School of the University of Seville. Currently available MRgFUS applications include treatment of uterine fibroids and palliative treatment of pain in bone metastases. Patient selection is based in published clinical and radiological criteria. Interested patients are required to fill out a clinical questionnaire including questions about previous abdominal surgeries, location and type of scar, Symptom Severity Score (SSS) scale, growth pattern of myomas, etc. We also ask them about fertility problems. A conventional contrast MR is performed to evaluate image features. Final decision about treatment is based on clinical and radiological data. Follow up consists in phone calls 24 hours after treatment to evaluate possible adverse effects, 48 hours after to check if the patient has returned to work, and after 3 months to ask if she has improved in symptoms. After 6 and 18 months, an MR is performed and symptoms are quantified using the SSS questionnaire.

Results & Conclusions: 42 treatments have been performed in our center since May 2008 (38 patients with 4 double treatments). Four women got pregnant after MRgFUS treatment. Volume of treated myomas was in the range 8-870 cc, and 88.4% had an intramural location. Sonications per treatment were between 50-250. Among our pregnant patients, 1 case was a cesarean section (due to previous myoma) at term, delivering a healthy baby with no complications during pregnancy. Two other cases are still pregnant, being deliveries expected for September and January. Two of these three women were nullipara, and two of them had a previous history of fertility problems before MRgFUS treatment. Time to achieve pregnancy was between one and four months after treatment. Another case had two term pregnancies before becoming pregnant two months after MRgFUS treatment. It ended up in a miscarriage on week 9. Our data agree with other published results. MRgFUS is safe for women that have not completed their fertility desire, and it may have also helped some women with fertility problems due to uterine fibroids. Being a very promising treatment option, larger data sets are still needed.

Acknowledgements (Funding): Work partially funded by a R&D Project by the Agency IDEA (Andalusian Regional Ministry of Innovation and Science, Spain) 2007-09.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-45

Characterization of Fibroids After Initial Treatment with MRgFUS and Survival Curves, Interesting Correlations Between Epidemiology and Imaging Features

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Background/Introduction: This study was undertaken to clarify the early effects of magnetic resonance-guided focused ultrasound surgery (MRgFUS) in the assessment of nonperfused ratios of a contrast enhanced image immediately after the procedure; as well as to know the decay volumes curves of fibroids after the ablation.

Methods: Retrospective analysis of 92 fibroids in 62 patients treated from August 2006 to January 2009, at the Magnetic Resonance Imaging Unit of the Medica Sur Hospital. The volume of treated fibroid and nonperfused volume (NPV) were recorded, while symptom outcome was assessed with a symptom severity score (SSS). Fibroids were classified as hyperintense or hypointense relative to skeletal muscle on pretreatment T2- weighted MR images. Fibroids were classified into 3 types based on the signal intensity of T2-weighted sequence as follows: type 1, low intensity; type 2, intermediate intensity; type 3, high intensity. Using Kapplan and Meyer Method, we obtained survival curves depicting the gradual decrease in size of three locations of fibroids (subserosal submucosal and intramural) volume after thermal ablation.

Results & Conclusions: The average age of patients was 38.9 ± 5.9 years (range 23 to 50 years). Ninety-two fibroids were evaluated, which showed T2 volume of 75.5 ± 98.9 cm3 (range 0.17 to 580 cm3). The PV was 72.3 ± 90.9 cm3. The volumes post MRgFUS were 47.9 ± 61.4cm3 NPV values and the FVP of 24.5 ± 41.9 cm3. The percentage of thermal ablation was 84.6 ± 101.15%. The comparison of the initial volume to final volume after treatment had a significant change with $p < 0.5$. The size decrease of fibroids showed: 50% of fibroid size reduction treaty reached to 200 days for the three different locations. 100% of subserosal and submucosal fibroids decreased in size in about 300 days. 100% of intramural fibroids decreased in size in about 500 days. The efficacy of MRgFUS correlates with the signal intensity of T2-weighted magnetic resonance images. The larger the NPV immediately after treatment, the greater the volume reduction and symptom relief achieved. This finding suggests that there is a strong link between the success of therapy and devascularization and/or necrosis. These findings may help both in selecting appropriate patients for MR-guided focused ultrasound surgery and in predicting patient outcome. Decay curves may alert about the follow-up times, which we should extended up to 500 days. The predominant symptoms were bleeding, abdominal pain, abdominal oppression, alteration of sexual life, urinary frequency, and fatigue pre- or post-treatment according to the location. Fibroids with extension submucosal bleeding showed a decrease of 90% to 48%, abdominal pain decreased by 65% and 23% in the pre and post-treatment respectively. Intramural fibroids that altered sexual life decreased by 35% to 17%, mass sensation fibroids with extension subserosal decreased by 38% to 27%.

Acknowledgements (Funding): The studied was sponsored by the Magnetic Resonance Unit at Medica Sur Hospital in Mexico City.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-46

Spontaneous Vaginal Expulsion of Uterine Fibroids After Magnetic Resonance-guided Focused Ultrasound Surgery

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Background/Introduction: Vaginal passage of treated fibroid tissue has been reported during other therapeutic procedure such as UAE and pureperium. The current study is the first to report a case of vaginal expulsion of uterine fibroids after MRgFUS, with complete endometrial recovery upon follow-up.

Methods: EA 38-year-old woman was referred to our hospital with severe menorrhagia. A transvaginal ultrasound showed the presence of submucosal fibroids as the likely cause of symptoms. A screening MRI was performed, which revealed two adjoining intramural-submucosal fibroids at the posterior wall of the uterus. The three months follow-up MRI showed a volume reduction of 36% in the treated fibroids (total fibroids volume of 80 cc). The treated fibroids showed an enhanced submucosal component and discontinuity with the endometrial lining on the T2 weighted sagittal image Two weeks later, the patient visited our hospital for symptoms of a palpable vaginal mass. We examined the MRI and found that the treated fibroids were situated in the vagina with a narrow stalk extending from the uterus. Two weeks after the initial detection of vaginal fibroid expulsion, there was no change in the status of the expulsed fibroids within the vagina. The fibroids were therefore removed by hysteroscopic resection without any adverse events. Follow-up MRI was performed 3 months after hysteroscopic resection, showing an absence of any residual fibroid tissue or abnormality in the endometrial lining.

Results & Conclusions: MRgFUS treatment may result in vaginal fibroid expulsion and restoration of the overlying endometrium. The expulsion of the treated fibroids following MRgFUS may be considered as a treatment outcome rather than a complication.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-47

Successful Magnetic Resonance-guided Focused Ultrasound Surgery for Recurrent Uterine Fibroid Previously Treated with Uterine Artery Embolization

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Background/Introduction: Different patient selection criteria are established for UAE and MRgFUS treatments. For UAE, submucosal and pedunculated fibroids may be considered relative contraindications as are previous internal iliac or uterine artery occlusion or recent GnRH analogue administration. In addition, there are insufficient data to advocate UAE as a means of preserving fertility. For MRgFUS, hyper intense fibroids and multiple fibroids may be considered relative contraindications as they are difficult to treat. In addition, in cases where the ultrasound beam is interrupted by anatomical structures, such as bowels, bones or nerves, MRgFUS treatment may be impossible without successful mitigation techniques. This is the first case to report MRgFUS treatment on a patient with recurring fibroid symptoms following UAE.

