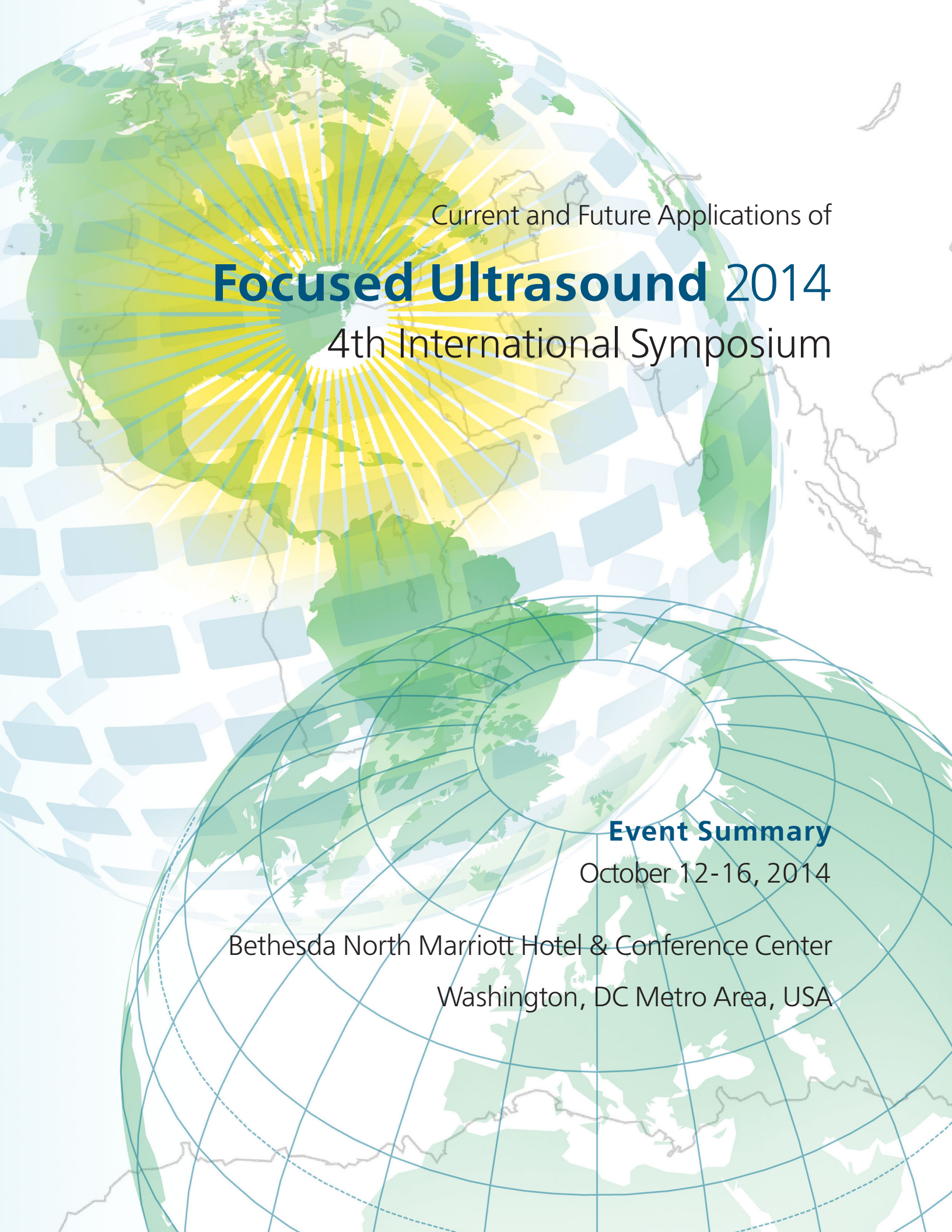


Current and Future Applications of

Focused Ultrasound 2014

4th International Symposium

Event Summary

October 12-16, 2014

Bethesda North Marriott Hotel & Conference Center

Washington, DC Metro Area, USA

Your partner *in advancing the field*

FOCUSED ULTRASOUND FOUNDATION

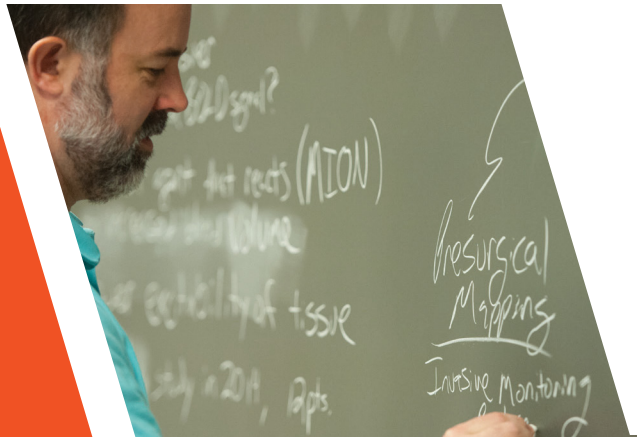
The Focused Ultrasound Foundation was created to improve the lives of millions of patients by accelerating the development and adoption of focused ultrasound.

We leverage our independent status to drive progress by:

Funding Research

A key priority for the Foundation is funding translational studies, applying the growing body of knowledge to complex problems.

We organize and conduct research internally and through an **External Awards Program**, which funds investigator-initiated clinical and technical research projects through a competitive peer-reviewed process.



Fostering Collaboration

We act as a global connector, hosting a variety of **workshops and biennial symposia** to stimulate innovation and increase awareness.

Overcoming Barriers

We **partner with industry** to help usher this technology through the regulatory and reimbursement processes and move the technology closer to patients.

Current and Future Applications of Focused Ultrasound 2014

A Summary of the Focused Ultrasound Foundation's 4th International Symposium

Contents

Welcome

Neal F. Kassell, MD, Founder and Chairman of the Focused Ultrasound Foundation and Professor of Neurosurgery at the University of Virginia in Charlottesville, Virginia

Welcome. The audience today includes more than 400 people from 24 countries. The purpose of this meeting is to disseminate knowledge and foster collaboration--and this year's theme is innovation. Because challenges exceed resources, the only way to bridge the gap is innovation. Only a few years ago, focused ultrasound technology had a handful of bioeffects, clinical indications, and commercial organizations. Today the physicians, scientists, and entrepreneurs in this room have explored more than 12 different bioeffects for 60 clinical indications and formed at least 25 companies. The potential of FUS to improve the quality of life for millions of people has never been greater, but the challenges are substantial. The reason that this meeting is designed to create opportunities to foster collaboration is because it is the collaborative initiatives that will overcome many of the barriers. Learn, share, enjoy yourselves, and get primed to innovate! On behalf of the Foundation, we thank the meeting's sponsors. Personally, I would also like to thank the hard work of the Symposium planning team.

Honorary President

Feng Wu, MD, PhD, Focused Ultrasound Consultant and Senior Clinical Scientist, Oxford University Hospitals, Headington, Oxford, United Kingdom

I am excited to serve as Honorary President of this Symposium. For 25 years I have worked on developing focused ultrasound to treat a range of solid tumors. I began in China and am now conducting research at Oxford. Just my experience alone is an example of how the field is expanding by breaking through geographic barriers to build on the value of global collaboration. I have personally seen a great change in focused ultrasound--it has grown from a concept into its own scientific discipline. It is an exciting time to come together. The pace of progress around the globe has accelerated, and this Symposium will help fuel further advances. The field is both expanding and deepening as focused ultrasound evolves from the laboratory to clinical trials and regulatory approval for treating more conditions. Everyone in this room is critical to defining the future of focused ultrasound. We have all left our laboratories and clinics to invest time to convene for the next few days. This is the opportunity for the world's leading focused ultrasound clinicians and scientists to learn from each other, and we should think of this Symposium as a giant laboratory for experimenting with ideas and building new connections that will propel the field forward. I encourage you to take full advantage of the opportunity – and to have fun! Lastly, I would like to thank the Focused Ultrasound Foundation for making this Symposium possible. They have put together a compelling and well-rounded program for us. We are lucky to have this independent organization dedicated to our mutual success and, ultimately, to the patients who will benefit the most. I hope to see you all again at the ISTU meeting in Utrecht in April and at the European Focused Ultrasound society meeting in London next October.

For more information, including the original abstracts from this meeting, go to:
www.fusfoundation.org

View the abstracts at:
http://www.fusfoundation.org/web/symposium/docs/FUSF_Symposium_2014_Program_Contents_ForWeb.pdf

Sign up to receive the FUSF Newsletter at:
http://www.fusfoundation.org/newsletter-signup

Keynote Speakers

Frederic Moll, MD, who helped establish the field of robotics to transform surgery, challenged attendees to take their ideas to the next level. In "Developing a New, Disruptive Therapeutic Modality: From Laboratory Research Tool to Standard of Care," he shared insights from his experience founding Intuitive Surgical, including his vision behind the technology, overcoming barriers to adoption, and lessons for focused ultrasound. Dr. Moll also serves on the Foundation's Board of Directors.

Andrew von Eschenbach, MD, addressed the importance of integrating discovery, development, and delivery to accelerate progress for medical solutions. In "The Virtuous Cycle of Discovery, Development, and Delivery: The 21st Century Paradigm for Advancing Bioscience," he elaborated on his experience with this continuum and how it can be applied to facilitate focused ultrasound's progress. A member of the Foundation's Board of Directors, Dr. von Eschenbach is the only person to have led both the U.S. Food and Drug Administration and the National Cancer Institute.

Rick Hamilton emphasized that strong global intellectual property systems encourage innovation and that innovation is key for growth and should be the top priority for business development. In "The New Innovation Economy," IBM's Cloud Offering Evangelist and Master Inventor discussed the rising importance of innovation in today's economy by examining the driving factors, how organizations are responding, and what it means to us as individuals.

Special Guests

U.S. Vice President Joe Biden delighted attendees with a visit to the Symposium's major networking event, the poster reception, where he perused posters on display and spoke with researchers about their work. "We extend our thanks to Vice President Biden for coming to see what the field of focused ultrasound is accomplishing," said Neal F. Kassell, MD, Chairman of the Focused Ultrasound Foundation. "To have him spend time engaging with researchers about their work energized the entire meeting."

Foundation Council members Tony and Jonna Mendez spoke publicly for the first time about Tony's battle with Parkinson's disease in a special session at the Symposium. They addressed his Parkinson's diagnosis, his recent deep brain stimulation treatment, and their hope that focused ultrasound might soon be a non-invasive treatment option for others. The discussion was moderated by Washington Post reporter Michael Rosenwald, and subsequently published in the Post.

Brain

The brain portion of the Symposium showed extreme growth over the past two years. The Foundation's dedicated brain program, whose activities include establishing technical and preclinical working groups and clinical trial steering committees, creating a resource library, hosting workshops, and sponsoring research, has promoted great progress. Clinical trials are underway or have been completed in essential tremor, Parkinson's disease, obsessive-compulsive disorder, depression, brain tumors, and opening the blood-brain barrier (BBB) to allow medications to reach previously unreachable areas of the brain. The field is adding new indications. Investigators are now studying the use of focused ultrasound (FUS) to treat intracerebral hemorrhage, epilepsy, and Alzheimer's disease.

Essential Tremor Jeff Elias from the University of Virginia (UVA) reported that enrollment is now complete for the essential tremor pivotal trial. Investigators at eight sites worldwide treated 76 patients in the first randomized controlled trial of unilateral MR-guided focused ultrasound thalamotomy with the InSightec ExAblate Neuro system. The study began in August 2013 and completed enrollment in September 2014. Patients with severe, medication-refractory essential tremor were enrolled after being assessed for tremor severity and disability and then randomized in a three-to-one fashion to receive either the focused ultrasound treatment or a sham procedure (to evaluate placebo effect). Participating patients are now being followed for one year. Treatment safety and efficacy are the study's primary endpoints, with secondary endpoints including durability at 12 months, quality of life (QOL), functional improvement, and comparison between the treatment and sham groups. During the follow-up period, an independent, blinded group of neurologists specializing in the management of essential tremor rate the clinical outcomes from videotaped assessments, and the patients will complete disease-specific QOL questionnaires. Results will be compiled by the end of 2015 and submitted to the United States Food and Drug Administration (FDA) for regulatory approval of the device. A group at Rambam Healthcare Campus in Israel is also conducting an essential tremor/Parkinsonian tremor combined study (see below).

Parkinson's Disease Five studies targeting three different areas in the brain are underway for FUS brain treatment of the tremor or dyskinesia associated with Parkinson's disease. Thalamotomy, palliodotomy, and staged subthalamotomy are each under consideration as possible lesioning locations.

Robert Dallapiazza updated the community on the pilot study for Parkinsonian tremor that is being conducted at UVA and Swedish Medical Center in Seattle. The randomized, controlled focused ultrasound thalamotomy study includes blinded and validated rater assessments and a sham comparative arm. The primary outcome variable is hand tremor. Twenty-four of 30 patients have now been enrolled, and 10 have reached the one-year follow-up period.

Menashe Zaaroor from Rambam Healthcare Campus in Israel described the work of their group in treating both essential tremor and Parkinsonian tremor by thalamotomy. Twelve patients with severe medically refractory essential tremor or Parkinsonian tremor have undergone unilateral ventral-intermediate nucleus FUS thalamotomy. Tremor stopped in the contralateral upper extremity in all patients immediately following the procedure, and two of the patients with Parkinson's disease also experienced a decrease in ipsilateral rigidity. Immediate side effects included vomiting, transient forehead pain, and transient vertigo during sonications. Scalp numbness and subjective transient gait unsteadiness occurred following the procedure in some patients. A severe adverse effect occurred in one patient when the FUS beam unexpectedly created a double focal point and ablated tissue that was a distance from the planned target. The patient developed gait ataxia and a problem with deep sensation in the leg. Overall in the study group, though, the clinical assessment changed from severe disability to no functional disability from tremor immediately after the procedure, and the treatment durability at 10 months shows sustained effect. No late side effects were noted. When asked about the double lesion, Dr. Zaaroor said that they are working with InSightec to determine why it happened but do not yet know why. When asked about the sharp pain in the forehead, he replied that most patients want to continue treatment despite the pain because it only lasts during the time of sonication and resolves rapidly. They think that it may be related to skull heating and the activation of pain fibers in the dura, and solutions may include increasing the energy but shortening the time.

Ronald Bauer presented a case study from a Swiss group of a 45-year-old man with medication-resistant, tremor-dominant Parkinson's disease where deep brain stimulation was contraindicated due to a bipolar disorder. The treatment targeted the pallidothalamic tract (fasciculus thalamicus) of the subthalamic area. The intervention resulted in a prompt and complete suppression of the tremor, improvement of gait, posturing (less rigidity), rigor (9 months follow up), and significant improvement in QOL. The patient now takes bigger walking steps, is

able to run and cycle, has a noticeable change in facial expression, and is no longer suicidal from his reduced QOL.

Jin Woo Chang and his group at Yonsei University College of Medicine in Korea presented their work performing the world's first FUS pallidotomy for Parkinson's disease in the GPi. The procedures to confirm efficacy and discover any potential side effects successfully demonstrated beneficial effects for improving levodopa-induced dyskinesia and motor symptoms. Although further investigation and follow-up are mandatory, the researchers measured increased lesion size at 1, 3, and 6 months after treatment. Dr. Chang also measures skull and marrow thickness in his patients because he believes that the amount of bone marrow affects the ability to increase treatment temperatures. When asked about the level of difficulty in creating lesions, Dr. Chang shared past research where his group discovered that skull thickness affected treatment outcomes because the pallidotomy is probably at the margin of the treatment envelope.

