MR guided Focused Ultrasound Symposium 2010
Chantilly, Virginia - October 17-20, 2010

The Focused Ultrasound Surgery Foundation held its 2010 symposium in Chantilly, Virginia on October 17-20, 2010. Over 320 people from 22 countries including clinicians, scientists and engineers from academia, industry and government agencies such as the FDA and the NIH attended this meeting.

Approximately 130 oral and poster abstracts were presented and included the growing number of new indications that are under development including stroke, epilepsy, Parkinson's disease, diabetes, back pain and tumors of the brain, thyroid, breast, liver, prostate, pancreas and bone.

This report provides a summary of the key topics discussed at the symposium.
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Overview: Current and Future Applications of Focused Ultrasound

Focused ultrasound is already approved for treating uterine fibroids in the U.S., Europe, Japan, Korea, Brazil and many more countries and for pain palliation of bone metastases outside the U.S. Researchers agree that the technology holds promise as a potential treatment for many other cancers and diseases.

The 2nd International Symposium on MR-guided Focused Ultrasound (MRgFUS), organized by the Charlottesville, Va.-based Focused Ultrasound Surgery Foundation, featured both current and future applications of focused ultrasound. MRgFUS continues to be studied in trials in patients with bone metastases, breast tumors and brain tumors, as well as prostate cancer and uterine fibroids. The technology is also in early research for liver tumors, stroke, epilepsy, movement disorders, pancreatic and kidney tumors, according to the foundation.

Approved by the FDA in 2004, the ExAblate® system developed by Israel-based InSightec Ltd. is the only U.S.-approved Magnetic Resonance (MR) guided Focused Ultrasound system for treating uterine fibroids. Outside North America, the Sonalleve® MR-high intensity focused ultrasound (HIFU) system has recently become available for fibroid therapy by Andover, Mass.-based Philips Healthcare.

HIFU (Ultrasound guided) is also approved to treat enlarged prostate and prostate cancer in Europe, Asia and other markets. The Sonablate 500, developed by Indianapolis-based Focus Surgery Inc., is used to treat localized prostate cancer and benign prostatic hyperplasia (BPH) in those countries where it is approved.

Ablatherm HIFU, manufactured by French device maker EDAP TMS, is approved for treating prostate cancer in Europe, Asia and other markets.

The Mounting Evidence

The U.S.-based Focused Ultrasound Surgery Foundation is working to accelerate the worldwide adoption of MRgFUS by hosting workshops and conferences and by funding studies of focused ultrasound surgery alone and in combination with therapeutics. Below are some of the highlights presented at the foundation’s October symposium.

Uterine Fibroids

Hysterectomies, in which the uterus is removed, are still the most common treatment for women with fibroids. Myomectomies, which require an abdominal incision, are designed to save the uterus and provide control over fibroid symptoms in about 80 percent of cases.

A study by Eva Bouwsma and her colleagues at the Mayo Clinic sought to measure the cumulative incidence of additional treatment following MRgFUS fibroid therapy at the Mayo Clinic. Of the 130 study patients, 27 underwent a subsequent fibroid treatment within a year or two. The cumulative incidence of additional fibroid treatment was found to be 9.7 percent and 24.8 percent, 12 months and 24 months post-treatment, respectively. Younger age at treatment and having a single fibroid were associated with the need for additional treatment.

The study group, which was largely comprised of Caucasian women, had multiple fibroids and a major complaint at baseline was heavy menstrual bleeding and bulk symptoms. Almost half of the study patients were overweight and more than 90 percent were premenopausal. Factors such as weight, symptom severity, total fibroid volume, smoking status and prior use of oral contraceptives were not found to be associated with treatment outcome, according to the abstract.
Previously, abdominal scars were considered to be a contraindication to MRgFUS fibroid therapy. But South Korean researcher Sang-Wook Yoon of the CHA Bundang Medical Center, Korea has found a way to potentially protect vulnerable abdominal scars from the ultrasound energy beam path by using a scar patch, developed by InSightec, composed of ultrasound blocking material. No serious adverse events were reported with the patch during the procedure or during the three-month follow-up period. The average size of the scar is 3.2 x 104.6 mm.

In another study of MR-HIFU fibroid therapy, Yoon and colleagues at Samsung Medical Center, of Seoul, Korea, found that higher acoustic power and/or ultrasound frequency could enhance the ablation efficacy for patients with a high Ktrans value, a significant predictor of poor treatment outcomes. Until now, the most important factor for poor prognosis of MR-HIFU therapy was high signal intensity of uterine fibroids on a T2-weighted MR image, according to the study abstract. (Philips Healthcare’s Bilgin Keserci also was among the authors of the Korean study to predict response).

