12th ICHO PROGRAM & ABSTRACT BOOK

SOCIETY FOR THERMAL MEDICINE

ESHO

ASIAN SOCIETY OF HYPERTHERMIC ONCOLOGY
ASHO

Table of Contents

Dear colleagues,

I want to welcome each of you to the 12th International Congress of Hyperthermia. The first multinational meeting, entitled "International Symposium on Cancer Therapy by Hyperthermia and Radiation" was held in Washington, D.C. in 1975. This meeting attracted over 100 participants and was organized by Eugene Robinson. The period from 1975-1990 was the heyday for the field. Hyperthermia was one of the most promising new agents for the treatment of cancer and many touted that it would be the fourth major treatment option, in addition to surgery, chemotherapy and radiation therapy. Interest in the field swelled during the1980's both in terms of the science being discovered, the conduct of clinical trials and commercial device development. For example the 6th Congress held in Tucson, AZ in 1992 attracted over 600 participants. However, as happens with many emerging cancer therapies that exhibit great promise, the initial enthusiasm diffused quickly into the hard work to establish best practices and to translate the most compelling biologic concepts into clinical trials. From these efforts, a deeply committed cadre of clinicians, engineers, physicists and biologists have banded together to push the frontier. New biologic discoveries and better therapeutic technologies that are tailored for specific cancers have galvanized the field. There is considerable excitement about new clinical trials, many of which will be summarized at this Congress.

What we realize now is that hyperthermia is but one aspect of "Thermal Therapies", which cover the temperature range from cryotherapy to thermal ablation. Thermal ablation therapy for various cancers is now a clinically established treatment modality for patients that are not candidates for surgery, radiation and chemotherapy, or is used to augment these traditional therapies. One of the reasons for this success is that – unlike for chemo- or radiation therapies – cancer cells do not have, and do not develop resistance to high-temperature thermal therapies. Experts that span the entire temperature range are present at this Congress. The advent of better technologies that cover this spectrum has energized the field and has led to FDA, European and Asian approvals for novel therapeutic applications, for example high-intensity focused ultrasound (HIFU). For several target sites HIFU now allows non-invasive tissue heating with mm precision, and combination with MRI based thermometry provides real-time 3D temperature monitoring capabilities. This may lead to exciting new clinical applications in temperature ranges covering both ablation and hyperthermia, for example image-guided drug delivery applications when combined with heat-activated drug carriers.

I personally became involved in the study of hyperthermia because the diversity of biologic effects was scientifically intriguing to me. Collectively, these diverse effects promote better anti-tumor effects of a range of therapies. Most promising on the horizon are the immunostimulatory effects, for example. Recent discoveries regarding how hyperthermia inhibits DNA damage repair has led to new clinical trial designs. Further technological developments in ferromagnetic fluids and other nanoparticles hold great promise for augmenting drug delivery to tumors in ways that simply cannot be achieved with unencapsulated drug. Such developments could revolutionize how drugs are delivered to tumors in therapeutically effective concentrations.

The logo of this Congress was designed to embrace the diversity of the physics and engineering developments as well as biologic effects that this therapy brings to the patient. Over the past 40 years we have learned many lessons, but we solved many of the challenges to emerge with modern and improved strategies. At this Congress, we will show that the promise and reality of thermal therapy remains stronger than ever.

With Regards,
Mark W. Dewhirst, DVM, PhD, FASTRO, FAAAS
Gustavo S. Montana Professor
of Radiation Oncology
Associate Director for Basic Science,
Duke Cancer Institute
12th ICHO President

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Society for Thermal Medicine Association Manager **Christopher Lapine** and Association Management Administrator **Katie Rempala** of Allen Press, Inc. and Meeting Planner **Tony Ballard** from Kansas State University Conference Services for their assistance with planning the 12th International Congress of Hyperthermic Oncology.

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Meeting info/maps

Registration Desk Hours of Operation:

Tuesday, April 12: 8:00am – 5:30pm - La Salle C Foyer

Tuesday, April 12: 6:00pm – 9:00pm - Frenchman Ballroom

Wednesday, April 13: 6:30am – 6:30pm - La Salle C Foyer

Thursday, April 14: 6:30am – 5:30pm - La Salle C Foyer

Friday, April 15: 6:30am – 5:30pm - La Salle C Foyer

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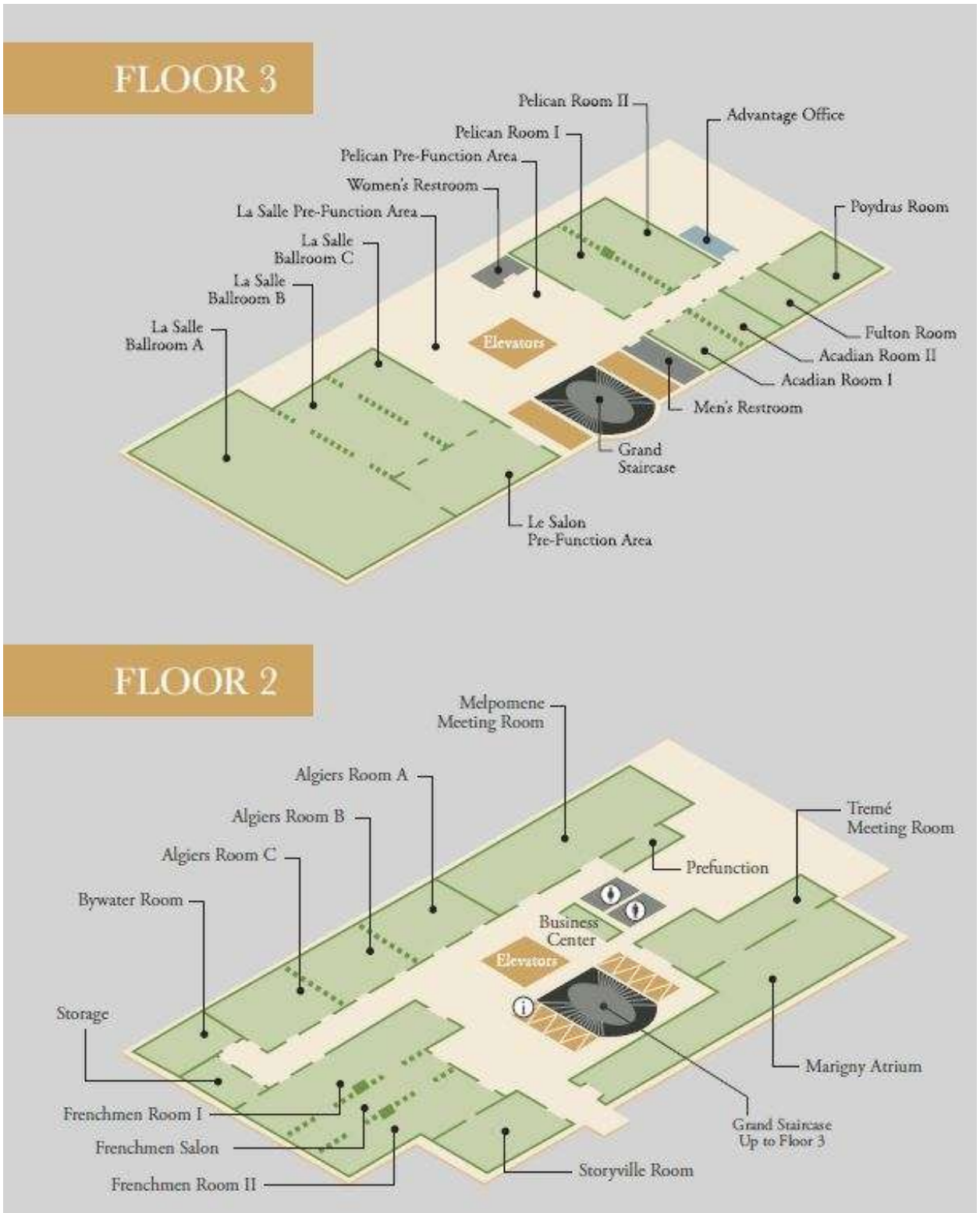
Meeting info/maps



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Society for Thermal Medicine

Mission Statement

The Society for Thermal Medicine is a 501(c)(3), non-profit organization whose mission is to significantly improve patient treatment outcomes by advancing the science, development and application of Thermal Therapy.

Our Society strives to:

- Promote new discovery in thermal biology, physics/engineering, and medicine.
- Sponsor high quality forums for education of medical professionals in the practice of thermal medicine.
- Advocate for increased patient access to appropriate, high quality, thermal therapies.

Governing Council European Society for Hyperthermic Oncology

Mission Statement

The object of the European Society for Hyperthermic Oncology (ESHO) is to promote for the public benefit, fundamental and applied research in physics, engineering, biological and clinical sciences relating to the use of hyperthermia in cancer therapy.

Moreover, the society wants to facilitate integration and exchange of information between different disciplines in the study of the biological effects of heat in the treatment of cancer either alone or combined with other cancer treatment modalities.

The European Society for Hyperthermic Oncology was established in 1987 in England. In 1992, the registered office of the Society was transferred to The Netherlands.

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Plenary Speaker
Dr. Damian Dupuy, MD

Plenary Session - Clinical Applications of Thermal Ablation
Wednesday, April 13, 2016, 8:15am - 9:00am
La Salle A

"Interventional Oncology: the Fourth Arm of Cancer Care"

Director of Tumor Ablation, Rhode Island Hospital
Professor of Diagnostic Imaging, Brown Medical School

Dr. Dupuy, is the director of Tumor Ablation at Rhode Island Hospital and a professor of Diagnostic Imaging at Brown Medical School.

Dr. Dupuy, a pioneer in the use of image-guided ablation, helped broaden clinical applications to successfully combat cancer involving the kidney, liver, lung, adrenal, head and neck and skeleton. Other newer technologies such as microwave ablation, and combination therapies using RFA with external radiation or brachytherapy have been pioneered by Dr. Dupuy who has been the principal investigator of two NCI funded multicenter trials.

Dr. Dupuy has published over 140 publications and given over 110 invited lectures in the field of radiology and image-guided ablation.

Plenary Speaker
Professor Chrit Moonen, PhD

Plenary Session - State of the Art in HIFU
Thursday, April 14, 2016, 8:15am - 9:00am
La Salle A

"State-of-the-art In High Intensity Focused Ultrasound (HIFU)"

Professor, Division of Imaging at the University Medical Center in Utrecht, the Netherlands.

Chrit Moonen did his Masters in Molecular Sciences and his Ph.D. in biophysics (Wageningen University). He did part of his studies with Nobel Laureate Wüthrich in Zürich, Switzerland. He went for a postdoctoral period to the University of Oxford (Sir Georg Radda). He then worked at the University of California at Davis as a Visiting Research Scientist before becoming head of the NIH In Vivo NMR Research Center from 1987-1996. He moved back to Europe (Bordeaux, France) in 1996 where he has been director of the laboratory "Molecular and Functional Imaging: from Physiology to Therapy" until 2011.

He is currently professor at the Division of Imaging at the University Medical Center in Utrecht, the Netherlands. He coauthored over 150 scientific papers. H-index is 54. He was President of the "International Society of Magnetic Resonance in Medicine" (2006), and of the "Society for Molecular Imaging" (2009). He received the European Magnetic Resonance Award 2000, is a Fellow of the International Society of Magnetic Resonance in Medicine, of the European Society of Magnetic Resonance in Medicine and Biology, and of the World Molecular Imaging Society. His recent work is mainly in molecular and cellular imaging, MRI guided Focused Ultrasound, and image guided drug delivery.

Plenary Speaker
Professor Michael B. Yaffe, MD, PhD

Plenary Session - Using Systems Biology of Signaling to Improve Cancer Treatment
Friday, April 15, 2016 , 8:15am - 9:00am
La Salle A

"Using Systems Biology of Signaling to Improve Cancer Treatment"
David H. Koch Professor of Biology and Biological Engineering, MIT
Attending Surgeon, Beth Israel Deaconess Medical Center, Harvard Medical School

Dr. Yaffe is the David H. Koch Professor of Biology and Biological Engineering at MIT and Attending Surgeon at the Beth Israel Deaconess Medical Center, Harvard Medical School. He is also a founder of Consensus Pharmaceuticals and Merrimack Pharmaceuticals. Dr. Yaffe co-founded The DNA Repair Company in 2004 and serves as Chairman of Scientific Advisory Board at the company. He also serves as Member of Scientific Advisory Board of Merrimack Pharmaceuticals, Inc. and Boston Biomedical Research Institute, Inc. He completed a residency in General Surgery, a Fellowship in Surgical Critical Care, Burns and Trauma at Harvard Medical School, and post-doctoral training in Signal Transduction with Lew Cantley in Cell Biology at Harvard. He received his B.S. degree in Materials Science and Engineering at Cornell University, and his M.D. in 1989 and Ph.D. degree in 1987 from Case Western Reserve University in Biophysical Chemistry.

ICHO President's Symposia Lecturers

Thursday, April 14, 2016, 1:30pm - 3:30pm
La Salle A

Christopher H. Contag, PhD
"Dynamic assessment of heat shock response and thermotolerance are enabled by use of novel reporter genes"
Stanford University, Stanford, California, USA

Dr. Contag, is a Professor in the Departments of Pediatrics, Radiology and Microbiology & Immunology at Stanford University, and a member of BioX Faculty for interdisciplinary sciences, and Immunology Faculty.

Dr. Contag received his B.S. in Biology from the University of Minnesota, St. Paul in 1982. He received his Ph.D. in Microbiology from the University of Minnesota, Minneapolis in 1988 where he did his dissertation research under the direction of Professors Ashley Haase and Peter Plagemann on the topic of viral infections of the central nervous system. He was a postdoctoral fellow at Stanford University from 1990-1994 in the Department of Microbiology where he studied mother-to-infant transmission of HIV, and then joined the faculty in Pediatrics at Stanford in 1995 with a joint appointment in Microbiology and Immunology and a courtesy appointment in Radiology.

Dr. Contag is the Associate Chief of Neonatal and Developmental Medicine, director of Stanford's Center for Innovation in In Vivo Imaging (SCI3) and co-director of the Molecular Imaging Program at Stanford (MIPS). Dr. Contag is a pioneer in the field of molecular imaging and is developing imaging approaches aimed at revealing molecular processes in living subjects, including humans, and advancing therapeutic strategies through imaging. His laboratory develops macroscopic and microscopic optical imaging tools and uses imaging to assess tissue

responses to stress, reveal immune cell migration patterns, understand stem cell biology and advance biological therapies. He is a founding member, and a past president of the Society for Molecular Imaging, and for his fundamental contributions in imaging, is a recipient of the Achievement Award from the Society for the Molecular Imaging. Dr. Contag is a Fellow of the World Molecular Imaging Society (WMIS) and currently President Elect of WMIS.

The research mission of the Contag laboratory is to develop and use noninvasive imaging tools that can simultaneously reveal the nuances of biological processes and provide an overall picture of disease states for the purpose of developing and refining novel interventions. These imaging tools are sensitive and image over a range of scales from micro- to macroscopic, and are well-suited for the in vivo study of cellular and molecular biology. For the purpose of studying tumor biology in vivo, the Contag group is developing, and using, advanced microscopic tools with the aims of detecting and studying cancer at high resolution in vivo. These approaches use micro-optics to develop miniaturized cofocal microscopes and Raman endoscopes that can reach inside the body to interrogate disease states. This is enabling point-of-care microscopy that is changing the diagnostic paradigm from biopsy and histopathology to in vivo pathology. The opportunity to study tumor margins with arrays of microscopes will enable improved tumor detection and guided resections.

ICHO President's Symposia Lecturers

Thursday, April 14, 2016, 1:30pm - 3:30pm
La Salle A

Silvia C. Formenti, MD
"CONVERGING HYPERTHERMIA AND IONIZING RADIATION (IR) TO CONVERT THE TUMOR INTO AN IN SITU VACCINE"
New York Presbyterian/Weill Cornell Medicine,
New York, NY, USA

Silvia C. Formenti, MD, is professor and chairman of the department of radiation oncology at the New York University School of Medicine in New York City. Before joining the NYU faculty in 2000, Dr. Formenti was a tenured associate professor of both Radiation Oncology and Medicine at the University of California School of Medicine in Los Angeles.

Dr. Formenti was born in Milan, Italy, and attended medical school at the Universita degli Studi di Milano. She completed residencies in internal medicine, medical oncology radiology and radiation oncology in Milan, before coming to the United States, where she completed an internship in general medicine and residency in radiation oncology before joining the faculty at USC.

Dr. Formenti has been the principal investigator in many important studies, and has recently received multi-year peer-reviewed grants from the American Cancer Society and the Breast Cancer Research Foundation. Her extensive research interests include developing a new model for the treatment of locally advanced breast cancer by assessing the molecular characteristics of tumors before starting treatment; and studying novel treatment regimens including hormonal treatment, chemotherapy, and radiation.

ICHO President's Symposia Lecturers

Thursday, April 14, 2016, 1:30pm - 3:30pm
La Salle A

Bradford Wood, MD
"Integration of functional imaging with interventional oncology: Molecular Interventions"
Center for Interventional Oncology, National Cancer Institute & Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA

Bradford Wood, MD, is Director of the NIH Center for Interventional Oncology, Chief of Interventional Radiology, and a Senior Investigator with Tenure at NIH. He earned both his undergraduate and graduate degrees from The University of Virginia, then completed an Internship in Internal Medicine, followed by Residency in Diagnostic Radiology at Georgetown University, where he was Chief Resident. He then went on to do double fellowships at Massachusetts General Hospital at Harvard in Abdominal Imaging and Intervention and Vascular & Interventional Radiology, and stayed on staff at Massachusetts General Hospital / Harvard after training, and is board-certified in Vascular and Interventional Radiology as well as Diagnostic Radiology.

Dr. Wood has practiced Interventional Radiology at NIH since 1998, when he was recruited from Harvard / Massachusetts General Hospital. He directed the Interventional Radiology Research Lab from 2004 to present, and was Acting Chief of Radiology - Science and Research and Acting Director of the Molecular Imaging Lab from 2006 to 2008. He holds appointments in several NIH institutes, including the NIH Clinical Center and the National Cancer Institute, Urological Oncology Branch, and is credentialed in surgery and radiology. He has received both the Clinical Center Director's Award and the NIH Director's Award, and has published widely in the field of Interventional Radiology and the emerging discipline in Interventional Oncology.

He directs a multidisciplinary team of scientists, students, research nurses, biomedical engineers, computer scientists, chemists, technologists, and physician-scientists within a collaborative environment focused on first in human clinical translational research and development with academic, industry, and government components.

His achievements include All-American in Lacrosse, multiple patents in the field, and pioneering several technologies from the bench to the patient, now in widespread use, including heat deployed chemotherapy combined with thermal ablation for liver cancer, “medical GPS” electromagnetic (EM) tracking for needle-based procedures like biopsy and thermal ablation, and smart needles and devices for minimally invasive, multi-modality, image-guided procedures.

He postulated and implemented bench to bedside Phase I trials of radiofrequency ablation for liver tumors, augmented with heat deployed chemotherapy (heat sensitive liposomal doxorubicin), which is currently post Phase III for hepatocellular carcinoma.

He was among the first physicians to perform radiofrequency ablation for kidney and liver tumors in humans in the mid-1990's, to use ablation devices plus heat-deployed drugs for liver tumors, to guide ablation and biopsy with "GPS-enabled" devices, to combine MRI and ultrasound for fusion guided prostate biopsy, "Medical GPS" fusion-guided ablation and biopsy, and RF ablation for patients with pheochromocytoma, lymphoma, adrenocortical carcinoma, liver abscess, chordoma, and intractable hematuria.

In the 2000's, NIH teams also deployed percutaneous methods for isolated liver perfusion (Chemosaturation) for regional liver therapy. NIH teams have performed over 12,000 needle procedures in over 850 patients with the tracking / fusion technology.

Translational research interests include fusion and navigation tools, minimally-invasive & image-guided tumor ablation tools and treatment planning, drug + device combination therapies, heat deployed nanoparticles activated with needles or ultrasound GPS-enabled medical and surgical devices, image-able drugs (drug eluting beads and liposomes), image-guided robotics, and HIFU for non-invasive ablation or "drug paint-brushing" of chemotherapy.

He is actively involved in the Society of Interventional Radiology and the Radiological Society of North America, and manages numerous government-academic-industry partnerships. He serves on the editorial boards of Interventional Oncology and the Journal of Therapeutic Ultrasound, is on the Board of Directors of the Academy of Radiology Research, and has close collaborations

with Duke University, Johns Hopkins University, Harvard / Massachusetts General Hospital, Georgetown University Medical Center, Utrecht Medical Center, Eindhoven University of Technology, Children's National Medical Center, and Innsbruck Medical University. Dr. Wood has been a visiting professor and invited faculty at many institutions around the world.

ICHO President's Symposia Lecturers

Thursday, April 14, 2016, 1:30pm - 3:30pm
La Salle A

Arlene Leonie Oei, MSc
"How hyperthermia works. How can we make hyperthermia work better?"
Department of Radiation Oncology, AMC, Amsterdam, The Netherlands

Arlene Leonie Oei, MSc. received her Bachelor degree in Biomedical Sciences at the Free University of Brussels (VUB) in 2011 and obtained her Master degree in Biomedical Sciences at the Radboud University Nijmegen in 2013. During her graduation project, performed at the Laboratory for Experimental Oncology and Radiobiology (LEXOR), Department of Radiation Oncology at the Academic Medical Center (AMC) in Amsterdam, Arlene studied the effect of the combinational treatment of hyperthermia, radiotherapy, cisplatin and PARP1-inhibitors. This aroused her interest in hyperthermia and she continued her work as a PhD student at the AMC. Her main research interest is to unravel the underlying mechanisms how hyperthermia and other agents sensitize tumor cells to radiotherapy. Furthermore, she is investigating the optimal treatment scheme for the combinational treatment of hyperthermia and radiotherapy. Her work has resulted in publications on the impact of hyperthermia on DNA repair pathways and HPV-positive cervical cancer cell lines. Arlene has been a recipient of several awards, such as the Best Poster Award at the OOA retreat in Renesse (2013), the Best Poster Award at the 40th Annual Meeting of the ERRS in Dublin (2013), the New Investigator Travel Award at the 31st Annual Meeting of the STM meeting in Minneapolis (2014) and the Young Investigator Award at the 30th Annual Meeting of the ESHO in Zürich (2015) and the Klaas Breur Travel Grant at the Spring Meeting of the NVRB in Utrecht (2015).

STM 26th J. Eugene Robinson Award & Lecture

Opening General Session
Tuesday, April 12, 2016, 3:00pm - 6:00pm
La Salle A

Zeljko Vujaskovic, MD, PhD
"The Re-Emerging Role of Thermal Therapy in Cancer Treatment"
Professor and Director
Division of Translational Radiation Sciences
Department of Radiation Oncology
University of Maryland Baltimore

Dr. Zeljko Vujaskovic is a seasoned radiation oncologist with internationally recognized expertise in the treatment of genitourinary malignancies, radiation-induced normal tissue injury, and hyperthermia cancer treatment. Dr. Vujaskovic earned his medical degree from the University of Zagreb, Croatia, in 1985, and his doctorate in radiation biology from Colorado State University in 1994. He began his academic career as an assistant professor in the Departments of Radiotherapy and Clinical Radiobiology at the University of Gröningen School of Medicine in The Netherlands. In 1999, Dr. Vujaskovic joined the Department of Radiation Oncology at Duke University where he rose through the ranks from Assistant to full Professor.

As a dedicated physician, Dr. Vujaskovic has led the way in optimizing cancer patient care since the beginning of his career. Since 1992, Dr. Vujaskovic has been at the forefront of combining hyperthermia treatment with radiation and/or chemotherapy for patients with chest wall recurrent breast cancer, bladder cancer, melanoma, sarcoma, and head and neck tumors. He served as co-Principal Investigator on an NIH funded hyperthermia program project grant and served as the Director of the Clinical Hyperthermia Program. One of Dr. Vujaskovic's important clinical contributions was in the field of multimodality treatment of soft tissue sarcoma. Dr. Vujaskovic led the Duke clinical team as the only US participating site in a multicenter Phase III

trial establishing a new multimodality treatment regimen for high-risk soft tissue sarcoma, the results of which were published in the world's leading medical journal, Lancet Oncology.

Dr. Vujaskovic's productivity in driving the field of hyperthermia forward has continued at the University of Maryland School of Medicine, where he relocated in 2012 to establish the new Division of Translational Radiation Sciences within the Department of Radiation Oncology. There, Dr. Vujaskovic created one of the largest clinical thermal therapy services in the United States. He has recently assumed leadership of the Maryland Proton Alliance, a joint effort between the School of Medicine and the newly opened Maryland Proton Treatment Center in Baltimore, where, among other research initiatives, he plans to explore synergies between proton beam therapy and thermal therapy. This significant, first-of-its-kind multimodality approach has the potential to open a new avenue for improving tumor control and overall survival.

For more than 30 years, Dr. Vujaskovic's career has been defined by transdisciplinary research that bridges the gap between basic science and clinical research to ultimately improve outcomes and long-term quality of life among cancer patients. As a testimony of his exceptional contributions to cancer research and clinical practice, Dr. Vujaskovic was awarded the 2009 R. Wayne Rundles Award for Excellence in Cancer Research. His impact on the field was recognized by his peers, who elected Dr. Vujaskovic to serve as medical councilor for the Society of Thermal Medicine from 2006-2010. In 2010, he was elected to serve as President of the Society for Thermal Medicine for 2011.

During his career, Dr. Vujaskovic has published more than 150 articles and book chapters on radiation therapy, radiation normal tissue injury, and hyperthermia. As a result of these important contributions, Dr. Vujaskovic is recognized as a leading national and international expert in radiotherapy/ hyperthermia cancer treatment.

ESHO/BSD Award & Lecture

Opening General Session
Tuesday, April 12, 2016, 3:00pm - 6:00pm
La Salle A

Stephan Bodis, Prof. Dr. med.
"Hyperthermic Radiation Oncology 2020: Evidence, Cure, Care, Visions"
Canton Hospitals Aarau (KSA) and Baden (KSB), University Hospital Zurich (USZ)

Born in 1958 in Basel, Switzerland, Dr. Bodis received his medical education at University of Fribourg and the Medical School of the University of Basel (1978-1984).

His Residencies in Internal Medicine were at the Canton Hospital Baden (1985 – 1987) and University Hospital Zurich (1987 – 1989), followed by a Clinical and Research Fellowship in the Departments of Hematology/Oncology and Molecular Pharmacology, Institute Gustave Roussy, Villejuif, Paris, France (1989-1991). He worked as a resident and obtained US Board Certification in Radiation Oncology at the Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA, USA (1991 – 1995), undertaking a Research Fellowship at the Dana Farber Cancer Institute and the Massachusetts Institute of Technology Cancer Research Center in addition.

Stephan Bodis served briefly as an attending physician in Radiation Oncology at Brigham and Women's Hospital in Boston before returning to Switzerland as an attending physician in the department of Radiation Oncology at University Hospital Zurich. Currently, Stephan Bodis is the Director of the Radiation Oncology Centers Aarau-Baden (2003 – present). He is also an Associate Physician in the Department of Radiation Oncology at the University Hospital Zurich (2012 – present).

In 1998 he was appointed Assistant Professor at the University of Zurich Medical School and was promoted to Full Professor in 2012.

Stephan Bodis' work concerns clinical aspects of molecular radiobiology, the application of photon and proton radiotherapy and the combination of hyperthermia with radiotherapy in the treatment of various cancers. He is a member of numerous national and international cancer organisations and international cancer congress organisations (e.g. Wolfsberg Meeting Series).

ASHO Award & Lecture

Opening General Session
Tuesday, April 12, 2016, 3:00pm - 6:00pm
La Salle A

Hideki Matsumoto, PhD
"Nitric oxide-mediated bystander responses induced by physical stress protect cells against its damage"
Department of Experimental Radiology & Health Physics, Faculty of Medical Science, University of Fukui, Japan

Dr. Hideki Matsumoto's research is dedicated to elucidating mechanisms of stress-induced bystander response, which is indirectly evoked in non-stressed cells by the factors excreted from stressed cells, improving efficacy of cancer therapies, especially thermo- and radiotherapies.

Dr. Matsumoto graduated from Ehime University with a BA in Biology, received his MS and PhD degrees from Kobe University in the area of Biochemistry and from Nara Medical University in the area of Radiation Biology, respectively. He initially worked as Assistant Professor of the Department of Anatomy, Nara Medical University (NMU), then moved to the Department of Biology, NMU.

Taking this opportunity, he was starting research in Radiation Biology, especially in p53-dependent cellular response after hyperthermia and irradiation with UV and ionizing radiation under the leadership of Professor Takeo Ohnishi. Afterward, he moved as Associate Professor to the Department of Experimental Radiology and Health Physics (Professor Eiichi Kano), Fukui Medical University (currently Faculty of Medical Sciences, University of Fukui). Here, he was starting research about stress-induced bystander response, then he led to a novel finding, 'stress-induced, nitric oxide-mediated bystander response'. He has over 80 peer-reviewed publications on various topics, such as heat shock proteins, p53, nitric oxide, bystander

response, adaptive response and radio-protective agent, in addition to several invited review articles.

Dr. Matsumoto has actively served the Japanese Society for Thermal Medicine as an auditor and a member of editorial board and Senior Editor for the Journal of Radiation Research since 2005.

Tsudomu Sugahara Award & Lecture

Thursday, April 14, 2016, 5:15pm - 6:15pm
La Salle A

Yoko Harima, MD, PhD
"Randomized clinical trials and predictive cancer related genes in patients with locally advanced cervical cancer for effectiveness of hyperthermia oncology"
Kansai Medical University, Japan

Dr. Yoko Harima's research is investigated a randomized clinical trial and its molecular research in patients with advanced cervical carcinoma treated with radiotherapy or chemo-radiotherapy combined with hyperthermia for a long time to clarify the role of hyperthermia. In addition, Dr. Harima proposed the prediction of advanced cervical carcinoma after thermo-radiotherapy from an aspect of molecular biology by using of the progressed molecular techniques such as microarray analysis for the gene expression after cancer therapies including hyperthermia. Dr. Harima is the pioneer of the scientists which studied hyperthermic oncology from the combination of clinical therapy and molecular biology.

Dr. Harima graduated from Kansai Medical University at Osaka in Japan, and completed a Postdoctoral Fellowship at Kansai Medical University of Radiology. Dr. Harima received her MD and PhD degrees from Kansai Medical University in the areas of Radiology. From November 2000, she was Associate Professor, Department of Radiology of Kansai Medical University. From January 2006, Dr. Harima was Director, Department of Radiology, Takii Hospital of Kansai Medical University. Dr. Harima has actively served the Society for Japanese Thermal Medicine- as a board member and President of the 32nd Japanese Congress of Thermal Medicine (JCTM) in September 4th to 5th 2015.

ICHO New Investigator Travel Award Recipients

$500 travel grants were awarded to New Investigators to encourage participation at the 2016 ICHO. Awards were given based on a competitive evaluation of submitted applications and abstracts by the ICHO Awards Committee.

Matthew Adams
"Development of MR-guided endoluminal ultrasound applicators for thermal ablation of pancreatic cancer: design and evaluations in ex vivo and in vivo porcine studies"
University of California, San Francisco, San Francisco, USA

Bassim Aklan
"Hyperthermia treatment planning: Impact of variation in manual tissue-segmentation on the simulated temperature distribution"
Radiation Oncology, University Hospital Erlangen, Erlangen, Germany

Kathleen Ashcraft
"Enhanced efficacy of radiotherapy by voluntary exercise is dependent on a thermoneutral environment"
Duke University, Durham, North Carolina, USA

Akke Bakker
"Scar tissue is more at risk of developing thermal skin damage in recurrent breast cancer patients treated with reirradiation and hyperthermia"
AMC, Amsterdam, The Netherlands

Sarah Brueningk
"A comprehensive model of hyperthermia and radiotherapy induced cell death"
The Institute of Cancer Research, Sutton, Surrey, UK

Mark Bucsek
"The impact of β-adrenergic signaling on radioresistance and anti-tumor immunity in murine tumor models"
Roswell Park Cancer Institute, Buffalo, New York, USA

ICHO New Investigator Travel Award Recipients

$500 travel grants were awarded to New Investigators to encourage participation at the 2016 ICHO. Awards were given based on a competitive evaluation of submitted applications and abstracts by the ICHO Awards Committee.

--CONTINUED--

Tejan Diwanji
"Multidisciplinary Management Of Unresectable Verrucous Carcinoma Of The Genitals, i.e. Buschke-Lowenstein Tumor, With Combined External Beam Radiation and Hyperthermia: A Case Report"
University of Maryland Medical Center, Baltimore, MD, USA

Kalyani Ektate
"Ultrasound monitoring of tumor temperature and drug delivery with echogenic thermosensitive liposomes"
Oklahoma State University, Stillwater, Oklahoma, USA

Samuel Fahrenholtz
"Laser ablation prediction via global optimization and cross-validation"
Department of Imaging Physics, UT MD Anderson Cancer Center, Houston, Texas, USA

Taylor Ibelli
"Photothermal Ablation of Streptococcus pyogenes and Staphylococcus aureus using Fluorescent Bio-Polymer Nanoparticles"
Wake Forest University, Winston-Salem, North Carolina, USA

Paras Jawaid
"Effects of nanoparticles on the cell killing induced by different physical stressors"
Toyama University, Toyama, Japan

Samir Jenkins
"Photothermal Treatment and Radiosensitization of Breast Cancer Cells using Targeted Polydopamine Coated Gold Nanocages"
University of Arkansas for Medical Sciences, Little Rock, AR, USA

Thomas Longo
"HEAT-TARGETED DRUG DELIVERY USING A NOVEL CONDUCTIVE BLADDER HYPERTHERMIA DEVICE"
Duke University Medical Center, Durham, NC, USA

ICHO New Investigator Travel Award Recipients

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--CONTINUED--

Eleanor McCabe-Lankford
"Near-Infrared Nanoparticle Mediated Hyperthermia In Colorectal Cancer Spheroids: A Tissue Phantom Study"
Wake Forest University School of Medicine, Winston-Salem, NC, USA

Daniel Meeker
"Designing novel antibiotic-loaded, targeted nanoparticles to eradicate Staphylococcus aureus planktonic cultures and biofilms"
University of Arkansas for Medical Sciences, Little Rock, AR, USA

Hendrik Thijmen Mulder
"Optimal path length correction for the Sigma Eye applicator for Hyperthermia Treatment Planning"
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Rupal Parikh
"Extreme Exotherms using Polyprotic Acids with Polyamines for Thermochemical Ablation"
Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Elles Raaijmakers
"An MRI-Compatible Hyperthermia Applicator for Small Animals"
Erasmus MC, Rotterdam, The Netherlands

Mati Ur Rehman
"Cold atmospheric helium plasma (He-CAP) and mild hyperthermia in combination causes enhancement in cell killing mainly via generation of reactive oxygen species"
Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

Stephanie Rice
"External thermal therapy (ETT) as an adjunct to radiation therapy in the treatment of soft tissue sarcoma"
University of Maryland Department of Radiation Oncology, Baltimore, MD, USA

ICHO New Investigator Travel Award Recipients

$500 travel grants were awarded to New Investigators to encourage participation at the 2016 ICHO. Awards were given based on a competitive evaluation of submitted applications and abstracts by the ICHO Awards Committee.

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Dario Rodrigues
"Towards integration of non-invasive temperature measurement with microwave radiometry for improved control of superficial hyperthermia array applicators"
Thomas Jefferson University, Philadelphia, PA, USA

Jan Sebek
"Sensitivity of microwave ablation models to tissue biophysical properties: application to model-based treatment planning"
Kansas State University, Manhattan, Kansas, USA

James Snider, III
"Concurrent Interstitial Thermal Therapy and Interstitial Brachytherapy for Recurrent and Bulky Pelvic Malignancies: A Single Institution Experience"
University of Maryland Medical Center, Baltimore, MD, USA

Frederik Soetaert
"Influence of magnetic nanoparticle location on the survival of SKBR3 cells"
Johns Hopkins University, Baltimore, MD, USA

Stefan Stangl
"Membrane associated Hsp70 as a tumor-specific target structure for theranostic in vivo targeting of a wide variety of malignancies"
Department of Radiation Oncology, Klinikum rechts der Isar, TU München, Munich, Germany

Caspar M. van Leeuwen
"The effect of the time interval between radiotherapy and hyperthermia on treatment outcome in cervical cancer"
Academic Medical Center, Amsterdam, The Netherlands

ICHO New Investigator Travel Award Recipients

$500 travel grants were awarded to New Investigators to encourage participation at the 2016 ICHO. Awards were given based on a competitive evaluation of submitted applications and abstracts by the ICHO Awards Committee.

--CONTINUED—

Joshua VanOsdol

"Targeted intratumoral doxorubicin delivery by ultrasound-imageable low temperature sensitive liposomes and high intensity focused ultrasound mild hyperthermia"
Oklahoma State University, Stillwater, Oklahoma, USA

Chencai Wang
"Heating Efficiency of Colloidal Magnetic Fluids with Nonlinear Loss Properties and Aggregate Formation"
University of California, Los Angeles, Los Angeles, CA, USA

ICHO Educational Session with CME Credits

The Congress will feature an Educational Session organized by R. Jason Stafford, prior to the kickoff of the meeting, which will focus on image-guided thermal ablation will be offered on April 12, 2016 from 8am -3pm. **6 CME credits will be available to participants.**

Image-Guided Tumor Ablation: Fire & Ice – What's hot and what's not

Educational Goals:

Experts in the field of tumor ablation will be outlining current concepts, devices, physical principles and biological rationale for therapy and associated systemic effects.

Upon completion of this Educational Session, Participants should be able to:

1. Identify the major physical principles which underlie ablative technology for cancer therapy
2. Recognize categories of thermal ablation procedures and equipment needed for delivery
3. Identify clinical opportunities in which thermal ablation is resulting in beneficial outcomes
4. Identify immunological and other biological changes associated with clinical benefit of ablative protocols
5. Recognize physical and biological differences between cryo-ablation and ablative technologies that depend upon heat.

Educational Session Schedule and Speakers:

8:00AM - 8:20AM: ***Thermal Ablation in the Clinic - Where are we and where are we headed?*** with David Woodrum

8:20AM - 8:30AM: Questions from audience

8:30 AM - 9:15 AM: ***Biological Concepts in Thermal Biology and Dosimetry for Ablation*** with Robert Griffin

9:15AM - 9:30AM: Questions from audience

ICHO Educational Session with CME Credits

The Congress will feature an Educational Session organized by R. Jason Stafford, prior to the kickoff of the meeting, which will focus on image-guided thermal ablation will be offered on April 12, 2016 from 8am -3pm. **6 CME credits will be available to participants.**

Educational Session Schedule and Speakers (Continued):

9:30 AM - 10:15AM: ***Immune Adjuvant Activity of Radiofrequency Ablation*** with Sharon Evans

10:15AM - 10:30AM: Questions from audience

10:30 AM - COFFEE BREAK

11:00 AM - 11:20AM: ***Physical Mechanisms of Ablation Delivery and Devices*** with R. Jason Stafford

11:20AM - 11:30AM: Questions from Audience

11:30 AM - 11:50AM: ***Overview of Clinical Cryoablation*** with Aradhana Venkatesan

11:50AM - 12:00PM: Questions from Audience

12:00 PM - Lunch - Box lunch as part of registration or on own

1:00PM - 1:45PM: ***Advances and Opportunities in Radiofrequency & Microwave Ablation*** with Muneeb Ahmed

1:45PM - 2:00PM: Questions from audience

2:00PM - 2:20PM: ***Clinical Applications of Laser Ablation*** with David Woodrum

2:20PM - 2:30PM: Questions from Audience

2:30PM - 2:50PM: ***Progress in High Intensity Ultrasound Ablation*** with Mark Hurwitz

2:50PM - 3:00PM: Questions from audience

3:00PM – Adjourn

ICHO Sponsor & Vendor Presentations

Wednesday April 13th, 1:00pm-1:30pm – Sponsor & Vendor Presentations - *La Salle A*

- *The New Universal*, Jason Ellsworth, Pyrexar Medical
- *Clinical Update on Lyso-Thermosensitive Liposomal Doxorubicin (LTLD, ThermoDox®)*, Nicholas Borys, Celsion
- *Focused Ultrasound at the Tipping Point: An update from the Focused Ultrasound Foundation*, Jessica Foley, Focused Ultrasound Foundation
- *The Verasonics Vantage: A programmable ultrasound system for therapy and imaging research & development*, Peter Kaczkowski & Mike Vega, Verasonics
- *Oncotherm Modulated Electro-Hyperthermia (mEHT), Science & Technology at Work*, Mark Elderfield, Teneovita Medical Innovations

Thursday April 14th, 1:00pm-1:30pm – Sponsor & Vendor Presentations - *La Salle A*

- *Sonalleve MR-HIFU, and alternative route to clinical hyperthermia*, Thomas Andreae, Philips Healthcare
- *High Resolution Photoacoustic in vivo Imaging in Preclinical Research*, Nuno Sacadura, FUJIFILM VisualSonics
- *Using water-filtered infrared A for whole-body hyperthermia and superficial hyperthermia*, Stefan Heckel-Reusser, Heckel Medizintechnik GmbH
- *Fiber optic temperature probes; the perfect tool for critical thermal monitoring*, Barry Feldman, FISO Technologies
- *Waters: the science of what's possible*, Sabrina Forni, Waters Corp

ICHO Sponsor & Vendor Presentations

--Continued--

Friday April 15th, 1:00pm-1:30pm – Sponsor & Vendor Presentations - *La Salle A*

- *Enabling the operating room of the future today*, Yeruham Shapira, Insightec
- *Sim4Life – Device Design, Treatment Planning and Optimization using Patient-Specific Simulations*, Wolfgang Wiedemair, ZurichMedTech
- *Novel Application: Using Image Guided Focal Irradiation in Combination with Hyperthermia and Ultrasound in Preclinical Models*, Carolyn Seitz, Xstrahl Life Sciences
- *Oncothermia: Where are we now?* Oliver Szasz, Oncotherm GmbH & Hospicare Co Ltd

Thank You Again to our Sponsors!

ICHO Refresher Courses

Refresher Course: Tumor Immunology
"Cancer Immunology & Immunotherapy: The heat is on!"
Elizabeth A. Repasky, PhD
Roswell Park Cancer Institute, Buffalo, NY, USA

Wednesday, April 13, 2016, 7:15am - 8:00am
Pelican I/II (3rd floor)

Refresher Course: 20 Years of Thermal Ablation: Progress, Challenges, and Opportunities
"Clinical Applications of Laser Ablation"
David Woodrum, MD, PhD
Mayo Clinic, Rochester, MN, USA

Wednesday, April 13, 2016, 7:15am - 8:00am
Melpomene

Refresher Course: Novel Drug Delivery Approach
"Thermosensitive Nanotechnologies for Drug Delivery: Basic Principles and New Directions"
Christine Allen, PhD
University of Toronto, Toronto, Canada

Thursday, April 14, 2016, 7:15am - 8:00am
Pelican I/II (3rd floor)

ICHO Refresher Courses

Refresher Course: Clinical Hyperthermia Trials

"An overview of the clinical trials in hyperthermia: Do we have the evidence?"

Dr. Niloy Ranjan Datta

Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland

Thursday, April 14, 2016, 7:15am - 8:00am

Melpomene

Refresher Course: Cryotherapy Overview

"Challenges and opportunities in application of thermal ablative therapies"

John C. Bischof, PhD

University of Minnesota, Minneapolis, USA

Friday, April 15, 2016, 7:15am - 8:00am

Pelican I/II (3rd floor)

Refresher Course: Evolving Technology for Superficial and Deep Hyperthermia

"EVOLVING TECHNOLOGY FOR SUPERFICIAL AND DEEP HYPERTHERMIA"

Paul Stauffer, PhD

Thomas Jefferson University, USA

Friday, April 15, 2016, 7:15am - 8:00am

Melpomene

Pyrexar Medical will offer its own "**Pyrexar Day**" at the event location, offering a collection of presentations including a brand new product announcement. See the schedule below, plus some added details to help schedule your time.

9:30am - 10:15am: Meet and Greet - Refreshments

10:15am - 11:00am: Exploration of BSD-2000 System Applied to Clinical Treatment of Tumors – *Dr. Sun Jinghua, Associate Professor, 2nd Affiliated Hospital of Dalian Medical University*

11:00am - 11:45am: Pyrexar New Product Prototype Review - *Gerard Van Rhoon, PhD., Erasmus Hospital, Netherlands*

11:45am - 12:45pm: Capacitive vs Phased Array Hyperthermia - *Paul Turner, CTO Pyrexar Medical*

12:45pm - 1:30pm: New Product Announcement & Presentation – *Jason Ellsworth, VP Pyrexar Medical*

1:30pm – 2:15pm: Hyperthermia Adjunct to Chemotherapy Sarcoma Study - *Dr. Rolf Issels, Ludwig-Maximilians-University of Munich*

2:15pm – 3:00pm: Using Chemotherapy plus Hyperthermia for Advanced Liver Cancer - *Xiao Shaowen, Associate Chief Physician. Beijing University*

3:00pm – 3:45pm: Proton Therapy and MR-Guided Deep Regional Hyperthermia - *Dr. Zeljko Vujaskovic, University of Maryland Medical Center*

3:45pm – 4:30pm: Quality Assurance of MR-Guided Deep Regional Hyperthermia in Children with Cancer – *Dr. Ruediger Wessalowski Heinrich-Heine University Duesseldorf, Germany*

4:30pm – 5:15pm: Hyperthermia and Pancreatic Cancer; Adjunct to Radiation, Chemotherapy or Both – *Dr. Curt Heese, Cancer Treatment Centers of America, Philadelphia*

5:15pm - 6:00pm: Concepts For Future Deep Phased Array Systems - *Paul Turner, CTO Pyrexar Medical*

This event is open to all Conference Attendees at no additional charge. The event schedule above may change.

Monday, April 11, 2016

STM Council Meeting
8:00am - 10:00am **Pelican I**

Pyrexar User's Meeting
9:30am - 12:00pm **Frenchman I**

STM 2017 Meeting Planning Committee
10:00am - 12:00pm **Fulton Room**

ASHO Council Meeting
11:00am - 12:00pm **Acadian I**

Buffet Luncheon for Committee Members
12:00pm - 1:00pm **Poydras**

Lunch for Pyrexar User's Group
12:00pm - 1:00pm **Frenchman I**

IAHO Council Meeting
1:00pm - 2:00pm **Pelican I**

STM Finance Committee Meeting
2:30pm - 4:00pm **Acadian I**

Pyrexar User's Meeting
1:00pm - 5:30pm **Frenchman I**

International Journal of Hyperthermia Editorial Board Meeting
4:00pm - 6:00pm **Acadian I**

Tuesday, April 12, 2016

Registration

8:00am - 9:00pm La Salle C Foyer

Exhibit Hall and Poster Set-up

8:00am - 5:00pm Le Salon (pre-function to La Salle A/B/C)

ESHO Council Meeting

8:00am - 12:00pm Acadian I

Educational Session (6 CME credits)

8:00am - 3:00pm Pelican I

Image-Guided Tumor Ablation: Fire & Ice – What's hot and what's not

An additional registration fee of 75USD is required to participate. Breakfast and lunch will be provided.

FACULTY:
David Woodrum
Robert Griffin
Sharon Evans
R. Jason Stafford
Aradhana M Venkatesan
Muneeb Ahmed
Mark Hurwitz

Opening General Session

3:00pm - 6:00pm La Salle A

STM Robinson Award – Dr. Zeljko Vujaskovic - *The Re-Emarging Role of Thermal Therapy in Cancer Treatment*

ESHO/BSD Award Lecture – Prof. Dr. med. Stephan Bodis - *Hyperthermic Radiation Oncology 2020: Evidence, Cure, Care, Visions*

ASHO Award - Dr. Hideki Matsumoto - *Nitric oxide-mediated bystander responses induced by physical stress protect cells against its damage*

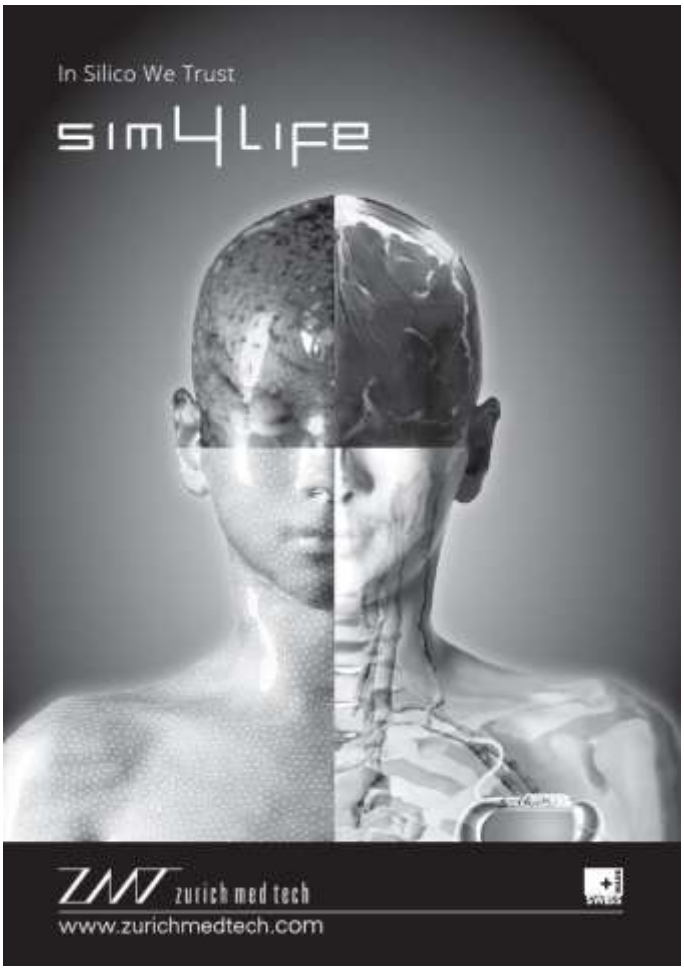
TUE 1 Nitric oxide-mediated bystander responses induced by physical stress protect cells against its damage

Hideki Matsumoto
Department of Experimental Radiology & Health Physics, Faculty of Medical Science, University of Fukui, Eiheiji, Fukui, Japan

Opening Reception

6:00pm - 9:00pm Frenchman Ballroom

with Jazz Sextet - Louis Ford & His New Orleans Jazz Flairs



Wednesday, April 13, 2016

Registration

6:30am - 6:30pm **La Salle C Foyer**

Speaker Ready Room - Available all day

Acadian I

Breakfast Buffet

6:45am - 8:15am **La Salle A**

Posters

7:00am - 5:00pm **Le Salon & LaSalle BC**

Exhibits

7:00am - 5:00pm **Le Salon & LaSalle BC**

Refresher Course: Tumor Immunology

7:15am - 8:00am **Pelican I/II (3rd floor)**

Speaker: Elizabeth Repasky

WED 1 Cancer Immunology & Immunotherapy: The heat is on!
Elizabeth A. Repasky
Roswell Park Cancer Institute, Buffalo, NY, USA

Refresher Course: 20 Years of Thermal Ablation: Progress, Challenges, Opportunities

7:15am - 8:00am **Melpomene**

WED 2 Clinical Applications of Laser Ablation
David Woodrum
Mayo Clinic, Rochester, MN, USA

Plenary Session - Clinical Applications of Thermal Ablation

8:15am - 9:00am **La Salle A**

WED 3 Interventional Oncology: the Fourth Arm of Cancer Care
Damian Dupuy
Rhode Island Hospital Brown University, Providence, RI, USA

Thermal Ablation

9:15am - 11:45am La Salle A Chair: Nahum Goldberg

INVITED SPEAKERS:

WED 4 Dr. Chris Brace: Overview of the various cutting edge ablative technologies including radiofrequency and microwave.

Prof. S. Nahum Goldberg: How thermal ablation can be combined with a host of adjuvant therapies to essentially potentiate improved tumor destruction.

Dr. Muneeb Ahmed: Recent emergence of data describing potential systemic effects of our focal tumor ablation therapies.

Thermal Ablation Session

S. Nahum Goldberg[1,2], Chris Brace[3], Muneeb Ahmed[2]

[1]Hadassah Hebrew University Medical Center, Jerusalem, Israel, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]University of Wisconsin, Madison, WI, USA

PROFFERERD PAPERS:

WED 5 The thermo-enhanced effect of transferrin as a thermosensitizer in the cancer treatment with the radiofrequency-induced hyperthermia

Seong-Tshool Hong

Department of Biomedical Sciences and Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Chonbuk, Republic of Korea

WED 6 Extreme Exotherms using Polyprotic Acids with Polyamines for Thermochemical Ablation

Rupal Parikh[1], Erik Cressman[2]

[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA

WED 7 Photothermal Treatment and Radiosensitization of Breast Cancer Cells using Targeted Polydopamine Coated Gold Nanocages

Samir Jenkins[1], Dmitry Nedosekin[1], Vladimir Zharov[1], Ruud Dings[1], Jingyi Chen[2], Robert Griffin[1]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

WED 8 Hyperchemical ablation: exothermic neutralization of organic amines with dichloroacetic acid.

Erik Cressman[1], Jonathan Partridge[1]

[1]MD Anderson Cancer Center, Houston, TX, USA, [2]University of Texas Austin, Austin, TX, USA

WED 9 Computer simulation of a clinically available microwave ablation system and comparison to infrared imaging data of ex vivo tissue studies
Garron Deshazer[1], Punit Prakash[2], Derek Merck[1], Dieter Haemmerich[3]
[1]Rhode Island Hospital, Providence, RI, USA, [2]Kansas State University, Manhattan, KS, USA, [3]Medical University of South Carolina, Charleston, SC, USA

WED 10 Nanodrug Combined with Ultrasound Hyperthermia and/or Thermal Ablation for Tumor Treatment
Li-Chen Chiu[1,2], Sheng-Kai Wu[1], Gin-Shin Chen[2], Win-Li Lin[1,2]
[1]National Taiwan University, Taipei City, Taiwan, [2]National Health Research Institutes, Miaoli Country, Taiwan

WED 11 Laser ablation prediction via global optimization and cross-validation
Samuel Fahrenholtz[1], Reza Madankan[1], Anil Shetty[2], Shabbar Danish[3], John D. Hazle[1], R. Jason Stafford[1], David Fuentes[1]
[1]Department of Imaging Physics, UT MD Anderson Cancer Center, Houston, Texas, USA, [2]Medtronic, Inc., Minneapolis, Minnesota, USA, [3]Department of Neurosurgery, Robert Wood Johnson Hospital, New Brunswick, New Jersey, USA

Nanotechnology – Ferro Fluids

9:15am - 11:45am Pelican I/II (3rd floor) Chair: Robert Ivkov & John Bischof

INVITED SPEAKERS:

WED 12 Multifunctional applications of near-infrared fluorescent magneto-albumin nanocarriers for cancer hyperthermia
Nicholas Zufelato, Gustavo Capistrano, Sonia Santos, Lorena Gomes, Ailton Sousa, Relton Oliveira, Eliana Lima, Elisangela Silveira-Lacerda, Andris Bakuzis
Federal University of Goias, Goiania, Goias, Brazil

WED 13 Hypofractionated Radiation-Magnetic Nanoparticle Hyperthermia-Immunotherapy Treatment of Spontaneous Canine Tumors
P. Jack Hoopes, David Gladstone, Alicia Petryk, James Petryk, Rendall Strawbridge, Susan Kane, Karen Moodie, Steven Fiering
Dartmouth College, Hanover, NH, USA

WED 14 X-ray guidance for magnetic hyperthermia of liver cancer: bench-to-bedside
Eleni Liapi[1], Anilchandra Attaluri[1,2], Sahar Mirpour[1], Robert Ivkov[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Rowan University, Glassboro, NJ, USA

PROFERRED PAPERS:

WED 15 Assess the effects and mechanisms of the combination therapy: heat therapy (HT) and external-beam radiotherapy (RT)
Shu-Han Yu[1], Jackie Stewart[1], Preethi Korangath[1], Charles G. Drake[3,4], Angelo M. De

Marzo[2,3], Robert Ivkov[1]
[1]Dept of Radiation Oncology, Johns Hopkins University, Baltimore, MD, USA, [2]Department of Pathology, Johns Hopkins University, Baltimore, MD, USA, [3]Department of Urology, Johns Hopkins University, Baltimore, MD, USA, [4]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

WED 16 Effects of magnetic nanoparticle-induced hyperthermia on DNA damage signaling
James Barnett, Anirudh Sharma, Robert Ivkov, Fred Bunz
The Johns Hopkins University School of Medicine, Baltimore, MD, USA

WED 17 Cumulative effect of thermal dose to total tumor regression in Sarcoma 180 murine model using magnetic nanoparticle hyperthermia at low field amplitude
Harley Rodrigues, Francyelli Mello, Gustavo Capistrano, Wanessa Carvalho, Nicholas Zufelato, Elisangela Silveira-Lacerda, Andris Bakuzis
Federal University of Goias, Goiania, Goias, Brazil

WED 18 Influence of magnetic nanoparticle location on the survival of SKBR3 cells
Frederik Soetaert[1,2], Mohammad Hedayati[1], Anirudh Sharma[1], Caleb Akers[3], Sri Kamal Kandala[1], Jackie Stewart[1], Haoming Zhou[1], Robert Ivkov[1]
[1]Johns Hopkins University, Baltimore, MD, USA, [2]Ghent University, Ghent, Belgium, [3]DePauw University, Greencastle, IN, USA

WED 19 In vivo Quantification of Iron Oxide Nanoparticle Biodistribution using Positive T1 Contrast with ex vivo Heating
Hattie Ring[1], Navid Manuchehrabadi[1], Jinjin Zhang[1], Katie Hurley[1], Qi Shao[1], Cathy Carlson[1], Djaudat Idiyatullin[1], Jack Hoopes[2], Christy Haynes[1], John Bischof[1], Michael Garwood[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Dartmouth, Hanover, NH, USA

WED 20 Microwave hyperthermia applicators - Optimization of SAR and temperature distribution by aid of ferromagnetic nanoparticles
Jan Vrba[1], Luca Vannucci[3], Jan Vrba[2], David Vrba[2], Ondrej Fiser[1], Ilja Merunka[1]
[1]Czech Technical University, Dept. of EM Field, Prague, Czech Republic, [2]Czech Technical University, Dept. of Biomedical Technique, Kladno, Czech Republic, [3]Czech Academy of Sciences, Institute of Microbiology, Prague, Czech Republic

WED 21 Magnetostructural characterization of iron oxide nanoparticles for cancer hyperthermia applications
Anirudh Sharma[1], Frederik Soetaert[1], Sri Kamal Kandala[1], Cindi Dennis[2], Robert Ivkov[1]
[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [2]Materials Science and Engineering Laboratory, NIST, Gaithersburg, Maryland, USA

WED 22 Nanoparticles and their targeting: A study in preclinical model of HER2+ breast cancer

Preethi Korangath[1], James Barnett[1], Shu-han Yu[1], Anirudh Sharma[1], Jacqueline Stewart[1], Sri Kamal Kandala[1,3], Saraswati Sukumar[2], Robert Ivkov[1]

[1]Department of Radiation Oncology, Johns Hopkins University, Baltimore, Maryland, USA, [2]Department of Oncology, Johns Hopkins University, Baltimore, Maryland, USA, [3]Department of Mechanical Engineering, Johns Hopkins University, Baltimore, Maryland, USA

Broad Spectrum Immune-Regulatory Activities of Thermal Stress

9:15am - 11:45am Melpomene Chair: Sharon Evans & Gabi Multhoff

INVITED SPEAKERS:

WED 23 Myeloid-derived Suppressor Cells Provide Novel Mechanism of Resistance at Thermally-Sensitive Vascular Checkpoints during Cancer Immunotherapy

Amy Ku, Jason Muhitch, Scott Abrams, Sharon S Evans

Roswell Park Cancer Institute, Buffalo, NY, USA

WED 24 Membrane associated Hsp70 as a tumor-specific target structure for theranostic in vivo targeting of a wide variety of malignancies

Stefan Stangl[1], Wolfgang Sievert[1], Isabel Riederer[1], Vasilis Ntziachristos[2], Florian Greten[3], Gabriele Multhoff[1]

[1]Department of Radiation Oncology, Klinikum rechts der Isar, TU München, Munich, Germany, [2]Helmholtz Zentrum München (IBMI), Munich, Germany, [3]Institute for Tumor Biology and Experimental Therapy, Georg-Speyer-Haus, Frankfurt, Germany, [4]Department of Medicine II, Klinikum rechts der Isar, TU München, Munich, Germany

WED 25 in situ vaccination to treat cancer using plant-derived viral like nanoparticles from compea mosaic virus

Patrick Lizotte[1], Amy Wen[2], Mee Rie Sheen[1], Pakdee Rojanasopondist[1], Nicole Steinmetz[2], Steven Fiering[1]

[1]Geisel School of Medicine at Dartmouth, Lebanon, NH, USA, [2]Case Western Reserve University, Cleveland OH, USA

PROFFERED PAPERS:

WED 26 Magnetic nanoparticle radiation sensitization

Alicia Petryk, Steven Fiering, P. Jack Hoopes

Dartmouth College, Hanover, NH, USA

WED 27 The impact of β-adrenergic signaling on radioresistance and anti-tumor immunity in murine tumor models

Mark Bucsek, Guanxi Qiao, Haichao Liu, Lauren Evans, Cameron MacDonald, Bonnie Hylander, Elizabeth A. Repasky
Roswell Park Cancer Institute, Buffalo, New York, USA

WED 28 Interleukin-6 Induced Acute" Phenotypic Microenvironment Promotes Th1 Anti-Tumor Immunity In Cryo-Thermal Therapy Revealed By Proteomics
Ting Xue[1], Kun Liu[1], Yong Zhou[2], Li Yang[2], Robert Moritz[2], Wei Yan[1], Ping Liu[1], Lisa X. Xu[1]
[1]Shanghai Jiao Tong University, Shanghai, China, [2]Institute for Systems Biology, Seattle, USA

WED 29 Can hypoxia/HIF- driven adenosine accumulation in the tumour microenvironment attenuate anti- tumour immune responses elicited by radio(chemo)therapy and hyperthermia?
Peter Vaupel
University Medical Center, Dept. of Radiooncology and Radiotherapy, Mainz, Germany

WED 30 SHOCKS, STRESSES, AND DRUGS: HURTING OR HELPING HSP90 INHIBITORS IN CANCER CHEMOTHERAPY
Michael Graner
University of Colorado Denver Anschutz Medical Campus, Aurora Colorado, USA

WED 31 Immunological enhancement & long-term remissions in HIV patients receiving only high-level whole body hyperthermia
Milton Yatvin
Reed college, Portland, OR, USA

WED 32 HOW CAN HYPERTHERMIA BE USED TO TREAT PATIENTS WITH LUNG CANCER?
Joan Bull
The University of Texas Medical School at Houston, Houston, TX, USA

Buffet Luncheon

12:00pm - 1:00pm La Salle A

Vendor Presentations

1:00pm - 1:30pm La Salle A

Pediatrics, Pelvic & Sarcoma

1:30pm - 3:30pm La Salle A Chair: Rudiger Wessalowski & Pavel Yarmolenko

WED 33 **INVITED SPEAKERS:**

Mild hyperthermia at temperatures between 41-43°C for chemo- and radiosensitisation in pediatric cancer

Ruediger Wessalowski[1], Eunike Velleuer[1], Oliver Mils[1], Christiane Matuschek[2], Patric Kroepil[3], Mariana Santos[4], Reinhart Willers[5], Ivo Leuschner[6], Uta Dirksen[7], Rolf Issels[8], Ewa Koscielniak[9], Gabriele Calaminus[10]

[1]Clinic of Pediatric Oncology, Hematology and Immunology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, [2]Department of Radiation Therapy and Radiooncology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, [3]nstitute of Diagnostic Radiology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, [4]Department of Pediatric Surgery,Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, [5]Institute of Statistics, Heinrich-Heine-University, Duesseldorf, Germany, [6]Institute of Pediatric Pathology, University of Kiel, Kiel, Germany, [7]Department of Pediatric Hematology and Oncology, University Children's Hospital, Muenster, Germany, [8]Department of Internal Medicine III, Klinikum Grosshadern Medical Centre, Ludwig-Maximilians-University, Munich, Germany, [9]Clinic Pediatric Oncology, Hematology, and Immunology, Olgahospital, Klinikum Stuttgart, Stuttgart, Germany, [10]Department of Pediatric Hematology and Oncology, University Children's Hospital, Bonn, Germany

WED 34 Hyperthermic intraperitoneal chemotherapy (HIPEC) in paediatric sarcomas: An initial phase 2 study

Andrea Hayes-Jordan[1], Holly Green[2], Lianchun Xiao[3], Keith Fournier[1], Winston Huh[4], Cynthia Herzog[4], Joseph Ludwig[5], Mary McAleer[6], Peter Anderson[7]

[1]University of Texas MD Anderson Cancer Center, Department of Surgical Oncology, Houston, Texas, USA, [2]Children's Hospital of Los Angeles, Los Angeles, California, USA, [3]University of Texas MD Anderson Cancer Center, Department of Biostatistics, Houston, Texas, USA, [4]University of Texas MD Anderson Cancer Center, Department of Pediatrics, Houston, Texas, USA, [5]University of Texas MD Anderson Cancer Center, Department of Sarcoma Medical Oncology, Houston, Texas, USA, [6]University of Texas MD Anderson Cancer Center, Department of Radiation Oncology, Houston, Texas, USA, [7]Cleveland Clinic, Department of Pediatric Hematology Oncology and Blood and Marrow Transplantation, Houston, Texas, USA

WED 35 Towards Non-Invasive Treatment of Osteoid Osteoma: State of the Art in Context of Accepted Methods

Karun Sharma[1,3], Pavel Yarmolenko[1], Ari Partanen[2], Haydar Celik[1], Avinash Eranki[1], Viktoriya Beskin[3], Domiciano Santos[4], Janish Patel[4], Matt Oetgen[5], Aerang Kim[6], Peter Kim[1]

[1]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, DC, USA, [2]Clinical Science MR Therapy, Philips,

Andover, MA, USA, [3]Radiology, Children's National Medical Center, Washington, DC, USA, [4]Anesthesiology, Children's National Medical Center, Washington, DC, USA, [5]Orthopedics, Children's National Medical Center, Washington, DC, USA, [6]Oncology, Children's National Medical Center, Washington, DC, USA

PROFERRED PAPERS:

WED 36 Feasibility, Safety, and Efficacy of Osteoid Osteoma Ablation in Children Using MR-guided High Intensity Focused Ultrasound

Pavel Yarmolenko[1], Ari Partanen[2], Haydar Celik[1], Avinash Eranki[1], Viktoriya Beskin[3], Dominiciano Santos[4], Janish Patel[4], Matt Oetgen[5], Aerang Kim[6], Peter Kim[1], Karun Sharma[1,3]

[1]Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, DC, USA, [2]Clinical Science MR Therapy, Philips, Andover, MA, USA, [3]Radiology, Children's National Medical Center, Washington, DC, USA, [4]Anesthesiology, Children's National Medical Center, Washington, DC, USA, [5]Orthopedics, Children's National Medical Center, Washington, DC, USA, [6]Oncology, Children's National Medical Center, Oncology, Children's National Medical Center, USA

WED 37 PROSPECTIVE IMAGING STUDY OF MAGNETIC RESONANCE THERMOMETRY QUALITY IN PEDIATRIC SOLID TUMORS

Theodore Laetsch[1,2], Robert Staruch[3], Korgun Koral[1,2], Rajiv Chopra[1]

[1]UT Southwestern Medical Center, Dallas, TX, USA, [2]Children's Health, Dallas, TX, USA, [3]Philips Research North America, Cambridge, MA, USA

WED 38 External thermal therapy (ETT) as an adjunct to radiation therapy in the treatment of soft tissue sarcoma

Stephanie Rice, Travis Dobbin, Shahed Badiyan, Shifeng Chen, Zeljko Vujaskovic

University of Maryland Department of Radiation Oncology, Baltimore, MD, USA

WED 39 Evaluation of doxorubicin containing phosphatidyldiglycerol ($DPPG_2$) based thermosensitive liposomes for the treatment of spontaneous feline soft tissue sarcomas

Katja Zimmermann[1], Martin Hossann[2], Johannes Hirschberger[1], Karin Troedson[1], Nina Kreutzmann[1], Christina Ratzlaff[1], Silke Baer[1], Michael Peller[3], Moritz Schneider[3], Andreas Brühschwein[4], Andrea Meyer-Lindenberg[4], Gerhard Wess[1], Melanie Wergin[1], Rene Doerfelt[1], Thomas Knoesel[5], Christine Baumgartner[6], Markus Schwaiger[7], Lars Lindner[2]

[1]Clinic of Small Animal Medicine, Centre for Clinical Veterinary Medicine, Ludwig Maximilians University of Munich, Munich, Germany, [2]Department of Internal Medicine III, University Hospital of Munich, Ludwig Maximilians University of Munich, Munich, Germany, [3]Institute for Clinical Radiology, University Hospital of Munich, Ludwig Maximilians University of Munich, Munich, Germany, [4]Clinic of Small Animal Surgery and Reproduction, Centre for Clinical Veterinary Medicine,

Ludwig Maximilians University of Munich, Munich, Germany, [5]Department of Pathology, Ludwig Maximilians University of Munich, Munich, Germany, [6]Center of Preclinical Research,Technical University of Munich, Munich, Germany, [7]Department of Nuclear Medicine, Technical University of Munich, Munich, Germany

WED 40 The effect of the time interval between radiotherapy and hyperthermia on treatment outcome in cervical cancer

Caspar M. van Leeuwen, Arlene L. Oei, Johannes Crezee, Arjan Bel, Nicolaas A.P. Franken, Lukas J.A. Stalpers, H.P. Kok
Academic Medical Center, Amsterdam, The Netherlands

WED 41 Concurrent Interstitial Thermal Therapy and Interstitial Brachytherapy for Recurrent and Bulky Pelvic Malignancies: A Single Institution Experience.