Jeff Elias and colleagues at UVA are also planning a clinical trial to investigate the management of medication-refractory motor symptoms associated with Parkinson's disease using a unilateral, focused ultrasound subthalamotomy performed in a staged fashion. They hope to enroll ten subjects with medication-refractory symptoms or side effects of advanced Parkinson's disease and treat them with a "sub-therapeutic" (stage 1) focused ultrasound subthalamotomy and then observe the patient for 30 days. A patient who develops severe and involuntary movements, such as hemiballismus, would be excluded from the second stage procedure, but those who tolerate subthreshold lesioning would then undergo a second, full subthalamotomy ablation (stage 2) with FUS. Validated Parkinson's disease rating scales, cognitive assessments, and MRI will be obtained before and after the procedures. When asked about this study, Dr. Elias discussed the difference between warming vs. killing tissue and suggested that the non-thermal effects of FUS may also be a way to manipulate neuronal circuits without damaging them.

In the Q & A session for the Parkinson's disease panel, Dr. Elias compared FUS to DBS for patient tolerance (similar), procedure duration (FUS lasts 2-3 hours, which is shorter than DBS), and invasiveness/patient comfort (patients do not like the drilling of a burr hole) but pointed out that FUS has a lot of room for improvement and should become faster. He thinks that FUS could be a wonderful tool when drugs do not help because patients with Parkinson's disease are often older and in poor condition. Dr. Chang cautioned that it is too early to make any conclusions about Parkinson's disease, but FUS has a certain role that is different from DBS (DBS is better for the really deep regions of the brain) and that essential tremor is a better indication right now. Neurosurgeons need to characterize and define this technology better, use caution, and let the results give us the answers. When asked about the histological outcome of these lesioning procedures, the panel responded that approximately 7 days after treatment, an area of edema forms and then resolves in the first month; after one year, the lesion is no longer visible on scans and becomes an area of scar tissue/gliosis. When asked about answering patient questions about focused ultrasound, Dr. Elias said that he tells them it won't take away all of the symptoms, it's more of a palliative procedure. He is hopeful that one day there will be a cure for Parkinson's disease so that we will not need these procedures.

Intracerebral Hemorrhage Because evidence suggests that liquefying and/or removing the clot after intracerebral hemorrhage (ICH) might be beneficial, Leodante da Costa and colleagues from Sunnybrook Research Institute in Toronto plan to test the feasibility of using FUS to safely and effectively cause clot lysis and provide good radiological resolution of the ICH. Six patients with a recent (< 72h) ICH and hematoma > 2 cm will be recruited to undergo FUS along with the same treatment as patients who are not in the trial. Feasibility and safety will be examined and analyzed, followed by radiological progression of the clot.

Obsessive Compulsive Disorder Jin Woo Chang and his group at Yonsei University in Korea have completed a 12-patient study using FUS to perform a capsulotomy in patients with intractable obsessive compulsive disorder (OCD). In this feasibility study, FUS was used to create bilateral thermal lesions in the anterior limb of the internal capsule (capsulotomy). Patient scoring tools for neurocognitive function and symptom improvement showed promising results that are comparable to DBS lesioning. A manuscript describing the study has been accepted for publication. Dr. R. Cosgrove congratulated Dr. Chang on the study and commented on the historical use of surgery, technology, and medication for psychiatric surgery and movement disorders. He stated that even with all of the advances, patients are asking for more help.

Although physiological feedback is not currently available during the procedure and the results are not immediately seen, the patients improve over time with this type of lesioning, and he predicts that these results will show continued improvement in 1 to 2 years. Dr. Kassell then recognized Dr. Chang's pioneering work and commented that no one has shown more courage in trying to improve the lives of large numbers of patients.

Jean-François Aubry's group at the Institut Langevin in Paris presented their studies on ultrasonic neuromodulation. Using a rat model, they applied low intensity US to produce pressure at the target site and achieve very specific motor responses, even with a large focal spot and diffuse field. Their simulations show that due to reverberations in the rat head, the pressure in the brain is higher than assumed in previous studies.

Brain Tumors Four presentations highlighted progress toward successfully treating brain tumors with focused ultrasound. A successful case of FUS ablation of malignant glioma was performed in Switzerland and has gained international media attention. Clinicians in Seattle are screening patients for inclusion into a metastatic brain tumor study. Other strategies, including microbubble-enhanced ablation and sonodynamic therapy, may further enhance the ability of focused ultrasound to treat brain tumors.

Nathan McDannold from Brigham and Women's Hospital/Harvard Medical School presented their research investigating non-thermal ablation with FUS plus an ultrasound contrast agent. This combination reduces the power needed to ablate tissue and could potentially eliminate skull heating, a method that may be useful for treating brain tumors. A low duty cycle prevents bulk tissue heating and promotes inertial cavitation. In a primate model, they injected a bolus of ultrasound contrast agent and then applied burst sonications slightly above the inertial cavitation threshold at a low ultrasound frequency (220-525 kHz) and a 1% duty cycle over several minutes. After 2-3 weeks, imaging revealed a lesion or cavity similar to surgical resection. White matter tracts seem to be resistant to this type of ablation, which may enable ablation directly adjacent to cranial nerves or the base of the skull. This method of ablation may work outside the thermal ablation treatment envelope, and offer advantages for tumor debulking. More work is needed to establish the viability of this technique in tumors and to understand how the method can be applied safely. This group has also developed a method to monitor the technique with acoustic emissions.

Sonodynamic therapy is the use of the energy from low-intensity ultrasound waves to activate sensitizing agents and induce apoptosis (cell death) without collateral damage to surrounding tissues. Because sensitizers like 5-aminolevulinic acid (5-ALA) and indocyanine green (IcG) have been shown to be preferentially taken up by glioma cells, Paul Schmitt and colleagues at UVA are hoping to prove that they can be effectively delivered to and detected in brain tumor cells and then targeted with FUS for treatment. This study demonstrated that both sensitizers were taken up in the tumor cells, in a rat model. The next study will attempt to determine the ability of low-intensity ultrasound to cause hyperthermia-induced apoptosis in the sensitized cells.

Javier Fandino and colleagues from Zurich, Switzerland reported the first successful non-invasive MR-guided FUS ablation of a brain tumor. The 63-year-old patient suffered from a centrally located malignant glioma in the left thalamic and subthalamic region. He underwent surgery five years ago but further surgery was not recommended due to the tumor's location within eloquent brain areas and previous radiotherapy and chemotherapy. The patient stayed awake and responsive during the intervention, was neurologically stable, and did not need medication after successful placement of the stereotactic frame. Follow-up MRI was performed immediately post-procedure and 1, 5, and 21 days afterwards. Perifocal edema developed around the thermal lesions but gradually disappeared during the follow-up period. The patient did well and had improved neurological function. This accomplishment supports the potential use of FUS for the non-invasive treatment of patients suffering from malignant brain tumors, especially in areas not amenable to conventional neurosurgical interventions. Further treatments in the context of this ongoing pilot study will be needed to assess the feasibility and safety of the procedure. If the results are positive, then a larger study in the future will be needed to demonstrate safety and efficacy. The current screening to patient selection ratio is 90:2. The case has been published in the Journal of Therapeutic Ultrasound.

Stephen Monteith from Swedish Medical Center in Seattle presented a clinical trial update on his group's intention to treat metastatic brain tumors using FUS. He shared the factors and challenges for recruiting patients into this study. Patients must have only 1 to 3 metastatic lesions, and they must be symptomatic but not have had any prior hemorrhage. Many lesions may have tiny microhemorrhages on gradient echo imaging without clinically occult manifestation or clinical relevance. The location of the metastatic tumors is problematic, as

they tend to present at the gray-white matter junction and not in the center of the brain, where the current clinical system is able to effectively treat. The group's experience with a large volume of screened patients has led them to suggest protocol modifications. Learning points, implications, and technological challenges were presented. Discussion followed regarding how prior hemorrhages, the size of the tumor, radiosurgery and radiation treatments, and prior craniotomy may affect patient selection.

Crossing the Blood-Brain Barrier Using FUS to open the blood-brain barrier (BBB) or as a way to improve the delivery of drugs or biologics was the subject of seven presentations. Advances have been made that demonstrate the potential to improve the treatment of glioblastoma and other types of primary and metastatic brain tumors as well as Alzheimer's disease and other neurodegenerative disorders.

Researchers at the University of Toronto/Sunnybrook Health Sciences Centre have been approved to begin a Phase 1 clinical trial using FUS to open the BBB and enhance the delivery of doxorubicin to treat glioblastoma. They will enroll 6 patients in a prospective, single-arm, nonrandomized trial and use an ultrasound contrast agent plus FUS to treat clearly defined malignant tumors that have been confirmed on biopsy or suspected based on imaging. The target size must be less than 2 cm in diameter or 8 cm3. They plan to compare imaging characteristics of the FUS treated and untreated regions to assess the delivery of the doxorubicin and whether it was enhanced by FUS.

Michael Canney from CarThera presented a clinical trial that has begun in Europe to open the BBB for chemotherapy administration. Although they do not use focused ultrasound, CarThera has developed a device that uses low intensity ultrasound waves to temporarily open the BBB prior to chemotherapy delivery to patients with recurrent glioblastoma. The Phase 1/2a clinical trial began last July, and has enrolled four patients at this time. A tiny ultrasound transducer is inserted into a standard burr hole, fixed to the surrounding skull bone, and covered with skin. The energy is delivered once a month when the device is connected to an external generator system via transdermal needle. The patient receives up to two minutes of pulsed ultrasound. At the same time, an ultrasound contrast agent is given and BBB disruption is monitored via MRI. As the BBB is opening with ultrasound, the chemotherapy is administered.

Nathan McDannold from Brigham and Women's Hospital/ Harvard Medical School presented an overview of data obtained in rodent tumor models that evaluated tumor growth rates and survival after ultrasound-enhanced chemotherapy delivery for a range of medications in both primary and metastatic tumors. The potential for this technology, either alone or in combination with focused ultrasound ablation, has been demonstrated and clinical translation is now needed. Focused ultrasound systems also need key improvements, including sonication of large volumes and the ability to monitor and guide the procedure outside the MRI.

Kullervo Hynynen from Sunnybrook Research Institute presented their work using FUS to open the BBB in mice with Alzheimer's disease. Mice received single or weekly FUS treatments using a 1.68 MHz transducer (10 ms pulses, 1Hz pulse repetition frequency, 120 second duration). Definity™ brand microbubble contrast agent was delivered at the onset of sonication. Effective BBB opening was confirmed using contrast enhanced MR images. After FUS, the mice showed improved performance on cognitive tests. The group found the repeated FUS treatments to be safe. Histologically, the mice treated with FUS also had reduced plaque burden in the brain and increased plasticity in the hippocampus, both of which have been correlated to improved learning and memory. Together these preclinical data demonstrate that FUS-mediated BBB opening can improve cognition (even in the absence of exogenous drug delivery) and suggests that FUS may have potential for incorporation into the overall therapeutic strategy for the treatment of Alzheimer's disease. In the future, this group plans to investigate whether stem cell delivery to the area where the plaque has been cleared could induce neuronal regeneration; their preliminary studies show promise in this area.

Elisa Konofagou and her colleagues at Columbia University are also studying ways to treat Alzheimer's disease. They are using FUS plus microbubbles to open the BBB and deliver neurotrophic (neuron-loving) molecules to potentially trigger neuroprotection and neurogenesis in a mouse Alzheimer's model. Brain-Derived Neurotrophic Factor (BDNF) is one of the most promising neuroprotective molecules for treating Alzheimer's disease and other brain disorders, but it does not cross the BBB. After opening the BBB with FUS, they were able to confirm that BDNF only crossed the BBB the treated region and that it entered the actual cell, not just the extracellular space. The group also investigated the effects of injecting two other neuroprotective agents: neurturin (NTN) and recombinant

adeno-associated virus (rAAV) for therapeutic gene delivery. The rAAV showed some neuroprotection and the NTN showed neuroregeneration (both preserved the number of neurons in the substatia nigra of MPTP mice).

Richard Price from UVA presented their work in delivering nanoparticles (NPs) across the BBB and the brain-tissue barrier (BTB) – the nanoporous, electrostatically charged tissue space – for the treatment of brain tumors and neurodegenerative diseases. They are using focused ultrasound (FUS) and contrast agent microbubbles to deliver drug- and gene-bearing NPs. To overcome the BTB, they coat the drug- and gene-bearing NPs with a dense layer of polyethylene glycol (PEG). After using FUS and microbubbles to deliver NPs with luciferase or mCherry plasmid DNA across the BBB in rats, they were able to visualize robust luciferase transgene expression that corresponded to a single focal site of FUS exposure. The intensity of gene expression correlated with the NP concentration. They were also immunochemically able to detect mCherry in both glial cells and neuronal cell nuclei. mCherry expression was homogeneously distributed throughout the sonicated area, demonstrating the benefit of combining FUS-mediated delivery across the BBB with brain-penetrating NPs. These studies represent the first evidence for brain transfection via the delivery of a nonviral gene NP across the BBB with FUS. Going forward, this approach may be used to deliver genes for neurotrophic factors for the treatment of neurodegenerative diseases.

James Keenan and scientists at Artenga worked with the National Research Council of Canada to develop a new method to efficiently and consistently load biologics onto microbubbles, including cerebral dopamine neurotrophic factor (CDNF), a novel neurotrophic molecule recently discovered at the University of Helsinki. Artenga's goal is to commercialize their technology to treat multiple diseases with different compounds and tumor-targeting agents. Their proprietary microbubble conjugation technology permits extremely high and consistent drug loading per microbubble for a wide range of compounds, including antibodies, proteins, antibody-drug conjugates, and genes. The covalent bond performs well in vivo, and the technology can also be adopted for cancer treatments. Indications that may be affected by this technology include Parkinson's disease, other CNS disorders, and different types of cancer (drug-loaded tumor targeting).

Neuropathic Pain Ernst Martin and his group at Zurich Children's Hospital described thalamo-cortical dysrhythmia (TCD) as chronic neuropathic pain that arises from thalamic deafferentation and leads to self-sustained thalamic oscillation. It is diagnosed using a quantitative EEG. They used FUS thalamotomy to treat 23 patients suffering from chronic neuropathic pain of various origins. They target the posterior central-lateral (pCL) nucleus of the thalamus with both unilateral and bilateral lesions, depending on the severity and extent of the clinical symptoms. The median pain relief was 56%, with an average reduction of maximal pain intensity of 34%, estimated by the patients on a numerical rating scale. Some patients may have subjective bias because they were no longer taking opiate medications, acted completely differently, or had a higher quality of life according to their family or psychiatrist. The researchers expressed the need for objective measurement tools for this patient population (e.g., QOL, ADL, pain medications, observations by others, psychiatric evaluation).

Neuromodulation Focused ultrasound can stimulate or suppress neural activity, depending on the parameters of the energy applied to neural tissue. Researchers are testing the safety and feasibility of using this bioeffect in the cortical, frontal, temporal, and primary somatosensory cortex areas of the brain. The five studies below show the diverse research that is being conducted in this area.