In a poster presentation, UCLA researcher Nelly Tan and colleagues, noted that there is limited published data on outcomes of patients who have had high volume of fibroids ablated. Their study of 25 patients found that the procedure was tolerated without complications, with the mean amount ablated 50.8 percent and the mean fibroid volume was 335.3 cm³ at an ablation volume of 123.1 cm³.

The Sheba Medical Center in Tel Aviv has been using MRgFUS for treating uterine fibroids since 2003. Even though the treatments have proven to be safe and effective for uterine fibroids, the system was limited in the number and type of patients that can be treated. In an ongoing study at the facility, fibroid treatments are being performed using InSightec’s advanced ExAblate system with the GE Signa 1.5T HDX MRI.

With the new system, the transducer allows higher amounts of energy per sonication, about 1.5 times more than the previous system, explained lead researcher Yael Inbar of Sheba. The system also allows bowel loops, pubic bone and scars to be avoided. Inbar said four patients had been treated so far using the new ExAblate system (5 treatments), with the goal of treating a total of 10. Improved treatment outcomes and no significant adverse events (no skin burns) were observed with the increased energy sonications.

Liver

In a disease where conventional therapy is lacking, liver lesions have responded well to focused ultrasound, UK researcher Wladyslaw Gedroyc of St. Mary’s Hospital, told symposium participants. Gedroyc, who is director of the London hospital’s MR Therapy Centre and a consultant radiologist, said that the liver may be the most important future application for focused ultrasound because the organ is so difficult to treat with current therapy.

The ribs, however, create a barrier for focused ultrasound targeted at the liver. One way around this problem, Gedroyc said, is to build larger transducers that can sonicate between the ribs.

Bleeding is the main cause of post operative complications in hepatic surgery, but HIFU-assisted hepatic resection during an open procedure reduced the median blood loss in an animal study conducted by French researchers at the Centre Leon Berard. Median blood loss was 68 mL in the group that had HIFU-assisted liver resection, compared to 194.7 mL and 200 mL, respectively, for the other two groups that had liver resection with or without triad clamping. The median duration of the surgical
procedure also was shorter in the HIFU-assisted liver resection group compared to the other two groups (12 minutes vs. 21 and 19 minutes). One case of hematic collection was observed and one death occurred in the two groups that did not undergo HIFU-assisted liver resection.

The ExAblate Conformal Bone system has demonstrated MR compatibility with a robotic arm used on human cadaver liver and kidney. UK researchers at the University of Dundee said MR guided positioning and sonication of liver and kidney on two human cadavers were performed to compare manual and robotic positioning. In addition, MR guided core biopsy needle positioning was conducted with the same set-up. The researchers concluded that automatic determination of robotic arm location makes MR guided biopsy (or other intervention) more accurate and also speeds up the process, the researchers concluded. The integration of the two technologies, they said, raises the possibility of a “one stop shop” for diagnosis and therapy, according to the abstract.

Bone Metastases
InSightec is studying its ExAblate system in an ongoing phase III trial in patients with painful bone metastases and multiple myeloma who are not candidates for radiation therapy, with results expected within a year. Results from phase I/II trials in patients with bone metastases were presented at the symposium and showed that the treatment was safe and provided significant improvements in pain. InSightec’s bone pain treatment, which has no ionizing radiation, is designed to destroy the pain-causing nerves in the bone surface surrounding the tumor. Only one treatment session would be needed in most cases, if the treatment is approved.

Other bone pain studies presented at the symposium were in line with published findings showing significant pain reduction following treatment with MRgFUS. But some researchers observed additional effects, suggesting that the technology may have other possible applications beyond the potential for bone pain reduction.

In an early stage study of InSightec’s ExAblate system, a team of Italian researchers at Sapienza University of Rome achieved tumor control as well as improved pain scores. And researchers in Spain at the Iberian Medical Research Institute and the University of Seville observed reduced pain in several patients and bone regeneration in one patient.

Back, Neck Pain & Other Applications
UK researcher Wladyslaw Gedroyc of St. Mary’s Hospital in London discussed an ablation technique that is designed to alleviate back and neck pain by targeting the facet joints in the spine. The procedure could provide an alternative to medications and localized injections.

