36TH ANNUAL MEETING OF THE SOCIETY FOR THERMAL MEDICINE

UNITING OUR STRENGTHS FOR A CURE

APRIL 28 - MAY 2, 2019 • ST. PETE BEACH, FLORIDA

2019 PROGRAM & ABSTRACT BOOK

ISSN: 0265-6736

IJH

INTERNATIONAL JOURNAL OF HYPERTHERMIA and thermal therapies

Taylor & Francis
Taylor & Francis Group

TABLE OF CONTENTS

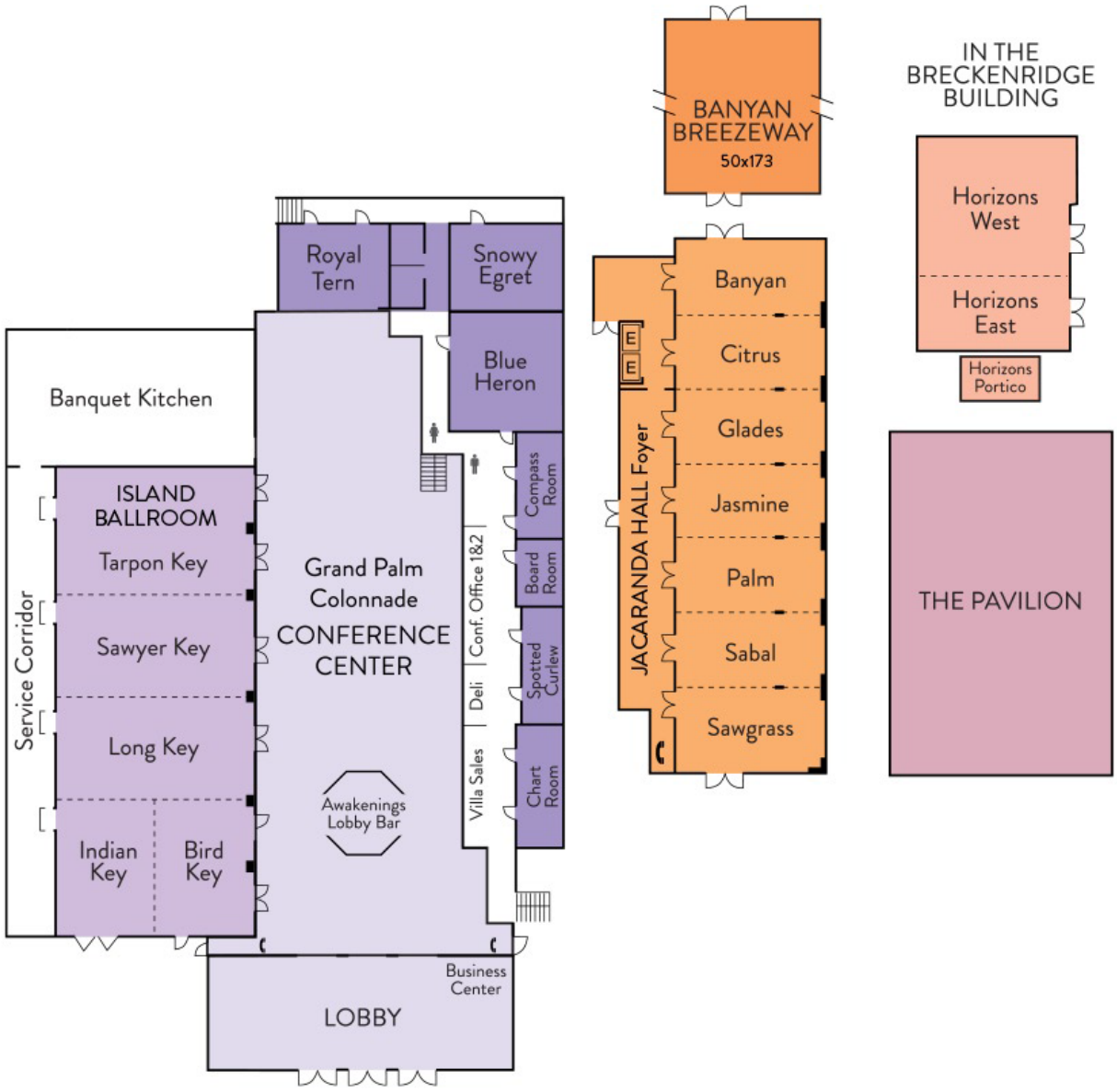
MEETING INFO/MAPS

Registration Desk Hours of Operation in the GRAND PALM COLONNADE WEST ▸

Monday, April 29th	7:00AM – 5:30PM
Tuesday, April 30th	7:00AM – 5:30PM
Wednesday, May 1st	7:00AM – 5:30PM
Thursday, May 2nd	7:00AM – 5:00PM

PROPERTY MAP

MEETING SPACE MAP



<table>
<tr><th>TIME</th><th>SUNDAY, APRIL 28</th><th colspan="2">MONDAY, APRIL 29</th><th colspan="4">TUESDAY, APRIL 30</th></tr>
<tr><td>7:00-7:30 AM</td><td></td><td rowspan="2">CONTINENTAL BREAKFAST
FOR WORKSHOP REGISTRANTS ONLY
PAVILION</td><td rowspan="15">REGISTRATION
GRAND PALM COLONNADE WEST</td><td colspan="3" rowspan="2">CONTINENTAL BREAKFAST FOR ALL ATTENDEES
PAVILION</td><td rowspan="15">REGISTRATION
GRAND PALM COLONNADE WEST</td></tr>
<tr><td>7:30-8:00 AM</td><td></td></tr>
<tr><td>8:00-8:30 AM</td><td rowspan="4">STM OTHER COMMITTEE MEETINGS
SNOWY EGRET</td><td rowspan="5">CLINICAL HYPERTHERMIA PRACTICE GUIDELINES WORKSHOP
TICKETED EVENT
PAVILION</td><td colspan="3">KEYNOTE #2
DR. MAY ABDEL-WAHAB
PAVILION</td></tr>
<tr><td>8:30-9:00 AM</td><td colspan="3">AM BREAK & EXHIBIT TIME
BANYAN BREEZEWAY</td></tr>
<tr><td>9:00-9:30 AM</td><td rowspan="2">BREAKOUT SESSION: TRADITIONAL HYPERTHERMIA: RECURRENT BREAST OR SKIN CANCER
BANYAN/CITRUS</td><td rowspan="2">BREAKOUT SESSION: ABLATION
BLUE HERON</td><td rowspan="2">BREAKOUT SESSION: MULTIPHYSICS MODELING
SNOWY EGRET</td></tr>
<tr><td>9:30-10:00 AM</td></tr>
<tr><td>10:00-10:30 AM</td><td rowspan="3">STM GOVERNING COUNCIL MEETING
SNOWY EGRET</td></tr>
<tr><td>10:30-11:00 AM</td><td colspan="3" rowspan="2">LUNCH - FOR ALL ATTENDEES</td></tr>
<tr><td>11:00-11:30 AM</td></tr>
<tr><td>11:30-12:00 AM</td><td rowspan="2"></td><td rowspan="3">WORKING LUNCH/ PANEL DISCUSSION - FOR WORKSHOP REGISTRANTS ONLY
PAVILION</td></tr>
<tr><td>12:00-12:30 PM</td></tr>
<tr><td>12:30-1:00 PM</td><td rowspan="4">STM FINANCE COMMITTEE MEETING
SNOWY EGRET</td></tr>
<tr><td>1:00-1:30 PM</td><td rowspan="2">QUALITY ASSURANCE SYMPOSIUM
BANYAN/CITRUS</td><td rowspan="2">BREAKOUT SESSION: HYPERTHERMIA AND RADIATION BIOLOGY
BLUE HERON</td><td rowspan="2">BREAKOUT SESSION: PELVIC THERMAL THERAPY - HIPEC- CRYOTHERAPY
SNOWY EGRET</td></tr>
<tr><td>1:30-2:00 PM</td><td rowspan="3">REFRESHER COURSES
PAVILION</td></tr>
<tr><td>2:00-2:30 PM</td></tr>
<tr><td>2:30-3:00 PM</td><td rowspan="4">IJH EDITORIAL BOARD MEETING
SNOWY EGRET</td><td colspan="3">PM BREAK - BANYAN BREEZEWAY</td></tr>
<tr><td>3:00-3:30 PM</td><td rowspan="3">PM BREAK
BANYAN BREEZEWAY</td><td colspan="3" rowspan="3">RESORT TIME</td></tr>
<tr><td>3:30-4:00 PM</td></tr>
<tr><td>4:00-4:30 PM</td><td rowspan="3">WELCOME & KEYNOTE #1 DR. BRIAN GASTMAN
PAVILION</td></tr>
<tr><td>4:30-5:00 PM</td></tr>
<tr><td>5:00-5:30 PM</td><td></td><td></td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>5:30-6:00 PM</td><td></td><td></td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>6:00-6:30 PM</td><td></td><td colspan="2" rowspan="2"></td><td colspan="3" rowspan="3">POSTER SESSION & COMPETITION
(WITH DRINKS AND HORS D'OEUVRES)
BANYAN BREEZEWAY</td><td></td></tr>
<tr><td>6:30-7:00 PM</td><td></td><td></td></tr>
<tr><td>7:00-7:30 PM</td><td></td><td colspan="2" rowspan="4">WELCOME RECEPTION
WITH HEAVY OER D'OUERVES
BRECK DECK NORTH</td><td></td></tr>
<tr><td>7:30-8:00 PM</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>8:00-8:30 PM</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>8:30-9:00 PM</td><td></td><td colspan="3"></td><td></td></tr>
<tr><td>9:00-9:30 PM</td><td></td><td colspan="3"></td><td></td></tr>
</table>

TIME	WEDNESDAY, MAY 1				THURSDAY, MAY 2			
7:00-7:30 AM	**CONTINENTAL BREAKFAST** *FOR ALL ATTENDEES* *PAVILION*			**REGISTRATION** *GRAND PALM COLONNADE WEST*	**CONTINENTAL BREAKFAST** *FOR ALL ATTENDEES* *PAVILION*			**REGISTRATION** *GRAND PALM COLONNADE WEST*
7:30-8:00 AM								
8:00-8:30 AM	**KEYNOTE #3 - DR. MARC S. ERNSTOFF -** *PAVILION*				**KEYNOTE #4 - DR. RUEDIGER WESSALOWKI** *PAVILION*			
8:30-9:00 AM								
9:00-9:30 AM	**AM BREAK & EXHIBIT TIME** *BANYAN BREEZEWAY*				**AM BREAK & EXHIBIT TIME** *BANYAN BREEZEWAY*			
9:30-10:00 AM	**BREAKOUT SESSION: TUMOR IMMUNOLOGY SPONSORED BY BTG** *BANYAN/CITRUS*	**THERMAL THERAPY TREATMENT PLANNING SYMPOSIUM** *BLUE HERON*	**BREAKOUT SESSION: NANOPARTICLES #1 - PHOTOTHERMAL THERAPY** *SNOWY EGRET*		**BREAKOUT SESSION: TEMPERATURE MONITORING** *BANYAN/CITRUS*	**HEAT SHOCK PROTEINS IN HEALTH AND DISEASE SYMPOSIUM - SPONSORED BY CELL STRESS SOCIETY INTERNATIONAL** *BLUE HERON*	**BREAKOUT SESSION: NANOPARTICLES #2 - IRON OXIDE** *SNOWY EGRET*	
10:00-10:30 AM								
10:30-11:00 AM								
11:00-11:30 AM								
11:30-12:00 AM	**STM PRESIDENT'S SYMPOSIUM: "HOT SCIENCE IN THE FACE OF A COLD REALITY" - INCLUDES LUNCH FOR ALL ATTENDEES** *PAVILION*				**STM BUSINESS MEETING - WORKING LUNCH -** *PAVILION*			
12:00-12:30 PM								
12:30-1:00 PM								
1:00-1:30 PM	**BREAKOUT SESSION: CRANIAL AND HEAD AND NECK** *BANYAN/CITRUS*	**BREAKOUT SESSION: ADVANCES IN IMAGE GUIDED THERAPY** *BLUE HERON*	**BREAKOUT SESSION: DRUG DELIVERY AND THERMAL SENSITIVE LIPOSOMES** *SNOWY EGRET*		**CAREER DEVELOPMENT WORKSHOP** *BANYAN/CITRUS*	**BREAKOUT SESSION: TRADITIONAL HYPERTHERMIA - DEEP HYPERTHERMIA OR PROTON THERAPY** *BLUE HERON*	**STANDARDIZING LANGUAGE AND DATA FOR THE THERMAL MEDICINE COMMUNITY: A JOINT STM-ASME WORKSHOP** *SNOWY EGRET*	
1:30-2:00 PM								
2:00-2:30 PM								
2:30-3:00 PM								
3:00-3:30 PM	**PM BREAK -** *BANYAN BREEZEWAY*				**PM BREAK -** *BANYAN BREEZEWAY*			
3:30-4:00 PM	**STM AWARDS SYMPOSIUM** *PAVILION*				**CLOSING PROGRAM/REMARKS**			
4:00-4:30 PM								
4:30-5:00 PM								
5:00-5:30 PM								
5:30-6:00 PM								
6:00-6:30 PM	**ROBINSON AWARD RECEPTION - TICKETED EVENT** *SOUTH LAWN/GAZEBO*							
6:30-7:00 PM								
7:00-7:30 PM								
7:30-8:00 PM	**ROBINSON AWARD BANQUET - TICKETED EVENT** *SOUTH LAWN/GAZEBO*							
8:00-8:30 PM								
8:30-9:00 PM								
9:00-9:30 PM								

LETTER FROM THE PROGRAM CHAIR

JENNIFER YU, MD, PhD

Dear colleagues, friends and sponsors of the Society for Thermal Medicine,

I am pleased to welcome you to the 36th Annual Meeting of the Society for Thermal Medicine, held on the shores of sunny St. Pete's Beach, FL.

Thermal medicine has come a long way since ancient times when it was recognized for its healing powers. Over the centuries, we have refined its delivery and improved our understanding of its biologic underpinnings. These insights have led to new technologies, including ablation, that have transformed care from traditional surgery to minimally invasive approaches. Advances in thermal modeling and temperature measurement have expanded care to the most sensitive organs, including brain, to permit treatment of diseases that may otherwise be considered too difficult to access surgically. Meanwhile, advances in nanotechnology and drug delivery that create heat or release drugs in a temperature dependent manner are improving clinical care. While these technological advances were being made, biologists have uncovered new mechanisms of action of thermal medicine. These include changes in cell stress responses, changes in cancer cells themselves, the tumor microenvironment and the immune system that facilitate a robust immunologic response.

The excitement in thermal medicine continues to build and span multiple disciplines. More than ever, building effective teams across disciplines to improve clinical care is paramount. This serves as the theme of our meeting: Uniting Our Strengths for a Cure.

Kicking off the meeting will be the inaugural Clinical Hyperthermia Practice Guidelines Workshop that offers practical information on starting and improving your clinical hyperthermia program. Following this workshop will be our Education Day workshop on April 29 that will provide a brief history of thermal therapy and discuss systemic effects of temperature on the immune system and microbiome.

The meeting officially opens with a keynote address by Dr. Brian Gastman, the lead surgeon who built a team to pioneer face transplantation and give new life to a young patient. Keynote addresses by leaders in medicine will open each following day. These speakers include Dr. May Abdel-Wahab, who serves at the United Nations as Director of Human Health at the International Atomic Energy Association who has brought new technologies and improved treatment standards around the world, Dr. Mark Ernstoff who has designed and led national immunotherapy clinical trials, and Dr. Rudiger Wesselowski who has pioneered thermal therapy with chemotherapy to improve outcomes for pediatric patients.

These keynote addresses will be rounded out by a diverse array of breakout sessions. We will hold a dedicated Quality Assurance Symposium and joint special STM-ASME workshop to improve quality and safety. We will hold multiple sessions devoted to the interplay between thermal therapy and biology, including effects on the immune system, DNA damage repair and cell stress responses. Multiple sessions will be devoted to advanced thermal modeling, clinical advances in traditional hyperthermia and ablation technology, and advances in nanotechnology and drug delivery. Education is also a priority, and we will hold a dedicated Career Development Workshop for young (and not so young) investigators.

This is a diverse meeting with presenters from all around the world encompassing subjects from basic science to physics to clinical medicine. This would not be possible without the generous support from our membership, sponsors and partnership societies, the American Society of Mechanical Engineers and Cell Stress Society International. We look forward to this exciting conference, and we are delighted to have you join.

Sincerely,

Jennifer Yu, MD, PhD
Program Chair, President-Elect, Society for Thermal Medicine
Associate Professor, Department of Molecular Medicine
Staff, Department of Radiation Oncology
Staff, Department of Cancer Biology
Director, Center for Hyperthermia
Co-Leader, Cancer Stem Cell Working Group, Case Comprehensive Cancer Center
Cleveland Clinic
Cleveland, OH, USA

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:

1. To encourage the advancement of thermal medicine in all areas of natural and medical sciences.
2. To facilitate cooperative research among the disciplines of physics, engineering, biology, chemistry, and medicine in the study of the properties and effects of thermal medicine.
3. To promote dissemination of knowledge in these and related fields through publications, meetings and educational symposia.

WE THANK OUR SPONSORS

PLATINUM LEVEL

Pyrexar MEDICAL

GOLD LEVEL

ASME
SETTING THE STANDARD

BTG

SILVER LEVEL

heckel
hyperthermia

MONTERIS®
MEDICAL

FRIENDS LEVEL

Focused Ultrasound Foundation

magnetic INSIGHT

stellar science

zurich med tech

SUPPORTING

IOP Publishing

Taylor & Francis
Taylor & Francis Group

36TH ANNUAL STM MEETING PLANNING COMMITTEE

Program Chair: Jennifer Yu, MD, PhD, Cleveland Clinic

Corporate Relations & Fundraising Chair: Zeljko Vujaskovic, MD, PhD, University of Maryland

Randy Burd, PhD, Long Island University

Rajiv Chopra, PhD, University of Texas Southwestern Medical Center

Erik Cressman, MD, PhD, University of Texas MD Anderson Cancer Center

Chris Diederich, PhD, University of California San Francisco

Mark Dewhirst, PhD, DVM, Duke University Medical Center

Rohan Fernandes, PhD, The George Washington Cancer Center

Steven Fiering, PhD, Geisel School of Medicine, Dartmouth College

Michael Graner, PhD, University of Colorado Denver School of Medicine, Department of Neurosurgery

Robert Griffin, PhD, University of Arkansas for Medical Sciences

Dieter Haemmerich, PhD, Medical University of South Carolina

Mark Hurwitz, MD, Thomas Jefferson University Hospitals

Robert Ivkov, PhD, Johns Hopkins University

Samir Jenkins, PhD, University of Arkansas for Medical Sciences

Nicole Levi-Polyachenko, PhD, Wake Forest School of Medicine

Alireza Mohammad Mohammadi, MD, Cleveland Clinic

Arlene Oei, PhD, Academic Medical Center Amsterdam

Elizabeth Repasky, PhD, Roswell Park Comprehensive Cancer Center

Dario Rodrigues, PhD, University of Maryland

Jason Stafford, MD, University of Texas MD Anderson Cancer Center

Paul Stauffer, PhD, Thomas Jefferson University

Christopher Lapine, STM Business Manager, Allen Press, Inc.

GOVERNING COUNCIL

Society for Thermal Medicine (2018 –19)

PRESIDENT:
Michael Graner, PhD
University of Colorado Denver
School of Medicine
Department of Neurosurgery
Aurora, CO

PRESIDENT-ELECT:
Jennifer Yu, MD, PhD
Cleveland Clinic: Department of
Radiation Oncology, Department
of Cancer Biology
Cleveland, OH

VICE-PRESIDENT ELECT:
Nicole Levi-Polyachenko, PhD
Wake Forest School of Medicine
Department of Plastic and
Reconstructive Surgery
Winston-Salem, NC

SECRETARY/TREASURER:
Rajiv Chopra, PhD
University of Texas Southwestern
Medical Center
Department of Radiology
Dallas TX, USA

PAST PRESIDENT
Robert Ivkov, PhD
Johns Hopkins School of Medicine
Radiation Oncology & Molecular
Radiation Sciences
David H Koch Cancer Research
Building
Baltimore, MD

EDITOR-IN-CHIEF OF
The International Journal of Hyperthermia
Mark W. Dewhirst, DVM, PhD
Duke University Medical Center
Department of Radiation Oncology
Durham, NC

Councilor: Biology /Chemical Sciences

2017–2019	Arlene L. Oei, PhD, Academic Medical Center Amsterdam
2018–2020	Elizabeth Sweeney, PhD, George Washington University, GW Cancer Center Washington, DC

Councilor: Clinical/Medical Sciences

2017–2019	Rolf D. Issels, Prof. Dr. med. Dipl. Biochem, Medizinische Klinik III Klinikum der LMU – Campus Großhadern, München, Germany
2018–2020	Joan Bull, MD, UT Health McGovern Medical School, University of Texas, Houston, TX

Councilor: Engineering/Physical Sciences

2017–2019	John Bischof, PhD, University of Minnesota, Deptartment of Mechanical Engineering, Minneapolis, MN
2018–2020	Dario Rodrigues, PhD, University of Maryland Department of Radiation Oncology, Baltimore, MD

INTERNATIONAL JOURNAL OF HYPERTHERMIA BOARD MEMBERS

INTERNATIONAL JOURNAL OF HYPERTHERMIA BOARD MEMBERS

2018 EDITOR'S AWARD WINNERS
INTERNATIONAL JOURNAL OF HYPERTHERMIA

These chosen papers were selected by the Editorial Board of the *International Journal of Hyperthermia* as the best of Young Investigator papers (in their respective categories) that were published in 2018. Authors self-nominate themselves with the criteria being that they are less than 35 years of age. The editors have rigorous scoring criteria to help them select the winning papers.Our congratulations go to the following recipients of the 2018 awards:

PHYSICS

SRI KAMAL KANDALA
Johns Hopkins University school of Medicine, Baltimore, MD, USA

Temperature-controlled power modulation compensates for heterogeneous nanoparticle distributions: a computational optimization analysis for magnetic hyperthermia

Sri Kamal Kandala, Eleni Liapi, Louis L. Whitcomb, Anilchandra Attaluri & Robert Ivkov

International Journal of Hyperthermia, Volume 36, 2019 - Issue 1
Published Online: 12 Dec 2018 -
https://doi.org/10.1080/02656736.2018.1538538

BIOLOGY

QI SHAO
University of Minnesota, Minneapolis, MN, USA

Engineering T cell response to cancer antigens by choice of focal therapeutic conditions

Qi Shao, Stephen O'Flanagan, Tiffany Lam, Priyatanu Roy, Francisco Pelaez, Brandon J Burbach, Samira M Azarin, Yoji Shimizu & John C Bischof

International Journal of Hyperthermia, Volume 36, 2019 - Issue 1
Published Online: 24 Jan 2019 -
https://doi.org/10.1080/02656736.2018.1539253

2018 EDITOR'S AWARD WINNERS
INTERNATIONAL JOURNAL OF HYPERTHERMIA

These chosen papers were selected by the Editorial Board of the *International Journal of Hyperthermia* as the best of Young Investigator papers (in their respective categories) that were published in 2018. Authors self-nominate themselves with the criteria being that they are less than 35 years of age. The editors have rigorous scoring criteria to help them select the winning papers.Our congratulations go to the following recipients of the 2018 awards:

CLINICAL

JIANMING LI

Beijing Friendship Hospital, Capital Medical University, Beijing, CN

Ultrasound-guided percutaneous microwave ablation versus surgery for papillary thyroid microcarcinoma

Jianming Li, Yujiang Liu, Jibin Liu & Linxue Qian

International Journal of Hyperthermia, Volume 34, 2018 - Issue 5

Published Online: 11 Apr 2018

https://doi.org/10.1080/02656736.2018.1453092

KEYNOTE SPEAKER #1

DR. BRIAN GASTMAN, MD

Cleveland Clinic, Cleveland, Ohio

IT TAKES A VILLAGE – TURNING MULTIDISCIPLINARY EFFORTS INTO CLINICAL SUCCESS - THE STORY OF KATIE – A FACE TRANSPLANT RECIPIENT

MONDAY, APRIL 29th, 4:00PM – 5:30PM / PAVILLION

DR. GASTMAN is the Surgical and co-director for Cleveland Clinic's Melanoma and High-risk Skin Cancer Program, Dr. Gastman is also Professor of surgery at Cleveland Clinic Lerner College of Medicine. He is double boarded in otolaryngology and plastic surgery, his research interests include melanoma, non-melanoma skin and soft tissue cancers specifically in tumor immune evasion and chemotherapy resistance; interaction between lymph node, tumor, and immune system; and less invasive sentinel lymph node surgery.

He is a member of the Society of Immunotherapy of Cancer's Melanoma Task Force, as well as on the National Comprehensive Cancer Network (NCCN) Melanoma and skin cancers Treatment Guideline Committee. Active with the NCI-based Cancer Immunotherapy Trial Network and ECOG-ACRIN, he is the national principal investigator for the largest Merkel Cell carcinoma trial. He is institutional PI on multiple trials as well. Dr. Gastman serves on the editorial board of Annals of Surgical Oncology. As a surgeon he is active in improving outcomes in reconstructive surgery and was the primary surgeon for two patients who underwent facial allotransplantation.

KEYNOTE SPEAKER #2

DR. MAY ABDEL-WAHAB, MD, PHD

Division of Human Health at the International Atomic Energy Agency (IAEA)

ADDRESSING CANCER CHALLENGES THROUGH NUCLEAR APPLICATIONS: THE ROLE OF THE IAEA

TUESDAY, APRIL 30TH, 8:00AM – 9:00AM / PAVILLION

DR. MAY ABDEL-WAHAB, MD, PHD is the Director of the Division of Human Health at the International Atomic Energy Agency (IAEA), a United Nations (UN) agency with over 170 member states world-wide. The IAEA's Division of Human Health conducts clinical trials, training and educational initiatives and provides expertise to technical cooperation projects in countries requesting support in radiotherapy, medical physics and diagnostic imaging, including particle therapy as well as missions and audit services to support radiotherapy quality assurance globally. Dr Abdel-Wahab has more than 30 years of experience in patient care, teaching and research in the field of radiation medicine. Prior to joining the IAEA Dr Abdel-Wahab was a Professor at the Cleveland Clinic Lerner School of Medicine, Case Western University and was Section Head of Gastro-Intestinal Radiation Oncology at the Cleveland Clinic, USA. A former residency program director, Dr Abdel-Wahab continues to hold a special interest in education and curriculum development, and has chaired numerous symposia and scientific meetings as scientific secretary. In addition to serving on FRS Board of directors, and several advisory and editorial boards, Dr Abdel-Wahab also served on various national and international committees, both as a member and/or chair, including the United Nations Interagency Task Force steering committee (UNIATF), the ASTRO Diversity and Disparity committee, Integrated Healthcare Enterprises in Radiation Oncology (IHERO) planning committee, and the Steering committee of the UN Joint Project on Cancer Cervix Prevention and Control, among others. Dr May Abdel-Wahab is a fellow of the American Board of Radiology, Fellow of the American Society of Radiation Oncology and was on the Best Doctors in America listing, among other honors. She is an avid lecturer and participant on scientific panels, served on expert panels for treatment guidelines and is published widely (over 150 publications). She has an interest in healthcare access and training, as well as novel solutions to address disparity and diversity issues in healthcare with an emphasis on radiation oncology.

KEYNOTE SPEAKER #2

DR. MARC S. ERNSTOFF, MD

Department of Medicine and Senior Vice President of Clinical Investigation at Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

THE ROLE OF ADRENERGIC STRESS IN CANCER IMMUNOLOGY AND IMPLICATIONS FOR THERAPY IN MELANOMA

WEDNESDAY, MAY 1st, 8:00AM – 9:00AM / PAVILLION

DR MARC S. ERNSTOFF, MD is Professor and Chair of the Department of Medicine and Senior Vice President of Clinical Investigation at Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA. Born in Brooklyn NY he studied History of Art at Emory University in Atlanta, GA and then medicine at NYU in NY, NY earning his MD degree in 1978. He completed his training in Internal Medicine at the Bronx Municipal Hospital and the Albert Einstein School of Medicine in the Bronx, NY and then oncology at Yale University New Haven, CT. He did a postdoctoral fellowship in cancer immunology and immunotherapy under the mentorship of Dr. John M. Kirkwood. Since then, he has focused his research on better understanding the immunobiology of cancer and on developing novel immune therapies for melanoma, renal cell carcinoma, myeloma, prostate cancer and gliomas. His research extends across a broad variety of immunotherapies including cytokine therapies, dendritic cell vaccines, immune checkpoint inhibition, targeted therapies and ex vivo expanded effector cells for adoptive transfer. Most recently he is investigating the role of tumor derived exosomes on the tumor microenvironment, and the impact of the beta adrenergic pathway on immune suppression. He currently serves on the Society for Immunotherapy of Cancer (SITC) and the American Society of Clinical Oncology (ASCO) Melanoma Guidelines committees, the SITC and National Comprehensive Cancer Network (NCCN) Immuno-oncology toxicity guideline committees, and the Cancer Immunotherapy Network (CITN) executive committee.

KEYNOTE SPEAKER #4

PD DR. RUEDIGER WESSALOWSKI, MD

Clinic for Pediatric Oncology, Hematology
and Clinical Immunology
Heinrich-Heine-University, Medical Faculty,
Düsseldorf, Germany

THE ROLE OF HYPERTHERMIA IN CHILD & ADOLESCENT CANCER

THURSDAY, MAY 2nd, 8:00AM – 9:00AM / PAVILLION

DR. WESSALOWSKI was born and raised in the Lower Rhine region of Germany, where he received his education. After he received his license to practice medicine in 1987, he obtained his MD degree from Heinrich-Heine-University Duesseldorf in 1993 and specialized in pediatric oncology and hematology. From 1991-2019 Dr. Wessalowski has been a Scientist within the Hyperthermia Study Group at Heinrich-Heine-University Duesseldorf, and since 2000 an Associate Professor in the Clinic for Pediatric Oncology, Hematology and Clinical Immunology in the Medical Faculty Duesseldorf, Germany, where he leads a clinical research program for regional deep hyperthermia for children, adolescents and young adults.

Dr. Wessalowski has devoted his research career to the development of hyperthermia strategies for children and translation of the hyperthermia technology to clinical practice in childhood cancer. His efforts led to the world's first prospective human trial of regional deep hyperthermia in infants and small children with refractory and/or recurrent cancer (Hyper-PEI protocol).

The hyperthermia strategy in childhood cancer according to the Hyper-PEI protocol - registered at the German Cancer Society (number 50-2732) - now has investigational approval in Germany, and is being evaluated clinically by the German Society of Pediatric Oncology and Hematology (GPOH) since 2004.

He has been honored for his work by the European Society of Hyperthermic Oncology with the ESHO-BSD-award in 2013. He is editorial board member of the International Journal of Hyperthermia (IJH) and deputy spokesman of the Interdisciplinary Hyperthermia Working Group (IAH) of the German Cancer Society.

In addition to the development of clinical hyperthermia therapy strategies in children, adolescents and adults, Dr. Wessalowski has explored the potential for non-invasive temperature measurement in the body of children and adults using BSD 2000-3D-Hydrid System. His interests include also the preclinical and clinical analysis of heat shock proteins as immune modulators, preclinical and clinical drug testing for thermosensitisation, and translation of experimental hyperthermia treatment strategies into clinical evaluation.

2019 GEORGE M. HAHN AWARD & LECTURE
AWARD WINNER

CHRIS J. DIEDERICH, PHD

Professor in the Department of Radiation Oncology and Director of Clinical Hyperthermia Physics and Thermal Therapy Research

University of California, San Francisco

WEDNESDAY, MAY 1, 3:30PM - 5:00PM / PAVILION

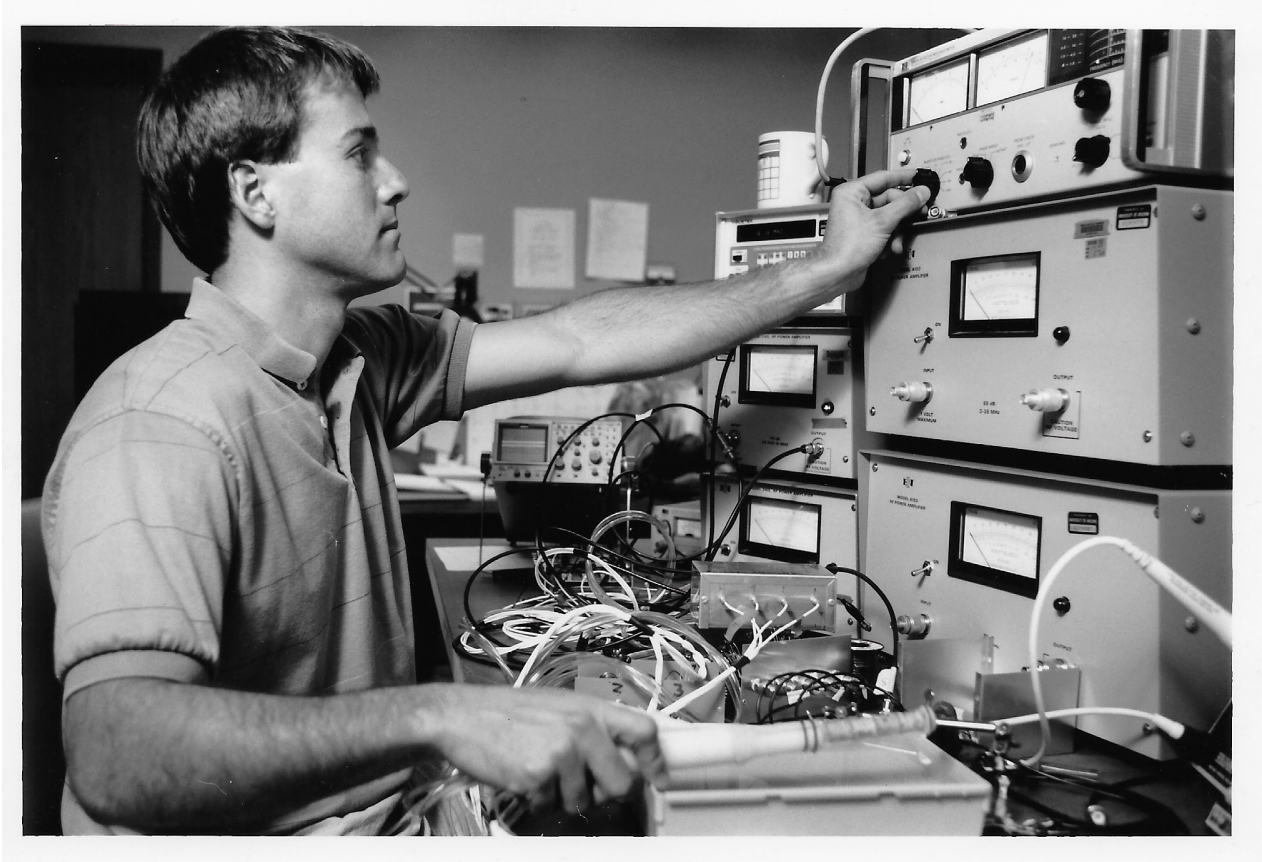
The George M. Hahn Award is presented every other year to an investigator whose research has contributed in a significant way to new clinical applications in thermal therapy. This lecture is named in honor of Dr. George Hahn who received the first Robinson Award in 1989. Dr. Hahn led a highly productive clinical program grant at Stanford for many years and his fundamental work in the heat shock response and in how hyperthermia modifies chemotherapy sensitivity still stand today as foundational work. His highly productive career exemplifies the translational attributes of this award.

Chris J. Diederich, PhD is a Professor in the Department of Radiation Oncology and Director of Clinical Hyperthermia Physics and Thermal Therapy Research at the University of California, San Francisco. He received his MSEE under Dr. Robert Roemer and his PhD under Dr. Kullervo Hynynen from the University of Arizona, and in 1990 joined the faculty and Hyperthermia Program at UCSF. Dr. Diederich has approximately 30 years of experience as a Medical Physicist in the field of Hyperthermia Therapy, with clinical applications of ultrasound and electromagnetic systems for delivering superficial, interstitial, and deep hyperthermia. He has contributed to numerous clinical studies including those combining heat with HDR/brachytherapy, Doxil, and ThermoDox. His research focus involves the use of experimental and theoretical approaches toward the development of ultrasound devices and treatment delivery strategies for targeted hyperthermia, thermal ablation therapies, drug delivery, and non-thermal tissue effects. This includes integration of MRTI and US image-guidance techniques for monitoring therapy delivery. Catheter based ultrasound technology developed by his group has been applied in clinical study of hyperthermia in conjunction with HDR brachytherapy for the treatment of locally advanced prostate and cervix cancer. He is an active and contributing member of the AAPM, ISTU and STM scientific societies. Dr. Diederich is a Fellow of AAPM, and currently serving on the Board of Associate Editors for *Medical Physics* and on the AAPM Scientific Program as Director of the Ultrasound Specialty Track. He is currently an Associate Editor of the *International Journal of Hyperthermia*. He has served on numerous committees and as Councilor, Secretary-Treasurer, and 17th President (2001) of STM/ North American Hyperthermia Society, and received the J. Eugene Robinson Award in 2010 in recognition of his contributions to the field of hyperthermia.

Hyperthermia's Wild Ride - Taking the Sound Approach

The support for and practice of hyperthermia and thermal therapy research has changed considerably over the last three decades in response to factors such as clinical trial outcomes, market forces, reimbursements, health care environment, regulatory requirements, NIH budget, and trending science topics. Further, clear needs for comprehensive

QA, changes to practice guidelines, and required improvements to device performance and dosimetry were established. I was "raised" in a culture of ULTRASOUND, with a mindset where problems/obstacles encountered with alternative heating modalities could be overcome through development of new and novel ultrasound technology. In part, this presentation will track changes within this environment and the influence on my research directions and collaborations – navigating toward development of endocavity, endoluminal, and catheter-based ultrasound technology with an intent to provide enhanced spatial control, depth of heating, and conformal targeting for applications of hyperthermia and thermal ablation. Image-guidance with MRI derived temperature and thermal dose mapping has been integrated for specific device applications, and plays a critical role for more precise therapy delivery and treatment verification. Examples include interstitial and endocavity devices applied for treating prostate and cervical cancer with hyperthermia in conjunction with HDR brachytherapy; highly conformal and directional interstitial ultrasound applicators for ablation in sites such as brain, liver, prostate, and spine; transurethral ultrasound applicators for ablation of prostate cancer and BPH under MRTI guidance; and recent development of site-specific ultrasound technology such as novel endoluminal applicators for MR guided applications targeting pancreas from within the GI tract, endobronchial ablation of pulmonary tumors, and non-thermal treatment of back pain. Additionally, general highlights and new directions across the field of image-guided therapeutic ultrasound will be discussed, extending well beyond thermal therapies and toward drug delivery, immunotherapy, and exploiting non-thermal effects of mechanical ultrasound. Finally, from a practical perspective, the (few if any :)) shortcomings of ultrasound technology will be positioned against significant advances in "alternative" technologies.



30TH J. EUGENE ROBINSON AWARD & LECTURE
AWARD WINNER

PD DR. RUEDIGER WESSALOWSKI, MD

Clinic for Pediatric Oncology, Hematology and Clinical Immunology

Heinrich-Heine-University, Medical Faculty,

Düsseldorf, Germany

WEDNESDAY, MAY 1, 3:30PM - 5:00PM / PAVILION

The J. Eugene Robinson Award is presented annually to an investigator who has made outstanding contributions to the field of hyperthermic oncology in one or more of the three main disciplines: Medicine/Clinical, Biology/Physiology, and Physics/Engineering. It is the highest and most prestigious award of the Society for Thermal Medicine. The award is named after J. Eugene Robinson who was a pioneer of hyperthermia research from the 1960's through the 1980's and a strong proponent of combined radiation and hyperthermia for cancer therapy.

RUEDIGER WESSALOWSKI, MD is an internationally recognized physician scientist and Associate Professor of Pediatric Oncology at the Medical Faculty of the Heinrich-Heine-University Düsseldorf. Dr Wessalowski`s research program fosuses on the understanding of synergistic interactions between anticancer drugs and hyperthermic temperatures in pediatric cancer. Preclinical findings from Dr. Wessalowski have guided in the development of a Phase I/II clinical trial (Hyper-PEI Protocol). He is being honored for over three decades of achievement in the field of thermal therapy, including the development of the first prospective clinical program of regional deep hyperthermia in refractory childhood cancer. His recent interest is the development of technology to enable non-invasive temperature measurement by MRI.

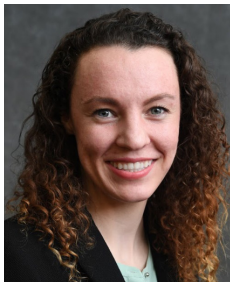
Dr. Wessalowski has actively served the Society for Thermal Medicine as board member and scientific program chair for the STM annual meeting in New Orleans, Louisiana and Cancun, Mexico. He is currently a Section Editor for the International Journal of Hyperthermia, and he is a previous awardee of the ESHO-BSD award from the European Society of Hyperthermic Oncology.

2019 STM SCHOLAR-IN-TRAINING TRAVEL AWARDS

We are pleased to announce that The Society for Thermal Medicine, is providing travel grants to 10 Scholars-in-Training to encourage participation at the 2019 STM annual meeting.

Awardees will receive a $500 travel grant, registration to the meeting and a 2020 membership in the society.

Travel Awards recipients are based upon a competitive evaluation of their submitted abstracts and New Investigator Award applications.



HEATHER CAMPBELL
Evaluation of a New Housing Apparatus for Laboratory Mice that Permits Self Selection of Ambient Temperature: Evaluation of Tumor Growth

Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

A. COLLEEN CROUCH
Sex and age mediate vascular response to core body temperature via redistribution of blood volume in arteries and veins: A Murine MRI Study

University of Michigan, Ann Arbor, MI, USA

PADRAIG DONLON
Using Microwave Thermal Ablation To Precisely Target The Adrenal Cortex, Taking A Minimally Ablative, Cortical-Sparing Approach

National University of Ireland Galway, Galway, Galway, Ireland

PEGAH FARIDI
Microwave ablation system integrated with MRI thermometry for experimental validation of 3D temperature profiles predicted by computational models

Kansas State University, Manhattan, KS, USA

MARLOES IJFF
Hyperthermia increases ionizing radiation induced cell reproductive death of cervical cancer cells by affecting two DNA DSB repair pathways.

Amsterdam UMC, Amsterdam, Netherlands

EMILY KOWALSKI
Concurrent External Thermal Therapy and Radiation in the Treatment of Cutaneous Malignancies: A Single Institution Experience

University of Maryland Medical Center, Baltimore, MD, USA

2019 STM SCHOLAR-IN-TRAINING TRAVEL AWARDS

PING LIU
A Novel Multi-Mode Thermal Therapy for Systemic Immunomodulation in Patients with HCC/CLM: A Pilot Study

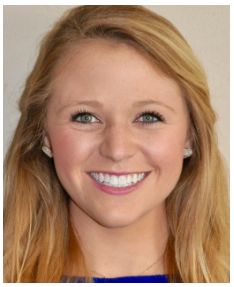
School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China

JIANNING SHAO
Stereotactic Laser Ablation for Treatment of Brain Tumors: Lessons Learned from 240 Cases Over the Past Decade

Cleveland Clinic, Cleveland, OH, USA

ANJAN MOTAMARRY
Real-time visualization and quantification of doxorubicin delivered by thermosensitive liposomes

Medical University of South Carolina, Chalreston, South Carolina, USA



EMILY THOMPSON
Applications of 19F Magnetic Resonance Imaging in Thermochemistry with Pathologic Correlation

The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

CLINICAL HYPERTHERMIA PRACTICE GUIDELINES WORKSHOP

MONDAY, APRIL 29, 8:00AM - 1:30PM / PAVILION

The goal of this workshop is to provide practical training for hyperthermia therapy personnel, including physicians, nurses, radiation therapists, and physicists. All speakers have clinical experience in their fields. Lectures from well-known experts on clinical, physics, and biology of hyperthermia will provide participants a comprehensive overview of practice guidelines to deliver safe and effective hyperthermia treatments. This multi-disciplinary workshop will also include talks on clinical workflow and reimbursement. The workshop is the first of its kind organized by STM and is open to STM2019 participants of all thermal therapy backgrounds.

7:00AM Breakfast

8:00AM Clinical Practice

1. **How to establish a hyperthermia program (30 min)**
   Dr. Zeljko Vujaskovic, University of Maryland, Baltimore MD
2. **Practice guidelines for superficial hyperthermia (25min)**
   Dr. Jason Molitoris, University of Maryland, Baltimore MD
3. **Practice guidelines for deep hyperthermia (25min)**
   Dr. Mark Hurwitz, Thomas Jefferson University, Philadelphia PA
4. **Practice guidelines for interstitial hyperthermia (25min)**
   Dr. John Hayes, Gamma West, Salt Lake City UT

Topics for clinical talks

- **Patient inclusion criteria**
- **Contraindications**
- **Types of tumors treated**
- **Monitoring recommendations**
- **Use of intraluminal and interstitial catheters**
- **Patient setup and comfort strategies**
- **Side effects and their management**

9:45 Coffee Break (15min)

10:00AM Physics of hyperthermia treatments

5. **Equipment, planning, and execution of MW superficial hyperthermia treatment (30min)**
   Dr. Paul Stauffer, Thomas Jefferson University, Philadelphia PA
6. **Equipment, planning, and execution of RF deep hyperthermia treatment (30min)**
   Dr. Dario Rodrigues, University of Maryland, Baltimore MD
7. **Assessment of hyperthermia treatments based on hypoxia imaging (30 min)**
   Dr. Mark Dewhirst, Duke University, Durham NC

11:30AM Clinical workflow and reimbursement

8. **Clinical workflow, documentation and reimbursement of hyperthermia treatments (30 min)**
   Erika Maynor, University of Maryland, Baltimore MD

12:00PM Working lunch and panel discussion (1h30min)

Sponsored by: Pyrexar MEDICAL

STM 2019 EDUCATION DAY WORKSHOP

LIGHTS, CAMERAS, AND THERMAL BIOLOGY IN ACTION

MONDAY, APRIL 29 2:00PM – 3:30PM / PAVILION

SPEAKERS

ALIREZA MOHAMMADI, MD

RUUD DINGS, PHD, MSC

ELIZABETH REPASKY, PHD

Thermal therapy has been shown to improve locoregional control in wide variety of cancers. However, its widespread adoption has been hampered by technical and clinical limitations. New improvements in temperature monitoring now permit non-invasive thermometry. Advances in thermal delivery have expanded treatment options for patients using minimally invasive hyperthermia or cryotherapy techniques. Additionally, the impact of thermal therapy on the cellular stress response, immune system and microbiome are now better appreciated. Designing effective strategies to take advantage of these biologic effects of thermal therapy may improve patient survival. In this education session, we will provide a brief history of thermal therapy including cutting edge technology that facilitates treatment in delicate organs including the brain, and discuss systemic effects of thermal medicine on the immune system and microbiome.

This session will feature:

History of Hyperthermia in Neuro-Oncology
Alireza Mohammadi, Cleveland Clinic, Cleveland, Ohio, USA

The crosstalk and impact of the microbiome on cancer initiation, progression and treatment modalities
Ruud Dings, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Using thermal therapy to fire up immunotherapy? Where are we now?
Elizabeth Repasky, Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

STANDARDIZING LANGUAGE AND DATA FOR THE THERMAL MEDICINE COMMUNITY:

A JOINT STM-ASME WORKSHOP

THURSDAY, MAY 2, 1:00PM – 3:00PM / SNOWY EGRET

MODERATED BY

DARIO RODRIGUES, PhD
University of Maryland School of Medicine, STM

JOHN BISCHOF, PhD
University of Minnesota, STM

ROBERT IVKOV, PhD
John Hopkins University School of Medicine, STM

RYAN CRANE,
Director, Codes and Standards Initiatives, ASME

CHRISTINE REILLEY
Director, Healthcare, ASME

LUIS PULGARIN
Project engineering advisor, Codes and Standards Initiatives, ASME

Why Attend?

- Learn about the latest developments in the creation of a lexicon covering key terms and definitions in thermal medicine.
- Explore the need for a standardized database of temperature-dependent properties.
- Be a part of the next steps of the joint STM-ASME projects aimed at bridging the communication gap among engineers, biologists, physicists, clinicians, and other experts on multidisciplinary thermal medicine teams.

Background

The Society for Thermal Medicine and STM and The American Society of Mechanical Engineers (ASME), recognizing the shared aspects of their vision, mission and knowledge base, held a kickoff workshop at last year's STM Annual Meeting where the following key challenges emerged following group discussions of more than 80 conference attendees:

- The thermal medicine community needs standardized language to resolve communication hurdles among the various players comprising multidisciplinary teams working in the field.
- A repository of temperature-dependent properties for a tissue properties database is required to advance thermal medicine research and development.
- There is a need for standardized computational anatomical models to promote an effective comparison between different thermal medicine techniques.
- The appropriate level of evidence necessary to support the use of computer simulations in the development of medical devices and treatment planning platforms needs to be identified.

Now in its second year, this joint STM-ASME interactive session offers an opportunity to discuss thermal medicine-related topics, applications, and standards needs and to build upon the opportunities uncovered in the 2018 session.

Who Should Attend?

- Clinical practitioners
- Medical physicists
- Bioengineers
- Medical device developers
- Researchers

2019 STM ANNUAL MEETING PRESIDENTIAL SYMPOSIUM

HOT SCIENCE IN THE FACE OF A COLD REALITY

Wednesday, May 1, 11:30am – 1:00pm / Pavilion

The Society for Thermal Medicine has long and tightly-held associations with two areas of seemingly ever-increasing interest: nanoparticles/nanomedicine and immunology/immunotherapy. Both of these realms of research have experienced peaks and valleys of perceived relevance and therapeutic credibility over the years. They are again in the white-hot spotlight of not only academic scientific and clinical attention, but are the subjects of significant investment by pharma and biotech. Also, a hopeful public reads and hears of apparent success in treating patients with such modalities, further promoting their appeal, but often generating unreasonable hype. As scientists, engineers, and clinicians, we need to maintain that unyielding sense of hope and wondrous curiosity, but must also temper that vision with doses of reality.

Our two speakers in today's Presidential Symposium are known among their peers and colleagues (and sometimes annoyed rivals) for their keen scrutiny of science amidst the inevitable hype and overstatement of things we wish were true. Their insights are based on both experience and perception; their outputs are based on hard work and rigor. Their respect for the history of scientific research is not nostalgia, but reflects the efficiency of avoiding past failures while nonetheless appreciating the efforts. This does not make them curmudgeons, but instead makes them realists.

Michael Graner, PhD
President, Society for Thermal Medicine

University of Colorado Denver
School of Medicine
Department of Neurosurgery
Aurora, CO

2019 STM ANNUAL MEETING PRESIDENTIAL SYMPOSIUM

Dr Rob Ivkov has played many roles in STM as Secretary-Treasurer, Vice President-Elect, Vice President, President, and Immediate Past President. He continues to bring expansive energy to STM and is a driver of outreach and outside-the-box thinking. His research touches on hard-core engineering, nanoparticle development, and now has delved into immunology with elements of "old-fashioned" nanoparticles. He has worked in industry, co-founded a company, ended up at Johns Hopkins, and attracted the attention of the Koskinas/Giovanis Foundation, resulting in lab funding for him and a major donation to STM for the outstanding 2017 Meeting. Among other editorial board appointments (including IJH), he is Editor-in-Chief of Convergent Science Physical Oncology, which is wholly and completely fitting for his views of the "interactome" of science. His talk today will cover his lab's efforts to probe the role of the immune microenvironment following iron oxide nanoparticle exposure, suggesting that immune-incompetent models may be inadequate to represent the effectiveness of such approaches.

Dr Tom Anchordoquy is a tenured Professor at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences. He holds numerous patents and patent filings for novel development of drug delivery vehicles, including some available on the market. He has co-founded companies and served as Director for one while maintaining an intensely active academic research lab. He sits on numerous editorial boards and NIH study sections and review panels; he has actually won awards as a reviewer, and has won several as an educator, as well. He is an internationally-known expert in drug delivery, liposome and nanoparticle formulation, and has recently focused research efforts on cow milk exosomes for oral drug ingestion of compounds that otherwise must be delivered intravenously due to toxicity. That work represents a convergence of "rational" particle design with what is biologically successful in nature. While the culmination of those efforts are likely yeas away, he has been in the national news with this work, with one hopeful patient thanking him for "having a curious mind", which aptly sums him up. His talk today will review successes and failures in areas of the nano-delivery field with injections of cold reality, but cloaked in the promise of something better.