Wonhye Lee from Brigham & Women's Hospital/ Harvard Medical School described the work of their group using FUS to mediate functional neuromodulation in a sheep model. To establish preliminary safety data prior to translational research into humans, researchers stimulated one somatosensory and one visual area of the cortical brain using an acoustic intensity of 1.4–15.5 W/ cm2 Isppa, tone-burst-duration of 1 ms, pulse-repetition frequency of 500 Hz (i.e. duty cycle of 50%), and a sonication duration of 300 ms. A batch of continuous sonications ranging from 50 to 150 ms in duration were also tested. Responses were measured, and histological testing of the tissue was performed at 1 week and at 2 months after sonication. With the exception of white matter tracts, the results support the theory that transcranial FUS may serve as a novel tool to transiently and reversibly modulate regional brain function, enabling electrophysiological functional assessment of an ablative target prior to FUS neurosurgery.

Nathan McDannold, also from Brigham & Women's Hospital/Harvard Medical School, presented a preclinical neuromodulation study where they attempted to use FUS to suppress visually evoked potentials in the primate brain. In seven sessions, a total of 133 sonications at 57 different targets on and around the LGN were evaluated.

While they were able to reliably obtain strong visually evoked potentials within the InSightec ExAblate system, they were unable to suppress them. In a few cases, large DC shifts that lasted several minutes were induced, perhaps indicative of cortical spreading depolarization. No tissue damage was evident in MRI, so it is unclear why these experiments failed. Potential reasons could be bad targeting, insufficient focal exposure, incorrect pulsing parameters, or other factors such as anesthesia.

Jean-Francois Aubry from the Institut Langevin Ondes et Images in Paris presented their work using FUS neuromodulation to stimulate the brain of monkeys. They targeted the frontal eye field and recorded baseline latency time vs. latency time after FUS. The latency time increased, and they were able to induce neurostimulation. The study demonstrates the feasibility of using focused ultrasound stimulation to causally modulate behavior.

A collaborative neuromodulation study between Brigham & Women's Hospital/Harvard Medical School, The Catholic University of Korea, and the Korea Institute of Science and Technology was presented by Seung-Schik Yoo. This group successfully used low-intensity FUS to stimulate the primary somatosensory cortex in 18 patients, eliciting sensory responses on the fingers and hand from 91.7% of the subjects. They measured the cortical EEG potential to quantitatively examine the effects of the FUS stimulation. Sonications elicited transient tactile sensations on the hand area contralateral to the sonicated hemisphere, with anatomical specificity of up to a finger, while EEG recording revealed the elicitation of sonication-specific evoked potentials. This study is the first evidence of active creation of stimulatory responses from the brain elicited by FUS in the absence of any external tactile stimulation. The stimulatory effects were transient and reversible and did not cause any discomfort or adverse effects across the participants.

Alexander Bystritsky from the University of California Los Angeles presented an approved clinical study to test the safety and feasibility of low-intensity FUS pulsations (LIFUP) to induce neuromodulation in patients with **temporal lobe epilepsy**. Although no patients have yet been enrolled, participants who have elected to undergo temporal lobe surgery are being recruited. Prior to the scheduled surgery, participants will undergo simultaneous LIFUP and functional MRI using various LIFUP pulsing paradigms to excite or suppress neural tissue. Safety and histological analyses will be conducted.

During the discussion period that followed the neuromodulation panel, a member of the audience asked "Why do some exposures cause activation and some cause suppression?" The panel responded that this is a wonderful comment on the current status of neuromodulation. We really don't know what is going on--we lack the mechanism behind it. There are a lot of different hypotheses – different parameters affect the various kinds of neurons differently, and more studies are needed. A poster by Michael Plasksin from the Israel Institute of Technology includes insights into cellular level changes during modulation, and it has a wonderful theory of what may be happening in terms of both suppression and activation.

Epilepsy Preclinical and clinical studies using focused ultrasound to treat different forms of epilepsy are underway. Along with the neuromodulation study listed above, medication refractory mesial temporal lobe epilepsy and subcortical epilepsy may be a good match for this technology's ablative abilities.

Stephen Monteith from Swedish Medical Center presented a laboratory feasibility study for FUS treatment of mesial temporal lobe epilepsy. Using cadaveric skulls filled with custom fitted thermo reactive gels and thermocouples strategically placed at anatomical areas of interest, researchers ablated a volume of temporal lobe structures similar to standard surgical excision. They created temperature maps in the treatment volume for various sonication parameters and monitored temperature at key structures, such as the base of the skull. The group successfully created a therapeutic-sized lesion. They noted that peripheral cooling was slower than medial cooling, but found this study to demonstrate feasibility of the method. Translation to clinical work might also involve blocking some beams to circumvent temperature rise in the anterolateral temporal fossa.

Nathan Fountain from UVA presented their work on the potential use of FUS for subcortical epilepsy surgery (FUSE study). This open label safety and feasibility pilot study will enroll 15 subjects with subcortical lesions as the cause of medically refractory epilepsy, including hypothalamic hamartomas, periventricular nodular heterotopia, focal "cortical" dysplasia that is sufficiently far from the skull, and hamartomas of tuberous sclerosis. Outcome measures will be safety, feasibility, and seizure reduction. Subjects will undergo a single MR-guided FUS treatment session. During the Q&A, a question was asked about treating children with hypothalamic hamartomas, and the response was that children would not be included at this time.

Treatment Envelope Focused ultrasound has been successful in treating targets in the center of the brain for movement disorders and neuropathic pain. To increase the treatment envelope (the area of the brain that can be safely and effectively treated) to include peripheral targets, researchers are investigating ultrasound contrast agents, simulation models to predict which parameter changes may create progress in this area, improved imaging capabilities, and design changes to the current clinical system.

Nathan McDannold from Brigham & Women's Hospital/ Harvard Medical School presented the work of his group in using ultrasound contrast agents to increase the treatment envelope. Microbubble agents respond strongly to an acoustic field, even at low intensities, and greatly magnify the bioeffects of FUS. The treatment envelope in the brain could potentially be expanded if scientists can reduce the time-averaged acoustic power needed for ablation. Introducing ultrasound contrast agents reduces the power needed to ablate tissue.

Jean-Francois Aubry and researchers at UVA, Institut Langevin, and the Focused Ultrasound Foundation are investigating the use of different simulation models and head phantoms to further expand the treatment envelope for FUS brain therapy. Simulations have been developed to create acoustic maps of the skull, and test treatment parameters prior to experimentation. Three different phantom models were developed and tested: cadavers, gel-filled skulls, and a head mold containing a skull and filled with gel that mimics the brain and the skin. Simulation models are ideal for investigating novel strategies, like transducer design and positioning, but experiments are mandatory to fully validate such approaches and test novel MR imaging techniques for better targeting, larger temperature monitoring volume, or shorter treatment time.

Navid Farr and researchers at the University of Washington in Seattle worked with Philips Healthcare to determine whether a commercially available FUS system could target and monitor boiling histotripsy and then characterize the volume and associated bioeffects of the final lesions. They successfully used MR to monitor the boiling histotripsy exposures and provide feedback on thermal effects within the target location and the surrounding region. The MRI was sensitive to the liquefaction of ex vivo bovine liver tissue produced during the histotripsy treatments.

Eyal Zadicario from InSightec discussed treatment considerations for their ExAblate Neuro transcranial FUS system. He reviewed the existing applications and the limitations of the current technology, including the size of the treatment envelope and the effects of different skulls on FUS delivery. Technological barriers need to be overcome, and patient selection criteria should be developed. The use of a lower frequency has the potential to widely expand the treatment envelope because 50% more energy can be delivered at a lower frequency; a dual-frequency system may be forthcoming. New safety measures and improving the focus are also underway.

Imaging Advancements in the use of imaging to visualize and monitor focused ultrasound treatment are continually expanding the current capabilities of the technology. Five presentations showed the diversity of projects in this area.

Kim Butts Pauly from Stanford University described the work in her laboratory with magnetic resonance acoustic radiation force (impulse) imaging (MR-ARFI). FUS has a temporal response; the tissue displacement at the focus will increase until the end of the pulse, creating shear waves that are proportional to the duration of the treatment. Using ARFI models for comparison, they performed in vivo verification of the focal spot, the focal quality, and the pressure intensity. Future studies will include tissue absorption and elasticity.

Dennis Parker and the University of Utah team are studying the use of volumetric thermometry for temperature mapping. Their work centers around creating a model that can predict the FUS temperature profile and optimizing the MR radio frequency (RF) coil's signal intensity (performance) through better and more specific coil design. For better transcranial FUS treatments, they predict that the FUS transducer and the coil will need to have an integrated design.

Rock Hadley from the University of Utah presented their work in improving the signal-to-noise ratio (SNR) of RF coils used with MR-guided focused ultrasound. Of all the options for increasing SNR, coils provide the greatest gains for the dollars spent, and a specific-purpose coil with a 40% SNR improvement over a general-purpose coil can achieve the same image quality in half the imaging time; a coil with twice the SNR can achieve the same image quality four times as fast. He presented the features of several different specific-purpose transcranial coil designs. Besides improving imaging, these coils also improve temperature accuracy, thermal dose measurement, and treatment planning.

Wilson Miller from UVA presented their work on MR bone imaging. Bone is highly relevant to clinical FUS, both because it can be treated with FUS and because it may surround other treatment areas. To use MRI to image bone, these researchers developed a technique using ultrashort echo time (UTE) that can create images from the very short signals produced by cortical bone. UTE pulse sequences are not yet available clinically on existing commercial scanners, but this may change over the next few years. With improved RF coils and aberration correction, bone thermometry may be possible.

Kullervo Hynynen from Sunnybrook Research Institute presented the work of their group detecting and mapping cavitation for brain imaging and therapy. FUS cavitation is being developed for opening the BBB and inducing sonothrombolysis for the treatment of stroke. Therefore, these researchers are studying methods for monitoring and controlling cavitation so that clinical studies can be conducted. They are also finding ways to use the cavitation signals to control treatments.

Discussion after the imaging session included the role of the body coil with specific-purpose transducers, skull heating and cooling, 1.5T vs 3T MRI systems, and transmit-only/receive-only coils.

Technology Wish List for Brain Applications When polled about technological needs, FUS brain system users asked for several improvements:

Imaging
- an integrated MR RF coil
- volumetric thermometry
- optimized central frequency correction
- diffusion and fMRI capabilities
- the ability to reduce artifacts from water and membrane motion
- the ability to see the focus for non-thermal effects
- ARFI focus verification and quality assessment

Treatment Planning
- an offline pretreatment simulation system that could help with patient selection
- skull efficiency prediction
- MR-based skull aberration correction
- a better understanding of neuromodulation
- multifocal stimulation capabilities

Workflow and Ergonomics
- optimized workflow to decrease treatment time
- a less cumbersome ability to position the transducer (robotic?)
- improved patient comfort

Safety
- cavitation localization
- bone thermometry

Additional considerations mentioned were transducer improvements to increase the treatment envelope and the ability to measure the temperature elevation in the skull during treatment (bone thermometry).

Monday Evening: Focused Ultrasound Showcase

Joseph Stancanello, Director, MR Applications and Workflow in Europe
GE Healthcare

Robert Sigal, President & CCO
InSightec Ltd.

Christopher Busch, VP, General Manager MR-Therapy
Philips Healthcare

Yuchi Chu, Director
Alpinion

Chrit Moonen, Board Member
ISTU

Peter Kaczkowski, Senior Scientist
Verasonics

Marc Oczachowski, President and CEO
EDAP

Jeff Keller, Sales Manager
Electronics & Innovation, Ltd

Andreas Melzer, President
EUFUS

Dan Pajek, President
FUS Instruments

Erik Dumont, President & CEO
Image Guided Therapy

Gerard Fleury, President & Marketing Manager
Imasonic

Kathy Dimeo, President
KAI Research

Kyle Morrison, Project Manager & Principal Engineer
Sonic Concepts

David Caumartin, President & CEO
Theraclion

Enhanced Immunotherapy

Tuesday, October 14, 2014

Panel Discussion: Enhanced Immunotherapy

An emerging application for focused ultrasound involves enhancing the body's immune response in the treatment of cancer. The heating and mechanical properties of focused ultrasound may have a role in the cancer-immunity cycle and in influencing the tumor microenvironment to allow the body's immune system to more effectively combat tumors. Several groups have begun studying focused ultrasound in this capacity. Researchers are looking at how focused ultrasound may enhance the ability of tumor-infiltrating lymphocytes to gain access to a tumor, cause upregulation of immunogenic cytokines to increase local and systemic effects, and assist in drug delivery by activating drug adjuvants to prevent recurrence, treat metastases, and increase survival. For background reading, Chen and Mellman's review article on the cancer-immunity cycle was published in Immunity in 2013, and Wattenberg's August 2014 Radiation Research manuscript was also suggested.

Elizabeth Repasky from the Roswell Park Cancer Institute led the panel and discussed how focused ultrasound could be used to boost immunotherapy in tumors. She described the cancer-immunity cycle and how FUS might play a role in the tumor microenvironment. FUS can change the tumor microenvironment by causing necrosis in the tumor, which releases tumor-associated antigens. T cells are activated through the signaling pathways of antigen-presenting cells, thereby stimulating the body's immune system to inhibit tumor growth and proliferation. This mechanism can then also be combined with other immunotherapies and cancer therapeutics to increase efficacy.

The Symposium's Honorary President, Feng Wu, from the University of Oxford presented FUS immunotherapy lessons that have been learned from preclinical and clinical studies. Tumor-infiltrating lymphocytes were found in tissue after FUS treatment for breast cancer, at a significantly higher concentration than in a control group. In a 2007 study of local expression of tumor antigens, epithelial membrane antigen and heat shock protein 70 (HSP-70) had positive expression. A preclinical study in a mouse model of liver cancer produced higher survival rates, and the researchers theorized that the thermal ablation modified the tumor's antigenicity and upregulated the expression of HSP-70 to increase the cellular immune response. FUS immunotherapy may play an important role in preventing local recurrence and metastasis of cancer. Future studies should determine if this response has clinical significance, determine its mechanism, target disease-specific tumors, and begin clinical trials.

Katherine Ferrara from the University of California at Davis discussed the immune activation properties of FUS from a drug delivery perspective. Immune adjuvants have been shown to be effective in treating metastatic cancer, and combining ablation with immune adjuvants is a promising technique. In her laboratory, they combined doxorubicin with copper to create a small crystal and then used FUS to release the crystals into the tumor in a mouse model. This targeted approach appeared to suppress tumor growth and increase survival (all viable tumor cells disappeared). The preliminary results are promising.

Mark Hurwitz from Jefferson University Hospitals presented his research using heat to augment immunotherapy. Because prostate cancer radiation causes a highly significant increase in HSP-70, he hypothesized that the heat from FUS could also create HSP release, dendritic cell (DC) activation, and adhesive changes. This would be an example of a local treatment inducing a systemic effect. Focused ultrasound has the potential to provide targeted heat and drug delivery to enhance immune effects arising from the heated but nonablated rim present with tumor ablation. Translating these effects into predictable and meaningful clinical responses poses a significant challenge.

To study the mechanical rather than the thermal effects of focused ultrasound with immunotherapy, Tatiana Khokhlova and her group at the University of Washington designed an experiment to determine whether they could use histotripsy to trigger the inflammatory cascade and induce an immune response

in a murine B16 melanoma model. While replicating Restifo's 2003 study, they replaced the tumor-fighting drug cocktail with ultrasound-guided boiling histotripsy. Although it destroyed the tumor tissue and doubled the macrophages and B cells, the boiling histotripsy had no effect on the tumor's growth rate.