Methods: A 45-year-old premenopausal woman, with a BMI of 22.1 and two previous pregnancies, complained of menorrhagia. In November 1998, she underwent a UAE and both her fibroids were treated. Approximately nine years later, in 2008, the patient reported the recurrence of symptoms. An MR angiography revealed the right fibroid to be lacking in blood supply, with nearly invisible right uterine artery. The left fibroid was supplied only by the narrow left uterine artery. The patient was recommended not to undergo an additional UAE, which made it difficult to approach the fibroid bilaterally and increased the risk for arterial perforation during a repeated UAE procedure. As the patient insisted on a non-invasive treatment for her symptoms, she was referred to our unit for MRgFUS treatment. Three months after the treatment, the patient reported significant symptom improvement. Contrast-enhanced T1-weighted and T2-weighted MRI, obtained at that time, revealed 49% shrinkage of the treated fibroid.

Results & Conclusions: MRgFUS treatment can be a good option for patients who were previously treated with UAE. Additional studies of the safety and efficacy of MRgFUS following UAE should be conducted.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-48

Analysis of Heat Shock Protein Upregulation and Evidence for Apoptosis in HIFU-Insonated Rabbit Thigh Muscle

Terry Matsunaga[1,3], Kyle McKeown[1], Ryan McFarland[1], Raymond Nagle[2,3], Edward Abril[2,3], Kathy McDaniel[2,3], Evan Unger[1,3]

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Background/Introduction: Focused ultrasound surgery is a viable alternative to surgery for treatment of uterine fibroids and metastatic bone pain palliation. This non-invasive approach uses focused ultrasound to produce intense heat that can be positioned within target lesions and destroy pathogenic cells with sub-millimeter precision. Our current efforts, however focused upon understanding the potential bioeffects in the peri-ablated region, if any, that could be occuring. We thus conducted a biochemical analysis of peripheral tissue viability by assaying for; 1) heat shock protein upregulation, an indicator of inflammation and cellular repair; and, 2) apoptosis. We assayed for these markers of cellular repair and damage using a HSP-70 monoclonal antibody assay and a cleaved caspase assay.

Methods: **A) Cleaved Caspase and HSP-70 Assays:** Routine H&E stains were performed on sections of tissue. Immunohistochemistry was performed using Cleaved Caspase and HSP-70 MAb. **B) Rabbit Thigh Muscle Studies:** i) New Zealand White rabbits were anesthetized, HIFU insonation was performed on both of the hind legs in the thigh muscle to prevent interference with bone or excessive fat, and to better simulate insonation through muscle tissue. Ultrasound experiments ranged from 500 W/cm2 - 1.6 KW/cm2 with varying insonation times

Results & Conclusions: For the HIFU samples, regions of necrosis and/or sub-cellular damage were identified. Tissue assays have did not reveal upregulation of HSP-70 or cleaved-caspase. Initial results seem to indicate that the tissue ablation to a significant extent remains localized to the ablated tissue and little damage occurs in the peri-ablated space. However, it may also be noted that the ultrasound intensities utilized in this experiment were less than those used by other researchers. In addition, the attenuation through the tissue, which at a penetration depth of 1.5 cm, is attenuated approximately 45% from the source (private communication, Artison Corp.), may be too small to induce significant damage, hence the variation in damage from sub-cellular to necrotic. In addition, lesions produced after the injection of 20 microliters/kg lipid-coated microbubbles did not appear to affect the lesion size of level of tissue damage. This observation could be the result of less vascularity in the thigh muscle region compared to other regions of interest (i.e. liver or kidney). .

Acknowledgements (Funding): We thank Kathy Stollbek and Patricia Payne-Kaltenberger in the University of Arizona Animal Care and William Meek in the TACMASS laboratory. Ken Coffey of Artison is greatfully acknowledged for his technical assistance and provision of a prototypical HIFU instrument for in vitro and pre-clinical research. The Focused Ultrasound Surgery Foundation is acknowledged for funding of this project and the Tissue Acquisition and Cellular/Molecular Analysis Shared Service (TACMASS Core, NIH CA023074) is also acknowledged.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-49

MR Guided Focused Ultrasound Surgery in Treatment of Diffuse Adenomyosis

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Background/Introduction: We at Jaslok Hospital and Research Centre have treated a case of diffuse adenomyosis. This was a 29-year-old female patient with heavy bleeding during periods for two years. Pretreatment MRI evaluation with T2 weighted images was done and revealed diffuse adenomyosis with focal posterior wall adenomyotic mass. The patient was treated with MRgFUS, and post treatment evaluation was done with post contrast MR images. There was appreciable reduction in symptoms after ablation of focal posterior wall adenomyotic mass (heavy bleeding to minor spotting during periods).

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-50

Magnetic Resonance Guided Focused Ultrasound Ablation of Symptomatic Uterine Fibroid: Short-term Outcomes Analysis

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Background/Introduction: There is limited published data on outcomes of patients who have had high volume of fibroids ablated. We review our initial experience with magnetic resonance-guided focused ultrasound ablation (MRgFUS) in the treatment of uterine fibroids, specifically patient improvement in symptom severity and impact on their quality of life.

Methods: After IRB approval, records of 25 self-referred patients who underwent MRgFUS for uterine fibroid related symptoms between August 2008 and May 2010 were reviewed. All patients opted to undergo MRgFUS in preference to hysterectomy, myomectomy, or UAE. MRgFUS was performed with the Exblate 2000 on a 1.5T magnet (HDx GE Medical Systems, USA). Patients completed the widely validated Uterine Fibroid Symptom and Health-related Quality of Life (UFS-QOL) questionnaire at baseline and following MRgFUS. The UFS-QOL was used to quantify several fibroid related symptoms including severity, concern, activity, energy, control, self consciousness, and sexual activity. The fibroid volume and ablation volume (as defined by absent perfusion on post gadolium imaging) was determined and the amount ablated was recorded. Statistical analysis to assess improvement was performed using a paired t-test. A p-value of 0.05 was considered statistically significant.

Results & Conclusions: A total of 25 patients underwent MRgFUS for uterine fibroids, and we had adequate follow up on 20 patients. The mean follow-up was 9.2 months (median 7 months). The mean fibroid volume was 335.3 cm3 (median 213 cm3), and the ablation volume was 123.1cm3 (median 125cm3). The mean amount ablated was 50.8% (median 48.5%). All patients tolerated the procedure without complications. Average UFS-QOL score prior to and post procedure was 109.7 and 73.5 points respectively (p=0.01). Significant improvement was observed in severity (p=0.01) with a mean score difference of 7.8. There were no differences in concern (p=0.13), control (p=0.14) energy (p=0.25), self consciousness (p=0.67), sexual activity (p= 0.27). MRgFUS is a safe and effective modality to provide short term symptom relief in patients with uterine fibroid related symptoms.

Session Topic: Uterine Fibroids
Presentation Type: Poster
P-51

Indian Experience in Treatment of Symptomatic Uterine Fibroid Patients with MR Guided Focused Ultrasound Surgery (MRgFUS) at Jaslok Hospital and Research Centre

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Background/Introduction: We have installed MR guided focused ultrasound machine at Jaslok Hospital and Research Centre. We would like to share our experience in treatment of the first 20 uterine fibroid patients with MRgFUS. Patient ages ranged from 25-45 yrs. All complained of menorrhagia, severe abdominal pain during periods. One of these patients had symptoms of urinary retention. All patients were evaluated with pretreatment screening with T2 weighted and post contrast MR images. Post treatment evaluation was done with post contrast MR images and non perfused volume was calculated. Two of these patients had midline vertical laparotomy scars. One of these patients had adherent bowel to the fundus of the uterus. There was significant reduction of symptoms post ablation.

Session Topic: Bone Tumors
Presentation Type: Oral
IS-16

MRgFUS for Treatment of Bone Metastases: Progress and Promise

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In the realm of oncology, management of painful bone metastases is a common and daunting clinical problem. Bone is the third most common organ involved by metastatic disease after lung and liver. Bone metastases are often associated with severe pain, which can be intractable. Previous studies showed that approximately half of patients with bone metastases receive only temporary pain relief with treatment. Advances in cancer detection and therapy have contributed to a protracted life expectancy for many patients. The resultant high incidence and prevalence of metastatic bone lesions has made the need for more effective palliative therapy ever more critical.