PROGRAM

SUNDAY, APRIL 28TH 2019

08:00 - 10:00	**STM Other Committee Meetings**	| Snowy Egret
10:00 - 12:00	**STM Governing Council Meeting**	| Snowy Egret
13:00 - 15:00	**STM Finance Committee Meeting**	| Snowy Egret
15:00 - 17:00	**IJH Editorial Board Meeting**	| Snowy Egret

MONDAY, APRIL 29TH 2019

07:00 - 17:30	**Registration**	| Grand Palm Colonnade West
07:00 - 08:00	**Continental Breakfast - For Workshop Registrants Only**	| Pavilion
08:00 - 12:00	***Clinical Hyperthermia Practice Guidelines Workshop** Chair(s): Dario Rodrigues & Zeljko Vujaskovic	| Pavilion

MON 1 | How to establish a hyperthermia program
Z. Vujaskovic, University of Maryland School of Medicine, Baltimore, MD, USA

MON 2 | Practice guidelines for superficial hyperthermia
J. Molitoris, University of Maryland School of Medicine, Baltimore, MD, USA.

MON 3 | Practice Guidelines for Deep Hyperthermia
M. Hurwitz, Thomas Jefferson University, Philadelphia, PA, USA

MON 4 | Interstitial Hyperthermia
J. Hayes, Gamma West Cancer Services, Salt Lake City, UT, USA

MON 5 | Equipment, Planning and Execution of Microwave
Superficial Hyperthermia Treatments
P. Stauffer, Thomas Jefferson University, Philadelphia, PA, USA

MON 6 | Equipment, planning, and execution of RF deep
hyperthermia treatment
D. B. Rodrigues, University of Maryland School of Medicine, Baltimore, MD, USA

MON 7 | A critical analysis of methods to image and quantify hypoxia in the context of hyperthermia and thermal ablation trials
M. Dewhirst, Duke University, DURHAM, NC, USA

MON 8 | Clinical workflow, documentation and reimbursement of hyperthermia treatments
E. Maynor, University of Maryland School of Medicine, Baltimore, MD, USA

*** Requires separate registration**

10:00 - 10:30 **AM Break** | Banyan Breezeway

12:00 - 13:30 **Working Lunch/Panel Discussion - For Workshop Registrants Only** | Pavilion

13:30 - 14:00 **PM Break #1** | Banyan Breezeway

14:00 - 15:30 **Education Day/Refresher Courses** | Pavilion

Chair(s): Jennifer Yu

MON 9 | History of Hyperthermia in Neuro-Oncology
A. Mohammadi, Cleveland Clinic, Cleveland, Ohio, USA

MON 10 | The crosstalk and impact of the microbiome on cancer initiation, progression and treatment modalities
R. Dings, University of Arkansas for Medical Sciences, Little Rock, AR, USA

MON 11 | Using thermal therapy to fire up immunotherapy? Where are we now?
E. Repasky, Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

15:30 - 16:00 **PM Break #2** | Banyan Breezeway

16:00 - 17:30 **Welcome & Keynote #1** | Pavilion

Chair(s): Jennifer Yu

MON 12 | It takes a village – turning multidisciplinary efforts into clinical success - The story of Katie – a face transplant recipient
B. Gastman, Cleveland Clinic, Cleveland, OH, USA

19:00 - 21:30 **Welcome Reception** | Breck Deck North

TUESDAY, APRIL 30TH 2019

07:00 - 08:00 **Continental Breakfast - for all attendees** | Pavilion

08:00 - 09:00 **Keynote #2** | Pavilion

Chair(s): Jennifer Yu

TUES 1 | Addressing Cancer Challenges through Nuclear Applications: The Role of the IAEA
M. Abdel-Wahab, International Atomic Energy Agency, Vienna, Austria

09:00 - 09:30 **AM Break & Exhibit Time** | Banyan Breezeway

09:30 - 11:30 **Breakout Session: Traditional Hyperthermia: Recurrent Breast or Skin Cancer** | Banyan/Citrus

Chair(s): Gerard van Rhoon & Emily Kowalski

***TUES 2 | Concurrent External Thermal Therapy and Radiation in the Treatment of Cutaneous Malignancies: A Single Institution Experience**

E. Kowalski, University of Maryland Medical Center, Baltimore , MD, USA.

TUES 3 | COMBINED RADIOTHERAPY AND INFRARED HYPERTHERMIA FOR IMPROVED NON-MELANOMA SKIN CANCER TREATMENT: A PILOT FEASIBILITY STUDY TO EVALUATE LOCAL CONTROL AND COSMESIS

E. Abraham, M.D., Hyperthermia Associates, LLC, Claremore, OK, USA.

TUES 4 | A Pilot trial of Hyperthermia in Combination with Olaparib in Breast Cancer Patients with Chest wall Recurrences

M. Hurwitz, Thomas Jefferson University, Philadelphia, PA, USA

TUES 5 | Hyperthermia and radiation for recurrent breast cancer

J. Zeng, Cleveland Clinic, Cleveland, OH, USA.

TUES 6 | Temperature and thermal dose during hyperthermia treatment for patients with recurrent breast cancer: a systematic review of the relationship to tumor response and hyperthermia associated toxicity

A. Bakker, UMCA, Amsterdam, Netherlands.

TUES 7 | A Single-Institution Experience of Concurrent External Thermal Therapy with Radiation Therapy as a Palliative Cancer Treatment

O. Siddiqui, University of Maryland, Baltimore, MD, USA

09:30 - 11:30 **Breakout Session: Ablation** | Blue Heron

Chair(s): Erik Cressman, Padraig Donlon & Emily Thompson

TUES 8 | Thermal ablation of musculoskeletal tumors: Indications, Techniques, and Results.

H. Ilaslan, Cleveland Clinic, Cleveland, Ohio, USA

***TUES 9 | Applications of 19F Magnetic Resonance Imaging in Thermochemistry with Pathologic Correlation**

E. Thompson, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

TUES 10 | Pilot survival study of catheter-based ultrasound thermal ablation of tumors in genetically engineered oncogenic pigs

E. Burdette, Acoustic MedSystems, Inc., Savoy, IL, USA.

*** 2019 Scholar-in-training Travel Award Winner**

TUES 11 | Endoluminal ablation of the main pancreatic duct as an exocrine pancreatic atrophy-inducing procedure: a pioneer method for an old need
E. Ewertowska, BioMIT, Department of Electronic Engineering, Universitat Politècnica de València, Valencia, Spain.

TUES 12 | Comparative assessment of experimental techniques for broadband tissue dielectric property measurements at ablative temperatures
H. Fallahi, Kansas State University, Manhattan, Kansas, USA.

TUES 13 | Transcriptome analysis indicates that combined thermal and osmotic stresses cause widespread compromise of cytoprotective responses in HepG2 cells
C. Guo, MD Anderson Cancer Center, Houston, TX, USA.

TUES 14 | MEK inhibition enhances sensitivity to thermal ablation by blunting HSF1 activation in HepG2 cells
C. Guo, MD Anderson Cancer Center, Houston, TX, USA.

TUES 15 | Combining laser ablation with other therapeutic modalities in high-grade glioma
D. Placantonakis, NYU School of Medicine, New York, NY, USA

09:30 - 11:30 **Breakout Session: Multiphysics Modeling** | Snowy Egret
Chair(s): Hana Trefna & Colleen Crouch

TUES 16 | Sex and age mediate vascular response to core body temperature via redistribution of blood volume in arteries and veins: A Murine MRI Study
A. Crouch, University of Michigan, Ann Arbor, MI, USA

TUES 17 | Evaluation of hydrogels as water bolus in hyperthermia treatment
H. Dobsicek Trefna, Chalmers University of Technology, Gothenburg, Sweden

TUES 18 | Targetability of sites in variable pelvic geometries using MR-guided high-intensity focused ultrasound (MRgHIFU) as assessed in an in vivo porcine model.
M. Altman, Washinton University in St. Louis, St. Louis, MO, USA.

TUES 19 | Bipolar Radiofrequency Ablation of the Brain Using a Virtual Patient Population: An Exploration of Lesion Size Dependency on Voltage Differential
E. Neumann, Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA.

TUES 20 | Mathematical model developments for thermoembolization
D. Fuentes, MD Anderson, Houston, Tx, USA

TUES 21 | Magnetic Nanoparticle Hypethermia for Treating Locally Advanced Unresectable Pancreatic Cancer: Role of Tumor size
A. Attaluri, The Pennsylvania State University – Harrisburg, Middletown, Pennsylvania, USA.

TUES 22 | Dual-Input Maximum Slope Model Assumption And Implications For Calculating Liver Tumor Wide-Array CT Perfusion Values
E. Liapi, Johns Hopkins University, Baltimore, MD, USA.

TUES 23 | Assessing specific loss power demands on magnetic nanoparticles in hyperthermia and nanowarming applications.
A. Sharma, University of Minnesota, Minneapolis, MN, USA.

11:30 - 13:00 **Lunch on own** | Pavilion

13:00 - 15:00 **Quality Assurance Symposium** | Banyan/Citrus
Chair(s): Paul Stauffer & Allison Payne

TUES 24 | Overview of recent ESHO sponsored QA guidelines: the summary of overall changes and current challenges
H. Dobsicek Trefna, Chalmers University of Technology, Gothenburg**,** Sweden

TUES 25 | Thermal monitoring strategies for superficial hyperthermia
A. Bakker, UMCA, Amsterdam, Netherlands

TUES 26 | Quality Assurance guidelines in Interstitial and superficial Hyperthermia and their potential impact on future clinical trial results
J. Crezee, Amsterdam UMC, University of Amsterdam, **Amsterdam,** Netherlands

TUES 27 | QA of radiative deep hyperthermia systems: refresher on available techniques. | Canyon I, III
G. van Rhoon, Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

TUES 28 | Quality assurance of MR-guided deep hyperthermia systems: an international multi-institution evaluation with an anthropomorphic phantom
S. Curto, Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

TUES 29 | Concepts in Quality Management for MR-guided Laser Ablation
R. Stafford, The University of Texas MD Anderson Cancer **Center,** Houston, TX, USA

TUES 30 | Quality assurance in magnetic resonance guided focused ultrasound therapy
A. Payne, University of Utah, Salt Lake City, Utah, USA

13:00 - 15:00 **Breakout Session: Hyperthermia and Radiation Biology** | Blue Heron

Arlene Oei, Marloes Ijff & Heather Campbell

***TUES 31 | Hyperthermia increases ionizing radiation induced cell reproductive death of cervical cancer cells by affecting two DNA DSB repair pathways**.
M. IJff, Amsterdam UMC, Amsterdam, Netherlands

TUES 32 | Differential effects of 42°C-hyperthermia on radiation response of breast cancer spheroids vs. normal human skin explants
A. Thomsen, Department of Radiation Oncology, Medical Center – University of Freiburg, Freiburg, Germany.

TUES 33 | Combination of radiation and hyperthermia in cancer treatment: Assessment of dose response in multicellular tumour spheroids
S. Michlíková, OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, TU Dresden and Helmholtz-Zentrum Dresden–Rossendorf, Dresden, Germany.

TUES 34 | Polymer Nanoparticles for Imaging and Ablation of Colorectal Cancer Tumor Organoids
B. McCarthy, Wake Forest University, Winston-Salem, NC, USA.

TUES 35 | Hyperthermia increases sensitization of proton beam therapy in chordoma cell lines
Z. Vujaskovic, Division of Translational Radiation Sciences (DTRS), Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland, USA.

***TUES 36 | Evaluation of a New Housing Apparatus for Laboratory Mice that Permits Self Selection of Ambient Temperature: Evaluation of Tumor Growth**
H. Campbell, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA.

13:00 - 15:00 **Breakout Session: Pelvic Thermal Therapy - HIPEC - Cryotherapy** | Snowy Egret

Chair(s): Nicole Levi & Brian Loggie

TUES 37 | Clinical applications of Hyperthermic Intraperitoneal Chemotherapy; a review.
R. Helderman, Amsterdam University Medical Centers, Amsterdam, Netherlands

TUES 38 | Prospective, single institution evaluation of HIPEC in ovarian cancer
T. Dellinger, City of Hope National Medical Center, Duarte, CA, USA

TUES 39 | Single Incision Laparoscopic Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy for Recurrent Cases of Pseudomyxoma Peritonei
B. Loggie, Creighton University, Division of Surgical Oncology, Omaha, NE, USA

*** 2019 Scholar-in-training Travel Award Winner**

TUES 40 | Towards thermal therapy treatment planning for hyperthermic intraperitoneal chemotherapy
D. Löke, Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands.

TUES 41 | ERAS Protocol Implementation for Cytoreductive Surgery with Heated Intraperitoneal Chemotherapy
E. Samlowski, Creighton University , Omaha, Nebraska, USA

TUES 42 | HIPEC models to predict tumor drug penetration in a dynamic 3D environment.
D. Löke, Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands.

TUES 43 | Magnetic Resonance Imaging-guided, Salvage, Percutaneous Cryoablation of Recurrent Prostate Cancer After Radical Prostatectomy: 24-Month Follow-up.
D. Woodrum, Mayo Clinic, Rochester, MN, USA

15:00 - 15:30 **PM Break & Exhibit Time** | Banyan Breezeway

18:00 - 20:00 **Poster Session & Competition (with drinks and hors d'oeuvres)** | Banyan Breezeway

POS 1 | Lidocaine-induced Potentiation of Thermal Damage in Skin and Carcinoma Cells
M. Purschke, Massachusetts General Hospital, Boston, MA, USA.

POS 2 | A new, tunable, multimodal strategy for ablation: exothermic reaction of thioglycolic acid for thermal denaturation whilst targeting disulfide bonds to alter protein structure
E. Cressman, MD Anderson Cancer Center, Houston, TX, USA

POS 3 | FIRST DETAILED PATHOLOGY OF HEPATIC THERMOEMBOLIZATION IN A SWINE MODEL
E. Cressman, MD Anderson Cancer Center, Houston, TX, USA

POS 4 | TISSUE MICROARRAY ANALYSIS OF MORPHOLOGY AND MECHANISMS OF TISSUE DAMAGE BY THERMAL, CHEMICAL, AND THERMOCHEMICAL MODALITIES
C. Guo, MD Anderson Cancer Center, Houston, TX, USA

POS 5 | MULTISITE SOFTWARE PLATFORM OF MRI-GUIDED FOCUSED ULTRASOUND HYPERTHERMIA APPLICATIONS
M. Siddiqui, University of Calgary, Calgary, Alberta, Canada.

POS 6 | Polarized macrophages interact specifically with antibody-labeled magnetic iron oxide nanoparticles
C. Yang, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

POS 7 | Systemically delivered antibody-labelled BNF are less toxic than BNF-plain under alternating magnetic fields
C. Yang, Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan.

POS 8 | Consistent evaluation of specific loss power in magnetic particle hyperthermia
S. Curto, Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

POS 9 | IRON OXIDE NANOPARTICLE PERFUSION AND REWARMING IN RAT HEARTS
Z. Gao, University of Minnesota, Minneapolis, MN, USA

POS 10 | Core-shell engineering of ZnxMn1-xFe2O4@ SiO2:zNd3+ nanoparticles for magneto-photothermal therapy and nanothermometry
A. F. Bakuzis, Institute of Physics, Federal University of Goiás, Goiania, Goias, Brazil

POS 11 | Thermally sensitive natural extracellular vesicles for cancer therapy
R. Griffin, University of Arkansas for medical sciences, little rock, Arkansas, USA

POS 12 | Characterization of Antigen Presentation and T Cell Response under Different Focal Therapeutic Conditions
M. Jiang, University of Minnesota, Minneapolis, Minnesota, USA

POS 13 | Photothermal elimination of Pseudomonas aeruginosa biofilm using Poly(3,4-ethylenedioxythiophene) nanotube/silicone nanocomposite
S. Yates, Wake Forest University Health Sciences, Winston-Salem, NC, USA

POS 14 | Characterizing miniature probes used for focal therapies on small animals
P. Ranjbartehrani, University of Minnesota, Minneapolis, MN, USA.

POS 15 | The use of gold nanoparticles for targeted leukemia cell ablation in mixed testicular cell cultures
A. Altamimi, Wake Forest University Health Sciences, Winston-Salem, NC, USA

POS 16 | The HSP-Accessorized Exosome: Presence in States of Danger, Disease, and Disruption
M. Graner, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA.

POS 17 | Finite element simulation of thermal effect of radiation therapy on breast tumor and tissue
E. Liapi, Johns Hopkins University, Baltimore, MD, USA.

WEDNESDAY, MAY 1ST 2019

07:00 - 17:00	**Registration**	| Grand Palm Colonnade West
07:00 - 08:00	**Continental Breakfast - for all attendees**	| Pavilion
08:00 - 09:00	**Keynote #3** Chair(s): Jennifer Yu **WED 1 | The Role of Adrenergic Stress in Cancer Immunology and Implications for Therapy in Melanoma** M. Ernstoff, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA	| Pavilion
09:00 - 09:30	**AM Break & Exhibit Time**	| Banyan Breezeway
09:30 - 11:30	**Breakout Session: Tumor Immunology - Sponsored by BTG** **Chair(s): Steve Fiering, Ping Liu & Heather Campbell** ***WED 2 | A Novel Multi-Mode Thermal Therapy for Systemic Immunomodulation in Patients with HCC/CLM: A Pilot Study** P. Liu, School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China. **WED 3 | Focal therapy with immunotherapy promotes formation of tumor antigen-specific CD8 T cells and tumor growth control** Q. Shao, University of Minnesota, Minneapolis, MN, USA **WED 4 | Immune checkpoint inhibitors enhance the abscopal effect of local thermo-radiotherapy in a metastatic mouse model** A. Oei, Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. **WED 5 | Stress-induced immunity by regional hyperthermia : A cold tumor becomes hot** R. Issels, Dept.of Medicine III, Munich, Germany. **WED 6 | Hyperthermia and radiation effects on the glioma immune microenvironment** C. Gilmour, Cleveland Clinic, Cleveland, OH, USA. **WED 7 | Better Than Expected Treatment Outcome of an Advanced Anorectal Squamous Cell Carcinoma Using Interstitial** Thermoradiotherapy, Possible Abscopal Immune Response J. Hayes, Gamma West Cancer Services, Salt Lake City, Utah, USA.	| Banyan/Citrus | Indigo

*** 2019 Scholar-in-training Travel Award Winner**

WED 8 | Prussian blue nanoparticles-based antigenicity and adjuvanticity trigger robust antitumor immune responses against neuroblastoma
J. Cano-Mejia, University of Maryland , College Park , MD, USA.

WED 9 | Tumour Ablation Induced Thermal Necrosis Modulates Immune-related Cytokines by Magnetic Resonance-guided Focused Ultrasound Surgery in Bone Metastatic Lesions
F. Hsu, Ph.D. Program for Transnational Medicine, School of Medical Science, Taipei Medical University, Taipei, Taiwan.

WED 10 | What about CAR-T Therapy? An Update of Immune Therapy & Potential of Thermal Therapy
J. Bull, UT McGovern Medical School, Houston, TX, USA

09:30 - 11:30 **Thermal Therapy Treatment Planning Symposium** | Blue Heron
Chair(s): Dario Rodrigues & Dieter Haemmerich

WED 11 | Computer support for ablative liver therapies
J. Strehlow, Fraunhofer MEVIS, Bremen, Germany.

WED 12 | Recent advancements in 3D patient-specific treatment planning for radiofrequency and microwave hyperthermia
P. Kok, Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

WED 13 | Treatment Planning for MR-Guided High Intensity Focused Ultrasound
P. Yarmolenko, Children's National Medical Center, Washington, DC, USA.

WED 14 | Data-driven methodologies for guiding treatment planning of MRgLITT
D. Fuentes, MD Anderson, Houston, Tx, USA

WED 15 | Requirements on HIPEC treatment planning to optimize treatment protocols and improve the efficacy of HIPEC cancer treatment
N. Hanna, University of Maryland School of Medicine, Baltimore, MD, USA.

09:30 - 11:30 **Breakout Session: Nanoparticles #1 - Photothermal Therapy** | Snowy Egret
Chair(s): Rajiv Chopra, Elizabeth Sweeney & Samir Jenkins

WED 16 | Mild hyperthermia enhances drug accumulation and photodynamic therapy efficacy
S. Jenkins, University of Arkansas for Medical Sciences, Little Rock, AR, USA.

WED 17 | Preclinical Safety and Clearance Profile of Plasmonic Gold Nanorods: Bringing Practical Photothermal Therapy to the Clinic.
L. Pagliaro, Siva Therapeutics Inc., Austin, TX, USA

WED 18 | Combined Nanoparticle-based Photothermal Therapy and Epigenetic Immunomodulation for Melanoma
D. Ledezma, The George Washington University Cancer Center, Washington, D.C., DC, USA.

WED 19 | Evaluating the immunological effects of nanoparticle-based photothermal therapy for melanoma
E. Sweeney, George Washington University, Washington, DC, USA.

WED 20 | A biocompatible nanoparticle platform for photothermal therapy of melanoma
S. Torres-Hurtado, The University of Texas at Austin, Austin, TX, USA.

WED 21 | IR820-Loaded PLGA Nanoparticles for Photothermal Therapy of Triple-Negative Breast Cancer
E. Day, University of Delaware, Newark, DE, USA

WED 22 | Sealing and Repair of Soft Tissues using Photothermal Nanomaterials
K. Rege, Arizona State University, Tempe, AZ, USA

WED 23 | EVALUATION OF A PHOTOTHERMAL NANOCOMPOSITE FOR DISTRUPTION OF STAPHYLOCOCCUS AUREUS BIOFILMS
P. Sanchez, Wake Forest School of Medicine, Winston Salem, NC, USA

11:30 - 13:00 **STM President's Symposium: Hot Science in the Face of a Cold Reality - includes lunch** | Pavilion
Chair(s): Michael Graner

WED 24 | Barriers to Successful Nanoparticle-Mediated Delivery
T. Anchordoquy, Skaggs School of Pharmacy and Pharmaceutical Sciences, Anschutz Medical Campus, University of Colorado, Aurora, Colorado, USA

WED 25 | The tumor immune microenvironment is reshaped after systemic exposure to magnetic iron oxide nanoparticles: A study in mouse models of breast cancer
R. Ivkov, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

13:00 - 15:00 **Breakout Session: Cranial and Head and Neck** | Banyan/Citrus
Chair(s): Ali Mohammadi & Jianning Shao

WED 26 | Laser Interstitial Thermal Therapy for Intracranial Lesions
P. Fecci, Duke University, Durham, NC, USA

WED 27 | Mechanisms of Blood-Brain Barrier Permeability by Laser Interstitial Thermal Therapy in a Mouse Model of Glioblastoma
A. Kim, Washington University, Saint Louis, MO, USA

***WED 28 | Stereotactic Laser Ablation for Treatment of Brain Tumors: Lessons Learned from 240 Cases Over the Past Decade**
J. Shao, Cleveland Clinic, Cleveland, OH, USA

WED 29 | Magnetic hyperthermia therapy of experimental glioblastoma in combination with chemoradiation
C. Hadjipanayis, Icahn School of Medicine at Mount Sinai, NYC, NY, USA.

WED 30 | MR guided Head&Neck Hyperthermia: Accuracy Through Integration
G. van Rhoon, Department of Radiation Oncology, Erasmus Medical Center Cancer Institute, Rotterdam, Netherlands.

WED 31 | MR thermometry phantom validation and modeling of a 915 MHz annular phased-array for treatment of brain tumors
D. B. Rodrigues, University of Maryland School of Medicine, Baltimore, MD, USA.

13:00 - 15:00 **Breakout Session: Advances in Image Guided Therapy** | Blue Heron
Chair(s): Chris Diederich & Pegah Faridi

WED 32 | Image-guided doxorubicin delivery for pediatric tumors using MRI-guided high-intensity focused ultrasound hyperthermia and temperature-sensitive liposomes
R. Chopra, UT Southwestern Medical Center, Dallas, TX, USA

WED 33 | Development and pre-clinical evaluation of a microwave ablation system integrated with an image-guidance and treatment planning platform for bronchoscopic transparenchymal lung access
P. Prakash, Kansas State University, Manhattan, KS, USA.

WED 34 | Thermochemical Ablation and the Necessity of a Multi-Modal Imaging Approach
E. Thompson, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

***WED 35 | Microwave ablation system integrated with MRI thermometry for experimental validation of 3D temperature profiles predicted by computational models**
P. Faridi, Kansas State University, Manhattan, KS, USA.

WED 36 | MRI-guided focused ultrasound robotic system for experiments with mice.
C. Damianou, Cyprus university of technology, limassol, Cyprus

***WED 37 | USING MICROWAVE THERMAL ABLATION TO PRECISELY TARGET THE ADRENAL CORTEX, TAKING A MINIMALLY ABLATIVE, CORTICAL-SPARING APPROACH**
P. Donlon, National University of Ireland Galway, Galway, Galway, Ireland.

*** 2019 Scholar-in-training Travel Award Winner**

13:00 - 15:00 **Breakout Session: Drug Delivery and Thermal Sensitive Liposomes** | Snowy Egret

Chair(s): Timo ten Hagen & Anjan Motamarry

WED 38 | CONVECTION ENHANCED DELIVERY OF THERAPEUTICS TO THE CNS: CHALLENGES AND OPPORTUNITIES
M. Vogelbaum, Moffitt Cancer Center, Tampa, FL, USA

WED 39 | The Drug Delivery Controversy
T. ten Hagen, Erasmus MC, Rotterdam, Netherlands

WED 40 | Effect of different hyperthermia methods on drug delivery with thermosensitive liposomes
K. Ramajayam, Department of Pediatrics, Medical University of South Carolina , Charleston, SC, USA.

WED 41 | Therapeutic efficacy of thermosensitive liposomal doxorubicin and short duration focused ultrasound hyperthermia in rabbit Vx2 tumors
M. Santos, University of Toronto, Toronto, ON, Canada.

***WED 42 | Real-time visualization and quantification of doxorubicin delivered by thermosensitive liposomes**
A. Motamarry, Medical University of South Carolina, Chalreston, South Carolina, USA.

WED 43 | The effect of thermosensitive liposomal doxorubicin dose on localized doxorubicin deposition and therapeutic index in Vx2 tumors using MR-HIFU mild hyperthermia
R. Chopra, UT Southwestern Medical Center, Dallas, TX, USA.

WED 44 | Development of a thermosensitive liposome formulation of the anti-cancer drug vinorelbine: parameters that influence drug loading and release
M. Regenold, University of Toronto, Toronto , Ontario, Canada.

15:00 - 15:30 **PM Break & Exhibit Time** | Banyan Breezeway

15:30 - 17:00 **STM Awards Symposium** | Pavilion

2019 George M. Hahn Award Presentation - Hyperthermia's Wild Ride: Taking the Sound Approach - Chris J. Diederich, PhD

30TH J. Eugene Robinson Award Presentation: Apoptosis or Necrosis – Mechanisms of Cell Death induced by Hyperthermia - Ruediger Wessalowski, MD

2019 STM Scholar-in-Training Travel Award Winners

2018 International Journal of Hyperthermia Editor's Award Winners

18:00 - 19:30 ****Robinson Award Reception** | South Lawn/Gazebo

19:30 - 21:30 ****Robinson Award Banquet** | Garden Courtyard

*** 2019 Scholar-in-training Travel Award Winner** **** Requires separate ticket**

THURSDAY, MAY 2ND 2019

07:00 - 17:00	**Registration**	| Grand Palm Colonnade West
07:00 - 08:00	**Continental Breakfast - for all attendees**	| Pavilion
08:00 - 09:00	**Keynote #4** Chair(s): Jennifer Yu **THUR 1 | The Role of Hyperthermia in Child & Adolescent Cancer** **R. Wessalowski, Heinrich-Heine-University, Medical Faculty, Düsseldorf, Germany**	| Pavilion
09:00 - 09:30	**AM Break & Exhibit Time**	| Banyan Breezeway
09:30 - 11:30	**Breakout Session: Temperature Monitoring** Chair(s): David Fuentes and Eleni Liapi **THUR 2 | Non-invasive intratumoral thermal dose determination during magnetic nanoparticle hyperthermia** A. Bakuzis, Federal University of Goias, Goiania, Goias, Brazil **THUR 3 | Preclinical demonstration of the application of magnetic resonance thermal imaging with the VectRx™ multi-applicator coil inductive heating system in swine** P. Floriano, NeoTherma Oncology, Wichita, KS, USA. **THUR 4 | Thermal imaging for monitoring tumor response of diffusing alpha-emitters radiation therapy in a murine model of breast cancer** E. Liapi, Johns Hopkins University, Baltimore, MD, USA **THUR 5 | MR Thermometry of Fat based on Synthesized Temperature Property of Methylene and Methyl Signals** K. Kuroda, Course of Electrical and Electronic Engineering, Graduate School of Engineering, Tokai University, Hiratsuka, Kanagawa, Japan. **THUR 6 | Feasibility of CT thermometry of laser ablations in ex-vivo porcine liver** M. Jacobsen, University of Texas MD Anderson Cancer Center, Houston, TX, USA.	| Banyan/Citrus

09:30 - 11:30 **Heat Shock Proteins in Health and Disease Symposium; sponsored by Cell Stress Society International** | Blue Heron

Chair(s): Michael Graner & Antonio De Maio

THUR 7 | THE HEAT SHOCK RESPONSE: FROM THE DISCOVERY TO THE NEW DOGMA

A. De Maio, Division of Trauma, Critical Care, Burns and Acute Care Surgery, Department of Surgery, University of California San Diego, La Jolla, CA, USA.

THUR 8 | HSP72, CANCER STEM CELLS, RESISTANCE TO THERAPY AND METASTASIS

S. Calderwood, Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston , MA, USA.

THUR 9 | Bridging Innate and Adaptive Immune Responses by Large Stress Protein for Cancer Immunotherapy

X. Wang, Department of Human & Molecular Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA.

THUR 10 | Stressed exosomes ("sexosomes"): stress balls or care packages in passaging stress phenotypes to recipient cells?

M. Graner, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA

THUR 11 | Hyperthermia induces peroxiredoxin antioxidant defenses through transcription factor Nrf2

D. Averill-Bates, Université du Québec à Montréal, Montréal, Québec, Canada

THUR 12 | Development of Heat Shock Protein Inhibitor-Containing Thermosensitive Liposomes for Combination Therapy with ThermoDox and Hyperthermia

M. Dunne, University of Toronto, Toronto, Canada.

THUR 13 | Intravascular Immune Suppression: Overlooked Checkpoint for Cancer Immunotherapy

S. Evans, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA

09:30 - 11:30 **Breakout Session: Nanoparticles #2 - Iron Oxide** | Snowy Egret

Chair(s): Rohan Fenandes & Hattie Ring

THUR 14 | PEG-Coated Iron Oxide Nanoparticles for Nanowarming

J. Pasek-Allen, University of Minnesota, Minneapolis, MN, USA.

THUR 15 | Distribution of Iron Oxide Nanoparticles in Hypothermic Perfused Tissues

H. Ring, University of Minnesota, Minneapolis, MN, USA.

THUR 16 | Novel insights into the possible mechanism of action by nanoparticle mediated tumor growth delay in a transgenic mouse model of breast cancer
P. Korangath, Johns Hopkins University, Baltimore, MD, USA.

THUR 17 | Hexagonal-disk magnetic nanoparticles emphasize the secondary role of Brownian rotation to heating and allow switching between domains of actuation
R. Chantrell, University of York, York, United Kingdom

THUR 18 | Eliciting an Immunological Response Through the Use of Mild Hyperthermia via a Vascular Targeted Iron Oxide Nanoparticle
G. Covarrubias, Case Western Reserve University, Cleveland, OH, USA

THUR 19 | Erythrocyte membrane-coated magneto-fluorescent nanocarriers for thermal therapy and heat-induced immunological responses
A. SOUSA-JUNIOR, Federal University of Goias, Goiania, Goias, Brazil

THUR 20 | Enhancing hyperthermia through magnetic nanoparticle clusters
R. Chantrell, University of York, York, United Kingdom.

THUR 21 | SCALABLE SILICA COATED IRON OXIDE NANOPARTICLES FOR NANOWARMING IN REGENERATIVE MEDICINE
Z. Gao, University of Minnesota, Minneapolis, MN, USA

11:30 - 13:00 **STM Business Meeting - working lunch(STM members only)** | Pavilion

13:00 - 15:00 **Career Development Workshop** | Banyan/Citrus

THUR 22 | A practical workshop to increase NIH grant success
M. Dewhirst, Duke University, DURHAM, NC, USA.
D. Haemmerich, Medical University of South Carolina
E. Repasky, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA
J. Yu, Cleveland Clinic, Department of Radiation Oncology, Department of Cancer Biology, Cleveland, OH, USA

13:00 - 15:00 **Breakout Session: Traditional Hyperthermia - Deep Hyperthermia or Proton Therapy** | Blue Heron

Chair(s): Gerard van Rhoon & Ruediger Wessalowski

THUR 23 | Early Outcomes of Locoregional Deep Hyperthermia with Pencil Beam Scanning Protons Indicate Modest Toxicity with the Promise of Increasing Efficacy
J. Molitoris, University of Maryland School of Medicine, Baltimore, MD, USA.

THUR 24 | Toxicity and Efficacy Outcomes of Concurrent Radiation and Hyperthermia in Soft Tissue Sarcoma
C. DeCesaris, University of Maryland Medical Center Department of Radiation Oncology, Baltimore, MD, USA.

THUR 25 | The effect of the time interval between radiation and hyperthermia on clinical outcome in 400 locally advanced cervical carcinoma patients.
G. van Rhoon, Department of Radiation oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands.

THUR 26 | Concurrent Pencil Beam Scanning Proton Therapy and External Thermal Therapy: Growing Clinical Experience with Promising Results
J. Snider, University of Maryland School of Medicine, Baltimore, MD, USA.

THUR 27 | Similar Rates of Skin Toxicity Associated with Concurrent External Thermal Therapy When Delivered with Pencil Beam Scanning Proton Therapy or Photon/Electron Techniques
S. Samanta, University of Maryland, Baltimore, MD, USA

THUR 28 | Improved Local Control with Hyperthermia (HT) Plus Proton Beam Therapy Compared to Electrons Plus Hyperthermia in Recurrent Breast Cancer?
E. Nichols, University of Maryland School of Medicine, Department of Radiation Oncology, Baltimore, MD, USA

13:00 - 15:00 **Standardizing Language and Data for the Thermal Medicine Community: A Joint STM-ASME Workshop** | Snowy Egret

THUR 29 | Overview of the ASME standards development process & Framework for verification and validation of computational modeling and simulation for medical devices
Dario Rodrigues, PhD, University of Maryland School of Medicine, STM
John Bischof, PhD, University of Minnesota, STM
Robert Ivkov, PhD John Hopkins University School of Medicine, STM
Ryan Crane, Director, Codes and Standards Initiatives, ASME
Christine Reilley, Director, Healthcare, ASME
Luis Pulgarin, Project engineering advisor, Codes and Standards Initiatives, ASME

15:00 - 15:30 **PM Break & Exhibit Time** | Banyan Breezeway

15:30 - 17:00 **Closing Program/Remarks** | Pavilion

ABSTRACTS

MON 1

HOW TO ESTABLISH A HYPERTHERMIA PROGRAM

Zeljko Vujaskovic

University of Maryland School of Medicine,, Baltimore, MD, USA

Abstract

Although hyperthermia therapy has been in use in the United States for several decades, the field has recently undergone renewed interest among the oncology community. Interest in the role of hyperthermia as an adjunct to radiochemotherapy has emerged due to the development of new technologies and positive results from randomized Phase II-III clinical trials. The purpose of this presentation is to provide audience with the key elements necessary to establish a successful hyperthermia program as an integral part of any clinical practice. The presentation will cover needs for technical requirements such as equipment and space. It will describe necessary personnel, their role in the treatment, required training, workflow process and coordination. Adequate cross training of physicians, therapists, physicists and nurses is a critical part of the integration process. Proper implementation and sustainability of hyperthermia program relies on accurate documentation and an effective reimbursement strategy. This will be described together with the importance of appropriate patient selection and indication for treatment as a part of well developed treatment protocols. Establishing reliable referral network is essential to maintain adequate patient volume. This presentation will set up the stage for subsequent lectures that will follow with more relevant details as part of the clinical practice guidelines workshop. In conclusion, successful establishment of hyperthermia program in any institution will depend on the ability to fully integrate hyperthermia clinical service with the rest of clinical operation.

MON 2

PRACTICE GUIDELINES FOR SUPERFICIAL HYPERTHERMIA

Jason K. Molitoris

University of Maryland School of Medicine, Baltimore, MD, USA. Maryland Proton Treatment Center, Baltimore, MD, USA

Abstract

This seminar will focus on development of guidelines to successfully select and deliver optimal hyperthermia treatments to patients with superficial disease, i.e., where the tumor is located within 4 cm from the skin surface. Hyperthermia is a well-known sensitizer of radiation and chemotherapy with a proven clinical record. Advances in the ability to safely deliver mild hyperthermia (39-44°C) has led to a resurgence of this adjuvant cancer treatment modality. Superficial hyperthermia (SupHT) can be delivered using relatively small devices that are not typically cost prohibitive. These devices allow for a versatile array of treatment to both small (e.g. head and neck nodule) and large (e.g., chestwall recurrent breast cancer) treatment areas. Our center has been utilizing SupHT concurrent with radiation for over 6 years and treated more than 150 patients.

Patient populations for which addition of SupHT is appropriate will be reviewed along with the absolute and relative contraindications to SupHT. This will include discussion of diagnoses, tumor location, and prior treatments that would influence consideration of SupHT. The importance of peer review and communication with the treatment teams will be highlighted with examples.

The basic strategies for SupHT delivery will be presented, focusing on microwave applicators that operate at 915 MHz. Guidelines for thermal dose including bolus and target temperatures will be reviewed along with recommendations for monitoring temperature including placement of the 8 available temperature sensors, use of thermal mapping, and role for interstitial versus superficial thermometry. Strategies to optimize patient set up for prolonged treatment and multiple sites will be revised. Finally, this presentation will also address wound management strategies associated with brisk tumor responses derived from the addition of SupHT to radiation therapies.

MON 3

PRACTICE GUIDELINES FOR DEEP HYPERTHERMIA

Mark Hurwitz

Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Deep regional hyperthermia has proven benefit in treatment of a wide range of malignancies as established in numerous clinical trials. The presentation will focus on widely available radiofrequency technology. Key considerations in utilization of deep regional hyperthermia including clinical indications, patient related contraindications, patient and treatment monitoring, strategies to optimize heating, patient set-up and comfort measures, as well as side effects and their management will be presented. The integration of new deep regional heating devices using non-invasive MR thermometry into the modern hyperthermia clinic will also be discussed. The potential impact of non-invasive thermometry and novel treatment paradigms on expanded use and acceptance of hyperthermia as a key part of multimodality cancer therapy will be reviewed.

MON 4

CLINICAL HYPERTHERMIA WORKSHOP---INTERSTITIAL HYPERTHERMIA

John Hayes, Thomas Skidmore, Keighley Swapp, Staci Buttars, Emily Hansen

Gamma West Cancer Services, Salt Lake City, UT, USA

Abstract

Clinical hyperthermia Workshop---Interstitial hyperthermia

Background: Interstitial hyperthermia (IHT) is typically used with interstitial brachytherapy (IBT), in a dual modality treatment that can be called interstitial thermo-radiotherapy (ITR). For lack of financial incentive and not science, IBT and IHT have been on the wane in the USA. Is now a time when ITR can come back from the brink? Can we encourage a new generation to pick up the baton of this clinical challenge? This presentation will focus on practical aspects of ITR treatment delivery.

Methods: Over the past 2 years we have performed ITR treatments on 74 patients with curative and palliative intent on de novo and recurrent tumors. Tumors types/sites we have treated include prostate, oral cavity, oropharynx, neck, breast, lung, skin, extremity soft tissue, abdominal, pelvic, anal, rectal, cervix and vulvar. The process requires image-guided placement of applicators, needles or catheters, using local, regional or general anesthesia. The applicators serve a dual function to deliver robotic IBT and IHT by means of 915 MHz interstitial microwave antennas. Recurrent and high-risk prostate cancer is a good model upon which to learn and gain confidence in ITR skills. IHT can be delivered immediately before or after IBT. The process involves placement of needles with TRUS and fluoroscopic guidance through a template on the perineum; CT imaging for IBT and IHT treatment planning; delivery of IBT treatment; hyperthermia setup that includes distributing the microwave antennas and interstitial thermometers throughout the target according to the treatment plan using the template to number and support the needles; application of 915 MHz power to achieve therapeutic temperatures of 42-44°C; patient monitoring and comfort measures; continuous temperature measurement; dynamic power adjustments to keep temperatures at therapeutic levels and within patient tolerance; calculation of thermal dose; documentation of IHT treatment; removal of needles; clinical follow-up to assess response and monitor side effects and complications.

Conclusions: We have effectively raised intra-tumoral temperatures into the range of 42-44°C for one hour with commercially available equipment and combined that thermal dose with large doses of IBT with encouraging clinical results and acceptable treatment related toxicity. In the quest for better tumor control probability, with abundant biological rational from preclinical research and encouragement from HT clinical trials, ITR is a treatment that needs investment in clinical application to train a generation willing to refine its clinical aspects and explore its use with chemotherapy and immunotherapy.

MON 5

EQUIPMENT, PLANNING AND EXECUTION OF MICROWAVE SUPERFICIAL HYPERTHERMIA TREATMENTS

Paul Stauffer

Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Background: The goal of this workshop is to provide a forum for practical training of hyperthermia treatment personnel to improve on the delivery of safe and effective superficial, deep and interstitial hyperthermia treatments. This presentation will focus on the clinical procedures necessary for planning and executing superficial hyperthermia treatments using microwave hyperthermia equipment that is generally available and approved for clinical use in the USA.

Procedures: This presentation will describe currently available clinical equipment and the typical procedures used to deliver heat treatments to superficial tumors located within 3-4 cm from the skin surface in any area of the body, with recurrent chest wall, neck nodes and melanoma being most common. It will explain procedures used to monitor and control therapy, and provide specific examples of the treatment planning, real time dosimetry, and post-treatment documentation required for each treatment. Special attention will be given to optimizing applicator coupling to tissue with easily fabricated custom water boluses and special applicator mounts that help accommodate heterogeneous tissue regions and contoured anatomy. Thermal monitoring strategies will be reviewed, along with correct interpretation of real time temperature data, patient comfort and toxicity avoidance techniques, and treatment methods to improve thermal dose uniformity over large regions.

Summary: This presentation will cover all practical aspects of delivering a superficial microwave hyperthermia treatment from initial planning and setup to real time clinical optimization and finally post-treatment documentation.

MON 6

EQUIPMENT, PLANNING, AND EXECUTION OF RF DEEP HYPERTHERMIA TREATMENT

Dario B. Rodrigues

University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Summary: Locoregional deep hyperthermia (DHT) is an adjuvant cancer therapy delivered concurrently with radiation therapy that targets solid tumors located more than 4 cm under the skin surface. This workshop aims to provide practice guidelines of DHT treatments of abdominal and pelvic tumors from a physics and therapy perspective.

Equipment: The most common DHT system is the BSD2000, which delivers therapeutic heating to solid tumors by applying radiofrequency (RF) energy at the frequency range 80-120 MHz. RF energy is transmitted to the patient via 8 dipole antennas that surround the patient's body in an annular phased-array configuration. This applicator requires the use of a water compartment (bolus) around the patient to couple RF energy into the body and provide cooling of superficial tissues. The DHT system also includes the ability to monitor temperature continuously during treatment via 8 RF-insensitive thermistors as well as provide multi-point thermal mapping along 1-8 internal catheters.

Planning: The DHT treatment plan requires the measurement of patient and tumor dimensions using CT/MR images; optimization of a patient-specific power deposition pattern (SAR) by means of power, frequency, and phase adjustments; location of internal and external temperature monitoring points using the SAR plan and patient's specific condition; and calculation of thermal mapping parameters for the intraluminal and/or interstitial catheters.

Execution: In preparation for treatment, the patient is placed on a suspended sling; catheters are inserted into the tumor and/or tumor surrogate, such as the bladder, the rectum, and/or the vagina; and temperature sensors are placed according to the treatment plan. The applicator is then positioned over the tumor region and the water bolus filled for snug contact with skin all around the patient. An additional water bolus is placed between the thighs to protect the genital and groin areas. The patient position is adjusted to be centered within the applicator and energy is focused electronically to the tumor region. The therapeutic goal is to achieve 40-43°C in the tumor for 60 min, which implies a total treatment time up to 2 hours including the setup preparations. Typical body reaction to this treatment is often compared to running and requires monitoring vital signs every 15-30 min and using creative comfort strategies, including multiple pillows for the neck, arms, and knees; as well as active cooling via fans and/or ice packs. Besides treatment delivery, this presentation will also cover calculation of thermal dosimetry and documentation required for each treatment.

MON 7

A CRITICAL ANALYSIS OF METHODS TO IMAGE AND QUANTIFY HYPOXIA IN THE CONTEXT OF HYPERTHERMIA AND THERMAL ABLATION TRIALS

Mark Dewhirst

Duke University, DURHAM, NC, USA

Abstract

Hypoxia is a critical determinant of treatment outcome for radiotherapy, chemotherapy molecularly targeted agents and immunotherapy. Despite overwhelming evidence of its importance, no method for measuring it has emerged as a standard of care. Accordingly, hypoxia is not used as a selection tool for using methods that could reduce hypoxia. The lack of ability to select patients who have hypoxic tumors for hypoxia modification trials undoubtedly contributed to failure of dozens of phase III trials, involving over 10,000 patients, where the goal was to demonstrate a therapeutic benefit of targeting hypoxic cells in combination with radiotherapy or drugs that are less effective in hypoxic conditions..

PET methods are the most well studied and validated methods to measure hypoxia, but the cost is prohibitive for most trials and the number of sessions that can be conducted per patient is limited because of patient safety as well as cost. Newer, relatively low cost methods, such as MRI and optics are becoming available and should be considered in future trials.

A variety of methods have been studied that could reduce hypoxia, including hyperoxic gases, drugs that alter perfusion, and drugs that selectively kill hypoxic cells. Hyperthermia has potential to reduce hypoxia, by changing perfusion as well as by reducing oxygen consumption rate. A number of pre-clinical studies have shown that hyperthermia is effective in reducing tumor hypoxia, yet, there only a handful of studies in canine/ human trials.

This review will provide an overview of methods that can measure and monitor changes in tumor hypoxia. Emphasis will be placed on the importance of considering such measurements in future human clinical trials involving hyperthermia.

MON 8

CLINICAL WORKFLOW, DOCUMENTATION AND REIMBURSEMENT OF HYPERTHERMIA TREATMENTS

Erika Maynor, Dario B. Rodrigues, Jamie Lepage, Zeljko Vujaskovic

University of Maryland School of Medicine, Baltimore, MD, USA

Abstract

Background: Hyperthermia therapy (HT) is becoming more prominent in Departments of Radiation Oncology (DROs) due to its ability to boost radiotherapy treatments (RT). A successful integration of HT in DROs requires an effective clinical workflow, documentation and reimbursement strategy.

Workflow and documentation: The HT clinical workflow starts with proper patient selection, which involves, medical, nursing and physics personnel. The next step is to collect insurance approval or an alternative reimbursement strategy. Once eligibility and finances are cleared, the patient schedule is established so that the timing between RT and HT treatments is minimized. Depending on the type of HT (superficial, interstitial, or deep), the overall time the patient spends in the HT room can vary from 90-180 min, which should be considered while planning the daily HT treatment schedule. A series of documentation is then generated that will later be associated with reimbursement billing codes. By chronological order, these documents are: consent, prescription, simulation order, special physics consult order, special physics consult, treatment planning, simulation summary, procedure summary, thermal dosimetry summary, and treatment summary. The use of such documents should be addressed in a standard operating procedure (SOP) with specific guidance for physicians, physicists, therapists, nurses, and administrators. Besides billing, an accurate documentation of the planning and hyperthermia treatments is extremely important for retrospective data analysis as well as treatment quality control.

Reimbursement: HT reimbursement poses some challenges that rely on awareness of all billing codes that should be charged and their compatibility with RT billing codes. Current Procedural Terminology (CPT) codes are the United States' standard for how medical professionals document and report health services, which are then used for billing purposes. The following CPT codes, their limited use when combined with radiation, and the required documentation will be reviewed: RT/HT Prescription (CPT 77470), physics consultation (CPT 77370), hyperthermia patient simulation (CPT 77280), custom water bolus (CPT 77332), thermal dosimetry (CPT 77300), externally-generated deep HT (CPT 77605), externally-generated superficial HT (CPT 77600) and interstitial HT (CPT 77610 or CPT 77615).

Summary: This presentation aims to provide hyperthermia professionals with specific knowledge not readily available in terms of HT clinical workflow, documentation and reimbursement strategies for hyperthermia treatments.

MON 9

HISTORY OF HYPERTHERMIA IN NEURO-ONCOLOGY

Alireza Mohammadi

Cleveland Clinic, Cleveland, Ohio, USA

Abstract

Focal hyperthermia has been used to treat cancer since 5000 years ago in ancient Egypt. Over time it has changed mostly because of limitation in technology. modern hyperthermia started more than a century ago when it was noticed that high fever can be helpful in treatment of in-operable cancer. also after invention of laser and possibility to deliver focal hyperthermia it was more enthusiasm in this field. in the field of Neuro-Oncology, recent advances in using MR-Thermometry as well as sophisticated laser probe designs resulted in a resurgence of the use of hyperthermia to treat brain cancer. In this topic,we will review evolution of hyperthermia treatment over time with a focus on neuro-oncology.

MON 10

THE CROSSTALK AND IMPACT OF THE MICROBIOME ON CANCER INITIATION, PROGRESSION AND TREATMENT MODALITIES

Ruud Dings

University of Arkansas for Medical Sciences, Little Rock, AR, USA

Abstract

Various microbial ecosystems reside on the human body consisting of commensal, symbiotic and pathogenic bacteria, archaea, protists, fungi and viruses. Locations include the gastro-intestinal tract, oral cavity, respiratory tract, urogenital tract, and skin. In the human intestine alone, the total number of bacteria is estimated to be around 1x10^14 (~2 kg), outnumbering the eukaryotic cells by a factor of ten or more. It is increasingly recognized that the microbiota is a key component in the development and homeostasis of a fully functioning immune system. Consequently, a disturbance in the composition of the microbiota, also termed dysbiosis, may result in an increase in the risk of cancer but also various other diseases, such as inflammatory (e.g., inflammatory bowel disease, Crohn's disease), autoimmune (e.g., celiac disease, arthritis, and multiple sclerosis), allergy-based (e.g., asthma and atopy), metabolic (e.g., diabetes, obesity, metabolic syndrome, and kwashiorkor), psychological/neurological (e.g., autism) in nature. Recent research shows that certain cancer therapies, conventional chemotherapeutics as well as immunotherapies, rely on the microbiota for its efficacy. Delineating how the microbiota impacts indigenous cancer immunosurveillance as well as treatment-induced immune responses has the potential for identifying new treatment strategies and hopefully more effective therapies and prophylactics.

MON 11

USING THERMAL THERAPY TO FIRE UP IMMUNOTHERAPY? WHERE ARE WE NOW?

Elizabeth Repasky

Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Abstract

The healing powers of heat have been recognized for hundreds of years. More recently, researchers have implicated increased tissue or body temperature in the regulation of the immune system, particularly in the settings of inflammation, autoimmunity and cancer. Both fever and hyperthermia have been linked to these changes in immune function. This educational session will review selected research, published in the last 15 years, with the goal of identifying major gaps in the field. Critical areas for future research will be highlighted, with a special emphasis on immunotherapies that could be enhanced by specific types of thermal therapy and to consider current barriers to achieving this goal.

MON 12

IT TAKES A VILLAGE – TURNING MULTIDISCIPLINARY EFFORTS INTO CLINICAL SUCCESS - THE STORY OF KATIE – A FACE TRANSPLANT RECIPIENT

Brian Gastman

Cleveland Clinic, Cleveland, OH, USA

Abstract

In all areas of medicine physicians and care givers take on major personal responsibility for their patients. Sometimes being able to accept that one does not know or cannot do everything on their own is a challenge for those in medicine. This is especially true as what drives so many in the medical field is their ability to take on complex challenges and see them through till their conclusion. The paradigm of working solo is changing as multidisciplinary clinics and approaches to patient care are ever increasing. In fact recent data from large databases like the national cancer database show that in cancer for instance, tertiary multi-disciplinary based centers offer the best outcome for patients which is a completely independent variable and that is on top of the fact that those same institutions are taking care of the most difficult patients, expected to have the worst outcomes. A face transplant is a rare and still considered experimental surgery, but is also the last option for patients with some of the most extensive pathologies in all of medicine. To achieve success in this field groups need to be constantly striving for improvement. But what is also clear is that these groups, e.g. surgeons are really a team working within a tapestry of a team of teams.