Discussion

• With regard to metastases, a Duke study determined that cancer cells are present in circulation long before a tumor can be detected and treated.
• HSP-70 is important in managing immunotherapy. It is specific to developing an immune response and has multiple roles. Other HSPs may have prognostic implications but the literature is most compelling for HSP-70.
• Tumor-specific factors will be important going forward and researchers who study the same tumor should work together. What makes one tumor more immunogenic than another is a critical question.
• Macrophage receptors and cytokines are important and could be measured to determine which is helpful and which is harmful.
•Whether using heat or mechanical effects, focused ultrasound alone may not be sufficient to induce a clinically significant tumor response; a combination approach that includes focused ultrasound plus immunotherapy drug(s) may be necessary for an effective and sustained clinical response.

Bone Non-Metastases

Tuesday, October 14, 2014

Osteoid Osteoma – Adult and Pediatric An osteoid osteoma is a small, benign bone tumor that is found most commonly in the vertebra and long bones, such as the femur and tibia. Three groups presented clinical studies using focused ultrasound to treat osteoid osteoma. Based on preliminary clinical evidence, the CE mark has been granted in Europe and other types of bone tumors are also being considered for focused ultrasound treatment.

Alessandro Napoli from the University of Rome presented their work using focused ultrasound to treat symptomatic osteoid osteomas, investigating its mid- to long-term efficacy. In their series of 29 consecutive patients (8 women; 21 men; mean age of 23), the treatment was safe and well-tolerated with no adverse events during and after 12-24 months follow-up. A mean of 4 ± 1.8 sonications at 894 ± 209 J was necessary to complete the treatment. Complete clinical response was found in 27/29 (93% CI 6–18) patients for pain relief. Two patients reported pain recurrence that required subsequent radiofrequency ablation. Strong anesthesia is required during the procedure, and nidus perfusion is important. The nidus is the highly vascularized core of an osteoid osteoma, and it is the primary target of thermal treatment because destroying it will prevent regrowth of this painful lesion.

Alberto Bazzocchi from the Rizzoli Orthopedic Institute in Italy presented their study of focused ultrasound treatment of superficial osteoid osteomas in the lower limbs of 7 consecutive patients (6 men, 1 woman; mean age 33.5±12.4, range 19-64 years old) using InSightec's ExAblate 2100 system. Six lesions were located at the femur, one at the tibia. The mean pain rating of 7.5 dropped to 0 after 1 month and remained at 0 in 6 patients (86%) after 6 months. No intraoperative complications or short/mid-term adverse events were observed. Focused ultrasound treatment of osteoid osteoma has attained the CE mark in Europe and should be expanded to treat other types of bone tumors.

Adam Waspe from the Hospital for Sick Children in Toronto presented their upcoming study using the Philips Sonalleve focused ultrasound system to treat osteoid osteomas in children and adolescents (6 months to 17 years). Ten patients will be recruited, complete age-appropriate and validated surveys for pain, medication usage, health-related quality of life metrics, and patients will undergo general anesthesia for the treatment. One patient with a 1-cm lesion on the left femoral head has already been treated.

Musculoskeletal Pathology Alberto Bazzocchi also presented a musculoskeletal pathology case review of five patients affected by diseases not commonly treated with focused ultrasound. Three patients with bone lesions of the femoral neck, one with a 1-cm sclerotic alteration of the 8th right rib, and a man with an aggressive a 10-cm fibromatosis on the left popliteal fossa were treated with InSightec's ExAblate 2100 system and followed up to 12 months. The patients with focal degenerative diseases showed an excellent response to treatment with significant improvement in hip mobility. The young lady with the rib lesion partially improved, and the man with the popliteal fibromatosis improved pain scores and quality of life. New and different applications for focused ultrasound in musculoskeletal disorders are promising because FUS decreases the pain and prevents the lesion from progressing.

Thermal Mapping Existing thermal measurement techniques do not provide temperature information within bone, so researchers are investigating ways to measure bone temperature during treatment. Two studies presented assessed MRI data correlation methods and simulation/modeling techniques that might be incorporated in the currently available clinical systems.

Collaborative research between Sunnybrook Research Institute, Philips Healthcare, and the University of Texas Southwestern was presented by Rajiv Chopra. The group is studying dual echo gradient imaging for simultaneous thermal mapping in cortical bone and soft tissue. Because existing MR-thermometry techniques do not provide temperature information within bone, focused ultrasound exposures in bone are currently monitored using temperature changes in adjacent soft tissues. In this study, a standard dual echo spoiled gradient echo (SPGR) sequence is proposed to simultaneously monitor thermal effects in both bone and soft tissue. The correlation of the temperature with magnitude and phase images at two different echo times was examined and found to be well-correlated temporally and spatially. This simple method can be easily translated onto existing MR imaging systems to improve the safety of focused ultrasound treatments.

Sin Yuin Yeo from the Eindhoven University of Technology in The Netherlands worked with scientists at Philips Healthcare to model bone temperature changes during focused ultrasound treatment for bone metastases. Understanding the interaction of focused ultrasound with bone and the temperature elevation in bone and surrounding tissues is very important for treatment planning, protocol design, and efficacy. They performed bone modeling and simulations complemented by phantom experiments to estimate the temperature increase in bone during focused ultrasound application. Their mathematical model used a ray tracing program to calculate the heat production in each spatial point followed by the actual temperature as a function of space and time by solving the heat transfer equation and using the heat production calculated from the ray tracing program as the source term. In addition, shear waves were incorporated into the calculation. The model was then validated using a porcine bone phantom with temperature probes inserted in the cortical bone for further temperature verification. Treatments were performed with the Philips Sonalleve system using 4- or 8-mm treatment cells positioned beyond the cortical bone (i.e. in bone marrow) and different combinations of power and heating durations. The model reliably simulated the temperature in bone during focused ultrasound and may serve as a treatment planning tool.

Session Q&A

Q. What are the limitations for treating bone with focused ultrasound? What conditions cannot be treated?
A. We try to stay away from targets on the spine or the skull, or if the lesion is located really deep in the bone. Generally most osteoid osteomas are found in the long bones and digits and are highly accessible.

Q. When you treated the rib, what was the pathway--did it pass through the lung?
A. As long as we stayed over the bone, it was safe enough. We were careful to watch the reflection from the air in the lung. The energy you need for bone is so low that it is a very safe profile. Thermometry is a problem, but so far it has worked out.

Bone Metastases

Focused ultrasound for the palliative treatment of bone metastases is approved in the United States, Europe, and other regions of the world. Clinical studies were presented by four groups and discussion included treatment consensus, increased adoption, combination therapies, comparative effectiveness data, and increased efficacy.

Merel Huisman from the University Medical Center in Utrecht, The Netherlands, shared their clinical experience with focused ultrasound for bone metastases. Overall, focused ultrasound for bone metastases has been proven as a safe and effective treatment that decreases pain 64% vs. 20% for placebo treatment and is now being reimbursed by some insurance companies. They sought to achieve international consensus to increase awareness, accelerate development, acceptance, and adoption, establish research priorities, standardize the procedures, and create a standard of care. They conducted a systematic literature review, held an expert meeting in 2013, and created a survey. A secondary palliative treatment option could now be included as a primary treatment option. Treatment simulation could optimize efficiency and make the treatments shorter. Future directions might also include local tumor control, treating vertebral metastases, and the use of focused ultrasound as a primary treatment for non—weight bearing bones, possibly in combination with radiotherapy. They may initiate a registry to conduct economic and logistical studies to evaluate cost effectiveness.

Joshua Meyer from Fox Chase Cancer Center presented their study that evaluated the safety of using focused ultrasound to treat painful bone metastases for patients who also received chemotherapy treatment. The retrospective analysis compared data for 104 patients (12% of the study population) who were treated in 17 medical centers worldwide as part of a randomized phase III study. Patients were followed for 3 months. No significant difference between the response rates of the chemotherapy group (71%) and the non-chemotherapy group (68%) ($p=0.78$) was found. Overall event rates were 57% for chemotherapy patients and 45% for non-chemotherapy patients ($p=0.38$). Sonication pain was not significantly different between the groups. No difference was found in efficacy or toxicity of focused ultrasound between patients receiving and not receiving active chemotherapy.

Alessandro Napoli from the University of Rome presented their study evaluating the efficacy of focused ultrasound for pain palliation of bone metastases in patients who had exhausted external beam radiation therapy (EBRT) or refused other therapeutic options. The prospective, single arm, multicenter study included 72 patients (24 women, 48 men, mean age: 61.6) with 87 non-spinal lesions who underwent focused ultrasound treatment with InSightec's ExAblate 2100 system. No treatment-related adverse events were recorded; 47.2% reported complete response to treatment and discontinued medications; 40.3% experienced a pain score reduction >2 points, and 12.5% had recurrence after treatment. They found statistically significant differences between baseline and follow-up pain score values, observed medication intake ($p<0.05$), and QLQ-BM22 scoring ($p<0.05$). Focused ultrasound should or could be used instead of radiation on accessible areas.

Alberto Bazzocchi and his group at the Rizzoli Orthopedic Institute in Italy evaluated the clinical outcome of 39 patients treated with focused ultrasound for painful bone metastases. Fifty-seven lesions affecting 17 men and 22 women (mean age 61.5± 7.9, 31-84 years old) were treated. Patients were clinically examined for pain and quality of life at baseline and 1-, 3-, 6-, and 12-months. Forty-five lesions were evaluated after 1 month; 31 reached 3 months (54.4%), 17 at 6 months (29.8%), and 8 at the 12-month (14.0%) point. Four patients died during the follow-up period from primary cancer—related events, and 3 lesions required retreatment. The pain score decreased an average of 42.01% at 1 month, 48.7% at 3 months, 57.8% at 6 months, and 53.6% at 12 months. Pain severity and pain interference decreased significantly between baseline and all follow-up points (both $p=0.001$). The size of the lesion was the only statistically significant measure of efficacy, with smaller lesions experiencing improved outcomes.

Prostate

Panel Discussion: Controversies in Prostate Cancer Treatment

Panel Moderators – Christian Chaussy, MD, and Howard Soule, PhD; Panelists – Rajiv Chopra,PhD, Albert Gelet, MD, Sangeet Ghai, MD, FRCR, Mark Hurwitz, MD, John Jurige, Jr., MD, and Stephen Scionti, MD

Christian Chaussy introduced the panel by discussing how prostate cancer patient care has changed in the last 20 years: patients are living longer with the disease due to early diagnosis. He said that invasive treatment is being challenged, that radical prostatectomy does not appear to save the lives of men with early stage disease, and that many do just as well with no treatment at all. He believes that active surveillance has limitations: patients leave due to anxiety and ask for an intervention even if it's not medically needed. The panel discussed their opinions on the following controversies:

1. Indications for focused ultrasound as a monotherapy.

The low-risk patient is the most appropriate population for monotherapy. Within this group, the 50-year-old men with a miniscule amount of prostate cancer are difficult because they go on active surveillance. Quality of life takes precedence over cancer control. In 2013, three major groups published long-term data on low- to high-risk cancer specific survival and metastases-free survival ten years after diagnosis. Low risk patients will do better with any ablative modality. Whether focused ultrasound, laser, or cryotherapy, we can reliably kill the tissue as long as we get energy to the tissue. Patient choice is an important concept. Not every patient wants surgery.

Between low, intermediate, and high risk patients, all are not equal. Gleason score, stage, and prostate-specific antigen (PSA) testing all should be taken into account. Who has the truly confined disease? In the surgical population, who does well and who doesn't? Who may need longer term hormonal therapy? For treatment, should PSA be no higher than 20? MRI can help decide who should get treatment and who should not. In a locally advanced prostate cancer study in Germany, 96% of the patients remained without hormone therapy

(specifically androgen deprivation therapy, ADT). Focused ultrasound delays the onset of ADT in locally advanced prostate cancer. It's not explainable by purely ablative therapies.

Which technique is best for salvage? Salvage focused ultrasound for locally radiorecurrent disease after EBRT represents an effective therapeutic option with curative potential and acceptable morbidity. Patients who fail RT generally are not evaluated for the possibility of local recurrence and the possibility of local salvage. Some are candidates for local salvage, but these therapies are generally unavailable in the US. Only 5% to 10% offer salvage cryoablation because of its complexity. This is where focused ultrasound may fulfill an unmet clinical need.

2. Indications for focused ultrasound as a combined therapy.

Should there be different sequential techniques, or can one technique solve all of the problems? When should combined treatment be done? Two possible sequences are 1) watch and wait, focal focused ultrasound, radical prostatectomy (RP) plus EBRT, ADT; or 2) transurethral resection of the prostate (TURP) plus focused ultrasound, a second focused ultrasound treatment, EBRT, and ADT. What is needed if monotherapy has an 85% success rate? It comes down to patient selection--50% or more of patients have an extracapsular extension.

What about localized patients? Is there a possibility of salvage radical prostatectomy? Look at the time frame of the studies. How does additional hormone ablation influence quality of life? The patient suffers more on hormone ablation than the studies report. A protocol combining radiation and hormonal ablation makes the patient impotent and adds cardiac risk factors. Could this be avoided? We need to define the appropriate population for hormone therapy because not every patient with intermediate risk needs hormone therapy. In the context of improving survival, what is the tradeoff? Weigh impotence vs. effects of long term radiation. We're talking about very minimal if not increased risk for the cardiac issues. Is the hormonal therapy needed? Is it to control disease outside of the prostate? It's not the local control that is the issue; it is that they harbor microscopic metastatic disease. We talk about long-term results, but what about quality of life? The patients change over time. Hormonal therapy is about preservation of life, not quality of life. Does hormonal therapy cause you to lose more quality of life than you expect? This is where salvage therapies could come in. The population that you want to keep away from hormonal therapies is the salvage population. The process of salvage local therapy needs to be treated as localized, and we should not be using hormonal therapy with this group.

Other concepts to consider: can focused ultrasound induce immunomodulation? Is a transurethral approach with good image guidance a way to ablate a larger volume in a shorter amount of time? The audience suggested that a new imaging technique called RSI (restriction spectrum imaging) developed in a GE system produced good results and is faster. A new device called a Euronav allows urologists to do the biopsy.

Prostate Session The prostate session included a variety of clinical studies using specific devices, comparative treatment data, image guidance, and risk assessment. Current systems use either a transrectal or transurethral approach. Ongoing preclinical work is addressing bowel motion interference, improved sonication/ feedback control, immunomodulation, and biomarker identification.

Albert Gelet from Edouard Herriot Hospital in Lyon, France presented their pilot study results on the focal treatment of prostate cancer with the Focal One Device. The prostate is first contoured via MRI and then on live ultrasound via a transrectal probe. The software creates a fused image whereas the live ultrasound volume is considered the reference volume and the MR volume is smoothly deformed to create a 3D contour of the prostate to guide the planning process. The probe can electronically vary the focal point along the acoustic axis. Ten patients with mono focal prostate cancer were treated between March 2013 and January 2014. The mean treated volume was 14 cc (7.3-20.4), which is 28% of the prostate gland. No incontinence was observed. A partial loss of potency (IIEF <17) occurred in two patients. The device achieved complete destruction of small prostate cancer using an elastic magnetic resonance-ultrasound (MR-US) registration system for tumor location and treatment planning. A multicenter trial is in progress.