MRgFUS is an emerging non-invasive technology that can address the need for new palliative therapies for osseous metastases. MR allows for precise targeting, detailed beam path visualization, real time non-invasive temperature measurement, and treatment feedback to ensure therapeutic goals are achieved. MRgFUS also has the potential to be used repeatedly as no ionizing radiation is used.

Results of phase I/II trials using MRgFUS to treat painful osseous metastases will be discussed. The Insightec ExAblate System has been shown in phase I/II trials performed by research teams in Haifa, Israel, Berlin, Germany, and Toronto, Canada to have an excellent safety profile and high rates of pain response for treatment of bone metastases. Significant improvement in pain defined as a ≥2 point improvement on the visual analog scale (VAS) was achieved for 77% of patients. Notably, most patients presented with pain refractory to standard treatments such as radiation. The safety profile of treatment has been excellent with no occurrence of related serious adverse events. Details of an international multi-center phase III trial building upon the initial clinical experience with MRgFUS for treatment of oncologic bone pain will be outlined. This ongoing phase III trial includes patients with painful bone metastases or multiple myeloma who are not candidates for radiation therapy. Patients are randomized 3:1 to MRgFUS or sham treatment with crossover to study treatment allowed for sham failures. The primary study endpoint is assessment of pain control over 3 months following treatment. In addition safety, quality of life, cost effectiveness analysis, and patient perceived clinical benefit are also being assessed. Details of the MRgFUS system, technical and clinical therapeutic parameters, use of real time non-invasive MR thermometry, and examples of patient treatments with use of MRgFUS to treat bone metastases will be presented.

New directions in use of MRgFUS including an update on development of a mobile applicator and integration of MRgFUS in multimodality oncologic care will also be presented. Specific strategies for integration of MRgFUS in combined modality treatment of malignant bone tumors including primary treatment in combination with radiation and use of nanoplatforms for heat sensitization will be presented to stimulate discussion of expanded use of MRgFUS for skeletal disease.

Session Topic: Bone Tumors
Presentation Type: Oral
BT-1

Palliation of Painful Bone Metastases Using High Intensity Focused Ultrasound Therapy with Magnetic Resonance Guidance: Cumulative Sheba Medical Center Experience

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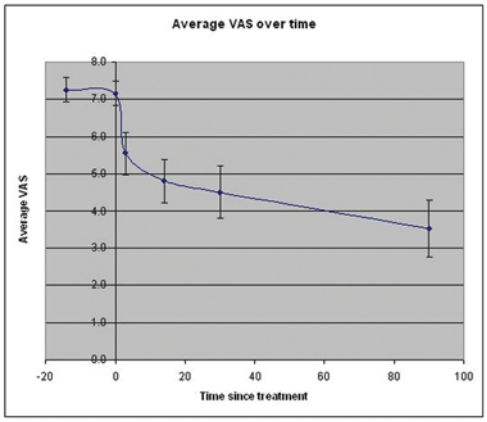
Background/Introduction: Magnetic resonance guided focused ultrasound, (MRg-FUS) has been used at the Advanced Technology Center, in Chaim Sheba Medical Center, since 2001, for the treatment of uterine fibroids, and other indications. In the past five years we have treated patients with painful bone metastases using MRgFUS on several IRB approved research protocols. We present here a pooled data analysis of based on the accumulated clinical experience in the treatment of these patients. MRgFUS combines the imaging capabilities of MRI with precise, monitored, delivery of thermal energy. The focused ultrasound beam heats the bone, which in-turn heats and ablates the periosteum surrounding the bone. Ablation of the periosteum results in partial or complete denervation of the painful area, and reduction in pain.

Methods: Two types of systems were used for bone treatments. The ExAblate® 2000 bone, (InSightec Haifa) which is a table based system, where the therapeutic transducer is mounted on a robotic arm and the ExAblate Conformal bone system, which has a mobile transducer that is strapped to the patient. Data was collected on pain levels of 34 lesions, from 33 patients, treated on three different research protocols, (all done under the IRB approval). Most of the patients were referred for treatment with MRgFUS due to persistent/recurrent pain following prior radiotherapy. The most common site of the targeted lesions were in the pelvis, although rib, scapula and extremity lesions were also treated. Treatments were performed in a single session, and in an ambulatory setting. Follow-up was done using VAS and QOL questionnaires, monitoring of pain medication intake, and monitoring of any adverse event.

Results & Conclusions: 33 patients were treated. Full 3 month follow up data was available on 22 patients. 11 patients were either lost to follow-up or are still in study and have not reached the 3 month follow-up visit. The pretreatment median VAS score was 7.3. 30 and 90 days after treatment the median score was, 4.5 and 3.5 respectively, 65% of pts achieved a reduction in the pain score of 2 point or greater at three months, About half of these, (35% of total), reported pain score of 0 at three months. No significant device related adverse event were recorded during this study. Conclusions: MRgFUS results in good pain relief in patients with painful bone metastases and may be particularly indicated in patients with persistent or recurrent pain following prior radiotherapy.
Acknowledgements (Funding): Insightec (Haifa) sponsored all the clinical studies.



Session Topic: Bone Tumors
Presentation Type: Oral
BT-2

Pain Palliation of Bone Metastasis Pain Using High Intensity Focused Ultrasound Therapy with Magnetic Resonance Guidance: Logistical issues

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[2]Sheba Medical Center, Radiology Institute, Tel Hashomer, Israel,
[3]Insightec, Haifa, Israel

Background/Introduction: Magnetic resonance guided focused ultrasound, (MRgFUS) has been used at the Advanced Technology Center, in Chaim Sheba Medical Center, since 2001, for the treatment of uterine fibroids, and other indications. In the past five years we have performed more then 40 treatments using MRgFUS for palliation of bone metastasis pain. In this work we present a pooled data analysis of based on the accumulated clinical experience in the treatment of patients with bone metastases. MRgFUS combines the imaging capabilities of MRI with precise, monitored, delivery of thermal energy. The focused ultrasound beam heats the bone, which in-turn heats and ablates the periosteum surrounding the bone. Ablation of the periosteum results in partial or complete denervation of the painful area, and reduction in pain. Patients suffering from painful bone metastases require timely treatment. MRgFUS therapy for bone lesions involves personnel from several departments to work together as a joint multidisciplinary team. These included radiation oncology and diagnostic imaging to select appropriate patients and to select the appropriate MRgFUS technique, and in addition anesthesialogy is required to provide sedation for pain relief during the actual treatment.

Methods: We have assembled a dedicated MRgFUS bone pain treatment team consisting of representatives of the relevant specialities in order to be able to offer treatment within several working days of referral. Candidate patients are seen by one of the radiation oncologists on the team within 24 hours of referral. The patient's imaging is viewed on the hospital PACS system together with the team radiologist and the appropriate treatment protocol is selected. After obtaining informed consent for treatment, additional screening CT or MR imaging is organized and a treatment slot is arranged. The pre-treatment screening MR in the treatment suite has the added benefit of allowing the team to evaluate the preferred approach to the lesion. The treatment is usually performed at the end of the regular working day to ensure availability of all necessary team members (anesthesiologist, interventional radiologist radiation oncologist, MR tech and nurse) and of the MR system and of an MR compatible anesthesia machine. A nurse co-ordinator has now been added to the team to improve patient flow.

Results & Conclusions: We can now offer treatment in a similar time frame to other palliative procedures such as external beam radiotherapy. We will present the workflow of the unit and describe the procedure for a typical patient receiving MRgFUS for bone pain. A MRgFUS program for treating bone metastases is feasible in a busy hospital setting but requires co-operation and co-ordination between all the involved departments.