It remains unclear what the optimal energy is for MRgFUS used in facet joints, but findings from a Japanese study led by Motohiro Kawasaki of Kochi Medical School showed favorable effects of the ultrasound treatment in elderly patients with low back pain who could not obtain anesthesia for a facet joint block or medical branch block procedure. The study, which evaluated InSightec’s ExAblate system, showed that low back pain significantly decreased, with a treatment time of 46-58 minutes and 8-18 sonications. While there were no adverse effects seen in the study, changes were observed on the MRI in the dorsal facet joint of one patient treated with focused ultrasound beams.

Kristin Dittmar and her colleagues at The Methodist Hospital Research Institute of Houston, studied the feasibility of targeting the pancreas with InSightec’s
ExAblate system in eight pigs. The results showed that energy deposited into the pancreas can result in necrosis after a certain threshold. Complications arose as the energy increased.

With the higher energy settings, the level of necrosis ranged from 45 percent to 65 percent. Other complications included abdominal wall muscle burns, necrosis of the duodenum and adjacent pancreas, gastric ulcers and reactive follicular hyperplasia in lymph nodes. Two pigs treated at the highest energy settings (peak temperatures were between 50 and 65 degrees Celsius) demonstrated evidence of pancreatitis and one had vomiting and needed pain medication. But most of the pigs tolerated the procedure well (20-30 seconds of treatment time and a 60-second cool-down).

Breast Cancer

In terms of current breast cancer treatments, “Existing therapies work very well which gives us a high bar,” Mitchell Schnall, chair of the American College of Radiology (ACRIN) Imaging Network, told the symposium.

ACRIN, a National Cancer Institute clinical trials cooperative group, planned to conduct a Phase III, single-arm breast cancer study, with a goal of 100 percent tumor necrosis. Schnall said that in negotiating the trial details with the FDA, the agency indicated that anything short of 100 percent ablation wouldn’t be acceptable, because excision currently is 100 percent effective. So based on that standard, the aim of the ACRIN breast cancer trial would be to achieve 100 percent ablation in 70 percent of patients using the InSightec focused ultrasound system. A week after the symposium, a spokesman at ACRIN provided an update on the study, saying that “due to ongoing regulatory issues, the trial’s sponsor decided not to go forward with the clinical trial.”

Researchers in Seattle are hoping to use the Sonalleve HIFU system to improve survival, by inducing the immune system to seek and kill microscopic metastatic disease in mice with breast carcinoma. Complete treatment of the experimental cohort and results of immunologic testing are pending, according to the study abstract, which was presented by lead researcher, Peter Eby of the University of Washington and Seattle Cancer Care Alliance. The anticipated results are that animals bearing HER-2/neu tumors treated with MRgFUS compared to untreated animals will demonstrate an increase in primed circulating HER-2/neu antigen specific effectors, and have low circulating antigen specific tolerogenic cells. The study is funded by the Focused Ultrasound Surgery Foundation and the Fred Hutchinson Cancer Center, with equipment and technical support from Philips Research.

University of Utah researcher Nick Todd and colleagues came up with a way to correct the phantom imaging of a mostly aqueous breast during free breathing, using an algorithm called temporally constrained reconstruction (TCR) to reconstruct an artifact-free image. But in the more difficult case of imaging in a mostly adipose (fatty) breast, an atlas-based correction method performed the best. Work is ongoing to test the entire approach on multiple female volunteers. The work is part of a project funded by the Focused Ultrasound Surgery Foundation.

Another team at the University of Utah led by Allison Payne sought to design a flexible, breast-specific transducer position, suspension tank and patient table using the engineering software SolidWorks. In this system, the breast is suspended in a cylindrical tank, water-coupled to the transducer, providing approximately 270 degree access around the treated breast. The patient table has been ergonomically designed for improved
comfort. The patient lies prone with the affected breast suspended in the cylindrical tank, while the nontreated breast is compressed. This design, the researchers found, provides a larger acoustic window than that of axially shooting transducers, yielding access to a wider population of breast tumors. It also provides increased signal-to-noise ratio to enable faster imaging and more accurate temperature monitoring.

**Prostate Cancer and BPH (Enlarged Prostate)**

MRgFUS has the potential to treat localized prostate tumors rather than the entire prostate, while also preventing or reducing the risk of incontinence and impotency, Vladimir Turkevich of Russia’s Petrov Research Institute of Oncology, explained in an oral presentation. Four patients with mapping-biopsy proven low risk prostate cancer have been treated so far using InSightec’s ExAblate system at Petrov. Initial efficacy is measured by prostate-specific antigen levels and patient completion of treatment related to quality of life questionnaires. No device or procedure-related adverse events occurred. A total of fourteen patients have been treated so far in Russia, Singapore, Rome and India sites.