Albert Gelet then presented their work comparing external beam radiation therapy (EBRT) to high intensity focused ultrasound (HIFU) for localized prostate cancer in patients with no previous or associated androgen deprivation (AD). A total of 256 eligible patients with intermediate risk prostate cancer (d'Amico classification) treated between 2000 and 2005 were prospectively followed and matched on a 1:1 basis following known prognostic variables: prostate-specific antigen (PSA)

level and Gleason score. Then 190 matched patients (95 in each group) were further analyzed for progression free survival. Other endpoints were secondary use of salvage therapy and survival rate without salvage palliative AD therapy. The progression free survival rate was not significantly different between the two groups, but the rate of patients who need palliative AD therapy was significantly different (85% after HIFU versus 58% after EBRT, p: 0.002).

Albert Gelet also presented the Lyon data on radical prostatectomy versus high intensity focused ultrasound (HIFU) for localized prostate cancer. The study evaluated oncologic outcome of patients treated with HIFU or radical prostatectomy by using a matched pair analysis. A total of 710 patients were prospectively followed and matched based on prostate-specific antigen (PSA) level, Gleason score, and clinical stage. After matching, 588 patients (294 in each group) were further analyzed. Primary endpoints were the start of salvage external beam radiotherapy (EBRT) or definitive palliative androgen deprivation therapy (ADT). Other endpoints were overall, cancer-specific and metastasis-free survival rates. The seven year EBRT free survival rate was significantly lower after HIFU than after RP (62% versus 78%, p=0.001). At nine years, the palliative ADT-free rate was not significantly different between the two groups and the overall, cancer-specific, and metastasis-free survival rates were similar. Matched pair comparison of HIFU and radical prostatectomy showed a higher rate of EBRT for HIFU.

Stephen Scionti from the Scionti Prostate Center presented his transrectal focal HIFU study on the use of MRI fusion for guiding treatment. Multiparametric MRI combined with systematic and fusion biopsy is being used worldwide to select patients for focal therapy. Commercially available, FDA-approved MRI to ultrasound fusion platforms are now readily available for use in the urology clinic setting; however, these have not yet been widely used to guide focal HIFU treatment. The workflow requires creation of a 3D MRI model using MRI images of the prostate (containing a lesion proven by targeted biopsy to be malignant), creation of a 3D model of the prostate using ultrasound images, rigid and elastic image fusion, and use of the fused images to guide treatment. This study used this process with SonaCare Medical's Sonablate system, wherein the radiologist and urologist work together. The Eigen Medical software (Profuse) is now available on the Sonablate platform, and the model is either loaded from the biopsy device to the treatment device or is on the same platform.

Sangeet Ghai from the University Health Network in Toronto presented preliminary outcomes from a multidisciplinary Phase 1 study on focused ultrasound for focal therapy of locally confined low risk prostate cancer with InSightec's ExAblate 2100 system. Four patients with low risk or very low risk disease have been treated with focal transrectal focused ultrasound under MRI guidance with real-time MR thermography. A total of six target lesions were treated. All four patients were MRI negative in their treated regions (100%), and three patients were clear of disease on biopsy (75%), representing successful complete treatment of five target lesions (83%). The sixth targeted site also showed a decrease in volume of Gleason 6 disease on biopsy. All patients had at least one low volume Gleason 6 positive core outside of the treated zone. Focused ultrasound seems to be a feasible method for ablating low-risk prostate cancers with low morbidity. The audience asked a question about the real time MRI. Dr. Ghai reported that the feedback is current every 3 seconds and indicates if they obtained the desired temperature. Another question was about the safety margin of the target, and Dr. Ghai said that if the average target size is 2cc, then they plan for 3.5 cc on average. Further discussion centered on estimating the size and shape of the tumor, since quite a lot of variation can be found. Some data suggest a 5 mm margin, but the safety margin is unknown, providing a challenge for truly focal therapy.

Rajiv Chopra from the University of Texas Southwestern Medical Center presented their work on transurethral HIFU for the treatment of localized prostate cancer. In contrast to transrectal approaches, transurethral applicators are simple in construction and designed for single use. Delivery of ultrasound from within the prostate gland avoids passing energy through sensitive structures and enables rapid tissue ablation. Tissue is coagulated radially outward from the urethra, with the depth of treatment controlled by feedback from MR thermometry. One challenge with this method can be reaching the outer boundary of the prostate gland. The transurethral approach is faster and allows higher energy delivery.

Profound Medical presented their Phase I clinical trial midterm outcomes on transurethral focused ultrasound prostate ablation. Their MRI-guided transurethral ultrasound ablation (TULSA) system is designed to provide local disease control with low morbidity using real-time MR thermometry and active temperature feedback control. This multi-center, prospective clinical study to determine safety, feasibility, and initial efficacy enrolled 30 patients with biopsy-proven, low-risk,

localized prostate cancer. Treatment was completed under general anesthesia. Drainage from a suprapubic catheter remains for 2 weeks. Median (range) prostate volume and treatment time were 47 (21-95) cc and 36 (24-61) min, respectively (n=30). MR thermometry measurements depict a continuous region of heating with a high degree of spatial control of the ablation volume, to within 0.1 ± 1.3 mm (n=30). Median PSA reduced by 90% at 1 month. The procedure was well-tolerated with no intraoperative complications, and no reported cases of urinary incontinence, fistula, or rectal injury. MRI-guidance enables accurate planning and real-time dosimetry and control of the thermal ablation volume. Midterm results indicate that MRI-guided TULSA is safe and clinically feasible with a well-tolerated, low side effect profile. During the discussion, questions were asked about the size of the treatment area and whether the necrotic material blocked the urethra.

Alain Schmitt from Sunnybrook Research Institute in Toronto presented their work on filtering bowel motion during MR-thermometry for transurethral prostate treatment. Accurate temperature is critical for precise heating and for preventing thermal injury of surrounding tissues. The PRFS thermometry method used is sensitive to tissue motion and change in the local magnetic susceptibility. Inconsistent temperature variations are detected and cancelled. Then spatial averaging using reliable voxels is applied in the artifact region to keep consistent heating distribution and maintain a low noise level. The two-step correction of the artifact-detected areas reduces the final standard deviation to levels similar to the original areas. Evaluation of the filter on patient data showed that most artifacts due to the presence of moving air bubbles in the rectum were detected and removed. A quantitative estimation of the filter capabilities shows a systematic improvement in the standard deviation of the corrected temperature maps, up to 2.2°C improvement.

Chris Diederich from the University of California, San Francisco presented their study implementing sonication and feedback control strategies for targeted prostate hyperthermia with the InSightec ExAblate 2100 endorectal focused ultrasound system. They devised specific beamforming, sonication, and control strategies to overcome the current software limitations of the system with the goal of delivering large contiguous volumes in prostate quadrants or hemi-gland targets. They used simulations with patient-specific modeling to compute 3D thermal distributions. The data were implemented on the ExAblate prostate array and experiments were conducted to confirm delivery of hyperthermia to focal cancer volumes. They hope that their work will translate into having several different beam patterns available for clinical applications as well as better control, monitoring, and feedback.

Karin Skalina from Albert Einstein College of Medicine presented their work on the immunomodulation induced by low energy focused ultrasound in a mouse model of prostate cancer. To improve local control and possibly induce a systemic therapeutic effect for successful tumor control, this group evaluated using low intensity focused ultrasound (LOFU) to induce sonic stress by raising the temperature without killing the cells. Tumor pre-treatment with LOFU prior to HIFU previously resulted in tumor growth retardation and a Th1 predominant immune response. Because LOFU induced expression of genes related to the unfolded protein response (UPR) and endoplasmic reticulum (ER) stress, they hypothesize that LOFU increases immunomodulatory surface signals, such as heat shock protein 70 (HSP70) and calreticulin. LOFU treatment was performed on the Philips Therapy and Imaging Probe System using 3W, 100% duty cycle, 1.5 seconds, 1 mm spacing. LOFU significantly induced cell surface HSP70 expression and calreticulin and induced immunomodulation in these cells.

Tatiana Khokhlova from the University of Washington presented their work with the Institute for Systems Biology and the University of Michigan to evaluate high intensity focused ultrasound-induced bubble stimulation to release nucleic acid cancer biomarkers and potentially reduce the morbidity and diagnostic limitations of the current methods of performing prostate cancer biopsy. Because nucleic acid cancer biomarkers like microRNA and mutant DNA show promise for improving cancer diagnostics, the group attempted to stimulate their release with two different HIFU approaches, using a mouse model of prostate cancer. In the first approach, tumor tissue was liquefied with boiling histotripsy. In the second approach, HIFU-induced inertial cavitation was used to increase the permeability of tumor tissue and vasculature. Both of the approaches significantly increased the relative plasma concentrations of some of the micro RNA suggesting a potentially useful clinical application of HIFU-induced bubbles for non-invasive molecular biopsy. Discussion of the work included using microRNA detection to help design treatment and comparison of this method of tumor disruption to what is currently done with biopsy.

The Journal-of Therapeutic Ultrasound Wadyslaw Gedroyc updated attendees on the progress of the Journal of Therapeutic Ultrasound (JTU). The online journal was founded 2 years ago to serve the focused ultrasound community, which will have published as many as 3,600 manuscripts across all journals by 2015. JTU has published scientific articles, case reports, descriptions of pilot work, and technological developments; they believe that the open-access format helps get information out more rapidly. They plan to begin a series of topical reviews and a series of debate articles on controversial subjects and have also been tasked with helping to advance regulatory and reimbursement issues. The journal is now indexed on PubMed, and is in the process of receiving an impact factor. Dr. Gedroyc asked the audience to please provide feedback, topics, and ideas to the journal editors.

Emerging Applications

Session moderators Larry Crum and Emad Ebbini invited discussion on presentations by eight groups on a diverse set of topics, including several preclinical studies exploring the role of non-thermal bioeffects of focused ultrasound as well as clinical studies using focused ultrasound to address unmet medical needs such as hypertension and soft tissue tumors.

Gail ter Haar presented work from the Institute of Cancer Research (ICR) addressing the need and challenges of conducting quality assurance (QA) and field characterization of focused ultrasound systems. Similar to comparable therapeutic techniques, focused ultrasound should match the rigorous QA and calibration practices needed for excellence in patient care. Well validated QA and field characterization techniques ensure that treatments can be planned and simulated and then compared between patients, centers, and machines. Relevant parameters include pressure distribution, total power, and the MR environment. ICR built an MR-compatible acoustic power measurement system designed to work in a clinical setting along with a positioning system that maps the pressure field. Their target water tank is designed to verify the precise (sub millimeter) location of the focal peak. Additional software will allow automated beam plotting in the bore of the MR scanner.

Linsey Moyer from the University of North Carolina presented collaborative work between UNC, UVA, and Sunnybrook Health Sciences Centre to compare direct nanodroplets and microbubbles for focused ultrasound ablation enhancement and safety. Because perfluorocarbon gaseous microbubbles and vaporized liquid droplets are known enhancers of thermal ablation, they designed a perfluorocarbon nanodroplet composed of a 1:1 ratio of dodecafluoropentane and decafluorobutane to shorten ablation procedures without sacrificing safety. These in-house manufactured nanodroplets change phase and activate at only 2 MPa peak negative pressure with common focused ultrasound pulse lengths and are stable at body temperature. They measured the effective circulation time of the nanodroplets and found the nanodroplets to be stable enough to enhance ablation for at least 1.5 hours, to avoid skin burns, and to provide a better option than microbubbles. These nanodroplets could potentially reduce focused ultrasound surgical procedure times by as much as 5 fold by more quickly ablating a larger region of tissue without compromising safety.

Jimin Zhang presented Kona Medical's data on their externally delivered focused ultrasound renal denervation clinical experience and simulation validation studies. To date, they have used their fully non-invasive, ultrasound-guided Surround Sound™ renal denervation system to treat 69 patients with hypertension under three different protocols (WAVE I, WAVE II, and WAVE III), with follow-up ranging from 3 months to more than 2 years. Clinical data in 58 patients who have reached 6 months follow-up show an average blood pressure drop of 24/10 from baseline and an acceptable safety profile. In this study, they chose a subset of 18 WAVE II patients for detailed numerical simulation analysis to evaluate safety, feasibility, and a specific dose strategy using a computational virtual model and then validated the simulations with human data. The simulations demonstrated that 1) the therapeutic dose creates a thermal lesion around the renal artery; 2) there are no significant pre-focal or post-focal regions of unwanted thermal or mechanical tissue damage in the kidneys, spine, and bowel; 3) the maximum peak temperature used in the clinical trials is below the threshold for thermally-induced cavitation using the most extreme clinical conditions and absorption coefficients; 4) the contribution of non-linear content in the acoustic waveform is minimal and is highly unlikely to result in any significant unintended mechanical biological effects such as cavitation; and 5) there is potential for unwanted heating starting from the fat/muscle interface and inside fat layer using the extremes of absorption coefficients and patients depths. Discussion followed and included the development of the dosing regimen and why they believe that Medtronic's renal denervation

study was unsuccessful (procedural issues rather than the mechanism). Kona has designed their clinical trials to avoid similar mistakes.

Pejman Ghanouni from Stanford University presented his group's preliminary experience using focused ultrasound to treat benign but locally aggressive or malignant soft tissue tumors of the extremities, including desmoid fibromatosis, arteriovenous malformations, and malignant sarcomas. Ten patients have been treated with the InSightec ExAblate focused ultrasound system under general or regional anesthesia (off-label use). Average treatment time was 4h10m ± 1h47m for an average tumor volume of 184 ± 288 cc and required an average 96 ± 53 sonications. Adverse events included injury to skin, nerves, and surrounding organs. Focused ultrasound could be a first-line therapy for benign tumors and a management tool for recurrent malignant tumors. Challenges include patient positioning, transducer coupling, reliable intraoperative treatment monitoring, and speed of treatment for large tumors. More technical development and evidence is needed.

Keyvan Farahani presented collaborative work between MD Anderson Cancer Center and the University of Texas Southwestern Medical Center to complete an American Association of Physicists in Medicine (AAPM) task group assignment to report peer-reviewed publications on the assessment of state-of-the-art clinical focused ultrasound technology, including the intrinsic system characteristics, quantitative metrics, sources of uncertainty, quality assurance measures, data types, nomenclature, and training issues for medical physicists. The task group will consider developing an open tool/public resource for the focused ultrasound research community. This presentation introduces the task group to the research community and solicits input about its current activities and future directions. The open tools may include a quality assurance phantom procedure. Findings will be presented at the July 2015 AAPM annual meeting.

Michael Bailey presented preliminary results from the University of Washington's initial human clinical trial using focused ultrasound to reposition kidney stones (expel small stones/fragments or dislodge obstructing stones) via ultrasonic propulsion. The three arms of the study are de novo stones, post-lithotripsy fragments, and large stones within the preoperative setting. Pain is rated immediately prior to and following propulsion, wherein a maximum of 40 push attempts are administered on either low (50 V) or high (90 V) power settings. Thirteen subjects have been enrolled with no treatment-related adverse events. The study uses a diagnostic system with a clinical probe under an IDE.

Christakis Damianou from Medsonic presented their work with the Cyprus Institute, the Frederick Research Center, and the Cyprus University of Technology to study the destruction of atherosclerotic plaque using pulsed ultrasound with a self-designed, planar rectangular transducer. In the feasibility study, they used mechanical mode ultrasound under MRI monitoring with a flat, rectangular (3x10 mm2) transducer operating at 5 MHz (average intensity of 10 W/cm2 for 120 s, DF of 10%, and a 1-ms pulse repetition period). The optimized protocol was applied in a rabbit model with a 2% cholesterol diet. Approximately 50% of the artery was covered by plaque 3 months after initiation of the diet. The mechanical protocol successfully destroyed the aortic plaque. When discussing the study, the researchers mentioned that this model may also work for Alzheimer's disease and that the effects were produced by mechanical, non-thermal, and measurable stable cavitation.