James Snider, III[1], Nasar Onyeuku[1], Tejan Diwanji[1], Jason Molitoris[1], Pranshu Mohindra[2], Pradip Amin[2], Zeljko Vujaskovic[2]
[1]University of Maryland Medical Center, Baltimore, MD, USA, [2]University of Maryland School of Medicine, Baltimore, MD, USA

WED 42 Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervix cancer after irradiation

Sun Young Lee[1], Dong-Hyu Cho[2]
[1]Department of Radiation Oncology, Institute for Medical Sciences, Chonbuk National University Medical School, Jeonju, Jeonbuk, Republic of Korea, Jeonju-si, Jeollabuk-do, Republic of Korea, [2]Department of Obstetrics and Gynecology, Chonbuk National University Hospital-Chonbuk National University Medical School, Jeonju, Republic of Korea, Jeonju-si, Jeollabuk-do, Republic of Korea

Bladder Cancer

1:30pm - 3:30pm **Pelican I/II (3rd floor)** **Chair: Brant Inman & Hideyuki Sakurai**

INVITED SPEAKERS:

WED 43 Review of currently available bladder heating devices

Hans Crezee
Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

WED 44 New hyperthermia technologies applicable to bladder cancer: a focused review.

Brant Inman
Duke University, Durham, NC, USA

WED 45 Current bladder cancer management: where hyperthermia might have an impact.

Thomas Longo, Brant Inman
Duke University Medical Center, Duke University Medical Center, USA

PROFFERED PAPERS:

WED 46 Heat-deployed liposomal doxorubicin for treatment of bladder malignancies
Andrew S. Mikhail[1], William Pritchard[4], Ayele H. Negussie[1], Ari Partanen[1,2], David Woods[1], Sam J. Brancato[3], Juan Esparza-Trujillo[1], Ivane Bakhutashvili[1], John Karanian[4], Piyush K. Agarwal[3], Bradford J. Wood[1]
[1]Center for Interventional Oncology, Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA, [2]Clinical Science MR Therapy, Philips, Andover, MA, USA, [3]Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA, [4]Center for Devices and Radiological Health, Food and Drug Administration, Laural, MD, USA

WED 47 Clinical Validation of a Thermophysical Bladder Model to Improve Hyperthermia Treatment Planning in the Pelvic Region
Gerben Schooneveldt[1], Petra Kok[1], Debby Geijsen[1], Akke Bakker[1], Edmond Balidemaj[1], Jean de la Rosette[2], Maarten Hulshof[1], Theo de Reijke[2], Hans Crezee[1]
[1]Academisch Medisch Centrum, dept. of Radiotherapy, AMSTERDAM, The Netherlands, [2]Academisch Medisch Centrum, dept. of Urology, AMSTERDAM, The Netherlands

WED 48 HEAT-TARGETED DRUG DELIVERY USING A NOVEL CONDUCTIVE BLADDER HYPERTHERMIA DEVICE
Thomas Longo, Ajay Gopalakrishna, Wiguins Etienne, Paolo Maccarini, Brant Inman
Duke University Medical Center, Durham, NC, USA

WED 49 Attenuated XPC expression is not associated with impaired DNA repair in bladder cancer
Joost Boormans, Kishan Naipal, Anja Raams, Geert van Leenders, Roland Kanaar, Dik van Gent
Erasmus MC, Rotterdam, The Netherlands

Advances in Image-Guided Therapeutic Ultrasound

1:30pm - 3:30pm **Melpomene** **Chair: Kim Butts Pauly & Chris Diederich**

INVITED SPEAKERS:

WED 50 Hyperthermia-enhanced targeted drug delivery using magnetic resonance-guided focused ultrasound in a genetic mouse model of pancreatic adenocarcinoma
Joo Ha Hwang
University of Washington, Seattle, WA, USA

WED 51 Combining ultrasound thermal therapy with chemo and immunotherapy

Katherine Ferrara, Matthew Silvestrini, Azadeh Kheirolomoom, Elizabeth Ingham, Lisa Mahakian, Sarah Tam, Josquin Foiret, Samantha Tucci, Neil Hubbard, Alexander Borowsky
University of California, Davis, CA, USA

PROFERRED PAPERS:

WED 52 Focused ultrasound hyperthermia mediated drug delivery using thermosensitive liposomes and visualized with in vivo two-photon microscopy

Marc Santos[1,2], Kullervo Hynynen[1,2], David Goertz[1,2]
[1]Sunnybrook Research Institute, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada

WED 53 Targeted intratumoral doxorubicin delivery by ultrasound-imageable low temperature sensitive liposomes and high intensity focused ultrasound mild hyperthermia

Joshua VanOsdol, Ramasamy Selvarani, Kalyani Ektate, Danny Maples, Jerry Malayer, Ashsih Ranjan
Oklahoma State University, Stillwater, Oklahoma, USA

WED 54 MR-HIFU MILD HYPERTHERMIA FOR LOCALLY RECURRENT RECTAL CANCER: TEMPERATURE MAPPING AND HEATING QUALITY IN FIRST PATIENT

William Chu[1,2], Robert Staruch[3], Samuel Pichardo[2,4], Yuexi Huang[2], Charles Mougenot[5], Matti Tillander[6], Max Köhler[6], Mika Ylihautala[6], Merrylee McGuffin[1], Gregory Czarnota[1,7], Kullervo Hynynen[2,7]
[1]Sunnybrook Odette Cancer Centre, Toronto, ON, Canada, [2]Sunnybrook Research Institute, Toronto, ON, Canada, [3]Philips Research, Cambridge, MA, USA, [4]Thunder Bay Regional Research Institute, Thunder Bay, ON, Canada, [5]Philips Healthcare, Markham, ON, Canada, [6]Philips Healthcare, Vantaa, Finland, [7]Medical Biophysics, University of Toronto, Toronto, ON, Canada

WED 55 COMPARISON OF ULTRASOUND AND MAGNETIC RESONANCE THERMOMETRY FOR GUIDANCE OF HIFU HYPERTHERMIA: PHANTOM STUDIES

Robert Staruch[1,2], Shriram Sethuraman[1], Matthew Lewis[2], Jochen Kruecker[1], Rajiv Chopra[2]
[1]Philips Research North America, Cambridge, MA, USA, [2]UT Southwestern Medical Center, Dallas, TX, USA

WED 56 Targeted antibiotic delivery using temperature-sensitive liposomes and magnetic resonance guided high-intensity focused ultrasound hyperthermia for chronic non-healing wound treatment

Ashish Ranjan[1], Chenchen Bing[2], Joshua VanOsdol[1], Danny Maples[1], Michele Wodzak[2], Joris Nofiele[2], Robert Staruc[3], Akhilesh Ramachandran[1], Jerry Malayer[1], Rajiv Chopra[2]

[1]Oklahoma State University, Stillwater, Oklahoma, USA, [2]University of Texas Southwestern Medical Center, Dallas, Texas, USA, [3]Philips Research, Briarcliff Manor, NY, USA, USA

WED 57 THE EFFECT OF HSP90 INHIBITION ON THERMAL CYTOTOXICITY

Petros Mouratidis, Gail ter Haar
The Institute of Cancer Research, Sutton, London, UK

WED 58 Use of Hyperpolarized C^{13} Imaging for Detecting HIFU-Sensitized Hyperthermic Region in Prostate Cancer

Jessie Lee, Chris Diederich, Vasant Salgaonkar, Robert Bok, Andrew Taylor, John Kurhanewicz
University of California, San Francisco, San Francisco, CA, USA

Breaking Advances in Hyperthermia Clinical Trial Results

3:30pm - 5:00pm La Salle A Chair: Gerard van Rhoon

INVITED SPEAKERS:

WED 59 RADIATION THERAPY COMBINED WITH HYPERTHERMIA OR CISPLATIN FOR LOCALLY ADVANCED CERVICAL CANCER: RESULTS OF THE RANDOMIZED RADCHOC TRIAL.

Ludy CHW Lutgens[1], Elzbieta M Van der Steen-Banasik[7], Jan J Jobsen[2], Peter CM Koper[8], Carien L Creutzberg[3], Hetty A Van den Berg[4], Petronelle B Ottevanger[5], Gerard C Van Rhoon[6], Helena C Van Doorn[6], Ruud Houben[1], Jacoba Van der Zee[6]
[1]Maastricht Radiation Oncology (MAASTRO) clinic, Maastricht, The Netherlands, [2]Medisch Spectrum Twente, Enschede, The Netherlands, [3]Leiden University Medical Center, Leiden, The Netherlands, [4]Catharina Hospital, Eindhoven, The Netherlands, [5]Radboud University Medical Center, Nijmegen, The Netherlands, [6]Erasmus MC, Rotterdam, The Netherlands, [7]Arnhem Radiotherapy Institute, Arnhem, The Netherlands, [8]Medical Center Haaglanden, Den Haag, The Netherlands

WED 60 An open-label, non-randomized, single-institution, phase 2 study, regional deep hyperthermia for salvage treatment of children with refractory or recurrent non-testicular malignant germ-cell tumors.

Ruediger Wessalowski
Clinic of Pediatric Hematology and Oncology, Medical Faculty, Heinrich-Heine University, Duesseldorf, NRW, Germany

WED 61 The European Experience of Regional Hyperthermia Combined With Chemotherapy as First-line Treatment in Soft-Tissue Sarcomas

Rolf D. Issels
University Hospital of the LMU - Campus Grosshadern, Munich, Germany

WED 62 Early Experiences of a Phase I Study of Targeted Delivery of Lyso-Thermosensitive Liposomal Doxorubicin by Focused Ultrasound Hyperthermia to the Liver (TARDOX)

Paul Lyon[1,2], Christophoros Mannaris[1], Michael Gray[1], Daniel Chung[3], Aarti Shah[3], Robert Carlisle[1], Feng Wu[2], Mark Middleton[4], Fergus Gleeson[3], Constantin Coussios[1]
[1]Institute of Biomedical Engineering, University of Oxford, Oxford, UK, [2]Nuffield Department of Surgical Sciences, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, [3]Department of Radiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, [4]Department of Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Poster Session 1 with Wine & Cheese Reception

5:00pm - 6:30pm Le Salon

POS 1 Using a Drug as a Reactant in Multiplexed Thermochemical Ablation: Thermal Profile of Valproic Acid, a Histone Deacetylase Inhibitor, in Reactions with Polyamines Multiplexed Thermochemical Ablation: Use of a Histone Deacetylase Inhibitor with Polyamines

Rupal Parikh[1], Erik Cressman[2]
[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA

POS 2 Anticancer effects of ß–elemene with hyperthermia in lung cancer cells

Zhibing Wu[1,2], Ting Wang[3], Shenglin Ma[1], Zhishuang Zheng[2], Shuhuan Yu[1], Saisai Jing[2], Sumei Chen[2]
[1]Nanjing Medical University Affiliated Hangzhou Hospital(Hangzhou First People's Hospital), Hangzhou,Zhejiang, China, [2]Hangzhou Cancer Hospital, Hangzhou,Zhejiang, China, [3]Yiwu Central Hospital, Yiwu,Zhejiang, China

POS 3 Heating by natural nano-technology

Oliver Szasz
Szent Istvan University, Biotechnics Department, Paty, Hungary

POS 4 Development of resonant cavity applicator system with non-invasive measurement of temperature distributions

Yuya Iseki, Takahiro Saito, Daisuke Anan, Eitaro Miura, Kazuo Kato
Meiji University, Kawasaki/Kanagawa, Japan

POS 5 An algorithm of measuring sub-pixel temperature distributions from ultrasound wave images

Daisuke Anan, Takahiro Saitoh, Eitaro Miura, Yuya Iseki, Kazuo Kato
Meiji University, Kawasaki/Kanagawa, Japan

POS 6 Complete neutralization of available nitrogen atoms in polyamines using dichloroacetic acid improves mass efficiency in thermochemical ablation

Erik Cressman[1], Jonathan Partridge[2]
[1]MD Anderson Cancer Center, Houston, TX, USA, [2]University of Texas Austin, Austin,

TX, USA

POS 7 Air Gap Filler Material for RF Capacitive Heating

Kazuki Kumagae[1], Kazuyuki Saito[2], Koichi Ito[2]

[1]Graduate School of Engineering, Chiba University, Chiba, Japan, [2]Center for Frontier Medical Engineering, Chiba University, Chiba, Japan

POS 8 Automatic evaluation of ablation zone boundary: a tool for quantitative evaluation of ex vivo ablation zone maps and comparison against numerical modelling results

Jan Sebek[1,2], Punit Prakash[1]

[1]Kansas State University, Department of Electrical and Computer Engineering, Manhattan, Kansas, USA, [2]Czech Technical University in Prague, Department of Circuit Theory, Praha 6, Czech Republic

POS 9 Magnetic particle imaging for magnetic hyperthermia treatment: quantitative evaluation of intratumoral magnetic nanoparticle distribution and prediction of therapeutic effect

Kenya Murase, Tomomi Kuboyabu, Isamu Yabata, Akiko Ohki, Marina Aoki, Kazuki Shimada, Yoshimi Inaoka, Natsuo Banura

Osaka University School of Medicine, Suita, Osaka, Japan

POS 10 Development of a system for heat transfer simulation for optimization and treatment planning of magnetic hyperthermia using magnetic particle imaging

Natsuo Banura, Atsushi Mimura, Kohei Nishimoto, Kenya Murase

Osaka University School of Medicine, Suita, Osaka, Japan

POS 11 Quantitative evaluation of tumor response to combination of magnetic hyperthermia treatment and radiation therapy using magnetic particle imaging

Akiko Ohki, Tomomi Kuboyabu, Mikiko Yamawaki, Marina Aoki, Kenya Murase

Osaka University School of Medicine, Suita, Osaka, Japan

POS 12 Quantitative evaluation of tumor early response to magnetic hyperthermia treatment combined with vascular disrupting therapy using a newly-developed method for magnetic particle imaging

Tomomi Kuboyabu, Mikiko Yamawaki, Akiko Ohki, Marina Aoki, Kenya Murase

Osaka University School of Medicine, Suita, Osaka, Japan

POS 13 Does whole thoracic regional hyperthermia increase the occurrence of radiation pneumonitis?

Takayuki Ohguri[1], Katsuya Yahara[1], Kyosuke Tomura[1], Hajime Imada[2], Yukunori Korogi[1]

[1]University od Occupational and Environmental Health, Department of Radiology, Kitakyushu, Japan, [2]Tobata Kyoritsu Hospital, Cancer Therapay Center, Kitakyushu, Japan

POS 14 Investigation of the threshold power density levels of millimeter wave exposures for the corneal damage under the CEM43ºC criterion by computer simulation

Yukihisa Suzuki[1], Masami Kojima[2], Jerdvisanop Chakarothai[3], Kensuke Sasaki[3], Kanako Wake[3], Masao Taki[1], Soichi Watanabe[3], Hiroshi Sasaki[2]
[1]Tokyo Metropolitan University, Tokyo, Japan, [2]Kanazawa Medical University, Ishikawa, Japan, [3]National Institute of Information and Communications Technology, Tokyo, Japan

POS 15 Hyperthermia: a possible adjuvant treatment for medulloblastoma to increase response rate and reduce late toxicity? - A literature review about the vascular characteristics of medulloblastoma -

H.P. Kok[1], H. Dobsicek Trefna[2], I.S.A. de Vries[1], R. Davila Fajardo[1], I.W.E.M. van Dijk[1], B. Lannering[3], K. Blomgren[4], M. Persson[2], J. Crezee[1]
[1]Academic Medical Center, Amsterdam, The Netherlands, [2]Chalmers University of Technology, Gothenburg, Sweden, [3]University of Gothenburg, Gothenburg, Sweden, [4]Karolinska Institutet, Stockholm, Sweden

POS 16 Optimal path length correction for the Sigma Eye applicator for Hyperthermia Treatment Planning

Daniel de Jong, Hendrik Thijmen Mulder, Ali Ameziane, Gerard Cornelis van Rhoon
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

POS 17 Increase in intra-tumor blood flow and sub-tumor temperature in cervix cancer by electro-modulated hyperthermia.

Sun Young Lee[1], Dong-Hyu Cho[2]
[1]Department of Radiation Oncology, Chonbuknational University Hospital-Chonbuk National University Medical School, Jeonju-si, Jeollabuk-do, Republic of Korea, [2]Department of Obstetrics and Gynecology, Chonbuk National University Hospital-Chonbuk National University Medical School, Jeonju-si, Jeollabuk-do, Republic of Korea

POS 18 The influence of a metal stent on the distribution of thermal energy during irreversible electroporation

Jantien Vogel[1], Hester Scheffer[2], Willemien van den Bos[3], Robert Neal II[4], Krijn van Lienden[5], Marc Besselink[1], Martin van Gemert[6], Cees van der Geld[7], John Klaessens[8], Rudolf Verdaasdonk[8]
[1]Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [2]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands, [3]Department of Urology, Academic Medical Center, Amsterdam, The Netherlands, [4]Department of Radiology, the Alfred Hospital, Melbourne, Australia, [5]Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands, [6]Department of Biomedical Engineering and Physics, Academic Medical Center, Amsterdam, The Netherlands, [7]Department of Mechanical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands, [8]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands

POS 19 Optical Microscopy Compatible Hyperthermia Applicator for Liver Tumors in Mice

P. Agnass[1], T.L.M. ten Hagen[2], A.B. Smolders[3], Gerard van Rhoon[1]

[1]Erasmus Medical Center — Daniel den Hoed Cancer Center, Rotterdam, Zuid-Holland, The Netherlands, [2]Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands, [3]Eindhoven University of Technology, Eindhoven, Noord-Brabant, The Netherlands

POS 20 Steering the Deep Regional Hyperthermia to Match the Hyperthermia Target Volume to the High-Dose Planning Target Volume in Helical Tomotherapy for Cervical Cancer –a Proposal and Preliminary Feasibility Test

Yu-Jen Chen[1,2], John Chun-Hao Chen[1], Yuen-Liang Lai[1,2], Meng-Hao Wu[1], Jie Lee[1], Kuo-Wei Lu[1], Hsu-Nien Huang[1], Kun-Yao Dai[1], Yu-Ming Huang[1], Tien-Chi Hou[1], Yi-Shueh Chen[1], Hung-Chi Tai[1], Shih-Hua Liu[1], Kou-Hwa Chang[1]

[1]MacKay Memorial Hospital, Taipei, Taiwan, [2]MacKay Medical College, New Taipei City, Taiwan

POS 21 Photoacoustic Imaging for Spectral Characterization and Thermography of ex vivo Thermochemical Ablation

Rupal Parikh[1,2], Trevor Mitcham[3,4], Richard Bouchard[3], Erik N.K. Cressman[2]

[1]Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA, [3]Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [4]University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences, Houston, TX, USA

POS 22 Preliminary in vitro evaluation of Oncothermia in a normal and a cancerous cell line

Marjorie McDonald[1], Stephanie Corde[1,2], Michael Lerch[1], Anatoly Rozenfeld[1], Moeava Tehei[1], Michael Jackson[1,2]

[1]Centre for Medical Radiaiton Physics, University of Wollongong, Wollongong, NSW, Australia, [2]Dept of Radiation Oncology, Prince of Wales Hospital, Sydney, NSW, Australia

POS 23 Primitive study of clinical applications of three-dimensional temperature distribution simulation for radiofrequency hyperthermia

Kenta Takada[1], Daisuke Kobayashi[2], Hideyuki Sakurai[1], Takeji Sakae[1]

[1]Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [2]Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan

POS 24 Deep regional hypethermia combined with chemotherapy: Greek Society of Hyperthermic Oncology.

Ioannis Gogalis, Ioannis Kouvaris, Alfred Baritz, Aias Papastaurou, Lazaros Daniilidis, Nikolaos Ouzounoglou, Vassilis Kouloulias

Greek society of hypethermic oncology, Athens, Greece

POS 25 Temperature dependent complex permittivity of agar phantom
Ilja Merunka, Ondrej Fiser, Jan Vrba, David Vrba, Jan Vrba
Czech Technical University in Prague, Prague, Czech Republic

POS 26 Tumor surface temperature measurement during magnetic hyperthermia in a murine model can differentiate distinct intratumoral heat deposition due to nanoparticle distribution.
Gustavo Capistrano, Nicholas Zufelato, Lorena Gomes, Sonia Santos, Elisangela Silveira-Lacerda, Andris Bakuzis
Federal University of Goias, Goiania, Goias, Brazil

POS 27 Heat transfer and electromagnetic modeling of magnetic nanoparticle hyperthermia in agar gel phantoms
Sri Kamal Kandala[1,2], Anirudh Sharma[2], Eleni Liapi[3], Cila Herman[1], Robert Ivkov[2]
[1]Department of Mechanical Engineering, Johns Hopkins University, Baltimore,MD, USA, [2]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore,MD, USA, [3]Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, Baltimore,MD, USA

POS 28 Enriching temperature measurements with simulations for 3D dosimetry during hyperthermia treatments.
Margarethus Paulides[1], Jifke Veenland[2], Valerio Fortunati[2], Theo Van Walsum[2], René Verhaart[1]
[1]Erasmus MC Cancer Insitute, Rotterdam, The Netherlands, [2]Erasmus MC, Rotterdam, The Netherlands

POS 29 Multidisciplinary Management Of Unresectable Verrucous Carcinoma Of The Genitals, i.e. Buschke-Lowenstein Tumor, With Combined External Beam Radiation and Hyperthermia: A Case Report
Tejan Diwanji, James Snider, Jason Molitoris, Michael Chuong, Shifeng Chen, Petr Hausner, Zeljko Vujaskovic
University of Maryland Medical Center, Baltimore, MD, USA

POS 30 Transarterial delivery of a dichloroacetyl chloride/Lipiodol mixture in porcine kidney: a proof of concept study for thermochemical embolization.
Chunxiao Guo, Christopher MacLellan, Megan Jacobsen, Jason Stafford, Erik Cressman
UT MD Anderson Cancer Center, Houston, Texas, USA

POS 31 Gain of radiation resistance induces hyperthermia resistance in lung cancer
Samir V. Jenkins[1], Kieng B. Vang[2], Robert J. Griffin[1], Ruud P.M. Dings[1]
[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas at Little Rock, Little Rock, AR, USA

POS 32 Influence of tumor infiltrating lymphocytes on local progression-free survival and disease-free survival in high-risk soft tissue sarcoma treated with combined neo-

adjuvant chemotherapy and regional hyperthermia

Rolf Issels[1], Eric Kampmann[1], Veit Bücklein[1], Elfriede Nössner[2], Lars H. Lindner[1], Michael Schmidt[3], Ulrich Mansmann[3], Wolfgang Hiddemann[1], Marion Subklewe[1], Thomas Knösel[4]

[1]Medical Clinic III, University Hospital of the LMU, Munich, Germany, [2]Helmholtz Zentrum München, Germany Research Center for Environmental Health, Institute of Molecular Immunology, Munich, Germany, [3]Institute of Medical Informatics, Biostatistics, and Epidemiology, Ludwig-Maximilians-University (LMU), Munich, Germany, [4]Institute of Pathology, Ludwig-Maximilians-University (LMU), Munich, Germany

POS 33 Characterization and evaluation of a tissue-mimicking thermochromic phantom for use in radiofrequency ablation

Andrew S. Mikhail[1], Ayele H. Negussie[1], Cole Graham[1], Manoj Mathew[1], Bradford J. Wood[1], Ari Partanen[1,2]

[1]Center for Interventional Oncology, Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA, [2]Clinical Science MR Therapy, Philips, Andover, MA, USA

POS 34 A phased antenna array for the treatment of cancer malignancies in the intact breast

Sergio Curto[1], Aleix Garcia-Miquel[2], Neus Vidal[2], Jose M Lopez-Villegas2[2], Punit Prakash[1]

[1]Kansas State University, Manhattan, KS, USA, [2]University of Barcelona, Barcelona, Spain

POS 35 Magnetically labeled mesenchymal stromal cells as theranostic platform for cancer

Shu-Han Yu[1], Marie Spitzner[2], Preethi Korangath[1], Jackie Stewart[1], James Barnett[1], Anirudh Sharma[1], Sri Kamal Kandala[1], Ralf G. Mundkowski[2], Robert Ivkov[1]

[1]Dept of Radiation Oncology, Johns Hopkins University, Baltimore, MD, USA, [2]Zentrum für Pharmakologie und Toxikologie Institut für Klinische Pharmakologie Schillingallee, Universität Rostock Medizinische Fakultät, Rostock, Germany

POS 36 A Case report of thermobiochemoradiation therapy using superselective intra-arterial infusion for carcinoma of the buccal mucosa with N3 lymph node metastases

Toshiyuki Koizumi, Kenji Mitsudo, Masaki Iida, Hideyuki Nakashima, Jun Ueda, Senri Oguri, Toshinori Iwai, Makoto Hirota, Mitomu Kioi, Iwai Tohnai

yokohama city university, yokohama,kanagawa, Japan

POS 37 Hyperthermia enhances the therapeutic efficacy of IL-13 cytotoxin in human oral squamous cell carcinoma.

Hideyuki Nakashima, Makiko Okubo, Mitomu Kioi, Akiyoshi Miyajima, Tomohiro Iisaka, Kei Sugiura, Itaru Sato, Toshiyuki Koizumi, Kenji Mitsudo, Iwai Tohnai

Yokohama City University Hospital, Yokohama, Japan

POS 38 Iron dextran as an ideal thermosensitizer in the radiofrequency-induced hyperthermia

Heui-Kwan Lee[2], Hea-Jong Chung[3], Hyeon-Jin Kim[3], Seong-Tshool Hong[1]
[1]Department of Biomedical Sciences and Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Chonbuk, Republic of Korea, [2]Deparment of Radiooncology, Presbyterian Hospital, Seonam University Medical School, Jeonju, Chonbuk, Republic of Korea, [3]JINIS BDRD institute, JINIS Biopharmaceuticals Co., Wanju, Chonbuk, Republic of Korea

POS 39 Preheating with bathtub markedly improves the whole-body heating with electrical heating chamber

Ihlbohng Choi, Sumin Chae, Chihwa Han, Taehang Lee
Cheju Halla General Hospital, Jeju, Republic of Korea

POS 40 Reirradiation+hyperthermia for recurrent breast cancer-en-cuirasse in previously irradiated area

Sabine Oldenborg[1], Hans Crezee[1], Yoka Kusumanto[1], Rob van Os[1], Bing Oei[2], Jack Venselaar[2], Paul Zum Vörde Sive Vörding[1], Coen Rasch[1], Geertjan van Tienhoven[1]
[1]Academic Medical Center, Dept. of Radiation Oncology, Amsterdam, The Netherlands, [2]Institute Verbeeten, Dept. of Radiation Oncology, Tilburg, The Netherlands

POS 41 Temperature Anomalies in Simulating Ultrasound Heating for Tissue Tightening with a Three-Layer Subcutaneous Structure

Huang-Wen Huang[1], Win-Li Lin[0]
[1]Tamkang University, Taipei, Taiwan, [2]National Taiwan University, Taipei, Taiwan

POS 42 Case report: Four years of local control of malignant fibrous histiocytoma by proton beam therapy combined with hyperthermia

Shota Maekawa, Shousei Shimizu, Takashi Iizumi, Haruko Numajiri, Masashi Mizumoto, Kayoko Ohnishi, Teruhito Aihara, Nobuyoshi Fukumitsu, Hitoshi Ishikawa, Toshiyuki Okumura, Hideyuki Sakurai
Tsukuba University Hospital, Tsukuba,Ibaraki, Japan

POS 43 A novel optimization approach for adaptive application of hyperthermia.

Domenica Iero[1], Tomas Drizdal[2], Lorenzo Crocco[3], Margarethus Paulides[2], Tommaso Isernia[1,3], Gerard Van Rhoon[2]
[1]Dipartimento di Ingegneria dell'Informazione, delle Infrastrutture e delle Energie Sostenibili (DIIES), Università Mediterranea di Reggio Calabria, Reggio Calabria, Italy, [2]Department of Radiation Oncology, Hyperthermia Unit, Erasmus Medical Center Rotterdam, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands, [3]Istituto per il Rilevamento Elettromagnetico dell'Ambiente (IREA-CNR), Consiglio Nazionale delle Ricerche, Napoli, Italy

POS 44 Early experience applying ultrasound-generated regional hyperthermia and radiation therapy to oligometastases in the abdomen and pelvis.

Phillip Beron[1], Oscar Streeter, Jr.[2], Cyrus Rafie[2], Sean Devlin[3], Nasha Winters[4], Eric Landau[2], Mitchell Kamrava[1]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, [2]The Center for Thermal Oncology, Santa Monica, CA, USA, [3]Institute of Integrative Medicine and Oncology, Santa Monica, CA, USA, [4]Optimal Terrain Consulting, Inc., Durango, CO, USA

POS 45 Effect of respiration on the quality of MR-guided thermal therapy: investigation in the neck region

Ghassan Salim[1], Paul Baron[1], Dirk Poot[3], Stefan Klein[3], Hendrik Thijmen Mulder[2], Maarten Paulides[2], Juan Hernandez Tamames[1]

[1]Erasmus Medical Center, Department of Radiation Oncology, Rotterdam, The Netherlands, [2]Erasmus Medical Center, Department of Radiology, Rotterdam, The Netherlands, [3]Erasmus Medical Center, Biomedical Imaging Group Rotterdam, Rotterdam, The Netherlands

POS 46 Local hyperthermia in treatment of late radiation-induced skin and soft tissue injuries

Orazakhmet Kurpeshev, Victor Pasov, Alyia Kurpesheva, Anastasia Orlova

A.F. Tsyb Medical Radiology Research Center, Branch, National Medical Radiology Research Center, Ministry of Health of Russia, Obninsk, Kaluga Region, Russia

POS 47 Outcomes of neoadjuvant thermochemoradiotherapy in soft tissue sarcomas

Orazakhmet Kurpeshev, Aleksei Zubarev, Aleksandr Kurilchik, Anastasia Orlova

A.F. Tsyb Medical Radiology Research Center, Branch, National Medical Radiology Research Center, Ministry of Health of Russia, Obninsk, Kaluga Region, Russia

POS 48 Thermochemoradiotherapy for locally advanced larynx cancer

Orazakhmet Kurpeshev, Viacheslav Andreev, Vladimir Pankratov, Igor Gulidov, Anastasia Orlova

A.F. Tsyb Medical Radiology Research Center, Branch, National Medical Radiology Research Center, Ministry of Health of Russia, Obninsk, Kaluga Region, Russia

Thursday, April 14, 2016

Registration

6:30am - 5:30pm **La Salle C Foyer**

Speaker Ready Room - Available all day

Acadian I

Breakfast Buffet

6:45am - 8:15am **La Salle A**

Posters

7:00am - 6:00pm **Le Salon & LaSalle BC**

Exhibits

7:00am - 6:00pm **Le Salon & LaSalle BC**

Refresher Course: Novel Drug Delivery Approach

7:15am - 8:00am **Pelican I/II (3rd floor)**

Speaker: Christine Allen

THU 1 Thermosensitive Nanotechnologies for Drug Delivery: Basic Principles and New Directions
Christine Allen
University of Toronto, Toronto, Canada

Refresher Course: Clinical Hyperthermia Trials

7:15am - 8:00am **Melpomene**

Speaker: Niloy Ranjan Datta

THU 2 An overview of the clinical trials in hyperthermia: Do we have the evidence?
Niloy Ranjan Datta
Centre for Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland

Plenary Session - State of the Art in HIFU

8:15am - 9:00am **La Salle A**

THU 3 State-of-the-art In High Intensity Focused Ultrasound (HIFU)
Chrit Moonen
University Medical Center, Utrecht, The Netherlands

HIFU #2

9:15am - 11:45am La Salle A Chair: Gail ter Haar & Mark Hurwitz

INVITED SPEAKERS:

THU 4 Low Intensity Therapy Ultrasound Approaches – Bubbles

Eleanor Stride[1], Dario Carugo[1], Joshua Owen[1], Jeong Yu Lee[1], Richard Browning[1], Anjali Seth[1], Anthony McHale[2], John Callan[2], Estelle Beguin[1], Shuning Bian[1], Miles Aron[1], James Kwan[1], Robert Carlisle[1], Robin Cleveland[1], Constantin Coussios[1]
[1]University of Oxford, Oxford, UK, [2]Ulster University, Coleraine, UK

THU 5 Interventional Oncology: Role of Focused Ultrasound (USgHIFU) in Pancreatic Cancer. Five Years Experience and Tumor Ablation Considerations in the Western Stage

Joan Vidal-Jove[1,2], Natalia Eres[2], Eloi Perich[2], Angels Jaen[1], Manuel Alvarez del Castillo[1]
[1]Hospital University Mutua Terrassa, Terrassa, Barcelona, Spain, [2]Institut Khuab, Barcelona, Spain

PROFERRED PAPERS:

THU 6 A comprehensive model of hyperthermia and radiotherapy induced cell death

Sarah Brueningk, Uwe Oelfke, Ian Rivens, Simeon Nill, Gail ter Haar
The Institute of Cancer Research, Sutton, Surrey, UK

THU 7 Method of Target Tracking in MR Guided HIFU using Image Matching Technique with 3D Liver Volumes Obtained via Time-resolved Volume Acquisitions

Etsuko Kumamoto[1], Daisuke Kokuryo[1], Kagayaki Kuroda[2,3]
[1]Kobe University, Kobe, Hyogo, Japan, [2]Tokai University, Hiratsuka, Kanagawa, Japan, [3]Center for Frontier Medical Engineering, Chiba University, Chiba, Japan

THU 8 Voxel-based radiobiological evaluation of combined radiotherapy and hyperthermia treatments: a basis for better informed clinical decisions.

Caspar M. van Leeuwen, Johannes Crezee, Arlene L Oei, Nicolaas A.P. Franken, Lukas A.J. Stalpers, Arjan Bel, H.P. Kok
Academic Medical Center, Amsterdam, The Netherlands

THU 9 AN INVESTIGATION OF THERMAL DOSE AS A PARAMETER FOR MODELLING THE THERMAL EFFECTS OF HIFU IN CANCER THERAPY

Petros Mouratidis, Gail ter Haar
The Institute of Cancer Research, Sutton, Surrey, UK

THU 10 Development of Ultrasound-Guided HIFU System with Non-Invasive Measurement of Sub-Pixel Temperature Distributions

Eitaro Miura[1], Daisuke Anan[1], Takahiro Saito[1], Yuya Iseki[1], Kazuo Kato[1], Akira Takeuchi[2]

[1]Meiji University, Kawasaki/Kanagawa, Japan, [2]LUKE CLINIC, Chuou-ku/Tokyo, Japan

THU 11 Development of MR-guided endoluminal ultrasound applicators for thermal ablation of pancreatic cancer: design and evaluations in ex vivo and in vivo porcine studies

Matthew Adams[1], Vasant Salgaonkar[1], Juan Plata[2], Peter Jones[1], Aurea Pascal-Tenorio[2], Donna Bouley[2], Graham Sommer[2], Kim Butts Pauly[2], Chris Diederich[1]
[1]University of California, San Francisco, San Francisco, USA, [2]Stanford University, Stanford, USA

THU 12 Development and preliminary in vivo assessment of an MRI guided hyperthermia platform implemented with a high-intensity focused ultrasound ablation array

Vasant Salgaonkar, Eugene Ozhinsky, Viola Rieke, Chris Diederich
University of California, San Francisco, USA

THU 13 Phased Array Techniques for Expanding the Transcranial Focused Ultrasound Treatment Range at the Skull Base

Alec Hughes[1,2], Ryan M. Jones[1,2], Aki Pulkkinen[3], Kullervo Hynynen[1,2]
[1]Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada, [2]Physical Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada, [3]Department of Applied Physics, University of Eastern Finland, Kuopio, Finland

Emerging Hyperthermia Biology

9:15am - 11:45am Pelican I/II (3rd floor) Chair: Chang Song & Mike Horsman

INVITED SPEAKERS:

THU 14 Dose reduction for stereotactic radiotherapy using nanomedicine and new thermal medicine capabilities

Robert J. Griffin[1], Azemat Jamshidi-Parsian[1], Nathan A. Koonce[2], Ganesh Narayanasamy[1], Ruud P.M. Dings[1], Peter M. Corry[1]
[1]UAMS, Little Rock, AR, USA, [2]National Center for Toxicology- Nanocore, Jefferson, AR, USA

THU 15 Enhancing the cytotoxic effects of hyperthermia by heat shock protein 90 inhibition

Lianne Vriend, Przemek Krawczyk
AMC, Amsterdam, The Netherlands

THU 16 Combination of Oncothermia with SBRT and Metformin *in vivo*

Wonwoo Kim[1], Mi-Sook Kim[1], Hee-jong Kim[1], Eunjin Lee[1], Jae-hoon Jeong[1]
[1]Research Center for Radiotherapy, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea, [2]Department of Radiation Oncology, Korea Institute of Radiological and Medical Sciences, Seoul, Republic of Korea

PROFERRED PAPERS:

THU 17 Thermosensitive cisplatin liposomes provide improved local control of triple-negative breast cancer

Michael Dunne[1], Yannan Dou[1], Tara Spence[1], Savio Gontijo[2], Christine Allen[1]
[1]University of Toronto, Toronto, ON, Canada, [2]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

THU 18 Lonidamine is a Potent Inhibitor of the Mitochondrial Pyruvate Carrier and Plasma Membrane Monocarboxylate Transporters

Bethany Nancolas[1], Lili Guo[2], Rong Zhou[2], Kavindra Nath[2], David Nelson[2], Dennis Leeper[3], Ian Blair[2], Jerry Glickson[2], Andrew Halestrap[1]
[1]University of Bristol, Bristol, UK, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Thomas Jefferson University, Philadelphia, PA, USA

THU 19 PARP1-inhibition allows substantial lowering of the cisplatin concentration in thermochemotherapy

Arlene L. Oei[1,2], Lianne E.M. Vriend[3], Caspar M. van Leeuwen[2], Rosemarie ten Cate[1,2], Hans M. Rodermond[1,2], Roland Kanaar[4], Johannes Crezee[2], H. Petra Kok[2], Przemek M. Krawczyk[3], Nicolaas A.P. Franken[1,2]
[1]Laboratory for Experimental Oncology and Radiobiology (LEXOR), Academic Medical Center (AMC), Amsterdam, The Netherlands, [2]Department of Radiation Oncology, Academic Medical Center (AMC), Amsterdam, The Netherlands, [3]Department of Cell Biology and Histology, Academic Medical Center (AMC), Amsterdam, The Netherlands, [4]Department of Cell Biology and Genetics, Erasmus Medical Center, Rotterdam, The Netherlands

THU 20 Enhancement of heat sensitivity of human cancer cells by inhibitor of HR but not NHEJ

Akihisa Takahashi[1], Eiichiro Mori[2], Atsuhisa Kajihara[2], Yosuke Nakagawa[2], Takeo Ohnishi[2]
[1]Gunma University Heavy Ion Medical Center, Gunma, Japan, [2]Nara Medical University, Nara, Japan

THU 21 Mild hyperthermia combined with DNAPK inhibition for Radioenhancement of cervical cancer treatment: In vitro and in vivo studies

Bregje van Oorschot[1], Giovanna Granata[1], Rosemarie ten Cate[1], Hans Rodermond[1], Johannes Crezee[2], Petra Kok[2], Nicolaas Franken[1]
[1]LexoR, dept of Radiotherapy, AMC, University of Amsterdam, Amsterdam, The Netherlands, [2]Dept Radiotherapy, AMC, University of Amsterdam, Amsterdam, The Netherlands

THU 22 Tri-modality treatment with chemotherapy, radiotherapy and mild-hyperthermia, in vitro

Helena C. Besse, Clemens Bos, Chrit T.W. Moonen, Roel Deckers

University Medical Center Utrecht, Utrecht, The Netherlands

HIPEC & Upper Abdominal

9:15am - 11:45am Melpomene **Chair: Zeljko Vujaskovic & Nadar Hanna**

INVITED SPEAKERS:

THU 23 CYTOREDUCTIVE SURGERY & HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR GASRIC CANCER; EXPERIMENTAL OR STANDARD THERAPY?
Nader Hanna
University of Maryland School of Medicine, Baltimore, MD, USA

THU 24 COMPREHENSIVE MANAGEMENT OF DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA
Paul Sugarbaker, Tristan Yan, Oswald Stuart, Dal Yoo
Program in Peritoneal Surface Oncology, Washington, DC, USA

PROFFERED PAPERS:

THU 25 Effect of Hyperthermic Intraperitoneal Perfusion Chemotherapy in Combination with Intravenous Chemotherapy as Postoperative Adjuvant Therapy for Advanced Gastric Cancer
Zhibing Wu[1,2], Shenglin Ma[1], Saisai Jing[2], Qinghua Deng[1], Zhishuang Zheng[2], Kan Wu[2], Juan Li[2], Sumei Chen[2], Rongjun Tang[2], Xiadong Li[1]
[1]Nanjing Medical University Affiliated Hangzhou Hospital(Hangzhou First People's Hospital), Hangzhou,Zhejiang, China, [2]Hangzhou Cancer Hospital, Hangzhou,Zhejiang, China

THU 26 Prolonged survival times in patients with advanced or metastatic pancreatic cancer after chemotherapy in combination with hyperthermia
Dr. med. Alexander Herzog
University of Sevilla, Sevilla, Spain

THU 27 Preliminary result of chemo proton beam therapy combined with hyperthermia in local advanced pancreatic cancer.
Takashi Saito, Nobuyoshi Fukumitsu, Haruko Numajiri, Masashi Mizumoto, Kayoko Ohnishi, Hitoshi Ishikawa, Teruhito Aihara, Toshiyuki Okumura, Hideyuki Sakurai
Tsukuba University Hospital, Tsukuba, Ibaraki, Japan

THU 28 Hyperthermia-based therapy is a promising approach to overcome treatment resistance in pancreatic cancer.
Tomoyo Yasuda[1], Takeshi Ishikawa[1,2], Tetsuya Okayama[1,2], Toshifumi Doi[1], Naoyuki Sakamoto[1,3], Satoko Adachi[1], Reiko Kimura[1], Satoshi Kokura[1,4], Yuji Naito[1], Yoshito Ito[1], Toshikazu Yoshikawa[2]
[1]Department of Molecular Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Department of Cancer Immuno Regulation,

Kyoto Prefectural University of Medicine, Kyoto, Japan, [3]Hyakumanben Clinic, Kyoto, Japan, [4]Kyoto Gakuen University, Kyoto, Japan

THU 29 Evaluation of the temperature increase during ablations with non-thermal irreversible electroporation in porcine liver and pancreas in vivo: effect of large vessels

Jantien Vogel[1], Hester Scheffer[2], Nina van Stolwijk[1], Krijn van Lienden[3], Hans Crezee[4], Petra Kok[4], John Klaessens[5], Martijn Meijerink[2], Marc Besselink[1], Thomas van Gulik[6,1]

[1]Department of Surgery, Academic Medical Center, Amsterdam, The Netherlands, [2]Department of Radiology and Nuclear Physics, VU University Medical Center, Amsterdam, The Netherlands, [3]Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands, [4]Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands, [5]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands, [6]Department of Experimental Surgery, Academic Medical Center, Amsterdam, The Netherlands

THU 30 Near-Infrared Nanoparticle Mediated Hyperthermia In Colorectal Cancer Spheroids: A Tissue Phantom Study

Eleanor McCabe-Lankford, Sneha Kelkar, Theodore Brown, Nicole Levi-Polyachenko

Wake Forest University School of Medicine, Winston-Salem, NC, USA

Buffet Luncheon

12:00pm - 1:00pm La Salle A

Vendor Presentations

1:00pm - 1:30pm La Salle A/B (3rd floor)

ICHO President's Symposium

1:30pm - 3:30pm La Salle A Chair: Mark Dewhirst

INVITED SPEAKERS:

THU 31 Dynamic assessment of heat shock response and thermotolerance are enabled by use of novel reporter genes

Christopher Contag

Stanford University, Stanford, CA, USA

THU 32 CONVERGING HYPERTHERMIA AND IONIZING RADIATION (IR) TO CONVERT THE TUMOR INTO AN IN SITU VACCINE
Silvia Formenti
NY Presbyterian/Weill Cornell Medicine, New York, NY, USA

THU 33 Integration of functional imaging with interventional oncology: "Molecular Interventions"
Bradford Wood
Center for Interventional Oncology, National Cancer Institute & Radiology and Imaging Sciences, Clinical Center, National Institutes of Health, Bethesda, MD, USA

THU 34 How hyperthermia works. How can we make hyperthermia work better?
Arlene Oei
Dept. Radiation Oncology, AMC, Amsterdam, The Netherlands

Poster Session 2 with Coffee and Beignet Break

3:45pm - 5:00pm Le Salon

Tsudomu Sugahara Award Presentation and Talk

5:15pm - 6:15pm La Salle A

THU 35 Randomized clinical trials and predictive cancer related genes in patients with locally advanced cervical cancer for effectiveness of hyperthermia oncology
Yoko Harima
Kansai Medical University, Moriguchi, Osaka, Japan

ICHO Banquet Dinner – Audubon Aquarium

7:00pm - 10:00pm Audubon Aquarium of the Americas

An additional fee of 100USD per person is required for this event. Dinner will include a multi-course meal, including appetizers, drinks and desserts. This event will be held at the world famous Audubon Aquarium of the Americas.

Friday, April 15, 2016

Registration

6:30am - 5:30pm **La Salle C Foyer**

Speaker Ready Room - Available all day

Acadian I

Breakfast Buffet

6:45am - 8:15am **La Salle A**

Posters

7:00am - 1:30pm **Le Salon & LaSalle BC**

Exhibits

7:00am - 1:30pm **Le Salon & LaSalle BC**

Refresher Course: Cryotherapy Overview

7:15am - 8:00am **Pelican I/II (3rd floor)**

FRI 1 Challenges and opportunities in application of thermal ablative therapies

John C. Bischof[2], Robert J. Griffin[1]

[1]UAMS, Little Rock, USA, [2]University of Minnesota, Minneapolis, USA

Refresher Course: Evolving Technology for Superficial and Deep Hyperthermia

7:15am - 8:00am **Melpomene**

FRI 2 EVOLVING TECHNOLOGY FOR SUPERFICIAL AND DEEP HYPERTHERMIA

Paul Stauffer

Thomas Jefferson University, Philadelphia, PA, USA

Plenary Session - Using Systems Biology of Signaling to Improve Cancer Treatment

8:15am - 9:00am **La Salle A**

FRI 3 Using Systems Biology of Signaling to Improve Cancer Treatment

Michael B. Yaffe

Koch Institute for Integrative Cancer Biology, Depts of Biological Engineering and Biology, Massachusetts Institute of Technology, and Dept. of Surgery, Beth Israel Deaconess Medical Center, Harvard M, Boston, MA, USA

Hot Abstracts #1

9:15am - 11:45am La Salle A Chair: Lars Lindner & Paul Stauffer

PROFFERED PAPERS:

FRI 4 Invasive temperature measurement in Soft tissue Sarcoma during hyperthermia using catheters: Analysis of side effects in 35 patients

Sultan Abdel-Rahman[1], Lars Lindner[1], Frederik Strobl[2,1], Houman Azam[2,1], Christoph Trumm[2,1]

[1]Department of Internal Medicine III, Munich, Germany, [2]Institute for Clinical Radiology, Munich, Germany

FRI 5 Infrared-based, clinical quality assurance in superficial hyperthermia treatments

Johannes Müller, Josefin Hartmann, Bassim Aklan, Oliver Ott, Rainer Fietkau, Christoph Bert

University Hospital Erlangen, Departmen of radiation oncology, Erlangen, Bavaria, Germany

FRI 6 Clinical implementation of the novel HYPERcollar3D applicator for deep hyperthermia treatment of cancers in the head and neck region

Margarethus Paulides, Gerda Verduijn, Gerard Van Rhoon, Netteke Van Holthe

Erasmus MC Cancer Institute, Rotterdam, The Netherlands

FRI 7 An MRI-Compatible Hyperthermia Applicator for Small Animals

Elles Raaijmakers[1,2], Margarethus Paulides[2], Rob Mestrom[1]

[1]Erasmus MC, Rotterdam, The Netherlands, [2]Eindhoven University of Technology, Eindhoven, The Netherlands

FRI 8 Comparison of Ultrasonic Thermometry based on the Change in Backscattered Energy with MRI Temperature Images

R Martin Arthur, William L Straube, Michael Gach, Michael Altman, Hong Chen

Washington University, St. Louis, MO, USA

FRI 9 Towards integration of non-invasive temperature measurement with microwave radiometry for improved control of superficial hyperthermia array applicators

Dario Rodrigues[1], Paolo Maccarini[2], Mark Hurwitz[1], Paul Stauffer[1]

[1]Thomas Jefferson University, Philadelphia, PA, USA, [2]Duke University, Durham, NC, USA

FRI 10 Laboratory prototype of UWB applicator for head and neck hyperthermia

Hana Dobsicek Trefna, Masoud Shafiemehr, Pegah Takook, Mikael Persson

Chalmers University of Technology, Gothenburg, Sweden

FRI 11 An integrated system for delivering hyperthermia to small-animal targets under 14 T ultra-high field MRI guidance

Sergio Curto, Leila Maurmann, Pegah Farid, Ron Jackson, Tej Shrestha, Matthew

Basel, Hongwang Wang, Deryl Troyer, Stefan Bossmann, Punit Prakash
Kansas State University, Manhattan, KS, USA

FRI 12 Feasibility of absolute MR thermometry for knee joint cartilage using spin-lattice relaxation time
Tomoya Kimura[1], Kenji Takahashi[2], Kagayaki Kuroda[1]
[1]Graduate School of Engineering, Tokai University, Hiratsuka, Japan, [2]Department of Orthopaedic Surgery, Nippon Medical School, Tokyo, Japan

FRI 13 Can we avoid interstitial thermometry during superficial hyperthermia?
Abdelali Ameziane, Gerard van Rhoon, Aleida Aangeenbrug, Audrey Wijngaarde, Netteke van Holthe
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

FRI 14 Modeling Scattering in Simulations of Focused Ultrasound Beam Propagation
Douglas Christensen, Matt Holbrook, Scott Almquist
University of Utah, Salt Lake City, Utah, USA

FRI 15 Optimization of Signal Processing in MR Thermometry using Resonance Frequency and Spin-lattice Relaxation Time for Breast HIFU
Yosuke Owaki[1], Yutaka Imai[2], Kagayaki Kuroda[1]
[1]Graduate School of Engineering, Tokai University, Hiratsuka, Japan, [2]School of Medicine, Tokai University, Isehara, Japan

Nanotechnology #2

9:15am - 11:45am Pelican I/II (3rd floor) Chair: Nicole Levi-Polyachenko & Jason Stafford

INVITED SPEAKERS:

FRI 16 Biodegradable plasmonic nanoparticles for cancer imaging and therapy
Konstantin Sokolov[1,2], Pratixa Joshi[2], Robert Stover[2], Soon Joon Yoon[2], Avinash Murthy[2], Ehsan Moaseri[2], Thomas Truskett[2], Stanislav Emelianov[3,2], Keith Johnston[2]
[1]The UT M.D. Anderson Cancer Center, Houston, TX, USA, [2]The University of Texas at Austin, Austin, TX, USA, [3]Georgia Institute of Technology, Atlanta, GA, USA

FRI 17 Synergistic Photothermal and Antibiotic Killing of Biofilm-associated Staphylococcus aureus using Targeted, Antibiotic-loaded Gold Nanoconstructs
Mark Smeltzer[1], Daniel Meeker[1], Samir Jenkins[2], Karen Beenken[1], Emily Miller[2], Jingyi Chen[2]
[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

PROFFERED PAPERS:

FRI 18 Engineering Polymer-coated Gold Nanocages for Photothermally-controlled Release of Therapeutic Agents
Jingyi Chen[1], Samir Jenkins[1], Emily Miller[1], Daniel Meeker[2], Mark Smeltzer[2]

[1]University of Arkansas, Fayetteville, USA, [2]University of Arkansas for Medical Sciences, Little Rock, USA

FRI 19 Hyperthermia -Induced Expandable Polymer Nanoparticles for Treating Breast Cancer

Nicole Levi-Polyachenko, Sneha Kelkar
Wake Forest University Health Sciences, Winston-Salem, NC, USA

FRI 20 Designing novel antibiotic-loaded, targeted nanoparticles to eradicate *Staphylococcus aureus* planktonic cultures and biofilms

Daniel Meeker[1], Samir Jenkins[2], Emily Miller[2], Karen Beenken[1], Allister Loughran[1], Jingyi Chen[2], Mark Smeltzer[1]
[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

FRI 21 Effects of nanoparticles on the cell killing induced by different physical stressors

Paras Jawaid[1], Mati Ur Rehman[1], Qing Li Zhao[1], Yusei Miyamoto[2], Masaki Misawa[3], Takashi Kondo[1]
[1]Toyama University, Toyama, Japan, [2]University of Tokyo, Chiba, Japan, [3]National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki, Japan

FRI 22 MRI T1-based marker for hyperthermia-induced release of doxorubicin and contrast agent from thermosensitive $DPPG_2$-liposomes

Michael Peller[1], Linus Willerding[1,2], Simone Limmer[2], Martin Hossann[2], Olaf Dietrich[1], Michael Ingrisch[1], Lars H. Lindner[2]
[1]Department of Clinical Radiology, University Hospital of Munich, Munich, Germany, [2]Department of Internal Medicine III, University Hospital of Munich, Munich, Germany

FRI 23 Heating Efficiency of Colloidal Magnetic Fluids with Nonlinear Loss Properties and Aggregate Formation

Chencai Wang, Yung-Ya Lin
University of California, Los Angeles, Los Angeles, CA, USA

FRI 24 Radiofrequency ablation + ThermoDox: Increased heating duration enhances drug delivery

Dieter Haemmerich, Christian Rossmann, Marvin Swindle
Medical Univ. of South Carolina, Charleston, SC, USA

Treatment Planning

9:15am - 11:45am Melpomene **Chair: Margarethus Paulides , Kagayaki Kuroda & Dieter Haemmerich**

INVITED SPEAKERS:

FRI 25 HIFU treatment planning for hepatocellular carcinoma using respiratory motion tracking system and 3D Slicer navigation system

Hiroyuki Fukuda[1], Noburaka Doba[1], Kazushi Numata[1], Yoshiteru Hao[1], Akito Nozaki[1], Koji Hara[1], Makoto Chyuma[1], Shin Maeda[1], Shigeo Takebayashi[1], Katsuaki Tanaka[1], Norihiro Koizumi[2], Kiyoshi Yoshinaka[3], Akira Kobayashi[4], Junichi Tokuda[5]
[1]Yokohama City University Medical Center, Yokohama, Kanagawa, Japan, [2]The University of Electro-Communications, Chofu, Tokyo, Japan, [3]Natioanl Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan, [4]National Institute of Radiological Sciences, Chiba, Chiba, Japan, [5]Brigham and Women's Hospital, Boston, Massachusetts, USA

FRI 26 Computerized Training of Prostate Cryotherapy

Yoed Rabin[1,2], Anjali Sehrawat[1], Robert Keelan[1], Kenji Shimada[1], Dona M Wilfong[2], James T McCormick[2]
[1]Carnegie Mellon University, Pittsburgh, USA, [2]Allegheny Health Network, Pittsburgh, USA

FRI 27 Treatment Planning for Magnetic Nanoparticle-Based Hyperthermia

Esra Neufeld[1], Hazael Montanaro[1,2], Myles Capstick[1], Niels Kuster[1,2]
[1]IT'IS Foundation for Research on Information Technologies in Society, Zurich, Switzerland, [2]Swiss Federal Institute of Technology (ETHZ), Zurich, Switzerland

PROFFERED PAPERS:

FRI 28 On-line hyperthermia treatment planning during locoregional heating to improve tumor temperatures and reduce hot spots

H.P. Kok, A. Bakker, L. Korshuize, M.W. Kolff, E.D. Geijsen, L.J.A. Stalpers, J. Crezee
Academic Medical Center, Amsterdam, The Netherlands

FRI 29 Potential of a low cost optical E-field probe as validation tool of hyperthermia treatment planning

Daniel de Jong, Maarten Paulides, Gerard van Rhoon
Erasmus MC Cancer Institute, Rotterdam, The Netherlands

FRI 30 Effect of Different Tissue Segmentation schemes on Precise Treatment Planning of Laser Induced Thermal Therapy: A Retrospective Study

Reza Madankan, Christopher MacLellan, Samuel Fahrenholtz, John Hazle, R.J. Stafford, David Fuentes
UT MD Anderson Cancer Center, Houston, TX, USA

FRI 31 Sensitivity of microwave ablation models to tissue biophysical properties: application to model-based treatment planning

Jan Sebek[1,2], Nathan Albin[1], Radoslav Bortel[2], Bala Natarajan[1], Punit Prakash[1]
[1]Kansas State University, Manhattan, Kansas, USA, [2]Czech Technical University,

Praha, Czech Republic

FRI 32 Hyperthermia treatment planning: Impact of variation in manual tissue-segmentation on the simulated temperature distribution
Bassim Aklan, Josefin Hartmann, Diana Zink, Hadi Siavooshhaghighi, Ricarda Merten, Florian Putz, Christoph Bert
Radiation Oncology, University Hospital Erlangen, Erlangen, Germany

FRI 33 Precise numerical analyses of microwave coagulation therapy
Kazuyuki Saito, Yuta Endo, Koichi Ito
Chiba University, Chiba, Japan

FRI 34 Designation of optimal frequency for multi-frequency phased array
Pegah Takook, Hana Dobsicek Trefna, Mikael Persson
Chalmers university, Göteborg, Sweden

Buffet Luncheon

12:00pm - 1:00pm La Salle A

Vendor Presentations

1:00pm - 1:30pm La Salle A

Breast, Head & Neck, Cervix, Superficial Cancer

1:30pm - 3:30pm La Salle A Chair: Nagrag Huilgol, Joe Hsu & Geertjan van Tienhoven

INVITED SPEAKERS:

FRI 35 Reirradiation and hyperthermia for locally recurrent breast cancer after salvage surgery, what to do?
Geertjan van Tienhoven
Dept of radiation oncology and hyperthermia, Academic Medical Center, Amsterdam, The Netherlands

FRI 36 CHEMO-RADIATION WITH RF-HYPERTHERMIA OF LOCALLY ADVANCED HEAD AND NECK CANCER
Nagraj Huilgol, Kailash Gandewar, Nilesh Deshmane, Neela Pai- Dhungat
Nanavati Super-specialty Hospitak, Mumbai,Maharashtra, India

PROFFERED PAPERS:

FRI 37 Addition of External Thermal Therapy to Radiation Therapy Results in Modest Toxicities with the Promise of Increased Efficacy: A Single Institutional Experience
Travis Dobbin[1], Jason Molitoris[1], Tejan Diwanji[1], James Snider[1], Mariana Guerrero[2], Zeljko Vujaskovic[2]
[1]University of Maryland Medical Center, Baltimore, MD, USA, [2]University of

Maryland School of Medicine, Baltimore, MD, USA

FRI 38 Superficial radio-hyperthermia with 433MHz: the university of Athens experience.
Ioannis Gogalis, Ioannis Kouvaris, Christina Armpilia, Christos Antypas, Anna Zygogianni, Zoi Liakouli, Vassilis Kouloulias
Aretaieion University Hospital, Athens, Greece

FRI 39 A multicenter randomized clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer
Yoko Harima[1], Takayuki Ohguri[2], Hajime Imada[3], Hideyuki Sakurai[4], Tatsuya Ohno[5], Yoshiyuki Hiraki[6], Koh Tuji[7], Masahiro Tanaka[8], Hiromi Terashima[9]
[1]kansai Medical University, Moriguchi, Osaka, Japan, [2]University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan, [3]Tobata Kyoritsu Hospital, Kitakyushu, Fukuoka, Japan, [4]University of Tsukuba, Tsukuba, Ibaragi, Japan, [5]Gunma University Heavy Ion Medical Center, Maebashi, Gunma, Japan, [6]Kagoshima University, Kagoshima, Kagoshima, Japan, [7]National Hospital Organization Minami Wakayama Medical Center, Tanabe, Wakayama, Japan, [8]Osaka City General Hospital, Osaka, Osaka, Japan, [9]Harasanshin Hospital, Fukuoka, Fukuoka, Japan

FRI 40 Thermography-controlled wIRA-hyperthermia and re-irradiation of large sized breast cancer recurrences
Markus Notter[1], Helmut Piazena[2], Peter Vaupel[3]
[1]Radioonkologie Lindenhofspital, Bern, Switzerland, [2]Medical Photobiology Group, Charité University Medicine, Berlin, Germany, [3]Dep. of Radiooncology and Radiotherapy, Technische Universität München, München, Germany

FRI 41 Scar tissue is more at risk of developing thermal skin damage in recurrent breast cancer patients treated with reirradiation and hyperthermia.
Akke Bakker, Willemijn Kolff, Linda Korshuize-van Straten, Rianne Oldenhof-de Kroon, Coen Rasch, Geertjan van Tienhoven, Hans Crezee
AMC, Amsterdam, The Netherlands

Hot Abstracts #2

1:30pm - 3:30pm Pelican I/II (3rd floor) Chair: Hans Crezee, Robert Griffin & Seongtae Bae

PROFFERED PAPERS:

FRI 42 Enhanced efficacy of radiotherapy by voluntary exercise is dependent on a thermoneutral environment
Kathleen Ashcraft[1], Elizabeth Repasky[2], Kingshuk Roy Choudhury[1], Mark Dewhirst[1]
[1]Duke University, Durham, North Carolina, USA, [2]Roswell Park Cancer Institute, Buffalo, New York, USA

FRI 43 A method to determine the increase in blood perfusion in human dermis during infrared hyperthermia

Leonid Dombrovsky[1], Victoria Timchenko[2], Michael Jackson[2]
[1]Joint Institute for High Temperatures, Moscow, Russia, [2]University of New South Wales, Sydney, Australia

FRI 44 Photothermal Ablation of Streptococcus pyogenes and Staphylococcus aureus using Fluorescent Bio-Polymer Nanoparticles
Taylor Ibelli, Christie Young, Sean Reid, Weedley Funeus, Ravi Singh, Nicole Levi-Polyachenko
Wake Forest University, Winston-Salem, North Carolina, USA

FRI 45 TRANSIENT (THERMAL) BIOLOGICAL DOSE-EQUIVALENT (TBDE) - APPROACHING SYNERGISM AND TIMING OF HYPERTHERMIA-RADIOTHERAPY (HT-RT)
Stephan Scheidegger, Rudolf M. Füchslin
ZHAW School of Engineering, Winterthur, Switzerland

FRI 46 Multiple Simultaneous Cell Death Predictions Provide A More Realistic Picture of Likely Ablation / Hyperthermia Effective Treatment Zones
John Pearce
The University of Texas at Austin, Austin,TX, USA

FRI 47 Microwave Interstitial Helix Applicators for Hyperthermia Cancer Treatment
Lucie Vojackova[1,2], Jan Vrba[1], Ilja Merunka[1], Ondrej Fiser[1]
[1]Czech Technical University, Prague, Czech Republic, [2]Czech Institute of Metrology, Prague, Czech Republic

FRI 48 A Patient Derived Logistic Model of Thermal Dose
Christopher MacLellan[1,2], David Fuentes[1,2], Heron Espinoza[1], Sujit Prabhu[1], Ganesh Rao[1], Jeff Weinberg[1], Jason Stafford[1,2]
[1]The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [2]The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas, USA

FRI 49 Combination of Alternating Magnetic Field Hyperthermia and Low Temperature Sensitive Liposome for Synergistic Bacterial Killing
Kaustuv Sahoo, Tengfei Sun, Danny Maples, Daqing Piao, Ashish Ranjan
Oklahoma State University, Stillwater, Oklahoma, USA

FRI 50 Modular hyperthermia applicator with closed-loop control and integrated treatment planning tool: First clinical results on animal patients
Marie-Christine Gosselin[1,2], Esra Neufeld[1], Myles Capstick[1], Carla Rohrer Bley[3], Susann Dressel[3], Niels Kuster[1,2]
[1]IT'IS Foundation for Research on Information Technologies in Society, Zurich, Switzerland, [2]Swiss Federal Institute of Technology (ETHZ), Zurich, Switzerland, [3]Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

FRI 51 Ultrasound monitoring of tumor temperature and drug delivery with echogenic thermosensitive liposomes.

Kalyani Ektate[1], Danny Maples[1], Selvarani Ramaswamy[1], Ankur Kapoor[2], Ashish Ranjan[1]
[1]Oklahoma State University, Stillwater, Oklahoma, USA, [2]Siemens Corporation Corporate Technology, Princeton, NewJersey, USA

FRI 52 Low-dose Short-time Ultrasound Hyperthermia can Significantly Improve Liposomal Doxorubicin Delivery and Antitumor Efficacy for Brain Metastasis of Breast Cancer
Sheng-Kai Wu[1], Chi-Feng Chiang[1], Yu-Hone Hsu[1,4], Houng-Chi Liou[2], Wen-Mei Fu[2], Win-Li Lin[1,3]
[1]nstitute of Biomedical Engineering, National Taiwan University, Taipei City, Taiwan, [2]Institute of Pharmacology, National Taiwan University, Taipei City, Taiwan, [3]Institute of Biomedical Engineering and Nanomedicine, National Health Research Institutes, Miaoli, Taiwan, [4]Department of Neurosurgery, Cheng-Hsin General Hospital, Taipei City, Taiwan

Cryotherapy

1:30pm - 3:30pm **Melpomene** **Chair: Dieter Manstein**

INVITED SPEAKERS:

FRI 53 Health Related Quality of Life (HRQoL) Outcomes in Active Surveillance (AS) and Primary Focal Cryotherapy (PFC) Men with Low-Grade Prostate Cancer (PCa)
David Habibian, Aaron Katz, Kaitlin Kosinski, Rose Calixte
Winthrop University Hospital, Garden City, NY, USA

FRI 54 Is Salvage Focal Cryotherapy Curative Treatment for Patients with Localized Recurrent Prostate Cancer?
Courtney Berg, Aaron Katz, Kaitlin Kosinski
Winthrop University Hospital, Mineola, NY, USA

PROFFERED PAPERS:

FRI 55 Cyro-thermal therapy eradicated implanted melanoma in mice by eliciting anti-tumor memory immune response
Kun He, Ping Liu, Lisa X. Xu
Shanghai Jiao Tong University, Shanghai, China

FRI 56 Cryosurgery with vascular disruptive agent and Immune Adjuvants to Address Local and Systemic Cancer
Qi Shao[1], Satish Ramadhyani[2], Vineel Vallapureddy[2], John Bischof[1]
[1]University of Minnesota, Minneapolis, MN, USA, [2]Galil Medical Inc., Arden Hills, MN, USA

FRI 57 Cold atmospheric helium plasma (He-CAP) and mild hyperthermia in combination causes enhancement in cell killing mainly via generation of reactive oxygen species
Mati Ur Rehman, Paras Jawaid, Qing-Li Zhao, Peng Li, Takashi Kondo

Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

Exhibit & Poster Teardown

1:30pm - 5:00pm

Must be out of space by 5:00pm

Debate Session #1 - HIFU is best for small deep tumors whereas EM phased arrays are best for large volume tumors

3:30pm - 4:15pm La Salle A Chair: Paul Stauffer

HIFU
Chrit Moonen
Joo Ha Hwang
Rajiv Chopra

EM
Rolf Issels
Ruediger Wessalowski
Margarethus Paulides

Debate Session #2 - house believes that measurement of thermal dose is essential for thermal therapy

4:15pm - 5:00pm La Salle A Chair: Paul Stauffer

In Favor
Gerard van Rhoon
John Pearce

Opposed
Peter Corry
Elizabeth Repasky

Closing Ceremony

5:00pm - 5:30pm La Salle A

ABSTRACTS FOR TUESDAY, APRIL 12, 2016

TUE 1

Nitric oxide-mediated bystander responses induced by physical stress protect cells against its damage

Hideki Matsumoto

Department of Experimental Radiology & Health Physics, Faculty of Medical Science, University of Fukui, Eiheiji, Fukui, Japan

Background: Nitric oxide (NO) is an important regulatory substance for the immune response, cytotoxicity, neurotransmission, and vasodilatation. NO is endogenously generated from L-arginine by NO synthase (NOS) isoenzymes, neuronal NOS (nNOS, also known as NOS1), inducible NOS (iNOS, also known as NOS2) and endothelial NOS (eNOS, also known as NOS3). In these fields of research on cellular response to physical stresses, it has been suggested that NO plays important roles in adaptation of the organism to many kinds of stresses, such as heat shock, radiation and ultraviolet (UV).