MR-guided pulsed HIFU may have great potential to improve the efficacy of docetaxel delivery in inhibiting prostate cancer growth, especially when combined with radiation therapy (RT), according to preliminary study results presented by Lili Chen of the Fox Chase Cancer Center in Philadelphia. But more experiments are needed for more reliable statistical analysis. In the study of male mice, treatment started with an InSightec ExAblate system and a 1.5 GE MR scanner. The relative tumor volume for mice treated with MRgFUS-docetaxel-RT was 1.0, compared to 1.4 for the docetaxel-RT group and 1.5 for the FUS-docetaxel group.

HIFU treatment prior to surgery significantly reduced tumor recurrence and also improved survival in mice, according to a poster presented by Duke University researchers. Prior to HIFU treatment, some groups were injected with CPA-7, a drug that kills cancer cells with high levels of the activated STAT3 molecule, but does not kill normal cells. Some 40 days after surgery, tumor recurrence was reduced by 50 percent and the survival rate increased by 50 percent in the CPA-7 treated groups. The results suggest that a rational combination of HIFU, immunotherapy and surgery may improve the overall treatment outcome for prostate cancer.

A group of Stanford University researchers led by Graham Sommer studied the performance of transurethral ultrasound applicators (multi-sectored tubuar transducer arrays) to ablate benign prostatic hyperplasia (BPH) in three canines. The device was designed to sonicate and ablate the anterior-lateral portions of the prostate gland between the bladder neck and the verumontanum. The results showed complete resorption of ablated regions at the time, with preservation of the prostatic urethra. BPH often results in lower urinary tract symptoms, which includes diminished urinary flow. Although medication is increasingly being used for BPH, surgical options such as transurethral resection of the prostate (TURP) are still commonly used for BPH, also known as enlarged prostate. The volume of surgeries in the U.S. for BPH is three to four times than that of radical prostectomies, the researchers noted. New minimally invasive techniques have been developed with the hope of fewer complications than TURP, with less anesthesia required, shorter hospital stays and fewer undesired side effects. But the durability of those treatments has proved limited, they said.

MR-guided transurethral ultrasound has been under development at the University of Toronto for several years, and has been successfully evaluated
in simulations, gel phantoms, and a preclinical canine model. The research team led by Laurence Klotz in the university’s urology division reported initial results in a study of eight men with low- to-intermediate risk prostate cancer who were scheduled for radical prostatectomy. According to the study abstract, the findings confirm the feasibility of generating precise spatial heating patterns in the prostate gland using transurethral ultrasound therapy and MR thermometry.

A strong, tumor-specific immune response was generated by using weekly cycles of the combination of low energy focused ultrasound (LOFU) and HIFU over three-weeks, in a study of mice presented in a poster by researchers at the Albert Einstein College of Medicine. This was in contrast to the tumor-specific antibodies predominantly generated after a high HIFU treatment. Control mice with untreated tumors had no detectable tumor-specific T cells. The treatment combination holds potential as an in situ tumor vaccination approach.

**Brain**

According to the Focused Ultrasound Surgery Foundation, the field of MR-guided focused ultrasound was ignited last year by news that Ernst Martin and his group of researchers had successfully used this noninvasive technology (InSightec’s ExAblate Neuro system) to treat patients in an area of the body most difficult to access – the brain. The landmark study has paved the way for clinical trials addressing a broad spectrum of brain disorders, including Parkinson’s disease, essential tremor, epilepsy, brain tumors, and stroke.

Long-term follow-up data for the Swiss study was presented by Ernst Martin. Twelve patients with chronic neuropathic pain who were treated with the ExAblate Neuro system have since undergone 3-month and one year followup MR imaging and neuro evaluations. Preliminary evaluation of these findings shows lesions that are visible on the MR image, yet smaller in size at 12 months versus 3 months post treatment. The prolonged suppression of the pain symptoms varies amongst the group of patients. Overall, the initial long-term findings suggest the potential of transcranial MRgFUS for precise functional neurosurgery procedures. More work in this field is warranted, and the symposium also offered a preview of the first North American patient study: a multicenter clinical trial evaluating the safety and efficacy of MR-guided focused ultrasound in treating medically-refractory essential tremor.