Here at the Cleveland Clinic, we performed our 3rd successful face transplant. More than any of the previous surgeries this one was by far the most complex and required the most coordination. In the end the technical, surgical feat was just one step of many which made the outcome what it is. Most striking was the coordination of over 200 care givers from dozens of disciplines all devoted to be a singular entity to make this once-thought-of fantasy, a reality. This talk will delve into the details of that process and give the audience an appreciation for multi-disciplinary care at the pinnacle of excellence. These efforts can now be translated into any field of medicine to break down a complex case or clinical field and through a group effort achieve success.

TUES 1

ADDRESSING CANCER CHALLENGES THROUGH NUCLEAR APPLICATIONS: THE ROLE OF THE IAEA

May Abdel-Wahab

International Atomic Energy Agency, Vienna, Austria

Abstract

Cancer continues to be a challenge globally. Increasing recognition of the importance of this issue is evident through the many new global initiatives, high level meetings and resolutions. As the world organizes, global cancer incidence continues to rise. From 2012 to 2018, new cancer cases increased from 14.1 million to 18.1 million, while deaths increased from 8.2 million to 9.6 million (Globocan 2018). Immediate concerted action is needed to support the prevention, diagnosis and treatment of cancer. Nuclear applications, including radiology, nuclear medicine and radiotherapy are essential for the management of cancer. However, access to these techniques is limited in many regions of the world. In addition, the quality and safety that ensure that patients glean the benefits of this technology can be a challenge, even in HIC. Furthermore, the technical complexity requires guidelines to ensure quality of delivery as well as appropriate education and training of the workforce. In addition, guidance in design of facilities and procurement of equipment can help avoid issues that can affect the delivery of care in the future. The IAEA is a UN agency with the nuclear mandate, including in health. The IAEA's efforts to address some of these challenges through activities, creation of opportunities, research and partnerships with other organizations will be presented.

TUES 2

CONCURRENT EXTERNAL THERMAL THERAPY AND RADIATION IN THE TREATMENT OF CUTANEOUS MALIGNANCIES: A SINGLE INSTITUTION EXPERIENCE

Emily Kowalski1, J.W. Snider2, Stephanie Rice1, Cristina Decesaris1, Osman Siddiqui1, Jason Molitoris2, Dario Rodrigues2, Zeljko Vujaskovic2

1University of Maryland Medical Center, Baltimore, MD, USA. 2University of Maryland School of Medicine, Baltimore , MD, USA

Abstract

Introduction: External thermal therapy (ETT) is an excellent radiosensitizer when delivered concurrently with radiation therapy (RT). Concurrent ETT and RT lends itself to safe and efficacious treatment of cutaneous malignancies with the promise of increased efficacy despite more advanced/bulky tumors.

Methods: At our institution, between 2013 and 2018, 20 patients were treated with this concurrent ETT/RT for cutaneous malignancies, most often with curative intent (n=17, 85%). Patients had a median age at diagnosis of 71 (range), were predominately white (81%), and male (55%). Histopathologies included squamous cell (n=11), basal cell (n=2), basosquamous (n=2), and merkel cell (n=1) carcinomas as well as melanomatous (n=5) skin lesions. One patient received two ETT courses for separate lesions. Three patients were known to harbor distant metastases. Eleven patients underwent prior surgical resection and four patients underwent prior radiotherapy. Greater than 50% (n=11) lesions treated were recurrent. Head and neck (n=9) and extremities (n=9) were the most common sites; however a scapular, chest, and inguinal lesion were also treated. The majority of patients underwent intensity modulated radiotherapy (n=9) or electron therapy (n=6) to a median dose of 58 Gy (range 25-74 Gy) in a median fraction size of 2.4 Gy (range 1.2-5 Gy). Patients were also treated with protons (n=3), HDR brachytherapy (n=1), and 3D-CRT (n=2). A median of 8 sessions (range 4-18) of ETT were delivered via the BSD-500 system; target temperature ranged from 40-44 degrees for 40-60 minutes. In a subset of patients, systemic therapy was administered concurrently (n=3) or after ETT (n=3).

Results: ETT and radiation were well tolerated. With a median follow-up of 15.1 months (range 2.6-60), the most common acute toxicities were grade 3 dermatitis (n=4), grade 1-2 dermatitis (n=14), grade 1-2 pain (n=13), grade 1-3 fatigue (n=13) and grade 1-2 hyperpigmentation (n=15). No grade 4 or 5 toxicities were reported. One patient experienced chronic would healing difficulties, while all other patients' toxicities were self-limited. Six patients (30%) experienced a local failure after treatment and eight patients (40%) died during follow-up.

Conclusions: Combined ETT/RT is a safe, efficacious and well-tolerated regimen for treatment of advanced cutaneous malignancies. While follow-up is early, initial results are promising and warrant further investigation.

TUES 3

COMBINED RADIOTHERAPY AND INFRARED HYPERTHERMIA FOR IMPROVED NON-MELANOMA SKIN CANCER TREATMENT: A PILOT FEASIBILITY STUDY TO EVALUATE LOCAL CONTROL AND COSMESIS

Edward H. Abraham, M.D.1,2, David M. Bower, M.D., Ph.D.2, Mark E. Pomper, M.D.2

1Hyperthermia Associates, LLC, Claremore, OK, USA. 2Horizon Medical Services, Tamarac, Florida, USA

Abstract

Introduction: The purpose of this study is to analyze efforts to integrate hyperthermia and radiotherapy for the management of non- melanoma skin cancers. While radiation therapy alone is adequate in a majority of cases of smaller tumors (> 90% local control of low to moderate grade basal and squamous cell carcinomas < 1.0 cm), we are testing whether addition of infrared hyperthermia and in some cases photo bio-modulation (PBM) can improve local control and enhanced cosmesis in the case of more aggressive tumors and/ or tumors in close proximity to critical structures such as the eyes, nose or ears. In these locations failures can be cosmetically and functionally debilitating or lethal. A secondary purpose is to investigate the optimal sequencing of the hyperthermia administration(s). We desire to compare the efficacy of HT before RT vs. hyperthermia after RT vs hyperthermia given both before and after RT.

Methods: Near infrared hyperthermia heating sources were used to generate skin heating temperatures between 43°C and 45°C. Heating was administered for twenty minutes before and/ or twenty minutes after administration of ionizing radiation. Target tissue temperatures were monitored with specialized RFID thermal monitoring chips and infrared thermometry. Hyperthermia was administered in conjunction with every radiation fraction. A general RT fractionation scheme consisted of treatments two non-sequential days per week with a fraction size from 250 cGy to 400 cGy and a cumulative dose from 2,500 cGy to 4,000 cGy at the end of five weeks. Centers utilized different sources of radiation therapy consisting of the following: 1. Superficial radiation x-ray machines (100 kV), 2. Electron-beam therapy generated on megavoltage linear accelerators, 3. Brachytherapy (either HDR or electronic). Additionally, some patients with larger lesions received laser PBM to normal tissue surrounding the tumor site in order to enhance in ingrowth of normal tissue to replace the irradiated tumor tissue.

Results: This approach has now been applied in several clinics with excellent patientacceptance and tolerance (~ 95%) of patients were able to complete the prescribed HT, absence of adverse effects (~97%) and excellent tumor control (~90%) and good cosmesis as judged by the patient and physician (~85%). Less than 5% of the treated tumors required surgical salvage.

Conclusions: The prevalence of skin cancers is rapidly increasing due in large part to past cumulative sun exposures; therefore, any efforts to improve therapy will have important societal benefits. We have demonstrated a convenient and effective method of improving treatment by integrating hyperthermia into clinical practice with excellent tumor control and cosmetic outcomes. No evidence of thermal resistance was noted even when in some cases hyperthermia was administered daily with 5 fractions a week for some large tumors. A future goal is determining how thermal doses and radiation fractionation can be optimized to minimize late effects while maintaining excellent tumor control rates.

TUES 4

A PILOT TRIAL OF HYPERTHERMIA IN COMBINATION WITH OLAPARIB IN BREAST CANCER PATIENTS WITH CHEST WALL RECURRENCES

Saveri Bhattacharya, Matt Schiewer, Rita Murphy, Parmila Rani Anne, Nicole Simone, Voichita Bar Ad, Maysa Abu Khalaf, Daniel P. Silver, Rebecca Jaslow, Frederick M. Fellin, Allison M. Zibelli, Ana Maria Lopez, Adam Berger, Paul Stauffer, Mark Hurwitz

Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Chest wall recurrences represent a significant source of morbidity for breast cancer patients, causing symptoms including bleeding, ulceration, infection and pain. Approximately 5 to 10% of breast cancer patients undergoing a mastectomy will have a chest wall or nodal recurrence within ten years after surgery. Unfortunately, after radiation, patients with unresectable isolated loco-regional breast cancer have very few treatment options.

In this novel trial, breast cancer patients with chest wall recurrences will be treated with olaparib, an oral targeted therapy that is an inhibitor of the poly ADP ribose polymerase (PARP), concurrently with chest wall hyperthermia. Hyperthermia induces degradation of the BRCA2 protein, thereby leading to defective homologous recombination DNA repair, and sensitization to PARP-1 inhibitors. Krawczyk and colleagues reported that mild hyperthermia (41–42.5 °C) induces degradation of BRCA2 and inhibits homologous recombination in cervical cancer cell lines. Hyperthermia can sensitize innately homologous recombination proficient tumor cells to PARP-1/2 inhibitors. Olaparib is a PARP inhibitor currently approved for metastatic ovarian cancer and metastatic breast cancer with BRCA1 or BRCA2 mutation. Our hypothesis is the combination of olaparib with hyperthermia will be a safe and tolerable combination for breast cancer patients with chest wall metastases.

We plan to treat patients with olaparib given twice a day at the appropriate dose level for 4 weeks in combination with chest wall hyperthermia (heating skin to 43 ° Celsius for 1 hour) for 3 weeks. No external beam radiation will be given at this time. We will assess the local progression free survival, one-year progression free survival, overall response and quality of life scores for these patients. We plan to obtain skin biopsies to evaluate biomarkers of homologous recombination deficiency including BRCA1, BRCA2, RAD51 as well as gH2AX as an indicator of DNA damage. We plan to evaluate the safety and the maximum tolerated dose of the combination of olaparib (at 100 mg BID, 200 mg BID, and 300 mg BID) and hyperthermia and intend to enroll sixteen patients in this clinical trial.

TUES 5

HYPERTHERMIA AND RADIATION FOR RECURRENT BREAST CANCER

Johnathan Zeng1, Sharvari Dharmaiaha2, Vinay Rao2, Zi Ouyang1, Tianjun Ma1, Kevin Yu1, Peng Qi1, Andrew Godley1, Ping Xia1, Jennifer Yu1

1Cleveland Clinic, Cleveland, OH, USA. 2Case Western Reserve University, Cleveland, OH, USA

Abstract

Background/Purpose: Treatment for locally recurrent breast cancer within a previously irradiated field poses a challenge because the benefits in local control must be weighed against the increased risk of side effects from repeat radiation. For these patients, hyperthermia has emerged as an adjunct treatment that can improve the radiosensitivity of cancer cells. The primary objective of this retrospective study is to evaluate local control with hyperthermia and radiation for breast cancer. The secondary objectives are to evaluate acute and long-term toxicity of treatment, dose to heart and lung, and overall survival rate.

Methods: This study is comprised of 36 patients (median age 59.5) who received concurrent hyperthermia treatment with radiation for recurrent breast cancer from February 2011 to April 2017. These patients previously progressed on multiple systemic treatments. Patients received adjuvant hyperthermia twice weekly prior to radiation (median dose 39.0 Gy, range 20.0 – 64.0 Gy). Median T90 was 40.2° C. Median follow-up was 11.5 months (range 1 – 137 months). Dose volume histograms to heart and lung were evaluated.

Results: Thirty patients (83.3%) previously received radiotherapy with a median dose of 60.4 Gy (range 50.4 – 66.0 Gy). Six patients were not previously irradiated. The median repeat radiation volume was 574 cc (range 11-3620 cc), using on-face electron beam, tangent beams, or IMRT techniques. Complete response (CR) was observed in 17 patients (47.2%), partial response (PR) in 5 patients (13.9%), stable disease (SD) in 11 patients (30.6%), and progressive disease (PD) in 3 patients (8.3%). Twenty-six patients experienced acute grade 1 and 2 toxicities, primarily pain and erythema, and twenty-six experienced long-term grade 1 and 2 toxicities, mainly hyperpigmentation and lymphedema. No grade 3 or higher grade toxicities were seen. Dose to heart and lung were acceptable. Heart and lung doses were higher for patients receiving IMRT technique compared to tangents or electrons.

Conclusions: Hyperthermia and radiation provide good local control with a favorable side effect profile in heavily pre-treated patients. Patients with large volume of disease may be treated with combined thermoradiotherapy for palliation. Patients with locoregional recurrent breast cancer should consider this as a viable treatment option.

TUES 6

TEMPERATURE AND THERMAL DOSE DURING HYPERTHERMIA TREATMENT FOR PATIENTS WITH RECURRENT BREAST CANCER: A SYSTEMATIC REVIEW OF THE RELATIONSHIP TO TUMOR RESPONSE AND HYPERTHERMIA ASSOCIATED TOXICITY

Akke Bakker1, Geertjan van Tienhoven1, Jacoba van der Zee2, Coen Rasch1, Hans Crezee1

1UMCA, Amsterdam, Netherlands. 2Erasmus MC, Rotterdam, Netherlands

Abstract

Background. Hyperthermia (HT), heating the tumor to 40-45°C, is a known radiotherapy (RT) and chemotherapy sensitizer. The additional benefit of HT to RT and chemotherapy has been proven, for example, in randomized trials concerning recurrent breast cancer. However, tumor response after RT combined with HT varied widely throughout these studies. We performed a systematic review to investigate whether there is a relationship between achieved temperatures and thermal dose during HT and tumor response and HT associated toxicity for patients with recurrent breast cancer.

Methods. Three databases, i.e. EMBASE, PubMed and Cochrane library, were searched with Medical Subject Headings terms (MeSH) "Breast Neoplasms" AND "Radiotherapy" AND "Hyperthermia, Induced". The final search was performed on October 9th 2017. The total number of records was 597, after removing duplicates 393. Based on title and/or abstract 320 records were excluded and an additional 51 were excluded based on the full text.

Results. Twenty-two papers were included in the systematic review, reporting a total of 2141 patients with recurrent breast cancer; 1671 patients with macroscopic disease (78.0%) and 470 patients with microscopic disease (22.0%). In total, 27 different thermal (dose) parameters were reported. Nine of the 22 studies (n=940) reported an univariate relationship between tumor response with thermal (dose) parameters, which remained significant in multivariate analysis in two studies (n=176; maximum temperature ≥42°C, maximum(minimum CEM43°C) and sum(minimum CEM43°C)). Duration of local control was significantly associated with thermal (dose) parameters in five studies for univariate analysis (n=524), and one study for multivariate analysis (n=59; average temperature). There was a significant association between overall survival and thermal dose in two studies (multivariate; n=280; median CEM43°C, sum(minimum CEM43°C) ≥ 6 minutes). HT associated toxicity (grade 2 and 3 blisters) was reported in eighteen studies, five studies found a significant association with maximum temperature in univariate analysis (n=418), which remained significant after multivariate analysis in one study (n=89; maximum temperature and % temperature >45°C).

Conclusion. Overall, temperature variables and thermal dose are poorly reported in studies concerning patients treated with RT+HT for recurrent breast cancer. Several studies report an evident relationship between the achieved temperatures and thermal dose during HT treatment and tumor response, duration of local control, overall survival and HT associated toxicity; i.e. higher temperatures result in more toxicity while improving tumor response.

TUES 7

A SINGLE-INSTITUTION EXPERIENCE OF CONCURRENT EXTERNAL THERMAL THERAPY WITH RADIATION THERAPY AS A PALLIATIVE CANCER TREATMENT

Osman Siddiqui, James Snider, Santanu Samanta, Cristina DeCesaris, Emily Kowalski, Stephanie Rice, Dario Rodrigues, Jason Molitoris, Zeljko Vujaskovic

University of Maryland, Baltimore, MD, USA

Abstract

Introduction: External thermal therapy (ETT) is a well-tolerated treatment which functions as an excellent radiosensitizer when used concurrently with radiotherapy (RT). Due to its ease of administration and promise of increasing treatment durability, our center has used ETT with increased frequency in both the curative and palliative settings. We hypothesized that this combination can provide improved symptomatic relief and local control in those patients with advanced disease requiring palliation without substantial added toxicity.

Methods: A retrospective IRB-approved review of all patients treated with ETT concurrent with RT with palliative intent was performed at our institution. We collected patient characteristics including age, gender, histology of disease, disease status, RT dose, technique, and ETT parameters to assess the disease control with our intervention. Local control was defined as start of treatment to date of local failure or last follow-up.

Results: Fifty-five patients from 2013-2018 with a median age of 60 (range, 33-92 years) were treated with palliative radiation therapy with concurrent hyperthermia in the University of Maryland's Department of Radiation Oncology. Two of these patients had multiple treatments for a total of 58 courses of therapy. Fifty-six (96.6%) of these treatments were completed with ETT while two involved interstitial hyperthermia. Forty-nine (84.5%) treatments were in the setting of recurrent disease and 18 (31.0%) had measurable distant metastatic disease at the time of treatment. Histologies included breast (n=26), sarcoma (n=7), renal (n=5), head & neck (n=3), skin (n=3), bladder (n=2), lung (n=2), pancreatic (n=2), adrenal (n=1), anal (n=1), endometrial (n=1), esophageal cancer (n=1), lymphoma (n=1), mesothelioma (n=1), multiple myeloma (n=1), and ureter cancers (n=1). Radiation treatments involved a median delivered dose of 44 Gy (10.0-70.0 Gy) using photons, electrons, protons, brachytherapy, or a combination thereof. ETT had the following characteristics, median (range): 7 (2-20) treatments per course to a target temperature of 43°C (40-44°C) over 60 minutes (16-60 minutes) of therapeutic time. Median local control was 100.5 days (9-1155 days) while overall survival was 177 days (9-1337 days). Of the 38 patients that died, 23 (60.5%) were locally controlled until death. Toxicity from these treatments generally involved skin reactions and pain, with six patients (10.3%) experiencing grade III dermatitis, and one experiencing grade III pain limiting self-care.

Conclusions: The combination of hyperthermia and radiation therapy for palliation has been utilized at our institution with limited significant toxicity. Further investigation is necessary to derive which populations benefit most from combined ETT-RT treatment.

TUES 8

THERMAL ABLATION OF MUSCULOSKELETAL TUMORS: INDICATIONS, TECHNIQUES, AND RESULTS.

Hakan Ilaslan

Cleveland Clinic, Cleveland, Ohio, USA

Abstract

The purpose of this presentation is to summarize image-guided thermal ablation of musculoskeletal tumors on the basis of clinical application including patient workup, procedural techniques, and post-ablation follow-up. Different techniques of percutaneous ablative treatments including radiofrequency/microwave ablation and cryoablation will be discussed. This minimally invasive treatment option can be combined with systemic treatment and other forms localized therapy such as cementoplasty or radiation.

TUES 9

APPLICATIONS OF 19F MAGNETIC RESONANCE IMAGING IN THERMOCHEMISTRY WITH PATHOLOGIC CORRELATION

Emily Thompson, Samuel Einstein, James Bankson, Erik Cressman

The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Introduction: Thermochemical ablation (TCA) is a novel treatment under development for hepatocellular carcinoma, a devastating disease with over 800,000 deaths annually.1 In TCA, an exothermic reaction induces tissue death via thermal and osmotic stresses. Accurate mapping of both mechanisms is required for dose determination and prediction of tumor response. We hypothesize that use of trifluoroacetic acid (TFA) will enable fluorine-19 magnetic resonance (19F-MR) as an imaging-based mapping technique. This work also evaluated the feasibility of 19F-MR relaxometry-based temperature imaging as a tool for evaluating thermal stress induced by TCA.

Methods: TCA was performed by using 10M TFA and NaOH into small ex-vivo porcine liver sections which were scanned with proton and 19F-MR performed with a Bruker 7T Biospec USR 70/30 and custom-built 19F volume coil tuned to 282.56MHz, the resonance frequency of 19F. A rapid acquisition with relaxation enhancement (RARE) sequence was used to image the acetate distribution with an acquisition time of approximately 5 minutes and 35 seconds. 19F images were superimposed onto proton images acquired under similar conditions. To evaluate the thermal imaging capabilities of 19F-MR, the temperature-dependent spin-lattice relaxation time constant (T1) of a 2.0M TFA solution was measured at various temperatures ranging from 14°C to 42°C. A saturation-recovery sequence (VTR-RARE) was used to measure T1. The spin-lattice relaxation rate constant (R1 = 1/T1) was calculated and plotted against temperature and a linear least-squares regression analysis was used to determine the linear fit. After scanning, tissue sections were fixated in formalin and prepared for histological analysis via hematoxylin and eosin staining to determine the extent of ablative damage.

Results: The distribution of TCA reaction products was successfully imaged with 19F-MRI. SNR proved sufficiently high to image with matrix sizes of 32x32 and 64x64, providing adequate resolution to determine relative location and concentration of fluorine in ex-vivo tissue. Histological analysis showed clear margins of tissue damage resulting from ablation. The thermometry study utilizing 19F-MR suggested a strong linear relationship between R1 and temperature ($R2 = 0.9529$) with a slope of -3x10-6 °C/ms.

Conclusion: Superimposition of 19F images onto proton images enabled correlation of fluorinated product distribution and anatomical location. Although preliminary, 19F-MR temperature data show promise in the development of 19F-MR thermometry. Our results support the hypothesis that 19F-MR can be used to determine the spatial location and thermal profile of TCA. Future experiments will further progress these techniques.

References

1. Global Burden of Disease Liver Cancer Collaboration. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol. 2017;3(12):1683–1691. doi:10.1001/jamaoncol.2017.3055

TUES 10

PILOT SURVIVAL STUDY OF CATHETER-BASED ULTRASOUND THERMAL ABLATION OF TUMORS IN GENETICALLY ENGINEERED ONCOGENIC PIGS

Lauretta Rund1, Emery Williams2, Goutam Ghoshal2, Paul Neubauer2, Chris Diederich3, Larry Schook1, Everette Burdette2

1University of Illinois, Urbana, IL, USA. 2Acoustic MedSystems, Inc., Savoy, IL, USA. 3University of California, San Francisco, San Francisco, CA, USA

Abstract

Background: Development of ablative therapies to solid organ malignancies is challenging due to the lack of larger animal models which can simulate the size and scale aspects of the physical environment and the clinical workflow characteristics encountered while treating a human patient. Thus far, no animal model has been reported that can selectively grow tumors that simulate size in animal model comparable to a human patient, which are well-suited for device technical evaluation. We propose to assess the treatment efficacy of 3D spatially-registered real-time image-guided catheter based ultrasound (CBUS) thermal therapy in an induced tumor grown in genetically engineered oncogenic pigs, specifically soft tissue leiomyosarcomas of the extremity and retroperitoneal regions.

Methods: A transgenic 'oncopig' line encoding a Cre recombinase inducible transgenic encoding KRASG12D and TP53R17H, a commonly mutated oncogene and tumor suppressor, respectively, in human cancers was created. Treatment of cells derived from these oncopigs with adenoviral vector encoding Cre (AdCre) led to KRASG12D and TP53R17H expression, which rendered the cells transformed in culture and tumorigenic when engrafted into immunocompromised mice. Injection of AdCre directly into these oncopigs led to the rapid and reproducible development of soft tissue sarcomas in the muscle and retroperitoneal areas. Once the tumor reached approximately 2cm by 3cm, it was treated with CBUS. A <1cm incision was made to insert catheter. Narrow-band sectored tubular transducers were used to precisely deliver energy to the treatment region. Ultrasound image guidance combined with 3D EM tracking were used to place the therapy catheter in the target region. The size of the tumor was monitored using ultrasound imaging post treatment during the 1-4 week survival period.

Results: Insertion of US therapy catheter under image-guided ultrasound was used for ablating intramuscular (IM) and retroperitoneal (RP) tumors. The tumors were treated for 6-9 minutes at 7Watts acoustic power (15-18W/cm2). Thermocouples inserted into the tumors (intratumorally and at tumor boundary) measured 55-65C during the treatment. Histopathology analysis showed coagulative necrosis, scar tissue development and complete ablation of the tumor using single US therapy catheter, configuration. Post ablation, the survival animal showed diminishing of tumor size based on ultrasound imaging and gross pathology indicated only fibrous connective tissue at the tumor site.

Conclusion: The results suggest catheter-based therapeutic ultrasound can be used to perform fast volumetric ablation of solid tumors. The tracked ultrasound image guidance is important to guide and accurately place the catheter at the target for precise volumetric treatment.

TUES 11

ENDOLUMINAL ABLATION OF THE MAIN PANCREATIC DUCT AS AN EXOCRINE PANCREATIC ATROPHY-INDUCING PROCEDURE: A PIONEER METHOD FOR AN OLD NEED

Ana Andaluz1, Elzbieta Ewertowska2, Xavier Moll1, Adrià Aguilar1, Felix Garcia1, Dolors Fondevila1, Rita Quesada3, Enrique Berjano2, Luis Grande3, Fernando Burdío4

1Departament de Medicina i Cirurgia Animals, Facultat de Veterinària, Universitat Autònoma de Barcelona , Barcelona, Spain. 2BioMIT, Department of Electronic Engineering, Universitat Politècnica de València, Valencia, Spain. 3Department of Surgery, Hospital del Mar, Barcelona, Spain. 4Department of Surgery, Hospital del Mar, Valencia, Spain

Abstract

Introduction: Radiofrequency energy has been used both experimentally and clinically to manage the pancreatic remnant after distal pancreatectomies. Our goal was to determine whether endoluminal radiofrequency (RF) ablation of the main pancreatic duct in large animals would be more efficient than glue occlusion as an exocrine pancreatic atrophy-inducing procedure.

Methods: Thirty-four Landrace pigs were assigned to either the transpapilar (n=16) or transection (n=18) groups. The transection implied the pancreas neck was severed. In each of these groups the remaining distal pancreatic duct was occluded either by a 3 Fr bipolar RF catheter or by hardening glue. The primary outcome analysis was based on the degree of atrophy in the transpapilar group or the development of postoperative pancreatic fistula in the transection group, respectively. Other factors examined in both groups involved intraoperative complications, weight increase, alterations in stool consistency and in histology preservation.

Results: In the transpapilar group complete and homogeneous atrophy and loss of the acinar component was observed in all the RF cases, while atrophy was incomplete in all the members of the glue subgroup. In both RF groups the major pancreatic duct was completely occluded and in the transection RF group the transection area was proven to be impermeable to the physiologic saline infused at necropsy through the main pancreatic duct. Duct patency was found in both glue groups. Consequently, all the animals in which RF ablation was performed experienced significant weight loss and alterations in stool consistency, contrary to the glue groups. The failure rate of the main pancreatic duct (usually expressed by a pseudocyst) in the transection groups was dramatically higher in the glue subgroup than the RF subgroups (9 out of 9 and 1 out of 9, respectively) and postoperative mortality occurred only in the glue subgroup (3 out of 9).

Conclusions: These results showed the superiority of endoluminal bipolar RF ablation over glue as an exocrine pancreatic atrophy-inducing procedure for main pancreatic duct occlusion, as seen by the degree of atrophy and fewer postoperative pancreatic fistulas.

TUES 12

COMPARATIVE ASSESSMENT OF EXPERIMENTAL TECHNIQUES FOR BROADBAND TISSUE DIELECTRIC PROPERTY MEASUREMENTS AT ABLATIVE TEMPERATURES

Hojjatollah Fallahi1, Jan Sebek1,2, Punit Prakash1

1Kansas State University, Manhattan, Kansas, USA. 2Czech Technical University, Prague, Czech Republic

Abstract

Introduction: Clinical microwave ablation systems operate at 915 MHz and 2.45 GHz, and systems employing other frequencies are under investigation. While data on temperature-dependent dielectric properties of liver tissue at 2.45 GHz have previously been reported, there is limited published data on temperature dependent dielectric properties at other frequencies. The objective of this study was to comparatively assess two methods for experimental measurement of broadband temperature-dependent dielectric properties of bovine liver.

Methods: An open-ended coaxial probe coupled with a vector network analyzer was used to measure the dielectric properties of the fresh bovine liver within the frequency range 0.5–6 GHz at temperatures over the interval 20–130 °C. A fiber-optic temperature sensor was placed flush with the dielectric measurement probe to record temperature of adjacent tissue. In the first technique, a 2.45 GHz insulated dipole antenna was used to heat the tissue samples, similar to previous studies. The dipole antenna was placed parallel to the dielectric sensing probe at a distance of 7–10 mm (n = 12, volume: 6x6x6 cm3). In the second technique, a hot plate and a custom-made copper container were employed to provide near-uniform heating of experimental tissue samples (n = 6, volume: 2x2x2 cm3).

Results: The rate of heating was faster and less variable when using the hot plate technique (0.91 ± 0.03 °C/s) compared with the microwave heating technique (0.70 ± 0.12 °C/s). Dielectric data measured at 2.45 GHz followed the same general trend as the previously published sigmoid model. However, dielectric data captured using the microwave heating technique followed the sigmoid model better at low temperatures (T < 70 °C), whereas data measured with the hot plate technique more closely followed the sigmoid model for T < 75 °C. Dielectric data measured with the hot plate approach attained their minimal value at ~100 °C compared to ~110 °C with the microwave heating technique. Less variability was observed in the dielectric data measured using the hot plate technique compared to the microwave heating technique, as evidenced by standard deviations of 3.68, 3.86 and 3.6 vs. 4.82, 5.50 and 4.61 at 915 MHz, 2.45 GHz, and 5.8 GHz for relative permittivity ,respectively, and 0.16, 0.14 and 0.40 S/m vs. 0.31, 0.25 and 0.64 S/m for effective conductivity.

Conclusion: Temperature-dependent dielectric property measurement using the hot plate technique provides an approach with reduced measurement variability, and allows improved control of the sample heating rate.

TUES 13

TRANSCRIPTOME ANALYSIS INDICATES THAT COMBINED THERMAL AND OSMOTIC STRESSES CAUSE WIDESPREAD COMPROMISE OF CYTOPROTECTIVE RESPONSES IN HEPG2 CELLS

Chunxiao Guo1, Michael Gustin2, Erik Cressman1

1MD Anderson Cancer Center, Houston, TX, USA. 2Rice University, Houston, TX, USA

Abstract

Introduction: The heat shock response promotes survival after thermal ablation and might contribute to local recurrence and remote metastasis. Therefore, targeting the cytoprotective heat shock response may lead to effective adjuvant therapy for thermal ablation. We previously observed that adding mild osmotic orthogonal stress to heat shock decreased HSF1 protein stability. Given the central role of HSF1 in heat shock response, we hypothesized that this osmotic stress would repress HSF1 mediated heat shock response in cells treated with combined thermal and osmotic stresses. Here, we demonstrated that osmotic stress altered the HepG2 transcriptome to favor hyperthermia-induced cell death.

Methods: Human hepatocellular carcinoma HepG2 cells were treated with 200mM sodium acetate for 2 hours for osmotic stress alone or with concomitant heat shock (43°C, 2 hours). Two hours after stress, total RNA was recovered by using a Qiagen total RNA isolation kit and mRNA was sequenced. 20 million reads from each sample were obtained by using Illumina paired sequencing (PE150). About 15,000 transcripts were identified from all samples. De novo assembly, genome alignment and reads counting were performed by using the RNA-seq pipeline at our institution. mRNA levels of HSP70 and HSP27 were also measured to validate mRNA sequencing data. Gene annotation and signalling pathway analyses were carried out by using IPA analysis from Qiagen.

Results: A mild heat shock of 43 0C altered about 6% of the transcriptome (cut-off: >2-fold increase or decrease, compared to control) of HepG2 cells. As expected, many heat shock protein genes were up-regulated. mRNA levels of HSP70 and HSP27 determined by qPCR were similar to those obtained from mRNA-seq reads count. Several pathways related to protein folding and quality control and stress response were upregulated including protein ubiquitination pathway, unfolded protein response and NRF2-mediated oxidative stress response. On the other hand, osmotic stress activated pathways modulating liver cell hyperplasia and proliferation such as TNF signalling pathways. Strikingly, combining this mild osmotic stress with mild heat shock decreased expression of most heat shock protein genes that were up-regulated by heat shock. Both heat shock and osmotic stress activated non-coding RNAs such as RN7SK, which was found to be a non-specific transcription repressor. Combined stress had highest levels of RN7SK expression levels among all sample, indicating unfavourable conditions for cancer cells.

Conclusions: Hyperosmotic stress compromised the cytoprotective heat shock response by down-regulating significant amount of chaperones induced by heat shock.

TUES 14

MEK INHIBITION ENHANCES SENSITIVITY TO THERMAL ABLATION BY BLUNTING HSF1 ACTIVATION IN HEPG2 CELLS

Chunxiao Guo1, Niloofar Karbasian1, Michael Gustin2, Erik Cressman1

1MD Anderson Cancer Center, Houston, TX, USA. 2Rice University, Houston, TX, USA

Abstract

Background: Efficacy and safety of thermal ablation in cancer therapy relies on susceptibility of cancer cells to hyperthermia induced cell death. Weakening cytoprotective heat shock response is thus a logical therapeutic strategy in developing adjuvant therapy. However, small molecule inhibitors targeting heat shock proteins have demonstrated limited efficacy. Heat shock response is largely mediated by a master transcription factor, heat shock factor 1 (HSF1). We previously reported iHSF115sensitized multiple cell lines to mild hyperthermia by directly targeting HSF1 transactivating downstream target genes. The activity of the MEK protein kinase is essential for phosphorylation and subsequent activation of HSF1 in NIH3T3 cells. In this study, we hypothesized that MEK inhibitors could enhance hyperthermia induced cell death in hepatocellular carcinoma cells by blunting HSF1 activation.

Methods: Human hepatocellular carcinoma cell line HepG2 was obtained from ATCC and cultured in a humidified CO2incubator at 37°C or for mild hyperthermia at 43°C (2 hours). Cells were pre-treated with MEK inhibitors AZD6244, GSK1120212 or U0126 for 1 hour before 2 hours mild hyperthermia. 24 or 48 hours after heat shock, cells were fixed with 4% formaldehyde and stained with 0.5% crystal violet to evaluate viability. Total RNA was recovered using a Qiagen total RNA isolation kit and mRNA levels of HSPA1A (HSP70) and HSPB1 (HSP27) (normalized to 18S RNA) were measured by qPCR. Total protein lysates were prepared and protein levels of ERK1/2, Phospho-ERK1/2, HSF1, HSF1 S326, HSP60, HSP90, HSP70, and HSP27 were examined by Western blots.

Results: MEK inhibition by AZD6244 or GSK1120212 significantly decreased HSF1 S326 phosphorylation while the total protein level of HSF1 remained unchanged. Either of these two MEK inhibitors inhibited HepG2 growth and sensitized these cells to mild heat shock. Expression of both mRNA and proteins for the downstream HSF1 target genes HSP70 and HSP27 were reduced by MEK inhibition. Other constitutively expressed heat shock proteins such as HSP60 and HSP90 stayed the same among all treatment groups. Overexpression of wild type HSF1, however, did not completely rescue HepG2 cells from death induced by combination treatment of MEK inhibitor and mild heat shock, suggesting involvement of pathways other than HSF1 signalling.

Conclusions: Inhibition of theMEK protein kinase-mediated activation of HSF1 in HepG2 cells compromised the cytoprotective heat shock response and effectively killed HepG2 in combination with mild hyperthermia. Importantly, both MEK inhibitors were effective at 50-100nM concentrations, which are easily achievable in animal models.

TUES 15

COMBINING LASER ABLATION WITH OTHER THERAPEUTIC MODALITIES IN HIGH-GRADE GLIOMA

Dimitris Placantonakis

NYU School of Medicine, New York, NY, USA

Abstract

High-grade glioma is an incurable brain malignancy. Standard of care therapy consists of safe surgical resection followed by conventional chemoradiotherapy. Unfortunately, these tumors evade therapy to invariably recur and progress.

Laser ablation has emerged as a novel cytoreductive approach in recent years, particularly in the case of otherwise inoperable tumors. However, the indications for its use and its therapeutic potential remain loosely defined.

I will discuss some of our own and published data on laser ablation and its comparison to other minimally invasive surgical approaches in the glioma space. I will also present an opinion on why laser ablation may present an appealing opportunity for synergy with other treatment modalities, based on our own clinical and laboratory experience.

TUES 16

SEX AND AGE MEDIATE VASCULAR RESPONSE TO CORE BODY TEMPERATURE VIA REDISTRIBUTION OF BLOOD VOLUME IN ARTERIES AND VEINS: A MURINE MRI STUDY

A. Colleen Crouch, Aditi Batra, Ulrich Scheven, Joan Greve

University of Michigan, Ann Arbor, MI, USA

Abstract

The cardiovascular (CV) system plays a vital role in thermoregulation because of its influence on heat transfer via forced convection and conduction by changes in blood distribution, blood velocity, and proximity of vessels/tissues. To fully understand the CV system's role in thermoregulation, blood distribution (influenced by cardiac output, vessel size, blood flow, and pressure) must be quantified, ideally across sex and age. The purpose of this study is to determine the influence of sex and age on the CV response to temperature.

Male and female, adult and aged, mice were anesthetized and imaged at 7T. Data were acquired from four co-localized vessel pairs (the neck [carotid/jugular], torso [suprarenal and infrarenal aorta/inferior vena cava (IVC)], periphery [femoral artery/vein]) at core temperatures of 35, 36, 37, and 38 °C. Sixteen CINE, ECG-gated, phase contrast frames with one-directional velocity encoding (through plane) were acquired perpendicular to each vessel: TR/TE ~180/5ms, field of view arteries/veins (20/25.6 mm)2, flip angle arteries/veins (60°/20°), matrix 1282 zero-filled to 2562, slice thickness 1 mm, 2 excitations, VENC 20-120 depending on the vessel). Each frame was analyzed for area, blood velocity, and volumetric flow across the cardiac cycle using a semi-automated in-house MATLAB script.

Blood velocity and volumetric flow were quantified in eight vessels at four core body temperatures. Flow in the infrarenal IVC linearly increased with temperature for all groups ($p=0.002$; adjusted means: male vs. female, 0.37 and 0.28 mL/(min • °C); adult vs. aged, 0.22 and 0.43 mL/(min • °C)).Comparing volumetric flow response to temperature, groups differed for the suprarenal aorta (adult < aged, $p<0.05$), femoral artery (adult < aged, $p<0.05$), and femoral vein (adult male < aged male, $p<0.001$). In aged animals, flow increases were driven primarily by velocity changes suggesting a diminished ability for structural changes in area.

Challenges associated with making measurements from core vessels has resulted in a lack of empirical information regarding how they change with core temperature and their role in thermoregulation. Researchers have begun to study vascular response in the leg, and we have expanded this to the whole body in both arteries and veins. With this work, we have been able to distinguish contributions from changes in area and blood velocity which would be important for more accurate bioheat modeling. These changes in blood velocity are also likely causing changes in wall shear stress, an important metric in cardiovascular disease progression.

TUES 17

EVALUATION OF HYDROGELS AS WATER BOLUS IN HYPERTHERMIA TREATMENT

Hana Dobsicek Trefna, Bastiaan Elling, Saul Llacer, Anna Ström

Chalmers University of Technology, Gothenburg, Sweden

Abstract

Introduction: The water bolus (WB) is an important part of the antenna applicator serving as a matching medium between the antennas and the body. Further, it is used to control temperature of the body surface. The present standard for WB is to circulate de-ionised water through plastic or silicone bags placed between the body and applicator. This conventional solution have however several drawbacks, such as inaccurate positioning, air pockets or even disturbances from a plastic materials. In this contribution we investigate the use of hydrogels as water bolus during microwave hyperthermia.

Methods: The dielectric, mechanical and rheological properties of commercially available polysaccharides commonly used in the fields of food and pharmaceutics. The polysaccharides are able to form ionic gels (calcium-alginate and HM-pectin/alginate) as well as neutral gels (xanthan/LBG and agarose). The mechanical properties of the gels were evaluated using stress and strain sweep as well as stress relaxation under uniaxial compression. Storage and loss modulus were determined as a function of temperature in order to define set and melt temperature of the gels. The LBG/xanthan/agarose gel was produced in real scale and used as a water bolus within a phased array applicator.

Results: The conductivity of gels formed using negatively charged polysaccharides (alginate and HM pectin) was too high, while the dielectric properties of the xanthan/LBG and agarose (total polymer concentration 1%) were close to water. Agarose on its own was however deemed too brittle to ensure close fitting between applicator and skin and Xanthan/LBG with excellent elasticity shown somewhat low melting temperature. The combination of both, the three-component xanthan/LBG/agarose gel provided a gel with high melting temperature and non-brittle deformation behaviour. We showed that cooling of the gel via water channels through the gel is feasible, although optimization of their size and number of the water channels still needs to be done. The final evaluation within the hyperthermia applicator showed excellent signal transmission from the antennas.

Conclusions: The results indicate that hydrogels have potential to overcome drawbacks of currently used water boli. However, the polysaccharides should be (close to) neutral, and ions should not be required for gelation to occur. A non-brittle gel with a melting temperature above 45C is further required, through which water channels can be formed. The next step is to verify the proposed solution in clinical conditions as well as testing other potential gels.

TUES 18

TARGETABILITY OF SITES IN VARIABLE PELVIC GEOMETRIES USING MR-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND (MRGHIFU) AS ASSESSED IN AN IN VIVO PORCINE MODEL.

Lifei Zhu1, Ari Partanen2, H Michael Gach1, Lauren Henke1, Jessika Contreras1, Dennis Hallahan1, Imran Zoberi1, Hong Chen1, Michael Altman1

1Washinton University in St. Louis, St. Louis, MO, USA. 2Profound Medical Corp., Mississauga, ON, Canada

Abstract

Purpose: A commercial MR-guided high-intensity focused ultrasound (MRgHIFU) system has the potential to deliver localized and accurate mild hyperthermia therapy (MHT, heating to 40-45°C) to a wide array of pelvic target sites. Previous studies have demonstrated this system can administer MHT to fairly homogenous tissue systems. This study uses an in vivo porcine model to assess the feasibility of targeting a wider variety of clinically relevant heterogeneous pelvic anatomical geometries.

Method: Fifteen MHT sessions were delivered to 1-3 sites in seven live pigs using a commercial 1.5 T MRgHIFU system (Sonalleve V2, Profound Medical Inc., Mississauga, ON): muscle adjacent to the ventral bladder wall (VBW, n=7), muscle adjacent to the distal bladder wall (DBW, n=3), and uterus (n=5). For each MHT session, an 18-mm diameter tissue region was heated using 100 W power for 30 minutes (±5%) with a target temperature of 42°C. Temperature maintenance via feedback control was provided by multi-plane MR temperature maps acquired every 3.2s. MR and temperature data were processed offline to evaluate the achieved temperature distributions. Gadolinium contrast-enhanced T1-weighted acquired before and immediately after heating, and gross pathology performed immediately after heating, were used to assess any potential tissue thermal damage.

Results: Average differences between the MR thermometry-measured average temperature (Tavg) and target temperature in the target region were 0.40°C, 0.40°C, and 0.58°C, for the VBW, DBW, and uterus, respectively. Across all MHT sessions, the standard deviation of voxels within the target region was 1.55°C, the average variation of Tavg across every 3.2s sample was 0.80°C, and the average difference between the 10th and 90th percentile temperatures in the target region was 4.5°C. The average time for a given MHT target to reach >41°C was 57.1s (maximum=133.3s), while the average time for the target to cool below MHT temperatures following sonication cessation was 51.90s (maximum=155.6s). No abnormally perfused tissue within the ultrasound beam path was detected in the contrast-enhanced MRI images, nor was any thermal damage evident in the gross pathologic examinations.

Conclusion: Multiple repeated 30 minute MHT sessions delivered to pigs in vivo show that treatments can be accurately and precisely administered to a variety of clinically relevant pelvic target geometries. This, along with the lack of observed thermal tissue damage, suggests that it may be safe and feasible to administer MHT to pelvic targets in human patients using the Sonalleve system.

TUES 19

BIPOLAR RADIOFREQUENCY ABLATION OF THE BRAIN USING A VIRTUAL PATIENT POPULATION: AN EXPLORATION OF LESION SIZE DEPENDENCY ON VOLTAGE DIFFERENTIAL

Erica Neumann1,2, Jorge Gonzalez-Martinez3, Ahmet Erdemir1,2

1Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA. 2Computational Biomodeling (CoBi) Core, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA. 3Epilepsy Center, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract

Introduction: Medically refractory epilepsy can be treated by surgical resection or laser ablation, however radiofrequency (RF) ablation may be completed at bedside following localization of the epileptic zone using stereoelectroencephalography (SEEG). While RF ablation using SEEG electrodes has been performed outside the United States, the lack of temperature monitoring during the procedure makes it difficult to determine the ablation volume, raising safety concerns. In a previous study, we used a virtual patient population to quantify the variation of lesion size during bipolar RF ablation using a fixed electric potential. To expand upon our previous work, the goal of this study was to determine the voltage differential that provides the largest lesion size within the previously defined virtual patient population.

Methods: A two-dimensional axi-symmetric finite element model of an SEEG electrode, incorporating thermo-electric coupling was developed. For simplification, only two platinum-iridium contacts were modeled with the remaining electrode surface modeled as plastic material. Material properties of the brain tissue were assigned from literature. Latin hypercube sampling was used to select thermal conductivity (tissue and perfusion), electrical conductivity, and heat capacity parameters to build the virtual population (n=160), while the remaining material properties were held constant. Ablation was performed for 30 minutes or until tissue temperature reached 100□, where RF power was modeled using a voltage differential of 20V, 25V, or 30V between two adjacent contacts of the electrode. The same virtual population was used for each voltage differential level for a total of 480 simulations. Lesion length, width, area, and volume, as defined by the 60□ isotherm, were used as response variables.

Results: Average (±SD) ablation area was 29.0±14.1 mm2, and 34.0±6.3 mm2, and 29.4±5.1 mm2 for 20V, 25V, and 30V, respectively. In addition, 11 (6.9%) samples did not reach a tissue temperature of 60□ at 20V, indicating that a lesion was not formed with the corresponding parameters at this voltage differential. The higher voltage differentials formed a lesion for the entire virtual population.

Conclusion: Our results suggest an optimum voltage differential of 25V, to achieve the largest lesion size across the population. In this study, a constant voltage differential was used to control RF energy. However, the in silico population used in this study may also be used to test other RF control parameters, such as temperature controlled energy delivery. Model validation will be performed using in vitro and in vivo models.

TUES 20

MATHEMATICAL MODEL DEVELOPMENTS FOR THERMOEMBOLIZATION

David Fuentes, Samuel Fahrenholtz, Chunxiao Guo, Emily Thompson, Megan Jacobsen, Rick Layman, Jason Stafford, Erik Cressman

MD Anderson, Houston, Tx, USA

Abstract

Background: Thermoembolization presents a unique treatment alternative for patients battling HCC. The approach delivers an exothermic chemical reaction through a transarterial catheter and combines the benefits of embolic as well as thermal- and chemical-ablative therapy modalities. The target tissue and vascular bed are subjected to simultaneous hyperthermia, ischemia, and chemical denaturation in a single procedure. Intuitively, embolic effects of this technique reduce blood flow near the burn zone and thus can reduce major heat-sink limitations observed with ablation of liver tissue. Simultaneously, inflammation in the periphery of the burn zone can enhance delivery of embolic material and the chemical denaturant by-products. Current ex-vivo efforts are promising and have demonstrated a 40:1 ratio of coagulated tissue volume to injected material and up to a 24.1 degC temperature rise. However, from a clinical standpoint, this potential for extensive tissue damage suggests a need for greater understanding of the behavior of these materials delivered by the endovascular route. The presented efforts develop a mathematical model for guiding the competing diffusive and convective effects observed in thermoembolization delivery protocols.

Methods: A mixture theory formulation is used to mathematically model thermoembolization as chemically reacting transport of an electrophile, dichloroacetyl chloride (CHCl2CCl3), within porous living tissue. Mass, momentum, and energy transport of each relevant constituent is considered. Specifically, dichloroacetyl chloride is injected in the vessels and exothermically reacts with water in the blood or tissue to form dichloroacetic acid and hydrochloric acid. Convective transport through the vessels is coupled with porous transport in the capillary bed. Neutralization reactions are assumed instantaneous in this approach. MR thermometry of the thermoembolization procedure performed in ex-vivo kidney is used to validate mathematical model predictions of temperature.

Results: Mathematical modeling predictions of tissue death are highly dependent on the vascular geometry, injection pressure, the intrinsic amount of exothermic energy released from the chemical species, spatially varying tissue properties, and are able to accurately reproduce the temperature distributions observed in MR thermometry.

Conclusion: Current efforts present a first step toward formalizing a mathematical model for thermoembolization and are promising for providing insight for delivery protocol optimization. While calibrated models capture observed experimental temperature measurements, numerical challenges in finite element mesh generation and efficient multi-physics simulations must be addressed to enable high dimensional procedure optimization.

TUES 21

MAGNETIC NANOPARTICLE HYPETHERMIA FOR TREATING LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER: ROLE OF TUMOR SIZE

Anilchandra Attaluri1, Sri Kamal Kandala2, Robert Ivkov 3

1The Pennsylvania State University – Harrisburg, Middletown, Pennsylvania, USA. 2University of Texas MD Anderson Cancer Center, Houston, Texas, USA. 3Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background: Due to the lack of specific symptoms and the aggressive nature of pancreatic cancer, more that 80% of the patients present with inoperable locally advanced tumors or metastatic disease at the time of diagnosis. Locally advanced unresectable pancreatic cancer (LAPC) patients have a five-year survival rate of < 12%. The standard of care, concurrent chemo-radiation therapy (CRT) typically stabilizes tumor progression for a time, and only 10% to 15% patients exhibit an objective response and is associated with significant toxicity. Magnetic nanoparticle hyperthermia (MNPH) allows for targeted and localized heat delivery which is a potent sensitizer for chemo and radiation therapies. In MNPH, magnetic nanoparticles (MNPs) are remotely activated with an alternating magnetic field (AMF) after endoscopic ultrasound (EUS) guided delivery into pancreatic tumors. Local control of large tumors with CRT presents challenges, whereas physics of heat deposition and control provides advantages for MNPH.

Methods: Finite element heat transfer analysis was used to solve Pennes bioheat equation and to model MNP heat transfer in tumor and surrounding tissues. Human body was approximated as a cylindrical human torso with a spherical pancreatic tumor. Constant blood perfusion and homogeneous tissue properties were used for the human torso and pancreas. Tumor volume-normalized MNP dose and fixed AMF conditions were used to study the role of tumor size on the achievable temperatures in the tumor. A uniform distribution of MNPs in half the tumor volume was considered as a constant volumetric heating rate to represent a EUS guided MNP injection.

Results: Large tumors realized a higher tumor thermal dose compared to small tumors when treated with tumor volume-normalized MION dose and fixed AMF amplitude and frequency. Simulation results are consistent with previously reported in vivo results. Non-specific eddy current heating is significant at the outer surface of the torso. Strategies for reducing the superficial non-specific eddy-current heating will be presented.

Conclusion: Treating LAPC with MNPH is feasible but approaches to minimize the superficial non-specific eddy-current heating are required. MNPH is effective at treating larger tumors > 3-4 cm.

TUES 22

DUAL-INPUT MAXIMUM SLOPE MODEL ASSUMPTION AND IMPLICATIONS FOR CALCULATING LIVER TUMOR WIDE-ARRAY CT PERFUSION VALUES

Rajeev Hatwar1, Sahar Mirpour1, Anilchandra Attaluri2, Alexandros Bouras3, Constantinos Hadjipanayis3, Robert Ivkov1, Eleni Liapi1

1Johns Hopkins University, Baltimore, MD, USA. 2Penn State Harrisburg University, Middletown, PA, USA. 3Icahn School of Medicine at Mount Sinai, NY, NY, USA

Abstract

Aim: Tumor and tissue blood perfusion are important components of the Pennes' bioheat equation. A novel and quantitative method of measuring blood perfusion is CT perfusion. In liver CT perfusion, the dual-input maximum slope (DI-MS) method is commonly employed for perfusion calculations. . For DI-MS to be applicable, the start phase (SP) of the spleen should occur before the SP of a liver tumor. The aim of this study was to examine this temporal relationship and how it affects DI-MS perfusion measurements in a large animal model of liver cancer with the wide-array CT perfusion technique. This study was part of our large animal preclinical image-guided magnetic hyperthermia protocol for enhancing chemotherapy effects in liver cancer, where we sought to assess tumor and tissue blood perfusion before and after magnetic hyperthermia.