Methods: To verify this hypothesis, we examined the effect of NO produced endogenously by heat-shocked or X-ray-irradiated cells on unstressed cells using a human cancer cell lines bearing wild-type *p53* (wt*p53*) or mutated *p53* (m*p53*) on the cutting edge.

Results: The accumulation of iNOS was induced by heat shock or X-ray irradiation in m*p53* cells but not in wt*p53* cells. The accumulation of Hsp70 and p53 was observed in unstressed wt*p53* cells co-cultivated with stressed m*p53* cells or exposed to the conditioned medium by pre-culture of stressed m*p53* cells. The accumulation of these proteins was suppressed by the addition of aminoguanidine (iNOS inhibitor) or carboxy-PTIO (NO scavenger) to the medium. In addition, the accumulation of Hsp70 and p53 in wt*p53* cells was induced by the administration of SNAP (NO generating agent) to the medium instead of giving such stresses. Finally, the thermo- or radio-sensitivity of wt*p53* cells was reduced in the conditioned medium prepared by culturing the heat-shocked or X-ray-irradiated m*p53* cells respectively, as compared with conventional fresh growth medium. Furthermore, we found that the accumulation of iNOS could be induced by exposure to radiation at non-lethal dose followed by exposure to radiation at lethal dose in wt*p53* cells. These findings lead us to a new approach for researching on cellular stress responses.

Conclusion: Our findings of the responses in NO-recipient cells co-cultivated with heat-shocked or X-ray-irradiated NO-donor cells provide the evidence for an intercellular signal transduction pathway *via* NO as initiator or mediator, so-called stress-induced, NO-mediated bystander responses.

ABSTRACTS FOR WEDNESDAY, APRIL 13, 2016

WED 1

Cancer Immunology & Immunotherapy*: The heat is on!*

Elizabeth A. Repasky

Roswell Park Cancer Institute, Buffalo, NY, USA

In recent years, immunotherapy approaches for the treatment of cancer patients have risen rapidly in popularity, largely because of recent, highly publicized clinical successes. In response to this growing excitement, many researchers want to include an analysis of immune responses in their own experiments. This Refresher Session will highlight basic principles of tumor immunology and summarize seminal discoveries which have catalyzed newly approved immunotherapies known as "checkpoint inhibitors" and "CAR T cells." Additionally, I will discuss recent literature in which a role for the immune response has been shown to be critical in the outcome of experiments using chemotherapy, radiation and thermal therapies.

WED 2

Clinical Applications of Laser Ablation

David Woodrum

Mayo Clinic, Rochester, MN, USA

Laser-induced thermal therapy (LITT) utilizes percutaneous placement of high-power laser fibers to produce focal tissue destruction which can be monitored and controlled with MRI guidance. The coupling of laser ablation with MR guidance provides a powerful clinical tool to ablate tumors throughout the body. This presentation will seek to address advances in laser hardware as well as discuss the integration of this technology with MR temperature mapping. The objective is to provide an introduction to laser ablation procedures, characterize the unique advantages, and to review clinical scenarios where it provides a tremendous clinical benefit. From this presentation, the audience should have an understanding of the clinical setup, clinical performance and potential clinical applications.

WED 3

Interventional Oncology: the Fourth Arm of Cancer Care

Damian Dupuy

Rhode Island Hospital Brown University, Providence, RI, USA

Cancer care in 2016 is a far cry from what it was 20 years ago. Most people think of chemotherapy, radiation and surgery as the only forms of cancer treatment. Advances in imaging and device technology now provide the fourth arm of cancer care in hospitals across the globe. Interventional oncology is the subspecialty field of interventional and diagnostic radiology that deals with the diagnosis and treatment of cancer and cancer-related problems using targeted minimally invasive procedures performed under image guidance. Interventional oncology has developed to be a separate, but highly collaborative pillar of modern oncology in which the majority of cancer patients utilize at some point in their care. Interventional oncology employs sophisticated image-guidance to guide miniaturized instruments (e.g. biopsy needles, ablation devices, intravascular catheters) allowing targeted diagnosis and precise treatment of solid tumors located in various organs of the human body, including but not limited to the liver, kidneys, lungs, adrenals, head and neck, prostate, breast, pelvis, soft-tissue and bones. Today we as interventional oncologists see patients in consultation and provide for many a single one shot outpatient diagnostic and therapeutic intervention whereby a small needle-like device or catheter is placed directly into the tumor or its blood supply under image guidance. The tumor can be biopsied and diagnosed as cancer with pathology expertise in the imaging suite and then destroyed locally with thermal energy with either extreme freezing or heating or intra-arterial drugs or radioactive beads. In patients with more advanced disease or larger tumors interventional oncologists work closely with the other three arms of cancer care to provide larger samples of tumor tissue with specialized biopsy devices and image-guidance. These tissue samples are analyzed to determine the exact genetic profile of that patient's particular cancer in order to tailor therapy. Radiation oncologists, medical oncologists, surgical oncologists and Interventional oncologists regularly combine their treatments to provide better local control or palliation of larger tumors that are poorly controlled with only a single therapy. Radiology advancements in the last 50 years and their impact on cancer care cannot be overstated. Advanced anatomic and functional imaging has given cancer specialists a better understanding of an individual's cancer type and burden. The advent of minimally invasive image-guided techniques to diagnose and treat cancers is a natural progression of these advancements and these less invasive and less costly outpatient cancer therapies provided by interventional oncologists are sure to increase.

WED 4

Thermal Ablation (Plenary Session)

S. Nahum Goldberg[1,2], Chris Brace[3], Muneeb Ahmed[2]

[1]Hadassah Hebrew University Medical Center, Jerusalem, Israel, [2]Beth Israel Deaconess Medical Center, Boston, MA, USA, [3]University of Wisconsin, Madison, WI, USA

Minimally-invasive, image-guided tumor ablation is now in widespread clinical use to treat small focal primary and metastatic tumors in the liver, kidney, lung, and other organs. Advantages include a lower associated morbidity and mortality compared to conventional surgery, use in patients who are not surgical candidates, and greater cost effectiveness. Relative ease of use coupled with clinical need have propelled this technique to widespread adoption with >100,000 treatments being performed yearly world-wide. These methods, of which radiofrequency (RF) and microwave (MW)-based systems are the most common, are based upon applying energy via needle-like applicators to generate high temperatures (50-100°C) and induce focal tissue injury. Thus, in essence, these techniques represent methods of using the highest thermal doses achievable to enable effective cancer therapy. Accordingly, this session will provide three lectures that highlight the scientific underpinnings of thermal ablation to demonstrate the potential benefit of extending hyperthermia to extreme thermal doses.

First, Dr. Chris Brace will provide an overview of the various cutting edge ablative technologies including radiofrequency and microwave. Specific emphasis will be placed on the key biophysical parameters that have enabled the technical breakthroughs that produce clinically acceptable volumes of ablation.

Next, Prof. S. Nahum Goldberg will discuss how thermal ablation can be combined with a host of adjuvant therapies to essentially potentiate improved tumor destruction. Many of these take advantage of strategies that use the hyperthermic temperatures surrounding a zone of thermal ablation. This includes the use of nanoparticles to preferentially deliver mechanistic based drugs to the hyperthermic zone. Agents targeting apoptosis and heat shock proteins will be stressed.

Finally, Dr. Muneeb Ahmed will discuss the recent emergence of data describing potential systemic effects of our focal tumor ablation therapies. Both potentially beneficial immunogenic processes and unwanted secondary systemic ablation induced tumorigenesis will be addressed.

WED 5

The thermo-enhanced effect of transferrin as a thermosensitizer in the cancer treatment with the radiofrequency-induced hyperthermia

Seong-Tshool Hong

Department of Biomedical Sciences and Institute for Medical Science, Chonbuk National University Medical School, Jeonju, Chonbuk, Republic of Korea

One therapeutic approach to treat cancer is hyperthermia in which malignant tissues are exposed to high temperature. Although various physical methodologies have been developed to induce heat in malignant tissues, the hyperthermia using 13.56 MHz radiofrequency electromagnetic wave to induce heat is most frequently used currently in oncology. However, the therapeutic efficacy of the radiofrequency-induced hyperthermia is marginal so that the radiofrequency-induced hyperthermia is typically used with chemotherapy or radiotherapy to treat cancer in modern standard cancer treatments. Therefore, development of a method to amplify the therapeutic efficacy of the radiofrequency-induced hyperthermia is required for the radiofrequency-induced hyperthermia to become another therapeutic option for cancer. Metal ions such as ferric ion have very strong dipole moment, which means that metal ions can interact well to generate heat. Considering the characteristics of metals ions, it would be an ideal thermosensitizer for radiofrequency-induced hyperthermia if non-toxic biological metal ion such as ferric ion could be specifically delivered to cancer. Here, I report that transferrin which contains ferric ions can be used as an ideal thermosensitizer for the radiofrequency-induced hyperthermia. Ferric ions loaded in transferrin were 1.8 times more actively transferred into cancer cells than non-malignant normal cells in vitro. As is the case of in vitro experiment, ferric ions loaded in transferrin was specifically accumulated in the tumor tissue of tumor xenografted mice so that the concentration of ferric ions were 1.5 ~ 3.7 times higher than normal tissues. Because ferric ions were specifically accumulated in the tumor tissue of tumor xenografted mice, ferric ions reacted with the electromagnetic wave-dependent hyperthermia to generate high heat. Therefore, increase in the temperature of the tumor tissue was 2.4 fold higher in the tumor xenografted mice under the 13.56 MHz radiofrequency-induced hyperthermia after injecting transferrin, compared to the 13.56 MHz radiofrequency-induced hyperthermia without transferrin injection. Surprisingly, the overall anticancer efficacy of the 13.56 MHz radiofrequency-induced hyperthermia using transferrin as a thermosensitizer was much better than paclitaxel, and completely eradicated cancer in the tumor xenografted mice.

WED 6

Extreme Exotherms using Polyprotic Acids with Polyamines for Thermochemical Ablation

Rupal Parikh[1], Erik Cressman[2]

[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA, [2]Department of Interventional Radiology, MD Anderson Cancer Center, Houston, TX, USA

Introduction: Implementing minimally invasive techniques leads to lower health care costs, improved mortality and morbidity, as well as decreased recovery time. Thermochemical ablation is a minimally invasive therapeutic modality that is being investigated for its use in treatment of tumors. Acid-base reactions lead to tissue ablation by multiple mechanisms. The purpose of this study is to evaluate two polyprotic acids, sulfuric acid and phosphoric acid, in exothermic reactions with organic polyamines for potential in thermochemical ablation (TCA) of solid tumors.

Materials and Methods: Triplicate aliquots of H_2SO_4 and H_3PO_4 (0.1-9M) were reacted with an equivalent of aqueous organic amines (diethylenetriamine [DETA], 1,3-Diaminopropane [1,3-DAP], and aminoethylethanolamine [AEEA]). The temperatures were measured every 2 seconds for a total of 5 minutes and averaged.

Results: Maximum temperatures were reached within 10 seconds. Exotherms were observed even at the lowest dilutions. Higher concentrations led to increased mean peak temperatures. For H_2SO_4 with AEEA, the peak temperatures at 9M ranged from 117.5-128.8°C (mean 124.2°C). For H_2SO_4 with DAP, the peak temperatures at 9M ranged from 114.6-150.3°C (mean 137.8°C). For H_2SO_4 with DETA, the peak temperatures at 9M ranged from 158.4-171.7°C (mean 166.7°C). For H_3PO_4 with AEEA, the peak temperatures at 9M ranged from 68.1-70.5°C (mean 69.2°C). For H_3PO_4 with DAP, the peak temperatures at 9M ranged from 101.3-110.1°C (mean 106.2°C). For H_3PO_4 with DETA, the peak temperatures at 9M ranged from 157.9-160.9°C (mean 159.6°C). Neutralization of DETA with H_2SO_4 led to the highest mean peak temperatures (at all concentrations). Overall, DETA led to higher mean peak temperatures compared to DAP and AEEA.

Conclusion: Based on these highly exothermic profiles and consistency in concentration dependence, neutralization of polyprotic acids with polyamines has potential for TCA. The increased exothermic yield of DETA compared to the other bases may be due to the presence of 3 nitrogen atoms. Further studies are warranted to evaluate the thermochemical profiles in *ex vivo* tissue.

WED 7

Photothermal Treatment and Radiosensitization of Breast Cancer Cells using Targeted Polydopamine Coated Gold Nanocages

Samir Jenkins[1], Dmitry Nedosekin[1], Vladimir Zharov[1], Ruud Dings[1], Jingyi Chen[2], Robert Griffin[1]

[1]University of Arkansas for Medical Sciences, Little Rock, AR, USA, [2]University of Arkansas, Fayetteville, AR, USA

Noble metal nanoparticles have shown great promise as photothermal therapeutic agents for treatment of a variety of tumors. Tumor targeting is a crucial consideration when designing nanoparticle-based theranostic agents for *in vivo* use. Despite the enhanced permeability and retention effect, the absence of targeting leads to low accumulation at the tumor site. Targeting nanomaterials to particular cells has been shown to increase tumor accumulation and decrease accumulation in normal tissue. Anginex is a synthetic 33mer that specifically targets galectin-1, which is secreted by malignant tumor cells and tumor vascular cells. The goal of the present study is demonstration of the photothermal destruction of triple-negative, galectin-positive breast tumor cells (4T1) using anginex-conjugated polydopamine-coated gold nanocages. Polydopamine was deposited on the nanocage surface using by an oxidative autopolymerization at elevated pH. Anginex was then conjugated to the surface via Michael addition, with binding on the order of 10^4 peptides per nanocage. Photothermal heating of the nanocages was used to induce local hyperthermia which resulted in significant, tumor cell killing in the laser-irradiated region, while little effect was observed in the absence of irradiation in vitro. The untargeted particle was also found to be a potent radiosensitizer and anginex conjugation increased this effect resulting in respective 2- and 4-fold reduction of surviving colonies, respectively compared to radiation alone. The combinatorial use of these two promising therapeutic modalities, as well as their underlying mechanisms, are under further investigation. Photoacoustic flow cytometry was used to demonstrate that nearly 100 % of cells treated with targeted nanocages had bound particles. Targeting of anginex-conjugated particles to these galectin-1 positive cells was further confirmed using darkfield and photoacoustic microscopy. Overall, we found that anginex functions effectively as a targeting agent for these nanomaterials, which may be useful for selective thermal treatment of tumors, for radiosensitization, and potentially as a vehicle for selective delivery of chemotherapeutics.

WED 8

Hyperchemical ablation: exothermic neutralization of organic amines with dichloroacetic acid.

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Purpose: To evaluate exotherms arising from the reaction of dichloroacetic acid (DCA) with five organic amines for potential in thermochemical ablation of solid tumors.

Materials and Methods: Triplicate aliquots of DCA (200µL, 1-9M) were reacted in test tubes with an equivalent of aqueous organic amines (Ethanolamine [EA], N-methylethanolamine[NMEA], Aminoethylethanolamine [AEEA], 1,3 Diaminopropane [DAP], and Diethylenetriamine [DETA]). The temperatures were recorded in five-second intervals for five minutes and averaged.

Results: Increasing concentration resulted in higher temperatures. **Peak temperature in selected trials reached 208°C**. Maximum temperatures were reached within 10 seconds for all trials. At 1M, the peak temperatures were 25.3-26.7°C, a 5°C increase over baseline. At 3M, the peak temperatures were 36.2°-39.9°C and began to differentiate. At 6M, the peak temperatures were 49.5-62.4°C. DAP was the most exothermic at concentrations up to 6M in these conditions. At 9M the average peak temperatures were **65.9-155.6°C** respectively. DETA was the most exothermic amine at 9M, over 50°C hotter than the second hottest amine, DAP.

Conclusions: Based on exotherms observed, the reaction of DCA with organic amines has substantial potential for applications in thermochemical ablation. The concentration-dependent nature of the exotherm allows for a measure of control in thermochemical ablation applications. Ethanolamines were consistently less exothermic than alkylamines, potentially due to the electron withdrawing effect of oxygen that may lower the basicity of the nitrogen. Further study is warranted on system performance with these exotherms ex vivo and in vivo.

WED 9

Computer simulation of a clinically available microwave ablation system and comparison to infrared imaging data of ex vivo tissue studies

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Introduction: Computational modeling techniques are under investigation for application to patient-specific planning of microwave ablation (MWA) treatments. The models often include multi-physics simulation techniques to compute the electric field profile in tissue. Knowledge of the antenna design as well as the temperature dependent tissue dielectric properties are necessary for accurate simulations. However, the proprietary design of applicators in current clinical use are often unknown. Alternative simulation techniques that characterize the power deposition pattern during MWA are needed in order to improve model accuracy without detailed information about antenna composition. The goal of this work is to show equivalency in the specific absorption rate (SAR) profile of between a multi-physics simulation and an experimentally measured SAR profile, given a commercially available antenna with known geometry. Given such concordance, it would be possible to simulate any arbitrary antenna based solely on its experimentally measured SAR.

***Methods*:** To characterize the MWA antenna an infrared (IR) camera (Mikron M7500) was used to determine the spatial SAR during MWA within a split ex vivo liver model. Perseon Medical's (Salt Lake City, UT) short-tip (ST) MWA antenna was placed on top of a tissue sample with the IR camera positioned above the sample. Additional thermocouples were placed at the tissue surface to calibrate temperature values derived from the IR camera. Microwave power (15 W) was applied for 5 min, while interrupting the power every 20 seconds to allow intermittent calculation of SAR. Tissue surface temperature was recorded via IR camera (20 fps, 320x240 resolution). SAR [W/kg] was calculated experimentally from initial rate of temperature rise, and intermittently based on slope before and after power shut-down; these data were compared to SAR profiles calculated from finite element method (FEM) simulations, implementing a coupled electromagnetic-heat transfer solver.

Results: The presented experimental setup allowed calculation of initial SAR, as well as changes in SAR pattern during heating. The SAR patterns derived from FEM simulations and the IR temperature measurements were within 1.5 mm agreement at the $5x10^5$ W/kg SAR isocontour.

Conclusion: The viability of an alternative characterization for MWA antennas via measurements of the specific absorption rate (SAR) within tissue was demonstrated. This method has potential for more accurately simulating MWA when the antenna geometry is unknown, as in most clinical situations.

WED 10

Nanodrug Combined with Ultrasound Hyperthermia and/or Thermal Ablation for Tumor Treatment

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Introduction: Anti-cancer nanodrugs can pass through leaky tumor vessels to achieve therapeutic purposes. When the tumor volume is large, the interior part forms coagulation necrosis, resulting in increased interstitial pressure and distance between blood vessels to hinder drug transport. The purpose of this study is to combine nanodrug (pegylated liposomal doxorubicin, PLD) with ultrasound hyperthermia to enhance the drug delivery in the peripheral region of tumors, and ultrasound ablation surgery for poor circulation region to achieve the overall treatment efficacy. **Methods:** In this study, murine breast cancer cells 4T1 were subcutaneously implanted into the BALB/c female mouse's back. Hyperthermia (HT) was induced by a 1-MHz plane ultrasound transducer, and ablation was conducted by a 0.47-MHz focusd ultrasound transducer. This experimental study included two parts: 5 mg PLD/kg and 3 mg PLD/kg. Each part was divided into four groups: control, PLD, PLD+HT(42°C 10 min), and PLD+ablation(56°C)+HT. When the tumor grew up to 250 mm^3, the first treatment was conducted and then five days later for the second treatment. Body weight and tumor volume were measured every day. The growth response of tumors was also quantified by an In-Vivo Image System (IVIS). H&E histological staining was used to study the tumor tissues. **Results:** The tumor size was significantly smaller for the PLD+HT group than the PLD group. For a dose of 5 mg/kg PLD, the tumor size was not significantly different between the PLD+HT group and the PLD+ablation+HT group, while the dose reduced to 3 mg/kg the tumor size of the PLD+ablation+HT group was obviously smaller than that of the PLD+HT group. The result of IVIS imaging showed that both 5 mg/kg and 3 mg/kg PLD resulted in lower photon signals than the control group. The groups conducted with both PLD and additional ultrasound therapies showed lower photon signals than the PLD alone group. Nevertheless, there was no significant difference between the PLD+ablation+HT group and the PLD+HT group. The H&E histological staining of tumors showed that hyperthermia could induce inflammation, and the ablated tumor tissues were loose and seriously destroyed. **Conclusion:** Hyperthermia could increase nanodrug accumulation in tumor tissues and improve therapeutic efficacy. When a high dose of PLD (5 mg/kg) was used, additional ablation could not significantly improve therapeutic results. On the other side, the combination of hyperthermia and ablation could significantly enhance the treatment efficacy for a low dose of PLD (3 mg/kg).

WED 11

Laser ablation prediction via global optimization and cross-validation

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Introduction: Computational modeling has the potential to aid MR-guided laser induced thermal therapy (MRgLITT) by providing neurosurgeons information guiding the number and location of laser applicators. A common impediment to *a priori* modeling has been a dearth of available parameter data. A possible solution is to use an inverse problem to infer the optimal parameter data from *a posteriori* patients and then predict on new patients. This abstract reports simulated 'prediction' scenarios by using leave-one-out cross-validation (LOOCV).

Methods: MR thermal images from N = 22 MRgLITT ablations using the Visualase 980 nm applicator were used as the training and cross-validation cohort. Given the large computational burden, a simple bioheat model is employed. It is a closed-from, steady-state point source that is repeated 50 times along a line segment to approximate the Visualase laser's line source. The point source is computed in a massively parallel GPU kernel, providing prodigious speed and allowing for global optimization of both microperfusion, ω, and the effective optical coefficient, μ_{eff}. During optimization, the objective function was the Dice similarity coefficient (DSC) between the model's 57 ^{o}C isotherm and the patient's Arrhenius damage at $\Omega = 1$ using Henriques 1948 parameters. DSC is an overlap metric comparing two regions; DSC values range from 0 to 1, and > 0.7 is considered a 'good' prediction. At the end of global optimization, the DSC is known for the entire μ_{eff}-ω space, sampled with 65 ω points by 176 μ_{eff} points = 11,440 total μ_{eff}-ω points. The ω space ranges from 3 to 16.5 kg m^{-3} s^{-1}. The μ_{eff} spaces ranges from 50 to 400 m^{-1}. The many DSC results from the 11,440 runs represent a look-up table that can rapidly execute the LOOCV algorithm without any subsequent bioheat model runs. LOOCV allows us to create simulated prediction runs.

Results: To four significant figures, the DSC results from LOOCV on the N = 22 patient datasets were: 0.7771 mean, 0.8297 median, 0.1288 standard deviation, 0.4791 minimum, and 0.9186 maximum. 17 of 22 patient datasets had DSC > 0.7 during LOOCV.

Conclusion: The use of a computationally efficient, trained model that is run within a GPU kernel allows for model training via global optimization of a large two-parameter space and cross-validation amongst a sizable patient cohort.

WED 12

Multifunctional applications of near-infrared fluorescent magneto-albumin nanocarriers for cancer hyperthermia

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Nanotechnology-based materials can be used to deliver heat mediated by the interaction of nanostructures with electromagnetic fields. Magnetic hyperthermia (MH) and photothermal (PTH) therapies are examples of this approach. Both treatment strategies have advantages and limitations, which need to be addressed in order to improve the efficacy for cancer treatment. In this work we report the development of a multifunctional nanocarrier for cancer hyperthermia. The nanoparticle platform consists of manganese-ferrite based magnetic nanoparticles surface coated with bovine serum albumin containing a near infrared heptamethine indocyanine dye, IR-780. The nanoparticle charaterisation was performed using several techniques (DLS, TEM, FEG-SEM, XRD, VSM, HPLC, among others). The nanocarrier has a spherical shape with a size around 100nm. In vitro studies demonstrate the applicability of such nanostructure for both therapies, PTH and MH. PTH was investigated using a laser with a wavelength of 800nm, while MH studies were performed in a broad range of field amplitudes (up to 200 Oe) and frequencies (100-800kHz). Dynamic hysteresis contribution to heat generation is confirmed from the frequency study. Also, the MTT cell viability tests demonstrate the chemotherapeutic potential of the nanoparticle due to IR-780. The in vivo studies were performed using the Ehrlich tumor model, which is a murine mammary carcinoma. Using the fluorescence molecular tomography (FMT) technique, operating at the first biological window, we were able to obtain the nanocarrier three-dimensional distribution. In vivo magnetic hyperthermia experiment is performed after intratumoral injection of the nanocarrier, which monitors in real-time the animal body surface temperature with infrared thermography. In order to compare those results with computer simulations, we reconstruct the body surface using optical tomography, while the tumor geometry was obtained from ultrasound images and the three-dimensional nanocarrier distribution was obtained from FMT. From this approach we are able to estimate the three-dimensional heat delivery in the tumor. Our results indicate that the multifunctional nanocarrier has high potential for cancer treatment. Finally, the perspectives of using the nanocarrier for cancer hyperthermia studies are briefly highlighted.

WED 13

Hypofractionated Radiation-Magnetic Nanoparticle Hyperthermia-Immunotherapy Treatment of Spontaneous Canine Tumors

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Introduction: The majority of current cancer cures are achieved with multimodality therapy. Radiation, surgery and chemotherapy are the most common and accepted approaches. However, altered radiation fractionation schemes, immunotherapy, nanotechnology and hyperthermia are promising adjuvants to these techniques. Although mathematical modeling, ex vivo testing, cell culture and rodent tumor experimentation are and have been important components of this research, the primary goal of this presentation is to demonstrate the safety and efficacy of optimally delivered hypo-fractionated radiation, iron oxide nanoparticle hyperthermia and intra-tumoral immunotherapy, in a cranially-based large animal spontaneous tumor model.

Methods: MRI/CT based tumor imaging and treatment planning, hypo-fractionated electron or photon radiation (6 MV/MeV) delivered in 3-6 fractions at a total dose of 36-40 Gy, intra-tumoral iron oxide nanoparticle hyperthermia delivered in 2 fractions at a minimum CEM of 30 / fraction, at the tumor normal tissue boundary, and intra-tumoral delivery of cowpea mosaic virus (CPMV) at a dose of 200 ug / treatment. Currently,15 dogs (all with life threatening invasive/malignant disease) have been treated; 12 oral tumors, 1 brain tumor, 1 nasal tumor, 1 digit tumor.

Results/Conclusion: although the potential for late effects remains, preliminary results show that this novel, mutimodality, translationally relevant treatment regimen is safe and capable of significantly extending the tumor free survival and life expectancy of these patients.

WED 14

X-ray guidance for magnetic hyperthermia of liver cancer: bench-to-bedside

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Introduction: Primary liver cancer is the third most common global cause of cancer-related death. Due to its indolent course, most patients have advanced disease at the time of diagnosis, leaving only non-surgical palliative treatment options. Among these, image-guided interventions have emerged as potent minimally invasive procedures that offer individualized tumour targeting. Yet, these procedures only modestly improve patient survival, creating a need for new technology. Magnetic iron oxide nanoparticles (MIONs) offer capability to provide both heating and imaging when localized within tumour tissue. An x-ray image-guided approach offers real-time visualization of MION distribution with feedback on effective tumour targeting and treatment planning, creating the potential for individualized therapy.

Aim: To review the current status of x-ray image-guided magnetic hyperthermia for treatment of liver cancer and to offer some insights of our effort to translate this technique to the clinic.

Materials: We have recently developed a MION formulation that provides dual imaging (x-ray and magnetic resonance), heating with low-power magnetic fields, and that enables co-formulation with standard chemotherapy agents. This formulation comprises MIONs, embedded in the oily medium of lipiodol. We will present our x-ray image guided approach for tumour targeting, iron quantification techniques using dual energy/dual source CT imaging, CT thermometry and CT perfusion for assessing tumour response to therapy.

Results: We will discuss future potential of x-ray guidance for magnetic hyperthermia and the factors needed to non-invasively plan magnetic hyperthermia treatment. We will present preclinical examples of this approach, using in vitro data, as well as data from the rabbit liver VX2 cancer model.

Conclusion: We will present the current status and role of x-ray guidance for magnetic hyperthermia of liver cancer, along with some preclinical examples of its utility.

WED 15

Assess the effects and mechanisms of the combination therapy: heat therapy (HT) and external-beam radiotherapy (RT).

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Background: Prostate cancer is one of the most common cancers in men worldwide, and choosing among available treatment options (radical prostatectomy, high-dose external-beam radiotherapy (RT), hormone ablation) remain the technical challenges because these treatments still carry high risks. Heating increases release of certain heat-shock proteins into the tumor microenvironment, which can also stimulate downstream immune activity. Previous studies have shown nanoparticle-mediated (MION) heat therapy (HT) produces tumor-specific immune-modulating effects. In this study, we hypothesize that a combinatorial therapy that includes MION-mediated HT with RT will produce local tumor control with potential for reduced total tumor burden.

Methods: We developed a male FVB mouse model bearing the hi-Myc expression prostate cancer cell line Myc-Cap. This mouse model was used to test our hypothesis that a combinatorial therapy that includes MION-mediated HT with RT will reduce total tumor burden. In this study, JHU-MIONs, an aqueous suspension of aggregated crystals of magnetic Fe_3O_4 /Fe_2O_3, was employed. MIONs were intratumorally injected into tumor. Then, mice were randomly divided into therapy cohorts (n=5), RT (3 GY), HT (30-60 CEM43), or RT+HT (3Gy+30CEM43). 24 hours after JHU-MIONs injection, alternating magnetic field (AMF) was applied to tumor to generate heat sufficient to significantly sensitize cancer cells. Temperatures are measured at one-second intervals with AMF-resistant optical fiber temperature probes. Mice were sacrificed 48 hours to one week after AMF treatment, and tissues were collected for iron quantification and histopathology.

Results: Preliminary data suggested that heat therapy (HT) and high-does external-beam radiotherapy (RT) alone can restrain local tumor growth. In addition, combination therapy with both HT and RT can produce immune-modulating alterations in the tumor microenvironment. Our data suggested that combing HT and RT can create a synergistic effect.

Conclusion: In conclusion, recognized synergistic interaction between heat and radiation creating a compelling tumor microenvironment to explore combinations with IT for enhanced efficacy with reduced toxic effect.

WED 16

Effects of magnetic nanoparticle-induced hyperthermia on DNA damage signaling

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Background: This study explores the hyperthermia-induced genotoxic effects of bionized nanoferrite (BNF) particles and their involvement in the activation of signal transduction pathways of DNA damage response (DDR). DDR is an extensive system of signaling pathways that responds largely to double (DSB) and single strand breaks (SSB). This repair network is essential for genomic stability, replication, cellular homeostasis and normal physiological development. ATM (ataxiatelangiectasia mutated) and ATR (ataxia-telangiectasia and Rad3–related) protein kinase are the regulators of DNA damage checkpoints that manage the progression, delay and arrest of the cell cycle. As a potent radiosensitizer, hyperthermia has also been shown to activate signaling pathways that are complementary to those induced by ionizing radiation. Elevated temperatures alter protein integrity and hinder DNA repair machinery, rendering cells susceptible to DNA damage through radiation. Macroscopic heating via hyperthermia of cancer cells has been shown to induce the phosphorylation of downstream effectors CHK-1 and CHK2. Although these finding are quite promising, delivery of a sustained thermal dose by other methods have not extensively been explored.

Methods: Magnetic nanoparticle-mediated heating via exposure to an alternating magnetic field was studied comparatively with water bath hyperthermia in human colorectal cancer (HCT116) cells. Cytotoxic activity was explored through clonogenic survival assays followed by further biological characterization. Western blot analysis was used to determine downstream phosphorylation of checkpoint proteins CHK-2 and CHK-1 (phosphorylated by ATM and ATR, respectively). ATM/ATR activation was investigated and visualized through confocal microscopy.

Results: The intracellular and extracellular presence of BNF particles at the observed concentrations suggested low cytotoxicity. A cytotoxicity profile of water bath hyperthermia was determined exposing HCT116 cells to temperatures between 42 to 45 degrees Celsius for comparison with nanoparticle-mediated hyperthermia. These results and evidence of signal transduction will be presented along with examination of gamma-H2AX foci abundance.

Conclusion: The results suggest that transient heating generated by nanoparticles may have unique effects on cellular communication and signalling.

WED 17

Cumulative effect of thermal dose to total tumor regression in Sarcoma 180 murine model using magnetic nanoparticle hyperthermia at low field amplitude

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In this work we evaluate the efficacy of magnetic hyperthermia (MH) therapy in murine tumor model (Sarcoma 180), which is a solid and subcutaneous tumor induced in swiss mouse. The heat centers consist of manganese ferrite-based nanoparticles with a mean size around 13nm and a size dispersity of 25 percent, as determined by transmission electron microscopy. Vibrating sample magnetization data, at quasi-static magnetic field conditions suggest, a superparamagnetic-like behaviour. The nanoparticles are able to produce a considerable amount of heat at quite low magnetic field amplitudes (around 10kA/m) at a frequency of 300kHz. The origin of heat generation is attributed to dynamic magnetic hysteresis. Four animal groups were evaluated, a control (n=2) not submitted to MH, and three others that passed through distinct number of 30-min hyperthermia procedures, namely one-session (n=2), two-sessions (n=2) and five-sessions (n=2). Our results indicate total tumor regression in some animals and decrease in the tumor growth rate in others, when compared with the control group. Animals were monitored up to 180 days after MH treatment. Although we always injected intratumorally the same amount of magnetic nanoparticles, the temperature profile between the animals were not the same. The surface temperature measurements were obtained using fiber optic thermometers and also infrared thermography with high temperature precision. Further, a surface CEM43 thermal dose (TD) was calculated for each animal and correlated with tumor evolution. We found no effect on tumor growth if CEM43 thermal dose is lower than 3. For CEM43 TD within the range of 40 to 80 we observe tumor regression, but unfortunately the tumor regrowth after 20 to 50 days. While total tumor regression was observed for a heat dose of higher than 150. In addition, we also performed a hyperthermia study in the S180 cell culture using heat bath, for 30 min, in a wide temperature range (41 to 60 degrees). The flow cytometry analysis corroborate with the in vivo results. In conclusion, we report total tumor regression using low magnetic field amplitudes and manganese-ferrite nanoparticles if thermal dose is high enough.

WED 18

Influence of magnetic nanoparticle location on the survival of SKBR3 cells

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Introduction: When exposed to an alternating magnetic field (AMF), magnetic nanoparticles generate heat that can be delivered to tumor cells. It was long hypothesized that intracellular hyperthermia is therapeutically superior to extracellular hyperthermia. Theoretical and experimental results have invalidated that hypothesis. However, recent work reports that membrane-bound and internalized antibody-labeled magnetic nanoparticles produce a significant reduction in cell viability following AMF exposure without a perceptible temperature rise. To elucidate the influence of the nanoparticle location on the cell viability, we study three distinct delivery modes: extracellular, intracellular and membrane-bound.

Methods: Bionized NanoFerrite (BNF) particles (80 nm) were conjugated to the humanized anti-HER2 monoclonal antibody, trastuzumab. These BNF-HER nanoparticles were incubated with cultured HER2-overexpressing SKBR3 cells. Immunohistochemistry, Prussian Blue staining and Scanning Electron Microscopy (SEM) were performed to confirm that the BNF-HER nanoparticles were bound to the cell membrane. To achieve intracellular hyperthermia, starch-coated BNF-particles (80 nm) were loaded into SKBR3 cells by means of Poly-D-Lysine. The same starch-coated BNF-particles were added to SKBR3 cells without loading agent to study effects of extracellular hyperthermia for comparison. The iron content of each sample was measured using a wet chemical (ferene-s) assay. Cell pellets in a range of 0.9×10^6 to 11.46×10^6 cells were exposed to AMF with a frequency of 150 kHz and amplitude of 36 kA/m for 30 minutes. Cell pellet surface temperatures were recorded with FISO temperature probes. Subsequently, thermal dose was calculated using the CEM43 method. Cytotoxicity was evaluated by clonogenic survival assay. Survival fraction was calculated relative to matched controls having the same iron concentration without AMF exposure.

Results: For all three nanoparticle-cell configurations, ferene-s assay results confirmed a mean iron concentration of 10 pg/cell. Net temperature increases of the cell pellets were linear with total iron mass. Rate of temperature rise for all three different nanoparticle-cell configurations exhibited the same slope, which was higher than predicted by the heat diffusion model. Measures of surviving fractions from clonogenic assay revealed no significant differences among the three sample configurations, and were consistent with water bath hyperthermia.

Conclusion: Current understanding of physics of heat transfer in fluidic systems predicts the measured macroscopic temperature rise to be identical in the three experimental configurations. Our results are consistent with this interpretation, and assays of heat-related cytotoxicity are also consistent with this prediction. These results challenge recently published findings suggesting alternate mechanisms of toxicity operate within cells harbouring membrane-bound nanoparticles.

WED 19

In vivo Quantification of Iron Oxide Nanoparticle Biodistribution using Positive T_1 Contrast with ex vivo heating.

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Iron oxide nanoparticles (IONPs) have great potential in the field of thermal medicine, due to their heat capabilities. The ideal IONP concentration for heating is 1 to 10 mg Fe/mL, however, this range is difficult to quantify with clinical available non-invasive imaging techniques (CT and MRI). Advancement of this application necessitates a method to non-invasively image and quantify IONP distribution. Herein, the most recent work to improve two important correlative areas, non-invasive IONP imaging and quantification and the corresponding SAR, is described.

MRI has been demonstrated to non-invasively quantify low IONP concentrations (< 0.1 mg Fe/mL), but fails at higher concentrations due to rapid signal decay. As a result IONPs appear as signal voids in images acquired with conventional gradient- and spin-echo pulse sequences. Sweep imaging with Fourier transformation (SWIFT) uses a time-shared excitation and acquisition, allowing an acquisition delay of only ~ 7 µs. In this way, SWIFT preserves signals from spins with extremely short signal decay, yielding quantifiable positive contrast images via T_1 decay. Previous reports have demonstrated positive contrast as high as 3 mg Fe/mL in agarose. This most recent work assess the effects of IONP intra-organ distribution, post-injection duration, and IONP surface charge on the linear correlation between R_1 (= $1/T_1$) and the tissue iron concentration. Quantifiable measurements as high as 3.2, 1.9, and 0.5 mg Fe/g tissue for the spleen, liver, and kidneys, respectively are demonstrated. This data was verified with Prussian blue histology, transmission electron microscopy, and inductively coupled plasma optical emission spectroscopy.

Ex vivo heating studies were performed on tissues acquired after in vivo imaging. An alternating magnetic field was produced at 190 kHz and 20 kA/m generated with a 1 kW inductive heating system with a 2.75-turn, water-cooled copper coil. A linear correlation in the liver between the iron concentration and the specific absorption rate (SAR) is evaluated based on changes in IONP surface charge and post-injection duration. Previous work with this IONP has demonstrated a consistent SAR (180 W/g Fe) in conditions mimicking biological environments. Interestingly, the SAR of IONPs in the liver demonstrated a dependence on IONP charge (114 and 246 W/g Fe for -19 and -32mV, respectively). Furthermore, an increase in SAR was observed between 24 h to 1wk (272 W/g Fe) in IONPs with a high negative charge. Continued work will focus on understanding the heating effects induced by the close proximity of nanoparticles caused by cellular uptake.

WED 20

Microwave hyperthermia applicators - Optimization of SAR and temperature distribution by aid of ferromagnetic nanoparticles

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Various kinds of ferromagnetic nanoparticles and various ways of EM field excitation of these nanoparticles were described till now to be used in cancer treatment by microwave hyperthermia. Our work is oriented on feasibility study of possible use of ferromagnetic nanoparticles to optimize SAR and temperature distribution of microwave hyperthermia applicators (e.g. waveguide type) working in the frequency range of 10^2 up to 10^3 MHz, i.e. the frequencies used typically for regional and/or deep local hyperthermia. In case of verification of this idea higher level of possible focusing of EM power into deeply situated tumours can be expected. The first evaluation step of possible effectiveness of nanoparticle heating by microwave hyperthermia system was done via numerical EM field simulation (SEMCAD X was used in this case). Models of two similar phantoms (one with 3 g of FeSi1416 nanoparticles and other one without nanoparticles) were created and their EM exposure was done by aid of rectangular waveguide applicator. Significantly increased heating effectiveness has been found for phantom with nanoparticles. The same kind of results we have got in second step of above mentioned idea verification, when we created real laboratory phantoms and we heated them by waveguide hyperthermia applicator at the frequency 434 MHz. Conclusions: By injecting ferromagnetic nanoparticles into treated tissue, the effectiveness of microwave hyperthermia treatment can be significantly improved. In particular, the depth of penetration can be increased and the focusing potential of the EM and thermal field can be improved.

WED 21

Magnetostructural characterization of iron oxide nanoparticles for cancer hyperthermia applications

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We provide a detailed characterization of the heating performance of various single-crystallite and multi-crystallite iron oxide nanoparticles as agents for thermal dose delivery in hyperthermia-based treatment of tumors. Ineffective heat treatment due to insufficient thermal potency of nanoparticles remains a major obstacle in cancer hyperthermia. Here, we provide optimal nanoparticle design criteria and alternating magnetic field (AMF) driving conditions for therapeutically relevant thermal doses in tumors.

The specific loss powers (SLP) of various commercial and proprietary iron oxide nanoparticles were experimentally evaluated as a function of externally applied magnetic field (AMF) magnitudes and frequencies. The measured SLP values were correlated with magnetostructural properties using SQUID magnetometry, electron microscopy, and X-ray diffractometry.

The magnetic, structural, and heating data will be presented in the context of prevailing models and with a view to applications for cancer hyperthermia in mouse models.

WED 22

Nanoparticles and their targeting: A study in preclinical model of HER2+ breast cancer

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Background:Nanoparticle-based therapies and drug delivery are emerging anticancer agents. Some nanoparticle constructs have received regulatory approval for use as carriers of anticancer drugs, yet their demonstrated ability to improve disease control often fails to surpass that of their small-molecule counterparts. Results of clinical trials often do not recapitulate the preclinical experience, halting further development. The size of nanoparticles provides new opportunities and challenges for cancer therapy that are unlike those with small-molecule drugs. Nanoparticles interact with the host immune system and the tumor microenvironment in ways that are unique to nanoparticles that may critically affect performance and tumor response. In this study we sought to systematically study the impact of the host immune system, targeting, and tumor biology on the distribution of ferrite nanoparticles in mouse models of HER2 overexpressing breast cancer by varying the immune status of the host.

Methods:To study uptake and distribution of ~80 nm diameter plain ferrite (BNF-plain) and Herceptin-conjugated ferrite nanoparticles (BNF-Her), we used HER2+ human breast cancer cell lines – MCF7/HER2 and BT474 and HER2- MDAMB231 and MCF-7. These cells were also used to generate orthotopic xenograft tumors in two strains of mice having varied immune status. Tumors were implanted in athymic nude mice and in NOD-SCID Gamma (NSG). For each animal model there were 4 groups of 5 animals bearing 2 tumors in the 4th mammary gland on either side. When tumor volume measured 150-200 mm^3, animals were randomized into 4 groups. Depending upon its designated cohort each animal received PBS, BNF-plain, BNF-Her or Herceptin intravenously. Mice were sacrificed 24 hours post injection to collect tumors, mammary gland, lymph nodes, lungs, liver, kidney and spleen. We compared the nanoparticle content and distribution among the tumors and between the two models using histopathology and inductively-coupled mass spectrometry.

Results:Both BNF-plain and BNF-Her particles accumulated in the vicinity of the tumor vasculature, but more accumulated in NSG mice than in nude mice, suggesting a more permissive environment. The distribution of BNF-plain nanoparticles was confined to sites near vascular structures; however, BNF-Her particles were distributed throughout the tumor tissue. BNF-Her infiltration into the tumor depended on the level of HER2 expression in tumor.

Conclusion:These results demonstrate that nanoparticle access to tumor vascular structures and retention within these depends upon host immune status; but, that significant nanoparticle distribution beyond the vicinity of blood vessels throughout the tumor will require molecular targeting of growth factor receptors on tumor cells.

WED 23

Myeloid-derived Suppressor Cells Provide Novel Mechanism of Resistance at Thermally-Sensitive Vascular Checkpoints during Cancer Immunotherapy

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Cancer immunotherapy has emerged as a promising approach to achieve durable responses in primary and metastatic cancer patients that are refractory to standard chemotherapy and radiotherapy. However, evidence that only a subfraction of cancer patients benefit from immunotherapy raises important questions about the underlying mechanisms of resistance. We have previously identified the tumor vasculature as a thermally-sensitive checkpoint controlling the efficacy of adoptive T cell immunotherapy in preclinical murine tumor models. The intrinsic adhesive properties of tumor vessels govern whether cytotoxic $CD8^+$ T cells gain access to tumors which is a necessary step to initiate contact-dependent lysis of tumor cell targets. We found that tumor vessels can be converted from low-to-high sites of cytotoxic $CD8^+$ T cell trafficking using thermal therapy regimens spanning a wide temperature range; i.e., systemic thermal therapy in which core body temperature is elevated to 39.5ºC for 6 hours, or radiofrequency ablation whereby local temperatures within tumor tissue are increased to 90ºC for 1 minute. We determined that a unifying feature of thermally-sensitive tumors was low infiltration by myeloid-derived suppressor cells (MDSC). However, tumors with a high intratumoral MDSC burden were refractory to adjuvant thermal therapy in the context of adoptive T cell transfer immunotherapy, as determined by the failure of tumor vessels to support E/P-selectin, CXCR3, and ICAM-1–dependent trafficking of cytotoxic $CD8^+$ T cell in preclinical models. MDSC located within the tumor microenvironment were further shown to be causal in blocking T cell trafficking across tumor vascular checkpoints through gain-of-function and loss-of-function approaches. Finally, we identified IL-10 as a key mediator of MDSC-induced inhibition of vascular function in tumors. Taken together, these studies identify a novel mechanism of immune evasion executed by intratumoral MDSC that subverts the immune-boosting activity of thermal therapy by preventing T cell access to tumor cell targets within the complex tumor microenvironment. Supported by grants from the NIH (CA79765 and AI082039) and the Jennifer Linscott Tietgen Family Foundation.

WED 24

Membrane associated Hsp70 as a tumor-specific target structure for theranostic *in vivo* targeting of a wide variety of malignancies

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Introduction: The major stress-inducible Heat shock protein 70 (Hsp70, Hsp1A1) is frequently overexpressed in a wide variety of human and murine tumor entities. Hsp70 plays a key role in development, viability and metastasizing capacities of tumor cells in vivo. We additionally could detect a membrane-associated form of Hsp70 on a wide variety of tumor entitites, while being absent in normal corresponding tissues. Hence, this tumor exclusive, membrane associated localization of Hsp70 might represent a tumor selective target structure. For therapeutic in vivo tumor targeting, we have generated the Hsp70 specific, monoclonal Antibody cmHsp70.1 for induction of antibody dependent cellular cytotoxicity (ADCC). Diagnostic in vivo tumor targeting with favourable biodistribution capabilities could be achieved by the 14mer "Tumor-cell Penetrating Peptide" TPP.

Methods: After systemic application into tumor bearing mice, the tumor cell selective accumulation of the Hsp70 specific compounds was determined using fluorescence imaging and positron emission tomography techniques. The ADCC mediated, therapeutic potential of the Hsp70 specific monoclonal Antibody cmHsp70.1 in tumor bearing mice was evaluated tracing the tumor growth delay and overall survival following repeated i.v. applications. Potential adverse on-target toxicity on normal tissue was screened in preclinical dose escalation studies.

Results: Immunization of mice with an Hsp70 derived peptide resulted in the generation of the IgG1 mouse mAb cmHsp70.1. The epitope recognized by cmHsp70.1 mAb, which has been confirmed to be located in the substrate binding domain by SPOT analysis, is frequently detectable on the cell surface of human and mouse tumors, but not on normal tissues. ADCC could be induced by cmHsp70.1 mAb in membrane $Hsp70^+$ tumor cells *in vitro* and *in vivo*, mediated by unstimulated mouse spleen cells. Three consecutive injections of cmHsp70.1 mAb into tumor bearing mice significantly reduced tumor growth and enhanced the overall survival. These effects were associated with infiltrations of NK cells, macrophages, and granulocytes. Biodistribution studies of cmHsp70.1 mAb and TPP peptide in tumor bearing mice revealed a significant, tumor-selective accumulation of the compounds with reduced off-target enrichment of the 1.5kDa TPP peptide in normal organ tissues, compared to the 150kDa IgG1 cmHsp70.1 mAb.

Conclusion: The tumor specific targeting potential of the Hsp70 specific monoclonal antibody cmHsp70.1 and subsequent induction of tumor-directed immune response was proven in preclinical mouse tumor models. Given the high proportion of membrane Hsp70 positive tumor entities might enable to establish a novel, tumor selective therapeutic targeting strategy with reduced adverse on-target side effects.

WED 25

***in situ* vaccination to treat cancer using plant-derived viral like nanoparticles from compea mosaic virus**

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Immunotherapy for cancer is making impressive impacts in the clinic. One strategy very relevant to thermal medicine is *in situ* vaccination This approach puts immunostimulatory reagents into an identified tumor to break the local immunosuppression, stimulate a local anti-tumor approach and most importantly stimulate systemic antitumor immune responses to eliminate metastatic disease. This is essentially an antitumor therapeutic vaccination, because the tumors provide the antigens and the adjuvants are the immunostimulatory reagents, thus "*in situ* vaccination". There are many immunostimulatory reagents that can be used and each has different capabilities. Here we report on plant-derived viral-like nanoparticles from Cowpea Mosaic Virus used in mouse cancer models. These particles are only composed of viral capsid proteins, have no nucleic acids and have no recognized immunostimulatory reagents. However, they are strongly immunostimulatory through unknown pathways and cause dramatic changes in the tumor microenvironment that lead to primary tumor reduction and potent resistance to metastatic tumors. The treatment is immune-mediated since it requires IFN-γ, IL-12, and adaptive immunity. Tumor reduction or elimination occurs in many anatomic locations and with multiple tumor types and in multiple strains of inbred mice. Treatment of a primary tumor by direct intratumoral injection mediates robust rejection of a rechallenge with the same tumor. The mechanisms and pathways of immunostimulation are under investigation. In addition to the inherent immunostimulatory adjuvant properties of these nanoparticles, they are a versatile platform to which other reagents for immune modulation can be attached. This demonstration of the value of viral-like nanoparticles for treatment of cancer opens a new avenue of cancer immunotherapy.

WED 26

Magnetic nanoparticle radiation sensitization

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Introduction: Research efforts have demonstrated increased sensitization of cancer cells to ionizing radiation (IR), when in the presence of iron oxide nanoparticles (IONP). This effect was further enhanced when localized, IONP mediated hyperthermia, was induced. Additionally, suppression of distant tumors has been demonstrated using localized IONP hyperthermia. Published work from our collaboration has shown that mild hyperthermia (heat in the 39-45°C range) applied by a combination of IONP directly injected into a tumor and heated by exposure to an AMF, can induce an antitumor immune response against re-challenge of melanoma tumors on the same animal. The goal of the proposed work was to combine these research efforts to investigate “abscopal” effects, which may utilize the yet to be determined mechanism of IONP-radiation interaction, as well as IONP-alternating magnetic field (AMF) hyperthermia. Objective/Hypothesis: Treatment of the primary tumor, with radiation, IONP and hyperthermia, may induce an immune-based systemic antitumor response, which may be advantageous for the treatment of distant disease.

Methods: Fractionated ionizing radiation (6 MeV, 3 Gy X 5) was used in the C3H/MTGB model. On days two and four, IONP were directly injected into the flank tumor and were allowed to incubate for four hours to allow for distribution and intracellular uptake, before receiving the radiation fraction. IONP-AMF induced hyperthermia followed irradiation for some treatment arms. Tumors were exposed to 43°C for 30 minutes. The cumulative equivalent minute (CEM) relationship was also used to describe thermal dose. Treatment outcome was measured by tumor regrowth, as indicated by the number of days it took to reach three times the initial treatment volume. Measurements were taken to determine leukocytes in blood and tumor, changes in cytokines and chemokines in blood and tumor, as an indication of immunostimulation.

Results: The use of IONP as a radiation sensitizer significantly improves local tumor regrowth delay when applied as part of fractionated radiation therapy. At the time of this submission, the study is ongoing, with immune-based systemic antitumor response continuing to be characterized.

Conclusion: With any ionizing radiation, there are potential short and long term toxicities. We propose, by using established ionizing radiation therapies, in combination with an adjuvant IONP protocol, the necessary radiation dose to achieve local control, may potentially be reduced. In addition to reducing the complications due to the radiation, the potential to treat undetected metastasis has the potential to significantly improve patient outcomes.

WED 27

The impact of β-adrenergic signaling on radioresistance and anti-tumor immunity in murine tumor models

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Our laboratory has demonstrated that mildly cool housing temperatures, a stress known to be mediated by sympathetic nerve activity and β-adrenergic receptors (β-ARs), can significantly enhance the growth and metastasis of tumors in murine models by suppressing anti-tumor immunity. Furthermore, we have shown that mild cool stress also decreases the sensitivity of cancer cells to several types of chemo- and targeted therapeutics. These data strongly suggest that in murine models, baseline levels of tumor growth and tumor immunology may be significantly influenced by housing temperature and the degree of adrenergic stress experienced by tumor bearing mice. To investigate the effects of increased adrenergic signaling on anti-tumor immunity, we used β-AR antagonists (β-blockers) to block β-AR signaling resulting from mild cold stress. The addition of β-blockade to mice injected with 4T1 breast or B16-OVA melanoma tumors significantly delayed tumor growth, recapitulating the slower tumor growth observed in mice housed at thermoneutrality where cold stress is alleviated. However, β-blockade had no effect on the growth of tumors in immunodeficient SCID mice indicating a dependence on the adaptive immune response. In mice bearing B16-OVA tumors, β-blockade also slowed tumor growth and this beneficial effect was negated by CD8+ T-cell depletion. Finally, we determined the effect of β-blockade on the efficacy of anti-programmed cell death receptor-1 (α-PD-1) immunotherapy. In both the 4T1 and B16-OVA models, reversing immunosuppression by β-AR blockade in combination with boosting the anti-tumor T-cell response with α-PD-1 significantly slowed tumor growth in mice at standard housing temperatures compared to either treatment alone. We also examined the effects of adrenergic stress signaling on radioresistance. We addressed this question by stimulating β-ARs on Pan02 (murine) and Mia-PACA2 (human) pancreatic tumor cells as well as 4T1 (murine) breast tumor cells *in vitro* and performed clonogenic assays. Treating the pancreatic cell lines with a β-agonist improved survival and proliferation at varying doses of radiation when compared to untreated controls similar to our earlier studies using chemotherapy. However, 4T1 does not express β-ARs, and likewise, β-AR activation had no impact on radioresistance compared to untreated controls. In summary, β-AR activity appears to play a fundamental role in the regulation of both anti-tumor immunity as well as intrinsic therapeutic sensitivity. Therefore, strategic combinations of β-receptor antagonists with chemo-radiation therapy, or immunotherapy may significantly improve tumor control.

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WED 28

Interleukin-6 Induced Acute" Phenotypic Microenvironment Promotes Th1 Anti-Tumor Immunity In Cryo-Thermal Therapy Revealed By Proteomics

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Cryo-thermal therapy has been emerging as a promising novel therapeutic strategy for advanced cancer treatment, which enhances remission of metastasis. To better understand the mechanism that boosts the anti-tumor activity, we utilized a spontaneous metastatic mouse model and quantitative proteomics to compare N-glycoproteome changes in 94 serum samples with and without cryo-thermal treatment. We quantified 231 highly confident N-glycosylated serum proteins using iTRAQ shotgun proteomics. Among them, 53 showed significantly discriminated regulatory patterns over the time course, in which the acute phase response emerged as the most enhanced pathway. The anti-tumor feature of the acute response was further investigated using quantitative parallel reaction monitoring proteomics and flow cytometry on 23 of the 53 significant proteins. We found that cryo-thermal therapy reset the tumor chronic inflammatory to an "acute" phenotypic state, with up-regulated expression of many acute phase proteins including interleukin 6 (IL-6) as a key regulator. The IL-6 mediated "acute" phenotype transformed IL-4 and Treg-promoting ICOSL expression to Th1-promoting IFN-γ and IL-12 production, augmented complement system activation and $CD86^{+}MHCII^{+}$ dendritic cells maturation and enhanced the proliferation of Th1 memory cells, and thus consequently shifted the tumor immunosuppressive to Th1 immunostimulatory. In addition, we found an increased production of tumor metastatic inhibitory proteins under such "acute" environment, favoring the anti-metastatic effect. In summary, we demonstrated that the cryo-thermal therapy induced, IL-6 mediated "acute" phenotypic inflammatory microenvironment restoring the anti-tumor activity of the host immune system, which provides important insights on improving the therapeutic effects for the advanced breast cancer treatment.

WED 29

Can hypoxia/HIF- driven adenosine accumulation in the tumour microenvironment attenuate antitumor immune responses elicited by radio(chemo)therapy and

hyperthermia ?

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Introduction: Development of hypoxia is a pathophysiological trait in solid tumours. Various mechanisms of action are discussed by which tumour hypoxia *per se* or through indirect actions (e.g., elevated HIF-expression) may contribute to a more aggressive phenotype, to an increased resistance to anticancer therapies, and finally to poor tumour control and patient outcome. In this context, it has been outlined that a hypoxia- or HIF- associated adenosine (ADO) accumulation in the tumour microenvironment (TME) may be one of the central drivers for the inhibition of innate and adaptive antitumor immune responses and promoting tumour progression, all in all resulting in poor disease outcome.

Methods: ADO and other purine catabolites were determined in snap-frozen tissue samples of experimental tumours using HPLC. Tumours of different volumes were investigated (0.5-2.5 ml) in order to correlate ADO-concentrations data with the extent of hypoxia.

Results: Enlargement of hypoxic subvolumes with increasing tumour sizes is associated with rising ADO-levels from 55-100 µM. This is in strong contrast to normal tissues with ADO-concentrations in the nM-range. Most probably, this accumulation is the result of (a) an intracellular generation from ADP by a cytosolic nucleotidase and subsequent ADO-export into the extracellular space through a (hypoxia/HIF-sensitive) nucleoside transporter, and preferentially (b) an extracellular cleavage by hypoxia/HIF-sensitive, membrane-bound ectonucleotidases (CD39 and CD73) upon release of nucleotides (ATP, ADP, AMP) from the intra- into the extracellular compartment of cancer (and stromal cells!) upon hypoxic stress. ADO- actions (adenosinergic effects) are mediated upon binding to surface receptors, mainly (hypoxia/HIF-sensitive) A2A-receptors on tumour and immune cells.

Localized hyperthermia (43°C for 60 min) further aggravates ADO- accumulations in the TME upon shut-down of the tumour microcirculation and thus increasing severity of tissue hypoxia. Immediately following hypoxia, ADO-levels were elevated approximately 4-fold as compared to normothermia (302 vs.72 µM).

Conclusions: Elevated extracellular ADO accumulation as a consequence of tumour hypoxia, a condition substantially aggravated following localized hyperthermia (43°C/60 min), can act through autocrine and paracrine pathways upon receptor binding. Several mechanism of action responsible for tumour progression are currently discussed: (a) ADO exhibits a broad spectrum of immunosuppressive properties (e.g., inhibition of NK-, CD4-, CD8- and dendritic cells, activation of M2-macrophages, Treg and MDSC-cells), (b) stimulation of cancer cell proliferation, migration and metastatic dissemination, and (c) activation of tumour angiogenesis. Thus, ADO-accumulation may counteract immune responses elicited by radio(chemo)therapy and moderate hyperthermia, and anticancer immunotherapy. Possible measures to counteract these ADO actions will be discussed.

WED 30

SHOCKS, STRESSES, AND DRUGS: HURTING OR HELPING HSP90 INHIBITORS IN CANCER CHEMOTHERAPY

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Background: Agents targeting Heat Shock Protein 90 (HSP90A family) and GRP94 (HSP90B family) are seldom tested in the context of heat shock or other forms of cellular stress such as the unfolded protein response (UPR). Tumour stress in general often activates HSPs and the UPR as pro-survival mechanisms. This begs the question of the effects of such stressors on the efficacy of chemotherapy agents, particularly those drugs that target proteins such as HSP90 or its endoplasmic reticulum paralog, GRP94. Here we tested the utility of a variety of HSP90 inhibitors, including PU-H71 (which also targets GRP94), on a unique primary canine lung cancer line under control, heat shock, and endoplasmic reticulum stress conditions.

Methods: We harvested and cultured cells from a high grade canine bronchoalveolar adenocarcinoma that showed high endogenous HSP90 and GRP94 expression; these levels substantially increased upon heat stress or UPR induction. We treated cells with the HSP90 inhibitors 17-DMAG, 17-AAG, or PU-H71 under standard culture conditions as well as under heat shock (42deg C, 2 hrs) or UPR stress (1 mM DTT, 4 hrs). Cell viability was measured by MTS assay, and cell survival was measured in soft agar assays. Protein (antibody) arrays measured intracellular signalling components and apoptosis profiles.

Results: Heat shock and the UPR had varying effects on cells treated with different HSP90 inhibitors; in particular, heat shock and the UPR promoted resistance to HSP90 inhibitors in short-term assays, but the combination of UPR stress and PU-H571 showed potent cytotoxic activity in longer-term assays. Array data indicated alterations in numerous signalling pathways, sometimes with apoptotic implications, but other times with pro-survival outcomes. UPR induction combined with a drug that targeted both HSP90 and GRP94 swayed the balance toward pro-apoptotic phenomena.

Conclusion: Cellular stresses, some of which are endemic to tumours, and others that may be interventionally inducible, can deflect or enhance chemotherapy efficacy, particularly when using drugs targeting chaperones. These stresses are likely not taken into account when testing new pharmacologic compounds or when assessing effectiveness of drugs already in use. A better understanding of the impacts of stresses such as the heat shock response or unfolded protein response on drug activities should be critical in improving therapeutic targeting and in discerning mechanisms of drug resistance in cancer treatments.

WED 31

Immunological enhancement & long-term remissions in HIV patients receiving only high-level whole body hyperthermia

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Latently infected HIV cells & free virus reside in anatomical or pharmacological reservoirs where they are inaccessible to antiretroviral therapy or immune regulation. Very likely, this is why neither a cure nor long term remissions occur after cessation of treatment with antiretroviral drugs. To address the problem we have developed a High Level Whole Body Hyperthermia procedure, HL-WBH, which by Its global nature, ability to up-regulate HIV production, and positive influence on immune function suggests that it is capable of addressing the HIV reservoirs. HL-WBH treatments involve raising a patient's core temperature to 43-43.5 degrees C in a water bath under general anesthesia. High frequency jet ventilation is used throughout the process, and vital signs are constantly monitored. Trial patients exposed to HL-WBH showed a marked increase in their CD4+ counts and a prolonged decrease of 1.8 logs in their viral load. The global nature of HL-WBH enables it to overcome physiological and anatomical barriers, which are partly responsible for the inability of current antiretroviral drugs to cure HIV infection. We believe that WBH could produce long-term remissions or cures through the following actions:

A) Inducing heat shock and HIV up-regulation

B) Activating NF-kB and HIV-1 transcription

C) Hsp90 stabilization of NF-kB inducing kinase

NIK for non-canonical pathway maintenance

D) Non-canonical induction of NF-kB results in

extended up-regulation of HIV infected cells

E) HL-WBH increases exposure of membrane gp41 and

gp120 epitopes which enables greater access to then by broadly

neutralizing antibodies.

WED 32

HOW CAN HYPERTHERMIA BE USED TO TREAT PATIENTS WITH LUNG CANCER?

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BACKGROUND: Patients with advanced non-small cell lung cancer (NSCLC) typically die within two years of diagnosis because the lung cancer recurs after initial response to standard radiation, chemo, and/or targeted therapies. More durable responses & longer survivals result when NSCLC is treated with immune therapy.

METHODS: What is immune therapy? Immune therapies stimulate host CD8+ T-cells to kill cancer cells. By obstructing the braking "checkpoint" signals that malignancies frequently use to block host effector T-cells, the checkpoint inhibitors amplify T-cell proliferation, tumor invasion and cytotoxicity. On the other hand, hyperthermia (systemic, local/regional or ablative) substantially boosts host immune response by increasing the number of CD8+ T-cells infiltrating the cancer and escalating the anti-tumor cytotoxicity of the effector T-cells.

RESULTS: New immune checkpoint inhibitors are proving to be powerful therapies to treat various malignancies. In NSCLC, the programed cell death-1 (PD-1) checkpoint inhibitors (e.g.: nivolumab, pembrolizumab, etc.) unleash host antitumor cytotoxicity if the cancer expresses the PD-L1 ligand. The PD-1 checkpoint inhibitor drugs have demonstrated increased responses, more durable responses, and significantly longer survivals in patients with advanced NSCLC compared to standard therapy. Unfortunately, the response rate of NSCLC to the PD-1 inhibitors is seldom over 30%. Responses can be increased by combining two different checkpoint inhibitors or by combining a checkpoint inhibitor with chemotherapy. Regrettably, toxicities are considerably increased by combining immune inhibitors together, or with chemotherapy. However, the combination of an immune PD-1 inhibitor with hyperthermia appears to be a compelling approach. While very likely to increase tumor response, the toxicities of hyperthermia are relatively minor. We must first, however, demonstrate that hyperthermia will increase durable lung cancer responses when combined with a PD1 checkpoint inhibitor in pre-clinical studies, then in clinical trials.

CONCLUSION: Clearly, the PD-1 immune checkpoint inhibitors are able to improve survival of patients with advanced NSCLC, albeit in a limited percentage of patients. The addition of hyperthermia--systemic, local or ablative—can be expected to increase the response rate of the immune inhibitors by increasing the infiltration of host CD8+ T-cells into the tumors, and escalating T-cell anti-tumor cytotoxicity. While the potential of hyperthermia combined with PD-1 inhibitors to improve treatment of advanced NSCLC appears obvious, it remains up to us in ICHO to test hyperthermia in combination with a PD-1 inhibitor to improve survival of patients with advanced lung cancer as well as other malignancies.