Acknowledgements (Funding): InSightec (Haifa) sponsor the clinical studies

Session Topic: Bone Tumors
Presentation Type: Oral
BT-3

Pain Palliation of Bone Metastasis: Initial Clinical Experience Using High Intensity Focused Ultrasound Therapy with 3T Magnetic Resonance Imaging Guidance

Alessandro Napoli, Carlo Catalano, Michele Anzidei, Luisa Molisso, Marco Mastantuono, Roberto Passariello

Sapienza University of Rome, Radiological Sciences, Rome, Italy

Background/Introduction: Bone is the third most common organ involved by metastasic disease behind lung and liver. Current treatments for patients with bone metastases are primarily palliative and include localized therapies (radiation and surgery), systemic therapies (chemotherapy, hormonal therapy, radiopharmaceutical, and bisphosphanates), and analgesics (opioids and non-steroidal anti-inflammatory drugs). Treatment with external beam radiation therapy (EBRT) is the standard of care for patients with localized bone pain, and results in the palliation of pain for many of these patients. Twenty to 30% of patients treated with radiation therapy do not experience pain relief. Re-treatment rates are generally reported in the range of 10-25%. In addition to relapse and re-treatment, there is an increased risk of pathologic fracture. A palliative treatment for painful bone metastases that is non-invasive, without long-term toxicity and having minimal complications would be highly desirable. Results of preliminary studies indicate that Magnetic Resonance guided Ultrasound (MRgFUS) treatment of painful bone metastases may be a beneficial treatment option. The MRgFUS system has the potential to achieve pain relief, preservation and restoration of functional levels and local tumor control. Purpose of our study was to determine the efficacy of non-invasive high intensity MRgFUS treatment for palliation of bone metastasis pain in patients not candidated for EBRT.

Methods: Under the IRB approval 18 patients and relative lesions underwent MRgFUS treatment using the ExAblate 2000 system (InSightec). 12 patients underwent prior EBRT with a mean 6 months recurrent pain. In 6 patients MRgFUS treatment was performed as first treatment modality. Treatments were done in a single session, in an ambulatory setting. Effectiveness of pain palliation was evaluated at follow-up using the visual analog pain score (VAS) and measurable changes in analgesics intake. For tumor control perfusion T1w-images were obtained pre- and post-treatment in order to determine the non-perfused sonication-related area (Fig1).

Results & Conclusions: All patients and all lesions were treated. Mean follow-up time was 4 months. At base line VAS was 7.1; it was 4.8 at 3 days, 3.0 at two weeks and 2.6 and 2.4 at one and four months respectively. No heating related adverse event were recorded during this clinical application; patient medication intake was considerably reduced. Variable degree on non-perfused volume was observed after treatment, mainly within the pericortical region (Fig2). Deeper penetration of the acoustic energy is at present desirable even if technically difficult to achieve with the current system. In wait of further technical advances, such as the conformal system that we are going to use next year, our limited experience indicates MRgFUS as a promising noninvasive treatment modality for successful palliation of bone metastasis pain in patients who are not candidate for EBRT.

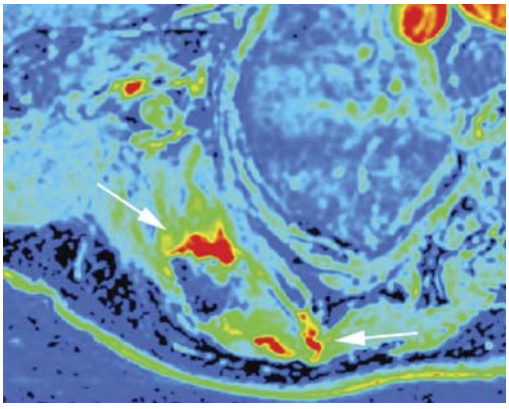


Figure 1

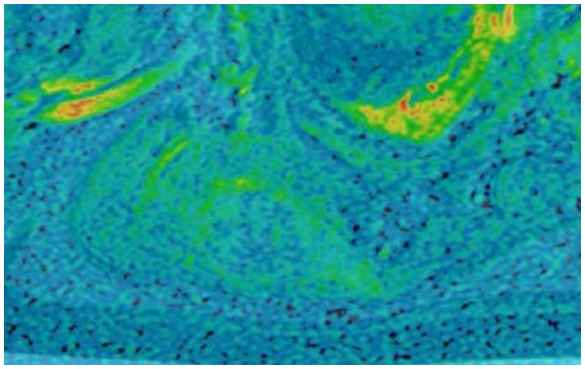


Figure2

Session Topic: Bone Tumors
Presentation Type: Oral
BT-4

Overview of Palliative MRgFUS Treatment of Painful Bone Metastases in Spain

María Valero[1], Emilio Gomez-Gonzalez[2], Pedro Valero[1], Araceli Sabino[1], Agustin Escorihuela[1], Helena Millan[1], Daniel Ramirez-Martinez[2], Andres Coca de la Torre[2], Elna G. Laffitte[1], Diego Valdes Cruces[1], Manuel A. Perales Esteve[2], Ana M. Marco-Ramirez[2], Francisco Villanueva-Martinez[1]

[1]Iberian Medical Research Institute - Instituto Cartuja, Seville, Spain,
[2]Group of Interdisciplinary Physics, ESI-University of Seville, Seville, Spain

Background/Introduction: Our site is the only MRgFUS site in Spain, located in the Scientific and Technological Park Cartuja 93, in Seville. We present the results of MRgFUS palliative treatment of pain in our initial series of bone metastases patients.

Methods: Equipment: ExAblate 2000 system (InSightec Ltd, Israel) in a 1.5T MR (GE Healthcare, USA). R&D is carried out in the frame of a Laboratory of Non Invasive Technologies for Tumor Treatment in collaboration between the author's institutions. Clinical activities are developed at Iberian Medical Research Institute-Instituto Cartuja and the scientific and technological duties at the Engineering School of the University of Seville. Currently available MRgFUS applications include treatment of uterine fibroids and palliative treatment of pain in bone metastases. After thorough clinical evaluation, patient selection is based on painful bone metastases in accessible locations for MRgFUS treatment. Conventional contrast MR studies are performed to evaluate image findings. Pain is measured using the standard Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (maximum level) in the pre-treatment evaluation, in a daily basis the week after and in routine follow-up. Total and partial responses to treatment are measured following published criteria.

Results & Conclusions: Our patient series comprises 6 patients since March 2009 (3 male, 3 female, age range of 45-75 years. Primary tumors were breast (3), colorectal (1), urothelial (1) and papillar (1) carcinoma of bladder. Treated metastases included 1 osteolytic rib metastasis, 1 located in coccyx, 1 pelvic, 1 in sacrum and 1 in pubis (in the same patient), 1 in femoral neck and 1 in distal femoral diafisis. Palliative chemo- and radiotherapy had failed in 3 male and 1 female patients. Pre-treatment pain score was in the range 7-10/10 VAS. Immediate relief to 4-6/10 VAS was achieved in 4 cases followed by further significant decrease in all 6 cases one week post-treatment. After a 2-month follow-up, stationary levels were in the range 0-4/10 VAS in 5 cases, without analgesics. After reducing pain from 10/10 VAS to 3/10 VAS, 1 patient deceased 1 week after treatment due to his primary pathology. In one breast case, new painful metastases appeared 45 days after treatment. In other case of primary breast cancer with a painful lytic lesion in the femoral neck, with elevated fracture risk, bone regeneration is observed after treatment. Currently, the patient has controlled pain, being back to normal life activities, including physical exercise. Although still a reduced, our data agree with other published results. A significant reduction in pain levels is achieved, with a very important improvement in the quality of life of patients and their families. Initial finding of bone regeneration after MRgFUS treatment is another possible effect of very important potential application.