Materials and Methods: Eleven New Zealand White rabbits, implanted with VX2 tumors in liver, were scanned using a liver 320-slice CT perfusion protocol. Times to peak (TTP) for arterial and portal slopes were recorded, as well as hepatic arterial perfusion (HAP), hepatic portal perfusion (HPP) and hepatic perfusion index (HPI) for liver and tumor using manual and automated methods. T-test comparisons and Bland-Altman plot analysis were performed.

Results: Mean tumor TTP occurred at 9.79 s (SD=3.41) and splenic TTP at 9.75 s (SD=4.47, p=0.98). In 3/11 (27.27%) cases, tumor SP occurred prior to spleen (mean difference=1.33 s, SD=1.15 s). In these cases, mean automated HPP values were 43.8% (SD=52.48) higher compared to manually computed ones. There were statistically significant differences between automated and manual methods for normal liver and tumor HPI and HPP ($p<0.01$ and $p<0.0001$, respectively), but not HAP values ($p=0.125$ and $p=0.78$, respectively). There was statistically significant variation between methods for tumor HPP and HPI ($p=0.001$, respectively).

Conclusion: In 320-slice CT perfusion of liver, we observed that tumor TTP occurred prior to splenic TTP in 27.27% of VX2 liver tumors. This temporal relationship affects tumor perfusion calculations and should be readily identified.

TUES 23

ASSESSING SPECIFIC LOSS POWER DEMANDS ON MAGNETIC NANOPARTICLES IN HYPERTHERMIA AND NANOWARMING APPLICATIONS.

Anirudh Sharma1, Zhe Gao1, Hattie Ring1, Bethanie Stadler1, Robert Ivkov2, Erik Finger1, John Bischof1

1University of Minnesota, Minneapolis, MN, USA. 2Johns Hopkins School of Medicine, Baltimore, MD, USA

Abstract

Introduction: We provide a detailed analysis of iron oxide nanoparticle (IONP) specific loss power (SLP) requirements and characterization of performance of different magnetic nanoparticle constructs in the context of two nanomedicine applications – magnetic hyperthermia-based cancer therapy and magnetic nanowarming of cryopreserved organs. Ideally, both these applications would benefit from a magnetic nanoparticle construct with a high SLP under clinically relevant alternating magnetic field (AMF) conditions. However, hyperthermia-based cancer therapy and nanowarming of cryopreserved organs, place different demands on optimal loss power requirements defined by (a) biological model – tumor vs organ (vascularity, physiology, bioheat transfer); (b) end-points defining clinical efficacy – tumor destruction vs organ viability, survival; (c) constraints/flexibility in the driving alternating magnetic field (AMF) conditions – Atkinson-Brezovich criteria, AMF modulation; and, (d) temperature range – cryogenic vs hyperthemic. These factors present obstacles for successful clinical translation.

Methods: We evaluated SLPs of commercial and proprietary MNPs as a function of clinically relevant externally applied magnetic field amplitudes (0-63 kA/m) and frequency (~160 kHz) conditions in aqueous solutions and cryoprotective agents. These SLPs were evaluated in two different temperature ranges – cryogenic (-150 to -20°C) and hyperthermic (41 to 45°C).

Results: We show that SLP varied with core structure (SLP of multi-crystallite cores > SLP of single-crystallite cores), surface-coating (Silica-PEG, PEG, starch, dextran) and temperature range (hyperthermic vs cryogenic). These results are discussed in the context of prevailing models of MNP heat generation and heat transfer. Additionally, we assess these results for their clinical relevance to (a) achieve optimal thermal dosimetry in hyperthermia-based cancer therapy; and, (b) achieve critical warming rates for maximum organ viability in nanowarming cryopreserved organs. This analysis is factored together with biocompatibility and scalability of MNPs to predict the nanoparticle constructs that are best suited for clinical translation in each application.

Conclusion: MNP SLPs measured over a wide AMF range exhibited significant deviation from predictions made by popular models such as linear response theory and depended on core magnetic structure. In CPAs, SLP varied significantly with surface coatings. Further, we show, with calorimetry measurements that SLPs of MNPs at cryogenic temperatures are higher compared to SLPs measured at room temperature or in the hyperthermic range. This is consistent with models that predict magnetic properties vary with temperature in this range. Finally, the constraints placed by eddy current heating on the applied AMF conditions are different in hyperthermia vs nanowarming, with nanowarming offering a wider AMF range to optimize IONP SLP.

TUES 24

OVERVIEW OF RECENT ESHO SPONSORED QA GUIDELINES: THE SUMMARY OF OVERALL CHANGES AND CURRENT CHALLENGES

Hana Dobsicek Trefna

Chalmers University of Technology, Gothenburg, Sweden

Abstract

Quality assurance (QA) guidelines are essential to provide uniform execution of clinical trials and treatment in the application of hyperthermia. The ESHO technical committee (ESHO-TC) has been established to provide QA guidelines for different hyperthermia applications to serve as the current standard. The guidelines aim to establish a single uniform level of quality assurance and control in hyperthermia treatments delivered in all multi-institutional studies initiated by the Atzelsberg Circle or under the auspices of the ESHO. The documents outline the clinical and technical consequences of the specific properties of various heat delivery techniques and specify recommendations for hyperthermia administration with superficial, interstitial and deep techniques.

This talk covers the recent efforts of the ESHO-TC to provide the users and developers of hyperthermia devices with tools to access the performance of their devices. It summarizes at high level the general concepts and overall changes from previous QA literature.

TUES 25

THERMAL MONITORING STRATEGIES FOR SUPERFICIAL HYPERTHERMIA

Akke Bakker

UMCA, Amsterdam, Netherlands

Abstract

Adequate thermometry is critical for successful superficial hyperthermia (HT) treatments. For various tumor types, e.g., sarcoma, melanoma, head and neck, and recurrent breast cancer, tumor response and local control were shown to be related to minimum temperature and minimum thermal dose achieved interstitially in the treatment area during HT. In addition, there is a clear relationship between maximum temperature and maximum thermal dose on the skin and HT associated toxicity; i.e. thermal burns.

Techniques to measure temperature during superficial HT include fiber-optic probes, thermistors and thermocouples. A disadvantage associated with these methods is that temperature is often recorded using a small number of temperature sensors. This results in under sampling in an area where significant temperature gradients are present, particularly within large treatment areas and macroscopic tumors. A low number of temperature sensors will result in an overestimation of the minimum temperature and an underestimation of the maximum temperature, which might result in undertreatment of the tumor and undesirable HT associated toxicity, respectively.

To prevent both, placement of temperature sensors should be done both interstitially and on the skin. The invasive temperature distribution is influenced by the presence of a silicone breast implant or a cavity filled with seroma. Close to a silicone breast implant the temperature is higher, while the temperature of seroma is higher than the surrounding tissue. Both might lead to HT associated toxicity when they are undetected during treatment. Skin temperature measurements are only weakly correlated to the temperature near the silicone breast implant. On the skin, temperature should be measured on both normal skin, tumor nodi, the transition of healthy tissue to tumorous tissue and on scars. Where scars are most at risk for thermal burns.

Recent retrospective analysis of clinical data showed that adequate coverage of the skin temperature distribution during superficial HT treatment requires the use of ≥50 stationary sensors per 400 cm2 applicator. Thermal mapping is a valid alternative technique that involves moving single sensor probes cyclically over a fixed trajectory to cover multiple measurement locations with a single sensor. Despite the lower temporal resolution, mapping significantly improves the spatial resolution.

To summarize, monitoring temperature during superficial HT should be done both invasively, to prevent undertreatment of the tumor, as well as on the skin, to prevent thermal burns. Silicone breast implants and seroma influence the invasive temperature distribution, whereas the presence of scars and macroscopic tumor influence the superficial temperature distribution.

TUES 26

QUALITY ASSURANCE GUIDELINES IN INTERSTITIAL AND SUPERFICIAL HYPERTHERMIA AND THEIR POTENTIAL IMPACT ON FUTURE CLINICAL TRIAL RESULTS

Johannes Crezee

Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

Abstract

Well-controlled, sufficiently high and uniform tumor temperatures are known to be predictive of treatment outcome, as demonstrated in many clinical hyperthermia studies. Treatment protocols should therefore incorporate safeguards to ensure that the equipment used is capable of achieving adequate temperatures, as well as ensure that a sufficiently large amount of thermometry data is available to assess the tumor temperature distribution in order to be able to execute high-quality treatments. Uniform rules are particularly important when conducting multicenter clinical trials.

Recently Quality Assurance (QA) guidelines of the technical committee of the European Society for Hyperthermic Oncology including senior STM members were published to safeguard quality for interstitial and superficial hyperthermia treatment delivery. Heating properties of equipment should be tested in advance to ensure that the entire target region can be covered. Important issues specific for both interstitial and superficial hyperthermia include the presence of steep temperature gradients within or close to the target region, requiring sufficient thermometry for reliable treatment monitoring. For clinical reasons extensive invasive thermometry is not feasible and thermometry is often at locations not inside but bordering to the target region, thus potentially not representative of the actual tumor temperature. the recently published QA guidelines give minimum requirements to ensure the presence of sufficiently representative thermometry, as well as an indication of the temperature level that should be achieved: the median tumor temperature T50 should exceed 41°C and T90 should exceed 40°C.

The clinical impact of implementing QA guidelines will be important to ensure good clinical results. Single and multicenter clinical trials incorporating the use of interstitial or superficial hyperthermia have yielded mixed results, sometimes not even finding a benefit for adding hyperthermia to radiotherapy or chemotherapy. Lack of adequate QA seems to have been the main cause for the negative results of these negative trials. Implementation of QA guidelines will lead to much better results of the addition of hyperthermia to radiotherapy and chemotherapy, possibly even surpassing the 20% difference in local control achieved in the positive randomized trials performed with superficial and interstitial hyperthermia.

TUES 27

QA OF RADIATIVE DEEP HYPERTHERMIA SYSTEMS: REFRESHER ON AVAILABLE TECHNIQUES.

Gerard C. van Rhoon, Sergio Curto

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Abstract

Background: Quality assurance (QA) is one of the cornerstones for comparing the performance of the available deep hyperthermia systems. During the past decades multiple approaches have been developed to perform QA-measurements as prescribed by ESHO or STM QA-guidelines.

Method: An inventory of the various available techniques to measure the required SAR/Temperature distribution has been made.

Results: An overview of the advantages and limitations for each method to assess the quality of the induced SAR/temperature distribution is provided. The oldest and most well-known approach for QA is the infrared split phantom technique. Alternatively, the temperature increase is measured with thermal probes either using a thermal mapping or multi-sensor probes (thermocouples, fiberoptic). The infrared measurement provides 2D SAR distribution patterns normalized to maximum temperature increase. Thermal mapping or multi-sensor thermometry has also the potential to provide 2D information but at a very poor resolution. A major disadvantage of QA-measurement by temperature increase is the long time interval needed to cool down the phantom to room temperature. Therefore, other measurement techniques were developed to measure directly the applied E-field distribution using 2D mounted LED, lamp or Schottky diodes arrays. A clear advantage of the latter systems is their fast measurement of the E-field enabling assessing SAR steering features of deep hyperthermia systems. Alternatively, a full 3D E-field distribution can be obtained by scanning the sensor through the whole phantom (time demanding). Clearly, for the later technique, but also for the LED or lamp technique a transparent and liquid phantom material is required. Recently, non-invasive MR-thermometry has been introduced as the most advanced technique to accurately assess a 3D distribution of the induced temperature increase in anthropomorphic phantoms. The MRI-technology provides an excellent platform to investigate the quality of the measured SAR/temperature distribution as function of the number of sampling points in 1, 2 or 3D.

Conclusions: For anthropomorphic phantoms only 3D measured distribution provide the best ability to carefully evaluate the quality of the induced SAR/temperature pattern and to perform realistic normalization of the temperature distribution. Reduction of the data set to a single 2D or 1D pattern demonstrate a large sensitivity of the result to exact location of the measurement plane.

TUES 28

QUALITY ASSURANCE OF MR-GUIDED DEEP HYPERTHERMIA SYSTEMS: AN INTERNATIONAL MULTI-INSTITUTION EVALUATION WITH AN ANTHROPOMORPHIC PHANTOM

Sergio Curto, Gerard C. van Rhoon

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Abstract

Background: Quality assurance (QA) measurements are essential to verify whether a system operates according to specifications. Multi-institution clinical trials should warrant similar treatments at different institutions for objective comparison of clinical outcomes. Currently, applicator QA measurements are implemented independently at each institution. The advent of magnetic resonance (MR)-guided deep hyperthermia systems not only allows temperature monitoring during treatment but also systematic experimental validation of applicator performance. This work reports the systematic QA measurements performed at the five institutions currently equipped with such systems. Two different hyperthermia applicators, the Pyrexar BSD2000-3D-MRI Sigma Eye and Universal Applicator, operating in three different 1.5 Tesla MR scanners (Siemens, GE and Philips) have been evaluated with the same set of phantoms.

Method: Human shape anthropomorphic phantoms containing plastic pelvic bones and spine have been specifically developed to evaluate the performance of the applicators. Catheters were positioned inside the phantoms for temperature measurements using Bowman sensor probes. Clinically relevant power of 600 watts was applied for 12.4 minutes to allow for 8 sequential MR-scans. The magnetic resonance thermometry (MRT) and Bowman probe sensor temperature, volumetric heating distribution, steering capabilities and presence of off-target heating were analysed.

Results: The maximum mean difference between MRT and Bowman probes for the devices at the different institutions was found to be 0.6 ± 0.1°C for both centric and eccentric targets. The evaluated devices shown comparable heating profiles. Although variations, which depended upon exact phantom positioning and applicator characteristics, were observed in the heating profiles, no significant difference was found in the average temperature distributions at the different scans for the evaluated institutions with ($p=0.61$) and ($p=0.18$), respectively for the centric and eccentric target.

Conclusions: This work provides pioneering results on the performance of different deep hyperthermia systems operating within three different MR scanners. Comparable heating profiles are shown for the five evaluated institutions. Subcentimeter differences in position substantially affect the results when evaluating the heating patterns. The integration of advanced phantoms and precise positioning into QA guidelines should be evaluated to guarantee the best possible patient care.

Acknowledgment: This work was performed within the framework of COST Action EMF-MED, supported by COST (European Cooperation in Science and Technology). The authors would like to acknowledge the financial support provided under unrestricted grants from the Dutch Cancer Society (KWF-DDHK 2013-6072) and Pyrexar Medical.

TUES 29

CONCEPTS IN QUALITY MANAGEMENT FOR MR-GUIDED LASER ABLATION

R. Jason Stafford

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

The minimally invasive approach of MR-guided laser ablation in brain and spine is an emerging alternative to surgical intervention for certain neurological and oncological indications. Because of the sensitive area in which the treatment is to be delivered, the procedure relies on accurate delineation of a target treatment volume, navigation of the treatment applicator(s) to the appropriate places for treatment delivery to cover the treatment volume, and precise delivery of treatment to the region. Often, owing to its soft-tissue contrast and temperature imaging capabilities, MR-imaging is a major part of the treatment planning, navigation, treatment monitoring and treatment verification process. Here we overview these procedures with an eye on the role and potential pitfalls of using MR-guidance during the procedure with particular on MR-guided navigation and MR-temperature imaging and thermal dosimetry for these patients.

TUES 30

QUALITY ASSURANCE IN MAGNETIC RESONANCE GUIDED FOCUSED ULTRASOUND THERAPY

Allison Payne

University of Utah, Salt Lake City, Utah, USA

Abstract

Magnetic resonance imaging-guided focused ultrasound (MRgFUS) is a non-ionizing image-guided interventional technology that couples the energy delivery capabilities of therapeutic focused ultrasound with magnetic resonance imaging. MRgFUS technology is complex and multi-faceted, requiring careful treatment planning, dosimetry, calibration as well as routine quality assurance (QA) and maintenance procedures. QA testing in MRgFUS takes on heightened importance due to the technical complexities of the system, the diversity of potential indications, known treatment uncertainties as well as the possibilities of adverse clinical outcomes if the MRgFUS equipment is not operating within defined specifications. This talk presents quality assurance procedures for MRgFUS as recommended by the American Association of Physicists in Medicine Task Group 241. Topics covered include acceptance and commissioning testing, recommended periodic testing and daily QA. Considerations for phantom design that allow quantification of the recommended QA metrics as well as evaluation of MRI performance with consideration of image signal-to-noise ratio will also be addressed.

TUES 31

HYPERTHERMIA INCREASES IONIZING RADIATION INDUCED CELL REPRODUCTIVE DEATH OF CERVICAL CANCER CELLS BY AFFECTING TWO DNA DSB REPAIR PATHWAYS.

Marloes IJff, Roxan F.C. Helderman, H. Petra Kok, Przemek M. Krawczyk, Lukas J.A. Stalpers, Johannes Crezee, Arlene L. Oei, Nicolaas A.P. Franken

Amsterdam UMC, Amsterdam, Netherlands

Abstract

Introduction: Chemoradiation (cisplatin with radiotherapy) is the standard treatment for advanced stages of cervical cancer, resulting in a five year overall survival of 65%. Adding hyperthermia to ionizing radiation (IR) has been shown to enhance the effect on the tumor significantly. Therefore, combining hyperthermia with chemoradiation might improve the survival rate. This can also be interesting for patients who are resistant to (high dose) chemotherapy. Adding PARP1 inhibitors to the treatment might enhance the overall patient survival even further. IR induces DNA double strand breaks (DSBs) as well as single strand breaks (SSBs). Hyperthermia inhibits DNA DSB repair pathway Homologous Recombination (HR) while PARP1 is responsible for repair of SSBs and is involved in DSB repair pathway AltNHEJ. Combining hyperthermia and PARP1-inhibition with IR increases tumor cell kill compared to a duomodality of IR and hyperthermia or IR and PARP1 inhibition. When cisplatin is added to the treatment, tumor cell kill can be enhanced even further, as this latter agent disrupts the Non-Homologous Endjoining repair (NHEJ). We hypothesize that tumor control will be improved when IR is combined with the three modalities that disable the DNA repair pathways.

Aim: To unravel the underlying mechanisms how hyperthermia sensitizes current treatment options.

Methods: Cervical cancer cells (SiHa, HeLa, C33A and CaSki) were treated with hyperthermia (42°C), IR (2–6Gy), chemotherapy (cisplatin, 0.3-0.5μM) and a PARP1-inhibitor (Olaparib, 4.0-5.0μM) in different combinations. Cell reproductive death was measured performing clonogenic assays. DNA DSBs were analyzed by the □H2AX staining and protein levels involved in the DSB repair pathways were measured.

Results: Combining hyperthermia and PARP1-inhibition with IR reduces the surviving fraction compared to chemoradiation. The expression of the DNA DSB repair proteins BRCA2 and Ligase III is lower in HT-treated cells.

Conclusion: Our results demonstrate that the combination hyperthermia, PARP1-inhibition and IR leads to a lower surviving fraction in cervical cancer cell lines compared to chemoradiation. Furthermore, the results demonstrate that hyperthermia does not only inhibit HR, but also affects AltNHEJ. It is concluded that hyperthermia in combination with PARP1-inhibition and IR is a good alternative for chemoradiation in cervical cancer due to its inhibitory effects on both HR and AltNHEJ.

TUES 32

DIFFERENTIAL EFFECTS OF 42°C-HYPERTHERMIA ON RADIATION RESPONSE OF BREAST CANCER SPHEROIDS VS. NORMAL HUMAN SKIN EXPLANTS

Andreas R. Thomsen1,2, Christine Aldrian1,2, Gabriele Niedermann1,2, Anca-Ligia Grosu1,2, Peter Vaupel3, Per G. Lund4

1Department of Radiation Oncology, Medical Center – University of Freiburg, Freiburg, Germany. 2German Cancer Consortium (DKTK), Partner Site Freiburg and German Cancer Research Center (DKFZ), Heidelberg, Germany. 3University Medical Center, Dept. of Radiooncology and Radiotherapy, Mainz, Germany. 4Department of Radiation Oncology, Ortenau-Klinikum, Offenburg, Germany

Abstract

Background: Recurrent tumors in previously irradiated regions remain a challenging situation, in which hyperthermia (HT) of 42°C serves to sensitize cancer cells to radiotherapy. For radiosensitization of superficial tumors, loco-regional HT can be applied in a contact-free manner by using water-filtered infrared A-(wIRA-) radiation. Starting from January 2018, our institution is treating patients with locally recurrent breast cancer using hypofractionated re-irradiation (5 x 4 Gy; 1x/wk.), shortly following wIRA-HT. Despite distinct response of cancer lesions, only grade I skin toxicities were observed. The biology underlying such favorable effects of combined treatment remains poorly understood. Therefore, this study aimed to follow the clinical protocol in vitro.

Methods: Human breast cancer cell lines were cultured as multicellular aggregates and treated weekly with HT at 42°C for one hour in a water bath. Hyperthermia was applied with or without simultaneous wIRA radiation (75 mW/cm²) to assess possible non-thermal effects of wIRA. Cultures were subsequently □-irradiated with a single dose of 4 Gy up to a total dose of 16-20 Gy. Additionally, T47D breast cancer cells were treated with different treatment schedules. Response was monitored by cell aggregate volume measurements for a total of 8 weeks and evaluated by paraffin histology. As a normal tissue model, skin biopsies were treated with a single fraction of water bath HT +/- wIRA radiation, subsequent □-irradiation and subjected to an ex vivo wound healing assay.

Results: Growth rates of normal cells and tumor cell aggregates were not impaired by HT or wIRA alone. When HT and □-irradiation were combined, a significantly higher 'cure rate' of breast cancer spheroids was found, compared to irradiation alone. Maximum treatment effects were obtained with simultaneous hyperthermia and irradiation, while increasing intervals between the two treatments continually reduced 'cure rate'. In skin explants, cell outgrowth declined with increasing irradiation doses, but was not significantly reduced by addition of HT +/- wIRA.

Conclusion: Hyperthermia (42°C, 1 hour, induced by water bath) radiosensitizes 3D breast cancer cell cultures. Simultaneous wIRA radiation did not cause any additional effect, so non-thermal effects of wIRA could not be observed in the in vitro models used. The synergistic effect of HT and □-irradiation was inversely correlated with time intervals between the two modalities, which emphasizes the role of adequate timing. Interestingly, the function of normal epidermal keratinocytes was not significantly impaired by addition of HT. These data thus support the clinical findings and may help to reveal the differential effect of thermo-radiation on malignant and normal tissue.

TUES 33

COMBINATION OF RADIATION AND HYPERTHERMIA IN CANCER TREATMENT: ASSESSMENT OF DOSE RESPONSE IN MULTICELLULAR TUMOUR SPHEROIDS

Sona Michlíková1, Adriana De Mendoza1, Jens Karschau1, Lisa Eckhardt1, Leoni A. Kunz-Schughart1,2, Damian D. McLeod1

1OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, TU Dresden and Helmholtz-Zentrum Dresden–Rossendorf, Dresden, Germany. 2National Center for Tumor Diseases (NCT), partner site Dresden, Dresden, Germany

Abstract

Hyperthermia is known to have a radiosensitizing effect in cancer treatment and thus presents a promising approach for combinatorial radiotherapy. However, the success of such treatment method is highly dependent on various parameters including treatment schedule and appropriate choice of thermal, as well as radiation dose. The thermal dose is defined by two further variables: time and temperature. This proves particularly difficult in determining the most effective combination of both treatment doses and several experimental models (both in vivo and in vitro) exist to predict that optimal combination. However, whilst on one hand in vivo models are time-consuming, expensive, and ethically problematic, less complex 2D cell culture models, on the other hand, insufficiently reflect the intricate tumour environment. As a good intermediate alternative, we use multicellular tumour spheroids (MCTS) as a tool for analysing tumour tissue dose response to both hyperthermia only treatment, as well as combinational treatment with photon irradiation. Most notably, the MCTS assay and analytical endpoints in the present study (growth delay and long-term growth control probability) reflect relevant pre-clinical and clinical endpoints and can be used to define and pre-select the best treatment settings for further in vivo validation. For our study we cultured spheroids from two head-and-neck squamous cell carcinoma cell lines in liquid overlay (radioresistant SAS and intermediately radiosensitive FaDu). Spheroids with a mean diameter of ~400 μm were subjected to different thermal (0-~800 CEM43) and/or single X-ray doses (0-25 Gy). Hyperthermia was applied via a thermal shaker. In combination treatments, irradiation immediately followed hyperthermia treatment. The integrity and size of hundreds of spheroids was monitored individually over a period of up to 60 days using semi-automated phase-contrast imaging. Spheroid control probability (SCP) curves were generated from the spheroid re-growth capacity after treatment; spheroid control dose 50% (SCD50), as the irradiation dose required to control ("cure") 50% of the spheroids, was calculated where appropriate. Volume growth curves and growth delay could be determined for treatment arms that showed 100% re-growth capacity. Our preliminary data indicate a threshold response to hyperthermia in spheroid cultures with different radiosensitivities. We also demonstrate the feasibility of the multicellular tumour spheroid model and the respective analytical endpoints for evaluating the response relationships in combinatorial hyperthermia/irradiation treatment regimes. Future experiments will include larger spheroids with a clear hypoxic core as well as the combination of hyperthermia with proton beam irradiation.

TUES 34

POLYMER NANOPARTICLES FOR IMAGING AND ABLATION OF COLORECTAL CANCER TUMOR ORGANOIDS

Bryce McCarthy1,2, Amit Cudykier3, Etai Sapoznik4, Shay Soker5, Nicole Levi-Polyachenko6

1Wake Forest University, Winston-Salem, NC, USA. 2Virginia Polytechnic Institute, Blacksburg, VA, USA. 3North Carolina State University, Raleigh, NC, USA. 4UT Southwestern Medical Center, Dallas, TX, USA. 5Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC, USA. 6Wake Forest University School of Medicine, Winston-Salem, NC, USA

Abstract

Introduction: Colorectal cancer (CRC) is the second deadliest cancer in the United States where a significant contributor to patient mortality is stromal-mediated chemoresistance. Theranostic nanoparticles, such as organic semi-conducting polymer nanoparticles, have been developed to both target and visualize tumors via fluorescence while being photothermally activated for ablation that bypasses chemoresistant pathways. Our group recently developed Hybrid Donor-Acceptor Polymer Particles (HDAPPs), hybrid organic semi-conducting polymer nanoparticles composed of fluorescent and heating polymers that can be activated and imaged within the near infrared (NIR) tissue-absorption minima. HDAPPs can be targeted to the CD44 receptor on CRC via hyaluronic acid (HA) functionalization of the surface. A major hurdle for the clinical translation of nanoparticles is their interaction with the 3D tumor microenvironment, where nanoparticle transport and photothermal heating may be isolated to the outermost shell of the tumor. To study the targeted imaging and heating potential of HDAPPs in the 3D microenvironment, we investigated their application within 3D constructs of hydrogel-embedded tumor and stromal cells (organoids) in vitro. Further, to monitor ablation in real-time via HDAPPs within these organoids, we demonstrated the utility of a unique fiber-optic-based (FOB) imaging system capable of laser-induced excitation and fluorescent imaging.

Methods: Selective binding and ablation of CT26 CRC cells cultured in 2D was demonstrated with HDAPPs and HA-HDAPPs under photothermal activation with an 800 nm laser. Next, photothermal ablation using HDAPPs and HA-HDAPPs of CT26 cells expressing green fluorescent protein (CT26.GFP) cultured in organoids with and without mouse mesenchymal stem cells expressing mCherry (mMSC.mCherry) was assessed to visualize the 3D-interaction of the nanoparticles with the tumor microenvironment. FOB imaging was used to monitor selective ablation of organoids with CT26.GFP cells treated with HDAPPs and HA-HDAPPs.

Results: Binding of HDAPPs versus HA-HDAPPs in 2D culture showed increased binding affinity of HA-HDAPPs to CT26 cancer cells relative to non-functionalized HDAPPs. Upon photothermal activation with laser, CT26 cells incubated with HA-bound nanoparticles had decreased viability. Finally, organoids were successfully imaged in real-time for photothermal ablation by detecting loss of fluorescence with FOB imaging.

Conclusion: Overall, we demonstrated the performance of a nanoparticle platform capable of targeted fluorescent imaging and photothermal ablation of CRC within a 3D cancer environment. Our work utilizes organoids with both tumor and normal cell components to capture treatment selectivity and intercellular effects on overall nanoparticle efficacy, where traditional 2D assays have failed to accurately assess treatment delivery and microenvironment interactions in nanotherapeutic development.

TUES 35

HYPERTHERMIA INCREASES SENSITIZATION OF PROTON BEAM THERAPY IN CHORDOMA CELL LINES

Javed Mahmood1, Prerna Singh1, John Eley2, Robert Malyapa1, Zeljko Vujaskovic1

1DIVISION OF TRANSLATIONAL RADIATION SCIENCES (DTRS), DEPARTMENT OF RADIATION ONCOLOGY, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE, BALTIMORE, MARYLAND, USA. 2DEPARTMENT OF RADIATION ONCOLOGY, SCHOOL OF MEDICINE, VANDERBILT UNIVERSITY, NASHVILLE, TN, USA

Abstract

Introduction: Chordomas are rare malignant tumors with a median survival in the United States of 7 years. Chordoma usually arises from remnants of the notochord and most commonly found in the clival and sacrococcygeal regions. The current standard of care is limited to en-bloc resection followed by adjuvant Radiotherapy (RT). RT is also given alone when surgery is not a viable option. However, chordoma is highly radioresistant and a high dose of RT increases the risk of toxicity to surrounding critical structures (pituitary, spinal cord, brain stem, cranial nerves). Therefore, novel strategies to improve the response of RT are warranted. Tumor-targeted hyperthermia (HT at 39-43oC) acts as a potent radiosensitizer and increases tumor blood perfusion. HT also enhances RT responses by inhibiting repair from RT-induced DNA damage of tumor cells. Current photon RT delivery to the tumor is often limited by doses that cause toxicity to the surrounding healthy normal tissues. Proton beam therapy (PBT) is a state-of-the-art RT technology that mitigates toxicities due to its characteristic spread of Bragg-peak (SOBP) leading to precise targeting of the tumor. We investigated whether PBT response can be further be enhanced in combination with HT as a radiosensitizer. We also explored whether there is any increased tumor cell killing at the end of the SOBP compared to the middle of the SOBP of PBT with HT. Method: Human Chordoma cell lines, U-CH2 and Mug-chor1 were treated with HT (43oC for 1 hour) followed by PBRT at both middle and distal SOBP with the dose of 4, 8, 12 and 16Gy for U-CH2 and 1, 2, 4, and 8Gy for Mug-chor1. Colony forming assay was performed for the dose-response survival and terminated after 14 days. All experiments were done in triplicates.

Results: HT significantly ($p<0.05$) decreased colony survival in combination with PBT at both middle and the distal SOBP for both cell lines. In U-CH2, HT with PBT significantly killed ($p<0.05$) cells at doses 4 and 8Gy and for Mug-Chor1 ($p<0.05$) at 1, 2 and 4Gy at both middle and distal SOBP. Interestingly, there was no statistical significance seen between the end and the middle of SOBP in both cell lines. We also found that Mug-chor1 is more heat-sensitive and radiosensitive while U-CH2 is heat-resistant and radioresistant.

Conclusions: Our results provide the first-time in vitro evidence about the effects of HT as a novel additive treatment to increase PBT effectiveness in Chordoma cell lines.

TUES 36

EVALUATION OF A NEW HOUSING APPARATUS FOR LABORATORY MICE THAT PERMITS SELF SELECTION OF AMBIENT TEMPERATURE: EVALUATION OF TUMOR GROWTH

Heather Campbell1, Sam Ministero1, Elena Nicholson2,1, Erin Kane1, Guanxi Qiao1, Bonnie Hylander1, Christopher Gordon3, Elizabeth Repasky1

1Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA. 2Benedictine University, Chicago, IL, USA. 3US Environmental Protection Agency, Research Triangle Park, NC, USA

Abstract

Previous work from our lab shows that laboratory mice, housed at standard, (IACUC mandated) room temperature are chronically cold stressed which also increases immunosuppression. This cold stress stimulates the sympathetic nervous system and increases the tumor growth rate in mice housed at standard temperature (ST, 22°C) compared to mice in which this stress has been alleviated by housing at thermoneutral temperature (TT, 30°C). In their natural habitat mice can self-regulate their temperature by moving to a warmer or colder environment. Therefore, we are testing a new housing model, which allows mice the opportunity to move between various temperatures. We developed "choice of ambient temperature" (CAT) system, where mice are housed at ST but have access to an area in which hand warmers are placed under the floor, creating warmer locations in their cage. We hypothesize that allowing mice to choose their ambient temperature will result in reduced thermal stress and an improved anti-tumor immune response similar to that seen in mice housed at TT. To test this hypothesis, mice housed at ST, TT, and CAT were injected with 4T1 mammary carcinoma, their tumor growth was measured every other day and their proportions of immune cells from their spleen and tumor were determined by flow cytometry. We found that mice housed at CAT have better tumor control than mice housed at ST and recapitulate what we observed at TT. This new model again demonstrates that chronic cool housing temperature is a stress to laboratory mice and for the first time, demonstrates that allowing mice to choose their optimal housing temperature environment can help to reduce cold stress and improve tumor growth. Understanding how cold stress impacts mouse models used to mimic human systems will help to explain variability in experimental results and will improve preclinical research.

TUES 37

CLINICAL APPLICATIONS OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY; A REVIEW.

Roxan F.C.P.A. Helderman, Daan R. Löke , H. Petra Kok , Arlene L. Oei , Pieter J. Tanis , Nicolaas A. P. Franken , Johannes Crezee

Amsterdam University Medical Centers, Amsterdam, Netherlands

Abstract

Peritoneal metastasis (PM) originating from gastrointestinal and gynecological malignancies are associated with a poor prognosis and rapid disease progression. Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment with curative intent. Hyperthermia enhances the cytotoxic effect of chemotherapeutic drugs, thereby killing microscopic tumors and reducing the risk of tumor recurrence. Eight parameters potentially have an impact on the degree of effectiveness of HIPEC: type of drugs, drug concentrations, carrier solution, volume of the perfusate, temperature of the perfusate, duration of the treatment, the technique of delivery and patient selection. In this review, a literature search was performed on PubMed and a total of 564 articles/abstracts were screened of which 168 clinical full papers were included that were written in English and reporting parameters. Although HIPEC is a successful treatment, there is no standardized method for delivering HIPEC and the choice of parameters is largely determined by institutional preferences. We observed both a geographical and institutional variation in the choice of parameters. Despite these variations, some regularities were also noticed. Drugs most often used in HIPEC treatments are mitomycin C and cisplatin. The prevalent choice of carrier solution is a saline or dextrose solution. Volume of the perfusate is either an absolute volume varying between 1 and 12 liters or dependent on the patient's body surface (often 2L/m2). The treatment duration varies between 30 minutes to 120 minutes. The temperature range between 41 and 43°C is considered to be the optimal temperature. Usually, high(er) temperatures are combined with a low(er) dose and/or for a short(er) period and low(er) temperatures are combined with high(er) dose and/or long(er) duration. The closed delivery technique is used in 50% of the institutes. It should be emphasized that patient selection has a major impact on the outcome of HIPEC. There is no clinical or experimental evidence indicating a superior choice of technique, carrier solution and volume. Type of drugs, concentration, temperature and duration were partially investigated in preclinical studies, but not for all clinically used schemes and drugs. The variability in each of the eight parameters is significant, resulting in a strong efficacy variation of the HIPEC treatment. In vivo, in vitro, in silico and other experimental studies are valuable tools to determine the importance of the individual parameters. Quantifying the effect of each parameter separately can help to optimize treatment protocols and thereby further improve the efficacy of HIPEC.

TUES 38

PROSPECTIVE, SINGLE INSTITUTION EVALUATION OF HIPEC IN OVARIAN CANCER

Thanh Dellinger, Ernest Han, Mark Wakabayashi, Stephen Lee, Mehdi Kebria, Maria De Leon, Lin Wei-Chien, Amy Hakim, Xueli Liu, Mihaela Cristea, Edward Wang, Robert Morgan, Mustafa Raoof, Byrne Lee

City of Hope National Medical Center, Duarte, CA, USA

Abstract

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) has demonstrated significant overall survival benefit in primary ovarian cancer. We report the preliminary results of a single institution feasibility study to determine safety and survival of HIPEC in patients with ovarian and endometrial cancer.

Methods: Eligible patients included women with newly diagnosed or recurrent Stage III/IV ovarian cancer (OC) or endometrial cancer (EC), who underwent cytoreductive surgery and HIPEC with cisplatin 75 mg/m2(over 60 minutes) from June 2014 - January 2018 as part of a single institution Phase I clinical trial. Primary endpoint included safety of HIPEC, and secondary endpoint included progression-free survival (PFS), overall survival (OS).

Results: A total of 18 underwent HIPEC, with 10 recurrent OC patients, 5 newly diagnosed (primary) OC, and 3 EC patients. Median age was 60 years. Median PCI score was 7. Complete cytoreduction (CC0) was achieved in 12 patients (67%). Median length of surgery was 6.7 hours. Median EBL was 300cc. Median length of hospital stay was 9 days (5-17 days). Median body mass index (BMI) was 28.4. The most common Grade 3 toxicities included anemia (9 patients), metabolic acidosis (5 patients) and aspartame aminotransferase elevations (4 patients). There were no Grade 4 toxicities, postoperative deaths or readmissions. Among 10 recurrent ovarian cancer patients, 7 patients progressed, and one died due to progression of disease (7 were platinum-sensitive, 3 platinum-resistant). In this recurrent ovarian cancer cohort, median follow-up was 17.5 months with 95% CI [16.0, NA]; median PFS was 13.4 months with 95% CI (7.6, NA), and median OS was 21.1 months (21.1, NA).

Conclusions: HIPEC in primary and recurrent ovarian and uterine cancer is feasible with a safe toxicity profile similar to that seen for patients undergoing surgical debulking without HIPEC. Additional follow up and further studies are needed to assess the efficacy of HIPEC on long-term survival.

TUES 39

SINGLE INCISION LAPAROSCOPIC CYTOREDUCTIVE SURGERY AND HEATED INTRAPERITONEAL CHEMOTHERAPY FOR RECURRENT CASES OF PSEUDOMYXOMA PERITONEI

Steven Cheung, Emily Griffin, Brian Loggie

Creighton University, Division of Surgical Oncology, Omaha, NE, USA

Abstract

Background: Cytoreductive surgery (CRS) with heated intraperitoneal chemotherapy (HIPEC) is the standard treatment for pseudomyxoma peritonei (PMP). With recurrence, the decision to operate is individualized based symptomatology, disease severity, previous surgeries, as well as short and long-term quality of life. Candidacy for HIPEC is dependent on completeness of tumor debulking. The midline celiotomy allows for wide exposure for tumor debulking but morbid and suboptimal when balanced against quality of life and in the setting of a complication, limits the transition to chemotherapy. Here, we describe a minimally invasive technique combining the use of single incision laparoscopic surgery (SILS) and the laparoscopic cavitron ultrasonic surgical aspirator (CUSA) handpiece to perform CRS for PMP.

Methods: Three consecutive patients with recurrent PMP, symptomatic obstruction, and moderate to high volume disease were prospectively selected to perform the minimally invasive CRS. All patients had previous midline celiotomy incisions that were marked in addition to other surgical incisions. Using preoperative MRI, a central 4-5 cm incision planned with minimal risk to underlying hollow viscus. After entry, debulking with the standard suction system or vacuum curettage device was performed when appropriate for initial debulking. Subsequently, flexible laparoscopy with both pneumoperitoneum via a SILS port or gas-less techniques used to obtain exposure to allow for resection with the laparoscopic CUSA. After resection completed, additional procedures performed as indicates prior to placement of catheters through the limited incision to perform HIPEC with carboplatin 900 mg for 1 hour at 42.5*C.

Results: The technique was successfully completed with HIPEC in all 3 patients without perioperative complications. The CUSA facilitated resection of 3700, 11050, and 1450 mL composing of 100%, 46%, and 61% of the total volume of tumor debulked respectively. For the second and third patient, additional subxiphoid incision made to perform targeted debulking of upper abdomen. Open conversion not necessary for any reason. Total lengths of stays were 7, 5, and 4 days.

Conclusions: Using the combined SILS and laparoscopic CUSA technique, higher volume tumor debulking can be performed while minimizing incision and thus, perioperative morbidity compared to traditional methods.

TUES 40

TOWARDS THERMAL THERAPY TREATMENT PLANNING FOR HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

D.R. Löke1, H.P. Kok1, R.F.C.P.A. Helderman1,2, G. Schooneveldt1, R. Zweije1, J. Sijbrands1, N.A.P. Franken1,2, J. Crezee1

1Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands. 2Department for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental and Molecular and Molecular Medicine (CEMM), Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

Abstract

Peritoneal metastasis (PM) originating from gastrointestinal and gynecological malignancies are associated with a poor prognosis and rapid disease progression. The only treatment option with curative intent is cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC). A problem often encountered in HIPEC treatments is the inhomogeneous distribution of the heated fluid (39-43 °C) containing the chemotherapeutics. The fluid is injected and drained through catheters at a flow rate of 1-2 liter/minute. The number and placement of these catheters determine the flow pattern inside the peritoneal cavity. Computational Fluid Dynamics (CFD) can thus be a relevant tool towards patient specific treatment planning software for HIPEC.

We use the OpenFoam software package to develop our own treatment planning software capable of mapping the transient thermal and drug distribution. We performed an experimental study, validating our software, on a simplified (closed) HIPEC model, testing for only natural convection. The model consisted of a polyvinylchloride (PVC) cube, measuring 7x7x7 cm, with two opposing vertical sides set at temperature differences up to 15 °C. Thermal probes mapped the temperature profile in the plane perpendicular to the opposing sides with a spatial resolution of 5-10 mm.

We predicted correct temperature profiles to within 0.1 °C, accurate enough for clinical hyperthermic applications. For future work, a similar model can be used for mimicking conditions resembling open HIPECs, including interactions with air.

These are the first steps towards the development of patient specific treatment planning software for HIPEC, reducing drug and thermal inhomogeneities and possibly limiting systemic toxicity.

TUES 41

ERAS PROTOCOL IMPLEMENTATION FOR CYTOREDUCTIVE SURGERY WITH HEATED INTRAPERITONEAL CHEMOTHERAPY

Erika Samlowski, Sarah Aurit, Gilman Plitt, Mark Reisbig, Brian Loggie

Creighton University , Omaha, Nebraska, USA

Abstract

Introduction: Enhanced Recovery After Surgery (ERAS) is a perioperative care plan designed to optimize the physiologic response to surgery and promote recovery. Cytoreductive Surgery (CS) with Heated Intraperitoneal Chemotherapy (HIPEC) is highly morbid surgery in complex patients. ERAS protocols have been successfully implemented and validated across a wide range of surgical specialties but has yet to be shown to have clinical benefit in this patient population.

Methods: Data was retrospectively collected from patients who underwent CS with HIPEC from September 2015 to January 2018 and analyzed for outcome differences pre versus post ERAS implementation. Mann-Whitney test was utilized for comparison of continuous variables and the Fisher's exact test for categorical variables. A multivariable Poisson regression model was utilized to predict length of stay and variable inclusion was considered if there was a significant unadjusted relationship. All analyses were conducted with SAS version 9.4, p-values < 0.05 were considered significant.

Results: Fifty one serial patients (15 men, 36 women, age 32-80, average 55.6 years) were reviewed. Narcotic PCA use dropped from 95.7% to 28.6% ($p< 0.001$.) 46.4% of ERAS patients received no narcotics in the post-operative period versus 4.3% pre ERAS ($p < 0.001$.) Return of bowel function was reduced from 4.6 days (SD 1.0) to 3.3 days (1.4) ($p=0.005$.) Days to normal diet was reduced from 4.9 days (SD 1.5) to 4.1 (2.1) days ($p=0.136$.) Length of stay decreased from 5.5 (SD 1.8) to 4.7 (SD 2.3) postoperative days ($p=0.180$.) 30 day readmission and morbidity rates were stable.

Conclusion: Implementation of the ERAS protocol for CRS HIPEC patients provided significant clinical benefit by reducing time to return of bowel function, time to general diet, and hospital length of stay. Narcotic use was drastically reduced compared to pre ERAS implementation.

TUES 42

HIPEC MODELS TO PREDICT TUMOR DRUG PENETRATION IN A DYNAMIC 3D ENVIRONMENT.

D.R. Löke1, H.P. Kok1, R.F.C.P.A. Helderman1,2, N.A.P. Franken1,2, J. Crezee1

1Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands. 2Department for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental and Molecular and Molecular Medicine (CEMM), Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands

Abstract

When diagnosed with gastrointestinal or gynecological malignancies in combination with peritoneal metastasis (PM), patients are faced with a grim prognosis. The only treatment with a curative intent is cytoreductive surgery (CRS), treating the macroscopic tumor load, followed by hyperthermic intraperitoneal chemotherapy (HIPEC) to treat residual microscopic disease. A strong prognostic factor for survival is the removal of all macroscopic nodules during CRS. During HIPEC, fluid (39-43 °C) is drained through multiple catheters, usually one or two inflows and around four outflows, at a flow rate of 1-2 liter/minute, which easily results in an inhomogeneous flow pattern throughout the peritoneum. This flow pattern causes a variety of local physical environments and numerical models incorporating these environments could be very useful to assess the effect on the penetration depth of chemotherapeutics. In this study we investigate the effect of tumor size, considering both spherical and ovoid nodules, type and dose of chemotherapy on the penetration depth.

Within the OpenFoam toolkit, we developed our own solver using a combination of the PISO (Pressure Implicit with Splitting of Operator) and SIMPLE (Semi-Implicit Method for Pressure-Linked Equations) algorithms. Models comprise a pipe-like structure resembling the peritoneal exterior and a necrotic core encapsulated by a viable tumor nodule, modeled as porous medium. Radii considered for spherical tumor nodules are 0.5 mm, 1 mm and 2 mm, investigating sizes relevant for a complete CRS. For ovoid geometries we used minor axis radii of 0.25 mm, 0.5 mm and 1 mm, varying shape and size for ovoid nodules. A flow was generated through the pipe at a flow velocity of 1 L/s at 42 °C with varying dose and type of chemotherapy, characterized by its diffusion constant. Inside the viable tumor region, uniform thermal and drug sinks were created to mimic the vascular structures, according to the Pennes bioheat equation and the work done by Baxter and Jain, respectively.

The penetration depth was not sufficient to expose all cancer cells inside the tumor to a sufficient dose of chemotherapy for any type of chemotherapy for tumor nodules with a radius of 1.25 mm or larger. Drugs with a lower density and molecular weight show a higher diffusion translating to larger penetration depths. Future studies with similar models could incorporate varying realistic velocities and temperatures to see the influence on penetration depth. These models can be used to further optimize current HIPEC treatments.

TUES 43

MAGNETIC RESONANCE IMAGING-GUIDED, SALVAGE, PERCUTANEOUS CRYOABLATION OF RECURRENT PROSTATE CANCER AFTER RADICAL PROSTATECTOMY: 24-MONTH FOLLOW-UP.

David Woodrum, Kristianne Kinsman, Robert McLaren, Derek Lomas, Krys Gorny, Christopher Favazza, Joel Felmlee, Aiming Lu, Lance Mynderse

Mayo Clinic, Rochester, MN, USA

Abstract

OBJECTIVE: To evaluate the effectiveness of MRI‐guided salvage cryoablation at 24 month follow-up in the treatment of recurrent prostate cancer limited to the prostate bed after radical prostatectomy.

MATERIALS AND METHODS: From retrospective review of recurrent prostate cancer patients with localized disease in the prostate bed treated with MR guided cryoablation from Feb, 2011 to June, 2015, 31 patients (mean age 66 years old) were treated with 1 lost to follow‐up after treatment. 18 patients had prior radical prostatectomy+radiation, 9 patients had radical prostatectomy with no radiation, and 4 patients had primary radiation therapy with local prostate bed recurrence prior to cryoablation. All patients had disease limited to the prostate bed by imaging MRI ± C-11 PET with congruent PSA levels to the lesion size based on experienced Urologist.Follow-up was MRI, PSA and clinic visit every 6 months for the 2 year follow-up with attempt at PSA measurements every 3 months.

RESULTS: Overall, 30 patients were treated with salvage MRI guided cryoablation with 2 year follow‐up. At 1 year followup, 18 of 30 (60%) showed no evidence of biochemical recurrence (PSA>0.2ng/mL) with 26 of 30 (87%) ≤ PSA 0.40. At 2 years, 5 of 30 had repeat treatments of MR guided cryoablation(3), radiation(1), and chemo-hormonal therapy(1). At 2 years of the remaining 25 patients, 16 (57%) showed no evidence of biochemical recurrence.

CONCLUSION: In this very difficult patient subgroup, MRI guided salvage cryoablation of biopsy proven, locally recurrent prostate cancer in the prostate bed who failed standard therapies is feasible and offers a valuable additional alternative therapy to patients who are running out of therapeutic options.

POS 1

LIDOCAINE-INDUCED POTENTIATION OF THERMAL DAMAGE IN SKIN AND CARCINOMA CELLS

Martin Purschke1,2, Adam Raff1,2, Carina Thomas1, Matthew Avram1,2, Rox Andrson1,2

1Massachusetts General Hospital, Boston, MA, USA. 2Harvard Medical School, Boston, MA, USA

Abstract

Lidocaine acts as a local anesthetic by blocking transmembrane sodium channel permeability, but also induces the synthesis of heat shock proteins and sensitizes cells to hyperthermia. A previous study reported two cases of deep focal skin ulceration at points corresponding to depot local lidocaine injection sites after treatment with non-ablative fractional resurfacing and it was hypothesized that lidocaine had focally sensitized keratinocytes to the thermal damage of laser treatment. The objective of this study was to investigate whether lidocaine potentiates hyperthermia damage to both normal and cancerous skin cells using an in vitro model. Normal skin cell lines (fibroblasts, keratinocytes), skin cancer cell lines (melanoma, basal cell carcinoma), and a mucosal cancer cell line (cervical carcinoma) were exposed to various concentrations of lidocaine (0-0.3%) with or without hyperthermia (37°C, 42°C). Compared to normal skin cells, we demonstrate that cancer cell lines show significantly increased cell toxicity when a moderate temperature (42°C) and low lidocaine concentrations (0.1-0.2%) are combined. The toxicity directly correlates with a higher percentage of cells in S-phase (28–57%) in the cancer cell lines compared to normal skin cell lines (13–19%; R-square 0.6752). These results suggest that lidocaine potentiates thermal sensitivity of cell cycle active skin cells. The direct correlation between cell toxicity and S-phase cells could be harnessed to selectively treat skin and mucosal cancer cells while sparing the surrounding normal tissue. Additional research pre-clinically and clinically using several different heat sources (e.g., lasers, ultrasound, etc.) and lidocaine concentrations is needed to confirm and optimize these results. Lidocaine-enhanced hyperthermia may provide a non-invasive, alterative treatment option for highly proliferating, superficial skin and mucosal lesions such as cancer or warts.

POS 2

A NEW, TUNABLE, MULTIMODAL STRATEGY FOR ABLATION: EXOTHERMIC REACTION OF THIOGLYCOLIC ACID FOR THERMAL DENATURATION WHILST TARGETING DISULFIDE BONDS TO ALTER PROTEIN STRUCTURE

Naadir Jamal1, Erik Cressman2

1Rice University, Houston, TX, USA. 2MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: Tumor ablation causes cell death primarily due to protein denaturation. The disulfide bond found in many proteins is a critical post-translational modification for stabilizing and maintaining structure and thus function of many proteins that are essential for life. Thioglycolic acid (TGA) can disrupt disulfide bonds, removing an essential stabilizing element in protein structure and facilitating denaturation. The purpose of the present study is to evaluate the potential of TGA in multimodal ablation by studying the exothermic reaction of TGA. Since TGA has two acidic protons, studies were done using either one or two equivalents of base. The combination of heat, nucleophilic disulfide bond disruption, and hyperosmolarity together would provide a powerful, multimodal denaturation in a single procedure.

Materials and Methods: Experiments were performed in triplicate. Small volumes (100-200 μL) of TGA (1-10 mol/L) were introduced into microfuge tubes and equilibrated with a thermocouple system for logging temperatures. One equivalent of NaOH at equal or twice the concentration but half the volume was rapidly introduced in a single portion with gentle agitation to ensure adequate mixing. Experiments were also conducted with two equivalents of base to assess the thermal potential for reaction of the free sulfhydryl group. Temperatures were recorded over 300 seconds and plotted as a function of concentration. Data were then compared to assess relationships between concentration, equivalents, and total mass.