WED 33

Mild hyperthermia at temperatures between 41-43°C for chemo- and radiosensitisation in pediatric cancer

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Background: Today, most children with malignant tumors have a good prognosis by using risk-stratified chemotherapeutic regimens. Despite these achievements, some of pediatric malignant tumors are refractory or recurrent and cannot be eradicated with salvage chemotherapy in conventional doses or reiterated surgical resections, or both. Our rationale for the use of microwave-induced regional deep hyperthermia (RHT) in the range of 41–43°C with cisplatin-based chemotherapy alone or in combination with additional radiotherapy in those cases was based on the observation that hyperthermia is a potent chemo- and radiosensitiser. We aimed to determine whether objective tumor response could be achieved in children with refractory or recurrent tumors with chemotherapy (cisplatin 40 mg/m^2 or adriamycin 30 mg/m^2, days 1+4; etoposide (100mg/m^2, days 1–4); and ifosfamid (1800 mg/m^2, days 1–4) with microwave-induced RHT (41–43°C, days 1+4) alone or in combination with radiotherapy (19·2–50·4 Gy) as salvage treatment.

Patients and methods: To answer these questions we analyzed the data of 160 children aged 7 months to 18 years (median 6 years 1 months). This analysis included 74 germ cell tumors, 35 rhabdomyosarcomas, 13 other soft tissue sarcomas, 8 Ewing- and osteosarcomas, 9 ovarian tumors, 4 intestinal tumors, 4 liver tumors and 13 others. The vast majority of tumors were located in pelvis (n=94) and abdomen (n=50); other tumors involved extremities (n=9) or head and neck (n=7). A total of 1658 RHT session were combined with chemotherapy (n=1486), radiotherapy (n=152), or both (n=18).

Results: We assessed thermometric records for all 1658 microwave-induced RHT sessions for quality control. The median intratumoral Tmax was 42.9°C (SD ± 0.52°C). The median time-averaged temperatures were 42.18°C (SD ± 0.46°C) for T20, 41.44°C (SD ± 0.37°C) for T50; 40.31°C (SD ± 0.34°C) for T90. CEM43T$_{90}$ was 5.63 min (SD ± 0.37min). In general microwave-induced RHT treatment was well tolerated in our patient group, with no severe skin burns after RHT treatments, probably thanks to fractionated sedation. Fractionated sedation did not increase the risk of burns. We report the response rates and long-term results of this salvage therapy for pediatric patients with refractory or recurrent malignant tumors.

Conclusion: The results for local tumor control, which is essential for a long-term cure, suggest that the use of microwave-induced RHT at temperatures of 41–43°C in combination with standard chemotherapy and/or additional radiotherapy should be introduced soon after initial treatment failure.

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WED 34

Hyperthermic intraperitoneal chemotherapy (HIPEC) in paediatric sarcomas: An initial phase 2 study

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Purpose: Desmoplastic Small Round Cell Tumor (DSRCT) is a rare sarcoma of childhood and adolescents. Overall survival is estimated 15%. Most patients present with dozens to hundreds of intra-abdominal metastasis. A safety trial has been completed for hyperthermic intraperitoneal chemotherapy in paediatric-type sarcomas. An efficacy trial has not previously been done.

Methods: Patients aged 23 months to 50 years old were enrolled on a phase 2 trial of cytoreductive surgery and HIPEC using Cisplatin, in DSRCT and other sarcomas. All underwent hyperthermic intra-peritoneal chemotherapy (HIPEC) at the time of cytoreductive surgery. Hyperthermia exposure was 90 minutes at 40.5 degrees Celsius using Cisplatin. All patients received neoadjuvant chemotherapy. All but one patient also received adjuvant chemotherapy.

Results: From January 2012 to December 2013, accrual was met and 20 patients were enrolled. Of 20 patients, 14 had DSRCT. DSRCT patients had a longer OS than patients with other sarcomas. 1-year overall survival rate was 93% (95% CI: 0.8, 1) for DSRCT patients and 67% (95% CI: 0.3, 1) for other sarcoma patients. (p=0.0073) The median survival was not reached for DSRCT patients. DSRCT patients had a longer RFS time (median=14.93 months with a 95% CI of 12.4 m to NA) than patients with other subtypes of disease. (4.01 months with a 95% CI of 2.96 m to NA) (p=0.0029) Three DSRCT patients relapsed in the abdomen, for a 77% local control rate. The overall survival for DSRCT patients was 80% (95% CI: 0.57, 1) at 2 years. Of 56 DSRCT patients evaluated the median age was 18 years (3-53yrs). Median follow-up was 28 months. Median overall survival was 31.8 mos. Hyperthermia was delivered at 1.5 degrees Celsius less than previous adult studies. There was no mortality from HIPEC. Major complications totalled 35%. Historic studies of HIPEC report ~45% post – HIPEC complications.

Conclusions: HIPEC may be effective in certain types of paediatric sarcomas. Lower temperatures may decrease morbidity without changing efficacy. Longer follow-up and a larger data set is necessary. DSRCT patients, despite abdominal metastases, have effective short term local control with hyperthermic intraperitoneal chemotherapy.

WED 35

Towards Non-Invasive Treatment of Osteoid Osteoma: State of the Art in Context of Accepted Methods

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There has been an evolution toward less invasive image-guided thermal ablation procedures to replace traditional surgical resection. These techniques include radiofrequency, cryo, laser and microwave ablation, and their use is driven by the desire to be less invasive, cause less collateral damage and morbidity and obtain faster recovery times. One example of this has been the treatment of osteoid osteoma. Traditional surgical resection was mainstream in 1980's and 1990's but gave way to CT-guided RFA in the late 1990's. This was much less invasive and offered very high success rates, and is the current standard of care across the world. In the last few years, Magnetic Resonance Imaging Guided High Intensity Focused Ultrasound (MR-HIFU) of osteoid osteoma has been introduced. This technology offers the advantage of no radiation and does not require any invasive procedures. This presentation will compare our initial experience with MR-HIFU ablation of osteoid osteoma to other, more conventional techniques, including minimally invasive procedures.

WED 36

Feasibility, Safety, and Efficacy of Osteoid Osteoma Ablation in Children Using MR-guided High Intensity Focused Ultrasound

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Background: Osteoid Osteoma (OO) is a benign but painful bone lesion that usually affects children between 10 and 20 years of age. The least invasive accepted treatment of computed tomography (CT)-guided radiofrequency ablation has high clinical success, but it is invasive and requires exposure to ionizing radiation. These shortcomings may be addressed through the use of Magnetic Resonance Imaging-guided High Intensity Focused Ultrasound (MR-HIFU). This therapeutic modality allows for spatially precise, radiation-free and non-invasive ablation of periosteal nerves and the nidus of OO deep inside the body, under MR image guidance. The treatment could thus reduce or eliminate pain, and potentially, penetrate into medullary cavity to treat subcortical lesions.

Methods: In an ongoing Phase I clinical study designed to evaluate MR-HIFU ablative therapy, 12 children with symptomatic osteoid osteoma will be treated with MR-HIFU. While complete follow-up is still pending, herein we report on the feasibility of patient positioning, sonication parameters, treatment times, and other technical considerations as well as treatment safety for the first 6 OO cases treated with MR-HIFU at the Children's National Medical Center (CNMC, Washington D.C., USA).

Results: Patient positioning on the HIFU table was feasible in all 6 cases, with OO locations in the tibia, femur (n=3), talus, and hallux (distal phalanx). Target distance from skin ranged 1.3-6.8 cm. Average acoustic power was 47±32 W per sonication and total energy deposition per therapy session was on average 10.0±6.3 kJ, resulting in complete ablation of the nidus in 4 of 6 patients, as indicated by non-perfused volume in post-treatment contrast-enhanced T1-weighted MRI. The treatment was well-tolerated without any serious adverse events.

Conclusions: Follow-up at 1 month is pending for 2 of the 6 patients, but the VAS pain scores improved in 4 out of 4 evaluated patients with complete pain resolution in 3 out of 4 patients evaluated thus far. While follow-up is ongoing, MR-HIFU has the potential to offer a fast, completely noninvasive, and radiation-free treatment option for children with painful OO.

WED 37

PROSPECTIVE IMAGING STUDY OF MAGNETIC RESONANCE THERMOMETRY QUALITY IN PEDIATRIC SOLID TUMORS

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BACKGROUND: Treatment of pediatric solid tumors is in many cases limited by cardiac toxicity induced by doxorubicin (DOX). The combination of local hyperthermia and liposomal DOX may result in enhanced DOX uptake in tumors, improving local control without increasing toxicity. Challenges in the delivery of localized hyperthermia may be overcome using HIFU guided by MR thermometry (MRT). In this imaging-only study, MRT was acquired in pediatric sarcoma and neuroblastoma patients already undergoing a diagnostic MR imaging study, to verify that the quality of MRT in pediatric solid tumors is sufficient to control hyperthermia delivered by MR-HIFU (precision and accuracy of approximately 1°C).

METHODS: Children with neuroblastoma or sarcoma who were scheduled for standard MR imaging to evaluate their tumor were eligible to participate in the study with consent from the parent or guardian. MRT data were acquired at the end of the patient's routine imaging study, using a 1.5T scanner (Intera or Achieva, Philips Healthcare). The MRT sequence continuously acquired echo-planar gradient echo images in 6 different planes every 3.2 seconds, over 2-5 minutes. MRT maps were calculated offline, and temperature in an 18mm diameter tumor region was evaluated for its precision and accuracy.

RESULTS: MRT data were acquired for 7 tumors in 6 pediatric cancer patients (ages 6-14). Tumor locations included 3 lower limb, 1 upper limb, 1 pelvis, 1 rib, and 1 paraspinal. Tumor types were osteosarcoma (n=3), Ewing sarcoma (n=3), and neurofibrosarcoma (n=1). 2/6 patients (upper limb and paraspinal) were sedated for their entire imaging study including MRT. Precision (spatial mean of temporal standard deviation) in lower limb tumors ranged from 0.14 to 0.42°C. In other tumor locations, which were affected by MRT artifacts from breathing motion near the tumor, precision ranged from 1.76 to 6.81°C. Accuracy (temporal mean of absolute deviation from baseline) was 0.15-0.35°C in lower limb tumors, and 2.75-4.26°C for other tumor locations. Uniformity (temporal mean of spatial standard deviation) was 0.34-1.25°C vs. 2.69-3.86°C.

CONCLUSION: MR thermometry quality in pediatric solid tumors of the lower extremities is sufficient to control MR-HIFU hyperthermia. Motion compensation or breath holds may be required to achieve reliable MRT in pelvic and abdominal tumors in pediatric patients. These findings have implications for initial clinical studies of MR-HIFU hyperthermia in pediatric solid tumors.

WED 38

External thermal therapy (ETT) as an adjunct to radiation therapy in the treatment of soft tissue sarcoma

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Background: Soft tissue sarcomas (STS) comprise a heterogeneous group of tumors that have a high propensity for local recurrence and hematogenous spread. Local tumor control is particularly difficult in non-operable tumors and tumors arising in previously irradiated tissue. Hyperthermia can be used an as adjunct to improve local control of STS when combined with radiation therapy.

Methods: A retrospective, HIPAA compliant database of patients treated with ETT at our institution between 2012 and 2015 was evaluated for patients with primary, radiation induced, or recurrent sarcoma. Information obtained included patient, tumor and treatment characteristics along with outcomes. ETT was given over 45-60 minutes using the BSD-500 microwave hyperthermia system with a maximum temperature of 44 degrees Celsius twice weekly with concurrent external beam radiation therapy (EBRT).

Results: 11 patients diagnosed with STS receiving ETT were available for review. 45% were female and 55% male with a median age of 65 years (range 25-82). 18% (n=2) were African American. 3/11 (27%) were radiation-induced (defined as a sarcoma arising within a prior radiation field). Histology included angiosarcoma (n=3), spindle cell sarcoma (n=2), synovial sarcoma (n=1), dermatofibrosarcoma (n=1), undifferentiated pleomorphic sarcoma (n=2), myxofibrosarcoma (n=1), not otherwise defined (n=1). Median follow-up was 27 months from diagnosis. 36% of patients received ETT for a primary occurrence while 64% were treated in the recurrent setting. One patient received two courses of ETT. Median lesion size was 6 cm (range 3.5-16 cm). Median radiation dose was 66 Gy (range 31-74.4 Gy). Median number of ETT treatments was 11 (Range 6-14) given twice weekly in all patients. 36% (n=4) of patients had a local recurrence. Median progression free survival (PFS) for the entire cohort after ETT was 7 mo (range 3-30 mo) while median PFS was 5.5 mo vs 7 mo for treatment in the primary versus recurrent setting, respectively (p=0.35). Acute toxicities from treatment included radiation dermatitis grade 0 (n=1), grade 1 (n=5), grade 2 (n=4) and grade 3 (n=1). One death occurred in our cohort as a result of distant progression of disease.

Conclusion: STS remains a clinically challenging disease. Despite small numbers in our cohort, the majority of our patients were treated in the challenging re-irradiation setting with good local control and an acceptable toxicity profile. Maturation of data is necessary to elucidate the full benefit of ETT, but early results support the addition of ETT in the treatment of STS.

WED 39

Evaluation of doxorubicin containing phosphatidyldiglycerol ($DPPG_2$) based thermosensitive liposomes for the treatment of spontaneous feline soft tissue sarcomas

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Aims: Feline soft tissue sarcomas (STS) are difficult to treat due to a high local recurrence rate after surgical resection and often cats are even presented with not resectable tumors at diagnosis. Similar to the situation in human STS, radiotherapy and doxorubicin (DOX) based chemotherapy are considered as effective treatment modalities to improve outcome. $DPPG_2$ based thermosensitive liposomes (TSL) loaded with DOX in combination with RF-hyperthermia (RHT) represent a powerful tool to further increase the effect of DOX. The aim of the study was to evaluate safety and effectivity of $DPPG_2$-DOX-TSL in feline STS.

Methods: 25 client-owned cats with histologically proven STS were enrolled in five dose groups. The cats were scheduled for six treatments with $DPPG_2$-TSL-DOX and simultaneous RHT in two-week intervals. RHT was performed with a superficial radiofrequency applicator (MA-151, BSD Medical) and intratumoral temperatures were measured with temperature probes. After reaching temperatures of 42 °C $DPPG_2$-TSL-DOX was administered i.v. over 15 minutes. RHT was continued for 45 minutes. After intraindividual dose escalation for the first 8 cats (0.1 - 0.4 mg/kg), at least 3 cats were treated at the dose levels 0.4 mg/kg, 0.6 mg/kg, 0.8 mg/kg and 1.0 mg/kg, respectively. Three cats treated with standard DOX 1 mg/kg + RHT served as control. Tumor volume was measured either manually or by pre- and post-treatment 2[18F]fluoro-2-deoxy-d-glucose (18F-FDG)-PET/magnetic resonance imaging (MRI) studies. Blood samples for PK-measurements were collected during treatment. All cats were carefully evaluated for treatment related side effects.

Results: The therapy with $DPPG_2$-TSL-DOX was overall well tolerated with no dose limiting toxicities whereas cats treated with standard DOX suffered from significant weight loss. All cats treated with $DPPG_2$-TSL-DOX at the higher dose levels (0.8 mg/kg and 1.0 mg/kg) showed objective responses whereas there was no response seen for the cats in the control group.

Conclusion: Therapy with $DPPG_2$-TSL-DOX offers a safe and effective treatment option for feline STS showing both significantly improved tumor responses and much better tolerability as compared to standard DOX.

WED 40

The effect of the time interval between radiotherapy and hyperthermia on treatment outcome in cervical cancer

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Introduction

The time interval between external beam radiotherapy(EBRT) and hyperthermia(HT) often varies in clinical practice, e.g. because of logistical considerations within a department, or because patients receive EBRT and HT at different institutes. The purpose of this retrospective study was to determine the effect of the time interval between EBRT and HT treatments on locoregional recurrence and overall survival of patients with cervical cancer.

Methods

This retrospective study included 59 women with locally advanced (stage IB2-IVA) cervical cancer, treated solely with radiotherapy and HT. Patients received four to five weekly HT treatments concurrent with 23-28 fractions (1.8-2.0Gy) EBRT and a brachytherapy boost (20-24Gy). On HT treatment days, HT was given after EBRT. For each patient, the mean time interval between corresponding EBRT and HT treatment fractions was calculated. The median thereof (79.2 min) was used to split the cohort in a 'short' (median 65.8 min, range 33.8-79.2 min) and 'long' (median 91.7 min, range 80.0-125.2 min) time-interval group.

Locoregional recurrence and overall survival were estimated using Kaplan-Meier analysis, and groups were compared by a log-rank test. To correct for potential confounding factors, a stepwise Cox regression analysis using backward elimination was used with time-interval group, age, FIGO stage, number of HT treatments, tumour temperature during HT treatment (T90), lymph node status and smoking as covariates.

Results

Locoregional recurrence was significantly lower in the short time-interval group (p=0.015). Recurrence rate at 2 years was 11% (95%CI 3-36%) in the short time-interval group compared to 49% (95%CI 30-73%) in the long time-interval group. The stepwise Cox regression identified time-interval (HR=6.7, p=0.008, short interval is better), T90 (HR=0.31, p=0.007, higher temperatures are beneficial) and age (HR=0.93, p=0.002, younger age is unfavourable) as significant prognostic factors, and shows a favourable trend for lower FIGO stage (HR=4.5, p=0.06).

Overall survival was also significantly better in the short time-interval group (p=0.023). Overall survival at 2 years was 60% (95%CI 39-75%) in the short time-interval group compared to 39% (95%CI 21-56%) in the long time-interval group. The stepwise Cox regression identifies a short time-interval (HR=2.2, p=0.014) and higher T90 (HR=0.57, p=0.008) as significant factors for a favourable outcome.

Conclusions

A short time interval between EBRT and HT results in a significantly lower recurrence and better overall survival for locally advanced cervical cancer patients. Furthermore, a higher tumour temperature during HT is associated with lower locoregional recurrence and better overall survival, stressing the importance of HT quality assurance.

WED 41

Concurrent Interstitial Thermal Therapy and Interstitial Brachytherapy for Recurrent and Bulky Pelvic Malignancies: A Single Institution Experience.

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Introduction:

Interstitial brachytherapy (IBT) is generally employed in bulky or recurrent tumors for which intracavitary applications or external beam radiation (EBRT) techniques would yield insufficient target coverage or would exceed the dose tolerances of nearby critical structures. The addition of concurrent hyperthermia to radiotherapy has also proven particularly useful in bulky/recurrent tumors by increasing the efficacy of radiotherapy without significantly augmenting toxicity. Interstitial thermal therapy (ITT) is an approach that can be combined with IBT to potentiate radiation response and potentially improve outcomes. However, the availability of this modality is currently limited to select institutions. We report our initial institutional experience with concurrent IBT/ITT.

Methods:

Since 2014, IBT/ITT has been performed in seven patients: cervical (2), rectal (1), vaginal (1), vulvar (1), bladder (1), and endometrial cancers (1). Median patient age was 68 (range 45-74), including 1 male and 6 females. Five patients were treated for recurrent disease, while 2 patients had bulky, primary disease. Four of the 5 patients with recurrent disease had received prior radiotherapy ranging in dose from 50.4-83 Gy. In the current course, 2 patients underwent re-irradiation by high dose rate (HDR) IBT alone; 2 patients underwent re-irradiation by EBRT+HDR-IBT; and 3 patients received primary EBRT+HDR-IBT. Total RT dose for the current courses ranged from 11 to 70 Gy. Each patient received either 1 or 2 ITT administrations immediately following IBT fractions to a goal temperature of 43 degrees Celsius utilizing the BSD-500 unit. Procedural placement of 10-18 catheters for IBT allowed for accurate, homogenous, and conformal ITT administrations utilizing 1-8 thermal antennae, monitored by 6-8 interstitial thermistors. ITT was delivered for 35 to 60 minutes/fraction.

Results:

ITT was generally well tolerated with only mild patient discomfort encountered during the procedure. No technical difficulties occurred, but two previously irradiated patients did experience brisk oncologic responses with frank tumoral necrosis during the course of therapy. All 5 patients receiving total RT of at least 40 Gy remain locally controlled (range, 1-21 months).

Conclusions:

A concurrent IBT/ITT program has been initiated successfully at our institution. The initial results are encouraging, though longer follow-up and a larger patient experience will be needed to evaluate oncological outcomes.

WED 42

Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervix cancer after irradiation

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Introduction: Survival in patients with recurrent cervical cancer after irradiation remains very poor. Chemotherapy combined with hyperthermia has been shown to improve the response rate. This study was performed to evaluate the effect of electro-modulated hyperthermia combined with conventional chemotherapy vs. chemotherapy alone on recurrent cervical cancer previously treated with irradiation.

Methods: Twenty patients were treated with chemotherapy alone, and 18 were treated with chemotherapy combined with electro-modulated hyperthermia. One patient was treated with chemo-radiotherapy as a primary treatment and then relapsed; the tumor was inoperable and radio-refractory after recurrence. Nearby metastases were included, such as metastasis of the para-aortic lymph nodes (PANs) and adjacent pelvic lymph nodes (PLNs), but distant metastases were excluded. Electro-modulated hyperthermia was performed three times per week beginning at chemotherapy initiation; patients underwent a total of 36 sessions.

Results: The overall response (CR+PR+SD/PD) to treatment was significantly greater in the group of patients who underwent chemotherapy combined with electro-modulated hyperthermia (p=0.0461), and at the evaluation conducted at the last follow-up examination, the reaction results were significantly greater in this group (p=0.0218). Additionally, severe complications were not reported.

Conclusion: In this study, for patients with recurring cervical cancer previously treated with irradiation, the overall response rate for patients treated with chemotherapy combined with electro-modulated hyperthermia was significantly greater than that for the group of patients who were treated with chemotherapy alone.

Keywords: concurrent chemo-modulated electro-hyperthermia, chemotherapy alone, recurrent cervix cancer, treatment outcome

WED 43

Review of Currently Available Bladder Heating Devices

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Hyperthermia is used in combination with radiotherapy and chemotherapy to increase the effectiveness of treatment in various stages of invasive and non-invasive bladder cancer. This has led to very promising clinical results, particularly for the combination of hyperthermia with concurrent intravesical instillation of Mitomycin C for Non-muscle invasive bladder cancer.

This review presents the currently available heating devices used for application of bladder hyperthermia. The technical features and temperature control of the different systems are evaluated.

WED 44

New hyperthermia technologies applicable to bladder cancer: a focused review.

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BACKGROUND

Bladder cancer is common and is highly sensitive to heat. A number of new hyperthermia-related technologies are evolving that could play a role in future bladder cancer management. In this presentation, I will describe some leading technologies that are developing and review the preclinical and/or early clinical data supporting their use.

METHODS

A systematic literature review was performed following PRISMA guidelines. Search terms included the MESH headings [urinary bladder neoplasms OR urinary bladder OR cancer] AND [hyperthermia OR heat OR thermal]. Meeting abstracts from key urological and oncological meetings were searched where electronically possible. Abstracts were screened for topic relevance and full text articles retrieved where possible and examined. Data was then abstracted from the relevant abstracts/ manuscripts and studies were categorized into one of three categories of scientific investigation: preclinical, early clinical (trials), and clinical. Preclinical and early clinical studies are the subject of this review. Common themes arising in the literature review are summarized in this presentation and selected technologies deemed by the author to be of interest are reviewed.

RESULTS

Using our broad search strategy, 54,292 PubMed indexed abstracts were initially identified and retrieved. After restricting this set to the subset of abstracts relevant to our topic, several hundred candidate publications were identified and individually screened for their content. From these, preclinical and early clinical technologies fell into several topic families, of which the following will be discussed: heat-mediated immunotherapy, heat-augmented chemotherapy, heat-augmented radiotherapy, heat-targeted chemotherapy, and nanoparticle-mediated hyperthermia.

CONCLUSION

Several new technologies exist that are applicable and translatable as treatments for human bladder cancer. Translation of these technologies into human trials is of paramount importance.

WED 45

Current bladder cancer management: where hyperthermia might have an impact.

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Introduction

Bladder cancer is common with an estimated 74,000 new cases in 2015 making it the fifth most common cancer. Bladder cancer falls into two phenotypes non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC). Nearly 80% of these cancers will be NMIBC and they have an excellent 5 year survival rate. Although it is uncommon for NMIBC to progress to MIBC, greater than 50% will have a recurrence. This high rate of recurrence and subsequent treatments makes bladder cancer the most expensive cancer to treat per patient. Unlike NMIBC, MIBC has a poor survival due to its propensity for metastasis.

Current Management

NMIBC is treated with a combination of complete transurethral resection of bladder tumor, and is typically followed by intravesical therapy. The bladder is easily accessible by the urethra and the urothelium acts as a barrier to systemic circulation. Less than 5% of small molecule drugs are absorbed into the systemic circulation. This allows for maximum tumor exposure to the therapeutic agent while minimizing the systemic side effects. Furthermore, bladder cancer displays field disease with abnormal tissue extending well beyond the area of gross tumor and intravesical therapy aims to treat this occult disease. Mitomycin C (MMC) is the primary intravesical chemotherapeutic agent used in the treatment of NMIBC, and BCG is intravesical immunotherapy. Many cases of NMIBC continue to recur, despite appropriate therapy and ultimately require bladder removal (cystectomy). MIBC gold standard treatment is systemic neoadjuvant chemotherapy followed by radical cystectomy and urinary diversion.

Role for Hyperthermia

Hyperthermia (HT) improves drug delivery to cancer cells, improves cancer cell sensitivity, and precipitates anti-cancer immune responses. Perhaps the biggest role for HT is in the management of NMIBC as an adjunctive therapy to reduce recurrence. HT has been combined with MMC to prolong cancer free survival and a relative risk reduction of recurrence by 59%. In fact,in a recent trial it has shown a superior recurrence free survival compared to BCG, the gold standard immunotherapy. Bladder sparing therapy remains elusive, but an obvious goal of treatment in MIBC that may involve HT in a novel protocol. HT may have a role as an adjunctive therapy, and has already shown promise with some of the newer immunotherapies. Effective adjunctive therapies carry the promise of relief for the financial, psychological, and tremendous physical burdens of the bladder cancer.

WED 46

Heat-deployed Liposomal Doxorubicin for Treatment of Bladder Malignancies

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Introduction: Cancer of the urinary bladder has a high rate of recurrence and progression despite locoregional therapy and tends to be metachronous, multifocal, and often superficial, all of which are amenable to new drug device combinations. Poor penetration and distribution of drugs in the bladder wall limit the efficacy of intravesical chemotherapy. Pre-clinical studies in our laboratory have demonstrated high levels of doxorubicin (DOX) in tumors when low temperature sensitive liposomes (LTSL) are administered intravenously with tumor-localized mild hyperthermia (40–42 °C). We hypothesized that intravenous delivery of DOX-loaded LTSLs (ThermoDox®, Celsion Corp.) during mild focal hyperthermia of the bladder will result in elevated drug accumulation and distribution in the bladder wall. The primary objectives were: 1) to demonstrate the feasibility of maintaining mild hyperthermia of the bladder and 2) to evaluate the microdistribution of drug in the bladder wall following IV administration of LTSL.

Methods: Female swine (53-63 kg) were divided into three treatment groups: 1) IV LTSL with bladder hyperthermia; 2) IV DOX with bladder hyperthermia; and 3) IV LTSL without bladder hyperthermia. The bladder was irrigated with warm water (group 1, 2: 45°C; group 3: 37°C) controlled using a custom in-line heat exchanger, peristaltic pump and an optical temperature probe. Thirty-minute intravenous drug infusions were administered and bladder irrigation was maintained for 1 hour. Distribution of drug was assessed in transverse bladder wall sections by qualitative visualization of DOX fluorescence. Quantitative analyses of drug penetration were performed in consecutive parallel bladder wall sections following drug extraction using liquid chromatography.

Results: Mild hyperthermia was successfully maintained in the bladder by irrigation with warm water. Elevated drug fluorescence was observed in bladder wall cross sections from the IV LTSL with hyperthermia group relative to IV LTSL without hyperthermia and free IV DOX with hyperthermia groups. Initial quantitative assessment of drug distribution in the IV LTSL with hyperthermia group confirmed high concentrations in the mucosa (mean: 119.8 μM, n=2) and muscularis (mean: 58.6 μM, n=2).

Conclusion: Preliminary results demonstrated high drug accumulation and distribution in the bladder wall following loco-regional application of mild hyperthermia to the bladder and systemic delivery of LTSL. This paradigm applies heat where drug is needed to selectively target delivery of chemotherapy to the bladder.

WED 47

Clinical Validation of a Thermophysical Bladder Model to Improve Hyperthermia Treatment Planning in the Pelvic Region

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Introduction & Aim

Optimal application of deep hyperthermia requires treatment planning to optimise phase and amplitude settings. Current treatment planning systems are accurate for most tissues but ignore the specific properties of the urinary bladder and its fluid contents, limiting their accuracy in the pelvic region. This may have clinical implications for treatment sites like the rectum, the cervix uteri, and particularly the bladder.

We extended our treatment planning system with a dedicated bladder simulation tool that takes into account the presence of convection and the absence of perfusion in the liquid bladder contents. We show the clinical validation of this tool by means of retrospective patient data analysis. We assessed the differences between the new and the conventional model, and compared both to temperature measurements made during treatment.

Materials & Methods

A CT scan with thermometry catheters in situ was obtained from three bladder cancer patients. A clinician delineated the bladder as part of the standard clinical work-flow. Based on the clinically applied antenna settings, we computed the electromagnetic field. This was used to compute the temperature distribution both with the conventional treatment planning system with a solid ('tumour-tissue-like') bladder, and with the expanded system with a convective fluid-filled bladder.

The convective thermophysical fluid model was based on the Boussinesq approximation to the Navier-Stokes equations; meaning we assumed all parameters to be temperature independent except for the mass density in the gravitational term. Clinical reference temperature measurements were obtained using copper-constantan thermocouples with 14 temperature sensors located at 0.5 cm intervals. Temperatures were obtained from treatment planning at the reference probe positions reconstructed from the CT scan. We subsequently calculated the differences between the resulting temperature distributions.

Results

The convective model results in a much more homogeneous temperature distribution within the bladder than the conventional model, in better agreement with the measurements. Within the bladder, differences between both methods can exceed 5 °C. Clinically relevant temperature differences of more than ±0.5 °C are limited to a region of 1.5 cm around the bladder.

Conclusion

The addition of the new convective modelling tool to the current hyperthermia treatment planning system leads to clinically highly relevant temperature calculations. Explicit fluid modelling is particularly important when the bladder or its direct surroundings are part of the treatment target area.

WED 48

HEAT-TARGETED DRUG DELIVERY USING A NOVEL CONDUCTIVE BLADDER HYPERTHERMIA DEVICE

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Introduction and Objective

Hyperthermia combined with intravesical chemotherapy, reduces the risk of recurrence and progression of non-muscle invasive bladder cancer. Currently no FDA-approved device exists for treating bladder cancer. We investigated a novel device (Combat BRS) that heats fluids, circulates them in an enclosed circuit, and thereby delivers heat by conduction to the bladder. Our goal was to map heat delivery to the bladder in 3D submillimeter space, determine the biological effects of heating, and use the device for heat-targeted drug delivery.

Methods

Female swine were chosen to model the human bladder. A multichannel array of submillimeter microprobes, custom manufactured for bladder heating, was surgically implanted in the bladder (urothelial surface, detrusor muscle, serosa, and transmural). Additional high resolution thermistors were placed in the esophagus, vagina, rectum, and internal iliac vein. Swine were then subjected to bladder heating using the Combat BRS device with a target temperature of 43°C for 1-2 hours. Temperatures were recorded and a 3D thermal map created using a CT image-based computer model of the swine. Swine were then treated with intravesical chemotherapy (mitomycin C) or a novel systemic heat-triggered liposomal drug containing doxorubicin (ThermoDox).

Results

Heat mapping demonstrated intravesical fluid temperatures of 42.9±0.14°C, which correlated closely with our target temperature (43±1°C). Thermal conductivity through the bladder wall occurred and serosal temperatures reached 41.5±0.6°C, albeit after ~45 min of heating. This indicates that a temperature gradient of ~1.5°C exists across the bladder wall when heated with conductive heat transfer but that deep bladder wall temperatures of were sufficient to allow triggering of ThermoDox (drug release occurs at 41°C). Adjacent organ temperatures only increased modestly, indicating that heating was biologically safe (vagina 41.8±0.5°C, rectum 39.1±0.4°C).

Conclusions

Comprehensive heat mapping demonstrated that the Combat BRS device effectively and safely heats the bladder transmurally. Drug delivery of mitomycin C and ThermoDox to the bladder is feasible using this heating device and is currently being evaluated. In particular, ThermoDox allows targeted release, and a 10-30 fold increase of doxorubicin levels within the tumor, allowing for reduced drug dose and overall systemic toxicity.

WED 49

Attenuated XPC expression is not associated with impaired DNA repair in bladder cancer

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Introduction: Attenuated expression of the DNA damage response protein Xeroderma Pigmentosum complementation group C (XPC) has been described in bladder cancer (BC). XPC is essential for nucleotide excision repair (NER) of UV-induced lesions, bulky DNA adducts and chemotherapy-induced intrastrand crosslinks. Hence, XPC protein might be a biomarker to guide therapy strategies in BC.

Methods: Freshly obtained human BC samples were ex vivo cultured as previously described (Naipal et al PlosOne 2015). Wild-type labelled human fibroblasts (C5RO) were added as controls. The 2D single cell layers were treated with 0, 2, 4, 6, and 8 J/m2 of UV-C radiation. DNA repair capacity was assessed by unscheduled DNA synthesis (UDS-assay) and XPC expression was measured by immunofluorescence (IF). The standardized XPC and UDS levels of tumour cells were calculated as: X= (avg. intensity tumour cells/avg. intensity C5RO cells) X 100%. The UDS assay measures the incorporation of a labelled nucleoside, 5-ethynyl-2'-deoxyuridine, after exposure to UVC, and is determined in cells that are not undergoing S-phase-dependent DNA synthesis. Lastly, IHC for XPC on FFPE tumours (n=47) was done. IRB approval was obtained (METC-2012-113).

Results: IHC showed in only 2/47 cases absence of XPC protein expression. Functional NER-activity was analysed in attached tumour cells from 36/47 cases using the UDS assay. The XPC-protein levels in the same cells were assessed by IF staining. 15/36 of the tumours expressed at least 2-fold lower levels of XPC protein than co-cultured fibroblasts (0-50%). Most tumours displayed near normal levels of XPC protein (50-180% of co-cultured fibroblasts). No XPC staining intensities of <5% were seen, a level typical for XPC-deficient fibroblasts (XP21RO). Remarkably, XPC expression showed very weak correlation with UDS in these tumours. Most tumours with relatively low XPC levels displayed normal UDS levels. Normal UDS (>50% of co-cultured fibroblasts) was observed in 34/36 samples. Two tumours showed reduced UDS (<50% of co-cultured fibroblast controls); one showed XPC and UDS levels similar to that of XPC-/- cells but in the other the UDS was close to 50%. Unfortunately, due to lack of material no further genetic analysis could be performed on these two tumours.

Conclusion: Functional NER deficiency is a relatively rare phenomenon in BC. Low levels of XPC expression can still support NER activity and decreased XPC expression does not necessarily influence NER activity in ex vivo cultured BC cells. In addition, XPC protein levels are not useful as a biomarker for NER activity in BC.

WED 50

Hyperthermia-enhanced targeted drug delivery using magnetic resonance-guided focused ultrasound in a genetic mouse model of pancreatic adenocarcinoma

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Pancreatic cancer is projected to become the second leading cause of cancer-related death in the United States by 2020. Current treatment with conventional chemotherapeutics is ineffective due to the presence of stromal desmoplasia and the reduced vascular network preventing the drug delivery. Hyperthermia produced by high-intensity focused ultrasound (HIFU) applied in combination with the systemic administration of a low-temperature sensitive liposomal formulation of doxorubicin (LTSL-Dox) can be used for targeted drug delivery to enhance delivery of doxorubicin to pancreatic tumors. Hyperthermia using a clinical magnetic resonance-guided (MR)-HIFU system was achieved in tumors of in mouse models of pancreatic cancerl. MR-HIFU, in combination with LTSL-Dox, resulted in significant increase in drug concentration within the tumor tissue. HIFU-induced hyperthermia in combination with LTSL-Dox is a noninvasive and effective method in enhancing the penetration of doxorubicin into pancreatic tumors.

WED 51

Combining ultrasound thermal therapy with chemo and immunotherapy

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The use of local therapies to generate an immune response has been shown to be a promising technique for immune activation. The combination of ultrasound and immunomodulatory agents has not been extensively explored but is a rational choice because of the primary effect of ultrasound on the immune environment and the augmented antitumor effects observed when immunotherapy is added. Further, certain chemotherapeutics have been shown to be a source of immunogenic cell death.

WED 52

Focused ultrasound hyperthermia mediated drug delivery using thermosensitive liposomes and visualized with *in vivo* two-photon microscopy

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Background: Preclinical studies have shown that MRI-guided focused ultrasound (MRIgFUS) can achieve spatially localized thermal exposures in the range of 41-43°C. It has been demonstrated through histology that MRIgFUS is capable of inducing the targeted uptake and release of doxorubicin (DOX) from thermosensitive liposomes (ThermoDox®, Celsion Corporation) in tumor models, and that this gives rise to potent antitumor effects. To enable the treatment of a broad spectrum of tumor types, improved heating approaches must be developed to overcome issues relating to respiratory motion, bone shielding, and large blood vessel cooling during MRIgFUS. To facilitate this process, it is important to gain insight into the microscale spatiotemporal release patterns induced by ultrasound mediated hyperthermia. Window chamber microscopy is well established as a method for investigating thermosensitive drug delivery, but to date it has generally employed water bath heating to control temperature. Here we describe the first integration of ultrasound mediated hyperthermia into a two-photon microscopy (2PM) setting, and report initial results with this approach.

Methods: GFP-tagged FaDu tumors were initiated in dorsal skinfold window chambers in nude mice 10-14 days before imaging. On experiment day, two type-T thermocouples were implanted to allow real-time temperature monitoring. A 'ring' transducer (1.2 MHz) was attached to the window chamber such that the ultrasound beam was directed into the tissue in a region that was co-incident with the optical field-of-view. Temperature based PID control of the acoustic power was used to maintain the tissue temperature at 41°C or 42°C for 20 minutes. Serial 3D vascular and DOX images were acquired before, during and after the FUS hyperthermia exposure in the presence of ThermoDox®.

Results: ThermoDox® drug release was successfully visualized with 2PM during FUS hyperthermia. The intra- and extravascular DOX signals were observed for up to 60 minutes following the initiation of treatments. The PID temperature controller was able to achieve a temperature response with variable rise time and maximum temperature to allow the investigation of different heating schemes. Work is ongoing to segment the vasculature and determine drug penetration as a function of distance to the nearest vessel under each exposure.

Conclusions: We have developed the use of 2PM to image the release of DOX from ThermoDox® in real-time under FUS hyperthermia in mouse tumors. This capability will enable the evaluation of different FUS schemes (stand alone or cavitation enhanced) for hyperthermia-mediated drug delivery with the goal of overcoming limitations on clinical MRIgFUS hyperthermia.

WED 53

Targeted intratumoral doxorubicin delivery by ultrasound-imageable low temperature sensitive liposomes and high intensity focused ultrasound mild hyperthermia

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Background

Ultrasound (US) imaging is extensively used for cancer diagnosis and to assess therapeutic success. However, translation of applications of High Intensity Focused Ultrasound (HIFU) to direct US-guided drug delivery from low temperature-sensitive liposomes (LTSL) have so far been limited. Objectives of this study were to: 1) develop an echogenic low temperature sensitive liposome (E-LTSL) co-loaded with an US contrast agent (Perfluoropentane, PFP) and doxorubicin, 2) determine E-LTSL doxorubicin delivery in a xenograft mouse model of colon cancer in combination with HIFU and 3) compare the ability of E-LTSL to report on real-time doxorubicin release compared to LTSL, non-thermosensitive echogenic (E-NTSL) and non-echogenic liposomes (NTSL).

Method: LTSL and NTSL containing doxorubicin were co-loaded with PFP using an innovative 1-step sonoporation method to create E-LTSL and E-NTSL, respectively. Athymic nude mice with C-26 colon cancer cells grown subcutaneously into the right hind leg were randomized into nine treatment groups: free doxorubicin, LTSL (+/- HIFU), E-LTSL (+/- HIFU), NTSL (+/- HIFU) and E-NTSL (+/- HIFU). Treatments (5 mg doxorubicin/kg) were administered via tail vein once tumors reached a size of 300-400mm^3. For the HIFU group, mild hyperthermia (40-41 °C) was applied to the tumors under ultrasound guidance after LTSL infusion for 1 hour. Doxorubicin concentrations in the harvested tumor, tumor adjacent and contralateral muscle and organ/tissue homogenates were determined by HPLC.

Results: Adding HIFU-induced hyperthermia to both E-LTSL and LTSL resulted in a ~ 5 fold increase in doxorubicin concentration in tumor compared to free doxorubicin and a ~2.5 increase in doxorubicin concentration in tumor compared to E-NTSL and NTSL. In comparison, tumor adjacent muscle demonstrated ~4 fold increase in doxorubicin concentration compared to contralateral muscles. Doxorubicin bio-distribution in non-tumor organs/tissues was similar between treatment groups. However, E-LTSL plus HIFU treated mice showed significantly greater drug delivery in heart tissue versus free drug ($p<0.05$, tukeys).

Conclusion: US guided HIFU-mediated drug release from imageable E-LTSLs showed comparable results with LTSLs and delivered more drug to the tumor than E-NTSLs and NTSLs.

WED 54

MR-HIFU MILD HYPERTHERMIA FOR LOCALLY RECURRENT RECTAL CANCER: TEMPERATURE MAPPING AND HEATING QUALITY IN FIRST PATIENT

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INTRODUCTION: Rectal cancer recurs in 5-15% of patients after surgery, radiation (RT), and chemotherapy (CT). Most patients with local recurrence (LR) are ineligible for salvage surgery, and undergo re-RT+CT with modest palliation and 5-year overall survival in <20%. We present early results from a prospective, single-center Phase I clinical study to assess treatment feasibility and acute toxicities of mild HT delivered using MR-HIFU, as an adjuvant to RT+CT for unresectable LR rectal cancer.

METHODS: The study is approved by the local Research Ethics Board. Patients with biopsy-proven LR rectal cancer who are not surgical candidates but are eligible for re-RT+ CT+MR-HIFU, are offered enrolment. Consenting patients receive the standard of care (30.6Gy over 17 fractions with daily oral capecitabine) plus delivery of MR-HIFU HT to the tumor before RT fractions 1, 6, and 11, with a goal of 42°C for 30 min. Primary objectives are to establish the feasibility of adding MR-HIFU HT to RT+CT and to assess acute toxicities (grade ≥3 GI or GU). Secondary objectives are to assess late toxicity, pain reduction, quality of life, HT accuracy and workflow, and radiologic response.

HT was delivered with the Philips Sonalleve MR-HIFU system under an Investigational Testing Authorization from Health Canada. MR thermometry (MRT) in 6 planes were used to regulate average temperature in an 18 mm-diameter target zone at 42°C, and to limit maximum temperature below 43°C. The target zone was heated using electronically-scanned HIFU at 1.0-1.2 MHz, and 40-80 W.

RESULTS: The first patient had a rectal recurrence in the pelvic sidewall that was unresectable due to proximity to the sciatic nerve. During MR-HIFU HT, the patient was under conscious sedation, and provided verbal feedback to the physician to decide when to pause HIFU energy deposition. The patient did not report pain, and has no adverse effects after 90 days of follow-up.

MRT outside the heated zone had an average elevation from baseline of <0.1°C, and temporal SD of 1.3°C. Median plateau temperature in the heated zone ranged from 39.8 to 41.2°C, with T90 and T10 of 38.3-39.3°C, and 41.2-42.5°C. Total durations in the range 41-45°C were 4.4, 7.5, and 18.4 min as the team gradually increased acoustic power. Quality of MRT and HT was limited mainly by patient motion.

CONCLUSION: We report the first clinical use of MR-HIFU for the delivery of mild HT. Therapeutic temperatures were achieved with no treatment-related toxicity.

WED 55

COMPARISON OF ULTRASOUND AND MAGNETIC RESONANCE THERMOMETRY FOR GUIDANCE OF HIFU HYPERTHERMIA: PHANTOM STUDIES

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BACKGROUND: Mild hyperthermia (HT) combined with radiation or chemotherapy can improve outcomes for many patients with cancer. Clinical evidence indicates that accurate and extensive thermometry is essential for safe and effective HT delivery. Non-invasive thermometry with image-based magnetic resonance (MR) thermometry is gaining acceptance, while ultrasound (US) thermometry may offer practical advantages including portability and cost. We present results from phantom experiments comparing temperature measurements made simultaneously using US and MR thermometry during HIFU HT.

METHODS: US thermometry in a gellan gum phantom was performed in an MRI (Ingenia 3T, Philips) using a single-element 5 MHz US transducer (Y109, Sonic Concepts) fitted within the central aperture of a single-element 1.1 MHz HIFU transducer (H102, Sonic Concepts); both had a focal distance of 59mm. Transducer location was controlled using an MR-compatible positioning system (RK100, FUS Instruments). US pulse-echo acquisition and HIFU energy deposition were interleaved using an open-architecture US acquisition system (Vantage 256 HIFU configuration, Verasonics). Filtered US signals were passed into the MR scan room through a grounded RF penetration panel. US echo shifts were tracked in the raw RF US data to derive thermally-induced strains which were calibrated to temperature rise. MR thermometry was calculated using the proton resonance frequency shift from RF-spoiled fast field-echo phase images (TE 12ms, 2mm in-plane resolution, 2 or 4 mm slice thickness) acquired across and along the US beam every 5 seconds. US and MR data were acquired simultaneously and asynchronously.

First, the temperature dependence of the US and MR data were calibrated in the phantom against fiber-optic semiconductor temperature sensors (T1C, Neoptix) during gradual, uniform heating using hot water pumped through a coiled tube. Second, US and MR thermometry data were acquired concurrently during rapid, localized HIFU heating.

RESULTS: MR and US measurements during slow, uniform heating from 19.6 to 44°C had comparable accuracy (-0.41±0.49°C vs. 0.20±0.69°C) and precision (0.15±0.08°C and 0.12±0.03°C). During HIFU, peak temperature measurements made using MR and US were highly correlated (R^2=0.82). MR measurements were consistently lower than US (bias -2.1°C, 95% limits of agreement -3.7 to -0.5°C) due to averaging in MR voxels larger than the width of the HIFU focus.

CONCLUSIONS: In stationary homogeneous phantoms, US and MR thermometry have comparable accuracy and precision in the HT regime. During HIFU, peak temperature elevations measured by US and MR were well correlated. Agreement was sensitive to voxel size and alignment with respect to the small heated volume.

WED 56

Targeted antibiotic delivery using temperature-sensitive liposomes and magnetic resonance guided high-intensity focused ultrasound hyperthermia for chronic non-healing wound treatment

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Chronic non-healing wound infections require long duration antibiotic therapy, and are associated with significant morbidity and healthcare costs. This results in both systemic and local infection to deeper tissues (e.g bones), thereby requiring long duration treatment (generally >6 weeks), resection of tissues, and emergence of drug resistance. Novel approaches for efficient, readily-translatable targeted and localized antimicrobial delivery are needed. The objectives of this study were to: 1) develop low temperature-sensitive liposomes (LTSLs) containing an antimicrobial agent (ciprofloxacin) for induced release at mild hyperthermia (~42ºC), 2) characterize in vitro ciprofloxacin release, and efficacy against *Staphylococcus aureus* plankton and biofilms, and 3) determine the feasibility of localized ciprofloxacin delivery in combination with MR-HIFU hyperthermia in a rat model. LTSLs were loaded actively with ciprofloxacin, and their efficacy was determined using a disc diffusion method, MBEC biofilm device, and scanning electron microscopy (SEM). Ciprofloxacin release from LTSLs was assessed in a physiologic buffer (serum and PBS), and in vivo in a rat model using MR-HIFU by fluorescence spectroscopy. Results indicated that > 95% loading of ciprofloxacin was achieved. Further, < 5% was released from the LTSL within 15 min at baseline (25 °C) and body (37°C) temperature, while > 95% was released at 42ºC. Sonication of rat muscles resulted in accurate and homogeneous temperature control within the heated ROI (42.0 ± 0.2 ℃), with a 90^{th} percentile (T10) and 10^{th} percentile (T90) of 43.2 ± 0.3 ℃ and 41.0 ± 0.3 ℃ respectively. Precise hyperthermia exposures in the thigh of rats using MR-HIFU during IV administration of the LTSLs resulted in a 4-fold greater local concentration of ciprofloxacin compared to controls (free ciprofloxacin + MR-HIFU or LTSL alone). The biodistribution of ciprofloxacin in unheated tissues was fairly similar between treatment groups. Triggered release at 42ºC from LTSL achieved significantly greater *S. aureus* killing and induced membrane deformation and changes in biofilm matrix compared to free ciprofloxacin or LTSL at 37°C. This technique has potential as a method to deliver high concentration antimicrobials to chronic wounds.

WED 57

The effect of Hsp90 inhibition on thermal cytotoxicity

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Background: High intensity focused ultrasound induces its biological effects, in part, due to an increase in the temperature of target tissue. These effects are associated with induction of necrosis and gene-directed forms of cell death including apoptosis and autophagy. In this study we aim to identify the proteins that may be associated with the response of cancer cells to heat. In addition we investigate whether regulation of these proteins can augment the cytotoxic effect of thermal exposures. **Methods:** The thermal dose concept was used to provide a parameter that allows comparison of different thermal treatments. Two human colon cancer cell lines, HCT116 and HT29, were subjected to ablative temperatures using a polymerase chain reaction (PCR) thermal cycler. Temperature was recorded using thermocouples. Cell viability was assessed using the MTT assay. The percentage of cells at different stages of the cell cycle was estimated by staining fixed cells with propidium iodide (PI). Induction of apoptosis was investigated using Annexin V / PI staining and FACS analysis. Basic heat stress response was determined by Western blotting using antibodies against Hsp70 and Hsp90. Regulation of CD47 and E-cadherin was determined using FACS analysis. Inhibition of Hsp90 was undertaken using targeted inhibition of the protein with an Hsp90-specific chemical probe **Results:** Exposure of colon cancer cells to EM_{43}s of 60, 120 and 240 minutes resulted in a decrease in the number of live cells one day after treatment. The remaining viable cells retained their clonogenic potential. Cells treated with an EM_{43} of 60 and 120 minutes showed signs of proliferation by day 2. A transient increase in the percentage of cells in the G1 phase of the cell cycle was evident in cells exposed to an EM_{43} of 240 minutes one day after treatment. An increase in the expression of Hsp70 was evident one day after treatment. Hsp90 protein levels did not change throughout the treatment. A time-dependent differential regulation of CD47 was observed. CD47 expression was reduced after 24 hours, but increased three days after treatment. The number of cells expressing E-cadherin was increased 4 days after treatment. The use of an Hsp90 inhibitor resulted in enhancement of thermally-induced cell death which was associated with a decrease in the number of cells expressing CD47. **Conclusions:** CD47 is associated with the response of cells to thermal exposures and may represent an important target in future hyperthermia treatments.

WED 58

Use of Hyperpolarized C^{13} Imaging for Detecting HIFU-Sensitized Hyperthermic Region in Prostate Cancer

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Background: Prostate cancer (PC) is the most frequently diagnosed noncutaneous cancer in men, and HIFU is being clinically investigated for focal ablation treatment of patients with low- or intermediate-risk PC. Real-time hyperpolarized (HP) ^{13}C MRI can be utilized during HIFU to improve treatment delivery strategies, provide treatment verification, and thus reduce the need for more radical therapies. The goal of this study is to develop imaging biomarkers specific to HIFU thermal therapy of PC that are capable of predicting the successful ablation of treated tissues and identifying tissues with sub-ablative hyperthermic exposure that are potentially sensitized to adjuvant treatment. The results of this study will provide the basis for evaluation of these biomarkers in human clinical trials of HIFU therapy for low- to intermediate-risk PC.

Methods: *In vivo* animal studies were performed using a transgenic prostate adenocarcinoma mouse model. Mice (n = 3) with solid prostate tumors received HIFU treatment (5.6 MHz, 160W/cm^2, 60 s,) and were imaged using a wide-bore 14T microimaging system. Imaging time points included a baseline 1 day before the treatment, and 1- and 5-day follow-ups post-treatment. Tumor metabolism was monitored by the conversion of injected ^{13}C-labeled pyruvate into the resulting metabolite lactate. Tumor perfusion was monitored using both C^{13}-labeled urea and DCE MRI (TE/TR=20/1200ms, acquired over 5 minutes). After the 5-day follow-up, tumors underwent histopathological analysis and were categorized into 3 regions: (1) the ablated region, (2) the sensitized region (tissues receiving sub-ablative thermal dose), and (3) the control group (untreated regions).

Results: Tissues in the ablated regions underwent sharp decreases in both metabolism and perfusion 1 day post-treatment, and showed no recovery by day 5. In the sensitized regions, lactate and urea underwent a 50% and 40% decrease by 1 day respectively, followed by recovery back to baseline by day 5, which can be indicative of tissues' healing response. In contrast, the area-under-curve of the clinical standard DCE remained constant through out the time course, showing its inability to detect the sensitized region.

Conclusion: This preliminary data shows that HP C^{13}-labeled urea and lactate are more sensitive than DCE MRI and its associated gadolinium-based contrast agent in indicating the hyperthermia-sensitized region following HIFU treatment, whereupon adjunct therapies (radiation/chemo therapy) can be applied to enhance treatment efficacy. Future work will include real-time MR thermometry and correlation of the thermal dose map to the imaging results to better assess treatment outcome and delineate the sensitized tissues.

WED 59

RADIATION THERAPY COMBINED WITH HYPERTHERMIA OR CISPLATIN FOR LOCALLY ADVANCED CERVICAL CANCER: RESULTS OF THE RANDOMIZED RADCHOC TRIAL.

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BACKGROUND: Chemoradiation (RT-CT) is standard treatment for locally advanced cervical cancer (LACC). This study tried to establish if radiotherapy combined with hyperthermia (RT-HT) should be preferred in bulky and/or FIGO-stage ≥III.

METHODS: In this open-label, multicenter randomized trial, patients with LACC were randomly assigned by a computer-generated, biased coin minimization technique to RT-CT or RT-HT. Central randomization was done with stratification by FIGO-stage, tumour diameter and nodal status. Primary endpoint was event free survival (EFS). Secondary endpoints were pelvic recurrence free survival (PRFS), overall survival (OS) and treatment related toxicity. Analysis was done by intention to treat.

RESULTS: The trial was closed prematurely (87 of 376 planned patients enrolled: 44 RT-CT; 43 RT-HT). Median follow-up time was 7.1 years. The cumulative incidence of an event was 33% in the RT-CT group and 35% in the RT-HT group. The corresponding hazard rate (HR) for EFS was 1.15 (CI: 0.56–2.36, *p*=0.7). Also the hazards for PRFS (0.94: CI 0,36-2,44) and OS (1,04; CI 0,48–2,23) at 5 years were comparable between both treatment arms as was grade≥3 radiation related late toxicity (6 RT-CT and 5 RT-HT patients).

CONCLUSION: After 25% of intended accrual, data suggest comparable outcome for RT-CT and RT-HT.

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WED 60

An open-label, non-randomized, single-institution, phase 2 study, regional deep hyperthermia for salvage treatment of children with refractory or recurrent non-testicular malignant germ-cell tumors.

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Background:

Although the survival of children and adolescents with malignant germ-cell tumors (GCTs) has improved greatly in recent years, the outcome remains poor for those with refractory or recurrent malignant GCTs. Because pediatric patients with non-testicular, primary GCTs mainly have their first recurrences in local regions, local tumor control is crucial to the long-term outcome in these children and adolescents. Intensification of systemic treatment could increase systemic toxic effects without adequately improving local tumor control, particularly in patients who undergo intensive pretreatment. The goal of cisplatin, etoposide, and ifosfamide (PEI)-regional deep hyperthermia is to enable tumor resection by down staging patients with otherwise unresectable malignant GCTs.

Methods: Patients with refractory or recurrent non-testicular malignant GCTs after standard cisplatin-based chemotherapy were treated prospectively with PEI chemotherapy (cisplatin 40 mg/m², delivered intravenously on days 1 and 4; etoposide 100 mg/m², intravenously on days 1–4; and ifosfamide 1800 mg/m², intravenously on days 1–4) plus simultaneous 1-h regional deep hyperthermia (41–43°C) on days 1 and 4. Patients received three to four treatment courses at 21-day intervals until residual tumor resection was possible; they subsequently received one or two additional courses of PEI-regional deep hyperthermia. Local radiotherapy was given for incompletely resected tumors. The primary endpoint was the proportion of patients who had an objective response and secondary endpoints were the event-free survival and overall survival after 5 years. This ongoing PEI-regional deep hyperthermia study (Hyper-PEI protocol) is registered at the German Cancer Society, number 50-2732.

Results: 44 Patients aged 7 months to 21 years (median 2 years 7 months) with refractory or recurrent malignant GCTs (9 poor response, 23 first relapse, 12 multiple relapses) were included in this study. Of the patients who had sufficient clinical and radiographical data available for response assessment, 86% had an objective response to treatment. 5-year event-free survival was 62%, and 5-year overall survival was 72%. The median follow-up of surviving patients was 82 months (range 9–195).

Conclusion: For recurrent and refractory extracranial non-testicular malignant GCTs in children and adolescents, a multimodal strategy integrating PEI-regional deep hyperthermia salvage treatment and tumor resection with or without radiation constitutes the best available strategy to increase local tumor control and achieve favorable long-term outcomes.

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WED 61

The European Experience of Regional Hyperthermia Combined With Chemotherapy as First-line Treatment in Soft-Tissue Sarcomas

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Introduction: Regional hyperthermia (RHT) was described as a targeted therapy and six hallmarks were recently proposed to define the pleiotropic effect of this therapeutic modality. In localized high-risk soft-tissue sarcomas (hr-STS) a randomized ESHO - EORTC Intergroup phase III study has proven the benefit of neo-adjuvant chemotherapy (NAC) combined with RHT (Issels et al. Lancet Oncol. 2010).This review reports whether the improvements are sustained and translate also into overall survival (OS) benefit.

Methods: Patients aged > 18years with localized hr-STS (size >5cm, FNCLCC grade 2 or 3) of extremity, trunk or retroperitoneal site were randomized to NAC or NAC +RHT. As induction therapy, NAC consisting of ifosfamide + doxorubiciand based chemotherapy was given first-line for 4 cycles q 3 weeks either alone or combined with RHT. Following local therapy (surgery, radiation) another 4 cycles of allocated treatment was given as adjuvant therapy.

Results: In total 341 patients were randomized (from July 1997 to November 2006), and 329 patients (167 NAC, 162 NAC+RHT) were eligible for the long-term analysis (withdrew consent: 5 NAC, 7 NAC + RHT). By December 2014, median follow-up was 74 months. Patients randomized to NAC + RHT had significantly prolonged OS compared to NAC alone (HR 0.74, 95CI: 0.55- 0.99; log-rank p = 0.047), with 5-year OS of 63 % vs 51 %, and 9-years OS of 54 % vs. 43 %. Median OS was 15.4 years for NAC + RHT and 6.2 years for NAC alone.

Conclusion: For patients with localized hr-STS the use of pre- and postoperative chemotherapy combined with RHT given first-line in addition to surgery and radiation resulted in significantly improved long-term OS benefit. This improved effect might be linked to the pleiotropic effect of hyperthermia by modulating the immune response. This treatment strategy is now used as standard treatment at our Sarcoma Center for hr-STS.

WED 62

Early Experiences of a Phase I Study of Targeted Delivery of Lyso-Thermosensitive Liposomal Doxorubicin by Focused Ultrasound Hyperthermia to the Liver (TARDOX)

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INTRODUCTION: The TARDOX study (Oxford, UK, NCT02181075) is a Phase I first-in-man proof-of-concept study which aims to demonstrate the safety and feasibility of targeted drug delivery using lyso-thermosensitive liposomal systems in combination with mild hyperthermia delivered non-invasively using focused-ultrasound (FUS). The primary endpoint of the study concerns demonstration of enhanced intratumoural delivery of doxorubicin to liver tumours for the same systemic dose of the drug, when given in liposomal form (Lyso-Thermosensitive Liposomal Doxorubicin, LTLD, ThermoDox®) and released locally by FUS hyperthermia.

We present the early results of this clinical study. At the time of writing four patients have received intervention; a single treatment cycle of 50mg/m^2 LTLD combined with FUS to a single target primary or secondary liver tumour using the ultrasound-guided extracorporeal FUS device (Model JC200 Focused Ultrasound Tumor Therapeutic System, Haifu Medical).

METHODS: Each treatment was performed under a general anaesthetic with the patient supine on the JC200. Using correlation with cross-sectional imaging, an 18-gauge co-axial needle was placed under ultrasound-guidance into the target tumour, allowing insertion of a clinically approved thermistor or a core biopsy needle according to the treatment protocol. Shortly following the 30-minute intravenous LTLD infusion, the JC200 beam was moved transcostally through the target tumour volume, containing the thermistor, in an automated plan to induce heating of the tumour to 40-44°C, monitored using the implanted thermistor. Heating strategies included single shot and moving beam and were optimised based upon *ex vivo* ox liver tissue experiments using the same system (presented at 3rd European Symposium on FUS Therapy, London 2015).

Core tumour biopsies were taken a) prior to drug infusion, b) following completion of drug infusion, and, c) following FUS, for analysis of intratumoral doxorubicin concentration and microscopy studies. Plasma samples were taken at simultaneous time points for pharmacokinetic analysis.

Dynamic contrast enhanced (DCE) MRI, perfusion CT and 18F-FDG PET-CT scans were performed the day prior to treatment and at approximately 2 and 4 weeks post-treatment with clinical review. An additional MRI was performed the day following treatment. Response evaluation was performed using principles of RECIST & CHOI and the SUV_{max} metric for the target tumour.

RESULTS: We present safety, thermometry and pharmacokinetic data and radiological outcomes.

CONCLUSION: We demonstrate the use of LTLD with extra-corporeal FUS hyperthermia for targeted drug delivery in human liver tumours is feasible, safe and can enhance intratumoral delivery of doxorubicin for a given systemic dose relative to LTLD alone.

POSTER SESSION ABSTRACTS FOR WEDNESDAY, APRIL 13, 2016 & THURSDAY, APRIL 14, 2016

POS 1

Using a Drug as a Reactant in Multiplexed Thermochemical Ablation: Thermal Profile of Valproic Acid, a Histone Deacetylase Inhibitor, in Reactions with Polyamines

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Introduction: Minimally invasive therapeutic alternatives are associated with lower health care costs and improved outcomes. Thermochemical ablation is a minimally invasive therapeutic modality that is being investigated for its use in the treatment of tumors based on thermal and chemical mechanisms. The purpose of this study is to evaluate valproic acid (VPA), a histone deacetylase inhibitor, in exothermic reactions with organic polyamines for potential in thermochemical ablation (TCA) of solid tumors.

Materials and Methods: Triplicate aliquots of neat VPA (6.24M) were reacted with an equivalent of aqueous organic polyamines (aminoethylethanolamine [AEEA], diethylenetriamine [DETA], N-methylethanolamine [NMEA], ethanolamine [EA], and 1,3-Diaminopropane [1,3-DAP],). In one trial, 9.0M DETA was used for neutralization to characterize the range of exothermic potential and in another trial, 3 equivalents of VPA were reacted with 6.24M DETA for full utilization of all 3 basic nitrogens. The temperatures were measured every 2 seconds for a total of 5 minutes and graphed.

Results: Maximum temperatures were reached within 30 seconds from a baseline temperature of 21.5°C. For VPA with NMEA and EA, the peak temperatures ranged from 35.4-43.5°C (mean 38.7°C) and 43.6-44.6°C (mean 43.7°C), respectively. For VPA with AEEA, DETA, and DAP the peak temperatures ranged from 33.9-36.8°C (mean 34.9°C), 33.8-40.7°C (mean 37.0°C), and 55.2-61.4°C (mean 55.2°C), respectively. 3:1 VPA:DETA at 6.24M yielded peak temperatures of 52.3-57.6°C (mean 54.6°C). For VPA with 9M DETA (1.5 fold excess), the peak temperatures ranged from 56.8-62.7°C (mean 58.6°C). Neutralization of VPA with excess DETA led to the highest mean peak temperatures.

Conclusion: Based on these exothermic profiles, neutralization of polyamines with VPA has potential for TCA. The moderate range of these exotherms may be due to the decreased solubility of VPA in aqueous solutions and the relatively weaker acidic potential of VPA (pKa ~4.8). The moderate increase in exothermic yield with the use of 3 equivalents of VPA with DETA may be due to the decreased solubility of VPA in the aqueous polyamine solution. However, a higher concentration of DETA driving the exotherm towards neutralization can further increase the energy yield. These exotherms can be further characterized by using multiple equivalents for full neutralization of the polyamines and utilizing other solvents for VPA. Further studies are warranted to evaluate these thermochemical profiles in *ex vivo* tissue and in animal models.

POS 2

Anticancer effects of β-elemene with hyperthermia in lung cancer cells

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Abstract

β-elemene is a novel anticancer drug extracted from herb which has been used to target various solid tumours and Hyperthermia is an adjuvant therapeutic modality to treat cancers.However, the underlying mechanisms associated with their efficacy are largely unknown.The aim of the present study was to evaluate the effects of β-elemene combined with hyperthermia in lung cancer cell lines. An MTT assay was used to determine the cell viability. The cell cycle and apoptosis were analyzed using flow cytometry. The morphology of cells during apoptosis was determined using a transmission electron microscope.The expression levels of P21, Survivin, caspase-9, Bcl-2 and Bax mRNA were detected using real-time PCR.β-elemene with hyperthermia inhibited proliferation of A549 cells.Also decreased S phase and induced apoptosis significantly.The morphological observation using transmission electron microscopy showed cross-sectional features of apoptosis: chromatin condensation, integrity of the plasma membrane, increased cellular granularity, nuclear collapse and the formation of apoptotic bodies.β-elemene promoted P21, bax mRNA expression and suppressed caspase-9, Bcl-2, Survivin mRNA expression in A549 cells.In conclusion, β-elemene with hyperthermia can significantly enhance the inhibitory effect in A549 cells. This occurs through decreasing S phase and inducing apoptosis via a increase in P21, bax mRNA expression and decrease in caspase-9, Bcl-2, Survivin mRNA expression.

Key words: Hyperthermia, Elemene, NSCLC, Apoptosis, Cell cycle

POS 3

Heating by natural nano-technology

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Introduction – The definite aim of curative hyperthermia is to kill the malignant cells selectively. Hyperthermia is a thermal approach where the tool of killing is the temperature. The tumour has a complex structure having various compartments, and only a part of it contains tumorous cells - which have to be our only target.

Method – Why do we heat up the complete tumour instead of the malignant cells only? This nanoheating technology selects and heats the malignant cells. The technology is widely used by various artificially added nano-particle applications. The technology of modulated electrothermia (mEHT, tradename: oncothermia) uses this knowledge [1], but no artificial additives are used for selective nanoheating of malignant cells [2]. The group of transmembrane proteins are naturally ready nanoparticles in the membranes of malignant-cells by definitely expressed lipid rafts [3].

Results – Make the energy absorption targeted to the rafts, gradual selection is made by various physiological specularities of malignancy: (1) the high metabolic rate makes conduction-selection by given radiofrequency (RF), (2) the robust change of intercellular connections of malignant cells orients the dielectric selection of RF, (3) the appropriate dispersion relation of the given modulated frequency chooses the rafts from their lipid environment, and (4) the dynamic (cooperative) changes in malignancy distinguish this tissue from their healthy counterpart, which is used by time-fractal modulation of the carrier RF. The nano-heating of rafts is thermal effect heating the rafts without direct heating of the mass of the tumour. It is measured that the rafts' temperature is at least 3°C higher than the lipids around it [4], which is the proven step of hyperthermia in nano-range. The proven part of the therapy (including lung, brain, liver) is successfully applied in numerous hospitals and clinics worldwide.

Conclusion – mEHT is a nano-heating technology by naturally present nanoclusters of the transmembrane proteins of malignant cells. This thermal method is under intensive studies at various universities; as well as clinical trials are in progress.