Acknowledgements (Funding): Work partially funded by a R&D Project by the Agency IDEA (Andalusian Regional Ministry of Innovation and Science, Spain), 2007-09.

Session Topic: Bone Tumors
Presentation Type: Poster
P-52

Magnetic Resonance Guided Focused Ultrasound for Palliation of Painful Bone Metastases

Vladimir Turkevich[1], Valentina Savelyeva[1], Igor Dunaevsky[1], Pavel Krshivitsky[1], Sergey Kanaev[1], Osnat Dogadkin[2], Martin Bernstein[2]

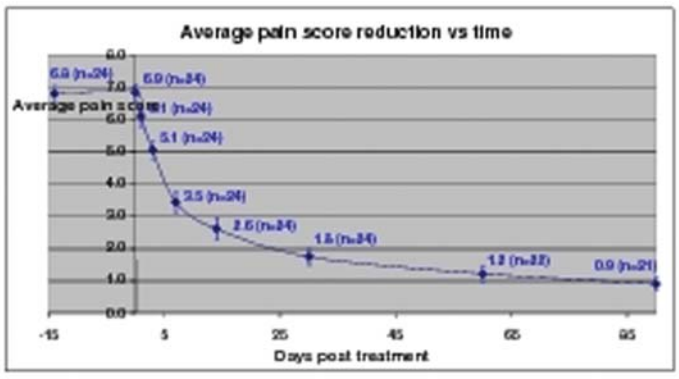
[1]Petrov Research Institute of Oncology, Radiation Oncology, St-Petersburg, Russia, [2]InSightec Ltd., InSightec Ltd., Haifa, Israel

Background/Introduction: Magnetic Resonance guided Focused Ultrasound (MRg-FUS) is a non-invasive treatment technique that recently has been shown to be effective for thermal ablation of a variety of benign and malignant tumors. We present here results of a clinical trial conducted in our facility. The main objective of the trial was to evaluate safety and effectiveness of MRgFUS treatment for palliation of pain caused by bone metastases.

Methods: 24 patients with painful bone metastases were treated with MRgFUS at Petrov Research Institute of Oncology, St. Petersburg, Russia. Immediately after their procedure, patients were examined for any adverse events; after a brief recovery, they were discharged in the care of a companion. Patients were followed up on at 1 and 3 days, 1 and 2 weeks, 1, 2 and 3 months post treatment. During each visit, treatment safety was evaluated by recording and assessment of device or procedure related adverse events. Effectiveness of palliation was evaluated using the standard pain scale (0-no pain/10-worst pain imaginable) and by monitoring changes in the intake of pain-relieving medications. Two types of pain scores were collected: the average and the worst pain in the last 24 hours. A reduction of 2 points or more on pain scale was considered a significant response to treatment. The study included 17 male and 7 female patients. Mean age was 55 years old (19-76). The base cancers were: 12 breast, 4 stomach, 2 bronchus, 2 bladder, 1 kidney, 3 other. Targeted lesions were 14 osteolytic; 4 osteoblastic and 6 mixed. 16 were pelvis metastases, 4 were located in the humerus bone and 4 were located in the ribs.

Results & Conclusions: No significant device or procedure related adverse events were recorded. Three patients died during the follow-up period due to disease progression, thus 3 months follow-up data includes only results of 21 patients. All patients reported significant improvement in pain with no change in their medication intake.

Conclusions: These results clearly show that MRgFUS can provide an effective, safe and noninvasive palliative therapy for patients suffering from painful bone metastases. The ability to achieve a rapid pain relief after only one treatment session combined with the high safety profile of the procedure implies that MRgFUS has a significant potential for both patients and physicians.



Session Topic: Bone Tumors
Presentation Type: Poster
P-53

Effects of Magnetic Resonance Guided Focused Ultrasound Treatment for Pain Palliation of Bone Metastasis on the Mechanical Properties of Bones

Boaz Liberman[1], Arik Hananel[2], Yael Inbar[3], Adlet Nurlai[1], Eran Avivi[1]

[1]Haim Sheba Medical Center, Orthopedic Oncology, Ramat-Gan, Israel,
[2]InSightec, Tirat-Hacarmel, Israel,
[3]Haim Sheba Medical Center, Radiology Department, Ramat-Gan, Israel

Background/Introduction: Magnetic resonance-guided focused ultrasound, (MRg-FUS), treatment is a novel method to non-invasively ablate soft tissue using MR images for targeting and MR thermometry for treatment control. This method has received approval, FDA, CE, MHLW, for ablation of uterine fibroids, and CE for pain palliation of bone metastasis. However, the effect of this treatment on the bone mechanical properties using the clinical treatment level parameters was never tested.

Methods: Following ethical approval, we have treated four mini-pigs with ExAblate 2000 for bone (InSightec Haifa), system. In each pig, we created a 2cm lesion on the right femur bone and six ribs, where the contralateral bone was used as control. Following treatment, MR and CT were used to evaluate lesion formation and effect on bone. Pigs were sacrificed immediately at 3, 7 and 9 weeks.

Results: At the time of writing this abstract, we still do not have the results from the mechanical lab analysis. By the October symposium, results will be ready for presentation.

Conclusions: Will be written based on the results.

Acknowledgements (Funding): Funding for this study provided by InSightec Ltd, Tirat-Hacarmel, Israel.

Session Topic: Bone Tumors
Presentation Type: Poster
P-54

Indian Experience in Treatment of Painful Bone Metastasis Patients with MR Guided Focused Ultrasound Surgery (MRgFUS) at Jaslok Hospital and Research Centre

Shrinivas Desai, Abhijit Patil, Ritu Kakkar

Jaslok Hospital and Research Centre, Imaging and Interventional Radiology, Mumbai, India

Background/Introduction: We have installed MR guided focused ultrasound machine at Jaslok Hospital and Research Centre. We have treated 3 patients (5 lesions) with pelvic and femoral neck metastasis with MRgFUS. All were male patients ranging in age from 28-75 yrs. The first patient was a case of PNET with femoral neck metastasis; the second patient was a case of CA Prostate with Ischial metastasis; and the third case was of CA Lung with Ilial and femoral neck metastasis. Pre treatment evaluation was done with T2 weighted and post contrast MR images. Post treatment evaluation was done with Post contrast MR images. Post Ablation there was significant reduction in pain score (NRS SCORE- 0-1) within 24- 72 hours.

Notes

Author Index

X

Y

Z

Young Investigator Award Program

The Focused Ultrasound Surgery Foundation has established the Young Investigator Award Program to encourage quality research by scientists-in-training and support them in presenting meritorious scientific papers at major venues such as the 2nd International Symposium on MR-guided Focused Ultrasound.

Open to graduate students, research fellows, clinical fellows and junior faculty members, awards are valued at up to $1,000 and cover transportation and lodging costs. Recipients also receive free symposium registration.

At the 2nd International Symposium on MR-guided Focused Ultrasound, Young Investigators will be acknowledged in several ways:

1. **Name Badges and Announcement**: Award recipients will receive unique name badges that indicate their status as Young Investigators. They will be acknowledged at the Symposium opening, and Senior Investigators will be encouraged to interact with them throughout the conference.
2. **Poster Session**: "Young Investigators" will have a designated section of the Poster Hall. On Tuesday, October 19, they will have an opportunity to present their work and showcase it to the larger focused ultrasound community.