Results: Temperatures increased in a concentration-dependent manner 4.8° - 58°C above baseline. A 2nd equivalent of base resulted in further increases in temperature, as did the use of base at twice the concentration but half the volume (less total thermal mass).

Conclusion: Temperature changes indicate TGA has potential as a multimodal ablation agent even without invoking disulfide bond cleavage or hyperosmolarity. Higher temperatures associated with a 2nd equivalent of base indicate reaction with the sulfhydryl group generated the highly nucleophilic thiolate anion. Protein denaturation via disulfide bridge disruption combined with heat energy appears to be a strategy worthy of further characterization in the preclinical animal setting.

POS 3

FIRST DETAILED PATHOLOGY OF HEPATIC THERMOEMBOLIZATION IN A SWINE MODEL

Elizabeth Whitley, Chunxiao Guo, Erik Cressman

MD Anderson Cancer Center, Houston, TX, USA

Abstract

Introduction: Chemoembolization therapy for hepatic tumors is performed by intra-arterial delivery of reagents causing toxic effects and vascular occlusion. Unfortunately, incomplete treatment is common and can provoke a more aggressive tumor response. Using a new method called thermoembolization, we performed exothermic chemical reactions in vivo. This is the first report of histopathological sequelae after thermoembolization induced a severe local pH imbalance with simultaneous release of substantial heat energy.

Methods: Using an in vivoswine model, focal hepatic segmental arterial thermoembolization was performed using a solution of 2 mol/L dichloroacetyl chloride in 400 μL of ethiodized oil, administered via fluoroscopically-guided microcatheter. Animals were euthanized 24 hours later and treated regions were collected and processed for histopathology. Acute effects of the method were evaluated microscopically using histochemical and immunohistochemical methods to characterize alterations in tissue architecture and cytomorphology, inflammatory responses, and mechanisms of cell injury and death. Fluorescent and chromogenic staining techniques were used to highlight polymerized actin of the cytoskeleton, myeloperoxidase in neutrophils, cleaved caspase-3 in apoptotic cells, and changes in nuclear morphology.

Results: A large zone of necrosis extended outward from the target artery, with relatively intact tissue architecture. Homogeneous, eosinophilic cytoplasm and loss of nuclear staining was present in hepatocytes and in cells comprising portal vessels, bile ducts, and stroma. This central area of necrosis was surrounded by a zone with prominent cell and nuclear lysis, infiltration by leukocytes, cleaved caspase-3-positive (apoptotic) hepatocytes, and, more peripherally, a crisp border with less-affected hepatic parenchyma. Adjacent lobules supplied by branches of the affected artery had smaller regions of injury.

Conclusion: Histologic features of hepatic injury are consistent with coagulative necrosis centered on portal structures and the adjacent hepatic parenchyma, with acute infiltration of polymorphonuclear leukocytes. The peripheral zone contained scattered apoptotic hepatocytes, indicating local expansion of damage after the initial injury. This may be in response to the release of danger signals from severely damaged regions and the resulting inflammation. Thermoembolization effects are likely mediated by a combination of acute pH injury, thermal injury, and ischemia with a delayed response component due to inflammatory mediators.

POS 4

TISSUE MICROARRAY ANALYSIS OF MORPHOLOGY AND MECHANISMS OF TISSUE DAMAGE BY THERMAL, CHEMICAL, AND THERMOCHEMICAL MODALITIES

Chunxiao Guo, Elizabeth Whitley, Kaleena Ramirez, Niloofar Karbasian

MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: A major therapy for early to intermediate-stage hepatocellular carcinoma includes hyperthermic and chemical ablation methods. These cause cell death through denaturation and coagulative necrosis, but recurrence and incomplete treatment are frequent. A new approach, locally applied thermochemistry, can release localized heat energy and a range of other alterations in the local environment simultaneously. Injurious stimuli can cause cell injury and death via several pathways, thereby resulting in distinct pathologic effects and, thus, differences in morphology. We report on the immediate morphologic effects of these factors, specifically thermal energy in the context of variations in pH and tonicity, which were examined using a custom-made tissue microarray.

Methods: Samples of fresh swine liver (0.5 cm x 0.5 cm x 0.5 cm) were exposed in vitroto heat (60°C/5 minutes) and/or to an excess of different carboxylic acids, bases (NaOH, Na2CO3) , or corresponding salts under conditions of high or low osmolarity (0.25M, 2.5M), alone and in combination. Tissues were then formalin-fixed, and processed as tissue microarrays for histologic examination. Patterns of tissue architecture and cell morphology including cytoplasmic proteins, cytoskeleton, and cell membranes were characterized using hematoxylin and eosin, phalloidin-AlexaFluor488, and 4□,6-diamidino-2-phenylindole (DAPI) staining.

Results: Thermal energy resulted in alterations in tissue architecture and clumping of cytoplasmic and extracellular proteins, with retention of nuclear morphology at milder conditions. Hepatocyte shrinking and erythrocyte lysis were present under acidic conditions. Alkaline conditions resulted in lysis of portal structures and, to a lesser extent, injury to hepatocytes, with alterations to nuclear membranes and regional karyolysis. Treatment with hypertonic saline resulted in cytoplasmic vacuolation, nuclear condensation, and, sometimes, karyolysis.

Conclusion: Thermal, acid, alkaline, and hypertonic treatments differ in the type and extent of tissue damage produced, with implications for selection of thermochemical conditions to target immediate tissue damage and generation of mediators of secondary inflammatory and immune responses.

POS 5

MULTISITE SOFTWARE PLATFORM OF MRI-GUIDED FOCUSED ULTRASOUND HYPERTHERMIA APPLICATIONS

Maryam Siddiqui1, Steven Engler2, Matthew MacDonald2, Craig Macsemchuk2, Jak Loree-Spacek1, Amanda Beserra1, Jeremy Tan3, Sam Raisbeck3, Elizabeth Morrow3, Lior Lustgarten3, Thomas Looi3, James Drake3, Adam Waspe3, Christine Allen4, Warren Foltz5, Laura Curiel1, Samuel Pichardo1

1University of Calgary, Calgary, Alberta, Canada. 2Lakehead University, Thunderbay, Ontario, Canada. 3The Hospital for Sick Children, Toronto, Ontario, Canada. 4University of Toronto, Toronto, Ontario, Canada. 5Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Abstract

BACKGROUND: The availability of robust, efficient and openly accessible software libraries facilitates the development of new applications in focused ultrasound. The tools MatMRI and MatHIFU (J. Ther. Ultrasound, 2013, 1,1–12) developed by our team enable researchers to control, respectively a Philips Healthcare-based Magnetic Resonance Imaging (MRI) system and the Sonalleve MRI-guided High Intensity Focused Ultrasound (MRI-HIFU) device from Profound Medical. In this communication, we present the software library Proteus, which is the next generation of a much more sophisticated software infrastructure aiming to facilitate the development of new therapeutic applications by providing a core of functionalities that are independent of MRI or MRI-HIFU vendors. Proteus facilitates multi-site collaborations and enables the research community to directly translate preclinical developments to new and innovative clinical directions. Although, this system poses a multi-modality advantage, here, we focus mainly on its application in hyperthermia experiments.

METHODS: Proteus is a series of libraries written in the Python language and includes modules for specific tasks such as treatment planning, real-time visualization and monitoring of MRI-HIFU delivery, cavitation detection, sensor data collection, data analysis and storage management, advanced MRI-based thermometry, proportional–integral–derivative (PID) controllers, and more. New variants of MatMRI and MatHIFU have been produced to integrate communication for low-latency data collection with other MRI vendors and control of HIFU hardware. By providing support to multiple hardware providers, Proteus facilitates collaboration among centers with diverse infrastructure.

RESULTS: We have successfully delivered hyperthermia based on MRI-HIFU in phantoms, rodent and pig models using very diversified hardware providers (Sonalleve, IGT, FUS Instruments) and MRI devices (Bruker, Philips and GE). Proteus facilitated using a common algorithm for spatial control of the hyperthermia delivery. Thanks to this multisite support, a current example of successful multi-center research based on Proteus is our collaboration between the University of Calgary, The Hospital for Sick Children (SickKids), and STTARR Facility (University Health Network) to advance the use of hyperthermia based on MRI-HIFU for breast cancer in adults and rhabdomyosarcoma in children.

CONCLUSIONS: Proteus represents a significant step forward in building a compelling collaborative model where the expertise of multiple centers is efficiently combined to overcome the many obstacles involved in the development efficient techniques of hyperthermia based on MRI-HIFU. We will apply this combined expertise for improving drug-delivery to tumours using thermosensitive liposomes in pre-clinical models of breast cancer and rhabdomyosarcoma.

POS 6

POLARIZED MACROPHAGES INTERACT SPECIFICALLY WITH ANTIBODY-LABELED MAGNETIC IRON OXIDE NANOPARTICLES

Chun-Ting Yang, Preethi Korangath, Robert Ivkov

Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background: Magnetic iron oxide nanoparticles (MIONs) have biomedical applications for drug delivery, image contrast, specific cell sorting and responding to alternating magnetic fields (AMFs) to generate heat. A majority of studies that demonstrate nanoparticle targeting with antibodies, toxicity, and changes to both the cell membrane and structure are in vivo studies conducted using mouse models. While it is accepted that MIONs interact with host macrophages, the nature of these interactions and their effects on the macrophages is less studied. To better understand the biological effects of systemic exposure to nanoscale materials, it is essential to study mechanisms of cellular responses in macrophages when exposed to MIONs. The aim of this study was to investigate, in vitro, the effects of macrophage polarization to differentiate between antibody-labeled and plain MIONs.

Method: MIONs used in the present study were starch-coated bionized nanoferrite (BNF) nanoparticles that have been used previously. BNF nanoparticles have demonstrated good biocompatibility, heating potential, and easy stable surface modification. BNF nanoparticles were labeled with either trastuzumab (aka Herceptin, or Her) or a polyclonal non-therapeutic human immunoglobulin G (IgG) antibody. RAW 264.7 macrophages were pretreated with M1 or M2 induction media for one hour and then exposed to various concentrations of nanoparticles for 24 hours at 37°C. Cell proliferation was measured with the WST-1 assay anda colony genetic assay was performed to assess the macrophage cell survival. qPCR was used to identify macrophage polarization properties (iNOS and Arg1).

Result: Macrophages induced to M1 state demonstrated a higher capacity to internalize more BNF nanoparticles as measured by iron quantification, with a strong preference for Herceptin-labelled BNF (BNF-Her) nanoparticles. The uptake demonstrated both dose and time of exposure dependence. On the other hand, M0 (uninduced) and (induced) M2 macrophages showed a slightly elevated internalization of BNF-Her nanoparticles than of either BNF-Plain and BNF-IgG, but this was 3-fold less than for M1 macrophages as measured by cellular iron content. For polarized macrophages in an induction medium, M2 macrophages grew faster than either M0 or M1, and formed spindle like structures within a condensed nucleus. For the M0 and M2 macrophages, BNF-exposed cells grew faster than with either BNF-Her or BNF-IgG groups for five days. No differences were observed in growth rates of M1 macrophages when exposed to any of the various BNF constructs. Results obtained from clonogenic assay demonstrated that M2 macrophage possessed a higher plating efficacy than either M0 or M1. M0 macrophages exposed to BNF-plain demonstrated a high survival rate, which was similar to M1 and M2. Elevated iNOS levels observed in both M0 and M2 exposed to BNF-Her nanoparticles demonstrates internalization of the BNF-Her construct initiated M1 induction, which was not observed after exposure to either BNF-Plain or BNF-IgG. Arg1 expression levels were elevated in M1 macrophages after exposure to BNF-plain suggesting exposure to BNF-Plain nanoparticles can initiate an M2 induction in M1 macrophages.

Conclusion: Murine macrophages exposed to various BNF constructs – Plain or bearing human antibodies – displayed complex cellular responses, that depended on both nanoparticle construct and macrophage polarity. M1 macrophages demonstrated significant capacity and preference to internalize Herceptin-labeled BNF nanoparticles. M2 macrophages exposed to BNF-Her were induced to the M1 state; however, BNF-Plain nanoparticles stimulated faster growth in M0 and M2 macrophages than did exposure to either BNF-antibody construct. These results demonstrate a complex set of cellular responses displayed by murine macrophages upon exposure to nanoparticle constructs that depends on both the nature of the nanoparticle and the polarity of the macrophages at time of exposure.

POS 7

SYSTEMICALLY DELIVERED ANTIBODY-LABELLED BNF ARE LESS TOXIC THAN BNF-PLAIN UNDER ALTERNATING MAGNETIC FIELDS

Chun-Ting Yang1,2, Preethi Korangath2, Jackie Stewart2, Chen Hu3, Wei Fu3, Sarah E. Beck4, Feng-Huei Lin1, Robert Ivkov2

1Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan. 2Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. 3Division of Biostatistics and Bioinformatics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. 4Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Background: Magnetic iron oxide nanoparticles (MIONs) have been a focus of biomedical research and applications for over fifty years because their magnetic properties enable imaging and therapy. From extensive use in preclinical and clinical studies, MION biocompatibility and toxicity is established, making them a subject of continued research for additional applications in medicine. For magnetic hyperthermia (MHT) treatments that involve heating a region of tissue following systemic delivery the potential therapeutic advantages of higher SLP (specific loss power) MIONs can be outweighed by the significant toxicity induced by overheating normal tissues and organs. In this study, the potential toxicity due to off-target heating of MHT following systemic delivery of MIONs was assessed in vivo.

Methods: 8-week old healthy female nude mice received tail vein injections of a single dose of hydroxyethyl starch-coated magnetic iron oxide nanoparticles (BNF) or a counterpart labeled with a polyclonal human antibody (BNF-IgG) at 1mg, 3mg or 5mg Fe/mouse on day1. On day 3, mice were exposed to an alternating magnetic field (AMF) having one of three different field amplitudes (32, 48 and 64 kA/m) at ~145 kHz for a duration of 20 minutes. 24 hours after AMF treatment, blood, liver and spleen were harvested from each mouse and analyzed with histopathology for tissue damage and with inductively-coupled plasma mass spectrometry (ICPMS) for iron content.

Results: Mice treated with different concentrations of BNF or BNF-IgG nanoparticles at different AMF conditions exhibited varying degrees of burn-related toxicity. Visible burn lesions were identified on skin of the chest region, with evidence of liver damage after treatment with BNF or BNF-IgG at higher concentration with high AMF amplitude. Mice receiving 3mg BNF combined with 48 kA/m appeared lethargic and ill, but were alive. At this BNF concentration and at 64 kA/m, all mice died following treatment. On the other hand, mice treated with 3 mg Fe of BNF-IgG and 64 kA/m AMF amplitude displayed were lethargic and appeared ill, but they survived. Analysis of histopathology of these groups also revealed widespread liver tissue necrosis. Following systemic delivery, BNF and BNF-IgG nanoparticles can accumulate in the liver and spleen, making these the sites of potential toxicity.

Conclusion: Toxicities associated with off-target heating of MIONs depend upon the distribution and off-target organ deposition of MIONs following systemic delivery. Antibody-labeling, often used to 'target' nanoparticles for solid tumor cancers, also alters off-target organ distribution thus modifying (reducing) potential toxicities. These results are promising and merit further investigation for clinical application.

POS 8

CONSISTENT EVALUATION OF SPECIFIC LOSS POWER IN MAGNETIC PARTICLE HYPERTHERMIA

Antonios Makridis1,2, Sergio Curto3, Gerard C. van Rhoon3, Theodoros Samaras1,2, Makis Angelakeris1,2

1Department of Physics, Faculty of Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece. 2Center for Interdisciplinary Research and Innovation (CIRI-AUTH), Balkan Center, Thessaloniki, Greece. 3Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands

Abstract

Introduction: Measurement of specific loss power (SLP) of magnetic nanoparticles (MNPs) is crucial to assert their heating potential in magnetic particle hyperthermia (MPH). Despite, the remarkable progress in this field, the evaluation process of SLP suffers from errors and uncertainties imposed not only by experimental parameters (particles, conditions and measurement) but by the estimation methodology as well. In this work, we propose a step by step standardization protocol, starting from the definition and recording of potential uncertainty and error sources, occurring in a typical magnetic hyperthermia procedure resulting to SLP evaluation.

Methods: We systematically investigate the heating properties of magnetite NPs with distinct magnetic features (ferromagnetic, superparamagnetic), when excited by an alternating magnetic field. Magnetic heating is performed using three different commercial induction heating setup systems to make feasible the diverse series of parameters and value ranges studied. The experimental results are collected over a wide range of field frequencies and amplitudes, with several optical fibre positions, using different coil geometries and different vessel sizes and types at an extent not found in the literature.

Results: Our results demonstrate that SLP is proportional to the square of field amplitude and to the reverse square of field frequency, confirming the ferromagnetic nature of the examined MNPs. Reducing the sample's volume by a factor of two (from 1 mL to 0.5 mL) may lead to underestimating the SLP value by half. In the contrary, a change in sample concentration (from 0.25 to 3 mg/mL) seems not to have a crucial effect on the total SLP (change less than 10%). According to our analysis, during a magnetic hyperthermia experiment performed under non-adiabatic conditions, the total extended uncertainty of the SLP value may be up to 14%. Meanwhile, different heating evaluation methods are assessed, with the "Modified Law of Cooling" proving to be the best choice under a wide range of experimental conditions.

Conclusions: In principle, SPL evaluation for MPH has a multi-parametric nature. The SLP parameters and their associated uncertainties presented in this work serve as a significant guide for performing a reliable MPH experiment. Such a parametric chart, is directly applicable in MPH laboratories and will ensure credible and consistent SLP evaluation and comparison between labs and MNP systems, opening the pathway towards safer MPH clinical protocols.

Acknowledging: Acknowledge the COST Action EMF-MED, supported by COST (European Cooperation in Science and Technology).

POS 9

IRON OXIDE NANOPARTICLE PERFUSION AND REWARMING IN RAT HEARTS

Zhe Gao, Baterdene Namsrai, Hattie Ring, Vasanth Ravikumar, Yugene Guo, Anirudh Sharma, Michael Garwood, Elena Tolkacheva, Erik Finger, John Bischof

University of Minnesota, Minneapolis, MN, USA

Abstract

Introduction: Many potential donor hearts are wasted due to only hours storage using conventional hypothermic stabilization. Long-term storage is feasible through cryopreservation, which entails perfusion of organs with cryoprotective agents (CPAs) and cooling to a vitrified (glassy) state. Rewarming of larger vitrified systems such as organs has not been achieved due to insufficient and nonuniform heating. We are studying the use of inductively heated iron oxide nanoparticles (IONPs) to rewarm vitrified materials by a technology called nanowarming. Here the IONPs and CPAs are deployed within the vasculature and chambers of the rat hearts to achieve uniform and rapid rates of warming, thereby contributing to cryopreservation success.

Methods: VS55, a CPA was perfused in rat hearts with step-wise concentration increases over 15-minute intervals at a constant flow rate (3 mL/min). IONPs including Ferrotec EMG308 and silica coated IONPs (sIONPs) were perfused into VS55 fully loaded hearts and unloaded with step-wise VS55 concentration decrease. The IONP-unloaded hearts were assessed visually to optimize cannulation method that allow maximum removal of IONPs. The unloading of IONPs from hearts (n=2) that prepared by the optimized cannulation method were assessed by MRI and ICP-OES for residual iron. Finally, CPA and IONP loaded hearts (n=2) were vitrified and nanowarmed to obtain physical data of cooling and nanowarming.

Results: Langendorff perfusion was able to keep hearts beating over 5 hours. Hearts were perfusion loaded and unloaded with VS55 and IONPs. The backwards pressure due to Langendorff perfusion shut the aortic valve and caused IONPs and CPA accumulation in the left ventricle. Therefore, a catheter was inserted into the left ventricle to drain IONPs and CPA. The sIONP unloaded heart was visually similar to the negative control. MRI indicated the presence of a low concentration of sIONPs, which was verified with ICP-OES (0.0006 mg Fe/mg dry weight). Hearts successfully loaded with sIONPs and VS55 were then vitrified at a cooling rate around 10°C/min and nanowarmed within a 15 kW coil (60kA/m, 185kHz). Nanowarming rates in the left ventricle, muscle and exterior of the IONP CPA loaded hearts were similar (66, 79, 83 °C/min, n=3).

Conclusion: Langendorff perfusion and special cannulation was used to efficiently load and unload CPAs and IONPs in to rat hearts. sIONPs were shown to effectively washout during unloading. VS55 and sIONP loaded rat hearts were shown to successfully vitrify and rewarm without crystallization or cracking. Future studies will focus on assessing biological and functional outcomes.

POS 10

CORE-SHELL ENGINEERING OF ZNXMN1-XFE2O4@SIO2:ZND3+ NANOPARTICLES FOR MAGNETO-PHOTOTHERMAL THERAPY AND NANOTHERMOMETRY

Navadeep Shrivastava, Marcus Vinícius-Araújo, Pedro H. Coelho Dias, Ricardo Costa de Santana, Andris F. Bakuzis

Institute of Physics, Federal University of Goiás, Goiania, Goias, Brazil

Abstract

Multifunctional nanoparticles (NPs) that are able to generate and monitor heat during thermal therapy have major challenges in nanomedicine, e.g. magnetic NP hyperthermia due to limit benefit of MRI thermometry for this therapeutic modality. Here, we report the synthesis and characterizations of ZnxMn1-xFe2O4@SiO2:zNd3+/CTAB (x = 0.2, and 0.3 mmol; and z = 0.3, 0.5, 0.7 mmol) core-shell NPs having dual capacity to act as both magnetic and photothermal agents along with potential for radiometric temperature feedback. Firstly soft nanomagnet ZnxMn1-xFe2O4/citric-acid NPs were prepared using hydrothermal method. Further, a modified Stöber method was used to prepare a shell (2-4 nm of thickness, as revealed by TEM) of SiO2 and SiO2:zNd3+/CTAB over the magnetic ZnxMn1-xFe2O4/citric-acid NPs. Additionally, Nd3+ doped SiO2 NPs (~ 20 nm) were prepared as control samples. Dynamic light scattering measurements indicated varying sizes of ZnxMn1-xFe2O4 (~ 80 nm), and ZnxMn1-xFe2O4@SiO2:zNd3+/CTAB (~ 145 nm) in aqueous media. We further, explored other key aspects of the as prepared NPs by analyzing structure, morphology, surface moieties, magnetic and photoluminescence properties. The nanoparticles' exposure to both: an alternating magnetic field and near-infrared laser irradiation (808 nm), were studied to understand heat generation in aqueous suspension at different concentrations. In the magnetic hyperthermia experiments, controllable heating at a fixed temperature of 45 °C was achieved by changing either the concentration of NPs in the aqueous solution or the intensity of the alternating magnetic field. SiO2:Nd3+ coated ZnxMn1-xFe2O4 showed lower heating rates, ranging from 17 to 26%, in comparison to non-coated NPs. Photothermal experiments using SiO2, and SiO2:Nd3+ NPs in aqueous medium as control samples were also performed. Further, ZnxMn1-xFe2O4@SiO2:zNd3+/CTAB NPs in different concentrations were tested, where Nd3+ doped nanoparticles showed higher heat generation (10%-15%) and longer cooling slopes (~ 15%) when compared to ZnxMn1-xFe2O4@SiO2 (15 mg/mL in 120 s). Finally, photoluminescent characteristics of ZnxMn1-xFe2O4@SiO2:zNd3+/CTAB NPs in the second/third biological windows suggests the possibility of using the ratio between the emitted intensity of Nd3+ ions at 860 nm (4F3/2□4I9/2), 1060 ((4F3/2□4I11/2),) and at around 1400 nm (4F3/2□4I13/2) as a thermometric parameters. In summary, these synthesized NPs encourages to adopt the combinatorial thermal response of magnetic and photothermal and show potential for nanothermometry.

POS 11

THERMALLY SENSITIVE NATURAL EXTRACELLULAR VESICLES FOR CANCER THERAPY

Rabab Hamzah1,2, Dmitry Nedosekin2, Fumiya Watanabe1, Alexandru Biris1, Robert Griffin2

1University of Arkansas at Little Rock, little rock, Arkansas, USA. 2University of Arkansas for medical sciences, little rock, Arkansas, USA

Abstract

Over the last several decades, synthesized nanoparticles have been developed to detect and treat cancer. The use of this technology offers exciting results such as the possibility of destroying tumors without harming healthy tissue and organs, as well as the recognition and elimination of malignant cells before they form tumors. Many types of nanomaterials have been used in the field of cancer treatment such as Graphene, gold-spheres, rods or cages, and iron oxide particles (IONPs) among others. Each nanoparticle has a unique set of characteristics for diagnosis and treatment of disease. For instance, particles heated by magnetic induction like (IONPs) show promise for thermally eradicating cancer cells without damaging healthy tissue. However, using IONPs has some limitation due to the toxicity of these particles when they accumulate in large amounts in some organs. Therefore, targeted drug delivery is a critical issue in achieving efficient cancer therapy. Endogenous vehicles, such as protein and polysaccharide nanoparticles, have been explored for drug delivery to obtain better therapeutic outcomes because of their biocompatibility and low toxicity. We are investigating the ability of exosomes, which are vesicles secreted by many if not all cell types, to act as carriers of nanoparticles or other materials into tumors or other pathological conditions. They are derived from a complex process of endosomal processing and release that produces a range of sizes. Exosomes are similar in size to a virus (30-150 nm), surrounded by a lipid bilayer. Because exosomes possess natural ability to be recognized and taken up by many cells, including tumor cells, we are working to utilize exosomes as carriers of nanoparticles such as IONPs. We have successfully isolate exosomes from cell culture medium and other fluids such as serum and plasma. The size and morphology of exososmes were characterized by using Transmission electron microscopy (TEM) and the purified exosomes have been electroporated with IONPs. We have used photoacoustic imaging to detect iron oxide nanoparticles inside exosomes after electroporation and see evidence of successful loading . We surmise that the resulting exosome-based drug/particle delivery vehicle may exhibit super paramagnetic behavior at room temperature, with a stronger response to an external magnetic field than individual super paramagnetic nanoparticles. The various approaches to utilize these naturally occurring nanovesicles as detection and treatment vehicles will be presented.

POS 12

CHARACTERIZATION OF ANTIGEN PRESENTATION AND T CELL RESPONSE UNDER DIFFERENT FOCAL THERAPEUTIC CONDITIONS

Minhan Jiang, Qi Shao, Stephen O'Flanagan, Samira Azarin, Brandon Burbach, Yoji Shimizu, John Bischof

University of Minnesota, Minneapolis, Minnesota, USA

Abstract

Minimally invasive cancer therapies (focal treatments) including thermal therapy (Heat), cryosurgery (Cryo) and irreversible electroporation (IRE) are increasingly being used for local cancer treatment. Our hypothesis is that antigen release and presentation after focal therapy can play a central role in engaging the immune system in combating local recurrence and metastasis. Previously we have shown that the choice of focal therapy method affects protein release, protein denaturation and T cell activation from B16 cells [1]. Here, we pursue this question further by asking whether the processing of the antigen, in this case ovalbumin (OVA) a model antigen, can be modified directly by focal therapy conditions.

OVA and the associated OVA peptide SIINFEKL were exposed to Heat (90°C, 30min), Cryo (-80°C, 30min) or IRE (1250V/cm, 50μs, 99 pulses and 1Hz) and incubated with antigen presenting cells (APCs) derived from differentiated bone marrow derived DCs. Antigen presentation is evaluated by quantifying the percentage of MHC I-SIINFEKL complexes while the T cell response is characterized by activation and proliferation of CD8 T cells specific to the OVA antigen. Activation markers include CD44+, CD69+ and CD62L- at 6 hours; proliferation is measured by CTV dilution after 3 days. B16 cell suspension (no antigen) was also exposed to the same focal therapy conditions except Heat (50°C, 30min) and then incubated with OVA and APCs for same analysis.

We found no significant difference in antigen presentation and T cell activation after applying focal therapy conditions to either pure SIINFEKL or OVA. However, OVA mixed with B16 cell lysates following treatments significantly improves T cell activation and proliferation (30-50% increase in CD69, 10-20% increase in CD44) when compared to pure OVA alone. This may suggest a crucial role of modulating immune priming by damage-associated molecular patterns (DAMPs) released by tumour cells. This work shows that the presence of antigen alone and it's presentation were relatively unaffected by focal therapy type under the conditions tested. Nevertheless, the increase in T cell response following OVA presentation with focal therapy lysates may suggest the need for further study of DAMP release after focal therapy. This in turn may increase our knowledge of immune modulation by focal therapy and guide optimization of conditions with or without adjuvants (e.g. check point blockade) which lead to sustained and systemic anti-cancer immune response.

[1] Shao et al. IJH In Press 2019

POS 13

PHOTOTHERMAL ELIMINATION OF PSEUDOMONAS AERUGINOSA BIOFILM USING POLY(3,4-ETHYLENEDIOXYTHIOPHENE) NANOTUBE/SILICONE NANOCOMPOSITE

Shaina Yates, Ken Vogel, Zhidan Xiang, Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, NC, USA

Abstract

Background: Endoscopes have become a familiar cause of infection across hospitals and endoscopy centers, with the risk of infection of 1-3 patients per 1000. These numbers can be attributed to the biofilms that form within endoscopes from remaining bacteria, due to insufficient cleaning of the channels of the endoscope after each use. The most effective mechanisms of sterilization involve high temperatures, such as autoclaving, but this is not possible for cleaning of endoscopes, due to the heat-sensitive components. Because of this, endoscopes are disinfected with chemical agents, which can have limited effectiveness. One of the common pathogens associated with endoscope contamination following routine cleaning is Pseudomonas aeruginosa, a gram negative bacterium capable of forming virulent biofilms. Recent literature has suggested that P. aeruginosa are more sensitive to antibiotics at elevated temperature, leading to reductions in biofilm mass bacterial viability. Based on this premise, the goal of the current work is to demonstrate that application of non-damaging temperatures may be able to improve the effectiveness of chemical endoscope cleaning agents.

Methods: Nanocomposites composed of silicone and photothermal poly(3,4-ethylenedioxythiophene) nanotubes (PEDOT NTs) were synthesized and evaluated for their optical absorption and heat-generating performance in the non-enzymatic detergent Liquiclean®. P. aeruginosa was grown on the nanopcomposite materials to establish robust biofilms. The samples were then exposed to near infrared (NIR) light to generate heat (45°C) in the presence of 8ml/L of Liquiclean. Bacterial viability was assessed via serial dilution, subsequent agar plating and colony counting for the determination of colony forming units per milliliter (cfu/ml). Biofilm mass was determined using crystal violet assays.

Conclusion: Preliminary data suggest that silicone coatings containing photothermal PEDOT NT, stimulated with NIR, is an effective mechanism for improving chemical agents used for cleaning medical devices, such as endoscopes, thereby reducing biofilm mass and viable bacteria.

POS 14

CHARACTERIZING MINIATURE PROBES USED FOR FOCAL THERAPIES ON SMALL ANIMALS

Pegah Ranjbartehrani1, Qi Shao1, John Bischof1, Satish Ramadhyani2

1University of Minnesota, Minneapolis, MN, USA. 2Galil Medical, Minneapolis, MN, USA

Abstract

Focal therapies, including cryoablation (Cryo), hyperthermia and irreversible electroporation (IRE) have been widely used in the treatment of cancer and other diseases. Cancer models in small animals (e.g. mice) offer cost-effective preclinical platforms for assessing focal therapy modalities and their adjuvant approaches. Nevertheless, application of clinical-sized focal therapy probes in small animals can be difficult to control or characterize, limiting our understanding of required energy dose to destroy diseased tissue. In this study, we designed several miniature probes for each of focal therapies and evaluated their performance in tissue-mimicking gel and ex vivo tissue.

The aforementioned miniature probes for Cryo, Radiofrequency (RF) ablation and IRE are built as follow: (1) Argon Joule-Thomson cryoprobe (1.2mm diameter) from BTG (2) RF probe (1.55mm diameter) from Angiodynamics and (3) Bipolar IRE probe (0.9mm diameter single needle) from Boston Scientific. The thermal probes have been characterized in ultrasound gel, using a thermocouple jig placed around the probe. Time-depended and spatial thermal behaviors were experimentally mapped 3 times. For IRE probes, the tissue destruction was evaluated using mouse liver tissue of which the lesion was visualized by histology. The volume of the lesion was then compared to the parameters of IRE including voltage (200-800V), frequency (1-10 Hz), pulse width (100-800 microsecond) and the number of pulses (10-99). All experiments were compared to 3D simulations by COMSOL Multiphysics using thermal and electrical properties of corresponding materials. In the case of cryoprobes, the corresponding phase change simulation has also been verified by Neumann analytical solution.

Temporal and spatial temperature distributions of the gel surrounding the thermal probes reveals that they are capable of destroying small-sized tumor (8-10mm) on mice. For cryoprobes, the measured temperature distribution and ice front location matches the computational model with most of the error resulted from the temperature boundary condition on the probe surface which is applied to the simulation. For IRE, the edge of lesion correlates to locations of electric field between 500 and 600 V/cm. In general, the lesion size grew for higher field, pulse length or pulse number.

This study focuses on understanding the behavior of specially designed miniaturized focal therapy probes. Moving forward, we will characterize these probes on an in-vivo cancer treatment and demonstrate performance in physiological context considering the effect of blood perfusion. The knowledge will ultimately be used in designing and optimizing focal cancer therapy in the future.

POS 15

THE USE OF GOLD NANOPARTICLES FOR TARGETED LEUKEMIA CELL ABLATION IN MIXED TESTICULAR CELL CULTURES

Afnan Altamimi, Omar Ahmed-Abdelaal, Hooman Sadri-Ardekani, Nicole Levi-Polyachenko

Wake Forest University Health Sciences, Winston-Salem, nc, USA

Abstract

Background: Pediatric patients suffering from leukemia frequently suffer from a loss of fertility due to chemotherapy regimens. Cyropreservation of testicular tissue can preserve future fertility; however, this tissue can also harbor leukemia cells within the spermatogonia cell population. This presents a significant problem for re-implantation of tissue engineered scaffolds containing these banked cells that could be used to re-establish fertility. Photothermal gold nanoparticles targeted to the leukemia cells only offer an advantage for selective ablation of the leukemia only, while sparing spermatogonia cells. The goal of the research is to demonstrate selective ablation of gold nanorods to leukemia cells.

Methods: Gold nanorods were functionalized with antibodies for CD1a, which is overexpressed on leukemia cells. Molt-4 leukemia cells were used to confirm binding of the nanoparticles via electron microscopy and flow cytometry. The number of nanoparticles needed per cell for sufficient binding was calculated and thermal inactivation parameters, including multiple heat cycles, for Molt-4 cells were determined. Near infrared light was used to stimulate the gold nanorods to generate heat and photothermal ablation assays of Molt-4 cells were performed.

Conclusion: Molt-4 leukemia cells are a suspended cell line and slightly more resistant to thermal death, and multiple cycles of hyperthermia led to enhanced cells death. Premliminary data confirm that CD1a-targeted gold nanorods appear to selectively attach to Molt-4 cells, allowing for photothermal ablation. The next step of the project involves a mixed culture of Molt-4 and spermatogonia cells to demonstrate that in a mixed cell population, targeted photothermal nanoparticles selectively eliminate cancerous cells without harming spermatogonia cells.

POS 16

THE HSP-ACCESSORIZED EXOSOME: PRESENCE IN STATES OF DANGER, DISEASE, AND DISRUPTION

Michael Graner1, Xiaoli Yu1, Mary Wang1, Anthony Fringuello1, Steve Griffiths2

1University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA. 2Minervagen Biotechnologies, Tucson, AZ, USA

Abstract

Heat shock proteins (HSPs) function as chaperones under both normal and pathologic conditions. As chaperones they assist in protein folding, in holding protein complexes for current or future activation, and in the degradation of senescent proteins for recycling of components and display for immune surveillance. During stressful situations, HSP quantities and/or activities are increased as cells and tissues seek protection from insults. On occasion, these insults can result in the cell surface display of HSPs, which can then lead to the surface display of HSPs on exosomes, membrane-enclosed vesicles released extracellularly after passage thru the endosomal system. HSPs present on the cell surface or in the extracellular space are regarded as "danger signals" in an ancient biologic paradigm. HSP-accessorized exosomes may act as "danger boli", carrying not only the HSPs, but hundreds of components of the stressed parental cell, capable of prompting immune responses, or possibly immune suppression, depending on the status of the recipient cell. Here we show that exosomes from the plasma of patients suffering from neurologic maladies (glioblastoma/GBM, traumatic brain injury/TBI, multiple sclerosis/MS) are precipitated by peptides designed to bind HSPs. The metabolome of such exosomes is distinct from that of blood exosomes from healthy donors (>80 distinct compounds in GBM exosomes, and TBI exosomes; >30 compounds in MS exosomes; all are unique to those groups). There are also numerous lipid and metabolic pathways linked to those compounds. Such HSP-accessorized exosomes thus possess metabolites with possible ties to the different CNS pathologies that may represent disease-specific biomarkers in a "liquid biopsy" setting.

POS 17

FINITE ELEMENT SIMULATION OF THERMAL EFFECT OF RADIATION THERAPY ON BREAST TUMOR AND TISSUE

Merav Ben-David1, Michal Tepper2, Eleni Liapi3, Israel Gannot4,3

1Tel Aviv University, Tel Aviv, Israel. 2Tel Aviv University, Tel Aviv, USA. 3Johns Hopkins University, Baltimore, MD, USA. 4Tel Aviv University, tel Aviv, Israel

Abstract

Aim: To provide with a computational model and a quantitative analysis of the thermal characteristics of breast tissue and tumors during radiotherapy. This numerical model was developed during a clinical study (ClinicalTrials.gov Identifier: NCT02776995) intended to investigate the effect of radiation therapy on the breast skin temperature in patients with breast cancer treated with radiation therapy and imaged with static infrared thermography.

Methods: Models of a multi-layered breast with and without a tumor were created and the COMSOL FEM software was used to perform the analysis. The effect of various parameters (tumor depth, metabolic heat generation, and blood perfusion rate) on the surface temperature distribution (measured with IR thermography) were analyzed.

Results: In normal breast tissue model there was a constant positive curve of thermal conductivity, with the temperature gradually increasing from skin to deep tissue. In the model of breast with a cancerous lesion, the thermal conductivity resembled a bell-shaped curve. For tumors located 2-4 cm beneath the skin, there was a temperature increase in the range 0.2 °K to 1.4 °K, which was accurately measured with a thermal camera. A reduction in metabolic heat production rates of 100,000 W/m3 to 10,000 W/m3 lead to a decrease in the temperature at the center by 2.5 degrees Celsius. Radiation caused an increase in perfusion, presumably due to inflammation. However, during radiation therapy, the area of the tumor became colder and in the normal tissue area became warmer. These results were correlated with the results of the clinical trial.

Conclusion: This computational model provides valuable insight on the thermal effects of radiation therapy in breast cancer and surrounding normal tissue, as measured with static infrared thermography. Observed results correlated well with the clinical trial observations.

WED 1

THE ROLE OF ADRENERGIC STRESS IN CANCER IMMUNOLOGY AND IMPLICATIONS FOR THERAPY IN MELANOMA

Marc Ernstoff

Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Abstract

Our growing understanding of the neuro-immune axis and its communicating pathways have opened new therapeutic models for cancer. During this presentation, we will review the observations, data and preliminary attempts to leverage this kowlegde for treatment.

The initial observation of epimorphic regeneration of a body part is dependent on nerve growth was described by T. J. Todd in 1823 in salamanders. In a cut limb, neurogenesis allows nerve fibers to inflitrate into the mesenchymal balastema enhancing limb regeneration. If the nerve is denervated, regeneration does not occur. It is now well established that nerve fibers innervate neoplasic tissue as well; if the nerve is denervative, like the limb, tumor growth is inhibited (Boilly). The interaction between the innervating nerves and the tumor microenvironment (TME) is dependent on neurotropic factors that support endothelial and mesenchemal cells allowing for angiogenesis, inflammation and tumor growth and metastasis.

Remarkably, innervation of lymph nodes have also been described (Felten). Innervation has been observed in the medullary region of the lymph node and other T cell rich area such as the cortical regions surrounding the germinal centers (Huang). Denervation of the nerve or depletion of norepinephrine decreases th abillity for a primary immune response to antigen.

The anectodatal observation of increase viral illness following a stressful time is supported by the experimental evidence that stress increases circulating concentrations of glucocorticoids, endophins, and andrenergic molecuIs has direct impact on a number immune cell populations including NK and T cells. Chronic stress appeas to show a greater level of ciruclation regulators and a more pronounced change in lymphocyte distributions (Pike). Reducing stess by emotional intervention can improve health outcomes (Pennebaker, Rosenberg). In expermental models of Simian Immunodeficency Virus (SIV) in rhesus macaques, Sloan and colleagues have shown that under stress, innervation of the nodal tissue is critical in mediating an increase in chatecolamines in the nodal tissue, a decrease interferon response and increase in viral replication (Sloan).

My colleagues at Roswell Park led by Dr. Elizabeth Repasky have been focused on the role of stress in cancer models and summarized the role of adrenergic signaling in supporting tumor growth and metastasis (Qiao). Adrenergic signaling plays multiple roles including tumorigenesis, angiogenesis, lympangiogenesis, immunosuprression, inflammation, epithelial mesenchymal transfomration, tumor cell proliferation and anti-apoptosis.b-adrenergic receptors specifically type 2 and 3 are noted on immune cells and .b-adrenergic signalling dcreases antigen-specific T cell frequency and function, supressing CD8+T cell productionn of IFNgand TNFa, decreases IL-2 production and proliferation of TH1 CD4+T cell, and can prevent T cell egress for the nodal tissues (Grebe, Estrada, Sanders, Pamer-Quinn, Nakai, Suzuki)

Dr. Repasky has aksi lead the investigation on thermal stress impacting immune response in mice models. Her group has demonstrated that cold stress activates the sympathetic nervous system leading to higher concentrations of norepinephrine in the circulation as well as the TME (Eng). Reduction of thermal stress improves outcomes of mice harboring 4T1 mammary tumors and this is mediated by adpative immunity

(Kokolus). In this model reducing thermal stress increases activated CD8+T cell infiltration into the TME. In another model of B16 melanoma-OVA, reduction of thermal stress or the use of a pan b-adrenergic receptor blocker propranolol enhances the immune response to immune checkpoint inhibition using anti-PD1 (Bucsek).

The role of b adrenergic receptor blocker in cancer therapies have been supported by observational data in melanoma from our group and the Penn State Milton S. Hershey Medical Center (Kokolus, Gandhi). Others have found similar finding in melanoma and other cancer too (De Giorgi, Lemeshow, Melhem-Bertrandt, Powe, Diaz, Watckins, Wang). The overwhelming retrospective and epidemiologic data for the role of b-adrenergic blockers along with one adjuvant therapy study in melanoma along with the laboratory evidence of the role of b-adrenergic blockers in mediating immune response has led our group to propose a multicenter phase I/II study of propranolol and pembrolizumab in patients with metastatic melanoma.

Drs. Shipra Gandhi, Manu Pandey and I have designed a study looking at three different doses of twice daily propranolol (10, 20 and 30 mg) in combination with a fixed dose of pembrolizumab in qualifying patients with metastatic melanoma as a first line therapy. We have completed the first two dose cohorts and will be analyzing b-adrenergic levels and immune enpoints to help identify the best dose to take to a phase II study. It is too early to provide clinical and biological data for this abstract at this time. The combination has been safe to give with no apparent increase in toxcity consistent with the retropspective data.

In conclusion, b-adrenergic pathways play a role in tumor and immune biology. Chronic stress can change the b-adrenergic concentrations in the circulation and TME. Modulation of his pathway using pan b-adrenergic blockers may provide therapeutic benefit and is currently being tested in a prospective clinical study.

Todd TJ. On the process of reproduction of the members of the aquatic salamander. The Quarterly Journal Science, Literature, and the Arts 1823;16:84

Boily B, Faulkner S, Jobling P, Hondermarck H. Nerve dependence: from regeneration to cancer. Cancer Cell 2017; 31:342-354

Felten DL, Livnat S, Felten SY, Carlson SL, Bellinger DL, Yeh P. Sympathetic innervation of lymph nodes in mice. Brain Res Bull. 1984;13(6):693-9.Sci Rep. 2013;3:1114.

Huang J, Zhu C, Zhang P, Zhu Q, Liu Y, Zhu Z, Wang M, Li W, Yang G, Dong N, Liu J, Chen L, Zhang Y, Yang R, Deng L, Fan J, Wang X, Liu J, Ma B, Fu Q, Wu K. S100+ cells: a new neuro-immune cross-talkers in lymph organs. Sci Rep. 2013;3:1114.

Marsland AL, Bachen EA, Cohen S, Rabin B, Manuck SB. Stress, immune reactivity and susceptibility to infectious disease. Physiol Behav. 2002;77(4-5):711-6.

Pike JL1 Smith TL, Hauger RL, Nicassio PM, Patterson TL, McClintick J, Costlow C, Irwin MR.

Chronic life stress alters sympathetic, neuroendocrine, and immune responsivity to an acute psychological stressor in humans. Psychosom Med. 1997;59(4):447-57.

Pennebaker, JW . Writing about emotional experiences as a therapeutic process. Psychological Science 1997;8:162–166.

Rosenberg HJ, Rosenberg SD, Ernstoff MS, Wolford GL, Amdur RJ, Elshamy MR, Bauer-Wu SM, Ahles TA, Pennebaker JW. Expressive disclosure and health outcomes in a prostate cancer population. Int J Psychiatry Med. 2002;32(1):37-53.

Sloan EK, Nguyen CT, Cox BF, Tarara RP, Capitanio JP, Cole SW. SIV infection decreases sympathetic innervation of primate lymph nodes: the role of neurotrophins. Brain Behav Immun. 2008;22(2):185-94.

Qiao G, Chen M, Bucsek MJ, Repasky EA, Hylander BL. Adrenergic Signaling: A Targetable Checkpoint Limiting Development of the Antitumor Immune Response. Front Immunol. 2018;9:164.

Grebe KM, Hickman HD, Irvine KR, Takeda K, Bennink JR, Yewdell JW. Sympathetic nervous system control of anti-influenza CD8+ T cell responses.Proc Natl Acad Sci U S A. 2009;106(13):5300-5.

Estrada LD, Ağaç D, Farrar JD. Sympathetic neural signaling via the β2-adrenergic receptor suppresses T-cell receptor-mediated human and mouse CD8(+) T-cell effector function.

Eur J Immunol. 2016;46:1948-58.

Ramer-Quinn DS, Swanson MA, Lee WT, Sanders VM. Cytokine production by naive and primary effector CD4+ T cells exposed to norepinephrine. Brain Behav Immun. 2000;14:239-55.

Sanders VM, Baker RA, Ramer-Quinn DS, Kasprowicz DJ, Fuchs BA, Street NE. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. J Immunol. 1997;158(9):4200-10.

Nakai A, Hayano Y, Furuta F, Noda M, Suzuki K. ΩControl of lymphocyte egress from lymph nodes through β2-adrenergic receptors.

J Exp Med. 2014 Dec 15;211(13):2583-98. doi: 10.1084/jem.20141132. Epub 2014 Nov 24.

Suzuki K, Hayano Y, Nakai A, Furuta F, Noda M. Adrenergic control of the adaptive immune response by diurnal lymphocyte recirculation through lymph nodes. J Exp Med. 2016;213(12):2567-2574.

Eng JW, Reed CB, Kokolus KM, Pitoniak R, Utley A, Bucsek MJ, Ma WW, Repasky EA, Hylander BL. Housing temperature-induced stress drives therapeutic resistance in murine tumour models through β2-adrenergic receptor activation. Nat Commun. 2015;6:6426.

Kokolus KM, Capitano ML, Lee CT, Eng JW, Waight JD, Hylander BL, Sexton S, Hong CC, Gordon CJ, Abrams SI, Repasky EA. Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature. Proc Natl Acad Sci U S A. 2013;110(50):20176-81.

Bucsek MJ, Qiao G, MacDonald CR, Giridharan T, Evans L, Niedzwecki B, Liu H, Kokolus KM, Eng JW, Messmer MN, Attwood K, Abrams SI, Hylander BL, Repasky EA. β-Adrenergic Signaling in Mice Housed at Standard Temperatures Suppresses an Effector Phenotype in CD8+ T Cells and Undermines Checkpoint Inhibitor Therapy. Cancer Res. 2017;77(20):5639-5651.

Kokolus KM, Zhang Y, Sivik JM, Schmeck C, Zhu J, Repasky EA, Drabick JJ, Schell TD. Beta blocker use correlates with better overall survival in metastatic melanoma patients and improves the efficacy of immunotherapies in mice. Oncoimmunology. 2017;7:e1405205.

Gandhi S, Pandey M, Ammannagari N, Wang K, Vona KL, Nestico J, Hamad L, Dy GK, Ernstoff MS ;Clinical and biochemical parameters as predictors of response to checkpoint inhibitors (CPI): A single institution experience. Proceeding ASCO 2017A

Powe DG, Voss MJ, Zänker KS, Habashy HO, Green AR, Ellis IO, Entschladen F. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget. 2010;1:628-38.

Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, Sood AK, Conzen SD, Hortobagyi GN, Gonzalez-Angulo AM. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol. 201129:2645-52.

De Giorgi V, Grazzini M, Gandini S, Benemei S, Lotti T, Marchionni N, Geppetti P. Treatment with □-blockers and reduced disease progression in patients with thick melanoma. Arch Intern Med. 2011;171:779-81.

Lemeshow S, Sørensen HT, Phillips G, Yang EV, Antonsen S, Riis AH, Lesinski GB, Jackson R, Glaser R. β-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev. 2011;20:2273-9.

Diaz ES, Karlan BY, Li AJ. Impact of beta blockers on epithelial ovarian cancer survival. Gynecol Oncol. 2012;127:375-8.

Watkins JL, Thaker PH, Nick AM, Ramondetta LM, Kumar S, Urbauer DL, Matsuo K, Squires KC, Coleman RL, Lutgendorf, Ramirez PT, Sood A. Clinical impact of selective and nonselective beta-blockers on survival in patients with ovarian cancer. Cancer. 2015;121:3444-51.

Wang HM, Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, Zhuang Y, Levy LB, Lu C, Gomez DR. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. Ann Oncol. 2013;24(5):1312-9.

WED 2

A NOVEL MULTI-MODE THERMAL THERAPY FOR SYSTEMIC IMMUNOMODULATION IN PATIENTS WITH HCC/CLM: A PILOT STUDY

Ping Liu1, Zan Shen2, Lichao Xu3,4, Kangwei Zhang1, Kun He1, Shengguo Jia1, Yue Lou1, Aili Zhang1, Wentao Li3,4, Lisa X Xu1

1School of Biomedical Engineering and Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China. 2Department of Medical Oncology, the 6th People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China. 3Fudan University Shanghai Cancer Center, Shanghai, China. 4Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Abstract

Background: Local radio-frequency ablation (RFA) has been accepted as the first-line therapy for patients with early-stage hepatocellular carcinoma (HCC) and resectable colorectal cancer liver metastases (CLM). Conventional RFA application in clinic is still hampered by issues such as limited ablation volume of probe, non-uniform heating, and control of tumor recurrence to increase patient survival time.

Methods: In this pilot study, a novel multi-mode thermal therapy was developed to locally freeze tumor followed by RF heating to break the tumor cells and microvasculature in situ using thermal and mechanical forces, for the maximal release of viable tumor antigens and immune stimulatory factors to stimulate systemic anti-tumor immunity. Forty patients bearing HCC/CLM (23/17) were recruited and randomly assigned to receive the multi-mode thermal therapy (n=19) or conventional radiofrequency ablation (RFA, n=21). The local treatment effect and systemic responses were evaluated by MRI imaging and examination of immune cells and cytokines in peripheral blood circulation.

Results: The multi-mode thermal therapy was well tolerated in all patients without major complications or procedure-related mortality. The new therapy could achieve similar or even better local control effects than RFA, e.g. for patients with CLM. More importantly, it induced DCs maturation, and a notable adaptive anti-tumor immune response characterized by significant up-regulation of CD4+Th1 that was well correlated with good prognosis in CLM patients. Marked increase of HSP70 and IL-6/IL-10 ratio were observed in peripheral blood that could help antigen presentation and CD4+T cell differentiation.

Conclusions: As a safe and minimal invasive modality for patients with HCC/CLM, this new multi-mode thermal therapy could achieve local tumor control while triggering systemic anti-tumor immune responses. Further study will be performed to quantify the thermal dose in relation to systemic anti-tumor immune response and clinical index for long-term patient prognosis.