Researchers at the University of California, San Diego, led by Thilo Hoelscher, demonstrated in vitro that HIFU could be used to achieve thrombolysis (breakdown of blood clots to restore blood flow in the brain) within seconds, without the need for the clot-busting drug tissue plasminogen activator (tPA). A total of 400 experiments were performed using InSightec’s ExAblate Neuro system. With transcranial MRgFUS, a maximum clot weight loss of 64.7 percent was achieved within 30 seconds in the absence of drugs like tPA. This team also reported initial results from an in vivo study that tested for sonothrombolysis of clots in carotid arteries of rabbits, using the ExAblate Neuro system. In the efficacy model, which evaluated the method in the carotid artery in six rabbits to date, thrombotic occlusion of the artery was achieved in all animals. Successful recanalization of the vessel via focused ultrasound was at least partially achieved in these animals. In the safety model, none of the12 rabbit brains that were evaluated showed abnormal behavior over 10 days nor pathological findings after histology.

Researchers at the University of Virginia have begun to investigate the use of the ExAblate Neuro system
for sonothrombolysis of intracerebral hemorrhage (ICH). Preliminary results have demonstrated the use of transcranial MRgFUS to target and lyse large blood clots in in vitro and in vivo models. Additional work is required to refine the focused ultrasound parameters for most efficient and safe transcranial clot lysis.

The blood brain barrier (BBB) has made it nearly impossible to use drugs in the treatment of brain disorders. But preliminary findings from a preclinical safety study in primates achieved localized, transient disruption of the BBB, using bursts of MR-guided focused ultrasound and microbubbles. The work was led by Nathan McDannold and his colleagues at Brigham and Women's Hospital and Harvard Medical School in Boston using the ExAblate system. In another preclinical study, McDonald and his team used the same approach to deliver chemotherapy across the BBB to tumors associated with metastatic breast cancer, representing the potential for targeted drug delivery.

**Targeted Drug Delivery (TDD)**

Another exciting field that has progressed significantly since the last MRgFUS symposium, is the use of focused ultrasound to enhance drug delivery and to aid in localizing the drug uptake to a small region of treatment. Targeted drug delivery uses many techniques and protocols to deliver the drug most effectively and with the fewest side effects of toxicity.

**Liposomes**

Liposomes are being studied as a potential vehicle for targeted drug delivery used with therapeutic ultrasound. A liposome is an artificially made tiny bubble (vesicle) that potentially could be used to deliver drugs for cancer and other diseases. The microscopic sacs, similar to the material of cell membranes, carry drugs through the blood to diseased tissue, such as tumors.

Drug delivery particles need to remain stable en route to the target tissue and efficiently release the encapsulated drug once at the disease site. The seemingly opposing properties may be reconciled by exposing drug-carrying sonosensitive liposomes to ultrasound in the tumor, according to researchers at INSERM Unit and Universite de Lyon in France, and Epitarget AS in Norway (LaFon et al.). In vivo experiments were performed on rats implanted with AT2 Dunning tumors. In the pharmacokinetic study, 18 rats were injected with liposomal doxorubicin 10 days after tumor implantation. Maximal tumor uptake of doxorubicin was observed at 11 and 12 days after tumor implantation. An increase in tumor signal intensity was observed after the application of ultrasound to animals injected with liposomes. The researchers also investigated the efficacy of a combined treatment with liposomal doxorubicin and ultrasound on tumor growth. Ultrasound alone did not induce any significant effect on the tumor growth. The group receiving both liposomes and ultrasound showed a significantly lower tumor growth compared to controls.

To minimize the leakage of liposomes while still retaining their quick release characteristics, researchers at the University of Helsinki (Tejera-García et al.) analyzed the thermal phase behavior of a number of lipid compositions. Special emphasis was placed on combinations of lipids with complementary effective shapes to help prevent voids and to obtain highly efficient packing at temperatures below the critical release temperature. This molecular engineering approach proved to be highly efficient, yielding quick drug release and very low leakage.

Drug delivery to solid tumors currently faces obstacles such as toxicity to healthy organs, insufficient and heterogeneous drug delivery and lack of knowledge of the concentration of the delivered drug. But image-guided targeted
drug delivery approaches may improve these shortcomings, according to researchers at the National Institutes of Health, Duke University and Philips Healthcare (Yarmalenko et al.). Combining image-able low temperature-sensitive liposomes (iLTSL) may enable spatial control and real-time noninvasive monitoring of content release for image-guided targeted delivery, the study found. The iLTSLs demonstrated consistent size and doxorubicin kinetics after storage at 4 degrees Celsius for seven days. The iLTSLs were co-loaded with an MRI contrast agent Gd-HPA D03A (also known as gadoteridol or ProHance) and doxorubicin. Faster, but incomplete doxorubicin release (approximately 70 percent) occurred in human plasma. In vivo, injection of iLTSL resulted in stable, roughly 30 percent signal enhancement relative to preclinical values in the heated portion of the tumor, following four 10-minute heating cycles.