Scott Burks from the National Institutes of Health (NIH) Clinical Center presented their work using pulsed focused ultrasound (pFUS) to inhibit interleukin 1-α, tumor necrosis factor-α, or cyclooxygenase-2 signaling, which suppress mesenchymal stem cell (MSC) homing to the kidneys. Maximal homing of iv-infused MSC may be critical for cell therapies. Molecular responses from the primarily mechanical effects of pFUS (i.e., mechanotransduction) in healthy or diseased murine kidneys generate a "molecular zip-code" that enhanced MSC homing. These findings may improve cell therapies for regenerative medicine. Since molecular signaling post-pFUS drives enhanced MSC homing, other drugs also aiming to treat disease could potentially interfere with molecular responses and subsequent cell migration to targeted tissue thus undermining cell therapy approaches. Cell counts from pFUS-treated kidneys were compared to untreated contralateral kidneys and ANOVA was used for statistical analysis ($p<0.05$). These findings suggest drug-host interactions could undermine cell-based therapies in regenerative medicine. This work may affect the way that acute kidney injury is treated, potentially preventing the onset of kidney failure.

Bioeffects

Wednesday, October 15, 2014
Panel Discussion: Beyond Thermal Ablation

Panelists: Jessica Foley, PhD, Brian Fowlkes, PhD, Mark Hurwitz, MD, Nathan McDannold, PhD, Brad Wood, MD

Because the junction of physics and biology is so great, we have only reached the tip of what focused ultrasound technology can do. The advancement of thermal ablation has opened clinical doors and can pave the way for many indications. Yet ablation is only the beginning for focused ultrasound. Why should we investigate other bioeffects? Many non-thermal regimes have been introduced and have highlighted a diverse field to explore. Other bioeffects may:

- change the way that cancers are treated
- break up tissue
- release drugs and genes precisely where needed
- Stimulate the immune system

Bioeffects such as hyperthermia could enhance multi-modality treatments by inducing complimentary and synergistic effects – e.g., sensitization to chemotherapy or radiation. Non-thermal effects offer significant promise as well.

- Immune sensitization may be used as a cyclic or interval therapy to control a disease that cannot be eradicated.
- Histotripsy is good for debulking tissue (benign prostatic hyperplasia and cancer).
- Safely delivering drugs across the blood-brain barrier opens up neuroscience far beyond where we are today and could enable treatment of tumors, Alzheimer's disease, and more.

Expanding utility for a focused ultrasound system beyond ablation adds an extra dimension and creates more opportunities for clinical sites to treat more patients, especially in conjunction with other treatments.

Moving forward, challenges include the regulatory barrier to bring the modality to patients. The Foundation could play an important role in that process by establishing collaborations with disease groups, medical societies, and drug companies to continue to expand the reach of focused ultrasound.

Breast

Breast Tumors Using focused ultrasound to treat breast cancer has reached clinical trials in Europe. Japanese research that began nine years ago is beginning to report good news on long-term follow-up with a low rate of recurrence after treatment plus radiotherapy.

Roel Deckers from University Medical Center Utrecht presented results from their Phase I clinical study on breast tumor ablation with a dedicated breast system. They reported safety, spatial accuracy, precision, and treatment efficacy. The group used the Philips Healthcare MR-HIFU system to treat ten women with i) pathologically proven invasive breast cancer after large-core needle biopsy and ii) tumor size ≥ 1 cm. Procedural sedation is used, and partial tumor ablation was performed to allow for histological analysis of viable versus ablated tumor tissue. The number of sonications performed per patient (1-5) and the acoustic power (50-90 W) used for each sonication was variable. Surgery was performed at least 48 hours after MR-HIFU, followed by histological analysis. More research is needed to correlate tissue damage to thermal dose and address minor adverse events. Patient recruitment for the study was difficult. During the discussion period, questions included sonication and cooling time, the amount of time needed to prepare the patient, and treatment time (1.5-2 hours on table for 3-4 sonications).

Hidemi Furusawa from the Breastopia Clinic presented updated results from their small breast cancer local recurrence study that has been ongoing since 2005. Their long-term patient follow-up protocol is designed to identify the incidence and cause of local recurrence after focused ultrasound treatment of the breast cancer. Inclusion criteria are 1) breast cancer diagnosed by needle biopsy, 2) receptor status confirmation, 3) tumor size ≥15 mm, and 4) well-demarcated mass on contrast-enhanced MRI. Needle biopsy performed within three weeks after ablation identified no residual viable cancer cells. Radiotherapy is continued every 3 to 6 months indefinitely. In the thirty-eight patients that have been followed-up for more than 60 months, no severe adverse events and no disease progression with metastases have been found, but one local recurrence developed seven years after the initial treatment. Causes of this local recurrence could be cancer displacement by the preoperative needle biopsy and/or developing residual cancer after focused ultrasound, according to the post-procedure needle biopsy specimen and the pathological inspection after the recurrence was excised. Focused ultrasound as a local treatment for small breast cancer

may someday replace invasive surgery; however, because radiotherapy can control local recurrence, careful follow-up is needed. During the discussion period, Dr. Furusawa said that next they would like to begin a comparative randomized trial between focused ultrasound and surgery/radiotherapy.

Breast Fibroadenoma Three international groups presented their data in using Theraclion's Echopulse system to treat breast fibroadenoma under various protocols. Discussion after the session included FDA approval procedures after additional studies, the possibility of eventually treating breast cancer, the quality of the ultrasound guidance, long-term follow-up for referring physicians, risk for future breast feeding, and the comparison of focused ultrasound to cryoablation.

Roussanka Kovatcheva from the University Hospital of Endocrinology in Bulgaria collaborated with researchers from University Medical Centre Ljubljana (Slovenia) to study the safety and efficacy of Theraclion's ultrasound-guided system for the treatment of breast fibroadenoma. The group studied efficacy and tolerability in 20 women (mean age, 29.4 ± 10.8 years) with 26 lesions. Follow-up at 1, 3, 6, 9, and 12 months was used to determine when the lesion's volume had been reduced to less than 50% of baseline. At that point, or when the absolute volume value exceeded 1.5 ml at the 6-month follow-up visit, a second ablation was performed between 6 and 9 months after the first treatment. The mean energy per treated volume was 11.8 ± 2.4 kJ/mL at the first session and 12.5 ± 2.9 kJ/mL at the second session (7 patients). The mean fibroadenoma volume decreased from 3.00 ± 2.81 mL to 1.87 ± 2.06 mL at 3-month follow-up ($p = 0.099$), 1.36 ± 1.40 mL ($p < 0.01$) at 6-month follow up, and 0.75 ± 0.66 ($p < 0.001$) at 12-months follow-up. By the 12th month, the volume reduction ranged from 47.2 to 92.6% (mean, 73.3 ± 10.9%). The volume reduction was significantly larger in the patients who received 2 treatments ($p < 0.05$). Mild transient complications such as subcutaneous edema or mild skin redness and irritation were observed in 7 patients. US-guided HIFU ablation is an effective and well-tolerated treatment for breast fibroadenoma, and repetitive treatment may provide even better results.

Mirjam Peek from King's College in London presented a feasibility study using the Theraclion Echopulse system to isolate the fibroadenoma from its blood supply, thereby decreasing treatment time and short-term complications. From December 2013, 13 patients underwent circumferential treatment, and seven patients opted for HIFU treatment due to pain or discomfort. Average treatment time for approximately 61 sonications (SD, 17 sonications), was 36 minutes (SD, 12 minutes). The circumferential treatment reduced treatment time an average of 44% (SD, 21%), which was significant ($P = 0.005$, two-tailed). Post-treatment follow-up at 2 weeks showed reduced pain in six of seven patients with resolution of pain in three of these. An additional patient developed new pain after two weeks. Short-term complications were erythema of the skin (n=4), ecchymosis (n=4), temporary numbness of the skin (n=1), and a first-degree skin burn (n=1). Circumferential HIFU ablation of fibroadenoma is feasible and significantly reduced treatment time. During the discussion, Dr. Peek noted that the patients noticed the lumps getting flatter, that they could no longer see the lump, and that they were happy with the treatment.

David Brenin from the University of Virginia has begun a study with the Theraclion Echopulse system to evaluate the safety and feasibility of ultrasound-guided focused ultrasound treatment of breast fibroadenoma. General patient safety, cosmetic outcome, tumor response, patient experience, physician/operator experience, and device performance will be assessed. They will enroll twenty patients in the single arm clinical trial. The computer-driven, continuously cooled, extracorporeal HIFU probe is mounted on an arm that is guided in real-time with an integrated ultrasound imaging scanner. The integrated probe is positioned by the operator, the lesion is imaged, and the treatment is automated, and then presented for review and approval on the computer screen. Tumor criteria were presented. Patients are evaluated immediately after treatment and at 3, 6, and 12 months for palpability of the lesion, pain, patient satisfaction, change in fibroadenoma volume, cosmetic outcome, investigator-rated evaluation of the device, incidence of adverse events, treatment parameters, and device energy settings. The UVA group hopes to complete enrollment by July 2015.

Liver and Pancreas

Panel Discussion: Liver Controversies

Wladyslaw Gedroyc, MD, Chrit Moonen, PhD, Gail ter Haar, PhD, Feng Wu, MD, PhD, Alessandro Napoli, MD, PhD

To begin the session, the panelists discussed the worldwide incidence of liver tumors, particularly in patients with hepatitis and cancer metastases. In Asia, hepatitis B is one of the largest causes of mortality, and no good treatment options exist because of the associated cirrhosis. The unmet clinical need is a proper and good treatment option for patients with cirrhosis and liver metastases.

Technical issues that prevent focused ultrasound research from quickly advancing include:

- The presence of the rib bones, which reflect the ultrasound energy back to the skin causing skin burns. Turning off the heating elements that are over the ribs reduces power and limits access to deep tumors.
- The movement of the liver during respiration creates a moving target behind an impenetrable curtain. The ribs move up and down and in a different plane than the liver. The geometry is always changing.
- The high vascularization of the liver tissue can cause a heat sink effect. Liver tissue is highly absorbing of focused ultrasound energy, and percutaneous ablation techniques work well.
- A good patient screening test is not standardized to date; centers may perform screening using ultrasound, MRI, CT, or even only a blood test.
- Patient positioning required for the use of general anesthesia is not optimal.
- A lack of focused ultrasound equipment that is specifically designed for this anatomic area. A better transducer with an active surface that is as large as possible is needed. Real-time measurement and localization are needed. MR guidance with good sedation allows for beam correction, but if it is not available, you have to correct for all types of motion including intestinal motion. An ideal system could access any portion of the liver, pancreas, and kidney.

The panel also compared focused ultrasound treatment to repeated radiofrequency ablation (RFA) and other percutaneous treatment options, which may induce cirrhotic hemorrhage. Additionally, significant cirrhosis could alter the way that the liver responds to focused ultrasound; the tumors are surrounded by cirrhosis with minimal blood supply, and when you put energy into the tumor there is no heat sink and potential for an overeffect. There is also the potential to combine drugs or gene therapy with focused ultrasound. Cavitation with drug delivery or the combination of microbubbles and existing medication has been shown in preclinical studies to be very promising.

During the Q&A session with the audience, topics raised included focused ultrasound as a future interventional radiology/oncology tool to target lesions that are in anatomically difficult locations; motion tracking under both MR and US guidance; focused ultrasound representation on the tumor boards; and relationships between the local interventional and surgical communities.

Liver and Pancreas Clinicians are advancing focused ultrasound for treating malignant stage II and IV pancreatic tumors and hepatocellular carcinoma. Scientists are evaluating imaging and simulation techniques to address the challenges of organ motion and accessibility through the ribs. Preclinical work is investigating effects of FUS on adjacent tissue, specific anesthesia protocols for effective treatment, and the role of non-thermal ablation using histotripsy.

Joan Vidal-Jove from the Hospital University Mutua Terrassa in Barcelona presented their study on ultrasound-guided high intensity focused ultrasound (USgHIFU) of malignant stage III and IV pancreatic tumors. Of 148 unresectable pancreatic tumors treated with USgHIFU hyperthermic ablation plus adjuvant chemotherapy, the first 43 (29 III/14 IV) from March 2010 to December 2013 were analyzed. Clinical responses (thermal ablation achieved) were measured with imaging techniques. Tumor ablation was achieved in 82% of the cases and sustained at 8 weeks post-procedure. They found 11 complete responses (25%) at the end of the combined treatment, 9 from stage III patients and 2 from stage IV. Major complications included severe pancreatitis with GI bleeding (1) and grade III skin burns that required plastic surgery (2). No deaths due to the procedure were registered. Overall median survival is 16 months (6 months – 3.4 years). USgHIFU is a potentially effective and safe modality for the treatment of malignant tumors and may prolong survival in unresectable stage III and IV pancreatic cancer. During the discussion, Dr. Vidal-Jove also reported a good response even when the tumor surrounded an important vessel and stated that the patients were on various chemotherapy protocols.

Alessandro Napoli from the University of Rome presented their data on focused ultrasound treatment

of moving organs for pain palliation and tumor control in locally advanced pancreatic cancer and hepatocellular carcinoma (HCC). MR-guided focused ultrasound treatment of pancreatic cancer and HCC is still in its preliminary phase. Therefore, this study attempted to evaluate its safety and effectiveness. They treated 5 patients with pancreatic cancer and 1 with unresectable right lobe HCC with the InSightec ExAblate 2100 system in a single ambulatory session. They obtained perfusion T1w images with contrast before and after treatment with follow-up exams 1, 3, 6, and 12 months later. The treatment was well tolerated with no heating-related adverse events and produced coagulative necrosis. The patients with pancreatic cancer showed a significant decrease in pain. No local progression was found during follow-up, but 2 patients with pancreatic cancer underwent radiotherapy, and one required a second focused ultrasound treatment. MRgFUS may be a safe and promising non-invasive treatment for patients with unresectable pancreatic cancer and HCC. During the discussion, Dr. Napoli mentioned that this procedure may provide a type of bridging therapy when other treatments are contraindicated; long-term survival is similar between radiotherapy and focused ultrasound, but focused ultrasound is nonionizing. The procedure lasted about 4 hours and produced good results for pain palliation. A question was raised about how to deal with the motion of the aorta.

Hong Chen from Columbia University presented their work to determine whether harmonic motion imaging (HMI) could be used to detect pancreatic tumors and to monitor focused ultrasound ablation. HMI uses ultrasound-induced displacement to assess tissue stiffness. This highly technical preclinical study found a high contrast between normal and malignant tissues (with an average lesion-to-normal displacement ratio of 2.4) and confirmed the feasibility of using HMI to detect pancreatic tumors and successfully monitor focused ultrasound ablation during the actual procedure. It is the first application of a radiation-force based technique to monitor focused ultrasound ablation of an abdominal organ.

David Melodelima from LabTAU - INSERM U1032 in France presented data from 21 patients with colorectal liver metastases who participated in a Phase I-II safety and feasibility study using intraoperative high intensity focused ultrasound to ablate liver metastases prior to hepatectomy. The transducer has a toroidal shape 70 mm in diameter and is divided into 32 ultrasound emitters of 0.13 cm2 operating at 3 MHz. The radius of curvature is 70 mm. A 7.5 MHz ultrasound imaging probe was placed in the center of the device for image guidance. Ablation was directed only at the part of the liver scheduled for resection. In Phase I, two single thermal lesions were produced in each patient. In Phase IIa, two ablations were precisely placed on a previously identified target and then at a distance from the target. In Phase IIb, metastases (20 mm maximal diameter) were ablated with safety margins in all directions. HIFU was feasible, safe, and effective in ablating large areas of liver scheduled for resection. They were able to access 95% of the hepatic volume with this method.