Keywords: Multi-mode thermal therapy, patients with HCC/CLM, thermal immunomodulation

WED 3

FOCAL THERAPY WITH IMMUNOTHERAPY PROMOTES FORMATION OF TUMOR ANTIGEN-SPECIFIC CD8 T CELLS AND TUMOR GROWTH CONTROL

Qi Shao, Stephen O'Flanagan, Meagan Rollins, Brandon Burbach, Samira Azarin, Yoji Shimizu, John Bischof

University of Minnesota, Minneapolis, MN, USA

Abstract

Introduction: Focal therapies not only destroy cancer cells, but also release antigens and other molecules (i.e. danger associated molecular patterns, DAMPs). Together, tumor lysates presumably with antigens and DAMPs can augment an adaptive immune response in which prime naïve CD8 T cells to become cytotoxic [1]. Additionally, immunotherapy alone with checkpoint blockade has been used to in cancer with sometimes excellence, but with often variable response rates. Our study investigates the potential of combining focal therapy with immune checkpoint blockade to generate cytotoxic T cells for control of tumor growth in a rodent cancer model.

Methods: TRAMP-C2 in C57BL/6 mice were studied. Primary tumors were inoculated by subcutaneous cancer cell injection; tumor of 4-6mm were treated (Day 0) by either by IRE (1500v/cm, 50 ms pulse width, 1 Hz and 2 trains of 25 pulses orthogonal directions) or cryotherapy (freezing to 0°C at the edge of tumor with BTG 1.2 mm cryoprobe at -160°C). Anti-CTLA-4 (200μg on day 1, 100μg on day 4, 7 and 10;) or anti-PD-1 (100μg on day 1, 3, 5 and 9) are given through IP injection. Tumor growth was monitor for 3 weeks before antigen-specific CD8 T cell in non-lymphoid tissues (NLTs) are analyzed.

Results: In the TRAMP model, combination treatment with IRE followed by anti-CTLA4 was associated with tumor stasis in 100% (15/15) of mice tested, and complete remission of residual tumor was achieved in the majority of cases. This combination therapy promoted a robust 50-fold expansion of proliferating (Ki67+) SPAS-1 tumor-specific effector CD8 T cells in the blood, and a 10-fold increase of tissue resident memory CD8 T cells (Trm) in several NLTs. In contrast anti-CTLA4 or IRE alone was associated with tumor outgrowth in all mice and failed to increase the number of SPAS-1 CD8 T cells, resulting in the presence of small populations of PD-1 hi tumor-specific CD8 T cells. Further, anti-PD-1 following IRE in TRAMP model did not control tumor growth. Further work with other cancers (i.e. B16, MC-38) and focal therapies is ongoing.

Conclusion: These results suggests that focal therapy, especially IRE, when combined with immunotherapy, promotes the activation and proliferation of antigen-specific CD8 T cells and the control of tumor growth. Further study and refinement may show that combining immunotherapy with focal therapy can serve a as potent in situ tumor vaccination strategy.

[1]. Shao et al. IJH 2019

WED 4

IMMUNE CHECKPOINT INHIBITORS ENHANCE THE ABSCOPAL EFFECT OF LOCAL THERMO-RADIOTHERAPY IN A METASTATIC MOUSE MODEL

Arlene L. Oei1,2,3, Preethi Korangath1, Mikko Helenius1, Jacqueline Stewart1, Brian Simons4, Coen R.N. Rasch3, Johannes Crezee3, Lukas J.A. Stalpers2,3, H. Petra Kok3, Nicolaas A.P. Franken2,3, Robert Ivkov1

1Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. 2Laboratory for Experimental Oncology and Radiobiology (LEXOR), Center for Experimental Molecular Medicine (CEMM), Amsterdam, Netherlands. 3Department of Radiotherapy, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands. 4The Brady Urological Institute, Department of Urology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Introduction: About 10-15% of all breast cancer patients suffer from an aggressive version and they will develop a recurrences or metastases within 3 years after diagnoses of the primary tumour. Both are correlated with (very) poor prognosis. Therefore, anticancer treatments should also be aimed to treat distant metastasis. This can be performed by combining classical therapies with treatment with immune checkpoint inhibitors.

Objectives: Radiotherapy, chemotherapy and hyperthermia are good strategies in treating primary tumours. And all these therapies have the ability to trigger parts of the immune system. This may prevent occurrence of metastases and/or secondary tumours for several years. However, in order to enhance the abscopal effect, immunological checkpoint inhibitors can be added to target metastases and improve the disease-free survival. In this study PD1-i and CTLA4-i are added to thermo-radiation, the combined treatment of radiotherapy and hyperthermia.

Methods & Results: To determine the effect of adding PD1-i and CTLA4-i to local radiotherapy and magnetic nanoparticle hyperthermia on the primary tumour and metastases, luciferin containing 4T1 cells (a highly metastatic breast cancer cell line), were injected into the BALB/c mouse mammary fat pad. One week after injection of cells, animals were treated with hyperthermia, radiotherapy and immune checkpoint inhibitors. Our data demonstrates suppression of the primary tumour growth when immune checkpoint inhibitors are added. Furthermore, the number of liver metastases was significantly lower after any treatment, and lowest after the triple combination. A similar trend was observed for the number of lung metastases. We show that all effects appear to be correlated to immune cell population in the tumour microenvironment. Finally, in this model, we found that in any combined treatment, mild hyperthermia (20 min at 43°C) resulted in a lower number of distant metastases compared to a treatment including partially ablative hyperthermia (5 min at 45°C + 15 min at 43°C).

Conclusion: The enhanced abscopal effect induced by immune checkpoint inhibitors in addition to local thermo-radiation can manipulate the tumour microenvironment in both the primary tumour and their metastases. This results in significantly better primary tumour control and lower numbers of metastases in distant organs.

WED 5

STRESS-INDUCED IMMUNITY BY REGIONAL HYPERTHERMIA: A COLD TUMOR BECOMES HOT

Rolf Issels1, Lars Lindner2, Michael von Bergwelt1, Peter Lang3, Christoph Rischpler4, Heinz Diem5, Judith Eckl6, Dolores Schendel6, Christoph Salat7, Oliver Stötzer8, Ruppert Handgretinger9, Thomas Kirchner10, Gabriele Multhoff11, Elfriede Nößner12

1Dept.of Medicine III, Munich, Germany. 2Dept. of Medicine III, Munich, Germany. 3Dept.of Pediatric Hematology/ Oncology, Tuebingen, Germany. 4Dept. Nuclear Medicine, Munich, Germany. 5Laboratory for Hematological Diagnostic, Munich, Germany. 6Medigene AG, Munich, Germany. 7Medical Center for Hemtology / Oncology MVZ, Munich, Germany. 8Medical Center for Hematology /Oncology MVZ, Munich, Germany. 9Dept.of Pediatric Hematology /Oncology, Tuebingen, Germany. 10Institute of Pathology, Munich, Germany. 11Radiation Immuno Oncology Group, Munich, Germany. 12Immunoanalytics Research Group, Munich, Germany

Abstract

Introduction Releasing breaks of T cells by checkpoint inhibitors has enforced cancer immunotherapy. Beside T cells, NK cells play a role in anti-tumor responses under stress conditions. NK cells target cells with an incompatible expression of MHC class I molecules (KIR-ligand -mismatch).T cells, when they differentiate into effector cells, are recruited to inflammatory milieus where they recognize and eliminate antigen - expressing target cells. NK cells, as well as cytotoxic CD8+ and CD4+ subsets of T cells express the lectin-like natural-killer group 2D (NKG2D) activating receptor and can receive co-stimulation through stress-induced NKG2D ligands (MICA/B, ULBPs), aiding their killing of tumor cells.

Methods We describe a young patient with alveolar rhabdomyosarcoma who finally failed all treatment options including haploidentical stem cell transplantation and donor lymphocyte infusion.She had progressive local disease with metastases and underwent regional hyperthermia and low-dose chemotherapy. We measured the lytic activity of NK cells and frequency of subsets, including NKG2D expression and expression of killer cell inhibitory receptors (KIR) .We assessed changes and frequencies of CD8 and CD4 T cells, as well as of regulatory T cells. We performed PET-CT imaging before and during the course of treatment.

Results In parallel with local response and regression of metastases, the initial proportion of the CD56bright NK cell subset increased two-fold from 15% to 35%. The patient's NK cells showed also a significant higher cytolytic activity. At the time of complete response, the patient had a high proportion of NK cells and of T cells expressing the activating receptor NKG2D. We found that NK cells expressed the CD158b receptor , but not the CD158a or CD158e receptor. At the time of complete response, at serial time points coincident with the measurements of the CD56bright NK cell subset, the frequency of primed effector CD8 and CD4 T cells increased by a factor of two with a reciprocal decline in the quantity of naïve CD8 and CD4 T cells. Among CD4 T cells, regulatory T cells (CD25+ FOXP3+) were initially elevated but declined during the course of treatment.

Summary The profound clinical activity provides strong evidence for a model in which hyperthermia serves to unleash the activity of NK cells and to prime T-cells.With the knowledge of checkpoint-mediated immunosuppression, the priming effect of regional hyperthermia in combination with checkpoints inhibitors should be addressed in a randomized clinical study.

WED 6

HYPERTHERMIA AND RADIATION EFFECTS ON THE GLIOMA IMMUNE MICROENVIRONMENT

Cassandra Gilmour1,2, Paul Pavicic1, Pat Rayman1, Marcela Claudia Diaz1, Jennifer Yu1

1Cleveland Clinic, Cleveland, OH, USA. 2Case Western Reserve University, Cleveland, OH, USA

Abstract

Glioblastoma is the most deadly form of primary brain cancer, with approximately 17,000 new cases per year. Glioblastoma is difficult to treat and patients live about 1 year. Re-occurrence of glioblastoma is high, which may be due to stem-like cells that evade standard of care radiation or chemotherapy. It has previously been shown that glioblastoma stem-like cells exhibit decreased survival when treated with a combination of hyperthermia and radiation compared to treatment with either alone. In mouse models of high grade glioma, we find that the tumor microenvironment is immunosuppressive and exhibits high levels of myeloid derived suppressor cells (MDSCs), specifically monocytic MDSCs. This cell population expands in cancerous environments and are thought to suppress the activity of T cells. We find that high grade gliomas secrete the chemokines MCP1 and MIP2 which are known to mediate the recruitment of monocytes. Hyperthermia and radiation synergistically increased pro-inflammatory cytokines MCP1 and IL8 and decreased TNF alpha. These data suggest that combined hyperthermia and radiation alters the immune microenvironment in the tumor; particularly the recruitment of monocytes, and may provide novel insights on integration of immunotherapy with hyperthermia and radiation.

WED 7

BETTER THAN EXPECTED TREATMENT OUTCOME OF AN ADVANCED ANORECTAL SQUAMOUS CELL CARCINOMA USING INTERSTITIAL THERMORADIOTHERAPY, POSSIBLE ABSCOPAL IMMUNE RESPONSE

John Hayes1, Ray Richards1, John Miller2, Thomas Skidmore1, Ryan Bair1, Brandon Fisher1, Joshua Bryant1, Melinda Forbush1, Keighley Swapp1

1Gamma West Cancer Services, Salt Lake City, Utah, USA. 2Utah Surgical Associates, St. George, Utah, USA

Abstract

Background: A 58-year-old male presented with a debilitating locally advanced low rectum/anal canal squamous cell carcinoma, T4 N1 M1, for further evaluation. At the time of presentation, the patient was disabled by pain and could not sit upright. At that time, he stated he had experienced progressive lower GI/obstructive symptoms for more than 12 months prior to seeking medical attention. Physical examination demonstrated a 7 cm partially obstructing mass occupying the entire anal canal and low rectum. Colonoscopy with biopsy led to the diagnosis of squamous cell carcinoma (SCC). PET-CT demonstrated metastases in the lung parenchyma and in mediastinal and left inguinal nodes. A colonic submucosal lesion at the hepatic flexure was biopsy positive for SCC. Considered incurable, he was offered chemotherapy or hospice therapy. His family sought alternative options. With focus only on pain palliation, he was treated with interstitial thermoradiotherapy (ITR).

Methods: His treatment plan included 4 outpatient interstitial procedures with subarachnoid anesthesia between 06/14/17 and 06/28/17. Each included a treatment with interstitial 915 MHz microwave hyperthermia immediately after an 800 cGy fraction of HDR brachytherapy (3200 cGy total).

Results: Average of parameters: needles, 23; target volume, 95cc; treatment volume, 137cc; V(100) 97.3%; active dwell positions, 575; D(100), 655 cGy; D(90), 881 cGy; Bladder (75), 0.0 cc; implant uniformity index, 0.73; MW antennas, 18; temperature probes, 5; Cumulative Effective Minutes at 43 °C, 38. The patient had gradually diminishing pain, decreased dependence on pain medications, and return to ADLs. PET-CT exams at 6-month and 12-month FU were devoid of all metabolic activity. EUA/colonoscopic exam at one year was NED with no mucosal erosions.

Conclusions: An initially "palliative" patient is now clinically NED 18 months following treatment with ITR. The well-tolerated treatment regimen reported here resulted in dramatic pain palliation, preservation of rectal function, return to ADLs and clinical, endoscopic and radiographic designation of NED at both 6- and 12-month FU exams. This regimen demonstrated a powerful local effect on a large primary tumor, while retaining function of the rectum/anus. It may also have triggered an abscopal effect on distant sites of metastatic disease by subsequent modulation of the innate and adaptive immune system against tumor cells. The NED status suggests either false positive readings on the presenting PET-CT or an abscopal effect from triggering the immune system.

WED 8

PRUSSIAN BLUE NANOPARTICLES-BASED ANTIGENICITY AND ADJUVANTICITY TRIGGER ROBUST ANTITUMOR IMMUNE RESPONSES AGAINST NEUROBLASTOMA

Juliana Cano-Mejia1,2, Michelle Bookstaver1, Elizabeth Sweeney2, Christopher Jewell1, Rohan Fernandes2

1University of Maryland, College Park, MD, USA. 2The George Washington University, Washington, DC, USA

Abstract

We describe the synthesis of CpG oligodeoxynucleotide-coated Prussian blue nanoparticles (CpG-PBNPs) that functions as a nanoimmunotherapy for neuroblastoma, a common childhood cancer. The CpG-PBNP-based nanoimmunotherapy is utilized to increase the antigenicity and adjuvanticity of treated tumors, consequently eliciting a robust antitumor immune response. The CpG-PBNPs are synthesized using a facile layer-by-layer coating scheme and the resultant nanoparticles exhibit monodisperse size distributions, multiday stability, and are not cytotoxic. The strong, instrinsic absorption of PBNPs in the CpG-PBNPs is leveraged to administer photothermal therapy (CpG-PBNP-PTT) that triggers tumor cell death releasing tumor antigens, which increases tumor antigenicity. Simultaneously, the CpG coating functions as an exogenous adjuvant that complements the endogenous adjuvants released by the CpG-PBNP-PTT (e.g. ATP, calreticulin, and HMGB1), increasing adjuvanticity. When administered in a syngeneic, Neuro2a-based, murine model of neuroblastoma, CpG-PBNP-PTT results in complete tumor regression in a significantly higher proportion (70% at 60 days) of treated animals relative to controls. Further, the long-term surviving, CpG-PBNP-PTT-treated animals reject Neuro2a rechallenge suggesting that our nanoimmunotherapy generates immunological memory. When CpG-PBNPs are used to treat a metachronous model of neuroblastoma, wherein the primary tumor is CpG-PBNP-PTT-treated and the secondary tumor remains untreated, 50% mice treated with our nanoimmunotherapy show complete eradication of both the primary and secondary tumors compared to conrols, which showed no survival efficacy. Our findings point to the importance of simultaneous cytotoxicity, antigenicity, and adjuvanticity using CpG-PBNP-PTT in generating robust and persistent antitumor immune responses against neuroblastoma.

WED 9

TUMOUR ABLATION INDUCED THERMAL NECROSIS MODULATES IMMUNE-RELATED CYTOKINES BY MAGNETIC RESONANCE-GUIDED FOCUSED ULTRASOUND SURGERY IN BONE METASTATIC LESIONS

Fang-Chi Hsu1,2,3,4, Hsin-Lun Lee1,2,3, Yin-Ju Chen5, Chia-Chun Kuo2, Jeng-Fong Chiou1,2

1Ph.D. Program for Transnational Medicine, School of Medical Science, Taipei Medical University, Taipei, Taiwan. 2Department of Radiation Oncology, Taipei Medical University Hospital, Taipei, Taiwan. 3Genomics Research Center, Academia Sinica, Taipei, Taiwan. 4Sydeny Kimmel Comprehensive Cancer Center, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA. 5Institute of Biomedical Engineering, School of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

Abstract

Magnetic Resonance-guided Focused Ultrasound surgery (MRgFUS) provides a non-invasive treatment strategy to ablate deep seated bone metastatic lesions and surrounding periosteal nerve endings. HIFU beam projects acoustic power at precise local bone cortex to generate thermal necrosis and results in pain relief. Local tumour control is also observed during a 3-month follow-up. It still remains unknown whether such a local palliative treatment might accompany anti-cancer effects that may lead to further disease control.

According to previous studies, thermal necrosis generates damaged molecular within tumour microenvironments and evokes acute inflammation.However, limited evidence suggests that release of cytokines is influenced by thermal necrosis but cytokine threshold of immune responses is still lacking. A prediction model to approximate post-ablation immune status by circulating cytokine activation is demanded.

In order to further understand cytokines changes in necrotic tumour burden, this study focused on patients' cytokine profiling in the circulation and the consequent primary tumour control. During 2014 to 2017, total 30 patients who received MRgFUS treatment in Taipei Medical University hospital was recruited and followed. All peripheral blood samples were taken with designed time points after MRgFUS treatments. These samples were used to analyze treatment-induced changes in immune-related cytokines and immune cell population. Inflammatory cytokine cluster, TNF-alpha, Il-6 and Il-1 beta, were observed that a significantly increasing ($p = 0.021$) in circulation within 24 hour as acute inflammation. Meanwhile, wound healing cytokines, such as VEGF and PDGF, and immune regulatory cytokines, TGF-beta, were also observed a significant decreasing after acute phase. In this phase, IL-6, IL-13, IP-10 and Eotaxin expression levels maintained a certain inflammatory level in situ.These cytokine changes also correlated with response rate of primary tumor control after acute periods. A maximum likelihood estimation was applied to test the correlation between cytokine concentrations and local control ($p=0.038$).

These results revealed a linkage between acute cytokine changes and immune responses after thermal based tumour ablation treatment. We also found that ablated bone lesions presented good responses of tumor control and immune activation. Hence, cytokine profiling may also indicate a potential direction of thermal immunotherapy which combines thermal ablation and immune checkpoint inhibitors in patients with multiple metastasis.

WED 10

WHAT ABOUT CAR-T THERAPY? AN UPDATE OF IMMUNE THERAPY & POTENTIAL OF THERMAL THERAPY

Joan Bull

UT McGovern Medical School, Houston, TX, USA

Abstract

BACKGROUND: CAR-T therapy has become a highly successful therapy in hematological malignancies but has been unsuccessful in epithelial cancers. Is there a potential of CAR-T therapy in epithelial cancers? Can thermal therapy help?

METHODS: There are new checkpoint inhibitors, new knowledge about predicting response and toxicity of checkpoint inhibitor therapy, antigen-specific adoptive cell transfer (ACT), CAR-T therapy, viral vector therapy are increasingly efficacious. The microbiome has become vital to immune therapies. We treat a burgeoning number of different malignancies with checkpoint inhibitors. Combining several or adding cytotoxic therapy improve response rates. As discussed before, a lack of CD8+ T-cells in the tumor environment excludes response to checkpoint inhibitors. CAR-T and ACT of antigen-specific T cells, both significantly increase the number of tumor-specific T-cells in the tumor microenvironment. Viral vectors of immune therapy also show clinical promise in difficult-to-treat cancers. It has become clear that the gut microbiome is crucial to both the occurrence of cancer and to therapy-induced response. The gut microbiome is particularly important to immune therapy. Antibiotics greatly lessen this vital resource.

RESULTS: Not all malignancies respond to immune therapy. Checkpoint inhibitors do not induce responses in many gastrointestinal (GI) cancers, yet GI and other cancers with mismatch repair defects respond well. In addition, antigen-specific ACTis a highly effective immune therapy in GI malignancies. Primary glial brain cancers do not generally respond to checkpoint inhibitors, yet there are anecdotal response to checkpoint inhibitors, CAR-T therapy, and viral vector therapy. All cancer patients want more and greater responses. We all recognize that all types of thermal therapy (both heat or cryotherapy) boosts host immune response and escalates the anti-tumor cytotoxicity of effector T-lymphocytes. Yet, we have not sufficiently investigated thermal therapy with checkpoint inhibitors and have never investigated thermal therapy with ACT, CAR-T cells or with viral vectors of immune therapy. In addition, how thermal therapy can alter will likely the microbiome, but lacks investigation.

CONCLUSION: The types of malignant diagnoses that respond to immune therapy continue to expand. Clearly survival of many patients has significantly improved with immune therapies. Yet, cancer patients require greater responses. As many know, thermal therapy increases response rates to immune therapies by increasing the ability of cytotoxic CD8+ T-cells to enter the tumors, recognize the cancer cells and thus increase tumor kill. However, even after five years of immune therapy, thermal therapy combined with immune therapy is much in need of investigation.

WED 11

COMPUTER SUPPORT FOR ABLATIVE LIVER THERAPIES

Jan Strehlow1, Torben Pätz1, Sabrina Haase1, Christian Rieder1, Christian Schumann1, Joachim Georgii1, David Black1, Tobias Preusser1,2

1Fraunhofer MEVIS, Bremen, Germany. 2Jacobs University, Bremen, Germany

Abstract

Introduction: Thermal ablation procedures like RFA, MWA, and Cryo play an increasing role in the treatment of malignant liver tumors. Planning of such interventions is complex and requires precise knowledge of the patient individual anatomies to select suitable access paths and instrument placements and, finally, to estimate the treatment effect. Furthermore, careful execution and assessment of the intervention influence the outcome considerably. Our work of the recent years is dedicated to supporting the clinician in these tasks with computer software.

Methods: We combine several state-of-the-art techniques of annotation, visualization, optimization, and simulation into our highly integrated treatment planning system SAFIR. The basis for patient-individual therapy planning is an accurate anatomical model. SAFIR offers several automatic and semiautomatic tools to efficiently and accurately delineate target, risk and other anatomical structures that affect the therapy, s.a. vessel systems and ribs. Based on the resulting patient model, the clinician can interactively explore suitable access paths to the target guided by advanced visualization methods and compare different instrument placements in a virtual 3D scene. Alternatively, the system can propose suitable access paths automatically. A unified and highly optimized numerical simulation system for RFA, MWA, and Cryo allows within seconds to estimate the resulting therapeutic effect and uncertainty margins. An approximation allows to preview the effect even during interactive planning. The resulting therapy plan can then be used during the execution of the intervention, potentially guided by auditory feedback. Finally, in the assessment phase, the coagulated region is delineated in post-operative imaging and can be compared with the planning data and the pre-operative simulation supported by a streamlined overview visualization.

Results: The optimization, visualization, and auditory feedback methods have been evaluated retrospectively on clinical data. The prediction of coagulation area based on numerical simulation is currently evaluated in ex-vivo experiments, in vivo animal experiments and retrospectively on clinical data. First results look promising but also point to limits of the modeling. For example, temperature-induced embolization is not yet covered by our simulation.

Conclusions: We present SAFIR, our ablation treatment support software which aims at reducing the uncertainties and the mental burden for the clinician in the planning phase of thermal ablative thermal interventions. Patient-individual planning supported by visualization, optimization and numerical simulation may be an enabling technology for the application of thermal ablation in a broader spectrum of indications and may leverage the full potential of current ablative interventions.

WED 12

RECENT ADVANCEMENTS IN 3D PATIENT-SPECIFIC TREATMENT PLANNING FOR RADIOFREQUENCY AND MICROWAVE HYPERTHERMIA

Petra Kok

Department of Radiation Oncology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands

Abstract

Achieving sufficiently high tumor temperatures during clinical hyperthermia is very important for tumor control and patient outcome. Hyperthermia treatment planning is a useful tool to assist clinical hyperthermia treatments and thereby improve treatment quality.

A correct high resolution patient model is crucial for reliable pre-treatment planning. Dielectric and thermal tissue properties determine the specific absorption rate (SAR) and temperature levels in the patient due to RF/MW heating, but these properties vary largely between patients. These uncertainties diminish quantitative reliability of pre-treatment hyperthermia planning for individual patients, but qualitative reliability of SAR and temperature simulations is very useful for adaptive strategies during treatment, as recent studies have demonstrated. Changes in predicted SAR and temperature levels correlate well with measured changes in temperature ($R2>0.5$) after phase and amplitude adaptations of the antennas. Fast simulation techniques make it possible to instantly update predicted SAR and temperature visualizations for on-line use. This allows routine use of 3D patient-specific hyperthermia treatment planning to optimize the temperature distribution in the patient.

For locoregional hyperthermia on-line assistance in phase-amplitude steering by treatment planning has been shown to effectively suppress treatment limiting hot spots while maintaining the same level of tumor heating. Additionally, on-line assistance by treatment planning in focusing the energy deposition to the tumor has demonstrated to improve tumor temperatures with about 1°C, without inducing hot spots. This is useful for common locoregional hyperthermia treatments of pelvic tumors (e.g. cervix and bladder), but also for more challenging tumor locations for which adequate thermometry at the tumor location is limited, such as pancreatic tumors. Treatment planning has been shown to be very helpful in determining adequate phase-amplitude settings for these patients, resulting in target temperatures in the therapeutic range.

For superficial and sub-superficial hyperthermia, treatment planning is very useful in applicator selection and positioning to optimize target coverage and minimize hot spots. In addition, thermal simulations can be supportive to determine the most effective water bolus temperature for superficial heating to guarantee therapeutic skin temperatures as well as sufficient penetration depth in the infiltrating tumor.

In conclusion, 3D patient-specific hyperthermia treatment planning is a very effective tool to optimize the quality of superficial and locoregional hyperthermia treatments. Based on the very positive results with clinical use of hyperthermia treatment planning so far, on-line assistance of treatments by planning is expected to increase in the near future.

WED 13

TREATMENT PLANNING FOR MR-GUIDED HIGH INTENSITY FOCUSED ULTRASOUND

Pavel Yarmolenko1, Haydar Celik1, Avinash Eranki1, Ari Partanen2, AeRang Kim1, Matthew Oetgen1, Domiciano Santos1, Janish Patel1, Peter Kim3, Karun Sharma1

1Children's National Medical Center, Washington, DC, USA. 2Profound Medical, Mississauga, ON, Canada. 3George Washington University, Washington, DC, USA

Abstract

MR-guided high intensity focused ultrasound (MR-HIFU) has gained traction in the clinic as a local ablative therapy. The technology is now being investigated as a means of treating malignant as well as benign tumors, and its array of applications continues to grow.

Techniques involved in planning these treatments are tailored to each application and each patient, albeit with some commonalities. Broadly, these common aspects include 1) identification of the target and nearby critical structures and assessment of risk to critical structures that must be spared, 2) identification of optimal position or positions that maximize likelihood of successful and safe treatment, 3) identification of an optimal approach to positioning the patient to achieve coupling of the HIFU transducer to the targeted anatomy, 4) selection of target-specific treatment parameters. Treatment planning approaches should consider input from the anesthesiologist as well as other members of the multidisciplinary team. The amount of time available for treatment planning may be limited, and therefore, the techniques involved should be as efficient as possible.

Several clinical trials evaluating safety and feasibility of MR-HIFU treatment in children with benign, as well as recurrent or relapsed malignant tumors are currently ongoing at our institution. We will present aspects of treatment planning from clinical cases we have encountered, with an emphasis on challenges and currently available solutions.

WED 14

DATA-DRIVEN METHODOLOGIES FOR GUIDING TREATMENT PLANNING OF MRGLITT

David Fuentes

MD Anderson, Houston, Tx, USA

Abstract

MR-guided laser-induced thermal therapy (MRgLITT) has an important role in treating patients with small volumes of pathological brain tissue. MRgLITT has shown favorable outcomes in treating metastatic disease, primary brain tumors, radiation necrosis and epilepsy. The minimally invasive nature and non-ionizing radiation unique to thermal therapies translates to low impact, repeatable procedures ideally suited for candidates that are not eligible for conventional treatment options. MR imaging and stereotactic surgical navigation provide important disease site targeting information during the procedure. Further, real-time MR temperature imaging (MRTI) of the treatment volume during laser heating provides a mechanism by which it is possible to deliver these therapies in both a safe and effective manner. Importantly, this imaging information may also be used to calibrate mathematical models to guide treatment planning of MRgLITT procedures. Currently, the neurosurgeon reviews MR images of the anatomy to plan the trajectory to reach the tumor with navigation software. Geometrical primitives (i.e., ellipsoid, cylinder) are used to overlay the maximum anticipated thermal dose onto the target lesion. Clinicians inherently use a combination of prior knowledge and pre-treatment imaging to plan treatment. Although this approach is acceptable within relatively homogeneous tissue environments, laser-induced heat transfer is largely unpredictable near heat sinks, such as large vessels and the ventricles in the brain. Similar to popular machine learning methodologies, a database of patient imaging provides important information that may be used calibrate mathematical models for guiding MRgLITT treatment planning in these heterogeneous tissue environments. This approach is clinically practical and uniquely integrated with routine imaging sequences to enable a priori model predictions of thermal damage to guide treatment planning. Results will compare predictions between this data driven approach and current treatment planning methods. Numerical techniques needed to incorporate uncertainties in tissue parameters and high dimensional optimization will also be discussed.

WED 15

REQUIREMENTS ON HIPEC TREATMENT PLANNING TO OPTIMIZE TREATMENT PROTOCOLS AND IMPROVE THE EFFICACY OF HIPEC CANCER TREATMENT

Nader Hanna1, Wim Ceelen2, Petra Kok3, Dieter Haemmerich4, Dario B. Rodrigues1

1University of Maryland School of Medicine, Baltimore, MD, USA. 2Ghent University, Ghent, Belgium. 3University of Amsterdam Academic Medical Center, Amsterdam, Netherlands. 4Medical University of South Carolina, Charleston, SC, USA

Abstract

The goal of this presentation is to identify the optimal treatment parameters and challenges associated with hyperthermic intraperitoneal chemotherapy (HIPEC), and explore the role of computational modeling for treatment planning to improve treatment delivery.

HIPEC is a technique used in combination with surgery to treat various gastrointestinal cancers, peritoneal mesothelioma and ovarian cancer that have spread to the peritoneum. During HIPEC treatment, the abdominal cavity is bathed with a heated perfusate (41-43°C) containing chemotherapeutic agents, thus, augmenting the anti-tumor effect of appropriate chemotherapeutic agents with mild hyperthermia. Application of this cancer treatment modality has increased exponentially over the past decades due to its improved clinical outcomes, including curative intent in selected patients with peritoneal malignancies. However, the choice of treatment parameters is largely determined by physician or institutional preference, which poses the need for standardization of HIPEC treatment planning and treatment delivery.

The main challenges for HIPEC delivery include the nonhomogeneous distribution of temperature and drugs in the abdominal cavity as well as heterogeneous organ size/distribution that leads to preferential and random flows in the abdominal cavity. So far, no studies have quantified the ability for HIPEC to effectively heat the entire tumor regions, which is often comprised of multiple nodules. In addition, the treatment duration required to effectively heat all tumor nodules and promote drug penetration has not yet been explored. Such efforts can be facilitated via computational modeling of flow dynamics, heat transfer, and pharmacokinetics between the circulating fluid and the tumor nodules in the cavity wall. The most relevant HIPEC modeling variables are the fluid flow parameters such as flow rate, pressure, and temperature as well as presence of stirring; tumor anatomy, especially size and dispersion of tumor nodules; tumor physiology, including accurate description of blood perfusion in the heterogeneous tumor; patient anatomy; number and location of temperature sensors; duration of treatment; drug type, concentration and carrier solution.

In summary, this presentation aims to challenge the hyperthermia community, especially computational modeling experts, to apply computational fluid dynamics, heat transfer and drug diffusion models to help optimize treatment protocols and thereby further improve the efficacy of HIPEC cancer treatment.

WED 16

MILD HYPERTHERMIA ENHANCES DRUG ACCUMULATION AND PHOTODYNAMIC THERAPY EFFICACY

Samir Jenkins1, Klressa Barnes1, Ruud Dings1, Gal Shafirstein2, Robert Griffin1

1University of Arkansas for Medical Sciences, Little Rock, AR, USA. 2Roswell Park Comprehensive Cancer Center , Buffalo, NY, USA

Abstract

Photodynamic therapy of tumors relies on the delivery of a small molecule, called a photosensitizer, to the tumor site, which is then activated externally by laser light. The effectiveness of the therapy is determined by the fluence and dose of the laser light, as well as the amount of photosensitizer delivered to the target tissue as well as availability of molecular oxygen to catalyze the reaction. Traditionally there are issues with dose limiting phototoxicity in the skin since the patient needs to wait for several days for enough photosensitizer to accumulate in the tumor to get some treatment benefit. To improve delivery, tumor areas were heated for 1 hour prior to or immediately following i.v. injection of the drug in an immunocompetent murine model. Our results suggest that time between drug and laser exposure can be shortened dramatically- a factor that would greatly improve clinical feasibility of PDT. Administration of heating caused a massive increase in therapeutic efficacy when a single laser treatment was applied only 2 hours following injection. Strikingly, in animals given only photosensitizer and irradiated 2 h later there was no measurable anti-tumor effect observed. Conversely, complete tumor growth inhibition was observed in the two days following treatment in the heated group, at clinical doses, and similar marked anti-tumor effects were observed as the dose was lowered from 10 mg/kg to 1.3 mg/kg. Additionally, histology showed the majority of the tumor tissue (~75%) was necrotic after two days when heat was combined with photodynamic therapy, while photodynamic therapy alone resulted in only ~25% necrotic tissue. Additionally, a significant increase in the efficacy was observed if the laser treatment was applied 24 hours later after heat and photosensitizer administration. This increase is in part ascribed to the increased accumulation of the photosensitizer in the tumor tissue and likely lasting effects on tumor blood flow and oxygenation in the heated vs. control groups.

WED 17

PRECLINICAL SAFETY AND CLEARANCE PROFILE OF PLASMONIC GOLD NANORODS: BRINGING PRACTICAL PHOTOTHERMAL THERAPY TO THE CLINIC.

Len Pagliaro, Colin Shepherd

Siva Therapeutics Inc., Austin, TX, USA

Abstract

Siva Therapeutics is developing a simple, safe, and effective cancer treatment termed Targeted Hyperthermia™, which generates therapeutic heat emanating from within solid tumors using systemically injected precision gold nanorods and an infrared light engine – technology termed photothermal therapy. Heat (~44°C) has several beneficial effects for solid tumors, including selective induction of apoptosis in cancer cells, stimulation of the immune system, inactivation of cancer stem cells, and increased perfusion resulting in improved drug efficacy. Targeted Hyperthermia provides precision heating of tumors with minimal collateral damage, using SivaRods™ polymer-coated gold nanorods and a SivaLum™ infrared light engine, and it promises to be a valuable adjunct to current drug therapies. While awareness of the therapeutic value of hyperthermia has been in the cancer community for many decades, implementing practical, safe, and cost effective hyperthermic cancer therapy has been challenging. Nanotechnology provides key tools for targeting heat to tumors, and photohermal therapy, in particular, has demonstrated efficacy, both in animal models, and now in the clinic. A critical hurdle for photothermal therapy has been scaling up manufacture of nanoparticles to pilot batch size, while maintaining plasmonic properties and uniformity of the material. Siva has accomplished pilot scale manufacturing and has completed full characterization of SivaRods through the Nanotechnology Characterization Laboratory program (https://ncl.cancer.gov/), which is supported by the National Cancer Institute, the FDA, and NIST. Systemically injected SivaRods have an excellent safety profile: they are neutral, inert, non-toxic, and excreted in both the urine and the feces. Additionally, Siva is developing a second-generation LED-based infrared light engine with the ability to illuminate regions of ~10 cm in diameter with high intensity infrared light to excite nanorods that have concentrated in tumors. Together, these advances have made nanotechnology-enabled photothermal cancer therapy safer, more practical, and more cost-effective than was previously possible.

WED 18

COMBINED NANOPARTICLE-BASED PHOTOTHERMAL THERAPY AND EPIGENETIC IMMUNOMODULATION FOR MELANOMA

Debbie Ledezma1, Juliana Cano-Mejia1,2, Elizabeth Sweeney1, Melissa Beaty1, Alejandro Villagra3, Rohan Fernandes1

1The George Washington University Cancer Center, Washington, D.C., DC, USA. 2University of Maryland, College Park, Maryland, USA. 3The George Washington Cancer Center, Washington, D.C., USA

Abstract

Introduction: Melanoma is a severe skin cancer that grows and spreads rapidly when undiagnosed and accounts for a majority of skin cancer-related deaths. Since many melanoma tumors are superficially accessible, nanoparticle-based photothermal therapy (PTT) may provide an effective treatment approach. To extend the local benefits of PTT to sites of melanoma dissemination, which is associated with a poorer prognosis, we propose to engage the immune system by using epigenetic drugs in combination with PTT. Several recent studies have described the antitumor immune effects of epigenetic drugs, including histone deacetylase (HDAC) inhibitors. Our approach comprises a single nanoparticle platform based on poly(lactic-co-glycolic acid) (PLGA) nanoparticles that encapsulate indocyanine green (ICG), a photothermal agent, and Nexturastat A (NextA), an HDAC6 inhibitor, to administer the combined photothermal-epigenetic therapy to melanoma. We test the effects of the combined therapy (using ICG-NextA-PLGA nanoparticles; INAP) on melanoma in vitro and in vivo.

Methods: INAPs were synthesized using an emulsion-evaporation synthesis scheme. INAP size distributions and stability were determined using dynamic light scattering. NextA encapsulation efficiency/drug loading was determined through UV-Vis spectrometry, and the photothermal heating characteristics were evaluated by illuminating the INAPs with an 808 nm NIR laser, measuring temperatures via a thermal camera. B16-F10 and B16-OVA melanoma cells treated with INAPs (± PTT) were assessed for viability, expression of NextA target proteins, and expression of immunogenic markers. In vivo studies assessed the effect of INAP-PTT on the expression of tumor-specific immune markers, tumor growth, and survival.

Results: Our optimized synthesis scheme yielded monodisperse and stable INAPs (200-300 nm, stable over 7 days) with 3-6% NextA drug loading. Illuminating INAPs with an NIR laser resulted in INAP concentration- and laser-power-dependent heating, achieving ablative thermal doses. Functional assays demonstrated that encapsulated NextA retained effective HDAC6 inhibitory activity in INAP-treated melanoma cells. Further, INAP-PTT treatment resulted in increased MHC1 and MHC1/OVA expression in B16-OVA melanoma cells suggesting increased antigen presentation, important for breaking tumor tolerance. Finally, INAP-PTT generated slower tumor progression and increased survival in the B16-OVA murine melanoma model, suggesting the potential of the combined photothermal-epigenetic therapy to treat melanoma.

Conclusions: Our study demonstrates the feasibility of using nanoparticles to combine disparate, yet complementary therapies such as PTT and epigenetic immunomodulation to treat melanoma. Ongoing studies are investigating the effects of the INAP-PTT on potentiating robust systemic antitumor immune responses, eliciting immunological memory, and validating our in vivo findings in other models of melanoma (B16F10 and SM1).

WED 19

EVALUATING THE IMMUNOLOGICAL EFFECTS OF NANOPARTICLE-BASED PHOTOTHERMAL THERAPY FOR MELANOMA

Elizabeth Sweeney1, Juliana Cano-Mejia1,2, Preethi Balakrishnan1, Rohan Fernandes1

1George Washington University, Washington, DC, USA. 2University of Maryland, College Park, Maryland, USA

Abstract

Introduction: Melanoma is a prevalent skin cancer, accounting for >9,000 deaths in the United States in 2018. Presenting on the skin, melanoma is readily accessible for photothermal therapy (PTT), a rapid and minimally invasive thermal ablation technique using near infrared (NIR) light-absorbing nanoparticles. Of increasing interest is the effect of PTT on potentiating a robust antitumor immune response because it has implications for targeting sites of tumor metastasis, which is associated with a dismal prognosis in melanoma. Our laboratory has developed a Prussian blue nanoparticle-based platform for PTT (PBNP-PTT). The goal of this study is to maximize the antitumor immune responses elicited by PBNP-PTT in melanoma to generate persistent treatment responses and immunological memory.

Methods: PBNP-PTT is performed by administering PBNPs to melanoma tumor cells in vitro or in vivo and illuminating them with an NIR laser for thermal ablation. We utilize two melanoma mouse models to test the effect of PBNP-PTT in vivo, SM1 and B16-F10 cells implanted in C57BL/6J animals. For vaccination studies, used to establish the optimal PBNP-PTT conditions, melanoma cells are treated in vitro with PBNP-PTT before injection into animals; subsequently, the mice are challenged with untreated melanoma cells to identify the PBNP-PTT conditions that maximize immune memory/tumor rejection. For therapeutic studies, melanoma cells are subcutaneously injected into mice. Once tumors are palpable, PBNP-PTT is administered at the previously optimized thermal ablation conditions.

Results: Our optimization studies have demonstrated that a higher thermal dose of PBNP-PTT (cumulative equivalent minutes; CEM) is required for effective melanoma cytotoxicity than in previously investigated models (e.g. neuroblastoma). Under these increased CEMs, PBNP-PTT is effective at eliminating primary tumor burden and maintaining significant tumor-free survival in melanoma-bearing mice. Further, PBNP-PTT-treated animals reject melanoma re-challenge, suggesting that PBNP-PTT generates immunological memory. Interestingly, when PBNP-PTT is combined with other immunotherapies (e.g. checkpoint inhibitors, exogenous immunological antigens and/or adjuvants), we find that the addition of these immunotherapies does not confer additional survival and tumor rejection benefit compared with PBNP-PTT alone suggesting that PBNP-PTT may already be maximizing the antitumor immune response in this primary tumor setting. However, these promising results need to be extended to animals bearing disseminated or metastasized melanoma tumors.

Conclusion: Our findings demonstrate the potential of PBNP-PTT to treat primary melanoma and engage a beneficial immunological response. Ongoing studies are looking into extending the observed tumor ablation/antitumor immune response benefits of PBNP-PTT from the primary to metastasized tumor setting in melanoma.

WED 20

A BIOCOMPATIBLE NANOPARTICLE PLATFORM FOR PHOTOTHERMAL THERAPY OF MELANOMA

Susana Torres-Hurtado1, Hieu Nguyen1, Niloofar Heshmati2, Tania Betancourt2, James W. Tunnell1

1The University of Texas at Austin, Austin, TX, USA. 2Texas State University, San Marcos, TX, USA

Abstract

Background: Nanoparticle-assisted photothermal therapy (nPTT) has been demonstrated as a means to treat solid tumors and alter immune responses that synergize with immunotherapy. A critical barrier to their use in humans is the potential toxicity of nPTT platforms. We have developed a biodegradable and biocompatible nanoparticle (NP) platform based on polymers with a long history of use in the biomedical arena that can be readily assembled via simple and scalable methods. Here, we present their physical and optical attributes, photothermal abilities, and cellular lethality in an in vitro model of melanoma.

Methods: Poly(lactic acid)-b-poly(ethylene glycol) (PLA-PEG-COOH) NPs were prepared through a precipitation process and loaded with indocyanine green (ICG) as a photothermal agent. Particle size distribution and optical absorbance were measured with dynamic light scattering and absorption spectroscopy, respectively. B16-F10 murine metastatic melanoma cells were seeded in a 96 well plates at a cell density of 1x104 cells/well and incubated overnight. nPTT in the cells was performed with NP concentrations ranging from 0.2 to 1.0 mg/ml and irradiated at 255, 474 and 693 mW for 3 min with an infrared (IR) diode laser of 808 nm. An IR camera was used to measure the temperature change of the cells. All experiments were performed in triplicate with the corresponding controls. Cell viability was evaluated by trypan blue exclusion assay 1 hour after irradiation.

Results: This method led to monodisperse NPs with mean sizes of approximately 75 nm and peak optical absorption of about 800 nm. Laser irradiated (= 808 nm) NPs in solution reached temperatures in excess of 50oC. Based on negative control (no laser; no NPs), high cell viability was observed for dark toxicity control (no laser; NPs at 1.0 mg/ml; cell viability >99%) and sham control (laser irradiation at 693 mW for 3 min; no NPs; cell viability ~97%). The temperature change for the sham control was ~2°C while the treatment groups showed increasing temperature changes up to 14°C. Cell death was observed in increasing amounts with increasing thermal dose (CEM43°C up to ~18 min with a corresponding cell viability of ~6%).

Conclusion: Our results demonstrate a nPTT platform with high translational potential. In vitro photothermal heating of these NPs in the presence of melanoma cells (B16-F10) result in cell killing in 3 min. Future work will investigate the impact of thermal dose on the release of damage associated molecular patterns associated with immunogenic cell death.

WED 21

IR820-LOADED PLGA NANOPARTICLES FOR PHOTOTHERMAL THERAPY OF TRIPLE-NEGATIVE BREAST CANCER

Danielle Valcourt, Megan Dang, Emily Day

University of Delaware, Newark, DE, USA

Abstract

Introduction: Triple-negative breast cancer (TNBC) accounts for 15-25% of breast cancers and is unsusceptible to current targeted or hormonal therapies. Photothermal therapy (PTT), which utilizes nanoparticles (NPs) to convert externally applied near-infrared light into heat to ablate tumors, is a promising alternative strategy, but it typically uses gold-based NPs that will remain in the body indefinitely with unknown long-term effects. To enable PTT with biodegradable NPs, we encapsulated the NIR-absorbing dye IR820 in poly(lactic-co-glycolic acid) (PLGA) NPs and evaluated their performance against TNBC in vitro and in vivo.

Methods: IR820-loaded PLGA NPs were prepared by single-emulsion solvent evaporation and their size, zeta potential, encapsulation efficiency, and stability evaluated using dynamic light scattering, transmission electron microscopy, and spectrophotometry. The temperature of free IR820 or IR820-PLGA NPs suspended in PBS upon laser exposure (808 nm, 5 min, 1.5 W/cm2) was measured by thermal camera. Each treatment's impact on MDA-MB-231 TNBC cell metabolic activity was assessed by MTT assay in the absence and presence of light. The mechanism of cell death induced by PTT was evaluated by flow cytometry using annexin V and propidium iodide staining. In vivo studies used female nude mice bearing subcutaneous TNBC xenografts. The distribution of IR820-PLGA NPs to major organs and tumors following intravenous injection was evaluated by imaging excised tissues with an In Vivo Imaging System. The tumor temperature in mice treated with saline, free IR820, or IR820-PLGA NPs during laser irradiation was measured with a thermal camera. To assess the impact of PTT on tumor growth, mice were treated with saline, free IR820, or IR820-PLGA NPs ± laser 1X/week for 4 treatments. Tumor volume was measured with calipers versus time and mice sacrificed after 30 days.

Results: IR820-PLGA NPs were spherical with hydrodynamic diameter of 60±13 nm, zeta potential of −40±6 mV, and encapsulation efficiency of >90%. IR820-PLGA NPs heated as well as free IR820, were more stable in water than free IR820, and were more cytocompatible in the dark than free IR820. Cells treated with IR820-PLGA NPs and light experienced a significant decrease in metabolic activity and the mechanism of cell death was primarily apoptosis. In vivo, IR820-PLGA NPs heated tumors more efficiently than free IR820, achieving temperatures >42°C. PTT mediated by IR820-PLGA NPs significantly reduced tumor growth compared to controls.

Conclusions: IR820-PLGA NPs can enable potent PTT of TNBC. These data support continued development of this platform for treatment of aggressive cancers like TNBC.

WED 22

SEALING AND REPAIR OF SOFT TISSUES USING PHOTOTHERMAL NANOMATERIALS

Kaushal Rege

Arizona State University, Tempe, AZ, USA

Abstract

Lacerations, tears, and incisions in soft tissues are typically treated using approximation devices including sutures or staples, which can be inherently traumatic. Laser-activated tissue sealing, also known as tissue welding, is an alternate strategy that facilitates rapid, fluid-tight approximation of ruptured tissues, but the lack of effective materials compromises efficacy. I will discuss our results on the generation, characterization and evaluation of laser-activated nanomaterials in which, gold nanorods (GNRs) are embedded within polypeptide matrices. Irradiation of these nanomaterials with near infrared (NIR) light facilitated a photothermal response, which, in turn, resulted in rapid, fluid-tight sealing and repair of soft tissues both ex vivo and in live animals. A combined experimental and modeling study of heat transfer resulted in identification of conditions that minimized tissue damage while maximizing sealing efficacy. Gold nanorods were also incorporated in polypeptide fibers, resulting in the formation of laser-activated sutures which combine the advantages of conventional clinical practice (suturing) with photothermal sealing in a single surgical device. Delivery of bioactive molecules, in concert with nanomaterial photothermal sealing, facilitated the acceleration of dermal wound healing and repair in live mice. We have recently also developed novel approaches for chromophore (e.g. GNR)-free sealing of soft tissues using light. Our results demonstrate that photothermal approaches can lead to effective sealing, repair, and regeneration in several applications including soft tissue trauma, wound healing and grafts.

WED 23

EVALUATION OF A PHOTOTHERMAL NANOCOMPOSITE FOR DISTRUPTION OF STAPHYLOCOCCUS AUREUS BIOFILMS

Pedro Sanchez, Anila Pullagura, Kenneth Vogel, Nicole Levi-Polyachenko

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

Abstract

Background: Staphylococcus aureus is culprit for biofilm-associated infections on medical devices.This is a major concern since biofilm-secreting bacteria, like S. aureus, develop an extracellular polysaccharide (EPS) matrix which encapsulates and protects them from both host-immune responses and the effects of antibiotics. Current methods for eradicating biofilm infections associated with medical devices involve antibiotics alone. However, activity of the antimicrobial agents is often inhibited.To enhance the effects of antibiotics against biofilm infections, disrupting the EPS matrix to enhance antimicrobial agents can be accomplished using heat. Heat-generating nanoparticle (NP)-doped silicone can induce hyperthermia for augmenting the efficacy of antibiotics for treating biofilm-associated infections on medical implants. In this study, it was hypothesized that the reduction of biofilms could be achieved by hyperthermic therapy by application of laser stimulation of nanocomposite treatment to biofilms of the engineered strain of S. aureus, Xen29, and augmenting the activity of gentamicin using heat.

Methods: Since silicone does not generate heat, Poly[4,4-bis(2-ethylhexyl)-cyclopenta[2,1-b;3,4-b'] dithiophene-2,6-diyl-alt22,1,3-benzoselenadiazole-4,7-diyl] (PCPDTBSe) nanoparticle (BSE NPs) were incorporated into silicone and stimulated with laser light. This in turn allowed for the generation of heat to the silicone. Xen29 biofilms were cultivated on either silicone only or BSe-silicone nanocomposites containing NP's at various concentrations (1, 5, and 10mg NP's/1g of silicone) for 24 hours. The samples were then laser treated with 5watt, 800nm laser light for 60 seconds (468.75 J/cm2) to induce hyperthermic temperatures of 48°C in the presence of gentamicin (0.0289mg/mL). The treated samples were quantified by serially diluting and culturing the biofilms onto nutrient broth 1 agar plates for determining the colony forming units (CFU's). Confirmatory analysis of the biofilms was determined via in vivo imagining system.

Results: Simultaneous treatment with photothermal therapy via laser light induced hyperthermic temperatures of 48°C using BSe-nanocomposites and enhanced the antimicrobial activity of the antibiotics against Xen29 biofilms. As a result of inducing hyperthermia by laser treatment, microbial biofilms cultivated on BSe-nanocomposites were decreased by 90%.

Conclusions:These experiments are the first confirmation that nanoparticle-doped silicone can induce hyperthermia for augmenting the efficacy of antimicrobial agents and decrease biofilm burden on silicone implants.

WED 24

BARRIERS TO SUCCESSFUL NANOPARTICLE-MEDIATED DELIVERY

Tom Anchordoquy

Skaggs School of Pharmacy and Pharmaceutical Sciences, Anschutz Medical Campus, University of Colorado, Aurora, Colorado, USA

Abstract

The use of nanoparticles as delivery systems is decades old and started with the introduction of liposomes in the 1960s. Although many magical properties have been attributed to these delivery systems, the predominant effect of nanotechnology on drug delivery is reduced toxicity, not improved efficacy. The majority of research in this field has focused on improving drug delivery to tumors, but studies have consistently shown that only 1% of the injected dose accumulates in tumors, and this dismal reality has not improved despite five decades of research. Although much has been learned about using "stealth technology" to achieve prolonged circulation, the vast majority of systemically-administered nanoparticles are cleared by the endogenous elimination mechanisms in the liver and spleen. Furthermore, even this "proven" technology has encountered significant problems that has resulted in the termination of some clinical trials due to adverse reactions and death. In an effort to overcome the toxicity associated with off-target effects, studies have attempted to deliver nucleic acids (DNA/RNA) with the hope of delivering cargo that specifically affects cancer cells. Unfortunately, the inability to overcome the same barriers that limit the efficacy of conventional nanoparticles (i.e., liposomes) prevent the "latest and greatest" nanoparticles from achieving clinical efficacy. The talk will review some of the major barriers to nanoparticle-mediated drug delivery, and provide a realistic perspective on what nanotechnology might be able to achieve in the foreseeable future.