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POS 4

Development of resonant cavity applicator system with non-invasive measurement of temperature distributions

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This paper describes the ultrasound-guided resonant cavity applicator system, which non-invasively measures sub-pixel temperature distributions during hyperthermia treatments. We have already proposed the resonant cavity applicator system for non-invasive hyperthermia treatments. The proposed applicator system consists of a resonant cavity with inner electrodes, a high frequency amplifier, an impedance matching unit and a loop antenna. In this applicator, a human body is placed in the gap between two inner electrodes inside the cavity, and is heated by electromagnetic fields stimulated inside the cavity without physical contact. It was shown that the applicator could heat deep seated tumors without creating unwanted hotspots. In addition, the resonant cavity applicator could control the heated area inside the tumors corresponding to the symptoms of the patients. During treatments, a real time monitoring system was used to acquire the targeted area and temperature distributions inside the human body. This was necessary for effectively treating tumors.

In this paper, we proposed the ultrasound-guided resonant cavity applicator system, which had the potential to measure sub-pixel temperature distributions inside the human body and to heat deep-seated tumors. The method of measuring temperature distributions was based on the thermal dependence of the local change in the speed of ultrasound and thermal expansion. Here, we described the method to measure temperature distributions inside the agar phantom heated by the developed ultrasound-guided resonant cavity applicator. First, we heated the agar phantom inside a hot water bath to show the effect of temperature increase on the ultrasound images. Next, we measured temperature distributions inside the agar phantom heated by the resonant cavity applicator using a diagnostic ultrasound imaging system. Also, we discussed the results of the measured temperature distributions inside the agar phantom for controlling the heated area. An infrared thermal camera was used to measure the two dimensional temperature distributions of the heated agar phantom. Heating power was 30 W and heating time was 60 minutes. When comparing the measured temperature distribution with the proposed method and the temperature distribution measured by a thermo-camera just after heating, both resulted in an error of approximately 1 ^{o}C.

From our heating experiments, it was confirmed that the proposed method was useful for non-invasively measuring temperature distributions and locating hotspots inside the heated object.

POS 5

An algorithm of measuring sub-pixel temperature distributions from ultrasound images

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A needle applicator is used in clinical practice to invasively heat tumors. Radio frequency (RF) interstitial hyperthermia treatment is the direct and local heating of an area around the needle. One of the major disadvantages of the needle applicator is that the heating area is small. Because the diameter of the needle is approximately 1mm, the energy for heating the object occurs around the needle. Therefore, it is not easy to measure a temperature distribution around the needle.

This paper presents an algorithm of measuring sub-pixel temperature distributions based on the changes in the ultrasound wave images before and after heating. The proposed algorithm consists of seven steps. The first step is to input ultrasound images. The second step is to apply a Gauss Filter to the images to avoid a peak rocking phenomenon. For the third step, we set up a small template and applied template matching to the images to measure the quantity of displacement of the images. The fourth step is to apply a median filter to the template matched images to remove a noise. The fifth step is to apply interpolation processing for the images after applying the median filter. The sixth step is to apply a moving average filter after interpolation processing. The last step is to apply a differential filter to the images after the moving average filter. The resulting ultrasound images show temperature distributions during heating. In our heating experiments, we used the RF interstitial hyperthermia system which consists of a RF generator, a connection box, a needle type applicator and a discoid electrode. We put the needle type applicator into an agar phantom and adhered the discoid electrode to the surface of the agar. Heating power was 2 W and heating time was 3 minutes. An infrared thermal camera was used to measure the two dimensional temperature distribution of the heated agar phantom. We applied the proposed method of measuring temperature distribution to the ultrasound images which have a subpixel order high resolution. The temperature measurement error was less than 1.0^{o}C when heating the agar phantom.

From our heating experiments, it was confirmed that the proposed method was useful for non-invasively measuring temperature distributions and heating hotspots inside the heated object.

POS 6

Complete neutralization of available nitrogen atoms in polyamines using dichloroacetic acid improves mass efficiency in thermochemical ablation

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Purpose: To evaluate the exotherms of organic polyamines with multiple equivalents of the monoprotic acid dichloroacetic acid (DCA) for use in thermochemical ablation (TCA).

Materials and Methods: Triplicate aliquots of DCA (200µL, 1-3M) were reacted in test tubes with an equivalent volume of 1M aqueous organic amines (Aminoethylethanolamine [AEEA], 1,3 Diaminopropane [DAP], and Diethylenetriamine [DETA]). Multiple equivalents of DCA were added either simultaneously or sequentially. Sequential neutralization studies were performed by using aliquots of DCA stepwise, cooling to baseline between addition of equivalents. Concentrations were capped at 3M due to reactivity of the reagents involved.

Results: DCA concentration was directly related to peak temperature up to complete neutralization of all nitrogen atoms present. With 1 equivalent of acid to neutralize one nitrogen atom in the organic bases, peak temperatures were 25.1-26.3°C, a 5°C increase over baseline. With full neutralization of AEEA and DAP (2 equivalents of acid), peak temperatures were 29.5-31.3°C. At 3 equivalents of acid (full neutralization for DETA), peak temperatures were 29.7-35.1°C. In sequential studies cooled to baseline in between stages (19.5°C), for the first equivalent, peak temperatures were 26.8-27.3°C. For the second equivalent, temperatures increased to 23.5-25.5°C. For the third equivalent, temperatures rose from baseline to 23.1°C.

Conclusions: Based on the exotherms observed, the use of multiple equivalents of acid in reaction with polyamines has potential for use in TCA and all basic nitrogens are reactive. As a triamine, DETA has the greatest exothermic potential under these conditions, and could be the most beneficial in TCA from a strictly energetic point of view. As protonation proceeds, the subsequent exotherms yield less energy, consistent with prior literature. Further study is warranted on the degree of exotherm relative to different volumes. These experiments suggest that polyamines could be preferable bases to monoamines for *in vitro* neutralization for TCA of solid tumors. Exploiting multiple reactive sites on a single molecule has the potential for a large exotherm with greater mass efficiency, resulting in a lower overall injection volume for ablation.

POS 7

Air Gap Filler Material for RF Capacitive Heating

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Purpose:

In the RF capacitive heating, the air gap between a human body and a bolus often causes a concentration of a current and may bring a burn injury. Therefore, the air gap frequently disrupts the treatment and inhibits the output power of the hyperthermic device. Then the low output power does not have enough capacity to achieve the sufficient temperature rise for the treatment of the tumor. Therefore we developed the air gap filler material.

Methods:

In this study, we made some kind of analytical models, they have different contact situations of the human body and the bolus. In the material insertion models, we made some types of air gap filler material models, which have different combinations of relative permittivities and conductivities. In addition we employed realistic high-resolution whole-body voxel models for finite integration technique (FIT) calculation. Then, we analyzed electromagnetic field and calculated specific absorption rate (SAR [W/kg]) distributions using Microwave Studio 2015 by CST.

Results:

As a result of numerical calculations, the biological tissue around the air gap has higher SAR value than the other models. Then the deviation of SAR distribution is improved by inserting the air gap filler material. From these results, it is considered that air gap filler material can improve the heating patterns of hyperthermic devices. When we compare the results, the air gap filler material, whose electrical properties are ε_r=80 and σ=0.1, is the most effective in this calculation.

Conclusions:

In this study, we calculated electromagnetic fields and the SAR distributions of some kinds of contact situations of a human body and a bolus. From the results of calculations, we confirmed that the air gap affect the heating characteristics and the air gap filler material can improve the heating patterns.

Challenges and future requirements:

As a future study, we will make the air gap filler material and verify the effectiveness of the material by an experiment.

POS 8

Automatic evaluation of ablation zone boundary: a tool for quantitative evaluation of *ex vivo* ablation zone maps and comparison against numerical modelling results

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Introduction: To evaluate the performance of applicators and energy delivery strategies for thermal ablation, the dimensions of induced ablation zones in *ex vivo* tissue samples are often described by visually examined maximal long- and short-axis diameters. Drawbacks of this approach are: (1) introduction of ambiguities due to the subjective assessments of achieved ablation zones and (2) ablation zones are parametrized as ellipsoids, even though the actual shape is more complex. We propose an automated technique for detecting the boundary of the ablation zone along its entire circumference from digital images of the tissue sample, which reject above stated problems. Methods: The proposed algorithm estimates the ablation border position with the use of set of discrete points. Following the parametric description of an ellipse, points at certain positions are generated and moved according to the gradient of the area median intensity such that the ellipse encompasses the ablated area. Next, the position of each point is further refined according to the ablation boundary by gathering radial intensity profile of pixels in its vicinity and fitting of this profile to the sigmoid function. 90% of the sigmoid maximum marks refined position. The algorithm was evaluated on a set of 4 images following ex vivo microwave ablation of bovine liver (n = 2) and porcine muscle (n = 2). Ablation was delivered using an insulated dipole antenna operating at 2.45 GHz, with 30 W supplied at the antenna input port for 10 minutes. Estimated ablation zone contours were compared against manually segmented ablation boundaries and measurements of ellipse parameters. Results: Overall, the mean discrepancy between visually observed parameterized dimensions of the ablation zone and those identified by the proposed algorithm were: 1.6 ± 0.6 mm and 1 ± 0.5 mm for the ellipse short- and long-axis diameter. The average root mean square error between the manually segmented ablation boundary, and that estimated by the proposed algorithm was 1.48 mm for muscle and 1.70 mm for liver tissue. Average computation time was 2 minutes at Athlon Dual-Core 2.1GHz processor. Conclusion: The proposed algorithm provides a promising automated technique for objective assessment of ablation zone following experiments in *ex vivo* tissue. This technique may: (1) facilitate more objective comparison of ablation zones predicted by biophysical models and experiment, and (2) provide more accurate representations of ablation zone for treatment planning and regulatory submissions. More robust objective functions of utilized gradient algorithms can provide enhanced performance.

POS 9

Magnetic particle imaging for magnetic hyperthermia treatment: quantitative evaluation of intratumoral magnetic nanoparticle distribution and prediction of therapeutic effect

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Introduction: Recently, a new imaging method called magnetic particle imaging (MPI) has been introduced. MPI allows imaging of the spatial distribution of magnetic nanoparticles (MNPs). We developed a system for MPI with a field-free-line (FFL) encoding scheme, in which the FFL is generated using two opposing neodymium magnets and the signals generated by MNPs are received by a gradiometer coil. This study was undertaken to investigate the usefulness of MPI for predicting the therapeutic effect of magnetic hyperthermia treatment (MHT) using phantom and small animal experiments.

Methods: First, we imaged phantoms filled with various iron concentrations of MNPs (Resovist®) using our MPI scanner and investigated the correlation between the iron concentration of MNPs and the MPI value (pixel value). We also heated the phantoms using an alternating magnetic field (AMF) with a frequency of 600 kHz and an amplitude of 3.1 kA/m and measured the temperature rise using an infrared thermometer. Second, we performed animal studies using tumor-bearing mice, which were divided into untreated (n=10) and treated groups (n=27). The tumors in the treated group were injected with Resovist® with iron concentrations of 500 mM (n=9), 400 mM (n=8), and 250 mM (n=10) and were heated using AMF. MHT was not performed in the untreated group. The mice in the treated group were imaged using our MPI scanner immediately before and immediately after MHT. We drew the region of interest (ROI) on the tumor in the MPI image and calculated the average MPI value by taking the threshold value for extracting the contour as 40% of the maximum MPI value within the ROI. We also measured the relative tumor volume growth (RTVG), which was defined as $(V-V_0)/V_0$ with V_0 and V being the tumor volumes immediately before and after MHT, respectively.

Results: In phantom experiments, the MPI value had significant correlations with the iron concentration of MNPs ($r=0.997$) and temperature rise ($r=0.981$). In animal experiments, the MPI value immediately before MHT had significant negative correlations with the RTVG values 5 days ($r=-0.696$), 7 days ($r=-0.666$), and 14 days after MHT ($r=-0.642$). The MPI value immediately after MHT had significant negative correlations with the RTVG values 5 days ($r=-0.658$), 7 days ($r=-0.667$), and 14 days after MHT ($r=-0.650$).

Conclusion: MPI can visualize the spatial distribution of MNPs in tumors and quantify their amount accurately. Our results also suggest that MPI will be useful for predicting the therapeutic effect of MHT.

POS 10

Development of a system for heat transfer simulation for optimization and treatment planning of magnetic hyperthermia using magnetic particle imaging

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Introduction: Magnetic particle imaging (MPI) allows imaging of the distribution of magnetic nanoparticles (MNPs) with high sensitivity, spatial resolution, and imaging speed. In addition, MPI can visualize MNPs in positive contrast without background signals from background tissues and can quantify the amount of MNPs with excellent linearity. Magnetic hyperthermia (MHT) is a strategy for cancer treatment using the temperature rise of MNPs under an alternating magnetic field. Accurate knowledge of the spatial distribution and amount of MNPs accumulated in the targeted region is crucial for designing optimal treatment planning of MHT to prevent insufficient heating of the targeted region and overheating of the healthy tissue. The purpose of this study was to develop a system for heat transfer simulation for optimization and treatment planning of MHT using MPI.

Methods: First, we performed phantom experiments to obtain the regression equation between the MPI value and the specific absorption rate (SAR) of MNPs. The MPI value was defined as the pixel value of the transverse MPI image obtained by our MPI scanner. The samples with various concentrations (50, 100, 125, 250, and 500 mM) of MNPs (Resovist®) were prepared by putting them into cylindrical tubes 6 mm in diameter and 5 mm in length. These samples were also heated using our apparatus for MHT, and the SAR was calculated from the initial temperature rise. The MPI value was converted to the SAR value in the simulation. Second, we imaged tumour-bearing mice injected intratumorally with Resovist® using our MPI scanner and X-ray computed tomography (CT) scanner. Third, we generated the geometries for use in the simulation by processing the X-ray CT and MPI images. The geometries and MPI images were then imported into software based on a finite element method (COMSOL Multiphysics®) to compute the time-dependent temperature distribution for 20 min after the start of MHT.

Results: There was excellent correlation between the MPI and SAR values ($r = 0.956$). There was good agreement between the time course of the temperature rise in tumours obtained by simulation and that obtained experimentally. The time-dependent temperature distributions under various blood perfusion rates in tumours and at various locations could be simulated, which cannot be easily obtained experimentally.

Conclusion: These results suggest that our system for heat transfer simulation using MPI will be useful for the optimization and treatment planning of MHT, because it enables us to investigate a large number of study conditions.

POS 11

Quantitative evaluation of tumor response to combination of magnetic hyperthermia treatment and radiation therapy using magnetic particle imaging

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Introduction: Magnetic particle imaging (MPI) is a new method of imaging the distribution of magnetic nanoparticles (MNPs). Accumulation and retention of MNPs in tumors are important factors to enhance the therapeutic effect of magnetic hyperthermia treatment (MHT). Radiation therapy (RT) has been reported to reduce the interstitial fluid pressure (IFP) in tumors, and is expected to enhance the retention of MNPs in tumors when combined with MHT. This study was undertaken to quantitatively evaluate the tumor response to MHT alone or combined with RT (MHT+RT) using MPI.

Methods: Colon-26 cells were injected subcutaneously into the back of 8-week-old male BALB/c mice. When the tumor volume reached approximately 100 mm^3, the tumor-bearing mice were divided into control (n=10), MHT (n=10), and MHT+RT (n=8) groups. In the control group, both MHT and RT were not performed. In the MHT group, the tumors were injected with MNPs (250 mM Resovist®) and were heated using an alternating magnetic field. The mice in the MHT+RT group were irradiated to a dose of 7.5 Gy with a 4-MeV linear accelerator and MHT was performed 3 days after RT. In the MHT and MHT+RT groups, MPI images were obtained using our MPI scanner immediately before, immediately after, 3 days, 7 days, and 14 days after MHT. After the MPI studies, we drew the region of interest (ROI) on the tumor in the MPI image and calculated the average, maximum, and total MPI values within the ROI. In all groups, tumor volumes were measured every day and the relative tumor volume growth (RTVG) was calculated from $(V-V_0)/V_0$, where V_0 and V denote the tumor volumes immediately before and after MHT, respectively.

Results: The RTVG value in the MHT+RT group was significantly lower than those in the control and MHT groups. Although the RTVG value in the MHT group tended to be lower than that in the control group, it did not reach statistical significance. The average MPI value in the MHT+RT group was significantly higher than that in the MHT group 3 days and 7 days after MHT. The maximum MPI value in the MHT+RT group was significantly higher than that in the MHT group 7 days after MHT. The increase in the average and maximum MPI values due to RT appears to reflect the decrease in IFP.

Conclusion: Our results suggest that MPI is useful for quantitatively evaluating the tumor response to MHT alone or MHT+RT.

POS 12

Quantitative evaluation of tumor early response to magnetic hyperthermia treatment combined with vascular disrupting therapy using a newly-developed method for magnetic particle imaging

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Introduction: Magnetic hyperthermia treatment (MHT) is a strategy for cancer therapy using the temperature rise of magnetic nanoparticles (MNPs) under an alternating magnetic field (AMF). Vascular disrupting agents (VDAs) selectively damage the endothelial cells of tumor blood vessels, inducing reduction of tumor blood flow and necrosis of tumor cells. Recently, a new imaging method called magnetic particle imaging (MPI) has been introduced, which allows imaging of the spatial distribution of MNPs. The purpose of this study was to evaluate the therapeutic effect and tumor early response to MHT combined with VDA (MHT+VDA) using MPI in comparison with those to MHT alone.

Methods: Colon-26 cells (1×10^6 cells) were injected into the back of eight-week-old male BALB/c mice. When the tumor volume had grown to 100-160 mm^3, the mice were divided into MHT+VDA (n=19) and MHT groups (n=12). In the MHT+VDA group, VDA (Trisenox®) was injected intraperitoneally at a dose of 4 mg/kg. Two hours after the injection of VDA, MNPs (250 mM Resovist®) were directly injected into the tumor and MHT was performed using an AMF (frequency: 600 kHz and amplitude: 3.5 kA/m). In the MHT group, only MHT was performed. In both groups, MPI images were obtained using our MPI scanner immediately before, immediately after, 1, 3, 7, and 14 days after MHT. After the MPI studies, we drew a region of interest (ROI) on the tumor in the MPI image and calculated the average MPI value by taking the threshold value for extracting the contour of the tumor as 40% of the maximum MPI value (pixel value) within the ROI. We also measured the relative tumor volume growth (RTVG), which was defined as $(V\text{-}V_0) / V_0$, where V_0 and V are the tumor volumes immediately before and after MHT, respectively.

Results: The RTVG value in the MHT+VDA group was significantly lower than that in the MHT group 1 to 3 days after MHT. The average MPI value in the MHT+VDA group was significantly higher than that in the MHT group 3 and 7 days after MHT, indicating that the retention of Resovist® in tumors was enhanced by use of VDA.

Conclusion: Our results suggest that the use of VDAs is useful for improving the therapeutic effect of MHT at early stage and for repeated applications of MHT. Our results also suggest that MPI is useful for evaluating the tumor early response to MHT+VDA in comparison with MHT alone.

POS 13

Chemoradiotherapy plus regional hyperthermia for thoracic esophageal cancer: Does whole thoracic regional hyperthermia increase the occurrence of radiation pneumonitis?

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Background: Several studies have demonstrated that the administration of a large distribution of low-dose radiation to the normal lung resulted in a higher risk of lung toxicity in esophageal cancer patients treated with chemoradiotherapy. For deep regional heating using an 8 MHz radiofrequency-capacitive regional hyperthermia (HT) system, the whole thoracic region should be heated with coupled large electrodes of 30 cm to elevate the temperature of the esophageal tumors. We hypothesized that whole thoracic HT may increase the risk of radiation pneumonitis because HT could inhibit the repair of sublethal radiation damage of the normal lung. The purpose of this study was to evaluate the relationship between whole thoracic regional HT and the occurrence of radiation pneumonitis (RP).

Methods: Between May 2005 and September 2012, 104 patients with esophageal cancer of the thorax were retrospectively analyzed. Whole thoracic regional HT using the 8MHz RF-capacitive regional HT system was performed during chemoradiotherapy in 42 of 104 patients (HT group) and was not used in the remaining 62 patients (non-HT group). The primary reasons for the lack of HT treatment in the non-HT group was a poor PS in 20 patients, obesity in 18 patients, patient rejection in 14 cases and advanced age in 10 patients. The number of treatments of whole thoracic regional HT using large electrodes (all cases, 30 cm in diameter) ranged from two to nine (median, five). The median total doses of radiotherapy in the HT and non-HT groups were 60 Gy (range, 50-70) and 60 Gy (range, 50-72), respectively. The median lung doses in the HT and non-HT groups were 7.5 Gy (range, 0.5-16.7) and 7.8 Gy (1.9-15.2), respectively. The median lung V20 for radiotherapy was 12.2% (range, 0.6-29.7) and 13.5% (3.2-28.9), respectively.

Results: RP of Grade 2 or higher was observed in three patients in the HT group (4.8%) (Grade 2: one patient, Grade 3: two patients) and four patients in the non-HT group (6.5%) (Grade 2: three patients, Grade 3: one patient), which was not significantly different. Symptomatic Grade 2 or higher RP was observed at a median of 6.0 months (range, 3–10) after RT. The dosimetric factors of the lungs (V5, V10, V15, V20, V25, and MLD) for radiotherapy were significantly associated with the development of Grade 2 or higher RP.

Conclusion: There was no relationship between whole thoracic regional HT and the occurrence of radiation pneumonitis in patients with esophageal cancer.

POS 14

Investigation of the threshold power density levels of millimeter wave exposures for the corneal damage under the CEM43ºC criterion by computer simulation

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Recently, the use of millimeter wave (MMW) technologies is developing in the field of communications, sensing, imaging, spectroscopy, and so on. Therefore, it is becoming public concern to consider the safety of the use of MMW technologies.

Against this background, we conduct the study to determine the threshold levels of ocular damage, especially within corneal region, under the MMW exposure from 40 GHz to 95 GHz. For this purpose, the mathematical model is proposed to estimate threshold incident power levels of MMWs based on CEM43ºC (cumulative number of equivalent minutes at 43ºC) criterion. CEM43ºC criterion is the index of "thermal isoeffective dose", which is originally applied for cancer therapy from 1984. Corneal damage induced by MMW is mainly caused by thermal dose, therefore it is reasonable to introduce the CEM43ºC criterion to the estimation of the threshold.

Coupled analysis for electromagnetic field (EMF) and heat transport (HT) is performed from 40 GHz to 95 GHz with 100μm spatial resolution. In the heat transport simulation, convectional heat transfer model, driven by aqueous humor in the anterior chamber, is considered. 3D time development temperature distributions are obtained during MMW exposure by varying incident power density from 50 mW/cm^2 to $300mW/cm^2$ at each frequency to obtain threshold. Moreover, 3D time dependent CEM43ºC index distribution within corneal region is calculated from these time dependent temperature data. Threshold levels of incident power density for 360 s exposure time is estimated from these CEM43ºC data in the condition of acute and minor damage as for cornea, which was described in past literature as 21 < CEM43ºC < 40 min. Consequently, threshold levels estimated by this mathematical model is consistent with those obtained by *in vivo* experiment. We think our proposed model with CEM43ºC criterion is feasible to estimate threshold power levels for corneal damage.

POS 15

Hyperthermia: a possible adjuvant treatment for medulloblastoma to increase response rate and reduce late toxicity? – A literature review about the vascular characteristics of medulloblastoma –

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Background: Standard treatment protocols for medulloblastoma include a combination of surgery, chemotherapy and cranio-spinal irradiation, yielding an 8-year overall survival of 50-60%. Unfortunately, radiotherapy causes severe late (neuro)toxicity. Hyperthermia, i.e. heating of tumors to 40-45°C enhances the effect of chemotherapy and radiotherapy. Effective hyperthermia would also allow to reduce the radiation dose, thereby decreasing side effects. The aim of this study was to explore literature data on vascular characteristics of medulloblastoma to determine whether hyperthermia could be effectively applied.

Methods: A PubMed search was performed with search terms medulloblastoma and vascular characteristics. This resulted in ten original studies describing the vascular pattern and different parameters that characterize the blood supply: microvessel density, vascular plasma volume, blood flow and vascular permeability.

Results: Medulloblastomas show a more heterogeneous vessel pattern compared to normal brain tissue. Although the microvessel density is comparable to normal brain tissue, the vascular plasma volume is slightly higher, implying a relatively good blood supply. Nevertheless, medulloblastomas are less perfused than the surrounding tissue, indicating that effective heating would be possible to increase the effectivity of radiotherapy and chemotherapy. The vascular permeability is higher than in normal cerebellar tissue, but relatively low compared to some other brain tumors. This suggests that increasing the vessel permeability by hyperthermia will enable improved chemotherapy drug delivery.

Conclusion: The vascular characteristics of medulloblastomas suggest that these tumors can be heated effectively. This would increase the effectiveness of chemotherapy and radiotherapy, which may increase clinical outcome and reduce late toxicity by radiotherapy dose reduction.

POS 16

Optimal path length correction for the Sigma Eye applicator for HTP

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Background

The Sigma Eye applicator has been designed to reduce the pressure of the water bolus on the patient's body compared to the cylindrical Sigma-60. Hereto, the shape of the Sigma Eye applicator closely resembles that of an ellipse, with a major axis of 540 mm and minor axis of 360 mm of the inner patient opening. In general the enhanced 3 dimensional control of the SAR distribution makes the Sigma Eye the applicator of choice to apply deep heating of pelvic tumors. To prevent high energy deposition in superficial tissues close to the EM-emitting dipole antennas a minimum distance of 40 mm water bolus must be present between the dipole surface and the nearest skin of the patient.

The elliptical shape of the applicator entails that the dipoles located at the top and bottom are closer to the center of the applicator than the left and right lateral dipoles. As a consequence a different path length exists between dipoles pairs at top and bottom with those at left and right.

In their manual BSD medical corporation has indicated a phase delay of 45° based upon a physical difference in path length of 43 mm, linear approach. It is assumed that the path length difference is calculated for a homogeneous permittivity comparable to that of water. Based on the physical shape of the Sigma Eye applicator and the fact that each antenna consists of a paired dipole we calculated a path length of 80 mm, again assuming a homogeneous water-like medium. This would translate in a phase delay of about 83°.

Methods

To decide what phase delay can be best applied, we use hyperthermia treatment planning to investigate the effect of the applied phase delay on the quality of the whole 3D SAR distribution in various cylindrical, elliptical and anthropomorphic phantoms.

Results/Discussion

Calculations of the 3D SAR distribution in a 220 mm diameter cylindrical phantom, permittivity ε_r =80 and electrical conductivity σ=0.5 S/m demonstrates that selection of the best phase delay is not a trivial decision. Even in a cylindrical phantom of homogeneous tissue adding a phase delay results in different sagittal and coronal SAR profiles. Depending on the relevance given to high SAR values at the more superficial tissue a phase delay between 60 and 90 seems best. Additional results will be provided to select the optimal phase delay for a central SAR focus.

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POS 17

Increase in intra-tumor blood flow and sub-tumor temperature in cervix cancer by electro-modulated hyperthermia.

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Introduction: It has been known that mild hyperthermia enhances the response of tumors to radiotherapy or chemotherapy by increasing tumor blood flow thereby increasing tumor pO2 or drug delivery. This study was performed to evaluate the changes in the intra-tumor blood flow and sub-tumor temperature in cervical cancers heated with electro-modulated hyperthermia.

Methods: Ten cervical cancer patients were treated with electro-modulated hyperthermia. Their mean age was 51.9 years (range, 37-81 years). The squamous cell carcinoma to non-squamous cell carcinoma ratio was 3 : 2. The mass nature was exophytic in 7 patients and endophytic in 3 patients. Patients were classified as stage IIb (5 patients), IIIb (4 patient), or IVb (1 patients). All patients received 1 hour hyperthermia on their pelvic area. Intra-tumor blood flow and sub-tumor temperature were measured at 30 min before hytherthermia (baseline), at 30 min and 60 min during hyperthermia, and 30 min after hyperthermia. Intra-tumor blood flow was measured with 3D Doppler ultrasound method . The sub-tumor temperature was measured with internal organ temperature probe.

Results: The mean sub-tumor temperature before heating was 36.8 ± 0.2°C, and it increased to 38.3 ± 0.5°C and 39.8 ± 0.7°C upon heating for 30 and 60 min, respectively, and 37.2 ± 0.3°C at 30 min after heating. The S/D (systolic/diastolic) ratios were 1.62 ± 0.21 at baseline, 1.38 ± 0.11 and 1.23 ± 0.08 upon heating for 30 and 60 min respectively. The RI (resistance index) indices were 0.41 ± 0.16 before heating, and 0.28 ± 0.14 and 0.20 ± 0.08 after heating for 30 and 60 min. The blood flow calculated using the RI and S/D values indicated that the tumor blood flow significantly increased during heating . The RI index varied considerably depending on the pathology of tumors (squamous cell carcinoma, p = 0.041). The increase in sub-tumor temperature was significantly different depending on the mass nature (exophytic, p = 0.003).

Conclusion: The sub-tumor temperature and intra-tumor blood flow in cervical cancers significantly increased during 30-60 min heating and for 30 min after heating. These increases were dependent on the nature of the tumor.

Keywords: intra-tumor blood flow, sub-tumor temperature, electro modulated-hyperthermia

POS 18

The influence of a metal stent on the distribution of thermal energy during irreversible electroporation

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Introduction: Irreversible electroporation (IRE) uses short duration, high-voltage electrical pulses to induce cell death via nanoscale defects resulting from altered transmembrane potential. The technique is gaining interest for ablations in unresectable pancreatic and hepatobiliary cancer. Metal stents are often used for palliative biliary drainage in these patients, but are currently seen as an absolute contraindication for IRE due to the perceived risk of direct heating of the metal and its surroundings. This study investigates the thermal and tissue viability changes due to a metal stent during IRE.

Methods: IRE was performed in a homogeneous tissue model (polyacrylamide gel), without and with a metal stent placed perpendicular and parallel to the electrodes, delivering 90 and 270 pulses (15-35 A, 90 µsec, 1.5 cm active tip exposure, 1.5 cm interelectrode distance, 1000-1500 V/cm, 90 pulses/min), and in-vivo in a porcine liver (4 ablations). Temperature changes were measured with an infrared thermal camera and with fiberoptic probes. Tissue viability after in-vivo IRE was investigated macroscopically using 5-triphenyltetrazolium chloride (TTC) vitality staining.

Results: In the gel, direct stent-heating was not observed. Contrarily, the presence of a stent between the electrodes caused a higher increase in median temperature near the electrodes (23.2 vs 13.3 °C [90 pulses]; p = 0.021, and 33.1 vs 24.8 °C [270 pulses]; p = 0.242). In-vivo, no temperature difference was observed for ablations with and without a stent. Tissue examination showed white coagulation 1mm around the electrodes only. A rim of vital tissue remained around the stent, whereas ablation without stent resulted in complete tissue avitality.

Conclusion: IRE in the vicinity of a metal stent does not cause notable direct heating of the metal, but results in higher temperatures around the electrodes and remnant viable tissue. Future studies should determine for which clinical indications IRE in the presence of metal stents is safe and effective.

POS 19

Optical Microscopy Compatible Hyperthermia Applicator for Liver Tumors in Mice

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Introduction: The temperature increase during hyperthermia can be used for controlled delivery and enhanced effectiveness of chemotherapeutic drugs that are enclosed in temperature sensitive liposomal nanocarriers to tumors. In order to apply hyperthermia in a tumor located in the liver of a mouse, a specific electromagnetic hyperthermia applicator (HA) for mice is designed and constructed. The HA must be simple, suitable for microscopic observations and it has to heat the tumor by 6°C in 60s.

Methods: The modelled HA consists of a water bolus, which is represented by deionized water tube enclosed in PVC tube. A quasi-static electric field is generated by four metallic semi-ring (SR) antennas that together encircle the water bolus.

Using a cylindrical phantom with approximate dimensions of a mouse, we investigated the most suitable frequency in SEMCAD X. For maximum power dissipation we changed some dimensions of the HA until we obtained $\log_{10}|S_{11} + S_{12}| < -15$dB. Further, the impact of a microscope with the objective immersed in a water layer just on top of the liver tumor, on the heating characteristics of the HA is investigated using EM-modelling. Thermal simulations are performed in SEMCAD X using the Pennes Bioheat Equation. The final version of the HA-model includes the mouse model from ITIS and a spherical tumor.

Results: For the HA including the phantom, 433.92MHz is proved to be a suitable frequency. To relocate the heat focus to the tumor region we symmetrically rotated the connection of the coaxial cables to SR to the opposite side of the tumor. The simulation results show that after application of input power of 20W, we obtained temperature increase of 6°C in 60s in the assumed tumor region. Moreover, the microscopic objective did not affect the applicator performance, i.e. $\log_{10}|S_{11} + S_{12}| < -15$dB. The model predicts that a temperature increase of 6°C in a large part of the tumor can be reached within 57s.

Conclusions: This study shows that our HA is simple, can rapidly increase the temperature of tumors located in the liver by 6°C in 60s while still providing to microscopically observations thermally induced biological effects.

POS 20

Steering the Deep Regional Hyperthermia to Match the Hyperthermia Target Volume to the High-Dose Planning Target Volume in Helical Tomotherapy for Cervical Cancer –a Proposal and Preliminary Feasibility Test

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Background: In clinical practice of combining regional hyperthermia with conformal radiotherapy (RT), the matching for target volumes in these two modalities is important. In RT of cervical cancer, the primary tumor and parametrium are regarded most risky area to develop recurrence. By using helical tomotherapy equipped with cone beam computed tomography (CBCT) scanners, the daily setup for image-guided radiotherapy (IGRT) could be achieved by registration of planning CT scan and CBCT images. However, the practical algorithms for precisely matching treatment volumes of hyperthermia and IGRT remain to be improved. To guide the steering of deep regional hyperthermia targeting region of interests concerned by physicians, we developed a proposal to match the hyperthermia target volume (HTV) to high-dose planning target volume (HD-PTV) of tomotherapy for cervical cancer treatment.

Methods: We defined a HD-PTV to cover primary cervical tumor and parametrium for cervical cancer. To test the feasibility of our proposal, a locally advanced cervical cancer patient receiving tomotherapy and regional hyperthermia was recruited. After RT planning by tomotherapy system, the HD-PTV was generated from gross TV and clinical TV. To ensure accurate RT to PTV, the CBCT images were obtained and image registration with identifiable anatomical markers were performed to guide the stereotactic localization for tomotherapy treatment, which also guided the identification of HD-PTV center. The x-, y- and z-axis distances between image-registered HD-PTV center (the same as HTV center) and pubic bone marker were then calculated to aid steering of deep regional hyperthermia. The coverage ratio of HD-PTV by HTV was estimated.

Results: By using thermal mapping, we found that the coverage ratio of HD-PTV by HTV was greater than 95%. The center of HD-PTV with CBCT image registration could be easily and precisely identified to be set as the center of HTV before steering regional hyperthermia. The newly designed center of HTV was located 4.4-cm caudally to the conventional center of hyperthermia (the middle between cranial margin of uterus and caudal margin of cervix/cervical tumor). No significant adverse effect related to hyperthermia was noted by using this proposal.

Conclusion: In the preliminary test, we found that this proposal by matching the hyperthermia target volume to high-dose planning target volume of tomotherapy as a guide for deep regional hyperthermia for cervical cancer might be feasible. This proposal is feasible in clinical unit possessing both hyperthermia and IGRT facilities.

POS 21

Photoacoustic Imaging for Spectral Characterization and Thermography of ex vivo Thermochemical Ablation

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Introduction: Minimally invasive therapeutic alternatives are associated with lower health care costs and improved outcomes. Thermochemical ablation is a minimally invasive therapeutic modality that is being investigated for its use in the treatment of tumors based on thermal and chemical mechanisms. The purpose of this study is to evaluate the use of photoacoustic (PA) imaging to assess local spectroscopic shifts and temperature changes during thermochemical ablation (TCA) of *ex vivo* porcine liver.

Materials and Methods: Using the VisualSonics Vevo® 2100-LAZR imaging platform, 3-D B-mode ultrasound (US), 3-D spectral PA nanostepper (sPA; 700, 740, 760, and 800 nm), and 2-D spectral PA (680-970 nm) images were acquired from each sample prior to injection and pre- and post-bisection of the ablated region after injection. Controls were saline, 5M diethylenetriamine (DETA), and 5M H_3PO_4. Total volumes were 200 µL, 400 µL, and 1000 µL of 1:1 DETA and H_3PO_4 for simultaneous injection into an *ex vivo* porcine liver phantom. Real-time 2-D PA imaging (760 nm) was achieved through the approximate center of the injection volume before, during, and following the TCA for thermography to correlate PA signal intensity with temperature change.

Results: Unablated tissue yielded a PA spectrum consistent with deoxyhemoglobin (HHb). Thermochemically ablated and H_3PO_4–infused tissue produced a PA spectrum lacking HHb's characteristic 758-nm local maximum. Real-time 2-D PA imaging yielded a drastic increase in PA signal amplitude coincident with the injection time point, followed by a generally monotonic decrease in PA signal to baseline. Injection of saline and DETA did not cause spectroscopic changes.

Conclusion: Loss of the 758-nm HHb local maximum in thermochemically ablated tissue is consistent with the PA ablation spectrum observed with other ablative modalities, including radiofrequency (RFA) and high-intensity focused ultrasound. Based on these consistent findings, PA imaging has potential for studying the spatial characteristics of TCA and RFA in tissue. Injection of H_3PO_4 likely resulted in spectroscopic changes due to immediate denaturing of proteins within the injection site, whereas DETA likely did not due to delayed effects of basicity on primary protein structure. Results suggest that real-time, single-wavelength PA imaging can be leveraged for the purposes of thermography, permitting the noninvasive characterization of the exothermic effect of TCA in tissue. Further studies are warranted to evaluate the efficacy of PA imaging of TCA in *in vivo* animal models.

POS 22

Preliminary in vitro evaluation of Oncothermia in a normal and a cancerous cell line

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Background: Oncothermia is a novel method of capacitive hyperthermia using 13.56 MHZ alternating electric fields. There is some controversial laboratory and clinical data to suggest an advantage over conventional hyperthermia but it is still far from being accepted as a conventional medical treatment. Synergistic effects are claimed when combining Oncothermia with radiotherapy and chemotherapy. This study looks at Oncothermia effects at the cellular level, alone or in combination with radiation, to compare with findings from the Oncothermia research community.

Material and methods: A rat brain tumour model cell line (9L) and a canine non-cancerous kidney cell line (MDCK) were chosen to assess the potential efficacy of Oncothermia treatment using the clonogenic assay as the endpoint. Cells suspended in 2ml cryogenic tubes were immersed in water and exposed for 30 minutes to 42°C, either with a conventional water-bath or with Oncothermia applied via the LAB-EHY 100 laboratory unit (Oncotherm GmbH, Germany). Oncothermia pre-treated cells and untreated cells were irradiated to 5Gy with 10 MV photons. After treatment, cells were sub-cultured at low density in Petri dishes and after 15 doubling times, colonies with more than 50 cells were counted as surviving. Treated samples were normalized to the untreated samples to establish the cell survival fraction (SF). All experiments were repeated three times.

Results and discussion: The MDCK cells have a similarly high SF for both the water-bath and Oncothermia treatment, 86.5% and 77% respectively. On the other hand, the 9L cell line shows a greater difference between the water-bath and Oncothermia treatments with a SF of 97.5% and 61.4% respectively. Thus the 9L cells are resistant to traditional heat treatment using the water-bath but not to the same temperature using Oncothermia. The results for MDCK illustrate no significant contribution of Oncothermia when used before a radiation dose of 5 Gy compared to radiation alone (SF 5.4% v 4.4%). Conversely, results for 9L clearly demonstrate an enhancement with the combined Oncothermia and radiation treatments (SF 35% v 13%). The 9L cell line is well known to be very resistant to radiation so the positive result with Oncothermia is potentially useful.

Conclusion: Selectivity of Oncothermia for the 9L cancer cells compared to MDCK non-cancerous cells has been observed. Similar preferential enhancement towards the 9L cancer cells was also observed when treated in combination with radiation therapy. Further experiments and analysis are still required to understand the effects of Oncothermia at the subcellular level.

POS 23

Primitive study of clinical applications of three-dimensional temperature distribution simulation for radiofrequency hyperthermia

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Introduction

Hyperthermia using radiofrequency (RF) capacitive heating has been performed since 2011 at University of Tsukuba hospital. The research interest in RF hyperthermia from the viewpoint of medical physics is the information about heat generation and the temperature distribution accompanying clinical heating. The data obtained by the temperature measurement using thermal sensors is one-dimensional (point) or two-dimensional (line) information. That is, it is difficult to acquire a three-dimensional temperature distribution correctly with measurement using thermal sensors only.

In this research, we aimed to construct a general-purpose simulation system that can evaluate the three-dimensional temperature distribution for RF hyperthermia.

Methods

The hyperthermia system used for the evaluation was RF-8 (YAMAMOTO VINITA).

First, we acquired the time-dependent temperature change of a gelatin phantom heated by clinical parameters (500 W) with the thermocouple sensors. Next, we built a simulation system for RF hyperthermia using Multiphysics (COMSOL), the temperature distribution simulation software. We optimized some physical-property parameters so that the time-dependent temperature change obtained by measurement could be reproduced for the built simulation system. Furthermore, we used an optimized simulation system and performed various evaluations.

Results

From the measurement results obtained using thermocouple sensors, we observed that the central temperature of the phantom proportionally increased with heating time. In the built simulation system, it was possible to acquire a three-dimensional temperature distribution in the phantom for RF hyperthermia. Moreover, in the simulation system with optimized physical-property parameters, it was possible to reproduce the time-dependent temperature change in the phantom in agreement with the measurement data.

The simulation results can be output as electronic data. Therefore, it was suggested that it is possible to superimpose the results with dose distribution or to evaluate the influence of the heterogeneous materials (for example, metal stent, etc.) on the temperature distribution using the simulation system.

Conclusion

In this study, we built a general-purpose three-dimensional temperature distribution simulation system for RF hyperthermia. In future, we will build a simulation system for a human model.

POS 24

Deep regional hypethermia combined with chemotherapy: Greek Society of Hyperthermic Oncology.

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Introduction: Hyperthermia has been used to treat a number of different types of localized cancer, including liver metastases, lung metastases, cervix, rectum, and bladder. This procedure in combination with chemotherapy or radiotherapy, or with both, may help to improve the effectiveness of these treatments.

Patients and Method

Between July 2012 and September 2015, 25 patients undergone combined chemotherapy and hyperthermia (EHY 2000 Line voltage:AC 230V/50Hz0, Power input:1600 VA, Output carrier frequency:13.56 (MHz), Output useful power:max. 150 W). Hyperthermia was performed for one hour in the temperature range of 43-45^{o}C. Anatomical regions included 11 liver metastases, 8 lung metastases, 4 cases of cervix and 2 cases of bladder. Patients were followed up three months post combined RT+HT.

Results

Complete response was achieved in 80% (liver metastases), 65% (lung metastases),

75% (cervix) and 50% (bladder) of patients with follow-up data.

Conclusion

Simultaneous hyperthermia combined with chemotherapy is able to enhance response and local control rates. Follow up in ongoing.

POS 25

Temperature dependent complex permittivity of agar phantom

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Microwave hyperthermia applicators are tested with agar phantoms at our university. Temperature of the agar material increases during a power measurement from 20 °C to 30 °C. Since complex permittivity of dielectric materials is generally temperature dependent, there should be also change in complex permittivity of agar phantom. In this contribution, we are studying a relationship between the temperature of the agar phantom and its complex permittivity. The main goal of this study is to establish a rate of change of complex permittivity along the temperature. Frequency range going from 50 MHz to 3 GHz was chosen to cover the frequencies used in microwave hyperthermia.

Small cylinder made from agar phantom material was inserted into a thermostatic water bath with temperature set to 20 °C. Temperature probe was placed inside the cylinder, in order to measure actual temperature of the phantom material. Temperature of the water bath was then increased in 1 °C steps to 35 °C. Enough time for temperature equalization was taken in every temperature step and complex permittivity of the material was then measured. Professional open ended coaxial probe connected to a vector network analyser was used to measure the complex permittivity. The coaxial probe was fixed in a laboratory stand and placed in the water bath too. Any movement of the probe was avoided after a calibration of the system. The measurement procedure was repeated several times.

Measured values of complex permittivity were compared at different temperatures. Debye model is going to be fitted to the data with a goal to create models for its temperature dependent coefficients. Results of this work contribute to the fields of new microwave hyperthermia applicators design and testing of microwave imaging systems.

POS 26

Tumor surface temperature measurement during magnetic hyperthermia in a murine model can differentiate distinct intratumoral heat deposition due to nanoparticle distribution.

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Monitoring heat delivery is very important to guarantee the success of a hyperthermia procedure. In particular, the development of non-invasive methods is of crucial importance, since the efficacy of a hyperthermia treatment depends on this information. Recently, we used thermography to monitor in real-time magnetic hyperthermia. In this type of treatment, it is believed that the nanoparticle distribution inside the tumor can have a strong influence on the three-dimensional heat deposition. In order to investigate the influence of the heat center distribution, we developed a near-infrared magnetic nanocarrier that reveals the intratumoral particle distribution. This particle localization information was obtained using fluorescence molecular tomography (FMT) technique after intratumoral injection. We used swiss albino 6-8 week-old mice in the experiments. The cancer model consists of Ehrlich tumor model. Non-invasive magnetic hyperthermia experiments were performed at 300kHz in a non-uniform field configuration. The surface temperature was monitored by infrared camera. Two distinct intratumoral injection procedures revealed different nanoparticle distributions in the tumor. The surface temperature profile at the surface monitored by thermography was very different suggesting a correlation with heat center localization. In order to investigate this further, 3D computer simulations were performed with the objective to match the surface experimental data. Using 3D reconstruction software we were able to reconstruct three-dimensionally the body of the mouse, while the tumor was reconstructed from ultrasound image sequences. As discussed before, FMT revealed the heat centers position. Computer simulations were performed using the software pachage Comsol Multiphysics, bio-heat transfer module. The simulation also considered blood perfusion rate temperature dependence. Comparison between computer simulations and experimental surface temperature measurements reveals the importance of distribution of nanoparticles and indicate that the intratumoral heat deposition might be determined non-invasively from surface temperature measurements in superficial tumors.

POS 27

Heat transfer and electromagnetic modeling of magnetic nanoparticle hyperthermia in agar gel phantoms

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Magnetic nanoparticle hyperthermia is the thermal treatment of tumors with nanoparticles when the region contacting the particles is subjected to an alternating magnetic field. Larger treatment volumes, or larger volumes of tissue exposed to AMFs, result in increased off-target heating of normal tissue due to generation of eddy currents. Thus, both heat transfer and electromagnetic modeling are needed to estimate power deposition and temperature distributions achieved in the tumor and surrounding healthy tissue. In this study, temperature distributions were computed in a cylindrical tissue model with and without nanoparticles subjected to an alternating magnetic field having frequency of 150 kHz and varying amplitude (0 – 16 kA/m). Experiments were carried out on agar gel phantoms (1% w/w, mimics soft tissues) in a 20cm coil with alternating magnetic field to validate the computational model. Three electrical conductivities were arbitrarily considered in the study by varying the salt concentration (0.017 M, 0.035 M, and 0.07 M NaCl) in the gel phantom. JHU nanoparticles were used in this study. Temperatures were measured at four points (in the center of the cylindrical gel phantom at equal distances along the radius) in the gel and compared with those estimated using the computational model. Good agreement was observed between the temperatures computed from computational model and those measured from gel phantoms. Also, with increased electrical conductivity higher temperatures were observed due to increased eddy current heating. Thus, the agreement between simulations/calculations and experimental results validates the model and this model can be used in subsequent studies to simulate and predict heating *in vivo* in a rabbit liver model.

POS 28

Enriching temperature measurements with simulations for 3D dosimetry during hyperthermia treatments.

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Background

24 phase III trials demonstrated the increased clinical outcome when hyperthermia is added to radiotherapy, chemotherapy or both. A number of investigations showed that this clinical improvement is temperature or thermal dose dependent. Treatment quality in hyperthermia is generally assessed by probe-based thermometry (very accurate, spatially limited) or MR thermometry (limited accuracy, high resolution). In this work, we present our first work on enriching thermometry with simulations for accurate 3D dosimetry.

Methods

For all patients, a CT was acquired with closed-tip thermometry catheters in place and the probe insertion into the catheter was documented before each treatment. Elastic registration was used to translate the measurement locations to the planning CT coordinate space. Based on the temperatures recorded during treatment, a constrained nonlinear optimization function was applied to minimize the cumulative difference between all measured and simulated temperatures using a leave one out approach. This procedure resulted in effective perfusion values (ω_e) and effective thermal conductivity values (k_e) per patient for the auto-segmented muscle, fat, and tumor regions. In step one (steady-state), we matched data for the 2-10 time-points of 17 patients when steady-state was detected. In step two (transient T), we optimized thermal tissue properties using the complete temperature profiles of 8 patients.

Results

In step one, a substantial improvement in simulation accuracy was observed compared to the accuracy obtained when using literature values for ω_e,and k_e: i.e. the average absolute difference reduced from 12.7°C (baseline values) and 4.4°C (thermal stress values) to 2.1°C (patient group optimized values). In step two, we demonstrated that the values optimized for the complete temperature profile and all patients resulted in a median temperature (T) prediction inaccuracy of 1.3°C and a median inaccuracy in T50 of 0.9°C, but that applying the optimized values from the previous treatment of the respective patient reduced the error to 1.0°C (T) and 0.4°C (T50).

Conclusion

The results show the high potential of our the new iterative reconstruction method and demonstrates the accuracies that can be obtained. We showed that limited data of probes can be converted into more reliable estimates of the applied 3D applied dose. In addition, we expect that this method can supplement MR thermometry in regions where it is inaccurate or at places outside the imaging field of view.

POS 29

Multidisciplinary Management Of Unresectable Verrucous Carcinoma Of The Genitals, i.e. Buschke-Lowenstein Tumor, With Combined External Beam Radiation and Hyperthermia: A Case Report

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Background: Condyloma acuminatum (CA) is a common, virally-mediated, sexually transmitted disease. By 1925, two physicians Buschke and Lowenstein had independently described a rapidly growing, aggressive variant that was initially called “carcinoma-like” CA and, eventually, Buschke-Lowenstein Tumor (BLT). Although there continues to be significant debate regarding the exact classification of these lesions, it is well recognized that they confer a substantial risk of malignant transformation. These tumors are very rare, and a variety of management options have been employed including surgery, topical chemotherapy, immunotherapy, and radiotherapy. Regardless of approach, however, high rates of local recurrence persist.

Methods: The reported patient was a 55 year-old white male with a 15-year history of slowly progressive condyloma involving the penile shaft, scrotum, abdominal wall, and perianal skin. Notably, he had no history of immunosuppression or HIV. He was evaluated by CT scan, confirming a large fungating mass enveloping the scrotum and penile shaft (Transverse – 17 cm, Deep – 3.8 cm, Tumor volume – 540 ml). The mass extended to the low rectus musculature without intraperitoneal involvement. Multiple incisional biopsies were performed revealing CA with associated invasive, keratinizing, squamous cell carcinoma (SCC). The condyloma tested positive for HPV 6/11 and 31/33, while the SCC was HPV-negative. PET-CT examination was negative for metastases. After multidisciplinary consideration, the patient was recommended for and underwent induction immunotherapy with cetuximab followed by definitive local therapy with radiation and concurrent hyperthermia. He received 4 months of cetuximab therapy q2weeks with an initial partial response. CT imaging at the 4 month follow-up revealed stable disease. The patient was then treated with daily Intensity Modulated Radiation Therapy (IMRT) to a dose of 59.4 Gy with concurrent External Thermal Therapy (ETT) administered twice weekly for 45-60 minutes to a maximum temperature of 43C.

Results: The tumor exhibited an exquisite response to IMRT/ETT with significant reduction in volume during the course of treatment. The patient required repeat CT simulation for plan adaptation based on the marked treatment response. The patient experienced expected skin irritation and desquamation. He also developed suprapubic ulceration from regression of the mass. Six-week post-treatment CT scan demonstrated a dramatic decrease in size of the mass (Transverse – 11cm, Deep – 1.8cm, Tumor Volume -200 ml), correlating with the remarkable clinical response observed.

Conclusions: Combined IMRT and ETT represent a potentially novel avenue for management of unresectable BLT.

POS 30

Transarterial delivery of a dichloroacetyl chloride/Lipiodol mixture in porcine kidney: a proof of concept study for thermochemical embolization.

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Introduction: Transarterial embolic procedures are widely adopted to treat liver cancers that are not resectable by surgery. Embolics such as Lipiodol and microspherical beads can substantially reduce the blood supply to tumors and result in ischemia that induces apoptosis of tumor cells. However, tumor cells may adapt to hypoxia and survive the embolic procedures. In previous studies, we found that the hydrolysis reaction of an acid chloride causes protein denaturation in liver tissue by generating heat and two equivalents of acid in situ. Here, we applied this concept to embolization and present a novel transarterial procedure named thermochemical embolization (TCE) that simultaneously delivers hypoxia, hyperthermia and low pH to tumors.

Methods: Dichloroacetyl chloride was dissolved in Lipiodol or mineral oil vehicle to a final concentration of 4M. Porcine kidneys were harvested and perfused with heparinized saline immediately after sacrifice to prevent thrombus formation. A 4 French sheath was inserted into renal artery before the bifurcation and secured by surgical ties. Dichloroacetyl chloride in vehicle was infused through this sheath using a 4 French catheter. Surface temperatures were monitored with an infrared camera. Temperatures at the upper and lower poles of the kidney were also recorded every 2 seconds with thermocouples deeper in the tissues. Magnetic Resonance (MR) thermal imaging was performed on a 3 Tesla GE MRI scanner.

Results: 8ml dichloroacetyl chloride/mineral oil in porcine kidney was infused over in 2 minutes. Temperatures at the upper and lower poles peaked at around 30-32°C 10 minutes after injection, indicating a 19-20°C gain from baseline. Similar temperature changes were also observed on the infrared surface images. Additionally, the infrared images showed that nearly 50% of kidney surface was heated up to 30°C. Consistently, gross pathology exam revealed that the same area appeared pale after the procedure, suggesting protein denaturation/coagulation in the area. A second kidney was perfused with 5ml dichloroacetyl chloride/Lipiodol mixture and subjected to MR thermal imaging. As expected, MR thermal imaging indicated that the highest temperature gain (around 30°C higher than baseline) occurred in the vessels and surrounding areas. The bisected kidney appeared pale, consistent with protein denaturation.

Conclusion: Intra-arterial hydrolysis of dichloroacetyl chloride in porcine kidneys occurred quickly, generating large areas of coagulation. Thermochemical embolization (TCE) may eradicate tumor cells more effectively than other embolization methods through the combination of hyperthermia, ischemia and pH change and thus warrants further study.

POS 31

Gain of radiation resistance induces hyperthermia resistance in lung cancer

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Despite the emergence of novel targeted treatments and immunotherapy, acquired resistance to therapy remains a significant challenge for the clinical success of any treatment modality. Unfortunately, this also holds true for radiation therapy. In order to identify the phenotypic and molecular characteristics associated with radiation resistance we generated a matched model of ionizing radiation resistance in human lung cancer. By exposing A549 cells (ATCC CCL-185) to 25 fractions of an accumulated 55Gy, we generated an acquired radiation resistant cell line, coined A549-RR. By means of cell viability and clonogenic assays we determined that A549-RR has up to a 2.5 fold increase in radiation resistance as compared to its parental counterpart. A549-RR displayed unexpected features of mesenchymal-to-epithelial transition (MET), confirmed by differential protein expression and functional assays. Namely, E-Cadherin was up regulated and Vimentin was down regulated. Functionally using the wound assay, A549-RR migrated significantly less than the parental cell line, 30% at 48hrs. Cumulatively, these results indicate a transition from the mesenchymal phenotype in A549 cells toward an epithelial phenotype in A549-RR cells.

Subsequently we wanted to see if this acquired radiation resistance was also associated with hyperthermia resistance. Clonogenic experiments showed acquired hyperthermia resistance was noted in A549-RR at 42°C for 60 minutes but not at 43°C for 60 minutes. Interestingly when combined with 2Gy radiation, hyperthermia at 42°C + 2Gy diminished the acquired radiation resistance.

The clinical relevance of our radiation resistant lung carcinoma model shows that radiation resistance is associated with a MET phenotype and coincides with hyperthermia resistance. Moreover, that combining hyperthermia with radiation overcomes the acquired resistance. Thus, the generated matched model of radiation resistance provides an opportunity for future in depth genomic and proteomic investigations of the key mechanisms for radiation resistance and potentially other treatment modality resistance profiles as well.

POS 32

Influence of tumor infiltrating lymphocytes on local progression-free and disease-free survival in high-risk soft tissue sarcoma treated with combined neo-adjuvant chemotherapy and regional hyperthermia

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Introduction: Clinical results showed significant improvement of local progression-free survival LPFS and disease-free survival (DFS) by adding regional hyperthermia (RHT) to neo-adjuvant chemotherapy (NAC) (Issels et al., Lancet Oncol 2010). Here, we investigated the hypothesis whether Tumor Infiltrating Lymphocytes (TIL) in high-risk soft tissue sarcoma (STS) biopsies predicts treatment outcome in this study.

Methods: The EORTC 62961- ESHO phase 3 study (NCT 00003052) investigated 341 patients (pts) with high-risk STS (grade2/3, > 5cm) comparing NAC with NAC + RHT. From 109 randomized pts (53 NAC, 56 NAC +RHT), 137 paraffin-embedded core biopsies were available before (84) or after (53) NAC + /- RHT treatment. TILs were assessed by counting in standard HE stained Tissue microarrays (TMA). IHC staining was performed for CD3, FOXP3 and PD-1. TILs were defined to be high (> 5TILs / TMA) or low (< 5TILs/TMA). Outcome was compared using Kaplan Meier and Cox estimations. IRB approval and written informed consent were obtained.

Results: In 84 initial biopsies, TILs were high in 17/84 (20.2 %) and low in 67/84 (79.8 %). By comparison, in the 53 post- treatment biopsies the high TILs fraction was increased and the proportion equally balanced: TILs high in 26/53 (49.1 %) and low in 27/53 (50.9%). PD-1+ infiltration did not change, whereas FOXP3+ (T-reg cells) were reduced after treatment .CD3 was 60-80 % expressed in TILs. Analyzing initial biopsies, survival outcome for high- vs low-TILs pts was not different (LPFS: HR 1.07; n.s.; DFS: HR 1.14 , n.s.) whereas after treatment the results were independent of grade significantly in favor of high-TILs pts (LPFS: HR 0.46. 95 % CI: 0.23 - 0.96; log- rank p=0.0325; DFS: HR 0.49 95% CI: 0.24 -0.98; log- rank p=0.040) .The % of high TILs in initial vs post-treatment biopsies after NAC +RHT increased nearly four-fold (15.8 % to 58.1 %) whereas this was not seen after NAC alone (23.9 % to 36.4 %).

Conclusion: We report first indication in STS that high TILs in response to therapy may be predictive for local control and survival. The effect of RHT to increase the fraction of TILs in tumor tissue as well as the depletion of negative regulatory T cells by chemotherapy suggest a new immune therapeutical potential for the combined application.

POS 33

Characterization and evaluation of a tissue-mimicking thermochromic phantom for use in radiofrequency ablation

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Introduction: Tissue-mimicking phantoms (TMPs) are used in a variety of applications including characterization of medical imaging systems and for device development, quality assurance, and training. Currently, measuring temperature in TMPs for evaluation of thermal therapies such as radiofrequency ablation requires invasive optical probes or costly magnetic resonance thermometry. This work describes characterization and evaluation of a tissue-mimicking thermochromic phantom (TMTCP) capable of providing direct visualization and quantitative determination of temperatures during thermal ablation.

Methods: TMTCP material was prepared using polyacrylamide gel and thermochromic ink that permanently changes color gradually from white to magenta when heated. Color vs. temperature calibration was performed by extracting RGB color values from photographs of phantom samples following water bath incubation at known temperatures. Color calibration was validated by visual comparison of heated test samples to samples exposed to known temperatures, or by computational comparison of RGB color intensities. For evaluation of phantom performance with RFA, a radiofrequency electrode (Radionics/Covidien) with 3 cm active tip connected to an RF generator (Radionics RFG-3E) was advanced into a TMTC phantom or ex vivo bovine liver. Temperatures in phantom or liver were measured at 0.5cm increments from the RF electrode during heating using fiberoptic temperature probes. Following RFA, the phantoms (n=3) and liver sample were bisected along the length of the RF electrode track and photographed at a set time. Temperature isotherms based on color changes in the phantom were generated in Matlab using the previously acquired temperature vs. color data.

Results: Heating of the TMTCP resulted in incremental, permanent color changes over a temperature range of 40-67°C, covering both mild and ablative hyperthermic ranges. Visual and computational methods of temperature estimation were accurate to within ±0.6°C and 1.6°C between 52-62°C, respectively. Real-time temperature measurements during RFA using fiberoptic probes matched closely with maximum temperatures as predicted by color change in the TMTCP. RFA heating profiles in the phantom resembled those in ex vivo bovine liver.

Conclusions: The TMTCP, designed for use with RFA, can be used in thermal therapy applications requiring quantitative temperature measurements in mild hyperthermic, sub-ablative, and ablative temperature ranges. Temperature estimations can be made visually or computationally based on permanent color changes in the phantom. The phantom provides an accurate and reproducible measure of absolute temperatures and ablation zone geometry with high spatial resolution, and can be used to model and evaluate modality and device dependent spatial heating characteristics in a controlled, predictable environment.

POS 34

A phased antenna array for the treatment of cancer malignancies in the intact breast

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Introduction: Currently available technology for delivering hyperthermia to breast cancer malignancies is not well suited to treating disease in the intact breast. We have previously reported a 915 MHz single element patch antenna applicator for delivering hyperthermia to the intact breast. Here, we report on the extension of the system to incorporate multiple antenna elements, with the goal of facilitating controllable power deposition profiles for treating disease at varying locations within the breast.

Methodology: A 3D-computational model was implemented to assess power deposition profiles with 915 MHz applicators incorporating a hemispheric groundplane and 1, 2, 4, 8 and 12 antenna elements. Hemispheric breast models of 90 mm and 150 mm diameter were investigated. Hyperthermia target volumes of 10 mm (small target) and 30 mm (large target) cubic side positioned at the center of the breast, and located 15 mm from the chest wall were considered. The average power absorption (aPA) expressed as the ratio of the power absorption in the target volume and in the full breast was evaluated. A 4-element prototype antenna was fabricated and experimentally evaluated. The ability to electrically steer power deposition profiles by adjusting the phase of the signal at antenna inputs was investigated.

Results: Computational models revealed that a 12-element constant phase array applicator (with antennas positioned at an angular offset of 22.5°) presented the highest aPA (1.5 for large target and 1.4 for small target) at deep targets in the large breast model. A 4-elements applicator presented the highest aPA for targets located at the center of the large (4.8 for small target and 4.5 for large target) and small breast (4.25 for small target and 3.75 for large target) models and deep targets in the small breast model (2.5 for the large target and 2.4 for the small target). An algorithm to maximize constructive E-field produced by the individual antenna element was implemented. A 4-element prototype was fabricated and experimentally evaluated within *ex vivo* chicken breast. With 7.5 W/antenna applied power, 10 min heating time and optimized antenna-phases, the temperature increased 7.5 °C in laterally positioned targets 22.5 mm from the breast center compared with the symmetrically located position, which temperature increased only 3 °C.

Conclusion: The proposed phased array hyperthermia systems shows strong potential for delivering conformal thermal therapy in the intact breast. Detailed experimental characterization is underway and will be presented at the meeting.

POS 35

Magnetically labeled mesenchymal stromal cells as theranostic platform for cancer

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Background: Magnetic iron oxide nanoparticles (MIONs) can be activated by an alternating magnetic field (AMF) to generate heat sufficient to significantly sensitize cancer cells for radiation therapy. Targeting strategies capable to effectively deliver sufficient concentrations of MIONs to sites of metastases remain among the technical challenges inhibiting clinical application. Recent studies have shown that tumor tropism displayed by mesenchymal stromal cells (MSCs) could be used to target therapeutic and diagnostic agents to tumors. The aim of this feasibility study is to ascertain the potential that MSCs can deliver sufficient concentrations of magnetic nanoparticles to tumors for therapeutic heating.

Methods: Analysis of tissue sections by histology was performed on tissues sections obtained from a previously conducted study using nude female mice bearing MDA-MB231. Briefly, MSCs obtained from bone marrows of GFP transfected C57B1/6 mouse (GmMSCs) were cultured and loaded with MIONs. Loading efficiency was confirmed by quantitative (ICP-MS) and qualitative (Prussian blue staining, electron microscopy) methods. FACS, differentiation, proliferation and stress assays were employed to test the influence of BNF nanoparticles on GmMSCs differentiation, morphology and proliferation. GmMSCs were intravenously injected into tumor-bearing mice (~1×10^6 cells) weekly for 7 weeks. Mice were sacrificed one week after final injection, and tissues were collected for iron quantification and histopathology.

Results: Quantitative analysis of iron and markers obtained from tissue confirmed the migration potential of MSCs to tumor tissue, the suitability of MRI to analyze the migratory fate of GmMSCs in vivo and the suitability of ICP-MS for quantitative analysis of the migratory fate of GmMSCs. Furthermore, Prussian blue staining and immunohistochemistry (with anti-GFP and anti-MSC antibodies) revealed that GmMSCs can migrate to tumor tissue, yet MION loaded GmMSCs exhibited significantly constrained migration to tumor tissues.

Conclusion: In conclusion, MION loaded MSCs analyzed by MRI and ICP-MS are a suitable tool to study the migratory fate of MSCs to tumor tissue in a quantitative manner; however, loading MSCs with MIONs to deliver therapy may be constrained by subtle impairments of tumor tropism that may depend upon intracellular concentrations of Fe. Histopathology data also suggested MION loaded GmMSCs exhibited constrained migration to tumor tissues.

POS 36

A Case report of thermobiochemoradiation therapy using superselective intra-arterial infusion for carcinoma of the buccal mucosa with N3 lymph node metastases

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We report a case of cancer of the buccal mucosa (T4bN3M0) treated successfully with thermobiochemoradiation therapy using retrograde superselective intra-arteial infusion, intravenous infusion of cetuximab and hypertheia. A 64-year-old man was referred to our hospital for treatment of a mass of the left buccal mucosa and left cervical swelling. CT images showed that the tumor had invaded masticatory space and pterygoid process and also large metastatic lymph nodes. The patients was diagnosed as squamous cell carcinoma of the buccal mucosa (T4bN3M0). As the patients wanted to preserve oral function and refused to undergo operation of the primary site excluding neck dissection, we performed intravenous biotherapy (cetuximab: total 1900mg/m^2), superselective intra-arterial chemotherapy via superficial and occipital artery (docetaxel: total 70mg/m^2, cisplatin: total 175mg/m^2) with daily concurrent radiotherapy (2Gy/day, total 70Gy) and thermoradiotherapy for cervical lymph node metastases (RF capacitive hyperthermia: 4 sessions). After the treatment, image examinations and the biopsy of the primary tumor were performed and diagnosed as pathological complete response of the primary site. So, only neck dissection was performed in eight weeks after the end of preoperative therapy. There were no findings of malignancy in the surgical specimen. One year and 6 months after the thermobiochemoradiation therapy, there were no recurrence of the primary tumor and cervical lymph node metastases, and no finding of distanat metastasis.

POS 37

Hyperthermia enhances the therapeutic efficacy of IL-13 cytotoxin in human oral squamous cell carcinoma.

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Background: Hyperthermia is often utilized together with chemotherapy and radiation as the increase in blood flow in tumor tissue results in increasing treatment efficacy. Previous studies showed that interleukin-13 receptor α2 chain (IL-13Rα2), a unique tumor-associated antigen, is a promising target for cancer immunotherapy. IL13-PE, a targeted cytotoxin composed of IL-13 and mutated *Pseudomonas* exotoxin, induces specific killing of IL-13Rα2 positive tumor cells. Our objective is whether hyperthermia treatment of oral squamous cell carcinoma (OSCC) can modulate the expression of IL-13Rα2 and increase their sensitivity to IL13-PE, especially in IL13-PE-resistant cells.