Young Investigator Award Review Committee

Matthew R. Dreher, Ph.D.
Radiology & Imaging Sciences
National Institutes of Health
Bethesda

Hannah Edelen, J.D.
Focused Ultrasound Surgery Foundation
Charlottesville

Keyvan Farahani, Ph.D.
Image-Guided Intervention Branch
National Cancer Institute
Bethesda

Joy Polefrone, Ph.D.
Focused Ultrasound Surgery Foundation
Charlottesville

Gail ter Haar, Ph.D. (Chair)
Joint Department of Physics
Institute of Cancer Research:
Royal Marsden Hospital, Sutton

2010 Focused Ultrasound Surgery Foundation Young Investigator Award Recipients

Esther Bouwsma, M.D.
Department of Reproductive Endocrinology
Mayo Clinic, Rochester

Caitlin Burke
Biomedical Engineering
University of Virginia, Charlottesville

Navid Farr
Department of Bioengineering
University of Washington, Seattle

Ronit Machtinger, M.D.
Department of Obstetrics and Gynecology
Brigham and Women's Hospital/
Harvard Medical School, Boston

Jonathon Pagan, M.S.
Radiation Oncology
University of Arkansas for Medical Sciences, Little Rock

Allison Payne, Ph.D.
Mechanical Engineering
University of Utah, Salt Lake City

Nick Todd, Ph.D.
Utah Center for Advanced Imaging Research
University of Utah, Salt Lake City

Urvi Vyas
Bioengineering
University of Utah, Salt Lake City

Marianne Voogt, M.D.
Department of Radiology
University Medical Center Utrecht, Utrecht

Katherine Watson
Biomedical Engineering
University of California, Davis

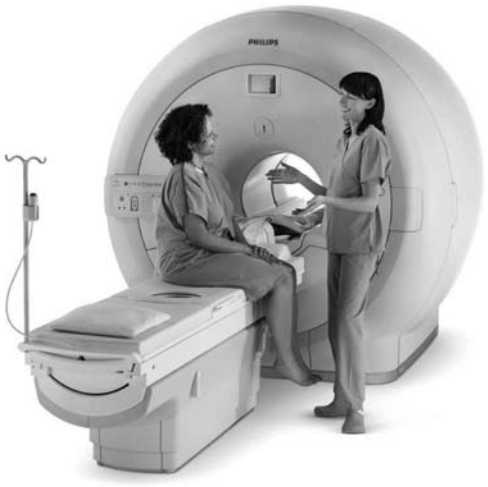
Sponsors & Vendors

Sponsors

Vendors

New, non-surgical treatment for uterine fibroids
A real alternative to surgery

High Intensity Focused Ultrasound (HIFU) has long been known as a non-invasive therapy technique. It uses focused ultrasound waves to heat and coagulate tissue deep inside the body without damaging intervening tissue. However, the lack of a suitable guidance and monitoring technique and long treatment times has prevented its widespread medical use.



The perfect combination

With Sonalleve MR-HIFU, Philips now presents a system that enables exciting emerging non-invasive therapies. It brings the advantages of two modalities together by integrating an advanced High Intensity Focused Ultrasound system into the patient table of the Philips Achieva MR system.

Focused ultrasound

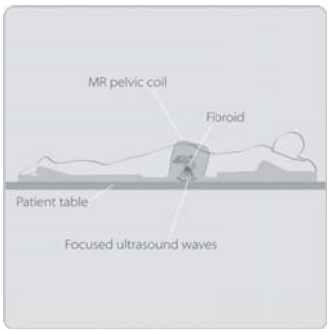
With High Intensity Focused Ultrasound therapy, a focused transducer is used to bundle ultrasound energy into a small volume at the target locations inside the body. During treatment, the ultrasound energy beam penetrates through the skin and soft tissue causing localized high temperatures only in the focus area, leaving the skin and intermediate tissue unharmed. Within a few seconds this produces a well-defined region of coagulative necrosis.

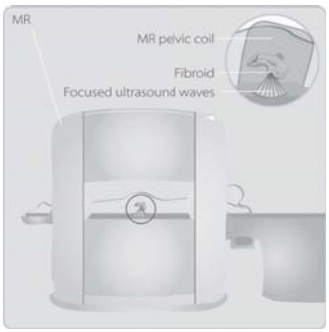
Combined with MR image guidance

3D anatomical images provide the reference data for treatment planning, while real-time temperature sensitive images follow the ablation process to provide information about treatment progress and monitor critical anatomical structures.

Ablation of uterine fibroids

Uterine fibroids are the most common benign tumors in pre-menopausal women. Fibroids occur in 20 to 50% of women of child-bearing age, and with increasing size produce pain, excessive menstrual bleeding, pressure, bloating and urinary and bowel compression symptoms. Fibroids may also cause infertility. Many women suffer from uterine fibroids but don't want to undergo surgery and continue to endure the condition in silence. Philips' new Sonalleve MR-HIFU system now offers a non-invasive treatment of uterine fibroids. The technique is much more convenient and comfortable than other therapeutic procedures such as hysterectomy, myomectomy or uterine artery embolization. These require hospital admission as an in-patient and sometimes weeks of recovery. In contrast, with Sonalleve fibroid therapy, patients can be treated as an out-patient, be out of the hospital the same day and almost fully recovered within a few days.





- Non-invasive therapy for uterine fibroids, a very common condition for women of child-bearing age
- Fast out-patient procedure with high patient compliance and short recovery times
- Safe and effective Procedure
- Volumetric heating with real-time feedback for high procedural efficiency and short procedure time
- Optimized MR system utilization through easy switching between diagnostic and therapeutic use

To learn more, please visit us at: www.philips.com/sonalleve

PHILIPS

FUS Instruments Inc.

Toronto, Ontario, Canada

FUS Instruments is a spin-off company formed in 2009 from the Focused Ultrasound Laboratory at Sunnybrook Health Sciences Centre (SHSC) in Toronto, Canada. The mission of the company is to lower the technology barrier that exists to investigate novel applications of focused ultrasound technology by producing turnkey solutions for conducting research in this exciting field.

Technology Description

FUS Instruments develops image-guided focused-ultrasound systems for preclinical scientific research**. The core technology produced by the company is a computer-controlled focused ultrasound system capable of operation within a magnetic resonance imager (MRI) or x-ray computed tomography (CT) scanner. This system was designed specifically for performing focused ultrasound experiments in preclinical animal models. The system is portable and can be used on MR scanners from all the major vendors at both 1.5 and 3.0 T. The setup and takedown of the system can be performed in a matter of minutes, making it a perfect solution for environments where a dedicated MRI-guided FUS system is not possible. In addition to the core FUS system, the company can provide accessories such as transducers, power meters, water degassers, and RF coils.

Applications of Technology

The system from FUS Instruments is designed for flexibility, enabling users to investigate both thermal and mechanical applications of focused ultrasound. The spatial precision of the system (0.1mm) makes it possible to deliver ultrasound energy to precise targets in small animals, while the large range of motion (up to 10x10x10 cm) permits experiments in large animal models.

Contact Names and Details

For more information, please contact the company at info@fusinstruments.com

** *The products sold by FUS Instruments are not intended for use in humans.*

Image Guided Therapy (IGT)

Bordeaux, France

Image Guided Therapy develops and produces MR guided focused ultrasound devices. The company focuses on two main applications: pre-clinical trials for breast cancer treatment using a dedicated FUS device and focused ultrasound mediated drug delivery.

Technology Description

Image Guided Therapy has developed a range of MR guided focused ultrasound systems featuring state of the art temperature imaging software, easy to use procedure planning tool, and a wide range of phased array transducers (from 16 elements ring arrays to 256 elements arrays) and MR compatible, remote controlled positioning systems. The systems are easy to site and function without interferences within the MR rooms.

Applications of Technology

IGT develops as part of a collaboration with the University of Utah a FUS system optimized for breast cancer treatment. The system is a 256 elements phased array device which enables rapid volumetric ablation of breast tumors. Reliability of the treatment is ensured by the real time adaptation of the procedure based on actual temperature images.