WED 25

THE TUMOR IMMUNE MICROENVIRONMENT IS RESHAPED AFTER SYSTEMIC EXPOSURE TO MAGNETIC IRON OXIDE NANOPARTICLES: A STUDY IN MOUSE MODELS OF BREAST CANCER

Preethi Korangath1, James Barnett1, Anirudh Sharma1, Elizabeth Henderson1, Jacqueline Stewart1, Shu-Han Yu1, Sri Kamal Kandala1, Chun-Ting Yang1,2, Mohammad Hedayati1, Todd Armstrong1, Elizabeth Jaffee1, Cordula Gruettner3, Xian Zhou1, Wei Fu1, Saraswati Sukumar1, Brian Simons1, Robert Ivkov1

1Johns Hopkins University School of Medicine, Baltimore, MD, USA. 2National University of Taiwan, Taipei, Taiwan. 3micromod Partikeltechnologie, GmbH, Rostock, Germany

Abstract

The factors that influence selective accumulation of nanoparticles into solid tumors remain an area of intense interest. Five tumorigenic human breast cancer cell lines with varying HER2 status were used to grow orthotopic mammary tumors in nude and NOD/SCID gamma (NSG) mice. A human HER2 overexpressing (huHER2) transgenic mouse (Genentech) was used to develop a syngeneic allograft model that was implanted across FVB/N (immune competent), nude, and NSG mice for comparative studies of tumor retention of nanoparticles. Starch-coated bionized nanoferrite (BNF) nanoparticles labeled with trastuzumab (BNF-HER), unlabeled (BNF-Plain), or PBS (control) were injected into tail veins of mice when tumors had a measured volume of ~150 mm ^ 3. 24 hrs following intravenous injection, mice were sacrificed and tissues harvested for analysis.

We demonstrate using inductively coupled plasma mass spectrometry and extensive histophathology analysis that unlabeled starch-coated magnetic iron oxide nanoparticles showed little accumulation in tumors regardless of tumor model or host strain. Surprisingly, retention of BNF-HER nanoparticles was evident across all tumor models, with little variation among the models. Further analysis showed that retention of the antibody-labeled counterpart in tumors depended more on immune status of the host than on presence of the target antigen.

In vitro, a TH1-type activation of murine macrophages and neutrophils led to preferential uptake of antibody-conjugated nanoparticles, suggesting nanoparticle retention in tumors was determined by an inflammatory tumor-microenvironment. In the immune competent huHER2 allograft model, accumulation of plain nanoparticles was minimal as observed in human xenograft models. Conversely, retention of BNF-HER nanoparticles in FVB/N mice bearing huHER2 tumors was dramatically higher than in nude or NSG mice bearing this tumor, with tumor retention occurring primarily in tumor-associated dendritic cells, neutrophils, monocytes, and macrophages as determined by magnetically sorted flow cytometry. An intact immune system with competent TH1 activation displayed preferential retention of antibody-labeled BNF nanoparticles.

Systemic exposure of immune intact allograft (implanted) huHER2 models to either plain or trastuzumab-labeled BNF nanoparticles delayed tumor growth and caused CD8+ T cell infiltration fourteen days after injection.

These findings demonstrate that the immune microenvironment of solid-cancer tumors can be a dominant factor that determines nanoparticle retention in tumors, and that systemic exposure to nanoparticles has potential to initiate systemic immune responses leading to adaptive immune-mediated tumor growth inhibition. Our results show that nanoparticle constructs offer anti-cancer immune-modulating potential that can be exploited for cancer immune therapy.

WED 26

LASER INTERSTITIAL THERMAL THERAPY FOR INTRACRANIAL LESIONS

Pakawat Chongsathidkiet, Cosette Dechant, Hanna Kemeny, Yang Liu, Ren Odion, Xiuyu Cui, Bridget Crawford, Chris Lascola, Tuan Vo Dinh, Peter Fecci

Duke University, Durham, NC, USA

Abstract

Brain metastases remain one of the most dreaded consequences of late stage cancer, yet their incidence has risen as survival from primary cancers has improved. More than 200,000 patients are affected annually in the United States, and treatment options remain limited.Recent technological advances include the minimally invasive use of lasers to thermally ablate intracranial lesions, converting phase change data from intra-operative MRI (iMRI) imaging into real time in vivo temperature monitoring. Laser Interstitial Thermal Therapy (LITT) has now emerged as a successful treatment for recurrent metastatic lesions, as well as primary brain tumors, that have failed therapy and have few remaining options. Furthermore, ample evidence suggests LITT opens the blood-brain barrier (BBB) for a period of time after treatment, improving otherwise poor access for other modalities, including immune-based platforms. Therefore, LITT is well-suited to intracranial lesions, proffering a novel treatment platform on its own while simultaneously licensing therapies that otherwise possess limited efficacy in the brain. Unfortunately, LITT remains handicapped by a small radius of treatment (lesions larger than 3cm provide a challenge) and a lack of treatment specificity for tumor. We have built a novel therapeutic platform that uses plasmon-activated gold nanotechnologies to obviate the current limitations of LITT, expanding treatment coverages and conferring specificity for tumor borders with surrounding normal brain. This talk will discuss current clinical uses of LITT, as well as our efforts to enhance the technology.

WED 27

MECHANISMS OF BLOOD-BRAIN BARRIER PERMEABILITY BY LASER INTERSTITIAL THERMAL THERAPY IN A MOUSE MODEL OF GLIOBLASTOMA

Afshin Salehi, Mounica Paturu, Matthew Caine, Robyn Klein, Albert Kim

Washington University, Saint Louis, MO, USA

Abstract

A major obstacle in the treatment of glioblastoma, the most common primary brain cancer in adults, is the blood-brain barrier (BBB), which prevents the entry of most therapeutic drugs. Our group previously demonstrated in human patients that minimally invasive laser interstitial thermal therapy (LITT) may increase local BBB permeability for several weeks following treatment. We thus established a LITT platform in a mouse model to examine the temporal and spatial characteristics of LITT-induced BBB and Blood-Tumor Barrier (BTB) permeability. We stereotactically introduced a 660 micrometer optical fiber through a burrhole into the mouse frontal cortex. A Fibertome 8100 laser generator set at 2W was used to treat C57BL/6J mouse brain along with a 400 micrometer thermocoupler inserted 1 mm anterior to the laser fiber to monitor and maintain hyperthermia at 43 degrees Celsius for various durations. In other experiments, mice were also stereotactically implanted with syngeneic GL261 tumor cells prior to LITT. We first performed a longitudinal analysis of BBB permeability using a quantitative fluorescein permeability assay. LITT disrupted the BBB up to 14 days post-LITT with a relative peak at 3 days post-LITT. Immunohistochemical analysis on mice treated with LITT demonstrated an increase in both Dextran 70 kDa and IgG extravasation in LITT-treated brain parenchyma compared to sham controls, indicating increased LITT-mediated BBB leakiness. Additionally, mice orthotopically implanted with GL261 tumor cells demonstrated an increase in Dextran 70 kDa and IgG extravasation in tumor compared to non-laser treated tumors, suggesting increased BTB permeability. Beyond mechanical disruption of blood vessels, we are currently examining the cellular mechanisms of prolonged BBB permeability, particularly in the penumbra of LITT-treated brain. These data suggest that LITT-mediated opening of the BBB and BTB can potentially enable therapeutic delivery of molecularly targeted or chemotherapeutic drugs, including antibody-based agents.

WED 28

STEREOTACTIC LASER ABLATION FOR TREATMENT OF BRAIN TUMORS: LESSONS LEARNED FROM 240 CASES OVER THE PAST DECADE

Jianning Shao, Nathan Radakovich, Krishna Joshi, Baha'eddin Muhsen, Hamid Borghei-Razavi, Alireza Mohammadi

Cleveland Clinic, Cleveland, OH, USA

Abstract

INTRODUCTION: Stereotactic laser ablation (SLA) is a novel, minimally invasive alternative to surgical resection for intracranial lesions, especially in patients with poor functional status and tumors close in proximity to eloquent structures. However, this technique is not uniformly optimal for all patients. As one of the first institutions to adopt this technology, we present a comprehensive case series detailing the evolution of patient selection, surgical trends, and lessons learned over the past decade in the largest patient cohort on SLA treatment in brain tumors to date.

METHODS : Retrospective review was performed on 240 patients with various brain tumors treated with SLA. Extensive data on patient demographics, surgical and tumor characteristics, temporary (resolved within 6 months) and permanent complications, and follow-up data were collected. Consecutive patients were categorized into two time periods (2011-2014, 102 patients; 2015-2018, 138 patients), and statistical analysis was performed.

RESULTS: Initially, SLA was predominantly utilized for upfront and recurrent gliomas (76.64%); recently, however, there has been a marked increase in SLA usage for metastases and radiation necrosis following radiosurgery failure (25 combined cases to 58 combined cases; 23.4% --> 42.65%). Additionally, there is a trend against SLA usage for large tumors (diameter > 4cm, 15.65% --> 9.57%) due to poorer outcomes associated with these lesions. Surgically, advances in SLA technology led to shorter operation times (6.25 hours to 3.6 hours) and better separation between tracts and the hyperthermic field, resulting in fewer temporary (39.17% --> 30.1%) and permanent (13.3% --> 7.5%) postoperative deficits. Lastly, better patient selection resulted in a lower mortality rate (decrease from 4.17% to 0.83%).

CONCLUSIONS: Our study shows the evolution of SLA usage at a single institution led to better patient selection and maturation of surgical panning, ultimately resulting in fewer complications and better outcomes.

WED 29

MAGNETIC HYPERTHERMIA THERAPY OF EXPERIMENTAL GLIOBLASTOMA IN COMBINATION WITH CHEMORADIATION

Constantinos Hadjipanayis1, Alexandros Bouras1, Keon Mahmoudi1, Dominique Bozec1, Joe Gerald Jesu Raj1, Eleni Liapi2, Robert Ivkov2

1Icahn School of Medicine at Mount Sinai, NYC, NY, USA. 2Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

INTRODUCTION: Glioblastoma (GBM) is a fatal brain cancer for which there is no cure. Fractionated external beam radiation therapy (RT) and chemotherapy (temozolomide; TMZ), known as chemoradiation (CRT), have provided the greatest benefit to GBM patients and are standard of care. Magnetic hyperthermia therapy (MHT) consists of intratumoral heat generation after deposition of magnetic iron-oxide nanoparticles (MIONPs) that are subjected to an external alternating magnetic field (AMF). MHT may potentiate the cytotoxic effects of CRT on tumor cells. We have developed MIONPs that demonstrate superior heating efficacy for MHT of GBM in combination with CRT.

METHODS: Intracranial heating efficacy and toxicity studies were performed in healthy mice using two concentrations (60 and 80 mg/ml) of MIONPs solutions with a clinically relevant AMF treatment (450kHz, 200G) after convection-enhanced delivery (CED). Both intracranial (ipsilateral and contralateral) and rectal temperatures were recorded. Bioluminescence imaging (BLI) was used to assess the in vivo efficacy of intracranial MHT in combination with fractionated RT in a mouse syngeneic GBM model. A pilot survival study of athymic nude mice with invasive, therapy-resistant orthotopic human GBM intracranial xenografts was completed after combination treatment with MHT and CRT. Quantification of TMZ levels in intracranial GBM xenografts and surrounding brain tissue after MHT was performed using liquid chromatography–mass spectrometry (LC-MS).

RESULTS: A concentration-dependent temperature increase by the MIONPs (60 and 80 mg/ml) after CED and an AMF was observed rapidly in the brain (40 and 43oC). No temperature elevation was observed in either the contralateral brain hemisphere or the rectum, supporting the localized intracranial heating effect. No severe acute and long-term side effects were observed after MIONP CED. A marked decrease in tumor size was found with MHT and RT by BLI. Significantly prolonged animal survival occurred with the combination therapy (MHT/RT/TMZ) in comparison to either treatment alone. Increased TMZ levels were measured in intracranial GBM xenografts and surrounding brain tissue after MHT and TMZ treatment.

CONCLUSIONS: We have confirmed the safety and feasibility of intracranial MHT in a rodent glioma model. Furthermore, we have demonstrated the chemoradiosensitivity enhancement of therapy-resistant human GBM xenografts after MHT. These data support the hypothesis that MHT of GBM can potentially enhance the effects of CRT.

WED 30

MR GUIDED HEAD&NECK HYPERTHERMIA: ACCURACY THROUGH INTEGRATION

Gennaro G. Bellizzi1, Kemal Sumser1, Tomas Drizdal2, Gerard C. van Rhoon1, Juan A. Hernandez-Tamames3, Desmond T. B. Yeo4, Margarethus M. Paulides5,1

1Department of Radiation Oncology, Erasmus Medical Center Cancer Institute, Rotterdam, Netherlands. 2Department of Biomedical Engineering, Czech Technical University in Prague, Prague, Czech Republic. 3Department of Radiology, Erasmus Medical Center, Rotterdam, Netherlands. 4Imaging and Bioelectronic Technologies, GE Global Research Centre, Niskayuna, NY, USA. 5Det. of Electrical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands

Abstract

Accurate temperature monitoring in hyperthermia (HT) treatments is highly needed. Invasive interstitial thermometry probes are currently exploited. Although with a 0.1-0.2°C accuracy these provide a limited spatial resolution and are uncomfortable for the patient. Magnetic resonance (MR) thermometry potentially forms a non-invasive 3D temperature monitoring approach. MR imaging can also visualize the treatment setup and tumor physiology during treatment, both of which provide crucial input for simulation-based MR-adaptive HT strategies. Hereto, a number of hybrid MR-hyperthermia applicator approaches have been developed, which we will review.

The first generation of systems for MR guided HT, i.e. "HT-only" inserts, led to one commercial system for deep pelvic HT, i.e. the BSD2000/3D/MRI (Pyrexar, Salt Lake City, UT, USA). This system relies on the MR scanner's body coil for imaging, which leads to a relatively low signal-to-noise-ratio (SNR) and single channel operation. Single channel coils and low SNR prevent enabling parallel imaging approaches for fast imaging and makes this approach very sensitive to motion, as e.g. observed in the intestines.

The second generation of HT inserts systems, i.e. "dual-function" devices, include "flex-coils" and are designed to improve SNR due to close-body signal pickup and imaging speed up by multi-channel operation. First dual-function systems, i.e., "integrated devices" [1,2], make use of the same coils/antennas for heating and imaging. "Dual-function" devices allow achieving high SNR and fast multi-channel ("parallel") imaging through dedicated coils/antennas. However, this approach involves tradeoffs between radiofrequency (RF) heating frequency, imaging frequency and design complexity. Research is needed to elucidate the best, and commercially most interesting, approach. A different subgroup of the second generation are "decoupled devices". One example is the MRcollar applicator [3] under development by our group for treatment of cancers of the head and neck. In this approach, separate heating and imaging arrays (carefully oriented for decoupling) are exploited. Besides the advantages of "dual-function" devices, this integration of two different systems for heating and imaging allows choosing the optimum working frequencies for heating and imaging independently. This is crucial for achieving a target conformal heating, enabling higher temperature, and performing imaging by clinically available MR scanners. Unfortunately, this integration of two complex RF systems poses major technological challenges.

Recent developments in lower-cost phased-array RF technology is strongly accelerating the development of commercially viable focused microwave (FoM: >300MHz) systems with up to 60 or more channels [4]. Such systems will require real-time MR thermometry guidance, so thorough investigation of all dual-function approaches regarding heating and imaging performance is urgently needed.

[1] Yeo et al., ISMRM, 2011 [2] Winter et al., Rad Oncol 2016 [3] Paulides et al., Phys Med Biol, 2014 [4] van Rhoon et al, STM 2013

Support by KWF-grant 2017-2/11368

WED 31

MR THERMOMETRY PHANTOM VALIDATION AND MODELING OF A 915 MHZ ANNULAR PHASED-ARRAY FOR TREATMENT OF BRAIN TUMORS

Dario B. Rodrigues1, Jason Ellsworth2, Martin Wadepohl3, Günter Futschik3, Zeljko Vujaskovic1, Paul Turner2

1University of Maryland School of Medicine, Baltimore, MD, USA. 2Pyrexar Medical, Salt Lake City, UT, USA. 3Dr. Sennewald Medizintechnik GmbH, Munich, Germany

Abstract

Background: Hyperthermia (HT) is a potent cellular radiosensitizer for the treatment of solid tumors, including brain cancer. Current strategies to heat deep-seated targets in brain are primarily invasive and existing deep HT applicators do not have appropriate frequency, geometry, and number of sources to focus at depth. This study presents a numerical and experimental investigation of a novel 915 MHz annular phased-array with 72 dipole antennas designed to target brain tumors.

Methods: The proposed applicator consists of 3 rings of 24 water-coupled dipole antennas (30×6 mm2) enclosed in a cylindrical frame with 26 cm diameter and 13 cm length. Two cylindrical head phantoms were analyzed with 14.2 cm diameter and 25.1 cm length: gel-based phantom with $\varepsilon r=76.4$ and $\sigma=0.799$ S/m and a solid phantom with $\varepsilon r=48.2$ and $\sigma=0.838$ S/m (915 MHz) that mimics brain dielectric properties. A cross-shaped array of catheters was inserted in the phantoms to facilitate temperature and electric field measurements using single-point sensors, which were compared with MR thermometry scans. Numerical simulations were implemented using a multiphysics software that couples electromagnetic and thermal physics to simulate SAR (W/kg) and temperature patterns in the phantoms. The antenna focus was characterized in terms of 50% SAR isovolume (SAR50).

Results: Using the center of the phantom as the target, simulations predicted a SAR50 focus of 3.4×1.4×1.5 cm3 with an ellipsoid shape. For the same antenna settings, MR images confirm the size and position of the central focus (4×1.5×1.5cm3). Using a forward power of 160 W split over 8 channels, the central focus increased 2°C within 3 minutes heating as measured by MR thermometry with an associated SAR peak of 98 W/kg. Moving the phantom off the central axis kept the focus in the middle of the applicator as expected. Similarly, electronic lateral steering generated the intended shift, but induced superficial SAR hot spots in the phantom. These hot spots were not observed using a 24-channel configuration. Simulations and temperatures measured with the single-point sensors and MR scans showed a good correlation within a 10% margin of error.

Conclusions: The feasibility of heating small targets in a head phantom using a novel microwave brain applicator is demonstrated with experiments and numerical simulations. The observed secondary SAR hot spots are expected to dissipate by highly perfused healthy brain and from convective cooling provided by the surrounding water bolus. The head phantoms confirm reliable and predictable steering focusing by phase or positional steering.

WED 32

IMAGE-GUIDED DOXORUBICIN DELIVERY FOR PEDIATRIC TUMORS USING MRI-GUIDED HIGH-INTENSITY FOCUSED ULTRASOUND HYPERTHERMIA AND TEMPERATURE-SENSITIVE LIPOSOMES

Rajiv Chopra

UT Southwestern Medical Center, Dallas, TX, USA

Abstract

Introduction: Doxorubicin (DOX) is widely used against many pediatric cancers, but it is associated with late-stage cardiotoxicity. Localized DOX delivery from thermosensitive liposomes (TSLs) using MR-HIFU mild hyperthermia (HT) might improve local control in solid tumors without increasing heart toxicity. Furthermore, MR-HIFU is non-ionizing and non-invasive, both of which are attractive characteristics for a pediatric intervention. In this project we evaluate the influence of hyperthermia and drug parameters on the therapeutic index, and also the tumor control effect of MR-HIFU and TSL's on a pediatric tumor cell line..

Methods: Rabbits bearing bilateral Vx2 tumors were treated with HE to one tumor. TSL-DOX (Celsion) was infused during HT over 5 min. In one study, the influence of exposure heating duration (10 vs 40 minutes) on drug distribution was evaluated. In a second study, the influence of injected dose on therapeutic index was evaluated. Once heating parameters were found with a good therapeutic index, the tumor control offered with this strategy was evaluated in a nude rat model bearing a human pediatric Ewings Sarcoma cell line ES1).

Results: Longer heating achieved more DOX delivery in heated tumors, without an increase in the systemic dose to the heart and other organs. This led to an increased therapeutic index with heating duration. The influence of injected dose on therapeutic index was not significant. In the case of the pediatric tumor study, the combined treatment of Thermodox+HIFU exhibited a significant delay in tumor progression relative to control groups of animals.

Conclusion: Our results confirm that there are strategies to increase the therapeutic index of DOX using TSLs are possible, with exposure duration being an important determinant.

WED 33

DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A MICROWAVE ABLATION SYSTEM INTEGRATED WITH AN IMAGE-GUIDANCE AND TREATMENT PLANNING PLATFORM FOR BRONCHOSCOPIC TRANSPARENCHYMAL LUNG ACCESS

Punit Prakash1, Jan Sebek1, Austin Pfannenstiel1, Yixun Liu2, Steve Kramer2, Justin Yu2, Rosilyn Noblejas2, Tom Keast2, David Biller1, Chanran Ganta1, Warren Beard1, Henky Wibowo2

1Kansas State University, Manhattan, KS, USA. 2Broncus Medical, San Jose, CA, USA

Abstract

Introduction: Image-guided bronchoscopic microwave ablation (MWA), combined with treatment planning and monitoring techniques, may enable safer and more effective treatment of lung nodules than current percutaneous ablation techniques. Our objective is to develop an MWA system for precise targeting of lung tumors, integrated with a clinically established approach for image-guided bronchoscopic transparenchymal nodule access and treatment planning system.

Methodology: We have developed a flexible 2.45 GHz cooled MWA applicator (1.5 m length, 1.8 mm O.D.), suitable for introduction to lung tumors via the working channel of a flexible bronchoscope. Proof-of-concept applicators were fabricated and experimentally characterized in ex vivo tissue with 30 – 45 W applied for 5 – 10 min. A prototype treatment planning system was developed to determine the optimal path for delivering the applicator to targets, and to estimate the extent of the ablation zone in vivo based on input generator parameters. Experimental studies are underway to assess the ability of the integrated system to create 1 – 3 cm diameter ablation zones in normal porcine lung in vivo.

Results: The diameter and axial ratio of ablation zones in ex vivo tissue ranged between 19 – 32 mm and 0.73 – 0.87, respectively, similar to ablation zones that can be achieved with rigid MWA applicators currently in clinical use for percutaneous ablation of lung tumors. A treatment planning platform has been developed and integrated within the Archimedes platform to: find the optimal path safely delivering the MWA applicator to the tumor; predicting the likelihood of achieving an adequate treatment margin; and suggesting suitable generator parameters for achieving the treatment margin. Results from in vivo studies, currently underway, will be presented at the meeting.

Conclusion: We have developed a flexible 2.45 GHz MWA applicator suitable for treatment of lung tumors via a bronchoscopic approach, and a treatment planning platform integrated with the Archimedes guidance and navigation platform. The proposed system may enable precise delivery of thermal ablation for treatment of early-stage lung tumors.

We gratefully acknowledge support through NIH grant R01 CA218357.

WED 34

THERMOCHEMICAL ABLATION AND THE NECESSITY OF A MULTI-MODAL IMAGING APPROACH

Emily Thompson, Samuel Einstein, Dodge Baluya, Chunxiao Guo, James Bankson, Erik Cressman

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Introduction: Hepatocellular carcinoma (HCC) has a grim prognosis and responds poorly to chemotherapy. Incidence is rising, and patients present frequently late in disease precluding surgery. Recurrence after radiofrequency ablation is common. Chemical ablation has been used but control of injections is challenging. Thus, new therapies and a means to monitor them are needed. Tracking and coregistration between imaging modalities are important tools to optimize procedural techniques. Thermochemical ablation (TCA), an acid/base neutralization reaction producing ablative quantities of heat is one of these new therapies that can be tracked with multiple modalities. Trifluoroacetic acid (TFA) can function as an agent in TCA and is visible on 19F magnetic resonance imaging (19F-MRI). At the same time, it can be imaged by mass spectrometry (MSI) and the data can then be correlated. We describe our first efforts in assessing performance and imaging using ex vivo tissues.

Methods: As components of TCA, 100 μL of 1.0M TFA and 1.0M NaOH was injected in fresh, sectioned ex-vivo porcine liver tissue. Tissue sections underwent 19F-MRI performed on a preclinical Bruker 7T Biospec USR 70/30 and custom-built 19F volume coil tuned to 282.56MHz, the resonance frequency of 19F. After scanning, ablated tissues were photographed and flash frozen with liquid nitrogen, cryosectioned at 10 μm for MSI. Data acquisition was performed in negative mode using a Waters Synapt G2-Si with data processing and images reconstructed using HDI 1,4 software.

Results: Using 19F-MRI, the compound was readily detected in all tissue sections. Signal from 19F atoms varied throughout the tissue sample, indicating the presence of a gradient. MSI showed injectate products in the ablated region with sharp margins indicating a clear separation of ablated and non-ablated tissue.

Conclusion: The results of this research demonstrate the ability of 19F-MRI to detect 19F in tissue at ablative concentrations of TFA. Variations of SNR indicate the potential of 19F-MRI to be used in ablation agent mapping. This work also demonstrates the effectiveness of MSI in evaluating chemical reaction products and location in ablated tissues. Future experiments will further investigate the agreement between 19F-MRI and MSI.

WED 35

MICROWAVE ABLATION SYSTEM INTEGRATED WITH MRI THERMOMETRY FOR EXPERIMENTAL VALIDATION OF 3D TEMPERATURE PROFILES PREDICTED BY COMPUTATIONAL MODELS

Pegah Faridi1, Paul Keselman2, Hojjatollah Fallahi1, Punit Prakash1

1Kansas State University, Manhattan, KS, USA. 2University of Kansas Medical Center, Kansas City, Kansas, USA

Abstract

Introduction: Computational models are widely used during the design and characterization of microwave ablation (MWA) devices, and have been proposed for pre-treatment planning. Our objectives were to: (1) develop an experimental MWA platform integrated with magnetic resonance thermometry (MRT) at 3T, and (2) employ the platform for comparative assessment of thermal damage profiles predicted by state-of-the art MWA computational models with measured MRT profiles during ablation experiments in ex vivo tissue.

Methodology: We performed MWA in ex vivo tissue (bovine liver and porcine muscle) under MRT guidance using a custom, 2.45 GHz water-cooled applicator (2.54 mm O.D.). MRT data were acquired on a 3T Siemens Skyra scanner in one coronal and two axial planes using a series of FLASH images (TR/TE = 50/12.3 ms, FOV = 128 x 128 mm2, matrix = 128 x 128, flip angle = 15°, slice thickness = 1.5 mm and acquisition time = 6.4 s). Data were acquired for 2 min prior to heating, during 5-10 min microwave exposures, and for 3 min following heating. Fiber-optic temperature sensors were used to validate the accuracy of MRT data (FO¬1 at 5 mm and FO2 at 35 mm radially from the applicator). A total of 10 ablation experiments were conducted using 30–50 W applied power. MWA computational models were implemented using the finite element method, and incorporated temperature-dependent changes in tissue physical properties. Model-predicted ablation zone extents were compared against MRT-derived Arrhenius thermal damage maps and visually observed ablation zones using the Dice similarity coefficient (DSC).

Results: Prior to heating, the observed standard deviation of MRT data was in the range of 0.3- 0.7 °C, similar to previously reported uncertainty in other studies. Mean squared error between MRT and FO¬1 and FO¬2 during heating was in the range of 3–4.5 °C and 0.5-2.6 °C, respectively. DSC between model-predicted ablation zones and MRT-derived Arrhenius thermal damage maps were 0.99 (30 W, 10 min, n=1) and 0.99, 0.82, and 0.79 (30 W, 5 min, n=3). For the same dataset, DSC between simulated and visually observed ablation zones were 0.99 and [0.99, 0.94, 0.95], respectively. High power microwave exposure, P > 40 W (n=4) was associated with extensive water vaporization in proximity to the applicator, which corrupted MRT data in these regions.

Conclusion: We have developed a system for 2.45 GHz MWA integrated with MRT at 3T, and applied the system experimental validation of MWA computational models.

WED 36

MRI-GUIDED FOCUSED ULTRASOUND ROBOTIC SYSTEM FOR EXPERIMENTS WITH MICE.

Marinos Giannakou, Christakis Damianou

Cyprus university of technology, limassol, Cyprus

Abstract

Introduction: An MRI-guided focused ultrasound (MRgFUS) system was developed that can be used for mice.

Materials and methods: The robotic system includes two linear axes. The motion of the robotic system is controlled using MR compatible encoders.

Results: The system was tested successfully in agar/silica/evaporated milk phantom for various tasks such as MR thermometry, and functionality. The ultrasonic absorption of the phantom was controlled to 0.4 dB/cm-MHz.

Conclusions: The system although simple is very effective in ablating mice. The system was tested for MR compatibility successfully in a 9.4 T MRI.

WED 37

USING MICROWAVE THERMAL ABLATION TO PRECISELY TARGET THE ADRENAL CORTEX, TAKING A MINIMALLY ABLATIVE, CORTICAL-SPARING APPROACH

Padraig Donlon1, Hojjatollah Fallahi2, Warren Beard2, Atif Shazad1, Lindsay Heflin2, Whitney Cox2, Brooke Bloomberg2, James Lillich2, Chanran Ganta2, Gerard O'Sullivan3, Giuseppi Ruvio1, Paula O'Shea3, Martin O'Halloran1, Punit Prakash2, Michael Dennedy1

1National University of Ireland Galway, Galway, Galway, Ireland. 2Kansas State University, Manhattan, Kansas, USA. 3Galway University Hospital, Galway, Galway, Ireland

Abstract

Introduction: Functioning adrenocortical tumours (FAT) are common (adult prevalence of 2-5%), causing hypercortisolism and primary aldosteronism. Mainstay therapy, adrenalectomy resects normal and abnormal tissue. Microwave thermal ablation (MTA) presents a plausible minimally-invasive therapeutic, to specifically target and ablate FAT, while preserving adjacent normal adrenal cortex.

Objective: To evaluate MTA as a precision ablation methodology for adrenocortical tissue, simultaneously evaluating effects on adjacent non-targeted tissue.

Methodology: A directional MTA applicator was used in vivo on adrenals of 8 male pigs: (i)sham (n=2); (ii)40W for 60s seconds (n=3); (iii)70W for 60 seconds (n=3). Blood was drawn intraprocedurally and at 48h for measurement of metanephrines, cortisol, ACTH and aldosterone (LCMS). Animal sacrifice/tissue harvest occurred at 48h. Ablation-zone volume was assessed by basic histology (H&E). Tissue damage was assessed using HSP-70 and HMGB1 (IHC). Tissue function was assessed by expression of CYP17 and CYP11B1 (IHC). Differential tissue immunology was assessed using CD3 and CD68 (IHC).

Results: A specific ablation zone (0.67+/-0.37cm3) was achieved, morphologicaly demonstrating coagulative necrosis. Non-targeted adrenocortical tissue was preserved functionally, shown by the presence of CYP11B1 and CYP17. Tissue integrity was retained in non-targeted tissue, demonstrated by the presence of HSP70 and HMGB1. The damaged and undamaged tissues were delineated by an immune cell infiltrate. Medullary damage occured in all ablated adrenals, consistent with transient intra-procedural hypertension.

Conclusion: For the first time, MTA is shown as a safe, effective method to precisely ablate adrenal cortex of volumes equivalent to FAT, while preserving adjacent non-targeted cortex. Intraprocedural alpha blockade is necessary to pre-treat possible intra-procedural medullary catecholamine surge. This presents exciting short-term translational potential for the therapy of FAT

Acknowledgements: This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 75308). Thanks to Dr Celso Gomez Sanchez for kindly gifting the steroidogenic antibodies for this study.

WED 38

CONVECTION ENHANCED DELIVERY OF THERAPEUTICS TO THE CNS: CHALLENGES AND OPPORTUNITIES

Michael Vogelbaum

Moffitt Cancer Center, Tampa, FL, USA

Abstract

Few systemically-administered therapeutic drugs have demonstrated meaningful clinical efficacy for the treatment of brain tumors, and a growing body of evidence indicates that one of the key causes of therapeutic resistance is the inability to generate physiologically relevant drug concentrations within tumor tissue or tumor infiltrated brain tissue.Other novel biological agents, including antibodies and viral vectors, also cannot reach therapeutic concentrations within the CNS. Barriers to delivery include the blood-brain-barrier (BBB), tissue pressure within bulk tumor, and biological resistance mechanisms present in malignant brain tumors. There have been a variety of alternative approaches to drug delivery to the CNS, including the application of brachytherapy seeds or drug eluting biodegradable wafers, and direct injection of therapeutics into brain tissue. While some of these approaches have demonstrated limited efficacy, they all have failed to provide sufficient exposure to areas of disease which often extends centimeters away from the bulk tumor.Convection enhanced delivery (CED) involves the implantation of one or several catheters followed by the slow, continuous infusion of a therapeutic for hours to days at rates on the order of microliters per minute. These low infusion rates, when applied over time, have been shown to be capable of producing effective delivery of multiple classes of therapeutic agents. Early clinical investigations involving CED were impaired by the lack of technology that could produce reflux-free infusion, and by study designs that did not permit the visualization of delivery. More recent studies have focused on the use of novel CED catheter designs and imaging of delivery by way of co-administration of radiographically visible tracers, and these studies have allowed investigators to more effectively relate the clinical and radiographic results to the pattern of therapeutic delivery. Several phase I and II clinical trials incorporating CED have recently completed enrollment and additional trials are planned. Opportunities for the development of novel agents delivered to the brain via CED will be discussed.

WED 39

THE DRUG DELIVERY CONTROVERSY

Timo ten Hagen

Erasmus MC, Rotterdam, Netherlands

Abstract

Chemotherapy of solid tumors is typically accompanied by side-effects, which are actually the first thing patients think of and, next to failure of the therapy, the most feared. Therefor it is important to focus research on treatment of cancer not only on new targets and new compounds, but also on improvement of delivery of drugs. This is not trivial as systemically administered chemotherapeutics arrive only in low levels in the tumor, which is caused by a number in intrinsic tumor characteristics and (often) also by properties of the therapeutics used. It can be argued that a straight forward approach is to change those properties which are working against delivery, while maintaining these which are favorable and were the initial reasons for the drug to be registered. Secondly, also the tumor can be changed, to allow more drug to reach the final destination.

To improve drug delivery we developed so-called smart drug delivery systems (SDDS), lipid-based nano-particles which change pharmacokinetics, biodistribution and intratumoral processing of the chemotherapeutic profoundly. Also, we use external or injectable factors which can change the tumor pathophysiology to improve drug delivery. We use in vitro and in vivo technologies to study the behavior of SDDS, their effect on tumors, and manipulation of the tumor pathophysiology with local hyperthermia by high resolution intravital microscopy in mice.

Here we show that SDDS can be constructed which respond to clinically applicable temperature changes (from 37 to 41°C) by rapidly releasing their content. These temperature-sensitive SDDS prolong circulation time of the mostly used chemotherapeutic doxorubicin (DXR), allow tumor specific release, increase local drug levels and augment tumor response. Importantly, we observed that not all doxorubicin delivered was retained in the tumor. We hypothesized that temperature-triggered drug release from SDDS saturated the tumor site, where cells cannot absorb the drug fast enough. We concluded that selection of doxorubicin may not be the right one in this setting, which is actually a loco-regional delivery method. Therefor we selected idarubicin (IDA), from the same family as DXR, but with a faster uptake by cells and a better intracellular retention. This drug, shows superior activity when delivery by SDDS.

Temperature-sensitive SDDS provide exceptional possibilities to improve chemotherapy. However, selection of chemotherapeutics needs reevaluation as the field shifts completely when SDDS are used. Here we show that selection of drugs should not be based on tumor type but on method of delivery.

WED 40

EFFECT OF DIFFERENT HYPERTHERMIA METHODS ON DRUG DELIVERY WITH THERMOSENSITIVE LIPOSOMES

Krishna Kumar Ramajayam1, Anjan Motamarry1, John Yost2, Michael Yost2, Dieter Haemmerich1

1Department of Pediatrics, Medical University of South Carolina , Charleston, SC, USA. 2Department of Surgery, Medical University of South Carolina, , Charleston, SC, USA

Abstract

Background: Thermosensitive liposomes (TSLs) are nanoparticles that encapsulate a drug and release it when exposed to hyperthermic temperatures (>40 °C), thus, achieving a targeted drug delivery. The goal of this study was to quantify and explain the impact of different hyperthermia methods on tumor drug uptake with TSL encapsulated doxorubicin (TSL-Dox).

Methods: We developed a 3-D coupled computer model that simulated both tissue heating and drug delivery. The drug delivery model simulated intravascular release from TSL-Dox, drug extravasation into tissue interstitium, and cellular uptake. A mouse hind limb was scanned by a 3-D scanner and the resulting geometry was imported into finite element modeling software. Three heating devices were simulated considering parameters used in prior in vivo studies: (1) water bath (42°C temperature), (2) thermistor probe (45 °C temperature), and (3) infrared (IR) laser (43 °C maximum tissue temperature). We simulated an infusion of TSL-Dox at a dose of 5 mg/kg over 30 s. 15 min post infusion, hyperthermia was applied for 15 min, followed by 10 min of cooling. We report the tumor temperature at the end of hyperthermia, TSL plasma half-life, and tumor drug concentration 10 min after hyperthermia conclusion.

Results: Water bath hyperthermia achieved uniform heating of the hind limb and tumor with an average tumor temperature of 40.4°C (range 40.0-40.9°C). The thermistor produced highly localized heating but did not achieve adequate release temperatures throughout the tumor (average 38.8°C, range 37.6-45.0°C). The IR laser produced localized heating with adequate tumor temperatures (average 41.1 °C, range 39.9-41.6 °C). The TSL Dox plasma half-life was 15.3, 19.0 and 16.6 min for water bath hyperthermia, thermistor and IR laser, respectively. Tumor drug concentrations for water bath, thermistor probe, and IR laser were: 3.8 μg/g (range 3.1-4.2 μg/g), 9.19 μg/g (range 5.7-14.6 μg/g), and 7.6 μg/g (range 6.8-8.4 μg/g). The large-volumetric heating via water bath resulted in rapid depletion of encapsulated doxorubicin in the systemic circulation, which explains the limited tumor drug uptake. The thermistor caused highest maximum tumor drug concentration due to smallest heating volume, but likely underdosed some tumor regions due to inadequate temperatures. The laser device exposed the whole tumor to adequate temperatures while limiting hyperthermia outside the target volume.

Conclusions: For optimal TSL-based drug delivery, localized hyperthermia is important to avoid rapid depletion of available encapsulated drug in systemic plasma as observed in the commonly used water bath method.

Keywords: hyperthermia, computer model, thermosensitive liposomes, drug delivery

WED 41

THERAPEUTIC EFFICACY OF THERMOSENSITIVE LIPOSOMAL DOXORUBICIN AND SHORT DURATION FOCUSED ULTRASOUND HYPERTHERMIA IN RABBIT VX2 TUMORS

Marc Santos1,2, Sheng-Kai Wu1,2, Maximilian Regenold1, Jessica Steigenberger1, Lucy Wang1, Christine Allen1, David Goertz1,2, Kullervo Hynynen1,2

1University of Toronto, Toronto, ON, Canada. 2Sunnybrook Research Institute, Toronto, ON, Canada

Abstract

Introduction: There is an urgent clinical need to improve the delivery of chemotherapy to solid tumors while minimizing harmful side effects for the patient. One promising strategy is to combine MRI-guided focused ultrasound (MRgFUS) hyperthermia with thermosensitive liposomal (TSL) drug formulations to achieve localized release of chemotherapy at the tumor site. To date the approach has been to maintain hyperthermic conditions in target regions for periods on the order of tens of minutes. However, in many clinical circumstances this is impractical to achieve for realistic tumor volumes due to issues of respiratory motion, bone shielding and large blood vessel cooling. It has previously been shown that applying the temperature elevation using FUS in short durations can mitigate the impact of blood vessel cooling and can be applied during a breath hold to overcome some of the limitations associated with MRgFUS hyperthermia for long heating durations. It remains an open question whether short duration MRgFUS hyperthermia can release enough drug from TSL chemotherapy to have a therapeutic effect. In this work we investigated short duration MRgFUS hyperthermia with TSL-Doxorubicin on its ability to treat rabbit Vx2 tumors.

Methods: Vx2 tumors were initiated in New Zealand white rabbit thighs and grown for 12 days whereupon experiments commenced. TSL-Doxorubicin was manufactured in-house and was administered at a dose of 1.67mg/kg of doxorubicin. Rabbits were assigned into 1 of 3 treatment groups: MRgFUS alone, TSL-Doxorubicin alone or the combination of MRgFUS+TSL-Doxorubicin. Sonications were conducted such that successive discrete 4mm diameter regions-of-interest (ROI) were heated that covered the entire tumor. Each ROI was sonicated for 30s to a temperature of 42°C for a total of 10 times. Tumor volumes were measured with contrast-enhanced T1w MRI scans on a weekly basis following treatment to evaluate treatment efficacy.

Results: At 14 days following treatment, tumor volumes in the group receiving MRgFUS+TSL-Doxorubicin (n=4) were reduced by 36-fold compared to the group receiving MRgFUS alone (n=1) and 17-fold compared to the group receiving TSL-Doxorubicin alone (n=3). Data collection is still underway.

Conclusion: We have provided the first in vivo demonstration of the therapeutic effect of short duration MRgFUS hyperthermia combined with TSL-Dox. The promising results from this study suggest that the strategy of applying MRgFUS hyperthermia in short durations can allow MRgFUS hyperthermia to be used to treat a more broad spectrum of tumor indications, specifically ones that are not amenable to long heating durations.

WED 42

REAL-TIME VISUALIZATION AND QUANTIFICATION OF DOXORUBICIN DELIVERED BY THERMOSENSITIVE LIPOSOMES

Anjan Motamarry1, Ayele Negussie2, Christian Rossman1, James Small1, Marissa A Wolfe1, Bradford Wood2, Dieter Haemmerich1

1Medical University of South Carolina, Chalreston, South Carolina, USA. 2National Institutes of Health, Bethesda, Maryland, USA

Abstract

Background: Thermosensitive liposomes encapsulating chemotherapy agent doxorubicin (TSL-Dox) are a drug delivery system that rapidly releases the contained drug in response to hyperthermia (>40ºC). Combined with localized heating, TSL-Dox allow highly localized delivery (~10-30x local dose compared to unencapsulated Dox). There are currently no methods that allow monitoring and prediction of tumor drug uptake in real-time, during hyperthermia. The goals of this study were: (1) Demonstrate ability to monitor drug delivery in real-time, during heating, via in vivo fluorescence imaging; (2) Quantify the ability of fluorescence intensity to predict tumor drug uptake; (3) Demonstrate the impact of hyperthermia duration on tumor drug uptake.

Methods: Nude mice carrying subcutaneous tumors (Lewis lung carcinoma) were anesthetized and injected with TSL-Dox at a dose of 5mg/kg. Localized hyperthermia was induced by heating tumors for either 0, 15, 30 or 60 min by a custom-designed hyperthermia probe (~2.5 mm diameter), heated to 50 °C, and placed on the skin above the tumors. In vivo fluorescence imaging (excitation 485 nm, emission 610 nm) was performed before, during (every 5 min), and for 6 min after hyperthermia. After imaging, tumors were extracted and drug uptake quantified by high-performance liquid chromatography (HPLC). Serum samples were obtained before and after the hyperthermia to quantify plasma concentration and determine pharmacokinetics.

Results: Local drug uptake could be visualized in real-time during hyperthermia, and fluorescence intensity correlated with amount of drug delivered to the tumor quantified by HPLC. Fluorescence increased by 4.6, 9.3 and 13.2 fold compared to unheated control tumors when hyperthermia was applied for 15, 30 or 60 min. Tumor drug concentration increased by 1.9, 2.9 and 5.2 compared to unheated control tumors when hyperthermia was applied for 15, 30 or 60 min. There was strong correlation ($R^2 = 0.67$) between the fluorescent intensity of the target tumor area and the drug delivered to tumors.

Conclusions: In vivo fluorescence imaging allows real-time monitoring of local drug delivery and is predictive of delivered tumor dose. Modulating the duration of hyperthermia allows control of locally delivered dose. Such a tool may provide a real-time window that facilitates optimization of drug-device combination therapies involving heat and TSL-Dox.

WED 43

THE EFFECT OF THERMOSENSITIVE LIPOSOMAL DOXORUBICIN DOSE ON LOCALIZED DOXORUBICIN DEPOSITION AND THERAPEUTIC INDEX IN VX2 TUMORS USING MR-HIFU MILD HYPERTHERMIA

Bingbing Cheng1, Chenchen Bing1, Robert Staruch1,2, Yu Hong1, Debra Szczepanski1, Noelle Williams1, Theodore Laetsch1,3, Rajiv Chopra1

1UT Southwestern Medical Center, Dallas, TX, USA. 2Philips Research, Cambridge, MA, USA. 3Children's Health, Dallas, TX, USA

Abstract

Introduction: Doxorubicin (DOX) is effective against many cancers, but its clinical use has been significantly limited by cardiotoxicity. Localized DOX delivery from thermosensitive liposomes (TSLs) using MR-HIFU mild hyperthermia (HT) might improve local control in solid tumors without increasing heart toxicity. Previously we have demonstrated that longer duration of heating can increase the DOX deposition from TSL-DOX in a target tumor without an increase in systemic exposure. In this study we investigate the effect of TSL-DOX dose on the relative deposition of DOX in heated rabbit Vx2 tumors compared to unheated tumors, heart, liver, kidney, muscle, spleen, and lung.

Methods: Rabbits bearing bilateral Vx2 tumors were treated with HT (42°C, 40 min) to one tumor. TSL-DOX (Celsion) was infused during HT over 5 min with three different doses 0.1 (n=11), 0.5 (n=13), and 2.5 (n=8) mg/kg. HT was delivered using a prototype software on a clinical MR-HIFU system (Sonalleve V2 and Ingenia 3T, Philips). Tissue samples were harvested 3 hours after drug infusion for DOX quantification using liquid chromatography-mass spectrometry. In vivo biodistribution of DOX concentration was compared. Therapeutic ratio, defined as the ratio between the DOX amount inside tumor and heart was calculated and compared among different groups. Student t-test with Holm-sidak correction was performed for the statistical analysis.

Results : MR-HIFU achieved stable and uniform HT of 10 mm diameter regions in rabbit tumors with mean, T90, and T10 of 42.0, 41.1, and 42.7 °C. The average time of temperature above 40 °C for 0.1, 0.5, and 2.5 mg/kg groups were 40.2±2.6, 40.4±2.6 and 39.9±2.3 min. DOX concentrations in all tested organs showed a significant dose-dependent deposition among 0.1, 0.5 and 2.5 mg/kg groups: heated tumor (2.1 vs10.8 vs 24.6 μg/g), unheated tumor (0.4 vs 1.8 vs 5.0 μg/g), heart (0.3 vs 1.6 vs 6.1 μg/g), liver (0.5 vs 1.7 vs 5.0 μg/g), kidney (1.1 vs 4.9 vs 32.8 μg/g), muscle (0.04 vs 0.2 vs 3.8 μg/g), spleen (1.3 vs 5.6 vs 28.9 μg/g), and lung (0.6 vs 2.9, and 10.4 μg/g). While the mean therapeutic ratio of 0.1 and 0.5 mg/kg groups (6.6 and 7.0) are higher than that of 2.5 mg/kg (4.1), no significant difference was found.

Conclusion: Our results confirm that there are no significant differences in therapeutic index among the tested doses in HT-mediated doxorubicin delivery from TSLs.

WED 44

DEVELOPMENT OF A THERMOSENSITIVE LIPOSOME FORMULATION OF THE ANTI-CANCER DRUG VINORELBINE: PARAMETERS THAT INFLUENCE DRUG LOADING AND RELEASE

Maximilian L. Regenold1, Jessica K. Steigenberger2, Heiko Heerklotz2, Christine Allen1

1University of Toronto, Toronto , Ontario, Canada. 2Albert-Ludwigs-University Freiburg, Freiburg, Baden-Württemberg, Germany

Abstract

Introduction: Studies have demonstrated the advantages associated with use of a thermosensitive liposome formulation of doxorubicin, in combination with hyperthermia, for treatment of localized cancer. Many other drugs may benefit from this same targeted and localized delivery approach as it can result in a significant improvement in therapeutic index. Our lab has developed a thermosensitive liposome formulation of the hydrophilic drug cisplatin. We are now interested in developing thermosensitive liposome formulations of vinca alkaloids, in particular vinorelbine (VRL). The physico-chemical properties of VRL differ significantly from that of doxorubicin and cisplatin, including the drug's lipophilicity (logPVRL>logPDOX>logPCDDP), pKa, molecular weight and amenability to loading via active gradient techniques. In this study, liposomes prepared with a lipid composition equivalent to that of ThermoDox, were used to evaluate the impact of formulation parameters on the loading and release of VRL from thermosensitive liposomes.

Methods: A series of systematic studies examined the impact of the following parameters on the drug loading and release rate of thermosensitive liposomes: external loading pH, loading temperature, initial drug-to-lipid ratio and concentration of intraliposomal buffer. Drug levels of VRL were measured using HPLC with MS detection. Differential scanning calorimetry (DSC) was used to assess the effect of drug entrapment on the gel to liquid-crystalline phase transition temperature (Tm) of the liposomes, as an indirect indicator of heat-triggered release. Temperature dependent drug release experiments, in pre-heated phosphate-buffered saline solution, were conducted to confirm the trends found via DSC.

Results: All formulation parameters were found to have a significant impact on drug loading with the initial drug-to-lipid ratio and loading temperature having the most pronounced effects. VRL was stably encapsulated into thermosensitive liposomes, at a high loading efficiency under the following conditions: external loading pH of 6.5, loading temperature of 35°C, initial drug-to-lipid ratio of 250g VRL/mol phospholipid, and internal buffer concentration of 0.65M. A sharp Tm was found for the optimal liposome formulation at 40.46°C with burst release of VRL observed within a few seconds of heating above 39°C.

Conclusion: The current studies provide insight into the many formulation parameters that must be considered in the successful design of a thermosensitive liposome formulation. Future studies will examine in vitro release of VRL from thermosensitive liposomes in the presence of serum protein as well as assessment of pharmacokinetics of VRL following intravenous administration in a mouse xenograft model with localized heating at the tumor site.

THUR 1

THE ROLE OF HYPERTHERMIA IN CHILD & ADOLESCENT CANCER

Ruediger Wessalowski

Heinrich-Heine-University, Medical Faculty, Düsseldorf, Germany

Abstract

Survival rates for children with malignant tumors have dramatically improved with advent of effective neoadjuvant chemotherapy protocols. However, tumor cell resistance (MDR) to anticancer drugs is the primary reason for treatment failure in childhood cancer. Resistance can exist at the onset of treatment or can become clinically apparent under selective pressure of drug exposure. In these special situations a selected number of researchers suggest hyperthermia - as a valuable treatment option - to improve conventional cancer therapy. Beside these hyperthermia effects against MDR, we know that temperatures in the range of 42 – 43°C for 60 minutes produce programmed cell death on tumor cells. In addition, hyperthermia > 40°C increases the effects of radiotherapy and/or chemotherapy by inhibition of DNA-repair enzymes, increment of drug uptake as well as modification of tumor blood perfusion and immunological reactions (environmental stress). In the field of pediatric oncology body weights can range from under 5 kg to over 60 kg. As a consequence, technical preconditions must be created to accommodate the wide range of anatomical dimensions. Beside the special body dimensions in children, their stress tolerance for hyperthermia treatment is considerably low, especially in smaller children and toddlers. Recently, quality assurance guidelines for clinical application of hyperthermia and temperature monitoring with respect to the pediatric patient population have been designed reflecting the experience and expertise from the early days of hyperthermia. In addition, numerous improvements in technical equipment have been made available and more importantly advanced hyperthermia treatment planning has been introduced.

In this talk, I will highlight hyperthermia concepts from the perspective of a pediatric oncologist. Among the possibilities are HIPEC, whole body hyperthermia, isolated limb perfusion, ultrasound, and microwave heating, which were reported to be useful as an additional treatment in pediatric patients with malignant tumors. Since oncological treatment concepts for children always aim at long-term cure and the possibility of a good quality of life, a complex picture of the tumor biology and the treatment strategies must be taken into account, depending on the child's age. Thus, in the future it will be necessary to change the indication for the use of hyperthermia procedures. Not the patient at the end of all therapeutic efforts and in the advanced stage, but the tumor with difficult characteristics - not responding to the appropriate first-line therapy - should represent the indication for additional hyperthermia strategies.