Methods: OSCC cell lines, HSC-3 and SCC-25 cells were heated with 43 ^{0}C for 1 hour. Then, the expression levels of IL-13Rα2 and HSP70/HSP90 were analyzed by RT-PCR. Cytotoxic activity of IL13-PE was evaluated by protein synthesis inhibition assay. We also determined whether IL13-PE after hyperthermia causes apoptosis in OSCC cells by TUNEL assay in vitro.

Results: The proliferation of heat-stressed OSCC cells showed > 50% growth inhibition compared to control cells. IL-13Rα2 was up-regulated after heating of OSCC cells. Western blot analysis of heat-stressed HSC-3 cells revealed that HSP70/HSP90 expression increased in time-dependent manner. Protein synthesis inhibition assay with IL13-PE showed that heat-stressed OSCC cells decreased the number of IC50 compared to that of without heated OSCC cells. The percentages of apoptotic cells increased in HSC-3 and SCC-25 treated with IL13-PE after hyperthermia compared with controls. In vivo study, combination therapy reduced the tumor growth compared to the control mice.

Conclusion: These data suggest that hyperthermia of human OSCC sensitize to IL13-PE most likely by up-regulating the expression of cell-surface IL-13Rα2. Now we are studying to observe the efficacy of IL13-PE after hyperthermia in a mouse model.

POS 38

Iron dextran as an ideal thermosensitizer in the radiofrequency-induced hyperthermia

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Treatment of cancer has been one of the toughest challenges that human race has been faced. Past 100 years of intensive researches on cancer treatment have developed surgery, chemotherapy, radiotherapy, hyperthermia, etc, for treatment of cancer. Among the current methodologies for cancer treatments, surgery, chemotherapy, and radiotherapy are dominated, and thermotherapy is used only in supportive care although the 13.56 MHz radiofrequency-induced hyperthermia recently is getting attention in clinics recently. Because the therapeutic efficacy of the 13.56 MHz radiofrequency-induced hyperthermia for cancer treatment is very marginal, the 13.56 MHz radiofrequency-induced hyperthermia is currently used mostly in combination therapy with chemotherapy or radiotherapy. Therefore, development of a method to amplify the therapeutic efficacy of the 13.56 MHz radiofrequency-induced hyperthermia is required for the 13.56 MHz radiofrequency-induced hyperthermia to become another therapeutic option for cancer. Metal ions such as ferric ion have very strong dipole moment, which means that metal ions can interact well to generate heat. Considering the characteristics of metals ions, it would be an ideal thermosensitizer for radiofrequency-induced hyperthermia if non-toxic biological metal ion such as ferric ion could be specifically delivered to cancer. Here, we report that iron dextran can be used as an ideal thermosensitizer for the 13.56 MHz radiofrequency-induced hyperthermia. Ferric ions in iron dextran are actively absorbed by apotransferrin to become transferrin. Because natural tendency of cancer cells strongly absorbs transferring, iron dextran were 1.9 times more actively transferred into cancer cells than non-malignant normal cells in vitro. As is the case of in vitro experiment, ferric ions loaded in iron dextran was specifically accumulated in the tumor tissue of tumor xenografted mice so that the concentration of ferric ions were 1.2 ~ 3.3 times higher than normal tissues. Because ferric ions were specifically accumulated in the tumor tissue of tumor xenografted mice, ferric ions reacted with the electromagnetic wave-dependent hyperthermia to generate high heat. Therefore, increase in the temperature of the tumor tissue was 2.4 fold higher in the tumor xenografted mice under the 13.56 MHz radiofrequency-induced hyperthermia after injecting iron dextran, compared to the 13.56 MHz radiofrequency-induced hyperthermia without iron dextran injection. Surprisingly, the overall anticancer efficacy of the 13.56 MHz radiofrequency-induced hyperthermia using iron dextran as a thermosensitizer was much better than paclitaxel, and completely eradicated cancer in the tumor xenografted mice.

POS 39

Preheating with bathtub markedly improves the whole-body heating with electrical heating chamber

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Whole-body hyperthermia improves the efficacy of certain chemotherapy drugs and also elevates host immunity. However, elevating and maintaining the whole-body temperature to therapeutic temperatures, e.g 40^{o}C, requires arduous efforts. We have discovered that preheating patients with 41^{o}C water using a bathtub remarkably improves the whole-body heating using a commercial electrical heating chamber. In our study, patients wearing swimming suit were first immersed in 41^{o}C water in bathtub for 20 min, which raised the body temperature by 1 - 2^{o}C. The patients were then placed inside a electrical whole-body heating chamber and heated. The body temperature of patients increased up to 40^{o}C in 20-30 min, The heating devise was then shot off, and the patients were covered with blankets and kept in the chamber for additional 3-6 hours. Because the patients were already wet, additional humidity control in the chamber was not needed. We found that this approach enabled that body temperature rise to about 40^{o}C rather quickly and easily and the remained at the same temperature for several hours. The patients were comfortable during the whole processes and many of them even refused to take sedatives.

In conclusion, preheating patients using a bathtub before heating with electrical heating chamber is an effective way to achieve whole-body hyperthermia.

POS 40

Reirradiation+hyperthermia for recurrent breast cancer-en-cuirasse in previously irradiated area

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Purpose: Cancer en cuirasse is a severe locoregional manifestation of breast cancer, usually occurring after a number of treatment failures. Treatment options are limited. One hundred and sixty-nine patients were treated with re-irradiation and hyperthermia (reRT+HT) from 1982 till 2006. Response and toxicity rates as well as the locoregional progression free interval were determined to assess the palliative value of this treatment.

Methods: All patients had received extensive previous treatments, including surgery, irradiation (median dose 50Gy with or without boost) and systemic treatments.. Seventy-five percent of patients had 1-7 previous locoregional recurrence episodes; 68% were treated with systemic therapies and 27% underwent salvage surgery.At start of re-RT+HT the tumor area comprised > 3/4 ipsilateral chest wall in 54% of patients. Fifty-two percent had areas of ulcerating tumor. Distant metastases were present in 45% of patients. reRT consisted typically of 8x4Gy, twice a week or 12x3Gy, four times a week. Superficial hyperthermia was applied once or twice a week using 434MHz Contact Flexible Microstrip Applicators (CMFA), heating the tumor area to 41-43˚C for one hour.

Results: The treatment was well tolerated; 154 patients completed treatment, only 15 patients did not, due to disease progression in 12, toxicity in 2 and refusal in 1 patient. Overall clinical response rate was 72% (30% CR; 42% PR), while only 6% showed PD. Median follow-up time was 7 months. The 1-year progression-free-interval was 24% with a 1-year survival rate of 36%. Acute ≥ grade 3 toxicity occurred in 33% of patients and consisted mostly of ulceration and dermatitis. The occurrence of radiation ulcera was significantly related to the presence of ulcerating tumor before the start of the reRT-HT (P=0.004, HR = 4.4). Conclusion: The combination of re-irradiation and hyperthermia is well tolerated and results in high response rates despite extensive disease and resistance to previous treatments. ReRT+HT is a worthwhile palliative treatment option for this patient group who suffer from extensive locoregional tumor growth and have a very poor prognosis.

POS 41

Temperature Anomalies in Simulating Ultrasound Heating for Tissue Tightening with a Three-Layer Subcutaneous Structure

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To simulate tissue-tightening and/or fat reduction with ultrasound energy, a planar circular ultrasound transducer is placed on the skin surface and then transmits the acoustic power vertically into a three-layer subcutaneous structure modelling skin, fat and muscle. Two interfaces (skin-fat and fat-muscle) need to be paid special attention when the interface is set as one node connecting two tissue layers with different thermal and acoustic properties during simulation study. Two interface conditions for the connecting nodes in this study are continuity of temperature and identical heat flux. Temperature anomalies exist in heat flux across two layers of different tissues when executing simulation for the heating process of tissue-tightening. With accumulation of thermal energy, hot spots may occur near the interfaces. The simulation results show that an abrupt thermal gradient appears near the interfaces due to different properties such as thermal conductivity, ultrasonic attenuation coefficient, blood flow, etc. It has shown the similar situation done by experiments using radiofrequency.

POS 42

Case report: Four years of local control of malignant fibrous histiocytoma by proton beam therapy combined with hyperthermia

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The first choice in the treatment of malignant fibrous histiocytoma (MFH) is a surgical operation. We present a case of MFH arising from the thigh, which is unresectable with conservative surgery, radically treated with proton beam therapy (PBT) combined with hypertehrmia. We report a case of a man in his sixties presented with left thigh mass. At first pathological examination of the resected specimen showed benign tumor, but four years later when the mass enlarged, re-biopsy specimen was diagnosed as MFH. The lesion extended diffusely to the left quadriceps femoris muscle, so a radical dissection, which meant amputation, was suggested to him. He refused the surgery and asked other hospital for heavy ion radiotherapy, however, for the extension of the mass, the tumor was judged out of therapeutic indications for heavy ion. After 3 courses of chemotherapy (CDDP + ADR) was not successful at shrinking the mass, he was referred to our hospital for PBT. He underwent PBT with two fields combined to cover all the 20 cm tumor involvement. After 40 GyE / 10 fx (5 times per week (P/W)) irradiation to a group of muscles in an anterior compartment of left femur, and one week pause of treatment, an additional of 32 GyE / 8 fx (5 times P/W) boost was irradiated. He simultaneously received local hyperthermia (800 Watts, 60 minutes, 1 time P/W, total 7 times). One year after completion of concomitant PBT and hyperthermia, response to the treatment was evaluated with magnetic resonance imaging (MRI) and positoron emission tomography-computed tomography (PET-CT). MRI showed tumor shrinkage and PET-CT showed decrease of fludeoxyglucose (FDG) accumulation at the site of tumor. After four years passed, complete response has obtained and there is no recurrence. As an acute side effect, grade 2 dermatitis was developed and was improved by conservative treatment. A late side effect was femoral muscle contracture. As the result, his left knee movement is partially restricted, but he is able to walk. We report a case of MFH which is successfully treated by PBT combined with local hyperthermia.

POS 43

A novel optimization approach for adaptive application of hyperthermia.

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Introduction

During hyperthermia therapy, the complex anatomy of the human body and of the thermal physiological phenomena set challenges that require performing patient-specific, i.e. adaptive, treatments. HT treatments are normally limited by undesired hot spots in healthy tissues, which can be avoided or minimized by optimizing the excitations of signals applied to the antenna array applicators.

Several optimization strategies have been presented in the literature. Most of them are rather efficient but they suffer from the inability of providing the optimal design solution while offering a customizable spatial power/field shaping. Earlier, the Optimal Constrained Power Focusing (OCPF) technique proved to be a valid alternative. In this work, we improved this technique for dealing with the clinical challenges imposed by an HT treatment.

Methods

Relying on a Convex Programming based formulation of the focusing problem, OCPF guarantees optimal conditions through the enforcement of upper bound constraints on the power deposition. This also allows to maximize the power deposition into the tumor location while specific restrictions on the different healthy tissues can be imposed. An adaptive OCPF procedure was developed to follow the body response to the heating by redefining the upper bound constraint according to the patient feedbacks and the current Specific Absorption Rate (SAR) distribution.

Results

The developed OCPF adaptive method has been assessed in the treatment of head and neck tumors performed by the HYPERcollar3D. SAR results have showed the capability of OCPF in shaping the signals in such a way that the power deposition in healthy tissues remains under specific bounds while the tumor region is covered.

We found that a comprehensive comparison of the novel OCPF method to the currently used Particle Swarm Optimizer (PSO) requires temperature simulations to address the improvement in the clinic.

Conclusions

The presented analysis shows the capability of OCPF in an adaptitave quantitative treatment strategy which will may lead to improved treatment quality and effectiveness.

POS 44

Early experience applying ultrasound-generated regional hyperthermia and radiation therapy to oligometastases in the abdomen and pelvis.

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Background: Advanced stage at presentation ovarian, sarcoma and rectal cancers often develop peritoneal and/or liver metastases, which inevitably fail chemotherapy treatment. However, many of these tumors have anatomically manageable tumor burdens (oligometastases) that can be treated in combination with radiation therapy and hyperthermia.

Patient Inclusion Criteria: Performance Status of ECOG-0 or 1 with minimal or no ascites who have measurable oligometastases in the abdomen (liver, peritoneal metastases).

Methods: Treat with hyperthermia and radiation, with most of these patients receiving during or after hyperthermia treatment chemotherapy based on molecular profiling with Caris™ Life Sciences with submission of fresh or archival paraffin-based tissue to determine drug combinations that are most likely to provide benefit at this point after failing other chemotherapy regimens. Liver oligometastases are treated using a unique method of radiation delivery that applies magnetic resonance imaging/radiation therapy technology to provide high-contrast pretreatment images and continuous soft-tissue imaging during treatment during beam-on irradiation capturing soft tissue images and adjusts radiation delivery on a sub second speed to insure that the metastatic lesion is treated and uninvolved tissue receives as minimal as possible dose while applying in less than two hours regional hyperthermia between these two modalities using an ultrasound generated hyperthermia applicator device for targets up to 15 x 15 cm in size to single or multiple tumor volumes.

Results: All patients obtain significant or complete symptom relief as well as partial or complete response in the lesions treated using the Response Evaluation Criteria in Solid Tumors (RECIST). There were no liver or gastrointestinal Cooperative Group Common Toxicity Criteria greater than 1.

Conclusions: Though this treatment it is not curative; it is a viable treatment option for patients that have failed other therapies. A phase II prospective trial is warranted.

POS 45

Effect of respiration on the quality of MR-guided thermal therapy: investigation in the neck region

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INTRODUCTION: MR-guided RF hyperthermia requires accurate ($\overline{\Delta T}$≤0.5°C) MR temperature measurements during the whole treatment duration (75 minutes) in the head&neck region [1]. Although the temperature changes may be measured via the shift in proton resonance frequency (PRFS) [2], this technique is sensitive to all other sources of magnetic field changes. One potential source of temporal magnetic field (B_0) changes in the neck region is respiration [3]. In this study, we investigated the influence of respiration on the apparent temperature changes measured in the neck region.

METHODS: The measurements were performed on an interventional 1.5T MRI scanner (GE Optima). A healthy volunteer lay supine in the bore of the scanner. A spoiled gradient echo scan was acquired dynamically (one image/3.9s) during 2 minutes of normal respiration and 1 minute of breath-hold, with TR/TE= 29/19.3ms, FOV= 400x400mm, slice thickness= 10mm, flip angle= 30°, acquisition matrix= 128x128, number of averages= 1. A slice in the axial plane was positioned though the center of the neck. The MR signal was received with a 6-channel flexible coil placed close to the neck. No heating/cooling was applied. The apparent temperature changes were calculated in a region of interest located in the spinal column, by using the standard phase-difference technique [2].

RESULTS: Over 1 minute of breath-hold the apparent temperature gradually decreased of 10°C/min. On the other hand, over 2 minutes of normal respiration we observed an oscillatory apparent temperature change of ±12°C at a frequency corresponding to the breathing cycle.

CONCLUSION: Respiration-induced magnetic field changes in the neck may cause significant errors in the MR temperature measurements if not accounted for. The order of magnitude is close to that measured by others in the breast [4, 5]. Future work will map out the spatial distribution of the field disturbance (including: eyes, brain, whole spinal cord, cheek) and consider whether respiratory gating will be necessary. Additionally, the effectiveness of corrections methods, such as fat referencing, will be explored.

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POS 46

Local hyperthermia in treatment of late radiation-induced skin and soft tissue injuries

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Introduction. Treatment of late radiation-induced injuries is a challenging problem. In some clinics, low-intensity laser radiation of a different wavelength, millimeter waves of extremely high frequencies, low-frequency electro- and magnetotherapy in combination with medicinal agents or without them are used to treat late radiation-induced injuries. These agents were found to have *anti-inflammatory* and analgesing *properties, to* improve microcirculation and tissue tropism. There are few publications on the use of hyperthermia for treating late radiation-induced injuries. The available data suggest that hyperthermia has a positive effect on post-radiation extremity edema and radiation-induced soft tissue fibrosis.

Methods. In the years 1988–2015, local hyperthermia (LHT) was given to 46 patients with radiation-induced fibrosis of the skin/subcutaneous fat, soft tissues of the neck, sub/supraclavicular, anterior abdominal wall and sacral region. All patients had previously undergone combination therapy for malignant pelvic tumors and Hodgkin lymphoma. The majority of patients had received combination treatment with preoperative and/or postoperative irradiation or chemoradiation therapy for malignant tumors. LHT was performed at 3–5 years after completion of therapy for underlying diseases. The presence of an active tumor process was an absolute contraindication to LHT. Hyperthermia treatment was carried out on the Yakhta-4, Yakhta-5 and Supertherm EP-40 machines. The temperature of heating (39-40°C) was monitored on the skin surface or in the fibrous tissue. The course of treatment consisted of 6–12 sessions at one- and two-*day intervals* (3–5 times a week). Repeated courses of LHT were administered 3–24 months later. The patients *were followed up* for 2–17 years.

Results. After LHT, hyperpigmentation almost completely disappeared in all patients, the *sensation* of gravity and pain in the area of fibrosis and below it considerably decreased. Upon *palpation*, reduced fibrous tissue density could be felt. According to ultrasound densitometry, it decreased from 12 to 6 units. The increase in tissue elasticity was noted. Doppler-sonography demonstrated improved *blood flow* in the fibrous tissue. However, the achieved effects were temporary. For this reason, some patients received 2-3 or 8-10 repeated courses of LHT at intervals from 3 months to 12-24 months. During the follow-up period, no recurrent diseases or distant metastases were noted.

Conclusion. LHT is an effective treatment for late radiation-induced fibrosis.

POS 47

Outcomes of neoadjuvant thermochemoradiotherapy in soft tissue sarcomas

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Introduction. Improvements in outcomes for patients with soft tissue sarcoma (STS) were resulted from the multimodal treatment including radiation therapy, surgery and chemotherapy. Our experience suggests that it is necessary to include local hyperthermia in treatment of STS.

Methods. From 2011 to 2015, combination therapy with the use of neoadjuvant thermochemoradiotherapy (NeoTCHRT) was given to 52 patients with locally advanced STS (T1b2bN0-2M0-1, G2-3), of whom 41 patients had primary tumors and 11 patients had recurrent tumors. Neoadjuvant chemotherapy (NeoCHT) consisted of 2-3 courses. The first course of NeoCHT was administered before radiation therapy (RT) and the 2-3 courses were administered after RT. Depending on the histological tumor structure and patient's condition, three chemotherapy schemes were used. Scheme 1: doxorubicin was given for 96 hours continuously, total 90 mg/m^2; cisplatin (100 mg/m^2) was given on day 6, once. Scheme 2: doxorubicin was given for 3 days continuously, total 75 mg/m^2; ifosfamide was given on day 1 and 4, total 7.5-10 g/m^2. Scheme 3: doxorubicin was given for 3 days, total 75 mg/m^2 (if there were marked changes in haematological and biochemical parameters of blood). RT was administered three times per week using daily dose fractions (3+3 Gy) at a 4-hour interval, bringing the total radiation dose to 30-36 Gy. During local hyperthermia (LHT), tumor temperatures was between 40 and 45° C, duration of heating was 40-90 minutes. During each course of NeoCHT one LHT session was used and during RT - 4 LHT sessions. Surgery was performed at 2–4 weeks after the last course of NeoCHT.

Results. After NeoTCHRT neither marked radiation reactions nor complications related to skin and underlying soft tissues were noted. There were no marked changes in haematological and biochemical parameters of blood. However, the patients with recurrent tumors, who had previously received CHT, showed more marked changes of blood. Immediately after NeoTCHRT, 37 (71%) patients achieved an objective tumor response: 31 (76%) of 41 patients with primary tumors and 6 (55%) of 11 patients with recurrent tumors. The 3-year overall recurrence-free survival rate was 94.5% for patients with primary tumors, and 91% for patients with recurrent tumors**.** During the first year of follow-up, distant metastases were detected in 5 (10.4 %) of 48 patients who had had no metastases prior to NeoTCHRT.

Conclusion. Neoadjuvant TCHRT does not lead to *severe local toxicity*. This treatment produces a marked immediate effect and a 3-year recurrence-free survival.

POS 48

THERMOCHEMORADIOTHERAPY FOR LOCALLY

ADVANCED LARYNX CANCER

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Introduction. The role of local hyperthermia in radiation therapy (RT) for locally advanced laryngeal cancer has been studied.

Methods: Nonrandomized trials enrolled two groups of patients with locally advanced laryngeal cancer (T3-4N0-3M0). In the control group (27 patients) only chemoradiotherapy (CRT) was performed, in the main group (31 patients) CRT was combined with local capacitive HF- hyperthermia (40.68 MHz). RT was given to all the patients up to a total tumor dose of 52-60 Gy. Radiation therapy (RT) was performed in the hyperfractionation (1 Gy + 1 Gy with an interval of 4-5 hours) 5 times a week to total dose (TD) 52-60 Gy with 2 week interruption after TD 30-40 Gy. Local hyperthermia (LHT) carried out 2 times a week before the 2nd fraction of RT. Number of LHT was 3-6 sessions. The first cycle of chemotherapy was administered at the beginning of RT, the second – after the break.

Results: The difference between groups by immediately reaction of the tumor and 5-year overall survival rate estimated at trends. Local control for T3 after CRT was 58%, TCRT – 88% (p=0,036), while T4 – 72% and 25% (p=0,028), respectively. Late radiation injuries of the larynx in the form of mucosal edema and perichondritis after CRT were diagnosed in 2 (7%) patients, after TCRT – 3 (10%).

Conclusions: TCRT locally advanced cancer of the larynx increase overall survival and local control compared with CRT and does not increase the frequency of perichondritis.

ABSTRACTS FOR THURSDAY, APRIL 14, 2016

THU 1

Refresher Course Title Thermosensitive Nanotechnologies for Drug Delivery:

Basic Principles and New Directions

Christine Allen, Ph.D.

Professor and GSK Chair in Pharmaceutics and Drug Delivery

Leslie Dan Faculty of Pharmacy

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Join me on the early morning of April 14th for a refresher course on thermosensitive lipid and polymer-based nanomedicines that have been explored to date for applications in oncology. The rationale behind these technologies as well as fundamental criteria that must be considered in their design will be discussed. Special attention will be given to the relationships between the composition and physico-chemical characteristics of thermosensitive nanotechnologies and their *in vivo* performance. The strengths and limitations of each of the lipid and polymer-based drug delivery approaches will be covered with an emphasis on technologies that have been evaluated *in vivo* in combination with thermal therapy. The latest and 'greatest' temperature sensitive drug delivery approaches will also be highlighted.

THU 2

Refresher Course Title Clinical Hyperthermia Trials

An overview of the clinical trials in hyperthermia: Do we have the evidence?

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Hyperthermia, one of the oldest forms of cancer treatment involves selective heating of tumor tissues to temperatures ranging between 39-43˚C. Recent developments based on the thermoradiobiological rationale of hyperthermia indicate it to be a potent radio- and chemosensitizer. This has been further corroborated through positive clinical outcomes in various tumor sites using thermoradiotherapy or thermoradiochemotherapy approaches. Moreover, being devoid of any additional significant toxicities, hyperthermia has been safely used with low or moderate doses of reirradiation for retreatment of previously treated and recurrent tumors, resulting in significant tumor regression. In addition, the technological advances over the last decade both in hardware and software have led to potent and even safer loco-regional hyperthermia treatment delivery, thermal treatment planning, thermal dose monitoring through noninvasive thermometry and online adaptive temperature modulation.

Even though there has been a steady progress in understanding the thermoradiobiology which has been ably complemented by developments in the hardware and software of hyperthermia treatment delivery, clinicians in general are still skeptical for integrating hyperthermia in their therapeutic armamentarium along with surgery, radiotherapy, chemotherapy and lately immunotherapy for curative treatments. This is despite positive outcomes reported through well designed randomized clinical trials in certain cancer sites.

One of the primary reasons that could be attributed to the skepticism amongst the clinicians could be due to the paucity of phase III randomized clinical trials with adequate sample sizes. Part of this could be ascribed to a relative reluctance of collaborating oncologists to enroll adequate number of patients in some of these well designed planed phase III trials. The other contributory factor could be the lack of widespread availability of hyperthermia treatment units, when compared to other treatments like radiotherapy and chemotherapy. Thus, it has essentially landed hyperthermia into a “Catch 22” phenomenon – with lack of hyperthermia facilities being attributed to lack of clinical evidence and *vice versa* resulting in difficulty in conducting well designed phase III clinical trials with statistically relevant patient numbers. Even then, individual centers have been reporting their experience with hyperthermia and/or chemotherapy, albeit with limited sample sizes.

Meta-analysis and recently network meta-analysis have been considered as effective statistical tools for providing a level I evidence to assess the effectiveness of various healthcare interventions. The procedure allows combining findings from independent published studies with uniform selection criteria pertaining to patient population, treatment interventions and outcome evaluation. Using the various estimates like odds ratio, risk ratio and risk differences between the study and the control groups, it could provide precise estimate of the treatment effect after giving due weightage to the size of the different studies included in the meta-analysis. A systematic review of all major databases to extract all relevant studies could be subjected to meta-analysis and network meta-analysis to evaluate the effect sizes, presence of heterogeneity, publication bias and also explore the robustness of the main findings using sensitivity analysis.

Thus, it is time to undertake meta-analysis in various common cancers in which hyperthermia has been used along with radiotherapy and/or chemotherapy to ascertain with certainty if hyperthermia could indeed improve the therapeutic outcomes. This could also provide a level I evidence on the clinical effectiveness of hyperthermia and pave the way for its claim for getting integrated in curative or palliative treatments. This refresher course therefore intends to present an overview of the various clinical trials in which hyperthermia have been used. The focus would be primarily on three common sites – locoregional recurrent breast cancers for palliative treatment, locally advanced head and neck cancers and locally advanced cervical cancers for curative therapy in which hyperthermia has been used along with radiotherapy alone or with chemotherapy in various studies.

THU 3

State-of-the-art In High Intensity Focused Ultrasound (HIFU)

Chrit Moonen

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Ultrasound can be focused within a region with a diameter of about 1 mm. The bio-effects of ultrasound can lead to local tissue heating, cavitation, and radiation force, which can be used for a variety of medical therapies such as tissue ablation, image guided drug delivery, and immune stimulation.

Tissue ablation

HIFU whether guided by ultrasound or MR imaging is a clinically approved technology for treatment of uterine fibroids, bone metastases and prostate cancer. Clinical research is ongoing in many other applications such treatment for essential tremor, breast cancer, liver, kidney and pancreas.

Image guided drug delivery (IGDD)

HIFU can be used in many different ways for IGDD: 1) local drug release from nanocarriers circulating in the blood, 2) increased extravasation of drugs and/or carriers, and 3) enhanced diffusivity of drugs. When using nanocarriers sensitive to mechanical forces or to temperature, their content can be released locally. Thermo-sensitive liposomes have been suggested for local drug release in combination with local hyperthermia more than 30 years ago. Microbubbles may be designed specifically to enhance cavitation effects. Preclinical work over the last 10 years has demonstrated that HIFU and microbubbles can lead to local and temporary opening of the blood-brain-barrier which is the most important impediment for pharmacological treatment of nearly all diseases of the central nervous system. Real-time imaging methods, such as magnetic resonance, optical and ultrasound imaging have led to novel insights and methods for IGDD Image guidance of ultrasound can be used for: 1) target identification and characterization; 2) spatio-temporal guidance of actions to release or activate the drugs and/or permeabilize membranes; 3) evaluation of biodistribution, pharmacokinetics and pharmacodynamics; 4) Physiological read-outs to evaluate the therapeutic efficacy.

Immune system stimulation

HIFU can be used for immune system stimulation in various ways. Its associated mechanical effects can release tumor antigens that can activate dendritic cells. With many drugs under development for immune system stimulation (or inhibition of tumor associated immune suppression), there clearly is a bright future for combinatory approaches, together with HIFU. It has been shown that ultrasound can decrease Alzheimer related plaques in the brains of animal models. This effect has been tentatively attributed to immune system stimulation.

THU 4

Low Intensity Therapy Ultrasound Approaches – Bubbles

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The biological effects of bubbles generated as a result of acoustic cavitation and boiling have been widely studied in the context of ultrasound safety and have the potential to induce significant tissue damage. Consequently the majority of exposure regimes for both diagnostic applications and high intensity focused ultrasound ablation are designed to minimise bubble formation. In the context of cancer therapy, however, both the mechanical and thermal effects produced by cavitation can be exploited to dramatically improve the degree to which treatment can be targeted to specific sites within the body. This talk will describe the ways in which specially designed cavitation nuclei in the form of solid, liquid or gas particles can be utilised to promote both direct thermal ablation and the controlled release and distribution of drug molecules for localized delivery in the treatment of cancer. First, the particles provide a means of encapsulating drugs to avoid interaction with healthy tissue and/or deactivation before reaching the target site. Second, the particles can be functionalized to enable them to be targeted to a specific tissue volume in order to maximize the concentration of the drug. Third, the release of the drug can be controlled temporally and spatially by using focused ultrasound to initiate cavitation only within the tumour. Fourth, the fluid motion induced by the cavitation activity significantly enhances transport of the drug throughout the tissue volume compared to passive diffusion; and finally, the acoustic emissions from the cavitation bubbles can be used to monitor the treatment from outside the body. The talk will conclude with discussion of a specific example of how cavitation mediated delivery is being utilized in the treatment of pancreatic cancer.

THU 5

Interventional Oncology: role of Focused Ultrasound (USgHIFU) in pancreatic cancer. Five years experience and tumor ablation considerations in the Western stage.

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Interventional Oncology has been proposed as a group of therapeutic procedures that are usefull at obtaining local disease control with minimal invasive techniques. We describe the experience of the HIFU Surgical Oncology Unit of Hospital University Mutua Terrassa (Barcelona, Spain) and the Interventional Oncology Unit of Institute Khuab Barcelona treating malignant tumors. We compare our both institution experience with the experience in the same hospitals with conventional treatments. We underline some considerations about the role of tumor ablation in the European oncology stage.

Materials and Methods: From February 2008 to April 2015 we have treated 150 malignant cases. Of those, 50 cases of non resectable pancreatic tumors were treated from March 2010 to April 2015, and we include the first 45 patients to the analysis. All of them underwent systemic chemotherapy with a standard combination.

Results: The distribution of the 150 cases treated reflects a majority of pancreatic and liver tumors. We specially analyze the 45 pancreatic tumors. Clinical responses (ablation obtained) were 82% in all cases. We obtained 11 complete responses (25%) at the end of the combined treatment. Major complications included severe pancreatitis (2), skin burning grade III that required plastic surgery (2), duodenal perforation (1). Median Survival is 16 month (6 mo – 3.4 year) and Overall Percent Survival is 33.5 % at 5 year follow up.

Conclusions: Focused Ultrasound is an effective and safe Interventional Oncology ablation of malignant tumors. Compared with same hospital data, it proves survival advantage in non resectable stage III and IV pancreatic cancer. Tumor ablation by means of Interventional Oncology needs to be considered as a novel group of therapies along Medical, Radiation and Surgical Oncology and re-defined at the light of this experience.

KEYWORDS: Interventional Oncology, High-intensity focused ultrasound ablation; HIFU; Pancreas, Cancer, Pancreatic cancer; Chemotherapy; Tumor Ablation

THU 6

A comprehensive model of hyperthermia and radiotherapy induced cell death

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Background: Hyperthermia (HT) induced radio-sensitization is believed to be due to a combination of impaired cellular repair mechanisms and enhanced cellular damage. For optimised treatment planning purposes, quantification of these biological effects is essential. Since experimental data are limited, mathematical modelling approaches are required for predicting treatment outcomes. Although cell survival modelling approaches exist for HT and radiotherapy (RT) treatments on their own, a framework which allows comparison and combination of the effects is missing. Here a cell survival model, which is equally applicable to RT and HT survival curves, is proposed, and validated experimentally.

Methods: Motivated by the biological effects of combined HT-RT treatments, a simple model which assumes that cellular damage is only repairable to a certain extent, and that the underlying repair capacity is in turn treatment dependent was developed. These effects are accounted for by a two case description of the surviving fraction as a function of (thermal) dose using three parameters: $\alpha_{0,}$ a measure of the initial damage, characterizes the slope of the survival curve at high doses. Repair is expressed as a first order Taylor expansion with parameters, α_R, and β. These indicate repair potential and the reduction of repair and provide a smooth transition of the curve from an exponentially linear-quadratic to an exponentially linear function of dose.

This new model and the linear-quadratic model have been fitted to clonogenic cell survival curves gathered from five published studies or obtained experimentally for human HCT116 cells treated with HT, RT or HT combined with RT. The resulting fit parameters were analysed for time-temperature, cell line and treatment modality dependencies.

Results: The proposed model fits survival curves with equivalent, or better, coefficient of determination than the linear-quadratic approach, independent of the treatment technique used. For HT data, the model delineates the characteristic shoulder of the curves and gives equal values of α_0 and α_R, which reduces the number of free parameters to two. These parameters have an exponential relationship with temperature. This allows an interpretation of cellular damage in terms of chemical reaction kinetics as described by Arrhenius equations. Combined HT and RT treatments are well fitted and the synergism of the techniques is accounted for by expressing the model parameters as a function of thermal and radiation dose.

Conclusion: The proposed model accurately describes cell survival curves from different treatment modalities (HT, RT and HT-RT), and holds great potential for planning of combination therapies.

THU 7

Method of Target Tracking in HIFU using Image Matching Technique with Liver Deformation Volumes Obtained via Time-Resolved Volume Acquisitions

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[Introduction] High intensity focused ultrasound (HIFU) treatment of abdominal organs, such as the liver, requires a tracking technique to “lock on” to the focal spot at the target tissue region during respiratory induced motion. Several target tracking methods based on the vessel of the liver have been proposed [1-2]. However, deformation in the liver organs caused by respiratory motion leads to the displacement of the estimated target position. To maintain sufficient tracking accuracy, both translation and deformation of the tissue need to be considered. In this study, we proposed target tracking technique using an image matching method with liver deformation volumes obtained via time-resolved volume acquisitions [3].

[Methods] Forty-two image sets of six interleaved slices from a healthy volunteer’s liver were acquired by 3.0T MRI with fast image employing steady state acquisition (FIESTA) under slow-paced free respiration. The images of each slice were sorted on one respiratory cycle based on diaphragm position. 113 image sets were rearranged, and each image set was interpolated to isotropic volumes. Several regions of interest (ROI), including branching vessels, were set and tracked using a 3D template matching method. The centre of the extracted region was set as the position of the relevant branching vessel. Å target was set on the first volume of image sets, and other volume targets were estimated using the finite element method (FEM). Tracking images were sequentially acquired sagittal images. Target position was estimated by getting the target position of the image set included the image of the highest degree of similarity to the tracking sagittal image.

[Results] Six positions of branching vessels were extracted by 3D template matching method. The average accuracy rate of detecting branching vessel positions was 94%. The tracking examination used the branching vessel that located centre of the other branching vessels as the target (focal spot). The target’s position was considerably shifted when the positions of branching vessels were failed to extract.

[Conclusion] The effectiveness of the proposed method to track target position with reconstructed 3D MR volumes based on FEM was demonstrated in a series of multiple sagittal images from a healthy volunteer’s liver.

[References] [1] Kuroda K, et al.: Thermal Medicine; 23(4):181-193, 2007. [2] Kokuryo et al. Magn Reson Med; 67(1):156-163, 2012. [3] Kumamoto E, et al.: Proc. of 23rd ISMRM, 1647, 2015.

THU 8

Voxel-based radiobiological evaluation of combined radiotherapy and hyperthermia treatments: a basis for better informed clinical decisions.

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Introduction: Hyperthermia(HT) significantly enhances the effect of radiotherapy(RT). Clinical decisions regarding the treatment scheme of combined RT and HT treatments are currently based on experience, but quantification of the radiosensitising effect of HT using radiobiological modeling would allow more scientifically based decision-making. Therefore, we developed a software package for voxel-based radiobiological evaluation of treatment plans for combined RT and HT.

Methods: The software package calculates equivalent radiation dose (i.e. the radiation dose yielding the same effect as the combined RT+HT treatment) at voxel level for combined RT+HT. Calculations use planned temperature and dose distributions as input and are based on an extended LQ-model, which applies radiosensitivity parameters that depend on both the achieved temperature and the time interval between RT and HT. The equivalent radiation dose can be evaluated according to conventional dose limits using DVHs, DVH-parameters, equivalent uniform dose(EUD) and tumor control probability(TCP).

Use of the software is illustrated by a clinical case of a patient with a solitary nodal metastasis of a melanoma in the left para-iliacal lymph node. The patient has been previously irradiated (13x2Gy) to the right para-aortic and para-iliacal lymph nodes, 10 years earlier. Two treatment schedules were evaluated: conventional RT (7x5Gy) and an RT+HT schedule designed to yield equivalent TCP (7x4Gy). Normal tissue effects were assessed using DVH-parameters. A 13Gy uniform dose was added to organs located in the center and right side to account for previous irradiation (assuming 50% long-term repair). TCP was assessed using a Poisson model with $\alpha=0.25Gy^{-1}$, $\alpha/\beta=3Gy$ and $\rho=10^8$ cells/cm^3.

Results: The following DVH-parameters were obtained, denoted as the values for the RT/RT+HT schedules respectively: bowel V_{45Gy}=247/182cm^3, bowel V_{60Gy}=146/12cm^3, bladder V_{50Gy}=43/30%, left hip $D_{0.01CC}$=49/41Gy. Other DVH-parameters easily satisfied clinical limits for both schedules. By design, the EUD and TCP were identical for both schedules (56.7Gy and 16% respectively). DVH parameters were superior for the RT+HT plan. Moreover, bowel V_{60Gy} exceeded acceptable limits for the conventional RT plan. Thus, the evaluation software showed that the RT+HT plan is preferable.

Conclusion: We developed a software package for voxel-based radiobiological evaluation of treatment plans for combined RT and HT. This software can be used to assist in a variety of aspects in clinical decision-making. As demonstrated, it can assess potential gain of RT+HT treatments compared to conventional RT. Other applications include assessment of the effect of different treatment parameters, such as the time interval between RT and HT treatments or temperature achieved.

THU 9

An investigation of Thermal dose as a parameter for modelling the thermal effects of HIFU in cancer therapy

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Background: The biological consequences of a tissue's exposure to heat depend on both the temperature rise, and the heating time. Thermal dose (TD) is a parameter that can be used to describe HIFU treatments in the clinic and allows comparison of thermal exposures delivered at different temperatures for varying times. Unlike for "slow" exposures at low temperatures, the validity of this concept has not been convincingly proven for "rapid" thermal exposures (<10 seconds) at ablative temperatures (>56^{o}C). In this study we investigate the validity of the thermal dose parameter for characterisation of the cytotoxicity of thermal exposures. **Methods:** Two human colon cancer cell lines, the HCT116 and HT29 cells, were subjected to EM_{43}s in the range of 120 to 1092 minutes using a polymerase chain reaction (PCR) thermal cycler for long exposure times (> 30 seconds) or a pre-heated water bath-based technique for "rapid" exposures. Temperature was measured up to a 100 times a second using fine wire k-type thermocouples. Cell viability was assessed using an MTT assay for up to 14 days following thermal insult. In addition, cells were visualised using fluorescent microscopy of actin microfilaments. **Results:** Exposure of HCT116 and HT29 colon cancer cells to an EM_{43} of 240 minutes achieved using 47^{o}C for 15 minutes resulted in a reduction of cell viability of up to 95% 4 days after treatment. The remaining viable cells had a rounded morphology and transiently lost their ability to attach to the substrate, while retaining their clonogenic potential. A proportion of these cells had attached to the substrate by day 4 after treatment. Proliferative activity was evident 7 days after treatment. A method was developed to expose cells rapidly (<10 seconds) to ablative temperatures (> 56^{o}C) and standardise treatments to the lowest EM_{43} detected in the thermal exposure chamber. Using this approach we showed that the reduction in cell viability observed after exposure of the cancer cells to EM_{43}s over 300 minutes depended on the method and duration of the thermal exposure. The use of "rapid" heating regimes which more accurately depict the in-vivo effect of HIFU exposure of tissue resulted in greater long term cell viability than for "slow" thermal exposures. **Conclusions:** Colon cancer cells can survive in an adherent and non-adherent "dormant" state for days without losing their clonogenic potential. The method of heat delivery was shown to play an important role on the outcome of the thermal treatment.

THU 10

Development of Ultrasound-Guided HIFU System with Non-Invasive Measurement of Sub-Pixel Temperature Distributions

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The Magnetic Resonance-guided Focused Ultrasound Surgery (MRgFUS) system was developed as a promising method to non-invasively treat tumors. A MRI was used to measure temperature distributions. However, when comparing diagnostic ultrasound imaging systems and MRIs, MRIs are very expensive and do not have high resolution. To overcome these problems, we have developed the ultrasound-guided FUS system. This system has a function of measuring 3-D temperature distributions with a high resolution of sub-pixel measurements inside the human body non-invasively. The method of measuring temperature distributions was based on the thermal dependence of the local change in speed of sound and thermal expansion. When drawing an image of the human body, ultrasound velocity was assumed to be a constant value passing through the human body. However, as the ultrasound velocity changed depending on the temperature increase inside the heated object, the ultrasound image was deformed. The temperature distribution could be measured from the degree of the deformation using image analysis techniques.

In the present paper, first, an algorithm of measuring temperature distributions using ultrasound images was proposed. Second, we heated the agar phantom inside a hot water bath to show the relationship between temperature increase and the resulting ultrasound images. Next, we measured temperature distributions inside the agar phantom heated by the FUS system. An ultrasound probe was fixed vertically in the direction that the ultrasound transmits inside the agar phantom, and a circular temperature distribution was measured. The three-dimensional temperature distribution of the heated area inside the agar phantom was constructed by taking several pieces of two dimensional temperature distributions, which were measured every several millimeters. The thermal image of a sagittal slice of the agar phantom was taken by an infrared thermal camera just after 5 seconds of heating with the FUS system. When comparing the thermal image results and the results of the temperature distribution, of the ultrasound images using the proposed method, both resulted in an error of approximately 1 ^{o}C.

From these results, it was confirmed that the proposed method using ultrasound images was useful for measuring temperature distributions with high resolution inside the heated object non-invasively.

THU 11

Development of MR-guided endoluminal ultrasound applicators for thermal ablation of pancreatic cancer: design and evaluations in *ex vivo* and *in vivo* porcine studies

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Introduction: Endoluminal ultrasound may serve as a minimally invasive option for delivering thermal ablation to pancreatic tumors adjacent to the gastrointestinal (GI) tract. This study's objective was to design, characterize, and evaluate prototype endoluminal ultrasound applicators capable of placement in the GI lumen for volumetric pancreas ablation under MR-guidance.

Methods: A family of MR-compatible endoluminal applicators, each containing a distinct two-element transducer array (~3.2 MHz) and delivery assembly at the tip of a flexible catheter, were designed and fabricated. Three transducer geometries were considered: 10x10 mm (planar), 8x10 mm with 20 mm radius of curvature (ROC) along the short dimension (lightly-focused curvilinear), and 9.3x11.4 mm with 25 mm ROC along the long axis (strongly-focused curvilinear). Radiation force balance and hydrophone measurements were performed to characterize each applicator. Device delivery into the upper GI tract and heating characteristics for treatment of pancreatic tissue were evaluated in MR-guided *ex vivo* and *in vivo* porcine experiments. MR-guidance techniques were developed for anatomical target identification, tracking/placement of the applicator, and PRF-based MR temperature imaging (MRTI), implemented in the real-time RTHawk software environment.

Results: *Ex vivo* porcine cadaver studies revealed capabilities of producing ablative temperature rise (ΔT>15 °C) contours in pancreatic tissue 4-28 mm wide and 4-40 mm deep for the planar transducer applicator (1-13 minute sonication duration, ~4 W/cm^2 applied acoustic intensity). Lightly-focused curvilinear transducers produced more selective heating with a narrower ΔT>15 °C contour width and depth up to 2-7 mm and 1-24 mm, respectively (1-7 mins, ~4 W/cm^2). *In vivo* MRTI-guided heating trials were performed in four pigs and demonstrated capability of ~15-20 °C temperature elevation in pancreatic tissue at 1-2 cm depths using the planar and lightly-curvilinear applicators (6-16 mins, 5-7 W/cm^2). Strongly-focused curvilinear applicators were capable of reaching higher temperature elevations of ~25-35 °C at 2-3 cm depths in shorter treatment durations (3-5 mins, ~5 W/cm^2). Dimensions of thermal lesions in excised pancreas ranged from 9-28 mm, 3-10 mm, and 5-10 mm in length, width, and depth, respectively, as verified through histopathological analysis of tissue sections. Multiple-baseline reconstruction and respiratory-gated acquisition were effective in suppressing motion artifacts for multi-slice thermometry during MRTI in the *in vivo* studies.

Conclusions: This study demonstrates the technical feasibility of generating volumetric ablation in porcine pancreatic tissue using endoluminal ultrasound applicators positioned in the GI tract, with integrated MR-guidance for target identification, device positioning/alignment, and MRTI treatment monitoring. (Supported by P01, NDSEG)

THU 12

Development and preliminary *in vivo* assessment of an MRI guided hyperthermia platform implemented with a high-intensity focused ultrasound ablation array

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Introduction:

Ultrasound systems have the potential to deliver precise and controlled MRI guided hyperthermia (MRgHT) to enhance anti-cancer regimens and newer multimodality treatment schema. We have implemented an MRgHT platform by performing operational modifications to a commercial high-intensity focused ultrasound (HIFU) ablation system that enable modulation of beam power and shape based on real time MR thermometry (MRT) feedback. Initial feasibility of long-duration hyperthermia (HT) to large contiguous volumes is demonstrated through preliminary *in vivo* experiments on an endorectal HIFU array currently in clinical trials for prostate ablation.

Methods:

Customized beamforming was implemented on the prostate array in the ExAblate 2100 ablation system (InSightec) to produce diffused heating through simultaneous multi-focus and cylindrical acoustic illumination patterns. A Windows-based sonication control software program was implemented to communicate with ExAblate's hardware interface and change power and phase input to the array elements based on MRT feedback. MRT application was developed with the RTHawk real-time MRI system (HeartVista) on a 3T MR scanner (GE Healthcare) and it enabled Proton Resonance Frequency Shift (PRFS) thermometry (SPGR, TE = 13.4 ms, 3 s/slice). The MRT software provided a custom interface for visualization, slice prescription, interleaved simultaneous multi-slice acquisition in different orientations and ability to place multiple ROIs for feedback control. MRT based feedback control was provided in form of (1) single-point proportional-integral (PI) controller that only changed array power output through duty-cycle variation by an external trigger, (2) multi-point binary controller that changed array power and phasing by communicating with sonication control software over a server connection established by the MRT application.

Results:

HT was demonstrated in porcine muscle *in vivo* with single-point PI controller (P_{max} = 15 W, 15 min, 6 or 8 ^{o}C set temperature). Sonications consisted of 4-point simultaneous foci with 5 mm lateral spread and 30 mm focal distance, 10 mm lateral spread and 40 mm focal distance, and diverging beam with 40-mm curvature. For multi-point binary control, the acoustic beam was scanned to sonicate the coolest among 4 ROI locations. Power was turned off when temperature in all ROIs exceeded 7^{o}C and restarted upon cool down to 6^{o}C. This scheme was demonstrated in a tissue mimicking phantom material (Pmax = 15 W, 15 min duration).

Conclusion:

Development and preliminary tests of an MRgHT platform with a commercial prostate HIFU ablation array show feasibility of long-duration large volume HT delivery (FUS Foundation, R01CA12276, R01CA111981, UCSF-RAP).

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THU 13

Phased Array Techniques for Expanding the Transcranial Focused Ultrasound Treatment Range at the Skull Base

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Introduction

The treatment envelope in transcranial focused ultrasound is a significant limitation to the treatment of various disorders at the base of the skull, such as trigeminal neuralgia (Monteith *et al*, J. Neurosurgery, 2013). With conventional phasing techniques, the skull base heats significantly during treatment deep in the brain, and as a result, renders potential treatments unsafe due to high levels of heating of structures adjacent to bone. We will present techniques using phased array controls for the expansion of the treatment range at the skull base, allowing for the potential to treat a range of neurological disorders.

Methods

A hybrid numerical simulation technique that couples ray acoustic (Sun and Hynynen, JASA, 1998) and full-wave methods (Pulkkinen et al, Phys. Med. Biol., 2014) is introduced, and is shown to allow for the rapid calculation of phased array controls in solid media at the base of the skull. This technique has the potential to allow for more advanced phased array controls and fast optimization techniques. The hybrid model is verified for a clinically-relevant phased array setup. It is then shown that using this fast numerical method, it is possible to reduce heating at the base of the skull using the concept of the anti-focus, while maintaining therapeutic levels of heating at the focus.

Results

Verification of this method shows that there is <10% error when comparing the acoustic field results with a full-wave numerical model. Differences in the phase of the acoustic fields between the full-wave and hybrid methods are demonstrated. It is also shown that it is possible to cause reductions in heating of >80% in the bone when using this hybrid technique for treatment planning using the anti-focus, where the reduced heating when using full-wave and hybrid phased array controls is compared to the resultant heating when using conventional phasing.

Conclusions

It is shown that by using phased array controls it is possible to expand the treatment range at the base of the skull, potentially leading to new treatments using transcranial focused ultrasound. A hybrid numerical technique for the rapid calculation of phased array controls at the skull base is introduced and verified against a full-wave model. Using this hybrid model, it is then shown that the anti-focus in solid media allows for the reduction of heating in bone while maintaining high temperatures at the focus.

THU 14

Dose reduction for stereotactic radiotherapy using nanomedicine and new thermal medicine capabilities

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Stereotactic body radiotherapy (SBRT, 1 to 5 fractions of 6-34 Gy) is widely being adopted with exciting efficacy in radiation oncology. It is also faced with limited application sites due to side effects and many anatomical sites having normal tissue tolerance dose limits well below the total dose normally delivered with SBRT. Therefore, dose reduction strategies could optimize effectiveness in patients presenting with tumor types/sites previously untreatable. We have found that thermal ablation and vascular damaging tumor necrosis factor (TNF)-coated gold nanoparticles can significantly improve the response of solid tumors to SBRT-relevant dosing by reducing the hypoxic tumor burden and destroying tumor vasculature, in agreement with Horsman et al (1). Importantly, establishing the dose reduction factor (DRF) obtainable with thermal ablation and/or anti-vascular drugs may open significant new avenues for SBRT. We have also recently reported on the existence of hypoxic blood vessels and endothelial cells in various tumor models (2). In current work, we are characterizing the amount of hypoxic radioprotection to be expected in endothelial and tumor cells in the SBRT dose range and the role of hyperthermia in enhancing radiation-induced cell killing by using clonogenic analysis. We found that endothelial cells have an oxygen enhancement ratio (OER) of 3.0 at 12 Gy and higher, while tumor cells had an OER of 2-2.5 above 12 Gy. It is known that hyperthermia can effectively inhibit DNA damage repair and increase radiation-induced cell killing but little attention has been given to its potential in SBRT or what effect it may have on hypoxic cells that may survive SBRT regimens. We observe that radiation-induced cell killing in vitro increases by 3-10 fold in hypoxic and aerobic conditions, respectively, when 42°C is applied for 1 h after 15 Gy radiation. These results suggest that both vascular targeting agents and a range of thermal therapy approaches using the improved technology now available (focused ultrasound among others) could reduce the total SBRT dose needed for tumor control, thus expanding the tumor types and sites amenable to curative treatment.

1. Horsman and Wittenborn, Acta Oncologica, 2015

2. Koonce N, Griffin RJ, PlosOne. 2015

THU 15

Enhancing the cytotoxic effects of hyperthermia by heat shock protein 90 inhibition

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Exposure of cells to exogenous stress, such as hyperthermia, can lead to unfolding and/or denaturation of proteins and impairment of their functions. Molecular chaperones, called heat-shock proteins (HSPs), normally responsible for protein folding and stability, protect normal as well as transformed cells from deleterious effects of (heat) stress. HSP90 belongs to intensively investigated chaperones because of its relevance in cancer and HSP90 inhibitors show promise clinical cancer treatment. HSP90 has also been implicated in DNA damage response, rendering it a potential therapeutic target in DNA-damaging combination therapies. Here we investigate the role of HSP90 in cellular responses to heat shock and show that HSP90 inhibition can boost the effectiveness of therapies combining hyperthermia with various DNA damaging agents, while showing only minor cytotoxic effects in non-heated cells.

THU 16

Combination of Oncothermia with SBRT and Metformin *in vivo*

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Oncothermia EHY-2000, a capacitive heating device utilizing 13.56 MHz RF, is widely used for treating various types of cancer. We studied the effect of oncothermia in combination with radiation against cancer using FSaII fibrosarcoma grown, s.c. in the right flank of C3H mice. The optimal sequence of radiation and oncothermia, was determined by heating tumors to 41 °C for 30 min 1 h before or after 6 Gy irradiating of the tumors. Heating the tumors with oncothermia before radiation was more effective than heating after radiation for suppressing tumor growth. We therefore, applied oncothermia before radiation in the subsequent studies. Recently, increasing numbers of cancer patient are treated with stereotactic body radiation therapy (SBRT), which treats tumors with high-dose radiation per fraction in 1-5 fractions. It has been reported that metformin, a drug used for type-2 diabetes, sensitizes tumors to SBRT and also hyperthermia. We therefore investigated the combined effects of oncothermia (41 °C for 30 min), SBRT (15 Gy) and metformin (150 mg/kg, i.p). The combination of oncothermia, SBRT and metformin was highly effective to induce apoptosis and suppress tumor growth. It has been shown that SBRT activates HIF-1a, thereby activating VEGF *in vivo*. Metformin suppresses upregulation of HIF-1a in hypoxic cells *in vitro*. We are investigating whether metformin suppress HIF-1a in the tumors treated with SBRT alone or in combination with oncothermia. Our study may reveal effective way to treat cancer with hyperthermia in combination with SBRT and metformin.

THU 17

Thermosensitive cisplatin liposomes provide improved local control of triple-negative breast cancer

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Introduction: Recent improvements in the treatment of metastatic breast cancer have resulted in a refocusing of research efforts on the treatment of primary disease, particularly in the case of locally advanced or recurrent tumours that are deemed inoperable. Several clinical trials have established the efficacy of cisplatin in treating primary triple-negative breast cancer (TNBC) tumours. Thermosensitive cisplatin liposomes (TCL) administered in conjunction with hyperthermia (HT) represent a promising treatment strategy for patients with non-resectable TNBC because the nanomedicine formulation allows a higher cisplatin dose to be administered while hyperthermic interventions boast desirable safety profiles and can be applied to breast tissue with relative ease. This study rigorously compares the efficacy of TCL to two clinically available cisplatin formulations (i.e. free cisplatin and Lipoplatin™).

Methods: TCL were prepared by high-pressure extrusion and characterized in terms of size, zeta potential, and cisplatin concentration. *In vitro* sensitivity of two human TNBC cell lines (i.e. MDA-MB-231 and MDA-MB-436) to cisplatin and HT (applied at 42°C for 1h) was determined using acid phosphatase, clonogenic, and spheroid growth assays. *In vivo* efficacy of TCL was compared to free cisplatin and Lipoplatin™ by administering each at their maximum tolerated dose ± HT. In order to elucidate mechanisms of thermotolerance, heat shock protein expression was measured *in vitro* using RT-qPCR and *in vivo* by histological staining and colour deconvolution quantitative image analysis.

Results: A differential sensitivity to both cisplatin and HT between the two cell lines was observed using both acid phosphatase and clonogenic assays. MDA-MB-231 cells had an IC50 of 22±4μM while MDA-MB-436 cells had an IC50 of 2.8±0.5μM. HT alone resulted in no significant effect in MDA-MB-231 cells compared to 40% cell death in MDA-MB-436. Neither cell line exhibited sensitivity to HT when treated as spheroids. Thermotolerant MDA-MB-231 cells expressed significantly elevated levels of heat shock proteins *in vitro* and *in vivo* ($p<0.01$) in response to the application of HT while MDA-MB-436 cells did not. In both tumour models the longest tumour growth delay and corresponding longest median survival times were in mice treated with TCL+HT ($p<0.05$).

Conclusion: Comparison of three *in vitro* HT sensitivity assays determined that spheroid growth studies are the most predictive of *in vivo* effects. The application of HT was sufficient to improve the efficacy of both traditional chemotherapy (i.e. cisplatin) and a stable nanomedicine (i.e. Lipoplatin™), however, regardless of cell sensitivity to cisplatin or HT, the most efficacious treatment was TCL+HT.

THU 18

Lonidamine is a Potent Inhibitor of the Mitochondrial Pyruvate Carrier and Plasma Membrane Monocarboxylate Transporters

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Introduction: Lonidamine (LND) sensitizes cells and tumours to hyperthermia with few side effects. Coss et al., (Int J Hypertherm. 2014) demonstrated that 150 μM LND reduced intracellular pH (pHi) in human DB-1 melanoma cells cultured at a tumour-like pHe 6.7, abrogated the induction of HSPs and sensitized cells to 42°C-hyperthermia. Conversely, cells cultured at a normal tissue-like pHe 7.3 were not acidified by LND and were not sensitized to 42°C. Here we show that LND inhibits the mitochondrial pyruvate carrier (MPC) and the plasma membrane monocarboxylate transporters 1, 2 & 4 (MCT), which account for many of its known effects on tumour cell metabolism and bioenergetics.

Methods: The methods are standard and are pending publication in Biochemical J.

Results: LND reportedly perturbs the bioenergetics of cells by inhibiting glycolysis and mitochondrial respiration while indirect evidence suggests LND inhibits L-lactic acid efflux from cells mediated by members of the proton-linked MCT family and also inhibits pyruvate uptake into the mitochondria by the MPC. Here we show for the first time that LND co-operatively inhibits L-lactate transport by MCT isoforms 1, 2 & 4 expressed in *Xenopus laevis* oocytes with similar $K_{0.5}$ values (36-40 μM; n, 1.65-1.85) and inhibits MPC activity in isolated rat liver mitochondria more potently (K_i 2.5 μM). LND inhibited the MPC in rat heart mitochondria with similar potency, but the uncoupled oxidation of pyruvate was inhibited more effectively (IC_{50} ~7 μM) than other substrates including glutamate (IC_{50} ~20 μM). In DB-1 melanoma cells 1-10 μM LND increased L-lactate output, consistent with MPC inhibition, but at higher concentrations (150 μM) L-lactate output decreased while $[L\text{-lactate}]_{in}$ increased >5X, consistent with MCT inhibition.

Discussion and Conclusions: The combined inhibition of the MPC and MCTs by LND prevents both efflux of glycolytically derived L-lactic acid from the cell and its oxidation by mitochondria. The resulting intracellular acidification inhibits glycolysis, and with the cell unable to compensate by oxidizing L-lactate/pyruvate, it experiences a bioenergetic crisis. This conclusion is supported *in vivo* by the selective effects of LND on L-lactate, pHi and ATP levels in DB-1 xenografts {Nath, Nelson, et al. 2013 #19096}. Why LND appears to be tumour-specific when all cells are dependent on the activity of either or both the MPC and MCTs could simply reflect the expression levels of MCT isoforms and the MPC relative to rates of metabolism dependent on them, e.g., the Warburg Effect. (Supported by R01-CA129544 and R01-CA172820.)

THU 19

PARP1-inhibition allows substantial lowering of the cisplatin concentration in thermochemotherapy

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Introduction

Cisplatin is a widely used cytotoxic drug damaging the DNA by the formation of single and double strand break (SSBs and DSBs). DSBs are critical DNA lesions, the majority of these lesions can be repaired via Non-Homologous End Joining (NHEJ). Besides inducing DNA breaks, cisplatin is cytotoxic by disrupting the NHEJ. The other major pathway for repairing DSBs is Homologous Recombination (HR). Hyperthermia can temporarily inactivate BRCA2, an essential protein in the HR. Moreover, hyperthermia improves the effectiveness of cisplatin by increasing the blood flow and vascular permeability. Adding a PARP1-inhibitor (PARP1-i) to the combination of cisplatin and hyperthermia is a logical next step since a PARP1-i blocks the Back-up End Joining, which gets activated if NHEJ or HR is disrupted. Without effective DSB repair mechanisms, errors in the DNA will accumulate, causing an increase in cell death and increased cytotoxicity. Our goal is to investigate the additional effect of PARP1-inhibition to the combination of cisplatin and hyperthermia.

Methods

To determine the effectiveness of hyperthermia (42˚C/60min), cisplatin (0.5 or 5µM/60min) and PARP1-i (NU1025; 100µM/continuously), apoptosis and cell survival assays were performed in R1, SiHa and HeLa cells. In order to explain the differences in surviving fraction, cell cycle analysis and γH2AX foci were studied. Tumor growth of R1 cells was investigated in the hind leg of rats, after 6 treatments with a PARP1-i (Olaparib 50mg/kg), cisplatin (2.0mg/kg) and hyperthermia (42˚C/90min).

Results

The combination of hyperthermia and 5µM/60min cisplatin is already quite effective by causing over 80% of cancer cell death. Adding a PARP1-i to this combination enhances tumor cell kill to almost 90%. In our in vivo models, the triple combination resulted in a tumor growth control in R1 tumors in rats, without observing any side effects. Even more interesting: a tenfold lower concentration of cisplatin of 0.5µM/60min combined with hyperthermia and a PARP1-inhibitor almost equals the results of 5µM/60min cisplatin with hyperthermia.

Conclusions

A tenfold lower concentration of cisplatin combined with hyperthermia and a PARP1-inhibitor results in almost equal tumor kill compared to the standard cisplatin-hyperthermia treatment. Therefore, the effectiveness of an extremely low dose of cisplatin combined with hyperthermia and a PARP1-inhibitor is a promising option for clinical application by minimizing systemic cisplatin-toxicity.

THU 20

Enhancement of heat sensitivity of human cancer cells by inhibitor of HR but not NHEJ

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Background: Recent work has revealed that DNA double-strand breaks (DSBs) play an important role in heat-induced cell killing. The cell can respond to the presence of DSBs, through two major repair pathways: Homologous recombination (HR) and non-homologous end-joining (NHEJ). HR works in the late-S and G_2 phases, because HR can repair DSBs by using homologous undamaged DNA as the repair template. On the other hand, NHEJ is active throughout the cell cycle. This study examined the effect of the inhibitor of HR or NHEJ for DSBs on heat sensitivity by using cancer cells, synchronized cells and DSB repair knockout cells.

Methods: We used the human non-small cell lung cancer cells, human glioblastoma cells and NHEJ-related *LIG4* or HR-related *Rad54* knockout mouse embryonic fibroblasts. Sixteen hours after seeding, cells were exposed to the inhibitor of HR-related Rad51 (B02, Calbiochem) or inhibitor of NHEJ-related DNA-PK (NU7026, Calbiochem) for 24 h. Cells were heat-treated at 44^{o}C with a water bath (Thermominder EX, TAITEC Co., Ltd) at 6 h after exposure to inhibitor. The heat sensitivity was measured by colony forming assays.

Results: Heat sensitivity was not affected by NU7026. On the other hand, B02 was able to enhance heat sensitivity. B02 was able to enhance heat sensitivity in G_2-phase cells, but the phenomenon was cancelled in G_1-phase cells which do not work HR repair. HR-deficient cells display a high heat sensitivity compared with HR-proficient cells. Moreover, B02 was able to enhance heat sensitivity in HR-proficient cells, but the phenomenon was cancelled in HR-deficient cells.

Conclusions: These results suggest that the heat sensitivity may be enhanced by the suppression of HR repair. In addition, these findings provide support for the concept that heat may lead to the induction of DSBs.

THU 21

Mild hyperthermia combined with DNAPK inhibition for Radioenhancement of cervical cancer treatment: In vitro and in vivo studies

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Background: Radiation therapy is based upon the induction of lethal DNA damage, primarily DNA double-strand breaks (DSB), in tumor cells leading to cellular death. Despite advances in tumor imaging, dose delivery and targeting, many tumors are poorly controlled by radiotherapy alone. Cancer cells who are able to evade or resist treatment might cause repopulation of the initial tumor. In mammalian cells radiation-induced DNA double strand breaks (DSBs) can potentially be repaired by non-homologous end-joining (NHEJ) or homologous recombination (HR). Suppression of DNA-DSB repair systems may offer new approaches for cancer treatment. In this study, cell survival, tumor growth delay and the effect of both DSB repair pathways after treatment with radiation, hyperthermia, the specific DNAPK-inhibitor, NU7441, and combined treatments are investigated.

Methods: Clonogenic survival assays of cervical cancer cell lines (SIHA, HELA), breast cancer cell lines (MCF7, T47D) and SW-1573 lung tumour cells were performed to determine radiosensitization after treatment with hyperthermia at 42°C (1h) and NU7441. Foci studies to determine accumulation of DSB repair proteins DNAPK, RAD51, MRE11 at the break ends after hyperthermia treatment was carried out with immuno-fluorescence. Levels of BRCA2 was measured with western blot. The effect of NU7441 on DNAPK was measured with a DNA dependent protein kinase assay. The combination treatment, radiation, hyperthermia and DNAPK-inhibitor was also tested in an *in vivo* xenograft system of human cervical cancer (SiHa) growing in nude mice.

Results: Clonogenic survival studies demonstrated clear radio-enhancement of mild hyperthermia treatment and the DNAPK-inhibitor. Subsequently, combination of both treatments enhanced the radiosensitivity to an even greater extent. This was confirmed by induced levels of apoptosis, a 2.5 fold increase after the triple treatment. The triple treatment also lead to a significant growth delay of the xenograft tumors as compared to the duo-treatments. No toxicities were observed. DNAPK activity was not decreased by hyperthermia treatment while NU7441 clearly inhibited the activity of this protein. Hyperthermia induced degradation of BRCA2 while this was not observed after DNA-PK inhibition. Foci studies demonstrated that hyperthermia did not prevent MRE11 to accumulate at the sites of DNA DSB while accumulation of RAD51 at the break ends was inhibited.

Conclusion: Results reported here show that combined treatment with hyperthermia for 1h at 42°C and a DNAPK-inhibitor radiosensitized cells by hampering proteins of the DSB repair pathways. Combined hyperthermia with DNA-PK inhibition might be an effective treatment for radio- and/or chemo- potentiation in cervical cancer.

THU 22

Tri-modality treatment with chemotherapy, radiotherapy and mild-hyperthermia, in vitro

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Background: Nowadays combination treatments of radiotherapy with chemotherapy or hyperthermia are increasingly used for anti-cancer treatments. Combinations of radiotherapy and chemotherapy, radiotherapy and hyperthermia and chemotherapy and hyperthermia show enhanced local control in the clinic[1]. There is a rationale for combining these three modalities[2], however there is limited pre-clinical and clinical data to support this. In this study the effect of concentration, temperature and timing of the tri-modality chemotherapy, hyperthermia and radiotherapy on the survival fraction of cells is investigated.

Method: HT1080, human fibrosarcoma, cells were maintained in MEM medium, supplemented with 10% fetal bovine serum, 1% L-glutamine and 1% sodium pyruvate. Cells were irradiated at 0, 2, 4, 6, 8 and 10 Gy using a linear accelerator (Elekta). 45 minutes before or 45 minutes after irradiation, the cells were incubated during 1 hour with doxorubicin (0, 0.02 or 0.06 µg/ml) at 37, 42 or 43°C in a water bath. Subsequently cell survival was measured using a clonogenic assay.

Results: Doxorubicin only showed synergistic effects when it was added before radiotherapy. Mild hyperthermia at 43°C, but not at 42°C, combined with radiotherapy resulted in synergistic effects. In this case the largest effect was achieved when radiotherapy preceded hyperthermia at 43°C. In contrast, doxorubicin combined with hyperthermia at 42 and 43°C resulted both in an enhanced chemotherapeutic effect. Finally for three modality treatment, only the combination of chemotherapy and mild hyperthermia at 43°C preceding radiotherapy resulted in a larger synergistic effect compared to any of the two treatment modalities.