Researchers from Philips Research Europe and Eindhoven University of Technology, both in the Netherlands (Heijman et al.), found that loading MRI contrast agents together with drug into the lumen of the liposomes allows for imaging and possibly quantifying drug release in situ. The researchers studied temperature-sensitive liposomes (TSLs) loaded with the chemotherapy drug doxorubicin (DOX) and the MRI contrast agent Gd-HPA D03A (also known as gadoteridol or ProHance) for temperature-induced drug delivery under MR image guidance. See Ruzics et al. JMRI 2008 Dec;28(6):1386-92).

TDD Technology for Cancer Therapy

Focused ultrasound is being studied as a possible drug delivery technology primarily in the area of cancer therapy. Studies have shown the synergistic effects between hyperthermia and chemotherapy. Clinical trials in image-guided drug delivery combine high temperature thermal therapy with chemotherapy agents, which are released in the heating zone via low temperature-sensitive liposomes (LTSL). The LTSLs can release their content within seconds upon heating above approximately 40 degrees Celsius. HIFU in combination with LTSL allows localized delivery of drugs with considerably higher concentrations compared to standard chemotherapy, according to findings presented at the October symposium (Gasselhuber et al.).

The study concluded that computer models may help to optimize drug delivery and the heating regimen, potentially maximizing local tissue concentration.

TDD for Tumor Growth Control

Celsion Corp., which presented preclinical abstracts at the symposium, is seeking to combine ThermoDox (lyso-thermosensitive liposomal doxorubicin) with MR-guided focused ultrasound, to control tumor growth.

Under a joint research agreement with Philips Healthcare, Columbia, Md.-based Celsion is developing a heat-activated liposomal encapsulation of doxorubicin, a drug frequently used for various cancers, including breast cancer. ThermoDox, administered intravenously and in combination with hyperthermia, enables high concentrations of doxorubicin to be deposited preferentially in a targeted tumor, according to Celsion. ThermoDox has been granted orphan drug status by the FDA and is in a pivotal 600-patient, global Phase III study in primary liver cancer under a special protocol assessment agreement with the agency. (Source: http://www.celsion.com/releasedetail.cfm?ReleaseID=520285).

In a preclinical study of rabbits, Canadian researchers (Staruch et al.) at the Sunnybrook Health Sciences Centre and University of Toronto demonstrated that ThermoDox concentrations in heated regions
of rabbit thighs were on average 15.3 +/- 8.1 times higher than in unheated contralateral thighs. The results, the researchers concluded, show the potential of MRI-controlled focused ultrasound hyperthermia to enhance local drug delivery with temperature-sensitive drug carriers.

Another preclinical study of ThermoDox (Ranjan et al.) investigated the combination of MR-guided HIFU and temperature-sensitive liposomes in rabbits with Vx2 tumors. Such tumors are implantable in fatty tissue. Philips’ Sonalleve system was used for sonications and MR guidance. Combining heating with MR-HIFU and low temperature-sensitive liposomes (LTSL) resulted in approximately five-fold greater doxorubicin concentration compared to treatment with LTSL alone. Analysis of individual fragments from each tumor demonstrated relatively heterogeneous doxorubicin distribution post MR-HIFU, suggesting that a more conformal hyperthermia treatment may further improve targeted drug delivery to a solid tumor, the researchers concluded.

A mild hyperthermia heating algorithm for accurate and homogeneous heating within the targeted region in rabbits bearing Vx2 tumors was developed by a group of researchers from the National Institutes of Health, the University of Helsinki, Philips Health Care, Duke University and Philips Medical Systems (Partanen et al.). The mean heating target was 40.5 degrees Celsius with a target 40-41 degrees C, and the standard deviation for homogeneity of heating was 1 degree C.

**Ultrasound Enhanced Drug Delivery**
A team of researchers at the University of California and the University of Bergen in Norway (Watson et al.) sought to determine the mechanism of ultrasound-enhanced drug delivery in an animal study.

Their study focused on the physiological mechanism responsible for liposomal particle accumulation enhancement. In the study, animals with mammary adenocarcinoma cells received intravenous injections after insonation with a modified Siemens Antares ultrasound scanner for 7 minutes. The therapeutic ultrasound treatment resulted in a 2.3-fold increase in accumulated liposomes 48 hours after insonation. Multiple mechanisms for increased accumulation were detected. Regardless of whether the tumor was insonified prior to or after euthanasia, the interstitial fluid pressure remained stable during heating to 42 degrees Celsius, but fell significantly when the temperature was maintained at 42 degrees Celsius.