IGT commercializes the first MR guided FUS system dedicated to small animal pre-clinical research, usable at all field strength, from the 1.5T clinical scanner to the 7T small bore research systems from Bruker.

Areas of Interest for Partnering

Drug delivery applications, Blood Brain Barrier opening, MR temperature imaging.

Contact Names and Details

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Phone: +33 5 56 46 47 05
Mob: +33 6 11 49 94 00
skype: Skype : erik.dumont-office

InSightec Ltd.

Neadquartered in Haifa, Israel with US offices in Dallas, TX.

InSightec Ltd. is a privately held company founded in 1999 and owned by Elbit Imaging, General Electric, MediTech Advisors, LLC and employees. InSightec is the pioneer and world leader in MR guided Focused Ultrasound (MRgFUS) technology with the first commercially available device for treating uterine fibroids (FDA approval 2004). The company's devices use MRgFUS to perform image guided robotic acoustic surgery for the next generation operating room.

Technology Description

InSightec's ExAblate devices incorporate the latest in phased array transducer technology for MRgFUS and many intelligent safety features. These systems, which comprise of a patient table, electronics cabinet and operator console, are compatible with GE Healthcare 1.5 and 3.0T Signa and Discovery (450 and 750) MRI. The combination of InSightec's focused ultrasound innovations and GE image quality has resulted in unparalleled efficacy and safety results over eleven years of collaboration.

The ExAblate family consists of three unique and customizable systems: ExAblate One—for womens health, ExAblate OR— the next generation operating room, and ExAblate Neuro—for transcranial MRgFUS applications. These devices are ergonomically and anatomically designed to treat a variety of indications and are optimized in terms of transducer geometry, frequency and energy output. The ExAblate OR incorporates interchangeable cradles allowing a single table to be used formultiple applications.

Applications of Technology

ExAblate One:

- Treatment of symptomatic of uterine fibroids
- Treatment of symptomatic adenomyosis*.

ExAblate OR*:

- pain palliation of bone mestastases
- treatment of prostate cancer
- treatment of breast cancer
- facet rhizotomy.

ExAblate Neuro*:

- brain tumors
- functional disorders
- stroke
- targeted drug delivery.

InSightec ExAblate OR—the next generation operating room, using MRgFUS for Image Guided Acoustic Surgery

* *All these applications are or will be requiring a full FDA Investigation Device Exemption for clinical trials in the United States. Not all applications are approved in all regions. Please consult your local representatives and read the product labeling specific for your region to determine approved indications for use.*

Areas of Interest for Partnering

InSightec welcomes academic, clinical, and corporate collaboration for technology and application development, as well as advancement and facilitation of clinical results and reimbursement. We believe there are many who share our company's vision in transforming MRgFUS applications from investigator initiated innovation to clinical practice.

Contact Names and Details

Oded Tamir, Chief Operating Officer
E-mail: OdedT@insightec.com

Philips Healthcare

Andover, MS
Business Unit MR-HIFU, Helsinki-Vantaa, Finland

Philips Healthcare is a global leader in healthcare and well-being with more than 30,000 employees globally, with research and manufacturing sites in the North America, Europe, Asia Pacific and Latin America, serving more than 100 countries around the globe and a portfolio across five business areas: Clinical Care Systems, Imaging Systems, Healthcare Informatics, Customer Services, and Home Healthcare Solutions.

The therapeutic ultrasound activities are concentrated in the global R&D and manufacturing center in Vantaa outside Helsinki, Finland. Customers are supported by the global Philips Customer Services organization on a local level.

Technology Description

Sonalleve MR-HIFU is an MR guided high intensity focused ultrasound system compatible with the Philips Achieva MR platform at 1.5T and 3.0T. The system comprises of an MR-HIFU tabletop replacing the standard diagnostic table top. The HIFU transducer is positioned with 5 degrees of freedom and positioning can cover a large treatment field. A dedicated RF receive coil for human pelvic therapy applications has been designed for optimum coverage, high resolution and speed for precise thermal imaging. The system features volumetric heating technology with real-time feedback for short procedure times and uniform heating patterns. For more details see www.philips.com/sonalleve

Applications of Technology

Ablation of uterine fibroids approved in Europe and Korea

Areas of Interest for Partnering

Philips drives development of this technology towards future applications in cancer treatment, both by ablation and HIFU mediated local drug delivery.

Contact Names and Details

Thomas Andreae, Ph.D., Marketing Director MR-HIFU, Philips Healthcare
Äyritie 4, P.O. Box 185, FIN-01511 Vantaa, Finland
thomas.andreae@philips.com

Profound Medical Inc. (PMI)

Toronto, Canada

Profound Medical Inc. (PMI), founded in July 2008, is a privately-held, venture capital financed medical device company, commercializing an MRI-guided thermal ultrasound device for the most accurate and precise treatment of localized prostate cancer. Most recently the 2010 recipient of the prestigious Ontario Premier's Catalyst Award for entrepreneurial innovation, the company's activities continue to be regularly rewarded with accolades from industry and independent judges.

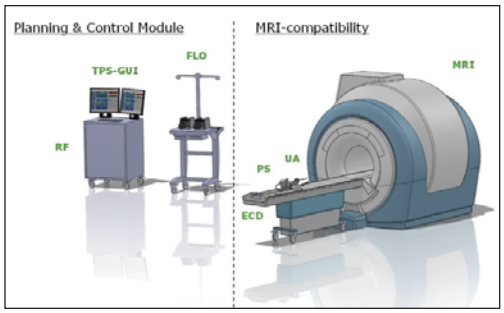
Technology Description

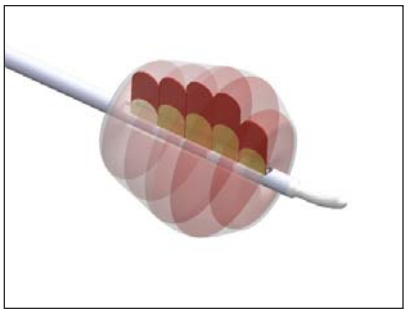
Arguably the best medical imaging tool in common use today, Magnetic Resonance Imaging (MRI) enables a clinician to detail the internal organs of a patient non-invasively. Ultrasound imaging and thermal coagulation therapy have proven utility in several medical applications. When combining the two methodologies in a unique manner, the opportunity exists for an optimal and thus vastly superior clinical outcome.

The company is finalizing data for an FDA-IDE submittal, and anticipates starting formal clinical trials in the USA and Canada in 2011.

Applications of Technology

PMI has developed a novel MRI-compatible system and ultrasound energy delivery wand to provide controlled thermal therapy to the cancerous regions of the prostate gland via a trans-urethral approach. The prototype has been extensively tested and delivered consistent and predictable proof-of-concept results in mathematical, gel, and most recently pre-clinical models.





Areas of interest for Partnering

TUS Clinical Trials, EU Clinical Trials., outsourcing of manufacturing.

Contact Names and Details

Paul Chipperton, CEO
T: ++1 647 291 8545
E: pchipperton@profoundmedical.com

SuperSonic Imagine

Aix-en-Provence, France

SuperSonic Imagine is leveraging unique disruptive ultrasound technology for use in both diagnostic and therapeutic applications.

The diagnostic device “Aixplorer” is commercially available.

Technology Description

Real time quantitative assessment of tissue stiffness leveraging the interaction of shear wave and longitudinal wave is a key technology developed by SuperSonic Imagine.