Discussion and conclusion: The results that were obtained by combining two modalities (doxorubicin, radiotherapy or mild hyperthermia) were in line with the literature [3-5]. The combination of the three treatment modalities resulted in an enhanced effect compared to the two modality treatment. For both the two and three modality treatments the timing of the modalities is an important factor. A larger effect was shown when doxorubicin was applied before radiation therapy, whereas for hyperthermia and radiotherapy this was achieved when hyperthermia was applied after radiotherapy. Only doxorubicin and mild hyperthermia before radiotherapy resulted in a synergistic effect; probably when radiotherapy is given prior to hyperthermia and doxorubicin the cells have time to repair the double strand breaks caused by radiotherapy before the doxorubicin is intercalated in the DNA.

References: [1]Falk, 2001, IJH [2]Jones, 2004, CCR [3]Li, 1977, EJC, [4]Watring, 1974 GO, [5]Hahn, 1979, CR

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THU 23

CYTOREDUCTIVE SURGERY & HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY FOR GASRIC CANCER; EXPERIMENTAL OR STANDARD THERAPY?

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Approximately one third of gastric cancer patients present with metastatic disease often seen as peritoneal carcinomatosis on imaging studies or discovered in up to 20% of patients with negative imaging studies undergoing attempt curative resection. Despite reported survival benefit of multimodality therapy in non-metastatic gastric cancer (INT-0116, MAGIC, and ACTS-GC trials), patients are at high risk of recurrent disease within 2 years with locoregional or peritoneal disease being most common and a component in over 70% of cases. Peritoneal carcinomatosis from GC is considered a terminal condition with poor prognosis and quality of life with reported median survival typically 3- 6 months even with modern but limited chemotherapy and cause of death in 60% of cases. The extent of peritoneal disease is frequently difficult to detect or underestimated by imaging modalities. Due to an inability to accurately measure tumor volume and treatment response, patients with peritoneal tumors usually do not meet the inclusion criteria for randomized trials. Gastric cancer is the only GI cancer in which addition of HIPEC to CRS for peritoneal carcinomatosis has been shown to provide a survival advantage. Single and multi-institutional trials have shown improved survival outcomes with CRS and HIEC in properly selected patients with limited synchronous carcinomatosis. Randomized trials of HIPEC as adjuvant treatment for prevention of carcinomatosis has also shown significant lower peritoneal recurrence rate and significant improved survival. Practice guidelines for considering prophylactic HIPEC and registry for patients undergoing curative intent D2 gastrectomy with high risk for peritoneal carcinomatosis should be developed for evaluating outcomes and best practices.

THU 24

COMPREHENSIVE MANAGEMENT OF DIFFUSE MALIGNANT PERITONEAL MESOTHELIOMA

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Background: In the past, diffuse malignant peritoneal mesothelioma (DMPM) has been regarded as a terminal condition. The length of the survival was dependent upon the aggressive versus indolent biology of the neoplasm, nevertheless cure was not considered as a reasonable expectation and the overall median survival was approximately one year.

Methods: A comprehensive literature review and a collection of pertinent data published on DMPM from the Washington Cancer Institute were used to construct this report.

Results: Recent publications from Bethesda MD, New York, Milan Italy, Lyon France and Washington DC have shown a remarkable prolongation in the median survival of this group of patients with approximately half the patients alive at 5 years. These prolonged survivors were treated with an intensive local-regional treatment strategy that included cytoreductive surgery (CRS) with peritonectomy and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) and some patients with early postoperative intraperitoneal chemotherapy (EPIC). As larger numbers of patients have been treated, clinical features by which to select patients most likely to benefit from this approach have been identified. Also, as the experience in the management of patients receiving these treatments has increased, the morbidity and mortality associated with their management is being reduced.

Conclusions: A new standard of care involves surgical removal of large disease deposits combined with perioperative intraperitoneal chemotherapy. Knowledgeable management uses selection criteria and incurs low morbidity and mortality.

THU 25

Effect of Hyperthermic Intraperitoneal Perfusion Chemotherapy in Combination with Intravenous Chemotherapy as Postoperative Adjuvant Therapy for Advanced Gastric Cancer

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Background/Aims: The aim of our study is to evaluate the preliminary efficacy and side effects of paclitaxel, 5-fluorouracil and leucovorin intravenous chemotherapy in combination with cisplatin hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) as postoperative adjuvant therapy for patients of locally advanced gastric cancer (GC) who was at high risk for recurrence after curative resection in our center.

Methodology: 41 GC patients who underwent radical gastrectomy with D2 lymphadenectomy were enrolled in the study. All patients received paclitaxel 135mg/m^2 on day 1, 5-FU 500mg/m^2 on days 1-5, LV 200mg/m^2 on days 1-5 intravenous chemotherapy and cisplatin 75mg/m^2 on day 5 HIPEC one month after surgery. It was repeated at 3 weeks interval and administered at least two cycles.

Results: A total of 181 cycles of chemotherapy were administered (median, 4 cycles). The median disease free survival time (DFS) of patients was 40.8 months. The median overall survival time (OS) was 48.0 months. The one-year, two-year and three year recurrence rate was 14.6%, 26.8% and 46.3% respectively. The main relapse patterns were remnant GC and metastases of retroperitoneal lymph nodes. The mobidity of grade 3 and 4 toxicities of myelosuppression, nausea/vomiting were less than ten percent. The side effects of grade 1 and 2 of hematologic toxicity, nausea and vomiting, abnormal function of liver, kidney or cardiac, fatigue and neurotoxicity were well tolerated.

Conclusions: Cisplatin HIPEC combined with paclitaxel, 5FU and LV intravenous chemotherapy regimen could improve the survival rate and decrease the postoperative recurrence of locally advanced GC. The side effects were slight with good tolerability.

Key words: gastric cancer; heat, regional hyperthermia, antineoplastic agents, cisplatin, hyperthermic intraperitoneal perfusion chemotherapy

THU 26

Prolonged survival times in patients with advanced or metastatic pancreatic cancer after chemotherapy in combination with hyperthermia

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Background:

Advanced or metastatic pancreatic cancer shows only a very short median survival times of 6-7 months after Gemcitabine. (11,1 months in selected and fitter patients after Folfirinox). The study was performed to see the outcome of patients treated with hyperthermia in combination with chemotherapy.

Methods:

Between 1/2002 and 12/2012 all patients treated in our hospital with advanced or metastatic pancreatic cancer were examined. In addition to chemotherapy (Gemcitabine or Folfox or FEM) the patients received hyperthermia treatments (short wave local hyperthermia. Some patients with metastatic disease fit enough also received whole body hyperthermia.

The average age of the patients was 58 years (33- 83), 45 % of the patients came for first line chemotherapy, 55 % received second or third line chemotherapy.

All patients received complementary treatments like infusions with vitamins and antioxidants, immune modulating therapies and physiotherapy.

Results:

The median survival time for all patients (n= 55) was 19,9 months, patients coming for first line chemotherapy (n=25) had a median survival time of 25, 8 months were as patients coming for second or third-line therapy (n=30) had a median survival time of 13,6 months. 74,5 % of the patients survived more than 1 year, 34,5% survived more than 2 years.

Summary:

In patients getting in addition to chemotherapy hyperthermia treatment much longer survival times than published in the world literature can be observed. It is difficult to estimate whether this difference in survival time is caused by hyperthermia alone and how much complementary treatments may have contributed to this effect. The sole selection factor was that all patients had chosen to come to a private hospital to get this treatment. As in this group of patient a randomizing is not possible for further clarification possibly matched pair analyses could be performed.

THU 27

Preliminary result of chemo proton beam therapy combined with hyperthermia in local advanced pancreatic cancer.

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【Introduction】

Pancreatic cancer is a representative refractory cancer. Many inoperable pancreatic cancer patients are obliged to receive chemotherapy or chemo radiotherapy. However, treatment outcome of chemo radiotherapy is not satisfactory, thus various treatment protocol has been conducted with chemo radiotherapy. Hyperthermia is one of them. The hyperthermia has a feature to kill the cancer cells which are radio-resistant. We have used hyperthermia to the pancreatic cancer patients since 2012. We reviewed the treatment outcome of inoperable loco-regional pancreatic cancer patients who were treated using proton beam therapy combined with chemotherapy and hyperthermia in our institute.

【Materials and Methods】

A total of 11 cases of pancreatic cancer patients treated in the University of Tsukuba since 2012 to 2015 were investigated (men 5, women 6, age: 44-84). Patients who had paraaortic node metastasis or distant metastasis were excluded. Clinical stage was Stage IIB in 1 case, Stage III in 10 cases according to UICC 7th. Median total irradiation dose was 67.5 GyE / 25 fr (range, 50–67.5GyE). All patients received concurrent chemotherapy and hyperthermia. As concurrent chemotherapy, gemcitabine and/or S-1 were used. Regional hyperthermia was performed once a week.

【Result】

The last follow-up was performed in December 2015. A total of 5 patients are alive and the remaining 6 patients are dead due to pancreatic cancer. One and two year survival rates were 64% and 53%, respectively.

Local recurrence was observed in 2 patients. Distant metastasis was seen in 5 patients. Median progression free survival time (PFS) was 13.5 months. One and two year local control rates (LC) were 88% and 66%, respectively.

【Conclusions】

Although definite conclusion is not stated for the small number of patients, local lesions were well controlled.

THU 28

Hyperthermia-based therapy is a promising approach to overcome treatment resistance in pancreatic cancer.

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Although powerful chemotherapy regimens to treat advanced pancreatic cancer such as FOLFIRINOX (combination of 5-FU, leucovorin, irinotecan, and oxaliplatin) and nab-Paclicaxel + Gemcitabine (GEM) have applied in clinical setting from the clinical trial results as demonstrating significant prolongation of overall survival, these roles are very limited because of their toxicity. At present, these regimens are regarded as good option for patients able to tolerate the side-effects. The treatment of advanced pancreatic cancer remains still very challenging field due to its aggressive nature and resistance to conventional treatments.

The reason why pancreatic cancer remains refractory is that it has some characteristics such as hypovascular tumor and collagen-rich stroma around tumor cells, which lead to the less delivery and infiltration of anticancer agents and immune cells into the tumor. Thus, we need to overcome these situations to improve the therapeutic outcome for patients with pancreatic cancer.

Hyperthermia as combined therapy with other treatments has the possibility that it could modify the tumor microenvironment thereby facilitating drug penetration and preventing the developing immunological tolerance.

We have reported that regional hyperthermia combined with GEM improved the prognosis of patients with unresectable pancreatic cancer, and we investigated the molecular mechanisms by which hyperthermia enhances the cytotoxicity of GEM. It is well known some anticancer agents activate the nuclear factor kappa B (NF-kB) in tumor cells, and NF-kB activation mediates the resistance to chemotherapy. We demonstrated that hyperthermia enhances the cytotoxicity by inhibiting GEM-induced activation of NF-kB. Recently, it has been reported that epithelial-to-mesenchymal transition (EMT) is crucial in cancer invasion and metastasis. Our in vitro study showed that hyperthermia suppressed TGF-□-induced EMT by blocking Smad2 phosphorylation in pancreatic cancer cell. In addition, we have recently obtained the results that GEM upregulated the expression of programmed death-ligand 1 (PD-L1), suppressive immune checkpoint molecule, on pancreatic cancer cells and hyperthermia inhibits the GEM-induced PD-L1 expression.

As mentioned above, hyperthermia combined with immune-based or non-immune-based therapies is a promising strategy. Hyperthermia can enhance antitumor effect of powerful chemotherapy and attenuate these chemotherapeutic drugs-induced toxicities. In addition, blockade of PD-L1 by hyperthermia should be considered when adoptive T cell transfer cell therapy is applied for cancer patients who received chemotherapy. In this presentation, we would like to discuss recent developments and future directions in this field.

THU 29

Evaluation of the temperature increase during ablations with non-thermal irreversible electroporation in porcine liver and pancreas in vivo: effect of large vessels

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Introduction: Irreversible electroporation (IRE) is a novel ablation technique used in locally unresectable tumors, not based on thermal destruction of tumors, but on permeabilization of cell membranes with electrical pulses. The non-thermal mechanism of IRE could be causing less damage of surrounding vital structures than thermal techniques, and not suffer from the heat-sink effect seen in thermal ablation techniques, where the presence of cool blood in nearby large vessels leads to ineffective ablations. However, some increase of temperature is expected to develop when applying a high voltage, high amperage, electrical potential on a lossy tissue. The aim of this study is to determine the significance of this thermal component of IRE and the effect of blood vessels in proximity of the ablation zone.

Methods: IRE-ablations were performed in-vivo in the liver and pancreas of 5 healthy pigs. Ablations were performed using 2-4 electrodes and clinical settings (i.e. 90 pulses, inter electrode distance 1.5cm, active tip 1.5cm, pulse length 90µsec, 15-35A, 1500V/cm). Electrodes were placed either proximate or distant from large blood vessels (i.e. liver-hilum vs peripheral in the liver and in the body/head vs tail of the pancreas). Additionally, the superior mesenteric vein (SMV) was blocked during a pancreatic head ablation. Temperatures were measured using fiber optic probes, placed between the electrodes.

Results: Thirteen ablations were performed (6 liver and 7 pancreas). In tissue distant from large blood vessels, the median temperature increase was in liver 5°C, 16°C and 29°C for 2,3 and 4 electrodes and in pancreas 9.5°C and 30°C for 2 and 3 electrodes. In tissue close to large blood vessels the temperature increase was 1°C, 6°C for 2 and 3 electrodes in liver and 0-3.5°C and 0-2°C for 2 and 3 electrodes in pancreas. Occlusion of the SMV led to a temperature increase of 3.5°C, which was not larger than without occlusion.

Conclusion: Temperatures increases significantly during IRE-ablation in absence of large blood vessels, while a negligible increase is seen in the proximity of large blood vessels. The absence of this increase seems to confirm the presence of a heat-sink effect. IRE thus consists of both a thermal and an electroporation effect. The question whether the thermal component contributes to the efficacy of the IRE-ablation is a subject of further research.

THU 30

Near-Infrared Nanoparticle Mediated Hyperthermia In Colorectal Cancer Spheroids: A Tissue Phantom Study

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Colorectal cancer is the third most common cancer and second leading cause of cancer-related deaths in the United States. This is primarily due to the challenge in accurate detection and treatment of micro-metastases once the disease has disseminated. Photothermal ablation therapy using specific formulations of nanoparticles, that can absorb light in the near-infrared (NIR) and emit the energy as heat, allows for more specific targeting and destruction of metastasis compared to standard radiation and chemo-based therapies. However, optimization of nanoparticle heat generation in vivo to destroy all metastases remains a challenge. In this study, we investigated the loss of nanoparticle heat generation relative to increasing thicknesses of a tissue-mimicking phantom. Our group has developed dual-purpose, fluorescent-heating nanoparticles, called PolyDOTS (Polymer Dynamic Theranostic Spheres), synthesized using various ratios of the fluorescent polymer -poly[(9,9-dihexylfluorene)-co-2,1,3-benzothiadiazole-co-4,7-di(thiophen-2-yl)-2,1,3-benzothiadiazole] (PFBTDBT10) to the heat producing polymer -poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b']dithiophene-2,6-diyl-alt-2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe). Here, three different ratios of PFBTDBT10 to PCPDTBSe were evaluated; 95:5, 76:24, and 0:100 respectively. Three-dimensional tumor spheroids with mouse CT26 colorectal cancer cells, made of type-I collagen (5 mg/mL) containing 100 µg/mL of the respective nanoparticles were used. Alginate tissue phantoms, comprised of 0.5% Intralipid and 0.08% bovine hemoglobin, were placed over the spheroids in thicknesses from 0-9 mm. A K-Laser system (800 nm), with parameters of 3W/60s, was used to induce photothermal ablation of the spheroids through the tissue phantoms. The spheroids were digested with collagenase and the cells were counted using Trypan blue. Data generated from this study showed that the 0:100 (PFBTDBT10:PCPDTBSe) nanoparticles had significant cell death up to 6 mm of tissue phantom, while the 76:24 and 95:5 PolyDOTS had significant cell death below 4.5 mm thicknesses. The depth of fluorescence detection for the PolyDOTS was determined using In Vitro imaging system/fluorimetry (IVIS). These data will help to determine the potential loss of heat generated by the nanoparticles at a specific tissue depth as well as to determine the maximum depth at which the nanoparticles can be detected in tissue.

THU 31

Dynamic assessment of heat shock response and thermotolerance are enabled by use of novel reporter genes

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Induction of heat shock protein (Hsp) expression correlates with a cytoprotection and reduced tissue damage and accelerated healing in animal models. Since Hsp's are trascriptionally activated in response to stress, they can act as stress indicators in burn injury or surgical procedures that produce heat and thermal change. A fast *in vivo* readout for induction of Hsp transcription would allow for the study of these proteins as therapeutic effect mediators and reporters of thermal stress/damage. For these purposes, we created reporter cell lines and transgenic (Tg) reporter mice in which luciferase expression is controlled by the regulatory region of the inducible 70 kilodalton (kDa) heat shock protein, Hsp70. We used these cells and Tg mice, in conjunction with *in vivo* bioluminescence imaging, to enable the rapid analysis of cellular responses to thermal stress/injury including laser-mediated stress and determine the duration dependence of Hsp70 expression by varying the duration of thermal stresses including the pulse duration of a CO_2 laser at 10.6 □m in wavelength from 1000 ms to 1 ms in transgenic mouse skin. We observed that Hsp70 expression levels were determined by both time and temperature and that cells could tolerate temperatures nearing 100°C for durations of several milliseconds and still respond with Hsp70 expression. We used luciferase expression patterns in the skin of Hsp70-luc mice to guide tissue sampling for analysis of mRNA levels and observed gradations of gene expression after laser-induced thermal stress. These studies identified potentially new genetic elements that may serve as more dynamic regulatory elements that could be engineered into reporter constructs to reveal levels of thermal stress. In general, we observed that Hsp70 induction varied with changes in laser pulse durations and radiant exposures, which defined the ranges at which thermal activation of Hsp70 can be used to protect cells from subsequent stress, and revealed the window of thermal stress that tissues can endure.

THU 32

CONVERGING HYPERTHERMIA AND IONIZING RADIATION (IR) TO CONVERT THE TUMOR INTO AN *IN SITU* VACCINE

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Both systemic temperature elevations and local hyperthermia directly impact the immune response to cancer.

Thermal stress increases neutrophil recruitment into tumors and enhances DC functions augmenting both their fagocytic capacity and IFN production (Knippertz *et al*. Int. J. Hyperthermia, 2011).

NK cells and lymphocytes are also affected by enhanced temperatures.

For instance, in preclinical models systemic treatment with 39.5°C ± 0.5°C for 6 hours activates IL-6 signalling that modifies the tumor vessels and enhances trafficking of $CD8^+$ effector/memory T cells (Fisher DT *et al*. JCI, 2011). In mice systemic hyperthermia increased LPS-induced signaling with enhanced phosphorylation of IKK and IκB. Moreover, NF-κB nuclear translocation and binding to the TNF-α promoter occurred in macrophages after subsequent endotoxin challenge (Lee CT *et al* PloS One, 2012). Similar to IR, hyperthermia upregulates MICA, the ligand of NKG2D receptor on the surface of NK and Lymphocytes (Ostberg JR *at al.* J. Leukoc. Biol., 2007; Ruocco MG *et al.* JCI, 2012).

Our group has successfully combined local radiotherapy with different immunotherapies to convert the irradiated tumor into an *in situ* vaccine (Formenti SC *et al*. IJROBP, 2012). Preclinical experiments in murine syngeneic tumor models have been validated in patients with metastatic solid tumors (Demaria S *et al.* JAMA Oncology, 2015; Golden E *et al.* Can Imm Res, 2013; Golden E *et al.* Lancet Oncology, 2015).

Because of the extensive preclinical and clinical experience in combining local hyperthermia with radiotherapy, it is compelling to explore the potential of a triplet approach, by adding immunotherapy to this combination. Issues of optimal selection of combinatorial immunotherapy as well as definition of optimal sequencing warrant extensive preclinical exploration.

THU 33

Integration of functional imaging with interventional oncology

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What is “molecular interventions for cancer”?

Molecular imaging in interventional oncology? Does that mean PET fusion-guided RFA? Personalized Oncology? Imaging drug delivery in vivo? Optical imaging in IR and the OR?

Interdisciplinary team science holds the keys to optimization of interventional oncology (IO) therapies. Visualization of the molecular processes underlying IO therapies in real time during the procedure may be a transformative paradigm shift, opening the door towards better understanding of the standard IO procedures of biopsy for drug discovery, thermal ablation, and regional drug delivery via DEB/TACE (Drug eluting bead / transcatheter hepatic arterial chemoembolization).

Image-able drug-eluting 70-150 micron microspheres may help optimize DEB/TACE and guide combination therapies by identification of tissue at risk for undertreatment. Optical endoscopy needles may detect signal from pre-injected ICG to help localize hepatomas and fluorescence corresponds with tumor differentiation. MRI-HIFU paintbrush to deliver and paint chemotherapy locally. Hypoxia-activated drugs for DEB/TACE. Checkpoint inhibition and ablation: a cancer vaccine. These are a few of the latest technologies and clinical trials on the molecular interventions horizon.

THU 34

How hyperthermia works. How can we make hyperthermia work better?

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Introduction

Hyperthermia has been applied since the early 1980s with excellent clinical results when used in combination with radiotherapy and chemotherapy in various tumor sites including melanoma, recurrent breast cancer, soft tissue sarcoma, head & neck tumors and cervical carcinoma. Debate has been ongoing on the underlying mechanisms that makes hyperthermia such a powerful radiosensitizer and chemosensitizer.

Biological Mechanisms of hyperthermia

One mechanism is that local tumor heating causes vasodilatation and thereby increases the blood supply to the tumor. Increased blood flow improves the delivery of chemotherapy to the entire tumor. Next to this, the increased blood flow also causes reoxygenation of the tumor, which enhances the effect of ionizing radiation which requires the presence of oxygen to induce the formation of DNA breaks, that are necessary in killing tumor cells.

A more direct mechanism on cellular level is that hyperthermia blocks a part of the DNA repair pathways. This is very relevant as repair pathways become active in tumor cells to restore any DNA damage caused by chemotherapy or radiotherapy, thereby undoing part of the effect of therapy. Research has shown that hyperthermia can block this unwanted DNA repair by causing a decrease in BRCA2, an essential protein required for the homologous recombination repair pathway, one of the major pathways in DNA repair. More recently hyperthermia was also shown to restore the activity of p53 in HPV positive cervical carcinoma, by enabling the complex formation of E6 (a viral protein) to p53.

Discussion

Knowledge of these mechanisms can be exploited to further enhance clinical effectiveness by combining hyperthermia, which blocks homologous recombination, with agents that block other DNA repair pathways. For example, currently the effectiveness of adding a PARP1-inhibitor to hyperthermia and cisplatin is investigated, as well as the effectiveness of the combination of these three modalities with ionizing radiation.

We expect that novel multimodality treatments which include hyperthermia will lead to even better clinical results with both increased tumor control and reduced normal tissue toxicity.

THU 35

Randomized clinical trials and predictive cancer related genes in patients with locally advanced cervical cancer for effectiveness of hyperthermia oncology

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From October 1994 to February 1999, we studied the efficacy of radiotherapy (RT) combined with hyperthermia (HT) for 40 FIGO Stage IIIB cervical carcinomas (CC) for both the clinical response and survival of patients treated with RT or RT+HT. All patients were divided randomly into the following two groups: the RT group of 20 patients who underwent RT alone, and the RT+HT group of 20 patients who underwent three sessions of HT in addition to RT. Both the 5-year overall survival (OS) and disease-free survival (DFS) of the patients who were treated with RT+HT (58.2% and 63.6 %) were better than those of the patients treated with RT (48.1% and 45%), but these differences were not significant. The 5-year local relapse-free survival (LFS) of the patients who were treated with RT+HT (79.7%) was significantly better than that of the patients treated with RT (48.5%) (P = .048, respectively). Next, between September 2001 and September 2013, to evaluate the efficacy of HT, we investigated a multicentre randomized clinical trial of concurrent chemoradiotherapy (CRT) alone versus CRT combined with HT (CRT+HT) in patients with FIGO stage IIA-IVA CC. Patients were randomly assigned to one of the following two groups: the CRT group of 50 patients receiving CRT alone, and the CRT+HT group of 51 patients receiving five sessions of HT in addition to CRT. Although not statistically significant, both the 5-year OS and DFS in the CRT+HT group (77.8% and 70.9 %) were better than those in the CRT group (64.8% and 61%). Logistic-regression analysis adjusting for age, stage, and histology indicated that the patients in the CRT+HT group were significantly more likely to achieve CR than those in the CRT group (OR, 3.993; 95%CI, 1.018-15.67; P = .047). CRT+HT were well tolerated and did not significantly add either acute or long-term toxicity over CRT alone.

To identify a set of genes related to thermo-radio-sensitivity of CC and to establish a predictive method. A total of 19 patients with CC who underwent definitive thermo-radiotherapy were included in this study. We compared the expression profiles of 8 thermo-radiosensitive and 11 thermo-radio-resistant tumors obtained by punch biopsy before treatment using a cDNA microarray. Some of these genes were already known to be associated with apoptosis (BIK, TEGT), hypoxia-inducible gene (HIF1A), and tumor cell invasion and metastasis (PLAU). We developed a “Predictive Score” system that could clearly separate the thermo-radiosensitive group from the thermos-radio-resistant one.

ABSTRACTS FOR FRIDAY, APRIL 15, 2016

FRI 1

Challenges and opportunities in application of thermal ablative therapies

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For thermal ablative technologies to be optimally applied in cancer and new cardiovascular and neural targets it is necessary to carefully assess impact in both the target tissue and adjacent tissues. Here impact is understood to mean the thermal response, the thermally mediated mechanism of action, and the resulting biological response (i.e. life or death) at the cellular or tissue level. For example, in addition to more traditional treatment of cancer, such as prostate and liver, new focal therapeutic targets now include pulmonary vein (atrial fibrillation) and arteries (renal denervation) and even nerves (pain and plantar fasciitis). These targets present unique challenges associated with the measurement and modelling of temperature in vivo and in thin or anisotropic biological structures of the target or adjacent structures (i.e. vascular or neural structures). Further, it requires a clear understanding of the mechanism of action associated with thermal injury. This usually relates to cell specific lipid, protein or water phase change and vascular/cellular interactions in tissue. Even further, it begs the question of whether heat, cold, or other energy based technology is best suited to achieve localized destruction without collateral injury in a given target. This talk will highlight a discussion of what is known about thermal response, mechanisms of action and biological response of cryosurgery, heat and other energy based technologies. The intent is to better understand the advantages and limitations of each therapy and therefore optimal application of focal ablative therapy to achieve disease control. The response of tissue and cells that survive focal thermal ablations may be as important as the amount of tissue destroyed in determining the ultimate usefulness and proper additional interventions needed to make thermal ablation a routine approach. Some of the better understood biology related to thermal dose distributions in solid tumors will be discussed to highlight the opportunities that are available to translate more rational, comprehensive treatment approaches into the clinic. For example, the immune stimulation caused by focal therapies, changes in the tumor microenvironment that may affect metastasis and sensitivity of residual primary tumor and possible ways to exploit these factors will be described. If collateral injury with complete ablation is unavoidable, what are the ways that other modalities might be used to fully destroy and control the tumor, as well as inhibit metastatic dissemination or growth or pre-existing micrometastases? These type of questions need to be answered for expanded use of ablative approaches.

FRI 2

EVOLVING TECHNOLOGY FOR SUPERFICIAL AND DEEP HYPERTHERMIA

Paul Stauffer

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Introduction: Many tumour types have proven responsive to hyperthermia treatments of 40-45°C for 1 hour, when combined with radiation and/or chemotherapy. However, existing heating technologies often fail to treat the entire disease which may extend outside the effective treatment volume of available applicators. The intent of this review session is to summarize heating characteristics of hyperthermia devices that have been used clinically to date and to differentiate their principles of operation as well as their typical performance in representative equipment systems. This presentation will cover heating technologies in current use for treating both superficial and deep lying tumours. It will also reveal several ongoing development efforts that should lead soon to enhanced heating capabilities in specific tumour sites. Because heating performance is intimately tied to thermal feedback, the associated thermometry and thermal dosimetry techniques will be described. And the impact of device and patient specific hyperthermia treatment planning will be introduced. Where possible, heating technologies will be correlated with typical performance in specific examples of clinical disease. The focus of this review will be on the ongoing evolution of heating technology that is replacing single element heat applicators with more adaptable multi-element applicators, including site specific phase or amplitude steerable conformal array applicators.

Conclusion: This course will end with a summary of advances in thermal therapy delivery approaches for superficial and deep hyperthermia which should fuel increasing optimism for the future of this field.

FRI 3

Using Systems Biology of Signaling to Improve Cancer Treatment

Michael B. Yaffe

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Synergistic tumor cell killing can be induced by combining particular signaling pathway inhibitors with cytotoxic therapies such as DNA damaging drugs. The enhanced anti-tumor response generally results from one of two distinct mechanisms: (1) inducing dynamic re-wiring of the cell injury or DNA damage response, cell cycle checkpoint control pathways or apoptotic networks to enhance cell killing, or (2) therapeutically exploiting pre-existing weaknesses in tumor cells that arose during tumor evolution, such as loss of p53 or oncogene addiction. In this talk, I will show examples of both types of synergy, along with insights into their mechanisms of sensitization that were uncovered using systems biology approaches. In the case of dynamic network re-wiring, I will show how time-staggered combinations of EGFR or FGFR inhibitors can re-wire apoptotic pathways in TNBC, NSCLC, and head and neck SCCs for increased death after doxorubicin or cisplatin-induced DNA damage. In the case of acquired tumor cell vulnerabilities I will present our ongoing work on cell injury and DNA damage signaling by the cell cycle checkpoint kinases Chk1, Chk2, and MK2 that has identified RNA-binding proteins as a major class of substrates that are required for cell cycle checkpoint competence in the absence of functional p53, and show how the targets of these RNA-BPs can be used to prognosticate the response of NSCLC patients to platinum-based chemotherapy. I will show how p53, when functional, suppresses these checkpoint kinase-controlled RNA-BP pathways to limit checkpoint arrest duration, and show how an RNA-BP focused approach to gene expression can be used to identify additional components of the cell injury response. Surprisingly, despite the growing clinical utilization of thermal therapies in solid tumor oncology, there has been little attention within the systems biology community directed at understanding the signaling mechanisms that underlie its beneficial effects. I will propose some straightforward investigations that could be pursued to address this unmet need.

FRI 4

Invasive temperature measurement in Soft tissue Sarcoma during hyperthermia using catheters: Analysis of side effects in 35 patients

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Purpose: Measured tumor temperature is a significant factor for treatment outcome of thermotherapy combined with chemotherapy and/or radiotherapy in different tumor entities. Invasive temperature measurement using closed-tip catheter delivers in RHT only limited data but it is still a means of quality control due to the lack of non-invasive thermometry. We investigate the technical success and complications in patients with high-risk soft tissue sarcomas (STS) undergoing CT fluoroscopy-guided closed-tip catheter placement before Thermo-chemotherapy treatment.

Material/Methods: This retrospective study comprises all patients referred for the insertion of thermometry probes before regional hyperthermia treatment from April 2010 to February 2015 at a single university center. Catheter placements were performed using a 128-row CT scanner (Siemens Healthcare, Forchheim, Germany) under local anesthesia and intermittent CT fluoroscopy-guidance (120 kV, 10-20 mA). The access chosen depended on the anatomic location of the tumor, which was individually different (thorax, abdomen, pelvis and extremity). Technical success, complication rate, duration of catheter insertion and Dose-Length Product (DLP) were analyzed. Technical success was defined as intratumoral catheter placement suitable for subsequent thermometry.

Results: 35 procedures were performed in 35 patients (52.4 ± 13.6 years; 22 male, 13 female). Localization of STS was in 48.6% (n=17) extremities, 25.7% (n=9) pelvis, 14.3% (n=5) thorax and 11.4% (n=4) abdomen. 34 out of 35 interventions (97.1%) were technically successful; in 1 patient (2.9 %) catheter placement was not feasible. No interventional complications such as bleeding occurred. Within a time interval of 30 days after the catheter insertions in n=25 patients (71.4%) neither intra- nor post-interventional complications nor technical failures were observed. In 9 patients (25.7%) post-interventional adverse events were observed comprising two major complications (abscess formation [n=1] and severe catheter dislocation [n=1]) as well as seven minor complications (catheter kinking [n=3]). A total of 55 catheters were placed, with a mean number of 1.7 ± 0.7 per patient. Catheters remained in place for a mean of 4.1 ± 1.8 days. Mean total DLP was 723.2 ± 355.9 mGy*cm.

Conclusion:
Catheter implementation under CT-control in deep seated tumors of the extremities as in pelvis/abdomen is safe and characterized by a high technical success rate.

FRI 5

Infrared-based clinical quality assurance in superficial hyperthermia treatments

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Although superficial hyperthermia (SHT) is a well proven treatment modality in oncology, feasible quality assurance (QA) methods for SHT treatments are widely limited to the use of temperature probes that are used either interstitially or placed on the patient's skin. However, the information provided by the probes is locally confined and therefore not capable of representing the global temperature distribution accurately. Infrared (IR) cameras represent a promising tool for QA in SHT treatments as they provide global temperature data. A trial was initialized to evaluate the feasibility of IR cameras for SHT treatment QA.

Currently the trial comprises eight patients with 5-10 SHT treatment sessions, each. All patients were treated with spiral antenna arrays (915MHz). The tumor entities mainly cover recurrent breast carcinoma, but also sarcoma and melanoma. IR images were acquired prior to and after the session, the heat dissipation after the applicator's removal was monitored with the IR camera for five minutes. The data were then analyzed under various aspects:

Firstly, the data of the IR camera were compared to the measured values of the three probes. Thus, the relevant parameters for IR image acquisition (e.g., emissivity) could be computed in order to ensure accuracy of the IR camera's data. Secondly, the temperature distribution of the treated skin areas before and after the treatment was evaluated with respect to the absolute and relative increase of the temperature. Thirdly, the measured overall maximal and mean temperature (T_{max} and T_{mean}) of the probes were compared to the IR camera's results to validate the probes. Lastly, the data collected from the cooldown phase were evaluated to gain insights into the influence of local perfusion on the achieved temperature distribution.

The emissivity could be determined satisfactorily, the method's uncertainty was ~0.7°C. The acquired IR images of the heated area allow assessing the homogeneity and the absolute and relative temperature increase comprehensively. The validation yielded deviations of (0.1±1.2)°C for T_{max}, T_{mean} is overestimated by (1.2±0.9)°C. The data collected from the cooling off phase of the skin indicate systematic spatial differences in body-temperature regulation: The temperature dropped faster in skin areas with extensive scar tissue than in areas with healthy tissue.

Generally, it was found that IR imaging complements currently implemented SHT QA methods well. Especially the information concerning homogeneity and extend of the temperature increase are considered to be of interest for the evaluation of SHT treatments. All patients received the camera positively.

FRI 6

Clinical implementation of the novel HYPERcollar3D applicator for deep hyperthermia treatment of cancers in the head and neck region

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Purpose

Multiple clinical trials show the benefit of adding hyperthermia to radiotherapy in patients with head and neck tumors, but the technology used allowed only heating of lateral locations. For deep heating in this region, we developed the HYPERcollar applicator. From 2007-2014, 45 patients were treated and treatments were always guided by both pre-treatment planning and a complaint-adaptive (discomfort indicated by the patient) treatment protocol implemented in our VEDO software. Based upon this experience, we developed the HYPERcollar3D, in which conformal heating capabilities, treatment reproducibility, and patient comfort are improved. In this work we report on this process and our early experience.

Methods

In the HYPERcollar3D, patient comfort and treatment accuracy/stability are improved by using a replaceable waterbolus and patient positioning according to the CT using specific immobilization and a laser alignment procedure. Using electromagnetic simulator SEMCAD-X (v. 14.8.6) we also improved the number of antennas and their locations. A clinical applicator prototype was constructed and quality assurance measurements were performed using an E-field scanning system. The novel applicator was clinically introduced in 2014.

Results

The simulation studies showed that the higher number of antennas, and their repositioning, allow for a substantially improved treatment quality: simulations predict a reduction of hotspots by 32% and a doubling of the clinically applied SAR to the target. Quality assurance measurements demonstrated good quantitative agreement in the region of interest (<10%). 12 patients have been treated with the HYPERcollar3D since its clinical introduction in 2014. Reliable thermometry could be applied in only 3/12 patients (25%), stressing the need for accurate simulations. Mean measured tumor temperatures in these three patients were 41.0 ^{0}C, 41.2 ^{0}C and 40.0 ^{0}C. SAR estimations, based on measured signals and simulations, indicate that indeed the mean applied SAR to the target was strongly increased, in two cases even above 300 W/kg.

Conclusions

First clinical experience confirm the simulations and focusing capabilities of the HYPERcollar. Earlier, we reported the excellent clinical results and toxicity for 6 patients (Van Holthe et al, ESHO 2015) but analysis of the results for this larger group of patients is ongoing.

FRI 7

An MRI-Compatible Hyperthermia Applicator for Small Animals

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Introduction

To design novel treatment combinations involving mild hyperthermia, pre-clinical trials are essential. These studies into treatment effectiveness require close monitoring of the temperature during testing. Invasive thermometry restricts testing of the link between hyperthermia and immune responses, so MRI-compatibility is a necessity. Next to that, the applicator must heat locally, and secondary hot spots especially in vulnerable regions like the spinal cord must be prevented. Lastly, the system must be non-invasive, for disturbances in the tissues studied interfere with the accuracy of the research.

With these goals in mind, we designed and built an applicator based on a novel water-embedded antenna design. In this study, we report the mode of operation for the head&neck region, but it can also be used for other tissues up to about 2 cm deep.

Methods

A simulation-based approach was used to design the antenna element, and the surrounding system including the load. Simulation programs SEMCAD and CST were used, both of which use a Finite Difference Time Difference (FDTD) calculation methods. SEMCAD was also used for Penne's Bioheat equation temperature predictions. The single antenna and array performance were assessed by simulating the power absorption distributions, i.e. the Specific Absorption Rate (SAR), and the temperature distribution.

The antenna was designed to achieve at least a -15 dB match to 50 Ω at 2.45 GHz. Furthermore, it was stabilized for various water temperatures and for disturbances in the air-water bolus boundary. The metal plates were designed to be thin enough to ensure MRI compatibility. The latter property was tested by inspecting MRI images for disturbances when the antenna plus related cables were scanned.

Results

According to our simulations, a single antenna operating at 5W power is able to heat tongue tissue to 42º C without creating hot spots in other areas. Next to that, experiments showed that the antenna stability required was achieved and a match of -19 dB was reached in all cases. Lastly, the MRI scan showed excellent compatibility in the area of interest.

Conclusions

Our novel setup provides operation within the specifications defined. Based on these promising results, we will now elucidate on the experimental validation of the heating performance of the single antenna setup and develop a phased array for deep heating.

FRI 8

Comparison of Ultrasonic Thermometry based on the Change in Backscattered Energy with MRI Temperature Images

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Background: Thermal therapies from cryosurgery to ablation would benefit from a non-invasive, safe, inexpensive and convenient 3D thermometer to monitor heating patterns. Ultrasound is a modality that meets these requirements. Agreement among predicted, simulated and measured change in the backscattered energy (CBE) from both our *in vitro* and *in vivo* experiments has shown that CBE can be used for temperature imaging (TI) in both 2D and 3D during non-uniform heating.

Methods: We compared TIs from CBE ultrasonic thermometry to TIs from MR images. For both modalities 1-2 cm thick turkey specimens were imaged during heating with hot water at 75^{o}C in a 1 cm silicon tube through the center of each specimen clamped in 10x10 cm lucite fixtures. Temperature for CBE thermometry was extracted from images measured with a Terason 3000 system with a 128-element array and 7.5 MHz center frequency. Heating was monitored with 7 thermocouples over the face of the fixture. For MRI thermometry, *Luxtron* Fluoroptic® fiber optic temperature sensors were used to monitor temperature, so that the fixture, sensors and the heating source could go into the Philips Ingenia 1.5T MRI system. The MR system executed Philips Sonalleve MR-HIFU V2 temperature software. Total heating time for each modality was 1200 sec.

Results: We compared the non-uniform heating patterns from each modality at 30-second intervals over the 1200 sec heating period. CBE computed using our stochastic-signal framework yielded temperature accuracy of 1^{o}C down to 2x2 mm region sizes over all frames from multiple experiments. MRI temperatures were also accurate to about 1^{o}C. Conclusions: Preliminary results suggest that heating patterns derived from CBE and MRI are similar and that CBE thermometry may be able to bring TI accuracy and precision to thermal therapies with a less expensive portable alternative.

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FRI 9

Towards integration of non-invasive temperature measurement with microwave radiometry for improved control of superficial hyperthermia array applicators

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Background: Current conformal microwave array (CMA) applicators can heat superficial tumors within the desired hyperthermia range of 41-45°C. However, efficacy of these treatments depends heavily on reliable thermal feedback from the heated tissue, which is currently limited to skin surface or invasive probe temperature measurements. This work addresses the use of microwave radiometry as a non-invasive thermometry technique to sense thermal radiation emitted from the tumor target under each aperture of antenna array applicators.

Methods: A CMA applicator is fabricated from thin, flexible, multilayer printed circuit board (PCB) material, with each independently controlled element of the array consisting of a square dual concentric conductor (DCC) 915MHz radiator for heating, combined with a passive antenna for radiometric sensing. Three microstrip antenna designs were evaluated numerically for the radiometric element: the DCC itself, an Archimedean spiral, and a tapered logarithmic spiral. The spirals were located concentrically within the central region of the square patch DCC antennas. Radiometric antenna performance was evaluated using an accurate 3D computational model of the human chest and a 6mm thick coupling water bolus. Each antenna was optimized using electromagnetic simulation software ANSYS® to maximize radiometric reception of thermal emissions from a target defined laterally by the DCC aperture and at a depth that includes typical maximum temperatures of superficial hyperthermia treatments: 3-7mm.

Results: Used as a radiometric receive antenna, the DCC aperture has a peripherally enhanced power collection pattern with peaks in the four outer corners and a broad minimum just above 50% of maximum centrally. In contrast, the spirals receive energy predominantly along the boresight axis of the spiral, thus confining the region of influence to tissue located within the central broad minimum of the DCC heating pattern. Both spiral antennas presented multiple wide bandwidths (>500Mz) for radiometric monitoring over the 1.2-3.5GHz range with predominantly circular polarization that enhances collection of randomly polarized thermal radiation. Overall, the received signal sensitivity from 1.2 to 3.5 GHz was approximately 2 (Archimedean) to 3 (logarithmic) times higher for the spirals than the DCC apertures.

Conclusions: The use of radiometric spiral antennas is compatible with current 915 MHz conformal microwave array (CMA) applicators and allows real-time readings of subsurface tumor temperature under each DCC heat antenna, paving the way for improved thermal dosimetry and treatment control of multi-element array applicators.

FRI 10

Laboratory prototype of UWB applicator for head and neck hyperthermia

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Introduction

Addition of hyperthermia to radiotherapy has been shown beneficial in management of Head and Neck tumors. In our work, we aim to develop H&N applicator that is capable of modifying the focus size according to tumor position and volume. This is achieved by varying operating frequency in addition to amplitude and phase optimization.

Methods

Due to differences in geometry of head and neck, we designed two exchangeable applicators. The neck applicator consists of 10 self-grounded bow-tie antennas arranged in one ring while the head applicator consists of 16 antennas arranged in two rings. Each antenna is placed inside a conical enclosure and cooled separately by circulated distilled water. The prototype of the neck applicator was manufactured to be a close approximation of the clinical version. The diameter is adjustable between 180 and 220 cm. As a water bolus a single inlet-single outlet thin plastic bag was used.

The focusing abilities of the applicator were experimentally evaluated on homogeneous cylindrical muscle phantoms representing the neck. The phantom diameters were 100 and 150 mm, while the diameter of the applicator was kept 180 mm. The experiment was carried out at room temperature, i.e both phantom and water bolus had temperature of 20°C and frequency 500MHz,

Results

The antenna operates in frequency band 450 MHz to 900 MHz, which is about 30 MHz higher than the simulated results. In all focusing experiments a minimal temperature rise of 1°C in 1 minute was obtained in the focal spot for applied powers of 30 to 70W. We achieved a good agreement between planned and measured data, in terms of the correct focusing and iso-SAR contours. The folders in the present water bolus cause dephasing of the applicator. Each time, a calibration procedure prior to the experiment must be performed. Therefore, as a next step, it is necessary to develop a new water bolus with predictable shape.

Conclusion

The developed UWB phased array applicator is capable of focused heating in the head and neck.

FRI 11

An integrated system for delivering hyperthermia to small-animal targets under 14 T ultra-high field MRI guidance

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Introduction: Moderate tissue heating is the subject of significant investigation with application to thermally mediated delivery and/or heat-triggered release of therapeutic agents (e.g. drugs, immune stimulatory agents) for treatment of cancer and benign disease. Ultra-high field magnetic resonance imaging (MRI) provides high-resolution (spatial and temporal) imaging of the tumor environment and vasculature. We propose the development of a 2.45 GHz microwave hyperthermia system integrated with a 14 T ultra-high field small-animal MRI scanner to facilitate real-time monitoring of physical and physiological changes induced by hyperthermia with submillimeter resolution, in conjunction with MR thermometry. This study reports on technical characterization of the hyperthermia delivery system, integration with MRI, thermometry, and preliminary *in vivo* evaluation.

Methodology: The proposed system incorporates a microwave hyperthermia applicator positioned adjacent to the small-animal target, directing microwave energy for localized treatment of tumors. A 3D electromagnetic-bioheat transfer model was used to optimize a directional 2.45 GHz antenna adjacent to the small-animal and inside the bore (30 mm diameter) of the 14 T ultra-high field MRI scanner (Bruker Avance III). Optimization objectives were: device miniaturization, impedance matching, and heating rate/profile of the target volume. The hyperthermia delivery device was fabricated from MR-compatible materials and integrated within the MR environment with band-pass filters (2.4 GHz ± 100 MHz) inserted in-line to mitigate any electrical interference between the scanner and the antenna. Impedance matching and heating performance were measured in tissue mimicking agar-based phantoms and *ex vivo* tissue. FLASH and EPI MR sequences were investigated for monitoring temperature with the proton resonance frequency shift technique.

Results: The high sensitivity of the 14 T scanner facilitated precise localization of antenna orientation and placement within the scanner. The optimized antenna yielded experimental S11 < -21 dB at 2.45 GHz. MR-derived temperature maps in agar-based phantoms were validated with fiber-optic temperature measurements. Maximum error between MR-thermometry and fiber-optic temperatures measurements was less than 0.3 °C at peak temperatures increases of 8 °C with antenna input power of 8 W. There was no observable electrical artifact introduced by operation of antenna within the MR environment. Susceptibility and flow artifacts were negligible and localized to submillimeter distance from the applicator.

Conclusion: The proposed system shows strong potential for delivering feedback controlled hyperthermia under ultra-high field MRI guidance in small-animal targets. Prototype *in vivo* animal experimental characterization is in progress and will be presented at the meeting.

FRI 12

Feasibility of absolute MR thermometry for knee joint cartilage using spin-lattice relaxation time

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Introduction Thermal therapy for osteoarthritis is becoming one of the options for pain-relief(1). In order to optimize the therapeutic effect, temperature visualization of the cartilage is necessary. We have demonsrated the feasibility of magnetic resonance (MR) temperature imaging of knee joint cartilage under thermal therapy using a phase mapping technique (2). This technique is suffered not only by the object displacement but also by the static magnetic field change due to the displacement. In order to develop a technique to measure temperature without an image subtraction, we have focused on the use of spin-lattice relaxation time, T1, for mesuring absolute temperature of the cartilage. As a feasibility study, we have examined the temperature dependence of T1 in the porcine knee joint cartilage in vitro.

Methods Proton spectra of cartilage segment samples collected from porcine knee joints were observed in a 9.4 T NMR spectrometer. The sample was immersed in deuterium oxide (D_2O, 99%, Sigma-Aldrich) in a NMR sample tube of 5 mm in diameter. Proton spectra were evaluated at various temperatures ranging from room temperature to 60 ^{o}C. The sample temperature was controlled with an air blower system equipped with the spectrometer. Then a conventional inversion recovery sequence with the following conditions yielded T1 of water proton in the sample; TR, 30 s; TI, 0.1, 0.2, 0.4, 1.0, 2.0. 4.0, 8.0, and 16 s, observation bandwidth, 8.012 kHz, and number of spectral points, 65536. The area of water peak was obtained over 4ppm around the center frequency at each temperature, and used for T1 calculation.

Results The spectrum of the cartilage sample exhibited a water signal with negligible (0.02-0.03%) fractions of the other components. The water proton T1 was in proportion to temperature with high correlation ($r \sim 0.99$). The temperature coefficient was 36.9 ms/^{o}C (1.28%/^{o}C at 30^{o}C) for heating period and 36.0 ms/^{o}C (1.24%/^{o}C at 30 ^{o}C) for cooling with no significant difference between, meaning that no hysteresis was recognized in the temperature range used in the present study. These results support that T1 is a strong candidate as a parameter for measuring absolute temperature in the cartilage.

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FRI 13

Can we avoid interstitial thermometry during superficial hyperthermia?

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Background

In the current clinical practice of superficial hyperthermia treatment, multi-sensor temperature probes are applied in tissue and on the skin to monitor the temperature during the treatment. In the study of Lee et al in three volunteers (Int. J. Hyperthermia 1994), the agreement between interstitial and skin temperatures was first studied. The objective of the current study was to investigate whether a correlation between interstitial and skin temperatures exists in a large group of patients. Based on such a correlation, one could consider to avoid interstitial thermometry.

Methods

The data of 30 patients were analysed that underwent the standard treatment procedure of 8 x 4Gy (2fr/wk) plus 4 fractions of superficial hyperthermia (1fr/wk) for their recurrent breast cancer in a previously irradiated area. For interstitial thermometry, closed-tip catheters were inserted into the tissue and left in place between treatments but removed after the last treatment or at the first indication of complaint of the patient. The depth of the probes was assessed by measuring the catheter depths using an ultrasonic imaging device. Prior to treatment, fibre optic temperature sensors were inserted in these catheters for continuous (every second) temperature measurement during hyperthermia treatment. To compare the interstitial with the superficial temperatures, a second fibre optic temperature sensor was placed at the skin exactly above the corresponding interstitial sensor. Mean differences between interstitial and superficial temperatures were calculated per patient per treatment per location.

Results

The data was collected for a total of 71 treatments and provided 229 matched interstitial and superficial temperature measurement locations. The applied water bolus temperatures were 37°C (3 treatments), 38°C (52 treatments), 39°C (13 treatments), 40°C (1 treatment) and 41°C (2 treatments). In 88% of the comparisons, the superficial temperature was lower than the interstitial temperature, though the difference varied over the treatment duration. Overall, a large variation (up to more than 5 °C) was observed in the overall differences, and this variation was not systematic and hence not predictable.

Conclusion

This study demonstrates that it is not possible to reliably deduce interstitial temperatures from superficial thermometry. Thus, for high quality SHT treatment monitoring it is strongly recommended to have both type of temperature measurements.

FRI 14

Modeling Scattering in Simulations of Focused Ultrasound Beam Propagation

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Introduction – The inclusion of scattering phenomena in numerical simulations of ultrasound beam propagation when modeling high-intensity focused ultrasound (HIFU) therapies is vital to the ultimate accuracy of the predicted results. This is especially important for transcranial applications where acoustic irregularities of the intervening skull provide numerous scattering sites that send portions of the propagating beam significantly off-axis. Including such effects in simulation software is not done regularly; the attenuation coefficient is often set equal to absorption only, neglecting scattering.

Methods – We include scattering effects into our 3D simulation software (called the hybrid angular spectrum, or HAS, method) in two ways depending upon the size of the scatterers: 1) explicitly if the scale of the variation in the medium's acoustic properties is larger than a voxel size of the numerical grid; or 2) implicitly for scatterers whose size is much smaller that the voxel dimensions. A key goal of this study is to determine the scattering characteristics that are needed to be instituted in Method 2 above by employing the results of high-resolution simulations using Method 1.

Results – Using Method 1 with a high-resolution numerical grid (voxel size 0.25 mm), we have modeled polyethylene scattering particles with a diameter nominally equal to 1/6 wavelengths randomly distributed in a gelatin phantom. We have shown a clear relationship between a decrease in transmitted beam power to the focal zone with increasing particle concentration, accompanied by a corresponding increase in absorbed power. The difference between the total power radiated by the source and the sum of absorbed power and power transmitted to the focus (after reflection is accounted for) is attributed to the scattered power in the form of an implied scattering coefficient. This coefficient is then inserted into a lower resolution simulation (and therefore a computationally more practical simulation– Method 2) of the same scattering configuration to demonstrate the effects of scattering.

Conclusion – Including scattering effects into numerical simulations of ultrasound beam propagation improves the validity of models of HIFU therapies.

FRI 15

Optimization of Signal Processing in MR Thermometry using Resonance Frequency and Spin-lattice Relaxation Time for Breast HIFU

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Introduction High intensity focused ultrasound (HIFU) therapy under MR guidance requires monitoring of temperature distribution around the target tissue. For aqueous tissues, proton resonance frequency shift of water signal can be used. This approach is not applicable to a voxel containing only fat, as proton resonance frequency of fat is not temperature dependent. Instead, spin-lattice relaxation time of methylene chain ($(-CH_2-)_n$) or terminal methyl (CH_3) proton is a promising parameter (1) for fat thermometry. Based on this rationale, we have proposed a novel technique using multiple flip angle and multiple echo time to map the spin lattice relaxation time (T_1) of methylene or terminal methyl proton for fat and the resonance frequency for water (2). In the present work, we have examined the effect of using prior information about frequency assignments and density ratios of the fat components to reduce the complexity of signal processing as well as to maintain the accuracy of T1 estimation.

Methods A numerical phantom comprising spoiled gradient recalled acquisition in steady state (SPGR) signals of water and 8 components of fat including methylene chain and terminal methyl was constructed. To this phantom, two different approaches were applied; one was with a model using the full 9-component model and the prior information on the frequency assignments and density ratios; the others was with a simpler model using only 2-components, water and methylene chain. The estimation accuracy of the methylene T1 was compared between the two approaches under signal-to-noise ratio (SNR) varied from 3.3 to 100.

Results The systematic error in T1 estimation was significantly smaller in the 9- component approach than in the simple 2-component approach ($p < 0.01$). The random error was also smaller in the 9-component model in the present SNR range. The corresponding temperature error was about 0.3 ^{o}C at SNR of 10 assuming that the temperature coefficient of methylene T1 was 1.79 %/^{o}C[1].

Conclusion The T1 estimation technique using the prior knowledge on frequency separation and signal intensity ratio in conjunction with the full component model was superior to the technique using a simple 2-component model.

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FRI 16

Biodegradable plasmonic nanoparticles for cancer imaging and therapy

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Many inorganic nanoparticles such as gold are intrinsically multimodal and, therefore, are of great interest in a number of critical clinical applications in cancer healthcare including early detection, diagnosis, image guided therapy, therapy monitoring, externally triggered drug delivery and enhancement of cancer immunotherapy. Presently, gold nanoparticles with a strong NIR absorbance are typically larger than ca. 30 nm that is above the threshold size of ca. 5 nm required for efficient renal clearance. As these gold nanoparticles are not biodegradable, concerns about long-term toxicity have restricted their translation into the clinic. Here, we present a strategy to development of biodegradable plasmonic nanoparticles (BPNs) with controllable size from ca. 20 to 100 nm and a strong NIR absorbance that covers the first (650-950nm) and the second (1000-1350nm) NIR windows. We showed that BPNs biodegrade in live cells such as macrophages to primary ca. 5 nm components which are highly favorable for body excretion. Furthermore, we demonstrated that BNPs do not cause any acute or liver toxicity in live mice and are excreted from the liver over time. We used directional conjugation chemistry to synthetize molecularly targeted BPNs and demonstrated their utility in highly sensitive imaging of cancer cells in animal cancer models in vivo. In addition, BNPs showed more than 4-fold increase in signal strength and superior photostability in PA imaging as compared to gold nanorods that is associated with cluster morphology of BPNs. Furthermore, our in vitro data show that nanoclusters formed by spherical gold nanoparticles can be used for highly specific killing of cancer cells using just a single ns pulse of near-infrared light. We have specifically focused on biodegradable gold nanoparticles with plasmon resonances in the NIR region. However, our platform can be easily extended to other inorganic nanomaterials such as iron oxide nanoparticles. The nanoparticles degrade to easily clearable components in the body and, therefore, can provide a crucial missing link between the enormous potential of metal nanoparticles for cancer imaging and therapy and translation into clinical practice.

FRI 17

Synergistic Photothermal and Antibiotic Killing of Biofilm-associated *Staphylococcus aureus* using Targeted, Antibiotic-loaded Gold Nanoconstructs

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Background. Resistance to antibiotics is a growing public health concern that is quickly out-pacing antibiotic development. This has led the Infectious Diseases Society of America (IDSA) to designate *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species as "ESKAPE pathogens" based on the decreasing availability of useful antibiotics. Moreover, many forms of bacterial infection are characterized by formation of a biofilm, the presence of which confers a therapeutically-relevant degree of intrinsic resistance to antibiotic therapy and host defenses. This emphasizes the urgent need for alternative therapeutic strategies to combat infections caused by these and other bacterial pathogens, particularly in the context of an established biofilm.

Methods. We used *Staphylococcus aureus* as a proof-of-principle pathogen to demonstrate that daptomycin can be incorporated into polydopamine-coated gold nanocages (AuNC@PDA) tuned to absorb light at a wavelength in the near infrared (NIR) range. Daptomycin-loaded AuNC@PDA (AuNC@Dap/PDA) were conjugated to antibodies targeting a species-specific surface protein (staphylococcal protein A; Spa) as a means of achieving selective delivery directly to the bacterial cell surface. Experiments assessing bacterial cell killing were then carried out with and without laser irradiation using *S. aureus* cells grown in planktonic culture as well as a catheter-associated biofilm.

Results. Our results confirm that laser irradiation at levels within the current safety standard for humans can be used to achieve both a lethal photothermal effect and controlled release of daptomycin and that this results in a degree of therapeutic synergy capable of eradicating viable bacteria even in an established biofilm. This was confirmed in both a methicillin-sensitive and methicillin-resistant strain of *S. aureus*. Targeting specificity was confirmed by demonstrating that AuNC@Dap/PDA had a reduced capacity to bind *S. aureus* cells and that AuNC@Dap/PDA-aSpa did not bind mammalian cells. Additionally, these synergistic effects were not observed with the Spa-negative species *Staphylococcus epidermidis*. Further confirmation of specificity, and the need for bacterial cell binding and that these synergistic effects were blocked in the presence of free anti-Spa. We also confirmed that achieving the desired effect was dependent on the ratio of AuNC@Dap/PDA-aSpa per bacterial cell.

Conclusions. We confirmed that laser irradiation can be used to achieve synergistic photothermal killing and antibiotic release to an extent capable of eradicating viable bacteria even within an established biofilm. Although we used *S. aureus* as our proof-of-principle pathogen, the system we developed should have broad applicability to other bacterial pathogens including other ESKAPE pathogens.

FRI 18

Engineering Polymer-coated Gold Nanocages for Photothermally-controlled Release of Therapeutic Agents

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Drug delivery systems with targeted capability and on-demand controlled release mechanism are particularly appealing for designing optimal medications in many disease treatments. One of such systems consists of polymer-coated gold nanocages (AuNCs) that are capable of converting light into heat and triggering the release of the encapsulated therapeutics. The release kinetics is dependent on the noncovalent binding affinity of the polymer-drug complexes. In this presentation, two examples will be discussed involving the poly(ethylene glycol)- (PEG-) coated AuNCs and polydopamine- (PDA-) coated AuNCs. The former (PEG-coated AuNCs) was particular suited for the delivery of hydrophobic porphyrin-containing photosensitizers. The latter (PDA-coated AuNCs) was applicable to deliver a hydrophilic antibiotic daptomycin. In both cases, the photothermal effect of AuNC can initiate an instantaneous release, and thus control of the release kinetics, demonstrating on-demand drug release. The surface of these polymer-coated AuNCs can be readily functionalized with specific moieties for targeting biomarkers at the pathological sites. Further utilizing the optical properties of AuNCs, these systems can achieve theranostics through diagnosis *via* AuNC contrast-enhanced molecular imaging and multi-modal treatment via photodynamic-, photothermal-, and chemo-/antibiotic- therapies.

FRI 19

Hyperthermia -Induced Expandable Polymer Nanoparticles for Treating Breast Cancer

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Oftentimes, heat is used directly to disrupt or ablate diseased tissues, including malignant lesions. Here, we report on the development of a new type of composite nanoparticle composed of two distinctly different polymer fractions. Near infrared light was used to stimulate heat in an electrically conductive polymer with the heat being directly imparted onto a bioresorbable elastomer to induce expansion of the elastomer. Inflation of the nanoparticles can be used for both intracellular mechanical disruption and break the nanoparticle into smaller nanoparticles to aid in clearance after therapy. Nanoparticles were synthesized using polycyclopentadithiophene benzoselenadiazole (PCPDTBSe) as the heating polymer and 1,8 poly(octanediol) citrate (POC) as the expandable elastomer. The amount of PCPDTBSe was the same in each formulation, and the amount of POC adjusted accordingly to prepare ratios of the polymers at 20/80, 50/50, and 80/20, and compared to particles composed of PCPDTBSe or POC alone. Nanoparticles were characterized using infrared and visible spectroscopy and all formulations containing PCPDTBSe had a major absorption peak near 760 nm. The size of the PCPDTBSe 20% and POC 80% ratio nanoparticles was 84.4 nm. After one application of 800 nm light at 230 J/cm^2, the nanoparticle size reduced to 34.5 nm, and after two applications of laser stimulation, size was reduced to 15.3 nm. This ratio of polymers produced nanoparticles with the greatest expansion. The heat generated by all formulations was similar, since the same total amount of PCPDTBSe was utilized. Upon laser stimulation of the polymer nanoparticles in 200 ul of water, using 230 J/cm^2, a 50°C temperature increase was observed. The various formulations of nanoparticles were evaluated in MCF 10A, MCF 7, and MDA MB 231 breast cancer cell lines. All of the formulations were capable of inducing heat sufficient for reducing the cell viability to below 10% when stimulated with 230J/cm2. Preliminary results indicate that as laser fluence is reduced, that the 20/80 ratio of PCPDTBSe/ POC nanoparticle formulation is capable of inducing cell death without significant amount of heat being delivered to surrounding media. This indicates that the heat induced by the PCPDTBSe polymer is remaining locally adjacent to the POC polymer and most likely inducing cell death by mechanical disruption occurring within the cells.

FRI 20

Designing novel antibiotic-loaded, targeted nanoparticles to eradicate *Staphylococcus aureus* planktonic cultures and biofilms

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Background: Antibiotic resistance is a growing public health concern with acquired resistance developing faster than new antibiotics can be developed and approved. This problem emphasizes the urgent need for alternative therapeutic strategies to combat infections caused by these and other bacterial pathogens. In addition to acquired resistance to antibiotics, the formation of a biofilm represents a serious clinical issue complicating antimicrobial therapy, particularly in the case of implant-associated infections. Biofilm formation results in a degree of intrinsic resistance to antibiotics, such that it is often necessary to surgically remove infected tissue/hardware to completely eradicate infection, but even surgical removal is not always sufficient for complete eradication.

Methods: We used *Staphylococcus aureus* as a proof-of-principle "ESKAPE pathogen" to demonstrate that an appropriate antibiotic (daptomycin) can be incorporated into polydopamine-coated gold nanocages (AuNC@PDA) and that daptomycin-loaded AuNC@PDA can be conjugated to antibodies targeting a species-specific surface protein (staphylococcal protein A) as a means of achieving selective delivery of the nanoconstructs directly to the bacterial cell surface. These gold nanoparticles can be tuned to absorb light at a wavelength in the near infrared range and release this energy in the form of heat. Experiments were performed with nanoconstructs and bacterial cells in planktonic culture as well as an *in vitro* catheter model of biofilm formation to demonstrate that cultures could be eradicated following irradiation of our antibiotic-loaded, antibody-conjugated nanocages.

Results: We demonstrate that near infrared laser irradiation at levels within the current safety standard for use in humans can be used to achieve both a lethal photothermal effect and controlled release of the antibiotic, thus resulting in a degree of therapeutic synergy capable of eradicating viable bacteria. The system was initially validated using planktonic bacterial cultures and was subsequently shown to be effective in the context of an established biofilm. Furthermore, owing to the conjugation to a species-specific antibody, we have shown that this system can be used to specifically eliminate *S. aureus* cells with minimal off-target effects.

Conclusions: Our results suggest that gold-based nanoparticles can be used to design novel therapeutic strategies to overcome acquired and intrinsic resistance to conventional antibiotic therapy.

FRI 21

Effects of nanoparticles on the cell killing induced by different physical stressors

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Background and Aim: Recently, nanotechnology is becoming popular due to the wide application of nanoparticles not only in material science but also in medical science. X-irradiation (x-ray) and Ultrasound (US) have been shown to induce apoptosis in cancer cells. We have under taken this study on the potential use of Platinum nanoparticles (Pt-NPs) and Gold nanoparticles (Au-NPs), in combination with x-ray (10 Gy) and US (1 MHz, at an intensity of 0.4 W/cm^2, 10 % duty factor, 100 Hz PRF, for 2 min) to further clarify the molecular mechanism involved in cell killing. **Material and Methods:** Human Lymphoma U937 cells were used for this study. The apoptosis induction, as detected by DNA fragmentation assay and Annexin V-FITC/ PI double staining was shown to be mediated by the both mitochondrial and caspase-8 dependent pathways, observed by Flow cytometry and Spectrophototmetry. Cell killing was confirmed by cell counting and microscopic examination. Apoptotic and autophagy-related proteins were detected by western blot, respectively. Intracellular reactive oxygen species (ROS) generation was detected by flow cytometry, while extracellular free radical formation was assessed by electron paramagnetic resonance spin trapping spectrometry. **Results:** Taken together, in this study we have shown for the first time that in combination treatment, Pt-NPs or Au-NPs protects x-ray and US-induced apoptosis. The inhibition of US-induced apoptosis by Pt-NPs or Au-NPs resulted in the enhanced US cell killing, which is due to change of cell death mode from apoptosis into particular ir-repareable pyknotic and non-apoptotic cell death; however, the underlying mechanism for this switch remains unclear. **Conclusion:** These findings showed that nanoparticles exerted differential effects depending on their internalization. These results indicate the potential use of Pt-NPs or Au-NPs in combination treatment and would further clarify the role of Pt-NPs or Au-NPs in x-ray-aided therapies while the combination of Pt-NPs or Au-NPs with US might be effective in cancer eradication.

FRI 22

MRI T1-based marker for hyperthermia-induced release of doxorubicin and contrast agent from thermosensitive $DPPG_2$-liposomes

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Effectiveness of anti-cancer drugs can be improved by tumor-targeting. Using thermosensitive liposomes (TSL) such targeting is achieved by tumor specific hyperthermia (HT) and visualization by loading the TSL with MRI-contrast agents (CA). So far correlation of MRI markers with DOX based on paramagnetic Mn-DOX complex or loading of Gadolinium based CA and DOX in the same TSL was used. To allow higher loading of the TSL and to simplify new TSL-formulations a third approach using a mixture of TSL loaded either with DOX or CA is applied here for T1-based quantification of hyperthermia induced doxorubicin (DOX) release in tumor.

Methods: In vivo experiments were performed in 5 male Brown Norway rats with a syngenic soft tissue sarcoma (BN175) located on each hind leg. Tumor temperature was monitored using an intratumoral fiberoptic temperature probe. In group A one tumor was selectively heated above 40°C by a diode laser and a MRI-compatible fiberoptic device. The second tumor on the other leg remained unheated for reference purposes. After a minimum temperature of 40°C was achieved, a bolus of mixed TSL (DPPC/DSPC/$DPPG_2$) loaded with CA (Gd-DTPA-BMA) or DOX was injected intravenously and hyperthermia continued for 1h. Thereafter the tumor was allowed to cool down to the temperature determined before the start of HT. In group B the same experiment was performed but without HT.