Therapeutic ultrasound can induce mild hyperthermia, providing a range of therapeutic effects, such as increased blood flows, enhanced microvascular permeability, extravasation of liposome particles, sensitization of tumor cells to radiation and release from temperature-sensitive liposomes.

The synergistic effect of heat with doxorubicin may be explained by several mechanisms, according to researchers at CapsuTech Ltd., InSightec Ltd., both of Israel, and the University of Dundee in the UK (Arditti et al.). One potential mechanism may be increased penetration of doxorubicin into the cells during heating. In addition, the researchers confirmed, ultrasound-induced cavitation causes necrosis, and cavitation effects were observed in detail, in real-time with high speed photomicroscopy.

Their study examined the viability of heat-treated human KB cells, and the cellular uptake of doxorubicin using MRgFUS. KB cells are a cell line derived from a human carcinoma of the nasopharynx. In the study, a significant decrease was seen in KB cell viability due to heat (temperatures higher than 41 degrees Celsius) in the presence of...
doxorubicin, compared with doxorubicin at normal culture temperature (37 degrees Celsius). But further investigation is needed, they said, to optimize the potential of MRgFUS to enhance cellular uptake of therapeutic agents.

A novel delivery nano-encapsulant developed by CapsuTech will be investigated with MRgFUS for its potential as a stimuli-responsive delivery system, including the possibilities of thermal and cavitation response mechanisms. Although ultrasound has been shown to enhance drug accumulation in tumors, differences in tumor phenotypes (epithelial, mesenchymal and transitional) must be accounted for in treatment planning, according to a study by researchers at the University of California, Davis (Watson et al.). In animals injected with mammary adenocarcinoma cells, well perfused epithelial tumors (insonified for 2 minutes at 42 degrees Celsius) demonstrated a 2.8-fold increase in accumulation 48 hours post-ultrasound. For tumors with mixed epithelial and mesenchymal phenotype, an increased mechanical index and insonation time to 7 minutes was required to enhance particle accumulation, a 2.3-fold accumulation increase. In fibrotic and poorly tumors, extended insonation time for 18 minutes produced a 3-fold increase, whereas a lower mechanical index or shorter treatment was unsuccessful.

Chrit Moonen, director of the molecular and functional imaging research team at the University Victor Segalen in Bordeaux France, described how the bioeffects of ultrasound can be used for local drug release from nanocarriers circulating in the blood. Real-time imaging such as MRgFUS is particularly useful in providing new insights to increase the therapeutic window with ultrasound, Moonen concluded. The circulation half-life may be increased by incorporating polyethylene glycol (PEG)-lipids in the lipid bilayer membrane.

Liposomes may carry drugs (hydrophilic and hydrophobic) in their aqueous interior as well as in the lipid bilayer. Drugs can be attached to the membrane surrounding the microbubble, they can be imbedded within the membrane itself, they can be bound non-covalently to the surface of the microbubble and can be loaded to the interior of the microbubble, either in an oil or aqueous phase, according to Moonen.

He noted that several recent publications have shown that ultrasound-triggered delivery is feasible (Descers et al. JMRI 2008 and JCR 2010; Frenkel et al. Adv Drug Del Rev 2008). The concept is not new. More than 25 years ago, thermosensitive liposomes were suggested for local drug release in combination with local hyperthermia. Image-guided ultrasound may be used for more than just drug delivery, the release or activation of drugs. According to the study, the technology also may be used to make cell membranes permeable, to identify and characterize targets, to evaluate biodistribution (pharmacokinetics and pharmacodynamics), and to provide physiological read-outs for evaluating therapeutic efficacy.

**Microbubbles**

University of Virginia researchers (Phillips et al.) examined microbubble radius and its effect on drug delivery and cell viability. The researchers used a model of vascular smooth cell proliferation, the primary cell type responsible for restenosis following angioplasty. The study goal was to deliver an anti-proliferative drug, rapamycin, to the cells via ultrasound-mediated delivery using microbubble carriers while minimizing cell death.

The hypothesis was that larger microbubbles would increase cell death, but also enhance drug delivery, thereby reducing proliferation of smooth muscle cells. The study showed that the effective drug
delivery width and the region of cell death both decreased with microbubble radius. A significant reduction in live cells was observed between groups treated with large microbubbles (62 percent alive) compared to small microbubbles (78 percent alive). Conversely, applying small microbubbles significantly reduced cell death by half, compared to large microbubbles (11 percent versus 23 percent). The permeable/dead cell ratio was 64 percent for large microbubbles and 98 percent for small microbubbles. The cells were differentiated using a fluorescent live/dead assay, where live was depicted as green, the color for dead was red and permeabilized was green and red.