Ulrik Carling from Oslo University Hospital presented results on the effects of focused ultrasound ablation of the swine liver in tissue that is adjacent to the hepatic and portal veins. To determine whether or not the heat sink effect would affect ablation and whether or not the ablation would damage the large vessels, two clusters of 6 to 7 lesions of 8 x 8 x 20 mm were placed around separate vessels in normal liver parenchyma. Although further analyses are needed, preliminary histopathology results indicated that liver parenchyma adjacent to vein walls can be ablated without damaging the vessel wall. During discussion, the technical challenges of the study were discussed, including adverse events, a long procedure time, and imaging issues.

Nobutaka Doba presented a Japanese study on the usefulness of a 3D slicer for planning and monitoring focused ultrasound treatment of hepatocellular carcinoma. 3D slicer imaging is a diagnostic imaging support system that can provide cross-sectional images on the same monitor screen using MRI data. This study used an interventional navigation system designed for focused ultrasound assisted by 3D slicer in a phantom. The Mianyang Haifu Tech ultrasound-guided system was used with open-source navigation software to connect images using an open network communication protocol (OpenIGTLink). A Polaris Vicra optical tracker (Northern Digital) was used. MRI scans (Signa HDX 3.0T system; GE Healthcare) were performed, and the 3D slicer was customized to combine MR images for the navigation. Testing was performed using an abdominal phantom (CIRS Model057). The 3D slicer successfully constructed multiplanar images of MRI displayed in the same sections of ultrasound. The synchronous movements of the same sections of US and MRI were shown in real time. Performance tests of the phantom show that the registration error of the system was 2.2 ± 1.8 mm within the liver (n=12). During the discussion, Dr. Doba said that they would like to add a respiratory tracking function to this system.

Tobias Preusser presented an update on the highly collaborative TRANS-FUSIMO (clinical TRANSlation of patient-specific planning for Focused Ultrasound in Moving Organs) project. Organ movement in abdominal organs (e.g., liver and kidney) presents a challenge for the application of focused ultrasound. Further complicating factors include the location of a lesion behind the rib cage, the physiology of the organs, and the effect of blood perfusion on energy deposition. Sophisticated software and advanced hardware are being developed and fully integrated into a focused ultrasound system to treat the liver.

The FUSIMO software uses dynamic organ models to simulate patient-specific anatomic deformation during breathing; ultrasound propagation, energy distribution, and tissue heating and cooling; and patient-specific tissue response. These models are integrated into software that compares them to patient-specific data. Phantom and ex vivo validation will be followed by a preclinical study and a two-arm clinical trial comparing neoadjuvant focused ultrasound plus resection vs focused ultrasound only. During the discussion, Dr. Preusser said that the FUSIMO system was able to detect breathing changes such as a cough and then showed a video of a moving liver with the focused ultrasound beam staying on the same spot.

Martijn de Greef from University Medical Center in Utrecht, the Netherlands presented their study on the feasibility of beam shaping for intercostal focused ultrasound treatment. Although beam shaping could theoretically protect the ribs from acoustic energy and enable sufficient energy delivery at the focal point, its feasibility in a clinically relevant volume remains untested. They evaluated acoustic energy exposure of the ribs and the near-field and measured the corresponding volumetric ablation rate to determine if it was clinically relevant. The preclinical work was performed on the Philips Sonalleve V2 HIFU platform and found that a collision detection method of beam shaping could effectively protect the ribs from excessive heating but raised the risk of excessive near-field heating, thereby limiting ablation volume and the volumetric ablation rate. Using more energy required longer cooling time between sonications.

In another presentation from the Utrecht group, Mario Ries explained their comparison of spontaneous breathing vs. mechanical ventilation for respiratory-gated focused ultrasound liver ablation. With respiratory gating, power output and image acquisition are limited to the resting phase of the diaphragm. Although they have previously used general anesthesia with mechanical ventilation (GA), procedural sedation and analgesia (PSA) has a lower risk of complications, shorter recovery, and lower associated costs than GA, and it can be performed by non-anesthesiologists. This preclinical study used the Philips Sonalleve system to investigate the feasibility of using respiratory-gated focused ultrasound ablation in the liver under PSA with spontaneous breathing. They found it feasible and comparable to GA and determined remifentanil to be particularly suited for this purpose (with an apnea risk that may require short-term ventilation of the patient).

Vera Khokhlova from the University of Washington presented their study to determine whether a clinical focused ultrasound system could be used to mechanically fractionate (via boiling histotripsy) tissue volumes in ex vivo bovine liver. While thermal ablation is being studied to treat liver cancer, long treatment times, skin burns, rib attenuation/aberration, heat diffusion, and perfusion provide challenges. This group's boiling histotripsy (BH) method could address these problems. To evaluate the feasibility of using a clinical focused ultrasound system for BH and develop exposure protocols for such treatments with real-time imaging, researchers tested two treatment protocols using the Philips Sonalleve system: a sequential treatment with a set number of pulses delivered at each target location, and a non-sequential treatment with consecutive HIFU pulses sent to different target locations (to diminish heat accumulation/thermal effects). Each treatment point received 30 pulses, and MR imaging was used for real-time monitoring and post-treatment lesion analysis. Lesions were also analyzed grossly and histologically. The clinical system produced MR visible, mechanically fractionated volumetric lesions using electronically steered BH. Successful sonications performed at 2 cm depth in tissue required less than 25% of the maximum system power, thus permitting implementation of this approach under clinically relevant conditions with greater attenuation. Homogenized lesions of 3 to 5 cm3 were produced at 1 Hz. Increasing thermal effects were observed for sonications produced at 3 to 10 Hz. With a 2 mm lesion separation, adjacent lesions merged to produce a single volume of fractionated tissue. Larger vessels could be spared while effectively fractionating surrounding liver tissue (the vessel structure was intact and unharmed, including microvessel).

Steven Allen from the University of Michigan presented their work evaluating real-time MRI feedback for histotripsy of liver tumors. Like other non-invasive surgeries, histotripsy requires a real-time feedback system that can estimate therapy location and dose.

MR thermometry is ineffective with histotripsy because histotripsy's time-average power output is very small, and the treatment region does not express a significant rise in temperature. A single-shot MR acquisition sequence can rapidly acquire a complete MR image and remain sensitive to histotripsy cavitation. Synchronizing each histotripsy pulse with incoherent motion-weighting gradients placed just before the readout portion of the sequence can give feedback on the location of every cavitation cloud applied to the target tissue. Cavitation sensitizing gradients reduce sensitivity to incoherent motion and other forms of motion are filtered out. MRI can capture a unique image for every bubble cloud in a 2 mm field of view.

Disruptive Effects in Medical Practice

Thursday, October 16, 2014

Panelists: Christian Chaussy, MD, Pejman Ghanouni, MD, PhD, Yael Inbar, MD, James Larner, MD, Matthias Matzko, MD, and Feng Wu, MD, PhD

How is focused ultrasound disrupting medicine's status quo? This panel introduced topics and controversies that may be arising as this new technology emerges, is purchased by hospitals, and is adopted and incorporated by the various medical specialties.

Topic 1: In which hospital department should focused ultrasound be located?

Patients, physicians, and manufacturers each have a different perspective. Since it is a multidisciplinary treatment, many think that creating a neutral location like radiology or the operating room is best because an experienced care team can be developed to assist various specialists. Alternatively, from a patient perspective, it should be the department with the most experience in their disease, where any complications could be handled. Another option would be location in the department with the greatest concentration of cases or most skilled individual physicians. The most cost effective location or the location that could obtain the best results for the patient and the most successful outcomes should also be considered.

Topic 2: Should focused ultrasound have a dedicated or shared MRI scanner?

Although some indications do not require MRI, when it is shared for diagnostic purposes, there is always pressure or tension. Research and clinical centers look at this issue differently because they have different funding sources. Clinically, the current lack of reimbursement affects both purchasing and scheduling priority. Because some care is economically driven and medical practice follows reimbursement, if focused ultrasound is fully reimbursed, it will be more competitive to perform the treatment. In Germany, providers used MRI data to show improved patient selection and outcomes, resulting in a positive reimbursement decision.

Topic 3: Is it possible to train a non-physician to be an expert operator of the system?

A physician with image-guided experience should perform the treatment because it is an intervention or operation. Decisions are often made during treatment, and the workflow is similar to radiation oncology in terms of the delivery of energy into the body. As the technology evolves, it may be easier to switch the workload to trained therapists, as is the case for many stereotactic radiosurgical procedures (e.g., Gamma knife). However, this will depend on the specific indication.

Topic 4: What is the best practice for tracking outcomes and collecting data?

For approved indications, some physicians perform follow-up scanning and tracking of treatment outcomes for up to six months. Others do no follow-up but send the patient back to the referring physician after confirming that the treatment was successful.

Topic 5: How do you obtain referrals for focused ultrasound treatment?

Some are current patients, some self-refer after becoming aware of the treatment via the internet, and some are referred from other physicians in the community. Educating referring physicians and marketing directly to patients may include creating brochures and using the internet, social media, or an expert board that answers questions. Multidisciplinary groups that offer various treatment options are successful in gaining patient trust because they offer an individualized solution, and this attracts patients. The perceptions of the medical community and the public are very important to generate referrals.

Uterine Fibroids

Researchers in Korea are testing a portable system for treating uterine fibroids, and a new skin cooling device may reduce the risk for skin burns. Decreasing treatment time by treating larger volumes of tissue or pretreatment with GnRH antagonists may be possible, and different thermal regimens could produce more favorable results. The effects of achieving reimbursement, the progress of an international registry, treatment of adenomyosis, and various studies on MRI screening were also presented.

Jae Young Lee from Seoul National University Hospital presented collaborative work with Alpinion Medical Systems on their clinical study of a portable focused ultrasound system with 3D electronic steering for the treatment of uterine fibroids. This prospective safety and efficacy study included 28 fibroids in 19 patients who were treated with focused ultrasound under 3D electronic steering. Treated volume ranged from 17.1 to 269.6 cm3, ablation volume ratio ranged from 28.3 to 100%, and ablation time ranged from 10 to 127 minutes. This newly developed portable system may provide a cost benefit and save time. During the discussion, Dr. Lee added that the patients were not sedated: pain control was provided with fentanyl and acetaminophen, but some patients had temporary back pain during the procedure despite angulating the probe around the sciatic nerve and spine. They used short pulse explosions to check beam focusing.

Nelly Tan from UCLA presented their multicenter trial using a novel focused ultrasound treatment algorithm for reducing uterine fibroid symptoms. Enhanced sonication (ES) is an ablation technique that uses nearly twice the amount of energy to ablate nearly twice the region of interest compared to standard sonications, resulting in a higher volume of uterine fibroids treated in the same amount of time. This single-arm trial from January 2010 to March 2013 evaluated the clinical efficacy of ES at seven institutions under an open label use with the InSightec ExAblate 2000 system. Of 245 screened patients, 115 women with an average age of 44 and average BMI of 24.9 underwent 164 treatment sessions (54 patients had a second treatment). Total fibroid volume per patient was 235 ± 220 cc, and the average non-perfused ratio was 65 ± 23%. Symptom severity scores improved from 66.7 ± 15.7 to 26.8 ± 16.2 after 6 months, and UFS-QOL scores also showed significant improvements overall and in the sub-scales between baseline and 12 months post treatment. After 12 months, 9% of the patients underwent alternative treatments. Sustained symptom relief was possible up to 12 months with the addition of ES to standard sonication. The higher dose of energy added discomfort and was not well tolerated by the patients, but no major complications were reported.

Johanna van Breugel from the University Medical Center in Utrecht, the Netherlands presented a proof of concept study that they performed in collaboration with Philips Healthcare to evaluate a new device for direct skin cooling (DISC) during volumetric focused ultrasound treatment of symptomatic uterine fibroids. Eight patients were treated with the DISC device, which was used to maintain a constant temperature (T≈20°C) at the interface between the focused ultrasound tabletop and the patients' skin. Technical feasibility was verified with a successful ablation procedure, and safety was evaluated through adverse events related to the DISC device within 30 days of follow-up. Two patients experienced coldness-related discomfort which resolved the same day. No serious adverse events were reported. It was technically feasible and safe to complete ablation with DISC, and it may reduce the risk of thermal injury to the abdominal wall. Reduced cooling times between sonications would significantly reduce treatment time.

Jaron Rabinovici from Sheba Medical Center in Israel presented their data on the effect of reimbursement of focused ultrasound treatment of uterine fibroids in a single tertiary center. In November of 2013, the procedure gained coverage by health maintenance organizations as a part of the Israeli National Health Insurance law. This retrospective analysis compared the number of patient visits to the focused ultrasound clinic before (December 2012 to February 2013, period I) and after reimbursement (December 2013 to February 2014, period II). In period I, 15 of 20 women (75%) met the basic criteria and were referred for MRI. Of the twelve who completed MRI, 7 were found suitable and 3 were ultimately treated. In period II, 39 of 63 women (61.9%) met the criteria for MRI. Of the 30 who underwent MRI, 12 were found suitable, and all underwent focused ultrasound treatment. The number of treated patients was significantly higher following the reimbursement ($p<0.001$). Reimbursement significantly increased the number of patients who attended the MRgFUS clinics and quadrupled the number of treatments.

Jaron Rabinovici then presented an update on the RELIEF Registry, which is designed to gather large-scale evidence on the safety and long-term efficacy of focused ultrasound treatment for symptomatic leiomyoma. The registry plans to enroll 1,000 patients in multiple sites worldwide and follow qualified patients for three years at sites that meet the registry's criteria. Treatment outcome

and follow-up data will be collected by a contract research organization and analyzed for safety and efficacy, and results will be compared to similar results in the literature. Subgroups will be selected and analyzed to address heterogeneity and usage of non-uniform treatment methods. Enrollment is now scheduled to begin in March 2015.

Heidi Coy from UCLA presented their study comparing the efficacy of using focused ultrasound ablation to treat localized adenomyosis versus its efficacy for treating uterine fibroids. An effective non-invasive therapy is needed for adenomyosis, especially for those who wish to preserve their fertility. This study compared the change in NPV in subjects with localized adenomyomas treated with focused ultrasound to those similarly treated for symptomatic uterine leiomyomas to determine if comparable results were achieved in the adenomyoma cohort. The retrospective review matched cases with leiomyoma-bearing controls based on total lesion volume, number of lesions, and age. They analyzed 10 lesions in 9 subjects, found similar baseline and post-treatment characteristics, and concluded that focused ultrasound may be a viable non-invasive treatment for patients with symptomatic adenomyosis and an alternative to conventional therapies. The discussion included considering concomitant endometriosis as a complicating factor.