Imaging was performed using a 3T MRI scanner. Before and after hyperthermia T1-mapping using variable flip angles was performed. Dynamic T1(t) was quantified throughout the experiment. T1-related parameters (absolute and relative differences before, during and after HT (ΔT1) or area under the curve (AUC)) were correlated with DOX concentrations in tumor tissue. DOX in tumor tissue was determined by HPLC after sacrificing the animal.

Results: A highly significant linear relationship of DOX and all investigated T1 parameters was found and used to calculate DOX in tumor tissue. The best match of DOX determined by HPLC and MRI was found using AUC T1(t) relative (correlation coefficient 0.811).

Conclusion: This was the first time that a mixture of TSL loaded with a clinically approved CA and TSL loaded with DOX has been investigated for *in vivo* chemodosimetry. The preliminary results show that visualization of the CA-release and possibly quantification of DOX in the treated tumor tissue is also feasible when using a mixture of CA- and DOX-TSL.

FRI 23

Heating Efficiency of Colloidal Magnetic Fluids with Nonlinear Loss Properties and Aggregate Formation

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Accurate evaluation of heating efficiency is particularly problematic in the clinical application of magnetic fluid hyperthermia, where injected magnetic nanoparticles that accumulate near the target tumor sites can generate local heating when exposed to an external alternating magnetic field. Previously proposed heating efficiency estimation models, such as the prevailing Rosensweig model, were derived assuming that: (i) magnetic nanoparticles are non-interacting in the colloidal suspension, and (ii) the magnetic susceptibility and the magnetic field amplitude are linearly related. As a result, the rough prediction of heating efficiency based upon those models is limited to small particle diameters under weak magnetic fields.

In magnetic resonance nanomedicine based on magnetic nanoparticle hyperthermia, both assumptions were found to be inaccurate for developing an accurate theoretical model to explain experimental results. In magnetic fluids as well as in vitro/in vivo applications, magnetic nanoparticles form aggregates, which experimentally affects the heating mechanisms and the magnitude of heat generated. Moreover, as the particle size and magnetic field amplitude increase, the heat generation mechanism becomes even more complicated since the linear regime only holds for the case of high temperature and/or weak magnetic field.

Therefore, in the interest of the clinical and pre-clinical applications of magnetic resonance hyperthermia, a new model was developed which includes the effect of aggregate formation and distribution, and the nonlinear relationship between magnetic susceptibility and magnetic field amplitude to accurately predict the heating efficiency and the specific loss power in the non-linear regime of a cluster-based magnetic fluid system. The complex susceptibility of the magnetic fluid is re-formulated to account for the cluster formation, while the relative cluster content is determined by the critical temperature. Calculations used our proposed theoretical model was then compared to previously published experimental data to assess the accuracy of this nonlinear cluster-based model. From the excellent agreement between the theory and experiments, it is concluded that our proposed new model is able to accurately predict the heating efficiency and the specific loss power as a function of mean magnetic nanoparticle size, even under strong magnetic fields. With the advances in magnetic resonance hyperthermia that intends to use high-performance NMR/MRI hardware for magnetic nanoparticle hyperthermia, this new model will become increasingly important, in order to understand the heating mechanisms and to optimize and control the heat efficiency of magnetic nanoparticle under strong magnetic field.

FRI 24

Radiofrequency ablation + ThermoDox: Increased heating duration enhances drug delivery

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Background: Radiofrequency ablation (RFA) is a clinically used cancer treatment utilizing localized heat delivered via an electrode placed in a tumor under image guidance. Recent studies suggest improved treatment efficacy when combining RFA with localized drug delivery by liposomal drug carriers that release doxorubicin (DOX) at hyperthermic temperatures, above ~40 ºC (ThermoDox). The purpose of this study was quantify the effect of heating duration on local drug accumulation in this combination therapy.

Methods: We used three dimensional computer models to simulate RFA for 5,12 and 30 minutes, to predict the amount of DOX in plasma, interstitium and cells considering temperature-dependent liposomal release from ThermoDox. In addition, porcine animal studies were performed, where ThermoDox (0.6 mg/kg) was infused over 30 min. Following drug infusion, a cooled needle RFA electrode (3 cm active length) was placed in a liver lobe under open surgery, and RFA was performed for either 5 or 12 minutes (n=4). The animal was euthanized 30 minutes after the final ablation, and the liver lobes were extracted and frozen. The liver samples were sliced orthogonal to the electrode direction, thawed, and DOX concentration profile around the electrode location was quantified via fluorescence imaging (520 nm excitation, 600 nm emission filter).

Results: In the computer model, the total amount of DOX deposited within the tumor tissue increased approximately linearly with total ablation time and was minimal for the 5 min and maximal for 30 min treatment (0.5 vs. 3 mg). Maximum DOX concentration after 12 min ablation was ~1.7x higher (computer model), and 2.7x higher (animal study) compared to 5 min ablation. In computer models, ablation for 30 min resulted in a further ~1.8x DOX concentration increase compared to 12 min ablation. In both mathematical models and in vivo studies, most DOX (80-95%) was delivered just outside the thermal ablation zone.

Conclusion: Extended ablation time resulted in enhanced drug delivery around the thermal ablation zone. This suggests a potential treatment benefit when extending the ablation time beyond standard duration (12 min) for this combination therapy.

FRI 25

HIFU treatment planning for hepatocellular carcinoma using respiratory motion tracking system and 3D Slicer navigation system

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Background/Introduction: HIFU is a non-invasive treatment for heaptocellular carcinoma (HCC). However, the present problem of HIFU for HCC is its long procedure time. The reasons for this is that the target lesions with respiratory movement are difficult to be detected clearly on the US monitor. In this study, we evaluated the usefulness of respiratory tracking system and 3D Slicer for the HIFU monitoring images of HCC.Methods: HIFU treatment were performed in 20 patients with HCC. The maximum diameter of the tumors measured on sonography ranged from 10 to 25 mm (mean, 20 mm; SD, 6.3 mm). The HIFU system (Mianyong Haifu Tech) was used under ultrasound guidance. By using the video images during the HIFU treatment, we evaluated the respiratory motion tracking system. Template matching method was applied to this respiratory motion tracking software. The open-source navigation software is connected together images using an open network communication protocol, OpenIGTLink. A Polaris Vicra optical tracker (Northern Digital, Ontario, Canada) was used. MRI and CT scans were performed, and 3D Slicer was customized to combine MRI and CT images for the navigation. Testing was performed using an abdominal phantom (CIRS Model057, Norfolk, VA).Results: 3D slicer could make the multiplanar reconstruction images of MRI and CT displayed in the same sections of US. The synchronous movements of the same sections of US, MRI and CT were shown in real time. Performance tests of phantom show that the registration error of the system was 1.8 ± 1.1 mm within the liver. In 15 cases of HCC, we evaluated the tracking system according to the tumor size, and the tracking of the tumor larger 16cm in diameter were successfully performed in all cases (n=10). On the other hand, the tracking of the tumor smaller than 15cm were performed successfully in 4 out of 5 cases. The reason for motion trackings were not performed well was thought to be that the tumor contour became unclear because the maximal cross section of the tumor go out of the plane by the respiratory movement. The tumor after HIFU treatment was also tracked well even after the presence of the hyperecho around the tumor. Conclusion The respiratory motion tracking using template matching method and 3D Slicer navigation system were successfully performed and have a possibility to shorten the HFU treatment time.

FRI 26

Computerized Training of Prostate Cryotherapy

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As a part of an ongoing effort to develop computation tools in the service of cryotherapy, the current study presents a proof-of-concept for a computerized tool for cryosurgery tutoring. The tutoring system lists geometrical constraints of cryoprobes placement, simulates cryoprobe insertion, displays a rendered shape of the prostate, enables distance measurements, simulates the corresponding thermal history, and evaluates the mismatch between the target region shape and a pre-selected planning isotherm. The quality of trainee planning is measured in comparison with a computer-generated planning, created for each case study by previously developed planning algorithms. Two versions of the tutoring system have been tested in the current study: (i) an unguided version, where the trainee can practice cases in unstructured sessions, and (ii) an intelligent tutoring system (ITS), which forces the trainee to follow specific steps, believed by the authors to potentially shorten the learning curve. In addition, two planning strategies have been examined, using (i) uniform and (ii) variable cryoprobes insertion depth. While the tutoring level in this study aims only at geometrical constraints on cryoprobe placement and the resulting thermal histories, it creates a unique opportunity to gain insight into the process outside of the operation room. Posttest results indicate that the ITS system maybe more beneficial than the non-ITS system, but the proof-of-concept is demonstrated with either system. System validation has been performed by collecting training data from surgical residents, having no prior experience or advanced knowledge of cryotherapy. In terms of match between a planning isotherm and the target region shape for the case of variable insertion depth, results demonstrate trainee performance improvement from 4.4% in a pretest to 44.4% in a posttest over a course of 50 minutes of training. In terms of combined performance, including geometrical match and constraints on cryoprobe placement, this study demonstrates trainee performance improvement from 2.2% in the pretest to 31.1% in the posttest. Given the relatively short training session and the lack of prior knowledge, these improvements are significant and encouraging.

FRI 27

Treatment Planning for Magnetic Nanoparticle-Based Hyperthermia

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Introduction: Superparamagnetic iron oxide nanoparticles (SPION) are used as MRI contrast agent. Coated and functionalized nanoparticles can specifically target cancer cells and thus be used to visualize secondary tumors and metastases. As SPIONs exposed to alternating magnetic fields deposit energy as a result of remagnetization losses (hysteresis) the targeting of functionalized nanoparticles can be used to apply localized hyperthermia therapy. When targeting is insufficient to produce the necessary particle density, particles can also be directly injected or be part of a cement formulation injected into brittle, tumor-affected bone. Treatment planning is required to determine the necessary SPION concentration, field strength, and expected outcome (safety and treatment success).

Methods: For that purpose an existing hyperthermia treatment planning platform (Sim4Life/HYCAT) has been extended. A magneto-quasistatic solver can be used to determine the local magnetic field generated by the applicator coils and the SAR distribution resulting from tissue conductivity losses. A physical model relating nano-particle density, frequency, temperature, SPION core and shell dimension, and magnetic properties of the nanoparticles to the specific loss power was derived. This analytical relationship which considers Neel and Brownian relaxation mechanisms can be used in combination with a particle density distribution to generate additional heat sources in the thermal modelling. The thermal modelling uses an extended Pennes Bioheat Equation (PBE) in combination with body-core heating, thermoregulation, and vascular impact models to determine the transient temperature and associated thermal dose distribution. Infrastructure is in place to load medical image data for the generation of patient specific anatomical models, co-visualize the images with the simulation model and results, but also to help extract the nanoparticle distribution.

Results: Simulations of a setup comprising a dog model inside applicator coils have been performed, featuring different generic nanoparticle distributions. Modelling has been used to investigate the impact of nanoparticle size, density, frequency, and magnetic field strength, resulting in the identification of optimal nanoparticle parameters. The current model does not consider the modified effective dielectric properties resulting from the presence of SPIONS and effects occurring in the case where multiple nanoparticles are in close proximity in clusters.

Conclusion: A treatment planning tool for magnetic nanoparticle (SPION)-based hyperthermia was implemented and used to model therapeutic application. Further experimental validation and the development of methodology to relate MRI data to quantitative particle density distributions are ongoing.

FRI 28

On-line hyperthermia treatment planning during locoregional heating to improve tumor temperatures and reduce hot spots

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Background: Adequate tumor temperatures during hyperthermia are essential for good clinical response, but excessive heating of normal tissue should be avoided. This makes locoregional heating using phased array systems technically challenging. On-line application of hyperthermia treatment planning (HTP) might yield an improved heating quality. The aim of this study was to investigate the possible clinical advantage of on-line use of HTP during treatment of pelvic tumors heated with the 70 MHz four waveguide AMC-4 locoregional hyperthermia system.

Methods: A graphical user interface was developed for on-line HTP. Electric fields were calculated in a pre-processing step using our in-house developed finite-difference based treatment planning system. This allows immediate calculation of the SAR or temperature distribution for user-selected phase-amplitude settings during treatment. The SAR and temperature distributions are projected onto the patient's CT scan for on-line visualization. The quality of heating can be visualized by the power absorbed in the target and a temperature volume histogram. The effect of this on-line use of HTP on hot spot reduction and tumor temperature was evaluated for locoregional hyperthermia patients. When tumor temperatures were inadequate or when complaints due to hot spots occurred, phase-amplitude settings were varied in the graphical user interface to obtain a better temperature distribution.

Results: The graphical user interface proved to be a user-friendly tool enabling on-line use of HTP, which is very helpful in improving heating quality. This allows reduction of hot spots and increasing tumor temperatures. One example is a cervical cancer patient with a hot spot near the sacrum. Based on HTP the phase of the dorsal antenna was changed from -67° to -47°, and the power ratio of the dorsal antenna was reduced from 1 to 0.75. This ratio change equally redistributes 25% of the power emitted by the dorsal antenna over the other three antennas. This reduced the hot spot temperature without affecting the measured tumor temperature(40.6°C). Another example is a patient with the deep-seated melanoma that was difficult to heat with standard phase-amplitude settings for pelvic tumors because of the eccentric location. HTP assisted in better focusing and the phase of the dorsal antenna was changed from 65° to 25°. This resulted in an increase in measured tumor temperature of 0.7°C.

Conclusion: On-line HTP is very useful to improve tumor temperatures and reduce hot spots. Implementation and analysis of automatic phase-amplitude optimization strategies to further improve the heating quality is subject of ongoing research.

FRI 29

Potential of a low cost optical E-field probe as validation tool of hyperthermia treatment planning

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Introduction

Implementation of hyperthermia treatment planning (HTP) as a standard step in the procedure of hyperthermia requires that the predicted energy distribution can be reliably and accurately transferred to the clinical environment. Analogue to radiotherapy this means that the mathematical model of the hyperthermia applicator integrated in the HTP must provide a reliable representation of the applicator. Hence, predicted energy distributions must be validated against real measured values. Most techniques to measure the energy distribution that an applicator induces in a phantom only provide relative distributions. Those systems that can provide absolute values are unfortunately very expensive.

Methods

An optical sensor was developed that measures the temporal E-field. Repeatability of the setup (probe & scanner) was tested by repeated measurement of the axial plane distribution of a Sigma-Eye applicator. Total field calibration was performed to obtain the respective contribution of each antenna to the amplitude and phase of the total E-field measured by the probe. Next, this calibration was used to retrieve amplitude and phase settings per antenna using the E-field measurements. Finally, using matching of measured and predicted E-fields at these 8 locations, using an earlier obtained “calibration” E-field distribution matrix, we could calculate corrected phase & amplitude settings in the antenna feed points for the set-up with the inward curved water bolus.

Results

Using the Gamma method, the repeated measurement in the Sigma-Eye applicator met the acceptance criteria at the 95% level for 1 mm / 4% (ΔE-field). The calculated amplitude and phase settings matched the applied settings within 6 W and 6° per channel on average, which is within the uncertainty of the amplifier settings. Using corrected feed point setting at each antenna a SAR distribution correction was obtained that is in close agreement with the one for a standard water bolus, i.e. the 25% iso-SAR contour coverage difference is below 5%.

Conclusion

This study shows the potential of E-field measurements to improve quality assurance in HTP.

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FRI 30

Effect of Different Tissue Segmentation schemes on Precise Treatment Planning of Laser Induced Thermal Therapy: A Retrospective Study

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Introduction: MR guided laser induced thermal therapy (LITT) is a safe and effective technique for heat mediated cancerous tissue destruction in brain. Precise modelling of the thermal ablation procedure is important for treatment planning and allows accurate risk assessment of the temperature fluctuations within critical structures. Precise knowledge of heterogeneous tissue boundaries (i.e. tissue segmentation) with distinct heat transfer properties is a limiting factor for accurate mathematical modelling of thermal ablation procedure using bioheat transfer equation.

Methods: The effect of using different MR imaging sequences for identifying thermally distinct tissues is studied with respect to the prediction accuracy of the Pennes bioheat transfer model. A Gaussian mixture model is applied to segment T1W (with and without contrast), T2W, FLAIR imaging. A Bayesian inverse problem scheme is utilized to estimate the most suitable tissue segmentation scheme by comparing the model predictions and MR thermometry data acquired during LITT in brain tumours.

Results: Results provide a comprehensive analysis of the effect of using different tissue segmentation schemes on performance of LITT mathematical simulation.

Conclusion: Results suggest that the proposed technique leads to realistic model predictions that achieve patient specific prediction accuracy and may be useful in therapy planning and inverse therapy planning.

FRI 31

Sensitivity of microwave ablation models to tissue biophysical properties: application to model-based treatment planning

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Purpose: Computational models of microwave ablation (MWA) are widely used during the design optimization of novel devices, and are under investigation for guiding delivery of treatments optimized for patient-specific anatomies. The impact of unknown patient-specific tissue biophysical properties on the accuracy of MWA models is unknown. The objective of our study was to assess the sensitivity of computational models of MWA to tissue biophysical properties.

Methods: The Morris method was employed to assess the global sensitivity of a coupled electromagnetic-thermal model, which was implemented with the finite element method (FEM). The FEM model incorporated temperature dependent tissue electrical and thermal properties. The variability of the model was studied using six different outputs to characterize the size and shape of the ablation zone, as well as impedance matching of the ablation antenna. Furthermore, sensitivity results were statistically analyzed and the absolute influence of each input parameter was quantified. A framework for systematically incorporating model uncertainties for treatment planning was suggested.

Results: A total of 1221 simulations, incorporating 111 randomly sampled starting points, were performed. Tissue dielectric parameters, specifically relative permittivity, effective conductivity and the threshold temperature at which they transitioned to lower values (i.e. signifying desiccation), were identified as the most influential parameters for the shape of the ablation zone and antenna impedance matching. Of the thermal parameters considered in this study, the nominal blood perfusion rate and the temperature interval across which the tissue changes phase were identified as most influential. The latent heat of tissue water vaporization and the volumetric heat capacity of the vaporized tissue were recognized as the least influential parameters. Based on the evaluation of absolute changes, the influence ratio between the most and the least important parameters (perfusion, volumetric heat capacity of vaporized tissue) was found to be approximately 40.23 for ablation area and 22.26 for deviation of ablation edge shape from sphere (permittivity versus latent heat of liver tissue vaporization).

Conclusions: Dielectric parameters, blood perfusion rate and the temperature interval across which the tissue changes phase were found to have the most significant impact on MWA model outputs. The latent heat of tissue water vaporization and the volumetric heat capacity of the vaporized tissue were recognized as the least influential parameters. Uncertainties in model outputs identified in this study can be incorporated to provide probabilistic maps of expected ablation outcome for patient-specific treatment planning.

FRI 32

Hyperthermia treatment planning: Impact of variation in manual tissue-segmentation on the simulated temperature distribution

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During regional deep hyperthermia treatment, the malignant tissues are heated to temperatures ranging between 40° and 43°C. For treatment planning 3D patient models are generated by manually segmenting normal and tumor tissues on CT images. The tissues are then assigned to dielectric and thermal tissue properties to calculate electric field and temperature distributions. The finite difference time-domain (FDTD) method is applied to calculate the temperature distribution in the patient. Since the manual segmentation is prone to observer variation, the aim of this study was to systematically investigate the influence of inter- and intra-observer segmentation variation on the temperature coverage of the target.

CT scans of six patients with cancers in the pelvic region acquired for radiotherapy treatment planning were used for the hyperthermia treatment planning. To study the effect of inter-observer variation, three observers (two medical physicists and one dosimetrist) manually segmented in the CT images of each patient the following organs: fat, muscle, bone and bladder. The gross tumor volumes (GTV) were contoured by three radiation oncology residents and used as hyperthermia target volume. For the intra-observer variation, one of the observers of each group contoured the structures of each patient three times with a time distance of one week between the segmentations. Since there is no histologic or clinical ground truth for the target segmentation, apart from each individual target contour of the three oncologists also the union of the three contours were regarded as a possible target structure. Each target structure was combined with each tissue segmentation for both inter- and intra-observer segmentations resulting into 144 temperature simulations. The spatial overlap between segmentation was assessed by the Dice similarity coefficient (DSC). Additionally, the minimal temperatures T10/T90 delivered to 10%/90% of the GTV, respectively were assessed for each combination.

The results of the segmentation similarity evaluation showed that the DSC of inter-observer variation of fat, muscle, bladder, bone and target was 0.68±0.12, 0.88±0.05, 0.73±0.14, 0.91±0.04 and 0.64±0.11, respectively. Similar results were found for the intra-observer variation. T90 and T10 were found to be on average (41.1±0.7)°C and (44.4±1.1)°C, respectively for inter-observer and (41.0±0.6)°C and (44.7±1.0)°C, respectively for intra-observer variations with statistically significant difference ($p>0.05$) in predicted target temperature.

Intra- and inter-observer variations in the definition of target structure, fat, muscle, bone, and bladder have a significant impact on the temperature coverage of the target. Studying the effect of segmentation variations in larger patient populations is currently ongoing.

FRI 33

Precise numerical analyses of microwave coagulation therapy

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In this study, to obtain a more accurate analysis of the temperature in microwave coagulation therapy (MCT) for hepatocellular carcinoma, the water content rations of liver tissue during the heating and the dependencies of the dielectric and thermal constants of the tissue on the water content ratios were investigated in microwave heating at 2.45 GHz.

In the MCT, the water content ratio [wt%] of the tissue around the heating antenna decreases along with heat-induced coagulation and evaporation. The decrease in the relative permittivity and conductivity of heated swine liver tissue is shown to depend on a reduction in the water content ratio. At boiling temperature (100 deg. C under atmospheric pressure), water contained in tissue evaporates by absorbing the evaporated latent heat (2,257 kJ/kg), and the temperature of the water does not rise until the evaporation is complete. This suggests that the reproduction of the biological tissue depending on water content ratios is necessary for high accuracy analyses of the electromagnetic field and the temperature around the antenna.

This study investigates the method of coupled analysis for electromagnetic field and temperature, employing tissue models of the dielectric and thermal constants which depend on the water content ratio. In these analyses, the dielectric and thermal constants of the biological tissues were expressed as functions of the water content ratio based on several measurements. First, the distribution of the specific absorption rate (SAR) in the liver was calculated by an electromagnetic field analysis employing the finite different time domain (FDTD) method. The resultant SARs were used as heating sources in the temperature calculation by the finite difference method. In the temperature analysis, based on the temperatures and absorbed heat quantities of the tissue, the water content ratios of the tissues were updated. These series of procedures were repeated until the total heating duration.

The results of the present study imply that more accurate analyses of the electromagnetic field and the temperature in heated tissue can be obtained by examine the effects of changes in the water content ratio of tissue. The findings of this study can also help to improve the safety of the MCT.

FRI 34

Designation of optimal frequency for multi-frequency phased array

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Introduction

Nowadays hyperthermia systems tend to operate at single frequencies. This is however not optimal as the focal spot needs to be variant according to the tumor size and position. In our work we are developing UWB system which allows for frequency selection in the range of 434-1000 MHz. In this paper we present a strategy to find the optimal frequency for a specific tumor. Here time reversal method is used to achieve focused heating in tumors. We study the impact of antenna numbers, tumor size and position on the optimum frequency of operation.

Methods

To find the optimum frequency, a 2D analysis is made in the center plane of an applicator including a circular phantom of radius 100 mm and immersed in water which contains a circular tumor with same tissue properties as the phantom. Considering 4-48 antennas, we have also changed the tumor center position from the surface to the center of the phantom, for 3 different tumor radiuses. Average power absorption ratio (aPA) in the tumor is used as a quality indicator to select the optimum frequency in each case. The analysis results are used to find the operational frequencies of realistic tumors in a head and neck phantom. One tumor of approximate radius 16 mm is located deeply in the head and the other with radius of 10 mm located near the surface of the neck. 16 and 10 number of antennas is considered to radiate into the tumors respectively.

Results

The obtained 2D analysis results of a circular phantom have been used to find the optimum frequency of two realistic tumors located in tongue and larynx of a head and neck phantom. Based on our 2D results, the optimal predicted frequency for the tumor in tongue is 400 MHz. For the second tumor in larynx 800 MHz has found as the optimum frequency.

Conclusion

Based on our 2D phantom analysis, for small superficial tumors, the lower frequencies are beneficial when the number of antennas is greater than 4 and less than 24.

The predicted optimum frequencies from 2D phantom analysis have found to be in agreement with 3D simulation results of realistic head and neck tumors in tongue and larynx.

FRI 35

Reirradiation and hyperthermia for locally recurrent breast cancer after salvage surgery, what to do?

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Reirradiation plus hyperthermia (RT-HT) is standard treatment for irresectable recurrent breast cancer in irradiated area. The complete response rate is up to 50% and the overall response rate 75-85%. Yet, patients are often referred after multiple lines of treatment with a huge tumour load, and longterm local control requires improvement with only 20-50%, depending on tumour size[1]. Early referral of patients may improve longterm results.

Locoregional recurrence after initial breast conservation or mastectomy is rare. Salvage surgery with or without irradiation is usually considered the treatment of choice but only sparse data exist concerning the subsequent locoregional control rates of this salvage treatment. In hyperthermia departments an increasing number of these patients are referred for adjuvant RT-HT after salvage surgery but there are no clear criteria for referral except belief in the merits of this treatment. In our experience, the subsequent 5 year local control rate of patients treated with RT-HT after salvage surgery for locoregional recurrent breatcancer is 70%[2,3]. Also in this cohort a proportion of patients received several lines of treatment for their recurrence(s) before being referred.

In a world of increasing multidisciplinary collaboration in the treatment of cancer it should be feasible to perform clinical studies to establish the optimal treatment of first, isolated locoregional breast cancer recurrence, despite its rarity. From a methodological point of view this would require an international multicenter trial with wide, pragmatic, 'real world' entry criteria. Theoretically a three arm trial: salvage surgery alone versus salvage surgery plus reirradiation versus salvage surgery plus reirradiation plus hyperthermia would be the optimal design. Second best would be to perform two studies: salvage surgery versus salvage surgery plus reirradiation + hyperthermia for non believers and salvage surgery + reirradiation versus salvage surgery + reirradiation plus hyperthermia for believers.

If we manage to conduct even one of these proposed studies we will as a side effect improve the visibility of hyperthermia in the greater breast cancer community, which may also reflect on earlier referral of patients with irresectable locoregional recurrence.

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FRI 36

CHEMO-RADIATION WITH RF-HYPERTHERMIA OF LOCALLY ADVANCED HEAD AND NECK CANCER

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Introduction: The outcomes following radiation alone or chemo-radiation do not yield more than 50 – 60 percent of control rates. Targeted therapies like Cetuximab and Nimutuzumab haven't really impacted outcomes. Hyperthermia, with a potential to enhances, the effect of radiation and chemotherapy may augment initial response, disease free survival and overall survival. Published randomised trials endorsing this assumption.

Materials & Methods;

The archived data was accessed for present analysis. All patients treated from2001 to 2012 were retrieved and only those who received chemo-radiation with hyperthermia were included for this study

Results:

This retrospective analysis looked at the achieved data since 2000. Total of 603 patients with head & neck cancer treated till 2012 were scanned. Only 195 of them underwent chemo-radiation with hyperthermia, of which 150 patients received either weekly Inj.Cisplatinum at a fixed dose of 50mgs or Inj. Paclitaxel at 60mgs. Nearly 82 % of the patients were staged III or IV.

98% of patients received a radical dose of 60 – 70 Gy while 90% of them received 4–7cyles of Chemotherapy. Hyperthermia was delivered every week for 30mins after pre-cooling. The initial response of 92.5% in stage III, 78.0% in stage IV & 54.7 in stage B was recorded. No significant toxicity due to hyperthermia was noted.

Discussion: The meta-analysis of chemo-radiation has consistently demonstrated improvements in survival of 4-8 percent. Hyperthermia with radiation also has shown similar improvements in outcomes. Hyperthermia with a potential to inhibit radiation induced injury and potential to enhance- perfusion, can improve survival. Excellent initial response attests to our assumption that addition of hyperthermia to chemo-radiation enhances response without increasing immediate toxicities.

FRI 37

Addition of External Thermal Therapy to Radiation Therapy Results in Modest Toxicities with the Promise of Increased Efficacy: A Single Institutional Experience

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Background: Hyperthermia is a well-known radiosenstitizer used to increase the effectiveness of radiation (RT). Advances in technology are allowing for increased availability of External Thermal Therapy (ETT) for superficial tumors, particularly those known to be hypoxic and/or recurrent. While ETT increases tumor response to RT, concern is prudent for radiation associated toxicity to surrounding normal tissues. The goal of this study is to report on the acute and chronic toxicities along with outcomes from our institutional experience.

Methods: Using data from March 2013 to December 2015, we retrospectively reviewed all patients who received ETT in our clinic and were concurrently treated with radiation of at least a BED(10) equivalent to 30 Gy in 10 fractions. Demographic variables acquired include gender, race, BMI, age at initial diagnosis of primary site disease, site of primary disease, histology, duration of treatment, RT dose, RT technique, ETT temperature, ETT duration, prior treatment and treatment following ETT/RT. Our primary focus was to evaluate the safety of ETT, specifically acute and late toxicities.

Results: Forty-one patients received ETT/RT to 44 treatment locations. The most common malignancies were breast cancer (32%), soft tissue sarcomas (32%), and skin cancers (16%). 34% of cases were primary lesions and 66% were recurrent disease. The median RT dose was 52Gy (24-70Gy); the median prescribed ETT treatment time was 60 minutes (45 – 60 minutes); and the prescribed ETT temperature was a max of 44 degrees Celsius, delivered utilizing the BSD-500. Median follow-up was 9.8 months. Of the 44 cases, acute grade 2 reactions included: moist desquamation in 10 (22.7%), pain in 1 (2%), and bleeding in 1 (2%). There were two (4.5%) acute grade 3 skin toxicities, one requiring treatment break and one leading to treatment discontinuation. One patient (2.2%), treated for a squamous cell carcinoma of the skin that developed over 15+ years, experienced late grade 3 soft-tissue fibrosis Median duration of local control was 10.2 months and 44.5% at 2 years despite the particularly aggressive/recurrent diseases treated. Progression-free survival was 6.6 months and 43% at 2 years.

Conclusion: Late toxicity was observed in one patient who had a chronic malignancy. Concurrent ETT/RT represents a generally well-tolerated combination with the potential to increase the oncologic efficacy of treatment.

FRI 38

Superficial radio-hyperthermia with 433MHz: the university of Athens experience.

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Introduction

Superficial hyperthermia has been used to treat a number of different types of localized cancer, including recurrent breast cancer, skin metastases, metastatic lymphnodes SCC. This procedure in combination with chemotherapy or radiotherapy, or with both, may help to improve the effectiveness of these treatments.

Patients and Method

Between July 2012 and September 2015, 75 patients undergone combined radiotherapy and hyperthermia (RT+HT) in the treatment of superficial carcinomas. Hyperthermia was performed with a 433MHz circular applicator with emitted power up to 80Watt for one hour 30 minutes after radiotherapy. The radiotherapy dose ranged from 30-50 Gy. In every session, temperatures were monitored with a multipoint sensor (thermocouple). T_{min} was 42.6^{o}C. Anatomical regions included 30 metastatic lymphnodes SCC (head and neck), 35 relapses from mastectomy, 6 cases melanoma and 4 cases of sarcoma. Patients were followed up every three months post combined RT+HT for one year.

Results

During follow up, complete response was achieved in 60% (head neck), 85% (thoracic wall), 80% (melanoma) and 75% (sarcoma) of patients with follow-up data. Grade 3 acute skin RTOG/EORTC toxicity was observed in 7-8% of patients.

Conclusion

Simultaneous hyperthermia combined with radiation is able to enhance response and local control rates. Follow-up is ongoing every three months.

FRI 39

A multicenter randomized clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer

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Cisplatin-based concomitant chemoradiation therapy (CRT) is generally administered in local advanced cervical cancer (CC). At the same time, hyperthermia (HT) has been shown to be effective for CC. However, there has hitherto been no randomized clinical trial comparing CRT+HT with CRT alone for patients with advanced CC. To evaluate the efficacy of HT for advanced CC, we investigated both the clinical response and survival of patients treated with concurrent CRT or CRT combined with HT (CRT+HT). The present study was conducted at five hospitals in Japan between September 2001 and September 2013. Patients with FIGO stage IIA-IVA CC undergoing definitive concurrent CRT using CDDP were eligible. After signing informed consent form approved by each center's institutional review board, patients were randomly assigned to one of the following two groups: the CRT group of 50 patients receiving CRT alone, and the CRT+HT group of 51 patients receiving five sessions of HT in addition to CRT. Primary endpoint was overall survival (OS). Secondary endpoints were disease-free survival (DFS), complete response (CR), and tolerability. OS and DFS were evaluated by Kaplan-Meier method and log-rank test. CR was analysed by Logistic-regression analysis. A total of 101 patients (median age, 64 years) were treated; patient characteristics, total dose of CDDP and radiotherapy were similar in both groups. Median follow-up for CRT group and CRT+HT group was 47.1 and 63.1 months, respectively. Although not statistically significant, both the 5-year OS and DFS in the CRT+HT group (77.8% and 70.9 %, respectively) were better than those in the CRT group (64.8% and 61%, respectively). CR was achieved in 77.6% in the CRT group versus 88% in the CRT+HT group. Logistic-regression analysis adjusting for age, stage, and histology indicated that the patients in the CRT+HT group were significantly more likely to achieve CR than those in the CRT group (OR, 3.993; 95%CI, 1.018-15.67; *P* = .047). CRT+HT, as delivered in this trial, was well tolerated and did not significantly add either acute or long-term toxicity over CRT alone. In conclusion, CRT+HT yielded significantly better treatment response than CRT alone for patients with locally advanced CC without adding acute or late toxicities.

FRI 40

Thermography- controlled wIRA-hyperthermia and re-irradiation of large- sized breast cancer recurrences

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Background Evaluation of the efficacy and possible side effects of a novel non-touching technique for superficial hyperthermia (HT) combined with re-irradiation (re-RT) to treat heavily pre-irradiated, large-sized breast cancer recurrences.

Methods Heating of tumor nodules and diffusely spreading cancer lesions was performed with water-filtered infrared-A irradiation (wIRA) under real-time thermographic temperature control. Records of 80 patients -involving 120 treatment fields- treated from 9/2009-10/2015 were retrospectively analysed. Hypofractionated RT consisted of 4 Gy once per week up to a median total dose of 20 Gy, and was stringently delivered within 1-4 min following wIRA-hyperthermia.

21 patients received re-re-irradiation and wIRA –HT using the same schedule.

Results Median follow-up was 9 months. Response rates: 71% CR, 23% PR, 4% NC and 2% PD. The maximum temperature of the skin overlying tumor nodules or lymphangiosis was 42.5-43.2°C. The minimum temperature was 41.5-42.2°C. Only grade 1 skin toxicities were observed.

Conclusions Application of thermographically controlled wIRA-HT combined with low dose re-irradiation provides good local control of heavily pretreated breast cancer recurrences. Despite substantially larger tumor extensions than reported in recent studies, the remission rates achieved are comparable to those obtained with other superficial HT-technologies. The novel technique guarantees for a sufficiently homogenous and most compliantly heat deposition up to a depth of 20 mm, adaptation to variable treatment fields by use of multi-applicator systems, and substantially reduces the time lags between HT and re-RT. The possibility of re-re-RT opens new therapeutic options for the future.

FRI 41

Scar tissue is more at risk of developing thermal skin damage in recurrent breast cancer patients treated with reirradiation and hyperthermia.

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Thermal skin damage (TSD) is reported to occur in 25-45% of patients treated with superficial hyperthermia, TSD can result in long-term toxicity. Current time-temperature dependent threshold values used in the clinic are based on research data of healthy human skin. Recurrent breast cancer patients however have had previous irradiation and/ or surgery. Radiation-induced fibrosis and scar tissue are less perfused than healthy skin and might be more at risk of developing TSD.

In this retrospective study temperature characteristics of hyperthermia treatment sessions were analysed in 263 recurrent breast cancer patients treated with reirradiation 8 x 4 Gy and 4 weekly hyperthermia sessions in the period of 2010-2014. Sixty-nine of these patients (26.2%) developed TSD after 80 sessions of hyperthermia, in total they received 341 hyperthermia treatment sessions. Temperature was measured using 42 (range 29-82) measurement points on the skin during every hyperthermia treatment session. Temperature characteristics of scar tissue and other skin tissue were compared. Also temperature characteristics of the same sites prior to development of TSD were compared. The probability of TSD was calculated for the achieved maximum temperature (T_{max}) and the cumulative equivalent minutes at 43°C (CEM43°C) of a measurement point during a hyperthermia session.

The sessions where TSD did not occur consisted of 10520 temperature measurements; 1970 (18.7%) on scar tissue, 8550 (81.3%) on other skin tissue. The 80 sessions prior to development of TSD resulted in 102 measurement points located at the site of TSD; 44 (43.1%) on scar tissue, 58 (56.9%) on other skin tissue. Scar tissue has a time-temperature dosage similar to that of other skin tissue, but with a slight shift (0.4°C) to higher temperatures; T_{max} 41.8±1.2°C versus 41.4±1.3°C ($p<0.001$). Much higher temperatures are present at TSD sites prior to development of TSD; T_{max} 44.4±0.8°C ($p<0.001$), with no difference between tissue types. The probability of TSD increases exponentially with the T_{max} and linearly with the CEM43°C. TSD development in recurrent breast cancer patients behaves time-temperature dependent in the 43-47.5°C range and starts occurring at 19 CEM43°C. The absolute temperature threshold for developing TSD appears to be 47.5°C.

Thermal skin damage occurs at similar maximum temperatures and CEM43°C thresholds in scar and other skin tissue in recurrent breast cancer patients treated with reirradiation and hyperthermia. However, during hyperthermia, scar tissue achieves a higher temperature than other skin tissue, thereby increasing the risk of developing thermal skin damage in scar tissue compared to other skin.

FRI 42

Enhanced efficacy of radiotherapy by voluntary exercise is dependent on a thermoneutral environment

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An anti-tumor effect of voluntary exercise has been established using multiple tumor models/exercise prescriptions. Our lab has previously demonstrated that voluntary wheel running reduces hypoxia in murine tumor transplants. Because radiation efficacy increases with improved oxygenation, we hypothesized that mice provided with voluntary running wheels would show greater tumor growth delay following radiotherapy compared to sedentary controls. Our initial study, conducted at the standard room temperature of 22C, confirmed previous studies showing that exercise alone slowed mammary tumor growth and improved tumor oxygenation. Bioluminescence analysis revealed that exercise disrupted the relationship between lung metastatic burden and primary tumor volume. However, surprisingly, tumor growth following radiation was similar between sedentary and exercising mice. To eliminate complications due to chronic mild cold stress which mice are known to experience when housed under standard room termperature, the experiment was repeated using mice housed at a thermoneutral temperature (30C), a condition which eliminates cold stress and enhances anti-tumor immunity. Under this condition, we now observed enhanced tumor control by radiotherapy and exercise compared to mice in a single treatment group. Our working hypothesis is that an ambient environment of 22C induced a mild chronic cold stress which compromised the anti-tumor immune response. We will address this hypothesis by immunohistological analysis of tumor tissue. Studies on the kinetics of metastasis growth under in sedentary vs. exercised mice, +/- radiation are also underway. This is the first study to examine the effects of radiotherapy when combined with voluntary exercise. The observation that exercise improves radiation-mediated growth delay only under thermoneutral conditions stresses the importance of considering ambient temperature when attempting to translate mouse work to clinical trials.

FRI 43

A method to determine the increase in blood perfusion in human dermis during infrared hyperthermia

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The local hyperthermia of superficial human tissues based on infrared irradiation of the body surface in the so-called therapeutic window can be used as a preliminary thermal treatment leading to an increase in the arterial blood perfusion. The latter is important to improve the results of subsequent tumour radiotherapy.

A computational model of heat transfer taking into account, not only the volumetric heat generation due to absorbed radiation and transient heat conduction, but also the blood perfusion in human dermis is developed. This model is a generalized version of the approach used by the authors to analyze the temperature field in human tissues under the action of water-filtered infrared-A radiation (wIRA).

A recently suggested method to retrieve the thermal properties of tissues is adapted to the problem under consideration. This method is based on the measurements of a period of quasi-steady oscillations of the body surface temperature generated in response to recurrent radiative heating based on the maximum and minimum temperature of the irradiated surface.

The effect of convective heat transfer from the body to ambient air on the period of temperature oscillations is not negligible and there will be variation in natural convection and perspiration intensity for individual patients and room conditions. Therefore, a series of calculations is used to obtain the intensity of forced convection at the body surface when the effect of blood perfusion on the period of temperature oscillations is sufficiently strong so that uncertainty in heat transfer conditions does not lead to significant errors in the retrieved value for blood perfusion.

The measurements of the body surface temperature are simple and the computational procedure is not time-consuming. Therefore, the method can be recommended for the validation of wIRA in clinical conditions.

FRI 44

Photothermal Ablation of *Streptococcus pyogenes* and *Staphylococcus aureus* using Fluorescent Bio-Polymer Nanoparticles

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The overuse of conventional antibiotics is at a concerning level in the United States. Each year, two million people become infected with antibiotic resistant bacterial strains and 23,000 die as a direct result. In cases of invasive infections caused by bacteria like *Streptococcus pyogenes* (*S. pyogenes*) and *Staphylococcus aureus* (*S. aureus*), the effectiveness of antibiotic treatment is critical to limit and destroy bacterial virulence. Given the current limitations of antibiotic potency, alternative treatments to mediate pathogenic virulence are necessary. One minimally invasive approach that has gained attention over the years is photothermal ablation. Photothermal ablation (PTA) is the process in which a material absorbs light and in turn generates localized heat sufficient for thermal ablation of adjacent cells. In this comparative study, our group looked at the effects of PTA on gram positive *S. pyogenes* and *S. aureus* bacteria using hybrid nanoparticles. Our nanoparticles are comprised of two polymers: Poly(3-hexylthiophene-2,5-diyl) (P3HT), used for its fluorescence abilities, and Poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b']dithiophene-2,6-diyl-alt−2,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) for heat generation. When synthesized together using Pluronic F-127, the biopolymer P3HT/PCPDTBSe has dual components for remarkable fluorescence and significant heat generation in the NIR window. In order to increase specificity of NP attachment and efficacy of PTA, P3HT/PCPDTBSe NP's were coated with polymeric β-1, 4-*N*-acetylglucosamine (chitosan), a biopolymer well known for its antibacterial activity and positive surface charge density. Chitosan coated P3HT/PCPDTBSe NP's were incubated with planktonic *S. pyogenes* and *S. aureus* for one hour after which samples were exposed to infrared light (5W, 800 nm, 1 minute). To assess PTA efficacy, viable bacteria (colony forming units) were counted after 24 hr incubation period. Our results showed that chitosan coated P3HT/PCPDTBSe NP's had significant killing in both *S. aureus* and *S. pyogenes* cultures. As a result, our study shows that hybrid nanoparticles with dual fluorescence and heat generation coated with chitosan is capable of eradicating *S. pyogenes* and *S. aureus.*

FRI 45

TRANSIENT (THERMAL) BIOLOGICAL DOSE-EQUIVALENT (TBDE) – APPROACHING SYNERGISM AND TIMING OF HYPERTHERMIA-RADIOTHERAPY (HT-RT)

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Introduction: To compare combined HT-RT treatments, different dose concepts have been developed, ranging from a temperature - dependent beta-term in the linear-quadratic law to dose quantities based on more sophisticated bio-physical models. However, a comprehensive framework covering the underlying dynamics of tumor response is still missing, especially for varying conditions of timing, fractionation and dose rates. We propose therefore a dynamic approach by using a transient dose-equivalent.

Materials and Methods: A transient biological dose-equivalent must be predictive regarding clinical outcome and therefore candidate quantities should fulfil the following requirements: (1) quantifying a relevant, measurable biological effect based on therapeutic input (e.g. temperature, absorbed radiation dose), (2) covering relevant transiency (rise according damage production rate, decay according repair rate). The second requirement can only be validated by performing experiments with varying dynamic conditions (e.g. varying dose rate or spacing of heating and RT fractions) and by acquiring time-resolved data. For experiments in vitro, cell survival, COMET assay data or induction of gH2AX-foci may serve as quantifiable biological effect, possibly including aspects of thermo-tolerance acquisition by cells. The feasibility for applying a transient dose concept was demonstrated for RT by the analysis of survival data in vitro and COMET data in-vivo from biopsy material of treated animals. For the model-based data analysis, the remaining DNA fragments in the COMET-tail have been estimated by the radiation-induced degradation of repair proteins. In principle, the same idea may serve for calculation of the heat-induced reduction of the cellular repair capacity. In this in silico - study, an Arrhenius-based approach for calculating a TBDE is used. We investigated first-order kinetics – based TBDE especially for temperatures between 42- 45°C, where the activation energy jumps.

Results: Kinetic calculations of the TBDE exhibit saturation when approaching 43°C. The saturation becomes more pronounced when adapting activation energy and pre-exponential factor of the Arrhenius law. Higher temperatures will not lead to higher TBDE due to this saturation effect.

Discussion and Conclusions: The thermal effects above 43°C as suggested by CEM43 are not covered by a TBDE based on a single biological effect. The effects above 43°C may be explained by changed speed of protein repair due to e.g. a second-step modification of proteins or an additive cell killing process in addition to the synergistic effect of heat and radiation. The findings suggest that a TBDE related to a single biological process can only be applied in a narrow temperature range.

FRI 46

Multiple Simultaneous Cell Death Predictions Provide A More Realistic Picture of Likely Ablation / Hyperthermia Effective Treatment Zones

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Introduction: For many years hyperthermic treatment effectiveness has been described by a single measure, CEM_{43}. Cellular response to elevated temperatures varies widely depending on the particular assay used and the cell type under study, as identified in the literature. For example, AT1 (rat prostate), PC3 (human prostate) and SN12 (renal CA) cells have extremely different thermal sensitivities when measured with the same assay, in this case Propidium Iodide (PI) uptake indicating severely compromised plasma membranes. These variations have been studied in numerical models to illustrate the wide-ranging response to thermal stress.

Methods: Finite element method (FEM) models of those cell types under magnetic nanoparticle heating were compared to *in vivo* experiment results in short term heating trials (less than 20 minutes). Further numerical studies were conducted over much longer heating times at hyperthermic temperatures (43 to 50 °C) to illustrate the relative kinetic differences. Cell death predictions for the PI assay follow Arrhenius kinetics for the AT1 and SN12 cells, while the PC3 cells require an additional temperature-dependent time delay to accurately match the cell survival curves, as do the classical CHO cell loss of clonogenicity curves from which the CEM_{43} method was derived. The appropriate time-delay for these processes has recently been determined.[1]

Results: Substantial differences among the cell death predictions were observed. In general the AT1 cells are the most thermally sensitive and PC3 cells the least. The AT1 cell response most closely paralleled the histologic results (collected within 5 minutes of the cessation of heating) in the mouse mammary CA tumor used in the experiments. Predicted cell death varied substantially in models of the experiments, from complete necrosis for the AT1 cells to very little response by the PC3 cells. The distribution in rates of cell death is reflected in the process activation energies: low energy processes are slow compared to high energy processes. Long-term activations sometimes invert the overall cell death expectation.

Conclusion: Realistic predictions and/or assessments of localized thermal treatment effective boundaries require the inclusion of multiple cell death processes to establish the probable limits of uncertainty in the heating protocol.

[1] Pearce, J.A. “Improving Accuracy in Arrhenius Models of Cell Death: Adding a Temperature-dependent Time Delay”, *Journal of Biomechanical Engineering*, v137, n6, pp. 121006, 2015.

FRI 47

Microwave Interstitial Helix Applicators for Hyperthermia Cancer Treatment

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In this paper we would like to present some of our results in the area of microwave interstitial helix applicators for hyperthermia cancer treatment. We studied the possibilities to create arrays of interstitial applicators as well. The applicators used in this work are the helix type and the operating frequency was 2.45GHz. For our studies based on numerical simulations two types of breast phantoms were used. The interstitial applicators, virtually organized in several configurations, were gradually inserted into these phantoms. The first model of breast was simply created by spherical segment. It was formed by three parts: a homogeneous breast tissue, skin and a spherical tumour. The second breast phantom was derived from magnetic resonance images (MRIs) and includes more parts which are anatomically realistic. The phantom includes a bit more complex shape of the tumour. For calculation of SAR characteristics created by these applicators a simulator of EM field SEMCAD X was used. A distribution of SAR value was especially monitored in the area where the breast tumour was placed. So we could compare the differences between the simplified breast model and the MRI-derived model. As an example of our results we would like to describe numerical simulation of our applicators placed in heterogeneous phantom. This configuration is with four applicators in 10mm distance between each other.

FRI 48

A Patient Derived Logistic Model of Thermal Dose

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Introduction: Accurate thermal dose modelling using magnetic resonance temperature imaging (MRTI) is integral for monitoring thermal ablation procedures, particularly in sensitive areas such as the brain and spine. Several thermal dose models approximate the onset of thermal damage (Ω) as an Arrhenius process. These models rely on threshold doses that have been derived using a variety of biological endpoints to make a binary distinction between viable and nonviable tissue. In this work, we aim to compare thermal dose from several Arrhenius models with changes observed on post-treatment contrast enhanced imaging that are commonly used as a surrogate for tissue viability.

Methods and Materials: MRTI-derived thermal doses and signal changes observed on post-treatment T1-weighted images were evaluated for 2,100 independent pixels extracted from 2 MR guided laser interstitial therapy procedures in human brain. Registration between the datasets was verified using the position of the laser fiber as a landmark. The non-enhancing center of the legion and characteristic enhancing ring were segmented manually on post-treatment imaging and resampled into the geometry of the MRTI acquisition. The regions immediately inside and outside the enhancing ring were determined to be nonviable and viable tissue, respectively. Using these classifications, a logistic analysis was performed using the thermal dose values from 4 Arrhenius models (Henriques (H), Weaver & Stoll (WS), Diller & Klutke (DK), and Brown (B)) as independent variables.

Results: The Henriques model provides the best fit as measured by the deviance of the logistic model. The commonly accepted Arrhenius threshold (Ω=1) corresponds to a 54% (H), 70% (WS), 61% (DK), and 36% (B) probability of tissue nonviability. Higher dose thresholds of 1.4 (H), 2.8 (WS), 1.8 (DK), and 4.6 (B) are required to achieve 90% chance of tissue nonviability. However, this increase in threshold has a negligible impact on the area of the nonviable region as the Dice Similarity Coefficient between the nonviable areas at these thresholds are 0.99 (H), 0.97 (WS), 0.98 (DK) and 0.95 (B).

Conclusion: We have compared 4 Arrhenius models of thermal dose to cell viability estimates derived from post-treatment contrast enhanced imaging using a logistic analysis. This technique allows a direct comparison of Arrhenius models to surrogate endpoints of tissue viability using retrospective clinical data.

FRI 49

Combination of Alternating Magnetic Field Hyperthermia and Low Temperature Sensitive Liposome for Synergistic Bacterial Killing

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Background: Deep seated bacteria infested bone infection requires long duration antibiotic therapy, and is associated with significant morbidity and costly complications. There is a critical clinical need to achieve efficient and readily-translatable targeted and localized antimicrobial delivery, enhance antimicrobial sensitivity to prevent drug resistance, and minimize the frequency and dose of treatment to improve patient compliance. Objectives of this study were to 1) investigate the combination of low temperature-sensitive liposomes (LTSLs) and alternating magnetic field (AMF) induced heating (~40-42°C) of superparamagnetic iron-oxide nanoparticle (SPION) on drug release and bacterial viability, and 2) determine the impact of AMF based hyperthermia on bacterial sensitivity to antimicrobial treatment.

Methods: LTSLs were loaded actively with a broad spectrum antimicrobial (ciprofloxacin) and were characterized for their size and their drug release by dynamic light scattering (DLS), and fluorescence spectroscopy. Hyperthermia (15min, 40-42°C) was generated using an AMF (~110Oe at 1.1MHz) and 3ml SPION (9~10nm core and 120nm average hydrodynamic diameter, 0.8mg/mL) containing a vial of model bacterial pathogen (1.5 x 108 colony forming unit (CFU)/mL of Salmonella typhimurium) and ciprofloxacin or LTSL (5μM). The ability of AMF and LTSL to induce Salmonella killing was determined by comparing the differences in mean CFU in various treatment groups.

Results: Results indicated that <5% ciprofloxacin was released from the LTSL at 37°C, while >95% was released at 42°C in physiological buffer. AMF-SPION mild hyperthermia triggered release of ciprofloxacin from LTSL at 42°C, and achieved ~7 log reduction in bacterial CFU compared to AMF alone. Additionally, hyperthermia (42°C) sensitization of S. typhimurium by AMF alone or in combination with ciprofloxacin improved bacterial killing (~1.2 log and 7 log reductions respectively) as compared to AMF (37°C) alone or in presence of ciprofloxacin.

Conclusion: Our initial data suggest that LTSL & AMF combination can improve antimicrobial sensitivity and achieve targeted antimicrobial release from LTSLs locally to enhance bacterial killing. Studies are currently underway to understand these mechanisms in a biofilm model with LTSL co-encapsulated ciprofloxacin and SPION.

FRI 50

Modular hyperthermia applicator with closed-loop control and integrated treatment planning tool: First clinical results on animal patients

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Hyperthermia in conjunction with conventional anticancer therapies (radiation-/chemo-therapy) has been reported to enhance treatment efficacy in cancers. Planning and administration of an adequate hyperthermia treatment is also beset with several technical difficulties, including a dearth of suitable planning tools, the complexity of treatment steering, and poorly controlled treatment application. We here present the first clinical results from the use of an improved hyperthermia system that integrates modular applicators – with closed-loop control useable in coherent and incoherent operation, a patient-specific treatment planning tool, and thermometry-based validation – on feline and canine patients.

Improvement of the hyperthermia treatment is achieved on several fronts. The closed-loop control provided by the applicators ensures treatment with the intended excitation signals. The placement of individual applicators can be optimized independently, with confirmation of their positions during treatment by means of integrated 3-axis accelerometers and, when multiple elements are used, with 3D-printed masks for fixed relative positioning. The electromagnetic and thermal simulation platform uses 'recipes' for the automatic assignment of simulation parameters, which leads to a flexible, efficient, and less error-prone planning. Thermoregulated perfusion is considered in the transient thermal simulations, leading to improved realism, as experimentally confirmed. Experimental data was also used to establish the modelling parameters of the water bolus, the water-temperature remaining one of the treatment optimization criteria. Validation of the temperature prediction provided by the treatment plan is achieved by CT-guided implantation of RFID-readable temperature sensors (1–3 per patient, depending on tumour size).

The new, integrated approach was applied as an adjuvant to radiotherapy for the treatment of sarcomas and malignant melanomas in cat and dog patients. The initial responses from the first six cases are encouraging beyond expectations. The achieved intra-tumour temperatures correlate well with the predictions from treatment planning. However, temperature readout currently requires that the applicator(s) be moved due to the limited range of the reader. While the impact on therapeutic temperatures can be minimized by rapid measurement, the frequency of measurement and the number of implanted sensors remains limited. To consider the anatomical change due to tumour-shrinkage observed between hyperthermia administration sessions, an image-based morphing tool is being developed to adapt the treatment plan and sensor locations.

The presented hyperthermia system provides a patient-specific, flexible, and yet semi-automated treatment planning pipeline, with improved treatment administration quality through closed-loop and positioning control. The validation tools confirm good correlation between the planned and applied treatments.

FRI 51

Ultrasound monitoring of tumor temperature and drug delivery with echogenic thermosensitive liposomes

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Background/objective: There is a critical clinical need to develop an alternative, less-constrained, contrast enhanced vascular imaging technology, such as ultrasound (US) that can reliably and accurately provide time-resolved absolute tumor temperature, while simultaneously reporting on drug delivery. Objectives of this study were to: 1) measure motion compensated temperature-induced state changes in acoustic impedance and Laplace pressure of echogenic low temperature sensitive liposome (E-LTSL), and 2) determine whether intravascular variation of E-LTSL contrast can be utilized for monitoring of doxorubicin delivery to tumors.

Method: LTSLs containing doxorubicin were co-loaded with an US contrast agent (Perfluoropentane, PFP) using a 1-step sonoporation method to create E-LTSL. To determine intensity variation with respect to the state change of E-LTSL in mouse tumor, acquisition of 12frames/second for about 20 min (or till wash out) at temperatures of 42°C, 39.5°C and 37°C was performed by securing mice (n=6) in a device that allowed only the leg with tumor to be submerged in water bath. To evaluate the correlation between US intensity variation, and doxorubicin release at various temperatures, treatment (5 mg doxorubicin/kg) was administered via tail vein once tumors reached a size of 300-400mm3, cine acquisition frames were acquired for 37° and 42°C, and mean intensity within regions of interest defined for each sample was computed over the collected frames and normalized in the range of [0,1]. A rigid rotation and translation was applied to each of the “key frames” to adjust for any gross motion that arose due to motion of the animal or the transducer. Doxorubicin concentrations of the harvested tumor at various temperatures were determined by HPLC.

Results: E-LTSLs demonstrated a 6-fold increase in within-ROI signal intensity after injection (once the liposomes reached a steady-state temperature greater than their transition temperature) *vs*. background (pre-injection). When motion-compensation technique was applied, a >2-fold drop in standard deviation in mean image intensity was observed, enabling a more robust estimation of temporal variations due to state change of E-LTSL. Consequently, a marked increase in peak intensity at 42°C compared to 37°C that corresponded with enhanced Dox delivery in tumors was obtained.

Conclusion: Our in vivo data suggest that co-encapsulation PFP in LTSLs can achieve a predictable change in tumor vascular contrast with temperature, and this could property could be applicable to nanomonitoring of drug delivery in real-time.

FRI 52

Low-dose Short-time Ultrasound Hyperthermia can Significantly Improve Liposomal Doxorubicin Delivery and Antitumor Efficacy for Brain Metastasis of Breast Cancer

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Background: The clinical application of chemotherapeutic agents for brain tumors remains a challenge due to inhibition of drug delivery caused by blood-brain barrier/blood-tumor barrier (BBB/BTB). Hyperthermia is able to enhance the delivery of chemotherapeutic agent into tumors.

Methods: In this study, we investigated the effects of low-dose short-time focused ultrasound hyperthermia (UH) on the delivery and therapeutic efficacy of pegylated liposomal doxorubicin (PLD) for brain metastasis of breast cancer. Murine breast cancer cells (4T1-luc2) expressing firefly luciferase were implanted into female BALB/c mouse striatum area and it was used as a brain tumor model. The mice were intravenously injected with PLD and then with/without 10 min transcranial pulsed-wave/continuous-wave UH (pUH/cUH) treatment on day 6 after tumor implantation. pUH (Frequency: 500 kHz, PRF: 1000 Hz, duty cycle: 50%) was conducted under the same acoustic power (2.2 Watt) and sonication duration as cUH. The amounts of doxorubicin accumulated in the normal brain and tumor tissues were measured with fluorometry. The tumor growth responses for the control, pUH, PLD, PLD+cUH, and PLD+pUH groups were evaluated with an IVIS spectrum system every other day starting from day 5. The PLD distribution and cell apoptosis were assessed with immunofluorescence staining.

Results: The Immunofluorescent examination and *in vivo* therapeutic results showed that pUH was better to enhance the PLD delivery into brain tumors than cUH and the brain tumor growth was further inhibited by a single treatment of PLD+pUH.

Conclusion: This study indicates that low-dose transcranial pUH is a promising modality to better enhance nanodrug delivery and improve the brain tumor treatment.

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FRI 53

Health Related Quality of Life (HRQoL) Outcomes in Active Surveillance (AS) and Primary Focal Cryotherapy (PFC) Men with Low-Grade Prostate Cancer (PCa)

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Background: The goals of PFC are to ablate localized cancer while leaving healthy tissue intact to maintain patients' HRQoL. PFC candidates may also be eligible for AS. To date, no studies have compared HRQoL between these men. Our institution has been following men over time who underwent PFC, as well as men on AS. Our objective is to measure differences in HRQoL and lower urinary tract symptoms over time in a single institution using validated questionnaires. Methods: Winthrop University Hospital maintains a database of 238 PCa patients, of which 80 are on AS and 35 received PFC between February 2002 and July 2015. HRQoL questionnaires were distributed via mail and anonymously completed every three months for one year. We used mixed effect models with a random intercept and random time for repeated measurements on the same patients. Baseline (BL) characteristics among the two groups are compared using two sample t-test, Wilcoxon rank sum test, and Fisher's exact test. Results: 47 AS and 25 PFC patients completed Expanded Prostate Cancer Index Composite (EPIC), International Index of Erectile Function (IIEF), and International Prostate Symptom Score (IPSS) surveys. Between AS and PFC men, there was no significant difference in mean age (66.4 ± 7.9 and 67.8 ± 7, respectively), use of PDE5 inhibitors (36% and 32%), Gleason score (6.15 and 6.63), number of positive cores (2.15 and 2.27), or percent of tumor involvement (24.4% and 38.2%). ANOVA revealed no significant difference in mean BL IIEF sexual desire scores, IPSS scores or EPIC sexual, bowel, and urinary scores. AS men's BL IIEF orgasmic function, intercourse, and overall satisfaction scores were significantly greater than that of PFC. PFC men initially reported lower sexual, erectile, intercourse, and overall satisfaction scores than that of AS. However, there was a marked improvement in each of these domains to greater than or equal to that of AS throughout the course of the study. Conclusion: PFC significantly decreases orgasmic, intercourse, and overall satisfaction scores. However, PFC patients reported increased sexual, erectile function, sexual summary, intercourse and overall satisfaction to scores greater than or equal to that of AS over time. PFC patients can expect to regain HRQoL over the course of their follow-up.

FRI 54

Is Salvage Focal Cryotherapy Curative Treatment for Patients with Localized Recurrent Prostate Cancer?

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Introduction and Objective: The salvage therapy options for patients with recurrent unilateral prostate cancer after primary radiation, or cryotherapy are limited. Salvage focal cryotherapy is becoming a more popular treatment option as it has shown success in its disease free survival rates. Salvage focal cryotherapy enables patients to delay or negate the use of hormone therapy which has many unfavorable adverse effects. The aim of this study is to report on the curative success of salvage focal cryotherapy in recurrent unilateral prostate cancer patients.

Methods: We identified patients that underwent salvage focal cryotherapy at Winthrop University Hospital between February 2011 and August 2015. Age at the time of treatment, follow up time, nadir PSA levels and follow up treatments were assessed.

Results: From 2011 to 2015, 88 patients underwent salvage focal cryoablation. Of these patients, 14 (15.9%) required another therapy treatment after salvage focal cryoablation. Hormone therapy was a necessary treatment for 9 patients. Only 6 patients (6.8%) went on to hormone therapy due to an MRI finding of a local, nodal, or distant relapses. Three (3.4%) patients went on to hormone therapy due to a rise in PSA.

Conclusion: Focal salvage therapy is associated with very low risk of clinical and radiographic progression of cancer. In our patients with radiation recurrent cancer we were able to prevent or delay the use of hormone therapy in the majority of these men.

FRI 55

Cyro-thermal therapy eradicated implanted melanoma in mice by eliciting anti-tumor memory immune response

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Current cancer therapies for metastases are unfortunately limited. Treatments that stimulate self-defense system of immune are bringing new hopes in the success of tumor therapy. Previously we developed a novel therapeutic modality of cryo-thermal treatment, which delivered greater therapeutic benefit in the study using 4T1 murine mammary carcinoma model. Currently we extended our studies to the B16F10 melanoma tumor model. The cryo-thermal treatment induced complete remission and resulted in long term survival, as well as protection against the tumor re-challenge. H&E staining was performed to confirm the reduction of tumor metastases after the cryo-thermal therapy, which indicated generation of a strong tumor-specific immune response after treating primary tumors. Mechanistically, flow cytometry assay analysis indicated that the cryo-thermal treatment targeted reducing MDSCs and increasing $CD4^+$ and $CD8^+$ T cells in peripheral blood, lung and spleen. Moreover, QPCR data showed that the differentiation of $CD4^+$ cells toward mainly Th1, $CD4^+$CTL and Tfh functional *phenotype*, especially high $CD4^+$CTL *phenotype* on day 90 after cryo-thermal treatment, as same as the differentiation of $CD8^+$ cells toward stem cell (T_{SCM}) memory $CD8^+$ T cells with high expression of stem cells antigen-1 (Sca-1) and IFN-γ, Perforin, Granzyme B, contributing to long-term anti-tumor immune response. Moreover, Significant increase of serum IFN-gamma and IL-7 associated with memory formation and maintenance was found after the cryo-thermal treatment by using ELISA. This study demonstrated the novel cryo-thermal therapeutic modality offered a new paradigm to generate persistent memory immune response for tumor eradication, inhibition of relapse and metastasis.

FRI 56

Cryosurgery with vascular disruptive agent and Immune Adjuvants to Address Local and Systemic Cancer

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Cryosurgery is an excellent method to control local cancer, however, alone it is not able to reproducibly address systemic disease. Our study tests the ability of adjuvants including anti-CTLA-4 and a nanoparticle delivered vascular disruptive agent (NP VDA) to address both local and systemic cancer.

Our previous experience with NP VDA has shown the ability to dramatically enhance local tumor destruction over thermal therapy alone. This is achieved by NP VDA "pre-conditioning" in the tumor that achieves increased vascular permeability while reducing overall perfusion between 2 to 6 hours after i.v. injection. Once "pre-conditioned", local cancer destruction can be enhanced by over 50% with the same thermal dose. We hypothesis that this enhanced destruction will also yield more antigen presentation to the immune system over cryosurgery or sham procedures.

To address systemic disease, local NP VDA thermal therapy will be combined with immunomodulation (anti CTLA-4) to stimulate NK and cytotoxic T-cell (CTL) cancer destruction as recently reported for cryosurgery alone. In this case the local thermal treatment provides cancer antigen to the NK cells and CTLs thereby further priming them to destroy cancer. Local thermal treatment provides cancer antigen to the NK cells and CTLs thereby further priming them to destroy cancer.

We hypothesize that the stimulated immune system is better able to address residual tumor, or tumor re-challenge, after NP VDA cryosurgery vs cryosurgery alone. Our carcinoma model (TRAMP) is being tested to show that CTLA-4 blockade cooperates with cryotherapy of a primary tumor to prevent the outgrowth of secondary tumors seeded by challenge at a distant site. Immunostimulation by anti-CTLA-4 will be administered. Cancer control will be measured by local regression or growth delay while systemic control will be measured by existing untreated tumor regression or secondary tumor challenge.

Immunotherapy following our NP platform's thermal and VDA pre-conditioning is expected to lead to enhanced antigen release that is expected to evoke tumor specific CTL tumor infiltration and improved survival through tumor growth delays (local cancer control). Growth of secondary tumors is mostly unaffected by thermal destruction or NP VDA alone, however, we do expect the combination treatment to slow growth or trigger rejection as previously reported for both immunomodulation and immunotherapy coupled with cryosurgery.

FRI 57

Cold atmospheric helium plasma (He-CAP) and mild hyperthermia in combination causes enhancement in cell killing mainly *via* generation of reactive oxygen species

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Introduction: Cold atmospheric plasma has been proposed as a novel therapeutic method for its anticancer potential. However, its biological effects in combination with other physical modalities remain to be elusive. This study was aimed to determine the effects of cold atmospheric helium plasma (He-CAP) on hyperthermia (HT)-induced apoptosis.

Methods: Flow rate of helium gas was 2 L/min. Cells were exposed to different doses of He-CAP and immediately after exposure cells were treated with HT at 42 °C for 20 min. Apoptosis was determined by observation of nuclear morphological changes, DNA fragmentation assay, and Annexin V-FITC/PI and cell cycle analysis. Detection of intracellular reactive oxygen species (ROS), mitochondrial membrane potential (MMP) and intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) was performed by using flow cytometry. Caspase-8 activation and the expression of apoptosis related proteins were detected by western blot.

Results: It was found that He-CAP, in combination with HT significantly enhanced apoptosis, which was accompanied by intracellular ROS production, loss of MMP, and caspase-8 and caspase-3 activation. However, no significant apoptosis was observed either by He-CAP or HT alone.

Conclusion: These findings suggest that He-CAP can enhance the cell killing effect of mild HT, might be due to increased in intracellular reactive oxygen species (ROS) generation, as He-CAP has been known to caused marked induction of ROS in the aqueous medium.

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