A separate study by researchers at the University of Virginia researchers and Philips Research North America (Klibanov et al.) sought to use ultrasound to destroy circulating microbubbles in the tumor vasculature and block tumor blood flow in mice with colon adenocarcinoma in the hind leg. As a result of microbubble destruction by ultrasound, transient reduction of blood flow in the tumor vasculature, was observed; most of the blood was restored minutes after treatment. Daily treatment during a two-week treatments study resulted in a significant suppression of tumor growth. In controls, where either microbubble injection or TIPS (vein shunt) treatment was not applied, tumor growth was not suppressed. The researchers concluded that the induction of local inflammation in the microbubble plus ultrasound-treated tissue may be the mechanism of the suppression of tumor growth.

The presence of blood vessels are an important cause of temperature inhomogeneity, preventing optimal temperature control during ultrasound exposure. Blood flow is the main parameter that determines temperature distribution in tissues. Adjusting the power deposition to take into account the presence of blood flow is an important step toward a better treatment with ultrasound, no matter which delivery method is used, according to researchers at the Methodist Hospital Research Institute in Texas (Sassaroli et al.). In their study, thermal treatment was simulated using three delivery methods, by an ultrasound focus stepped up through the mid-plane of the computational domain, in a sequential manner or through a spiral trajectory. In all three cases, a more uniform thermal dose distribution was observed, but under-dosage around the thermally significant vessels still remained. The preliminary results suggest the importance of treatment planning that takes into account the presence of blood vessels and blood flow.

Researchers at the University of Utah and Image Guided Therapy Inc. in France (Payne et al.) assessed a new MRgFUS system developed by the French firm to treat small animals. The system was used in both ex vivo and in vivo environments with a TIM Trio 3T MRI scanner by Siemens Medical Solutions of Germany. Ex vivo tissue experiments use MRI temperature mapping to valuate the system’s capabilities. Ex vivo tissue results showed the accuracy and ease of use of the new system. In vivo experiments were performed on mice with a subcutaneous pancreatic tumor model to evaluate the effects of unloaded and paclitaxel (PTX)-loaded perfluorocarbon nanoemulsions. The in vivo experimental results provided qualitative data that confirm results seen in phantom studies.

### Thiel Technique

For centuries, cadavers have been used in medicine for research and educational purposes. The Thiel technique has been used to soft-embalm cadavers using a mixture of salt compounds and very low amounts of volatile formaldehyde. That method is used for training purposes with cadavers in ultrasound-guided anesthesia of the cervical region. Researchers at the University of Dundee in the UK...
and InSightec Israel (Volovick et al.), demonstrated another promising use of Thiel cadavers in MRgFUS procedures, to study the targeting of organs behind the ribcage in focused ultrasound surgery, and for targeted drug delivery. Thiel soft-embalmed human cadavers were used to evaluate the accessibility and efficacy of FUS for various internal organs, such as liver, kidney, pancreas, etc.

The experiments were conducted using InSightec’s ExAblate system. Various MRI sequences were used for the imaging of ribs. The best visualization of ribs was achieved using echo planar imaging (EPI), the researchers found. Thiel embalmed human cadavers, they said, are promising as an MRgFUS model, and the same cadaver can be used more than once to repeat experiments. An investigation is under way on perfusion of the vascular system and breathing motion by pressurizing the lungs.

**Challenges Ahead**

Continued technological improvements in picture quality, beam precision and MR compatibility could allow a wider range of diseases and tumors to be treated with focused ultrasound, and address some of the limitations of the technology.

Collaborations between academia, radiology and biotechnology should work to advance the area of targeted drug delivery in cancer and other diseases. Larger studies over a longer term that show positive outcomes for MRgFUS would likely be the key to gaining greater acceptance from health plans and professional societies.

Unlike other medical applications of ultrasound, no guidance or standards documents have been developed for Focused Ultrasound. However, standards organizations are making progress toward that end. The FDA’s Center for Devices and Radiological Health, has announced that its Ultrasonic Laboratory is developing test methods and computational techniques for analyzing the safety and effectiveness of ultrasound ablation devices.

For more information on the Focused Ultrasound Surgery Foundation, go to [www.fusfoundation.org](http://www.fusfoundation.org).

You can also sign up to the MRgFUS newsletter, [http://www.fusfoundation.org/Newsletter-Subscribe/newsletter-signup](http://www.fusfoundation.org/Newsletter-Subscribe/newsletter-signup)