Jia Liu from Peking University First Hospital presented collaborative work with Philips Healthcare to review treatment outcomes when using different intraprocedural thermal parameters during focused ultrasound ablation of uterine fibroids. Since the temperature curve (i.e., temperature change as a function of time) is a relatively accurate manifestation of the fibroid's reaction to sonication, this study retrospectively studied the relationship of the T2WI signal intensity to the temperature curve. A total of 15 patients (mean age, 44.7 ± 5.4 years) underwent MRI screening in an Achieva TX scanner. The fibroids were classified as Type 1 (n=7), Type 2 (n=7), or Type 3 (n=1). Treatment thermometry data were used to create temperature curves. Matlab software was used to analyze the temperature curve to generate heating slope, decay slope, the area under heating curve, heating time, maximum temperature, and the time to peak. The temperature curve for Type 1 fibroids ascended quickly, descended quickly, had the longest plateaus, and the most effective therapy. The temperature curve of Type 2 fibroids ascended slowly, descended slowly, had shorter plateaus, and less effective therapy. The temperature curve of Type 3 fibroids ascended slowly, descended most slowly, and had the least effective therapy. The efficacy of focused ultrasound treatments based on temperature curves correlates well with the T2WI signal intensity of uterine fibroids. This study did not measure symptom improvement, but Dr. Liu believes that improvement depends on the vascularity of the fibroid.

Young-sun Kim from Samsung Medical Center in Korea presented data obtained in collaboration with Philips Healthcare to develop an MRI-based screening prediction model for therapeutic response of focused ultrasound ablation of uterine fibroids. Ideal screening criteria would comprehensively consider multiple influencing factors for treatment planning. A prediction model was developed to retrospectively evaluate 160 symptomatic uterine fibroids (diameter 8.3cm, range 3.1-15.0cm) in 112 women (age 43.3, range 25-55) treated with focused ultrasound. The three parameters chosen for evaluation were subcutaneous fat (mm), relative peak enhancement (%), and signal intensity. Prediction models were created with regard to ablation efficiency and ablation quality using generalized estimating equation analysis. Cut-off values for successful treatment were determined based on receiver operating characteristic curve analyses. The analysis created simple equation models to predict therapeutic response of focused ultrasound ablation for uterine fibroids, and these are easily applicable to screening MRI. The positive prediction values were quite high.

Young-sun Kim then presented their work correlating T2 signal intensity in uterine fibroids with semi-quantitative perfusion MR parameters. Although T2 signal intensity and perfusion MR findings are both important factors in predicting therapeutic response of uterine fibroids to focused ultrasound ablation, T2 signal intensity is easier to assess. This retrospective study evaluated the relationship between T2 signal intensity and semi-quantitative perfusion MR parameters in order to determine whether T2-weighted imaging can replace perfusion MRI for procedural screening. The analysis included 170 uterine fibroids (mean diameter 7.3 cm) in 170 women (mean 43.5 years). Semi-quantitative perfusion MRI data included peak enhancement, relative peak enhancement, time to peak(s), wash-in rate, and wash-out rate. Submucosal protruding fibroids failed to show a significant correlation, but significant correlations were noticed in all other types of fibroids (submucosal, intramural, transmural, and subserosal). T2 signal intensity of non-degenerated uterine fibroids had an independently significant positive correlation with relative peak enhancement of semi-quantitative perfusion MRI in cases other than the submucosal protruding type.

Mathias Matzko presented their single center study using MRI to predict clinical success in focused ultrasound treatment of uterine fibroids. To assess their technical and clinical results, 252 women (mean age, 42.1 ± 6.9 years) with uterine fibroids underwent focused ultrasound treatment using the InSightec ExAblate 2100 system with MRI screening prior to treatment. Results were evaluated with respect to non-perfused volume (NPV), symptom severity score, re-intervention rate, pregnancy, and safety data. NPV ratio was significantly higher in fibroids with a low T1 signal intensity and in fibroids that are distant from the spine (>3 cm). NPV ratio was lower in fibroids with septations, with subserosal component, and in skin-distant fibroids ($p < 0.001$). NPV ratio was in high correlation with clinical success: an NPV of more than 80% resulted in clinical success in more than 80% of patients. The re-intervention rate was 12.7% (mean follow-up time, 19.4 ± 8 months; range, 3-38). Expulsion of fibroids (22%) significantly correlated with a high clinical success rate. No severe adverse events were reported. Adequate patient selection and correct treatment techniques, based on the learning curve of this technology, combined with technical advances of the system, lead to higher clinical success rates with low complications rate, comparable to other uterine-sparing treatment options. During the discussion, septated fibroids were described with a capsule around the fibroid that differentiated them from fibroids without a capsule around them.

Alessandro Napoli from the University of Rome presented a retrospective outcome analysis of MRI screening for uterine fibroids with treatment selection between focused ultrasound (FUS), uterine artery embolization (UAE), or surgery. A total of 451 women (group A, mean age 39 ± 5 years) referred for FUS between July 2010 and March 2014 underwent pretreatment evaluation to assess symptoms and fibroid characteristics. Patients not eligible for FUS underwent UAE (group B) or surgery (group C). Primary endpoints were symptoms severity score (48.6 ± 13.4), volume shrinkage (Group A and B), and necessity for further treatment. Of the 451 patients, 131 underwent FUS (29%; Group A), 123 underwent UAE (27%, Group B) and 157 underwent surgery (35%, Group C). The remaining 40 patients (8%) were lost at follow-up or refused treatment. Although FUS is a reliable, non-invasive method for treating symptomatic uterine fibroids, only 30% of patients are suitable candidates based on MRI screening exams. Patients who are not suitable for FUS should undergo surgery or UAE, but both alternatives have significantly lower patient tolerance rates. One FUS patient experienced transient nerve damage that caused problems lifting her foot.

Kelli Bryant from University MRI in Florida presented their data using MRI characterization of uterine fibroids to predict success of GnRH agonist therapy prior to their focused ultrasound treatment. GnRH agonists can reduce fibroid volume by as much as 30% to 40% and decrease vascularity in large uterine fibroids, and this may enhance focused ultrasound treatment outcomes. To examine the responsiveness of fibroids to pretreatment GnRH agonist therapy in relation to their appearance on T2 weighted images and analyze this response in focused ultrasound treatment outcomes, 15 women (age 34-52) with fibroids in excess of 10 cm or a fibroid volume greater than 300 cc were pretreated for 3 to 6 months or more with a GnRH agonist prior to undergoing treatment with the InSightec ExAblate device. The fibroids were classified by their T2 weighted intensity relative to normal myometrium (hypointense, isointense, or hyperintense as well as tissue homogeneity or heterogeneity). A total of 17 hypointense, 3 heterogeneously hypointense, 1 heterogeneously hyperintense, and 1 isointense fibroid were treated (n=22). Fibroid volume reduction after GnRH administration, Joules of energy delivered per cc of fibroid tissue ablated, and the final non-perfused volume (NPV) were investigated. The average reduction in fibroid size from the GnRH treatment ranged from 44% (isointense) to 22% (hypointense). The average Joules of energy delivered per sonication ranged from 4550 J for isointense to 2654 J for hypointense. Additionally, the volume of tissue ablation per Joule of energy applied was significantly larger for the heterogeneously hypointense (0.066 cm3) and heterogeneously hyperintense (0.057 cm3) than for the isointense fibroids. The NPV per fibroid was greatest for the heterogeneously hyperintense (85%) and lowest for the isointense (32%) fibroids. Fibroid image characteristics may be used to predict the effectiveness of GnRH agonist therapy prior to MRgFUS treatment. While more vascular fibroids require greater energy to treat, they show a more favorable response to pretreatment with a GnRH agonist in terms of fibroid volume reduction and thermoablative treatment effectiveness than hypointense fibroids. Discussion included using GnRH therapy to decrease focused ultrasound treatment time and the negative side effects of the treatment.

Marijn van Stralen from University Medical Center in Utrecht, the Netherlands presented their multi-parametric analysis tool for review of focused ultrasound uterine fibroid treatment data. Because of the lack of an analysis environment that can process a spectrum of imaging and treatment data as a whole--and that can assess correlation between data sets--this group developed a new program that will be made available to the research community to i) accelerate developments in the field, ii) enable effective use of advanced imaging in focused ultrasound research, and iii) stimulate collaboration between centers. They have created a modular framework to analyze treatment, with tools to access treatment and imaging data, treatment cell geometry and parameters, and intraoperative thermometry data. Image registration of these data was implemented, and analysis tools were developed to enable correlation of treatment data with imaging parameters based on the targeted treatment geometries. The program also interfaces with popular data processing software.

Christopher Dillon from the University of Utah presented their work quantifying perfusion-related energy losses during focused ultrasound treatment. The power required for successful ablation of uterine fibroids varies substantially between patients and within single treatments. Fibroids with high T2 signal intensity require increased power to achieve adequate temperature for ablation; thus, T2-weighted signal intensity has been suggested to predict treatment response. Physiologically, high T2 intensity may represent vascularization, fluid-rich tissue, or degeneration. Quantifying perfusion-related energy losses (Qb) could help link energy loss with MR perfusion imaging, and this knowledge could improve biothermal modeling of focused ultrasound fibroid treatments and potentially predict treatment response and outcome. Preclinical experiments were performed in a phantom, and deviation of a thermal model that excludes perfusion effects from the experimental temperatures was used to quantify Qb. Estimates of Qb were obtained at the time of each MR acquisition during cooling, transformed into perfusion values via the Pennes bioheat transfer equation, and averaged to mitigate the effects of noise. High perfusion values correspond to regions of increased cooling and likely indicate locations of discrete vasculature. Constant, uniform perfusion values ranged from -0.7–0.1, 1.6–3.9, and 3.4–4.4 kg/m3/s for 0, 20, and 40 mL/min flow rates, respectively, following anticipated trends with perfusion approximately zero for the no flow case and increasing with flow rate. Future work will relate MR perfusion imaging to Qb, which should eliminate the need for tissue heating for improved biothermal modeling. Obtaining perfusion estimates from 3D MR temperature data is feasible and has the potential to improve biothermal models of focused ultrasound uterine fibroid treatment.

Closing Remarks

Neal F. Kassell, MD, Founder and Chairman of the Focused Ultrasound Foundation and Professor of Neurosurgery at the University of Virginia in Charlottesville, Virginia

It's been a good meeting, and with your feedback we can further improve upon the program. The Foundation's goals have been achieved. We've heard great results and details about new studies that are starting. We've heard the sizzle, but it's time to get the steak: we need results backed up by robust data. We've heard about hurdles like reimbursement, and the answer to these hurdles is data. In terms of collaboration, new relationships have been developed, and old friendships have been renewed. On the topic of biomechanisms, we have direction. Immunomodulation is the new kid on the block, and we will be pursuing that. Allow us to be involved and to help you. Thank you, especially the participants. Upcoming meetings include the Winter School, ISTU, the 3rd European Symposium in London, and our 5th Symposium in 2016. We had a really good time – thank you.

Young Investigator Awards

Steven Allen, PhD candidate in biomedical engineering at the University of Michigan in Ann Arbor, Michigan. Awarded for "Quantifying Perfusion-related Energy Losses During Magnetic Resonance-guided Focused Ultrasound."

Alberto Bazzocchi, Consultant Radiologist for clinical and research activity at the "Rizzoli" Orthopaedic Institute (Bologna, Italy). Awarded for "Palliation of Painful Bone Metastases: The "Rizzoli" Experience."

Kelli Bryant, Currently a second year medical student at the Florida Atlantic University Charles E. Schmidt College of Medicine. Awarded for "MRI Characterization of Uterine Fibroids May Predict Success of GnRH Agonist Therapy Prior to Magnetic Resonance Focused Ultrasound (MRgFUS) Treatment."

Ulrik Carling, Research fellow at the Department of Radiology and Nuclear Medicine at Oslo University Hospital. Awarded for "MRgHIFU – Experimental Perivascular Volumetric Ablation in the Liver."

Hong Chen, Postdoctoral research scientist at the Department of Biomedical Engineering at Columbia University. Awarded for "Harmonic Motion Imaging for Pancreatic Tumor Detection and High-intensity Focused Ultrasound Ablation Monitoring."

Christopher Dillon, Postdoctoral research associate in the Department of Radiology at the University of Utah. Awarded for "Quantifying Perfusion-related Energy Losses During Magnetic Resonance-guided Focused Ultrasound."

Merel Huisman, Clinical researcher from the department of Radiology, University of Utrecht in The Netherlands. Awarded for "International Consensus on Use of MR-guided High-Intensity Focused Ultrasound for Bone Metastases: Current Status and Future Directions."

Christina Keravnou, Currently pursuing a PhD degree in Mechanical Engineering at the Biomedical Ultrasound Laboratory of the University of Cyprus. Awarded for "Image-Guided Sonoporation in an Ex vivo Machine Perfused Porcine Liver."

Young Goo Kim, Clinical Fellow of Stereotactic and Functional Neurosurgery at Yonsei University College of Medicine. Awarded for "Unilateral Magnetic Resonance Guided Focused Ultrasound Thalamotomy for Essential Tremor: Practices and Clinicaoradiological Outcomes."

Wonhye Lee, Research fellow at the Department of Radiology, Brigham and Women's Hospital, Harvard Medical School. Awarded for "FUS-mediated Functional Neuromodulation for Neurophysiologic Assessment in a Large Animal Model."

Mirjam Peek, Sixth year Technical Medicine student from the University of Twente in The Netherlands. Awarded for "High Intensity Focused Ultrasound (HIFU) in the Treatment of Breast Fibroadenomata: a Feasibility Study."

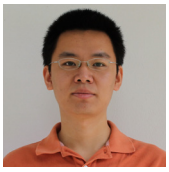
Michael Plaksin, PhD student in the Israeli Technion Nanoscience and Nanotechnology program. Awarded for "A Unifying Framework for Understanding Ultrasonic Neuromodulation Mechanisms."

Continued, next page

Young Investigator Awards (continued)

Karin Skalina, 4th year student in the Medical Scientist Training Program at Albert Einstein College of Medicine in Bronx, NY. Awarded for "Immunomodulation of Prostate Cancer Cells after Low Energy Focused Ultrasound."

Pamela Tebebi, Currently a biomedical engineering PhD student at The Catholic University of America. Awarded for "Re-establishment of Perfusion in Critical Limb Ischemia Model with Pulsed Focused Ultrasound (pFUS) and Mesenchymal Stem Cells in Aged Mice."



Yuan Zheng, Physics PhD candidate at the University of Virginia. Awarded for "High Speed, High Sensitivity PRF Shift MR Thermometry."

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Graduate students, research fellows, clinical fellows and junior faculty members are eligible to apply for the awards, which include complimentary event registration and up to $1,500 in reimbursement for travel and lodging expenses. The 2014 Young Investigator Awards are funded in part by a $5,000 grant from the National Cancer Institute (R13CA171719). The funding comes from the National Institutes of Health (NIH) Conference Grant Program which supports high quality conferences that are relevant to the scientific mission of the NIH and to public health.

Symposium Organizer

About the Focused Ultrasound Foundation

The Focused Ultrasound Foundation is a medical technology research, education and advocacy organization dedicated to improving the lives of millions of people with serious medical disorders by accelerating the development and adoption of focused ultrasound.

Positioned at the nexus of the large, diverse group of stakeholders comprising the focused ultrasound community, the Foundation functions as an independent, unbiased third-party, aligning organizations into a cohesive ecosystem with a single goal: To make this technology available to patients in the shortest time possible. It strives to catalyze progress while instilling a patient-centric sense of urgency.

The Foundation works to clear the path to global adoption by organizing and funding research, fostering collaboration, building awareness at our various workshops and symposia, and cultivating the next generation through internships and fellowships.

The Foundation is on the leading edge of the venture philanthropy and social entrepreneurship movements and is a model of how private philanthropy can work in concert with academia, industry and government to bridge the gap between research and commercialization.

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

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