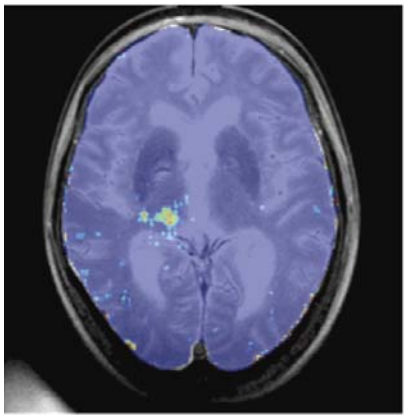
In the arena of therapeutic, the key technology is time reversal to correct for skull bone aberration. Elastography is to be used to assess the location and extent of the necrosis created in tissue.

Applications of Technology

Diagnostic product “Aixplorer”: early breast cancer detection, liver fibrosis assessment, prostate cancer evaluation…

Therapeutic device: brain (essential tremors, lesion necrosis.)

Picture of the set up with the cadaver head in place



Necrosis generated in cadaver brain through the skull

Areas of Interest for Partnering

Transducer development for HIFU application

Contact Names and Details

Jacques Souquet, Ph.D. CEO ; Jacques.souquet@supersonicimagine.fr

Claude Cohen-Bacrie, CTO: claude.cohen-bacrie@supersonicimagine.fr

www.supersonicimagine.fr

Symposium Abstracts Addendum

Monday,
October 18, 2010

Special Lecturer
9:55–10:15

The Role of CDRH's Office of Science and Engineering Laboratories in the Regulatory Process

Steven Pollack
Food and Drug Administration, Center for Devices and Radiological Health (CDRH), Office of Science and Engineering Laboratories (OSEL), Silver Spring, MD, USA

The Food and Drug Administration is a science-led regulatory organization. The complexity and range of medical products regulated by the Center for Devices and Radiological Health necessitates the availability of scientists and engineers whose knowledge is at the cutting edge of medical device technologies. The Office of Science and Engineering Laboratories (OSEL) in the Center for Devices and Radiological Health provides technological consultancy and the generation of independent scientific and engineering data to support pre- and post-market regulatory efforts of Center.

In this talk, Dr. Pollack will describe the structure and function of OSEL and how it engages with the other Offices of CDRH, other FDA centers, and external stakeholders to ensure that the most current scientific and engineering knowledge is brought to bear in the review of medical devices to ensure their safety, effectiveness and availability to the public.

Tuesday,
October 19, 2010

Breast Applications Session
14:30–16:05

IS-11

MRgFUS of Early Breast Cancer: Efficacy and Safety in Excisionless Study

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Background: The loco-regional lymph nodes have been recognized not to work as the defense against cancer cells spreading to the whole organ. The prognosis in approximately 60% of the breast cancer patients depends on the local treatment alone. The other 40% depends on the local and systemic treatments. Breast conserving therapy has been proven to be as good as mastectomy for breast cancer in several clinical trials. The aim of local treatment is to completely eradicate the cancer cells from the breast. MRI is the best modality in spatial resolution for the detection of breast cancer ductal spread. Two phase II clinical studies (*excision* studies) to investigate pathological efficacy and clinical safety of MR-guided focused ultrasound surgery (MRgFUS) were conducted and their outcomes have been published. Unfortunately, the FDA has not approved the ACRIN 6674 in North America for four years.

Purpose: To inspect the efficacy and safety of MRgFUS followed by radiotherapy in an *excisionless* study.

Methods: The inclusion criteria include: 1) tumor diagnosed by needle biopsy under ultrasound; 2) receptor status of cancer cells confirmation; 3) tumor size ≤ 15mm; 4) well demarcated mass in contrast enhanced MRI. The exclusion criteria include: 1) pure type mutinous carcinoma; 2) invasive micro papillary carcinoma; 3)skin dimple or dimpling sign, previous surgical scar of the skin above the tumor; 4) location of the tumor requires a high sonication angle. Needle biopsy was performed again within three weeks after ablation and no residual viable cancer cells were identified by Hematoxylin-Eosin stain and single strand DNA immunohistochemical stain. The following radiotherapy is whole breast (50Gy) and boost (10Gy).

Results: Fifty seven patients entered this study and forty-seven lesions were treated from April 2005 to August 2010. The median age was 58 years old (37-72). The average tumor size was 11.0mm (6mm – 15mm). The median follow up period was 44 months (3 months – 64 months). Thirty-four cases were followed up for more than 24 months. There were no severe adverse events, local and distant recurrence cases.

Conclusions: Although the number of cases is still small and the follow-up period is short, MRgFUS has the potential of replacing usual breast conserving surgery. Strict selection of cases is essential.

Symposium Presenter Changes

Tuesday, October 19

FUS Vendor Profiles | 7:00–8:25

Supersonic Imagine
New presenter: Mickaël Tanter, Institut Langevin, Ecole Supérieure de Physique et Chimie Industrielles, Paris, France

Liver Applications | 13:30–14:30

L-3 ***High-Intensity Focused Ultrasound (HIFU)-Assisted Hepatic Resection in an Animal Model***

New presenter: Aurélien Dupré, Centre Léon-Bérard, Oncologie Chirurgicale, Lyon, France

Prostate Applications | 16:05–17:35

PC-4 ***Focal Magnetic Resonance Guided Focused Ultrasound Treatment of Low Risk Prostate Cancer***

New presenter: Vladimir Turkevich, Petrov Research Institute of Oncology, Radiation Oncology, St. Petersburg, Russia

Poster Session | 18:00–20:00

P-37 ***Simulation Validation and In-Vitro Demonstration of 3D MRI-controlled Transurethral Ultrasound Prostate Therapy***

New presenter: Ilya Kobelevskiy, Sunnybrook Health Sciences Centre, Imaging Research, Toronto, ON, Canada

Wednesday, October 20

Bone Tumors | 11:30–12:45

BT-2 ***Pain Palliation of Bone Metastasis Pain Using High Intensity Focused Ultrasound Therapy with Magnetic Resonance Guidance: Logistical issues***

New presenter: Tatiana Rabin, Sheba Medical Center, Oncology Institute, Tel Hashomer, Israel

Lunchtime Discussion Groups

Overview: Non-moderated and free-flowing, these hour-long group discussions will give participants a chance to share lunch while posing questions, exchanging information, building relationships and identifying new collaborative opportunities. Space is still available both days for sessions held in the amphitheater. While boxed lunches are no longer available, we hope you'll grab a sandwich in the dining room and join in on the discussions happening down in the amphitheater—Monday's session covers Experimental Models and Micro-FUS and Tuesday will host a discussion on Brain Applications of focused ultrasound.

Monday, October 18 | 12:30–13:30

Session A:
Experimental Models and Micro-FUS
Location: Amphitheatre
Status: Seats available; box lunch reservations closed

Models for pre-clinical studies of MR-guided focused ultrasound will be this group's focal point. Discussion is expected to pick up where the Monday morning session on micro-FUS systems leaves off. Appropriate disease models will also be addressed.

Session B:
Reimbursement
Location: Westcott Room
Status: Session is full—standing room only

Expanding reimbursement is a major challenge for the MR-guided focused ultrasound community. This group will discuss issues and solutions related to private payer reimbursement in the U.S. as well as successful models of acceptance in Europe. Discussion will continue at the symposium's Accelerating Development & Adoption session on Wednesday, October 20.

Tuesday, October 19 | 12:30–13:30

Session A:
Brain
Location: Amphitheatre
Status: Seats available; box lunch reservations closed

A lively discussion is anticipated about MR-guided focused ultrasound applications in the brain. This group will continue conversations begun during the symposium's Brain Applications session on Monday.

Session B:
Prostate
Location: Westcott Room
Status: Session is full—standing room only

Scheduled to meet just before Tuesday afternoon's session on Prostate Applications, this group is open to everyone interested in prostate cancer and BPH, prevalent conditions that could be the next major clinical uses for MR-guided focused ultrasound.

Focused Ultrasound Surgery Foundation

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