THUR 2

NON-INVASIVE INTRATUMORAL THERMAL DOSE DETERMINATION DURING MAGNETIC NANOPARTICLE HYPERTHERMIA

Gustavo Capistrano, Clever Gomes, Nicholas Zufelato, Elisangela Silveira-Lacerda, Andris Bakuzis

Federal University of Goias, Goiania, Goias, Brazil

Abstract

Non-invasive clinical thermal dose determination is traditionally obtained by the analysis of magnetic resonance data during the thermal medicine therapeutic procedure (RF ablation, HIFU, photothermal therapy, among others). This technique, however, has limited application on magnetic nanoparticle hyperthermia (MNH), since the magnetic moment of the nanoparticles is blocked inside the MRI permanent magnet, and therefore is not able to generate heat. To solve this problem we started developing a near-infrared magnetic nanocarrier that is able to be intratumorally localized by Fluorescence Molecular Tomography. The animal body reconstruction is obtained using photogrammetry, while the 3D tumor shape is determined using ultrasound. Those informations are then included in COMSOL Multiphysics and used as an input for computer simulations. Comparison between the surface temperature of the tumor monitored experimentally by thermal camera and the computer simulations, taking into account the perfusion temperature dependence and a pixel dependent heat generation function that accounts for the non-uniform particle distribution, were performed. The criteria for a good simulation were established when higher than 50% of the area under analysis (25 pixels X 30 pixels – 16mmX19mm), corresponding to 750 non-invasive thermometers, was in accordance within the temperature error associated to the experimental setup. Four animals that passed through 30-minute magnetic nanoparticle hyperthermia therapy, after intratumoral injection of the multifunctional nanocarrier, were analysed. One was sacrificed after the MNH for histopathological analysis, and served as a control. The tumor was cut in 110 slices and the total necrotic area of the treated tumor was found. Computer simulations predictions were then used to determine the critical parameter for irreversible lesion in the Ehrlich murine tumor model through the comparison with histopathological data. The other three animals were monitored up to 600 days, where one showed tumor recurrence and the other two complete regression, that correspond to a 67% survival rate. The method is than successfully applied to explain the pre-clinical observations, i.e. from the simulations we found that animals that showed complete regression had higher than 96% of irreversible lesion in the tumor, while for the animal that showed cancer recurrence we found a much lower value, 53%. The results suggest that it is possible to determine non-invasively the intratumoral thermal dose through the surface temperature monitoring during MNH if the heat centers localisation and the three-dimension tumor shape are well known.

THUR 3

PRECLINICAL DEMONSTRATION OF THE APPLICATION OF MAGNETIC RESONANCE THERMAL IMAGING WITH THE VECTRX™ MULTI-APPLICATOR COIL INDUCTIVE HEATING SYSTEM IN SWINE

Pierre Floriano1, Charles Anderson1, Allison Payne2, Henrik Odeen2, Rock Hadley2, Dennis Parker2, Paul Stauffer3

1NeoTherma Oncology, Wichita, KS, USA. 2University of Utah, Salt Lake City, UT, USA. 3Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Background: Pancreatic cancer (PC) patients face dismal odds and little hope with current conventional therapies. A recent review (van der Horst, Int J Hyper 2017) showed that thermal treatment (TTx) could be effective in PC, but temperature was measured in the tumor in only 3 out of 14 clinical studies, using invasive temperature probes. Based on proprietary magnetic induction technology, the VectRx system can heat deep tissue and functions within an MRI to allow collection of MRI data for high resolution temperature measurements. Most MRTI protocols currently used clinically (with HIFU) are designed to accurately measure temperature during relatively short ablation periods (1-2 minutes) in regions not affected by significant motion. Conversely, TTx of abdominal targets require accurate monitoring of very small temperature increases over long time durations in the presence of respiratory, cardiac, and peristaltic motions. We evaluated the precision and accuracy of novel MRTI pulse sequences as compared to invasively placed fiberoptic probes (FP), in a correlation study where swine were subjected to thermal treatment in the range of 39.5°C-43°C.

Methods_ Four healthy Yucatan mini pigs were anesthetized for probe placement in multiple organ locations and within the pancreas. Animals were then placed within the VectRx treatment system on the couch of a 3T Siemens Prisma MRI scanner. Animals were subjected to targeted heating of the pancreas for ~60 minutes. Multiple regions of interest (ROIs) were defined in the pancreas and surrounding area, and 3D temperature maps from candidate MRTI pulse sequences were correlated to discrete FP measurements. Following treatments, the pigs were euthanized, necropsied and histopathologically examined.

Results: Bland Altman plots were constructed to demonstrate agreement and bias between multiple MRTI sequences and invasively placed FP. The pancreas target temperature was safely maintained for the desired ~60 min during treatments and MRTI precision and accuracy was shown to be maintained for the duration of the treatments.

Conclusions: Non-invasive monitoring of volumetric temperature throughout the treated region (pancreas and surrounding tissue) can be done in high resolution with MRTI in near real-time. This has great implications for future clinical use of the VectRx system not only for safety but also to ensure and characterize therapeutic thermal dose delivery in the targeted tumor region. These efforts pave the way for a VectRx Investigational Device Exemption (IDE) from the FDA and the initiation of a first-in-human feasibility study of the VectRx device in pancreatic cancer patients in 2019.

THUR 4

THERMAL IMAGING FOR MONITORING TUMOR RESPONSE OF DIFFUSING ALPHA-EMITTERS RADIATION THERAPY IN A MURINE MODEL OF BREAST CANCER

Merav Ben-David1, Michal Tepper1, Eleni Liapi2, Israel Gannot1,2

1Tel Aviv University, Tel Aviv, Israel. 2Johns Hopkins University, Baltimore, MD, USA

Abstract

Aim: To investigate whether thermal imaging may detect temperature changes and indirectly, tumor response, in a murine model of breast cancer treated with diffusing alpha-emitters radiation therapy (DART).

Methods: 10.5 weeks old female Balb/c mice were each injected with 5·105DA3 murine breast carcinoma cells (in a 150μL PBS solution) below their mammary glands. In the first experiment, three mice were thermally imaged on nine different occasions during the period between 13 and 46 days (days 13, 14, 18, 27, 33, 36, 39, 42, and 46 of the experiment) after tumor injection (Mouse 3 was imaged only eight times, starting from day 14). Treatment was initiated 33 days after the tumor cells were injected. In the second experiment, nine mice with single main tumors were thermally imaged on four different occasions during the period between 15 and 29 days (days 15, 18, 22, and 29 of the experiment) after the tumor injection. Treatment was initiated at day 15, 14 days after the tumor cells were injected. The images were captured using a ThermoVision A40 (FLIR©) thermal camera. This camera can detect thermal differences as low as 0.08 °C, with a spatial resolution of 1.3 mrad, and produces thermal images of 240´320 pixels. The thermal camera was placed 30 cm from the mouse to capture and record its temperature.

Results: On average, DART treated tumors increased in area by 78%, whereas tumors with inert wires increased in area by 165%. Temperature difference (either average or maximal) of the tumor as a function of the area seemed to decrease as tumor area increased. There was a statistically significant difference in the ratio of changes in average tumor temperature difference to changes in tumor area between treated and control mice.

Conclusion: Thermal imaging successfully detected differences in temperature related to tumor are and treatment with DART. Future studies are warranted looking into the validation of thermal imaging as a means of evaluating breast cancer response to therapy.

THUR 5

MR THERMOMETRY OF FAT BASED ON SYNTHESIZED TEMPERATURE PROPERTY OF METHYLENE AND METHYL SIGNALS

Kagayaki Kuroda1,2, Kenichiro Kurihara1, Yoritake Nakata2, Yutaka Imai3

1Course of Electrical and Electronic Engineering, Graduate School of Engineering, Tokai University, Hiratsuka, Kanagawa, Japan. 2Department of Human and Information Science, School of Information Science and Technology, Tokai University, Hiratsuka, Kanagawa, Japan. 3Department of Radiology, Tokai University School of Medicine, Isehara, Kanagawa, Japan

Abstract

Background: In thermal therapy of tumor in breast or abdominal organs, noninvasive MR thermometry for fat tissues is useful for protecting surrounding normal tissues and maximizing therapeutic effect. As fat tissue has no temperature dependence in proton resonance frequency, various techniques have been studied to use relaxation times like T1 and T2(1-3). For accurate temperature measurement, it is preferable to consider the difference of temperature dependence of T1 and T2 of different chemical shift components(4). In this study, use of synthesized temperature property of T2 of the two major proton components, methylene chain (-CH2-) and terminal methyl (-CH3), was examined.

Methods: Fat has nine chemical shift components according to the composition of the hydrogen sites. The primary components are stemmed from -CH2- and -CH3. Assuming that the contribution from the other small chemical shift components are negligible, a "synthesized" temperature calibration of the primary components was derived based on our previous MRS observation results at 9.4T using five different bovine fat samples in vitro(3). Temperature imaging experiments were performed on bovine fat samples in vitro under laser heating. Values of T2 of mixed -CH2- and -CH3 signals were obtained after using CHESS pulses to suppress water and other chemical shift components of fat. The imaging conditions were as follows; TR, 3000 ms; TE, 40.5, 121.5, 202.5, 283.5, 364.5, 445.5, 526.5, 607.5 ms; ETL, 8-13; FOV, 25 x 25 mm; matrix, 64×64. T2 value at each voxel was estimated by nonlinear LMS. The T2 value were then converted to temperature based on the calibration.

Results: The CHESS preparation suppressed the small proton signals of chemical shift components of fatty acid around water effectively leaving the -CH2- and CH3 signals. The synthesized temperature coefficient of T2 was 3.5ms/oC (2.3%/oC at 30 oC). The resultant temperature images clearly and quantitatively showed the laser induced temperature elevation in the sample.

Conclusion: Use of the synthesized temperature property of -CH2- and -CH3 of fatty acids with CHESS-prepared CPMG is effective to image fat tissue temperature. The ETL and TE settings should be optimized.

References: (1) Mikael P et. al. J Magn Reson Imaging, 2016;43:1171-1178.(2) Nick T et. al. Magn Reson Med, 2013;69:62-70. (3) Kuroda K et. al. Magn Reson Med Sci, 2011;10(3):177-183.(4) Kuroda K et al. Therm Med, 2012; 28(4):87-96.

THUR 6

FEASIBILITY OF CT THERMOMETRY OF LASER ABLATIONS IN EX-VIVO PORCINE LIVER

Megan Jacobsen1, Emily Thompson1,2, Samuel Fahrenholtz1, Christopher MacLellan1, Jason Stafford1, Erik Cressman1, Rick Layman1

1University of Texas MD Anderson Cancer Center, Houston, TX, USA. 2University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences, Houston, TX, USA

Abstract

Background: Real-time temperature imaging during laser ablation therapy is typically performed using magnetic resonance (MR) temperature imaging. However, these techniques are limited in cases where there may be magnetic susceptibility interfaces, such as the boundary between the lung and liver, or patients have implanted devices that are not MR compatible. Computed tomography (CT) can improve the temporal resolution of real-time temperature monitoring. Due to thermal expansion of tissue during heating, the CT number of tissue decreases during ablative therapies, and may be used as an alternative method for monitoring relative temperature change during interventional procedures.

Methods: Ex-vivo porcine liver was placed in a plastic container along with a bag of water to simulate a small body. A Visualase Neurosurgical Laser Ablation system (BioTex, Inc., Houston, TX) was used to perform the ablations with a wavelength of 980 nm. The laser fiber was positioned in the liver, and a fiber-optic temperature sensor (FISO Fiber-Optic Temperature System, #THR-NS-1165B, Quebec, Canada) was placed approximately 5 mm from the laser fiber. Two ablations were performed (5 W for 45 seconds and 4 W for 75 seconds), allowing the tissue to return to the baseline temperature between heating. CT scans were acquired every 10 seconds (Edge CT, Siemens Healthineers, Forchheim, Germany), and the CT number of tissue was monitored with a small rectangular region-of-interest (n = 36 voxels) at the estimated position of the temperature probe.

Results: Following the ablations, the CT number of tissue rose as the tissue temperature decreased. The laser caused optical interference with the temperature probe, limiting acquisition of temperature data to the cooling phase. The CT number varied linearly with temperature, with slopes of -0.52 and -0.37 following the first and second ablations, respectively. There was approximately a 10 HU difference at 25ºC between the end of the first and end of the second ablation, indicating potential hysteresis.

Conclusion: CT may be used to monitor temperature changes in ex-vivo liver tissue following laser ablation. Future work will characterize the heating curve and hysteresis curves of ablated tissue.

THUR 7

THE HEAT SHOCK RESPONSE: FROM THE DISCOVERY TO THE NEW DOGMA

Antonio De Maio

Division of Trauma, Critical Care, Burns and Acute Care Surgery, Department of Surgery, University of California San Diego, La Jolla, CA, USA. Department of Neurosciences, School of Medicine, University of California San Diego, La Jolla, CA, USA

Abstract

When cells are exposed to dramatic stresses, they respond by activating a robust response to preserve homeostasis, which was first observed over 50 years ago by a talented Italian scientist, Ferruccio Ritossa. Later, it was found that this response was mediated by the expression of heat shock proteins (hsp), which comprised a large family of polypeptides located in various subcellular compartments. The function of these proteins is to repair cellular damage and protect from further stresses. Subsequently, hsp were found to be present in normal physiological conditions playing a major role in the folding of newly synthesized polypeptides, an observation that lead to their referral as molecular chaperones. Hsp were identified in the middle of the molecular cloning bloom and their genes were rapidly sequenced indicating a large homology across species. The field of hsp biology has expanded dramatically and we currently know that they participate in many other cellular functions, including scaffolding protein complexes and signal transduction. More recently a new twist in the biology of hsp was observed as demonstrated by their ability to interact with lipid membranes in a not completely understood fashion. Moreover, hsp have also been found outside cells exported by an alternative mechanism to the ER-Golgi pathway. These extracellular hsp act as signaling molecules activating the immune system as a form of systemic stress response to avoid the propagation of the stress, which has been described as the "Stress Observation System (SOS)." The discovery of new functions for hsp is not over yet and it is very likely that new paradigms will be developed in the near future.

THUR 8

HSP72, CANCER STEM CELLS, RESISTANCE TO THERAPY AND METASTASIS

Stuart Calderwood1, Ben Lang1, Ayesha Murshid1, Jianlin Gong2

1Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston , MA, USA. 2Boston University, Boston , MA, USA

Abstract

We have examined the role of Hsp72 in mammary tumorigenesis by crossing mice that develop spontaneous mammary carcinoma (MMT) with mice knocked out for the hspa1a and hspa1b genes (depleted in Hsp72). In such KO mice, spontaneous tumors develop slowly and metastasis to lung is extremely rare. This loss of tumorigenesis was related to the depletion of cells expressing the Sca-1 and CD44 surface stem cell markers in mouse mammary tissue. Sca-1+CD44+ MMT cells were highly enriched in activated HSF1 and Hsp72 and loss of Hsp72 led to the depletion of breast cancer oncogene phospho-c-MET.

In addition, in cell cultures exposed to cytotoxic therapies (chemotherapy, radiotherapy), a large fraction of the population exhibited a similar cancer stem cell (CSC)-like phenotype, with increases in Sca1, CD44 and ALDH1. The cells additionally exhibited a powerful resistance to additional therapy and highly increased capacity to invade and metastasize to the lymph nodes and lungs of tumor bearing mice. The effects of radiation were mediated by secreted products, and conditioned medium from irradiated cells conferred stem-like properties and invasiveness on recipient cultures. These effects of radiation or conditioned medium could be entirely reversed by inhibitors of cyclooxygenase 2 (Cox2). Furthermore, we showed that the Cox2 product prostaglandin E2 (PGE2) was responsible for mediating these effects through its receptor EP4 and was reversed by EP4 antagonists. This appeared to be a common response and was observed in 4T1, MMT and MCF7 mammary cancer and MC38 colon carcinoma. Interestingly this property was lost in MMT / hsp70-/- cells – indicating a requirement for Hsp72 in therapy response, resistance and metastasis.

These experiments indicate an important role for Hsp72 in mammary cancer progression and treatment response and strongly suggest its targeting in therapy.

THUR 9

BRIDGING INNATE AND ADAPTIVE IMMUNE RESPONSES BY LARGE STRESS PROTEIN FOR CANCER IMMUNOTHERAPY

Xiang-Yang Wang1,2,3, Chunqing Guo1,2,3, Elizabeth A. Repasky4, John R. Subjeck5

1Department of Human & Molecular Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA. 2Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond, VA, USA. 3Institute of Molecular Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA. 4Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA. 5Department of Cellular Stress Biology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Abstract

While serving as an intracellular molecular chaperone to mitigate stressor-triggered proteotoxicity, large stress proteins (e.g., glucose-regulated protein 170 or Grp170) extracellular milieu can act as a delivery cargo to present antigens to the immune system and consequently generate an antigen-specific immune response. Our work reveals that, in addition to antigenic polypeptides, the Grp170 can interact with and amplify pathogen-associated 'danger' signals, e.g., microbial DNA, resulting in improved clearance of invading microbes. These dynamic interactions lead to improved innate and adaptive antitumor immunity when tumor antigen is present in this multi-component chaperone complex. Building on these findings, molecular engineering has been used to create a novel immunostimulating chimeric chaperone molecule, which is equipped with a superior capability to cross-present tumor antigens and concurrently to strengthen the functionality of antigen-presenting cells by providing crucial immune co-stimulation. Strategic use of this next-generation chaperoning-based immune modulator for cancer vaccination and its potential for targeting immunologically 'cold' cancers to normalize their response to immune checkpoint inhibitors will be highlighted. Additionally, a rational design of combinatorial immunotherapy and radiotherapy using this agent to promote immunogenic cancer cell death and 'abscopal' effect of radiation treatment will also be discussed.

THUR 10

STRESSED EXOSOMES ("SEXOSOMES"): STRESS BALLS OR CARE PACKAGES IN PASSAGING STRESS PHENOTYPES TO RECIPIENT CELLS?

Michael Graner, Xiaoli Yu, Anthony Fringuello, Jerry Yang

University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA

Abstract

Cancer cells undergo a number of stresses, many of them self-inflicted, but often do not appear to suffer the consequences of those stresses. In some cases, the stress responses may actually prove beneficial to the tumor cells, providing them with potent resilience to their less-than-hospitable environments. Consistent tumor stress responses include the Heat Shock Response and the Unfolded Protein Response (UPR), which combined encompass cytoplasmic, nuclear, and endoplasmic reticulum organellar activities in response to a wide variety of stressors. These stress-management systems may be incorporated by tumors into their stress portfolios to survive or even thrive amidst their environmental insults. We propose that exosomes from stressed cells (stressed exosomes, or "sexosomes") are able to induce stress response phenotypes in recipient, unstressed cells, thus enabling stress responses without having to experience the actual stress. Here we examine the impacts of heat shock and induction of the UPR on a meningioma cell line, a type of brain tumor that originates in the meningeal layers surrounding the brain and spinal cord. From transcriptome analyses we note that the stresses invoked drive significant changes in the tumor cells. Further, unstressed cells that receive "sexosomes" from the stressed cells prompt nearly identical pathway and network outcomes in the recipient cells as occur from the stresses themselves. Thus, exosomes may "distribute" stress throughout the tumor, potentially providing resistance phenotypes in cells that do not themselves undergo the stress. The implications for general tumor biology, and in particular, therapeutic resistance, are highlighted.

THUR 11

HYPERTHERMIA INDUCES PEROXIREDOXIN ANTIOXIDANT DEFENSES THROUGH TRANSCRIPTION FACTOR NRF2

Diana Averill-Bates, Marceline Tchouagué, Mélanie Grondin, Audrey Glory

Université du Québec à Montréal, Montréal, Québec, Canada

Abstract

Hyperthermia is a promising anticancer treatment used in combination with radiotherapy and/or chemotherapy. It uses heat (42-45°C) to kill cancer cells. Low doses of heat at milder temperatures (39-41°C) induce thermotolerance, an adaptive survival response that upregulates defense molecules to protect cells against subsequent exposure to toxic stress. There is still much to learn about cellular mechanisms of hyerthermia. This study aims to understand the role of reactive oxygen species (ROS), antioxidants and the antioxidant transcription factor Nrf2 in cellular stress responses to mild and lethal heat shock. Mild thermotolerance (40°C) and hyperthermia (42-43°C) caused increased expression of the antioxidants peroxiredoxin-3 (Prx2) and Prx2, and its hyperoxidized form Prx-SO3. Heat shock-induced increases in Prx3 and Prx-SO3 were inhibited by antioxidants (PEG-catalase, MnTBAP) and a Nrf2 shRNA. Glucose metabolism by the pentose phosphate pathway produces NADPH, which maintains the antioxidant glutathione in its reduced form, GSH. Heat shock increased GSH levels, expression of glucose transporter GLUT1, and enzymatic activity and expression of glucose 6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme in the pentose cycle. Heat-induced increases in GSH levels and G6PD expression were inhibited by antioxidants (PEG-catalase, MnTBAP) and a Nrf2 shRNA. These results suggest that heat shock-generated ROS were involved in induction of the cellular defense molecules Prxs, GSH and G6PD through Nrf2 activation. Our study sheds new light on the role of Nrf2 and antioxidants in cellular responses to heat shock at both mild and lethal températures.

THUR 12

DEVELOPMENT OF HEAT SHOCK PROTEIN INHIBITOR-CONTAINING THERMOSENSITIVE LIPOSOMES FOR COMBINATION THERAPY WITH THERMODOX AND HYPERTHERMIA

Michael Dunne1, Brittany Epp-Ducharme1, Alexandros Marios Sofias2, Maximilian Regenold1, Christine Allen1

1University of Toronto, Toronto, Canada. 2Utrecht University, Utrecht, Netherlands

Abstract

Introduction: ThermoDox® is the most advanced thermosensitive anticancer nanomedicine, however clinical dose is limited by the toxicity of doxorubicin. In clinical oncology, dose limiting toxicities are most commonly managed by combining chemotherapeutics. The most appropriate drug pair for ThermoDox would also leverage the intrinsic advantages of heat-activated drug delivery, such as increased intratumoral drug accumulation and increased cytotoxicity. This research aims to identify and formulate in a thermosensitive liposome, a drug that is synergistic with doxorubicin and enhanced by hyperthermia.

Methods: In vitro screening of several heat shock protein inhibitors in a panel of breast cancer cells assessed synergistic activity in combination with doxorubicin and hyperthermia-mediated enhancement of cytotoxicity. The most promising heat shock protein inhibitor, alvespimycin, was used to prepare thermosensitive liposomes using traditional high-pressure extrusion and pH gradient active loading. Thermosensitive doxorubicin liposomes equivalent to ThermoDox were prepared for comparison and used in all studies. Liposomes were characterized in terms of size and size distribution, zeta potential, bilayer transition temperature, and drug loading. Temperature-dependant drug release was measured for both drugs between 37-44°C in the presence of albumin with aliquots being sampled every 30sec for 5min. Pharmacokinetics and normal tissue biodistribution of both formulations were assessed in healthy SCID mice. Accumulation of both drugs was measured in MDA-MB-231 human breast cancer tumors implanted in the mammary fat pad of female SCID mice. Tumors were preheated to 42.5°C for 5min using an external laser-based heating apparatus and single-point fibre optic temperature sensor. Liposomes were administered intravenously and tumors were heated for 20 additional minutes prior to tumor resection and drug quantitation.

Results: Chou and Talalay combination indices <0.7 indicated strong synergy between doxorubicin and alvespimycin across a wide range of drug ratios. Hyperthermia reduced the IC50 of doxorubicin 1.8-fold and alvespimycin 4.6-fold. Thermosensitive liposomes with identical lipid compositions containing either doxorubicin or alvespimycin were successfully prepared with a diameter of 108 ± 6nm and a surface charge of -28 ± 4mV. Both drugs were effectively loaded at a 1:20 (wt:wt) drug:lipid ratio with encapsulation efficiencies $>98\%$ and drug concentrations >2.5mg/mL. Encapsulation of both drugs was stable at 37-38°C, while relatively slow release occurred at 39°C, and fast and efficient release was observed at higher temperatures.

Conclusion: Analogous thermosensitive liposome formulations of doxorubicin and alvespimycin have been prepared and characterized. The chemical and functional equivalence of these formulations allows controlled delivery of synergistic ratios of the drugs to solid tumors.

THUR 13

INTRAVASCULAR IMMUNE SUPPRESSION: OVERLOOKED CHECKPOINT FOR CANCER IMMUNOTHERAPY

Amy Ku, Michelle Appenheimer, Colin Powel, Minhyung Kim, Jason Muhitch, Joseph Skitzki, Scott Abrams, Sharon Evans

Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA

Abstract

Significant advances in onco-immunotherapeutics have changed the treatment landscape for cancers including difficult to treat breast carcinoma. Therapeutic success depends on activation of systemic T cell immunity within lymph nodes as well as cytolytic activity of T cells within the tumor microenvironment. While durable responses occur in a subset of breast cancer patients treated with adoptive T cell transfer therapy or inhibitors of immune checkpoints (e.g., PD-1/PD-L1 axis), the majority of patients are non-responsive to current immunotherapy. Recent hyperthermia studies provide insight into the mechanisms by which non-cancer cells contribute to resistance to cancer immunotherapy. In orthotopic murine models of breast cancer and other solid malignancies, we found that tumor-induced myeloid-derived suppressor cells (MDSC) inhibit systemic antitumor immunity by cleaving the extracellular domain of the L-selectin lymph node homing receptor on target T cells. Studies of systemic thermal therapy (STT) strongly suggest that L-selectin loss is an active biological process rather than a bystander effect stemming solely from high blood concentrations of MDSC. Specifically, L-selectin loss on target T cells is not detected when neutrophil counts in tumor-free mice are elevated following acute exposure of mice to STT. We further found that even modest L-selectin loss on T cells substantially reduces T cell homing and antigen-driven T cell priming and expansion within lymph nodes. Vascular stimulation by STT only partially overcomes defective CD8+ T cell homing in lymph nodes, confirming the importance of MDSC in regulating T cell access to intranodal antigen depots. Findings that MDSC are excluded from lymph nodes provides an explanation for why contributions of MDSC to systemic immune suppression have been largely overlooked in previous studies. Our data indicate that MDSC act remotely, i.e., outside the lymph node microenvironment, to suppress systemic T cell immunity. Investigation into the site of MDSC activity unexpectedly revealed that MDSC cause L-selectin loss on T cells via a contact-dependent mechanism operative within the fast-flowing blood. These findings demonstrate that T cell-based antitumor immunity is subverted by an unprecedented mechanism of intravascular immune suppression mediated by blood-borne MDSC. Thus, the blood compartment emerges as an important checkpoint for immune resistance in cancer. (Supported by the NYS Peter T. Rowley Breast CancerGrant, Roswell Park Alliance Foundation, Breast Cancer Coalition of Rochester, the Jennifer Lescot Tietgen Family Foundation, and the NCI).

THUR 14

PEG-COATED IRON OXIDE NANOPARTICLES FOR NANOWARMING

Jacqueline Pasek-Allen1, Zhe Gao1, Anna Rudie1, Rameshu Rallabandi2, Jon Rainier2, John Bischof1

1University of Minnesota, Minneapolis, MN, USA. 2University of Utah, Salt Lake City, UT, USA

Abstract

Background: The inability to preserve donor organs for more than a few hours significantly contributes to organ shortages, poor organ matching, and poor quality of life for transplant recipients. Using radiofrequency excited iron oxide nanoparticles (IONPs) dispersed in cryoprotectants (CPAs), we have successfully rewarmed vitrified biological samples. We used mesoporous silica coated IONPs (msIONPs) to improve colloidal stability in CPAs, but msIONP fabrication is both expensive and difficult to scale. A simpler, biocompatible polymer (i.e. polyethylene glycol PEG) coated IONP that can remain stable in CPAs is needed. To address this need, we designed a small-molecule linker (PLink) with phosphonate, which has a high affinity to iron oxide. This linker enables ligands to bind to IONPs, giving the IONPs crucial functionality.

Methods: We synthesized PLink by adding a phosphonate group to a carboxyl ended molecule, which then coupled to hydroxyl group on the ligand (herein, monomethylether PEG MW=500, 2000, 5000 Da). The phosphonate was deprotected after PEG attachment and bound to IONPs through ligand exchange. Commercially available hydrophobic EMG 1200 and hydrophilic EMG 308 IONPs (Ferrotec Inc.) were functionalized with increasing amount of PEG added to the reaction (0.02 – 0.9 mmol PEG/g Fe). The PLink IONPs were characterized by dynamic light scattering, thermal gravimetric analysis (TGA), and inductively coupled plasma optical emission spectroscopy. Colloidal stability was determined visually in CPA, VS55, at specific time points for 35 days at 20oC. Heating performance, (specific absorption rate (SAR)), of IONPs in water was measured using a 1 kW inductive heating system at 360 kHz and 20 kA/m.

Results: We determined ligand exchange success on hydrophobic EMG1200 from increased stability in water, hydrodynamic size, and TGA measurements. PLink EMG1200 SARs in water increased from 20 to 150 W/g with higher PEG coverage due to better colloidal stability. PEGylation had no negative affect on heating and colloidal stability of hydrophilic EMG 308s and the SARs were 300W/g Fe regardless of PEG coverage. Stability of PLink IONPs in VS55 CPA increased with increased PEG coverage, from minutes (uncoated) to over 24 hours with maximum coating (0.9 mmol PEG/g Fe).

Conclusion: This work shows that designing proper PEG coating (size and coverage amount) can produce colloidally stable IONPs in CPAs without affecting heating properties. The simplicity of this approach suggests that it can contribute to inexpensive and scalable manufacturing of a wide range of PEG coatings for commercially available IONPs for nanowarming and other biomedical applications.

THUR 15

DISTRIBUTION OF IRON OXIDE NANOPARTICLES IN HYPOTHERMIC PERFUSED TISSUES

Hattie Ring1, Zhe Gao1, Anirudh Sharma1, Charles Lee2, Kelvin Brockbank3, Elizabeth Greene3, Kristi Helke3, Zhen Chen3, Lia Campbell3, Bradley Weegman4, Monica Davis4, Michael Taylor4, Sebastian Giwa4, Gregory Fahy5, Brian Wowk5, Roberto Pagotan5, John Bischof1, Michael Garwood1

1University of Minnesota, Minneapolis, MN, USA. 2University of North Caroline - Charolette, Charolette, NC, USA. 3Tissue Testing Technologies LLC, North Charleston, SC, USA. 4Sylvatica Biotech, Inc, North Charleston, SC, USA. 521st Century Medicine, Fontana, CA, USA

Abstract

Background: Nanowarming is a recent innovation where iron oxide nanoparticles (IONPs) produce rapid and uniform heating of cryopreserved living tissues, thereby maintaining tissue viability. Quantitative IONP imaging methods are essential for optimization of parameters to produce the most effective perfusion methods within organ systems. Often quantitative imaging is only performed through measurement of transverse (T2) relaxation using conventional sequences such as spin echo (SE). When IONPs are present, the rapid T2 signal relaxation overwhelms signal detection of longitudinal relaxation (T1) methods. However, the use of newly emerging ultrashort T2 insensitive pulse sequences, such as swept imaging with Fourier transform (SWIFT), it is possible to acquire quantitative T1 maps of IONPs which correlate with the heat produced through magnetic fluid hyperthermia [1]. This work focuses on the benefits of MR imaging within an IONP perfused tissue, and to our knowledge, this is the first demonstration of quantitative iron imaging of tissue perfused ex vivo with IONPs.

Methods: Rat hindlimbs, rat livers, rabbit kidneys, and porcine ovaries were perfused with Euro-Collins solution, or a cryoprotective agent (VS55 or M22), with or without IONPs. Quantitative magnetic resonance images were acquired using SWIFT (T1) and SE (T2) on room temperature tissues at 9.4T. Tissues were histologically assessed using Prussian blue (iron) staining and CD31 (blood vessel) staining.

Results: With T1- and T2-weighted images, the localization of IONPs is observed in tissue perfused with IONPs. We were able to acquire quantitative images for complex tissues perfused with up to 36 mg Fe/mL which is far above previous demonstrations of upper limit detection in agarose (2 mg Fe/mL) [2]. However, the lowest T1 values within the tissue (~0.25 ms), are higher than those measured within agarose (0.05ms) [2], indicating a lower IONP concentration. Finally, The improved IONP uniform distribution through changes in perfusate medium (Euro-Collins, VS55, and M22) and IONP coating were assessed with MRI.

Conclusion: Using MRI, we assessed the distribution of IONPs throughout tissues varying in complexity. Furthermore, Prussian blue histological staining, the gold standard for iron distribution assessment was observed to be inadequate for a system wherein IONPs largely remain in the vasculature. Additional studies are necessary to better understand this system and validate the calibration between T1 measurements and SARv.

References:

1. Zhang, J., et al., Magnetic Resonance in Medicine, 2017. 78(2): p. 702-712.

2. Ring, H.L., et al., Magnetic Resonance in Medicine, 2017. 79(3): p. 1420-1428.

THUR 16

NOVEL INSIGHTS INTO THE POSSIBLE MECHANISM OF ACTION BY NANOPARTICLE MEDIATED TUMOR GROWTH DELAY IN A TRANSGENIC MOUSE MODEL OF BREAST CANCER

Preethi Korangath1, Lu Jin2, Chun-Ting Yang1, Todd Armstrong1, Elizabeth Jaffee1, Cordula Gruettner3, Saraswati Sukumar1, Robert Clarke2, Robert Ivkov1

1Johns Hopkins University, Baltimore, MD, USA. 2Georgetown University, Washington DC, Washington DC, USA. 3 Micromod Partikeltechnologie GmbH, Rostock, Germany

Abstract

Introduction: Nanoparticles possess unique properties that can be modified to enhance their effectiveness in science and medical applications. By virtue of their size, nanostructured materials may possess intrinsic immune adjuvant properties. In a previous study comparing uptake and retention of magnetic iron oxide nanoparticles containing a therapeutic human antibody in allograft tumors grown in 3 different strains of mice showed higher uptake and retention of nanoparticles by fully immunocompetent mouse tumors. Further studies revealed widespread changes in the immune population in the tumor microenvironment after 24hrs of systemic nanoparticle injection, with tumor growth suppression manifesting at longer times post injection. Here we evaluated the therapeutic effect of nanoparticle constructs in a spontaneous murine transgenic breast tumor model.

Methods: Human HER2 overexpressing transgenic mice (FVB/N, n=6-8/group) that develop spontaneous mammary tumors around 8-11 months were used. When tumors were detected, mice were treated with a single intravenous injection of either PBS, Bionized nano ferrite plain nanoparticles (BP), BP conjugated with Herceptin (BH) or free Herceptin (Her). Tumor growth was followed by measuring tumor volume twice weekly up to 31 days. On the 31st day, all animals were sacrificed to dissect tumors and fix in 10% formalin. Tissue slides were stained for T cell markers by immunohistochemistry. Tissues were also harvested to purify RNA for gene expression analysis by Nanostring for identifying differentially expressed genes. Allograft tumors transplanted in FVB/N mice were subjected to different treatments (n=5-6/group) on day 10 and sacrificed at different time points to collect tumors and to evaluate immune cell populations by flow cytometry.

Results: A significant delay in tumor growth was measured in animals treated with BP, BH or Her treated animals when compared to the PBS injected group. An increase in CD3+ and CD8+ T cell populations was detected in BH and Her treated tumors on the 31st day. Nanostring analysis showed significant changes in TH1 and TH2 activation pathways with altered T and B cell signaling. Flow cytometry analysis revealed a time dependent activation and infiltration of T cells into the tumor microenvironment.

Conclusion: Systemically delivered BNF nanoparticles alter the immune population in the tumor microenvironment that delays spontaneous tumor growth in transgenic mice. We also discovered a pseudo infection like response to systemically delivered nanoparticles. Our studies on the gene expression changes in the tumor microenvironment after nanoparticle treatment reveal novel insights into the mechanism of tumor growth inhibition by the nanoparticles.

THUR 17

HEXAGONAL-DISK MAGNETIC NANOPARTICLES EMPHASIZE THE SECONDARY ROLE OF BROWNIAN ROTATION TO HEATING AND ALLOW SWITCHING BETWEEN DOMAINS OF ACTUATION

David Serantes1, Akira Satoh2, Roy Chantrell3

1Universidade de Santiago de Compostela, Santiago de Compostela, Spain. 2Akita Prefecture University, Yuri-Honjo, Japan. 3University of York, York, United Kingdom

Abstract

Background/Introduction: Accurate understanding of the heat dissipated by magnetic nanoparticles under an applied AC receives extra complexity due to the fact that the particles may rotate in the embedding viscous biological environment. This has often led to interpretations of experimental data in terms of a competition between Néel and Brown rotations as heating mechanisms. This is based on the availability of a simple analytical approach based on the linear response theory [1], despite it being well known that it is the nonlinear magnetisation response which produces significant energy losses: the rotation just changes the amount of dissipation via Néel reversal [2]. The goal of this work is to help understanding the large difference in the heating of both contributions by disentangling the effects, by setting a highly favourable scenario for Brownian losses: large aspect-ratio disks with coherent magnetisation reversal, which enhance the viscous interaction with the environment.

Methods: To clearly distinguish among reversal contributions we have used a theoretical approach, combining Brownian dynamics to account for reorientation/displacement effects, and micromagnetic simulations to account for the inner magnetisation reversal mechanisms. The theoretical framework is matched with experimental samples of hexagonal-shape magnetic nanodisks providing the same features.

Results: Our results [3] show that the energy losses associated with viscous (Brownian) origin are only really relevant in the frequency range around 103 – 104 Hz, i.e. well below the relevant range for hyperthermia applications. In the hyperthermia regime (105 – 106 Hz), the Brownian contribution to heating is about 2 orders of magnitude smaller than the Néel one. This is to say, only when Néel losses do not appear the Brownian ones become relevant. Interestingly, we have observed that such scenario may lead, when both effects are well disentangled (as with the hexagonal-shape disks presented here) to efficient alternation between magneto-mechanical response and heating just by changing the amplitude of the AC field.

Conclusion: Our results clearly illustrate the secondary role of Brownian rotation as itself a heating mechanism in the usual magnetic nanoparticle hyperthermia regime. Importantly, we have observed how a clear disentangling between Néel and Brown reversal mechanisms provides an efficient alternation between heating and magneto-mechanical action within the same frequency range.

[1] R. E. Rosensweig, J. Magn. Magn. Mater. 252, 370 (2002).

[2] S. A. Shah et al., Phys. Rev. B 92, 094438 (2015).

[3] D. Serantes et al., Phys. Chem. Chem. Phys. 20, 30445 (2018).

THUR 18

ELICITING AN IMMUNOLOGICAL RESPONSE THROUGH THE USE OF MILD HYPERTHERMIA VIA A VASCULAR TARGETED IRON OXIDE NANOPARTICLE

Gil Covarrubias, Abdelrahman Rahmy, Georgia Loutrianakis, Pubudu Peiris, Efstathios Karathanasis

Case Western Reserve University, Cleveland, OH, USA

Abstract

Standard of care for inoperable malignancies consist of chemotherapy and radiation therapy. These treatments are often impressively effective in the short-term; however, as a tumor proliferates it gains resistance to such therapies over time. On the contrary, immunotherapies including immune checkpoint inhibitors and cancer vaccines have shown to exhibit prolonged anti-tumor response resulting in tumor suppression, and in some cases establishment of anti-tumor immunologic memory. In particular, the success of checkpoint inhibition therapies such as the combinatorial administration of anti-CTLA-4 and anti-PD-1 are limited by the availability of intertumoral cytotoxic lymphocytes and natural killer cells. Without the presence of such effector cells, tumor response rates are hindered often yielding a poor prognosis.

Mild hyperthermia, or a slight elevation of temperature from baseline, has shown to induce an immunological cascade stemming a recruitment of cytotoxic lymphocytes and natural killer cells to these heated regions. In the case of cancer, mild hyperthermia relinquishes inflammatory cytokines and induces a production of tumor neoantigens. These inflammatory markers signal professional antigen presenting cells (i.e. dendritic cells) to malignant lesions cascading into the development of adaptive immunity – or a recruitment of cytotoxic effector cells. In this context, nanoparticles have successfully generated tissue hyperthermia in vivo. When magnetic nanoparticles are subjected to an alternating magnetic field, they can act as heating foci.

By functionalizing the outer shell of a nanoparticle you can traffic it to the site of interest. This can yield precise tumor targeting and consequentially homogenous tissue heating. A combination treatment of mild hyperthermia using magnetic nanoparticles and a check point inhibitor blockade therapy effectively induce a more profound tumor response rate. We have developed a new class of nanoparticles termed nanochains; a multi-component structure comprised of 3-5 linearly linked iron oxide spheres. In addition to hyperthermia, the chain-like nanoparticle has a unique ability to effectively and precisely target the near-perivascular regions of tumors, resulting in superior deposition of the nanoparticle throughout the entire tumor volume. We tested this therapeutic strategy in a mouse model of metastatic triple-negative breast cancer. Upon the deployment of the nanochain induced hyperthermia in combination with the use of checkpoint inhibition therapy, the size of the tumor was significantly reduced. Most importantly, metastatic spread of the disease was mitigated.

THUR 19

ERYTHROCYTE MEMBRANE-COATED MAGNETO-FLUORESCENT NANOCARRIERS FOR THERMAL THERAPY AND HEAT-INDUCED IMMUNOLOGICAL RESPONSES

Ailton SOUSA-JUNIOR, Sebastiao MENDANHA, Marcus CARRIAO, Gustavo CAPISTRANO, Nicholas ZUFELATO, Francyelli MELLO, Wanessa PIRES, Clever GOMES, Elisangela SILVEIRA-LACERDA, Andris BAKUZIS

Federal University of Goias, Goiania, Goias, Brazil

Abstract

Cell membrane-based nanotechnology is a promising strategy for the treatment of several diseases, with applications spanning from drug delivery, photothermal therapy, detoxication to immune activation. Indeed, heat-triggered immunological responses might be a useful therapy for effective treatment of metastatic cancers. More specifically, photothermal therapy locally applied to a solid tumor could lead to the regression of distant non-treated tumors, a phenomenon known as abscopal effect. In this work, we developed a long circulation lifetime nanocarrier with both magnetothermal and photothermal capabilities, consisting of manganese ferrite nanoparticles coated with IR-780-labeled erythrocyte membranes (magneto-fluorescent nanoghosts, MFGs). We then studied their pharmacokinetics (PK), with particular focus on their tumor uptake (delivery efficiency) using a subcutaneous solid Ehrlich tumor model in Swiss immunocompetent mice. Blood and tumor amounts of MFGs were monitored over time by fluorescence molecular tomography (FMT), after intravenous (retro-orbital) administration in mice (n=4). A 3-compartment PK model was adopted, encompassing: (1) blood and highly-perfused organs (central compartment); (2) normal tissues and organs (peripheral compartment); and (3) tumor tissue (tumor compartment). Monolix, a well-known PK software suite, was used to fit this 3-compartment PK model simultaneously to the two experimental data sets: amounts of MFGs in blood and within the tumor over time. The so-derived PK model parameters (intercompartment exchange rates) were then used to obtain numerical solutions to the proposed PK model. Analytical solutions were also derived, showing excellent agreement with the numerical ones. We demonstrate how the delivery efficiency and the time of maximum tumor uptake can be predicted as a function of the model parameters. MFGs show relatively high tumor uptake, further confirmed by histopathology analysis. Initial pre-clinical results reveal that systemically administered MFGs can deliver temperatures above the hyperthermia range upon near-infrared (808 nm) laser irradiation. Additionally, abscopal effects were observed in mice (n=5) after photothermal treatment, with manganese ferrite nanoparticles injected intratumorally (subcutaneous solid Sarcoma 180) acting as photothermal conversion agents. Anti-tumor responses were consistently observed even after rechallenge for one of the assessed mice. Taken together, our results indicate that MFGs can accumulate adequately in solid Ehrlich tumors, and might be suitable both for systemic magnetothermal and/or photothermal treatment and to trigger long lasting anti-tumor heat-induced immunological responses.

THUR 20

ENHANCING HYPERTHERMIA THROUGH MAGNETIC NANOPARTICLE CLUSTERS

Roy Chantrell1, Ondrej Hovorka2, David Serantes3, Teresa Pellegrino4

1University of York, York, United Kingdom. 2University of Southampton, Southampton, United Kingdom. 3Universidade de Santiago de Compostela, Santiago de Compostela, Spain. 4Istituto Italiano di Tecnologia, Genova, Italy

Abstract

Background/Introduction: A big challenge in magnetic nanoparticle hyperthermia (MNH) is to enhance the heating efficiency of nanoparticles so that their dosage can be minimized. However, the intricate interdependence between the material properties of particles, embedding media and applied magnetic field parameters of clinical use results in poorly controlled heating response. For example, ample experimental and theoretical evidence suggests that particles tend to aggregate in the viscous cellular media and interparticle interactions have a strong effect on the heating performance. However, reconciling theory and experiments in most of these studies is challenging as it needs to merge well-controlled experimental conditions in vivo and in vitro with efficient modelling techniques to study interacting particle systems. Here, we report on our advances in this area through combination of novel synthesis protocol for the preparation of controlled magnetic particle clusters, and by well matched experiments and simulations, we establish the role of interparticle interactions in enhancing the hyperthermic heating efficiency [1].

Methods: Experiments: we report about the synthesis of 20 nm iron oxide nanocubes assembled into dimers, trimers, and higher ordered clusters; TEM imaging and magnetometry-based magnetic characterisation of these clusters combined with specific adsorption rate (SAR) measurements under variable physical conditions. Simulations: we applied a kinetic Monte Carlo technique which accounts for distributions of particle properties, thermal fluctuations, frequency dependence and interparticle interactions [2].

Results: The experiments show that assemblies of dimers and trimers exhibit enhanced SAR in comparison to isolated particles or larger centrosymmetric clusters. Kinetic Monte-Carlo modelling reveals that the enhanced SAR is not necessarily correlated with saturation magnetisation, as expected in case of isolated particles, but it is due to the dominant dipolar interactions resulting from the relative differences between the geometries of particle clusters. We demonstrate excellent agreement between our experiments and simulations, which also support the previous work [3].

Conclusion: Accurate control of interparticle interactions in dimers and trimers lead to enhanced hyperthermia performance in comparison to single particles or larger particle clusters. For these clusters, interactions play a dominant role and the value of saturation magnetic moment has a secondary effect on the heating performance.

[1] D. Niculaes et al., ACS Nano 2017, 11, 12121-12133.

[2] S. Ruta et al., Sci. Rep. 2015, 5, 9090.

[3] R. di Corato et al., ACS Nano 2012, 6, 3080−3091.

THUR 21

SCALABLE SILICA COATED IRON OXIDE NANOPARTICLES FOR NANOWARMING IN REGENERATIVE MEDICINE

Zhe Gao, Hattie Ring, Baterdene Namsrai, Anirudh Sharma, Erik Finger, Michael Garwood, Christy Haynes, John Bischof

University of Minnesota, Minneapolis, MN, USA

Abstract

Introduction: The ability of iron oxide nanoparticles (IONPs) to heat in an inductive RF field has led to numerous biomedical applications. Nanowarming, which exploits heat produced by IONPs after perfusion through a tissue, requires high concentrations of IONPs to achieve adequate heating. As this technology may allow the rewarming of banked vitrified organs, there is considerable interest in developing an affordable, scalable IONP for this purpose. We developed a silica coated iron oxide nanoparticle (sIONP) that is affordable (< $0.5/mg Fe) and scalable (> 1 g Fe/batch) and this presentation will be focused on the physical properties of sIONPs and their performance in nanowarming applications.

Methods: sIONPs were produced by coating EMG308 (Ferrotec) with silica and modified with PEG (9-12 units) and a trimethyl group. The effect of shell thickness (10 – 45 nm) on sIONP heating and magnetic properties were studied. The cytotoxicity and cellular interaction of sIONPs and EMG308 with human dermal fibroblast (HDF) was assessed via viability assay, TEM and ICP-OES. HDFs were then cooled and rewarmed with sIONPs in an RF field as a proof of principle for nanowarming. Finally, sIONPs and EMG308 were perfused into rat kidneys and then removed. The residual iron was studied by MRI and ICP-OES.

Results: The silica shell thickness did not affect the IONP heating ability, saturation magnetic moment or r1 relaxivity. The silica coating provided a barrier between the iron oxide cores thereby reducing the inter-particle interactions at high Fe concentrations (i.e. aggregation or dipole interactions) and maintaining a constant high heating (400 W/g Fe) as opposed to EMG308 which has more inter-particle interactions (- 12% SAR) at 15mg Fe/mL in water. Further, sIONPs showed minimal HDF cell association and no toxicity after 24-hour exposure. HDF viability remained high (85%) after vitrification and nanowarming. Perfusion loading and unloading of sIONPs in kidneys showed the majority of sIONPs could be removed after loading while EMG308 were stuck in the kidneys causing higher perfusion pressure and confirmed by ICP-OES and MRI.

Conclusion: This work shows that silica shell thickness did not affect heating and magnetic properties, sIONPs are biocompatibility with low cellular interaction. Proof of principle experiments show that sIONPs can be used to nanowarm cells, and load and unload the vasculature of organs. Future work will demonstrate physical and biological outcomes from nanowarming organs loaded with CPA and sIONPs.

THUR 22

A PRACTICAL WORKSHOP TO INCREASE NIH GRANT SUCCESS

Mark Dewhirst1, Jennifer Yu2, Elizabeth Repasky3

1Duke University, DURHAM, NC, USA. 2Cleveland Clinic, Cleveland, OH, USA. 3Roswell Park Cancer Institute, Buffalo, NY, USA

Abstract

In the current funding climate, competition for grants is fierce and success rates are fairly low (<15% for most grant types). Given the low success rate, how can one compete? Having a good idea is not enough to guarantee funding. A lot of applicants have good ideas. What is most important is using the grant application as a vehicle to provide a compelling argument for why your grant must be funded, amongst a large group of grants that also contain good ideas.

Despite the importance of learning how to communicate ideas clearly and concisely, students receive virtually no training on how to do this. In this workshop, we will focus on the importance of the Aims page in selling a grant. We will critically review Aims pages from actual grant applications, to demonstrate how ideas can be presented in ways that drive reviewers to advocate for you. We will provide attendees with practical tools for how to write winning grants. Emphasis will be placed on the new NIH requirements about data reproducibility and rigor.

This workshop will be conducted by Dr. Dewhirst, who has published on methods to be more successful in the grants market. Panel participants will include Dr. Yu, who has had relatively recent experience in being on study section and Dr. Repasky, who has extensive NIH study section involvement.

Questions from the audience will be encouraged.

THUR 23

EARLY OUTCOMES OF LOCOREGIONAL DEEP HYPERTHERMIA WITH PENCIL BEAM SCANNING PROTONS INDICATE MODEST TOXICITY WITH THE PROMISE OF INCREASING EFFICACY

Jason K. Molitoris1,2, Dario Rodrigues1,2, James W. Snider1,2, Ankur Sharma1,2, Sina Mossahebi1,2, Mark Zakhary1,2, Kara Lehman2, Zeljko Vujaskovic1,2

1University of Maryland School of Medicine, Baltimore, MD, USA. 2Maryland Proton Treatment Center, Baltimore, MD, USA

Abstract

Introduction: Hyperthermia is a well-known radiosensitizer when delivered concurrently with radiation. Our group recently commissioned a Locoregional Deep Hyperthermia (DHT) unit in a Pencil-Beam Scanning Proton Therapy (PBT) facility. This combination has the potential to improve outcomes for advanced or recurrent malignancies.

Methods: Retrospective single institution IRB-approved review of all patients treated with concurrent DHT and PBT. All patients were required to have locally advanced or recurrent abdominal or pelvic tumors with the ability to measure temperature within the tumor or a proximal intracavitary surrogate. We collected patient characteristics including age, gender, primary disease site, histology, RT dose, and DHT parameters to evaluate acute toxicity in an initial patient cohort. Treatment time was determined based on a therapeutic temperature minimum of 40°C for tumor and 39°C for tumor surrogates. Thermal parameters are reported as the maximum temperature (Tmax) and maximum thermal dose (TDmax).

Results: Nine patients have received DHT/PBT with a median age of 70 (range, 19-75 years). Histologies included rectal cancer (n=5), sarcoma (n=2), bladder cancer (n=1) and prostate cancer (n=1). Seven patients (78%) were treated with locally recurrent disease and with re-irradiation. Median PBT dose was 40.8 Gy(RBE) (31.2-57 Gy[RBE]) and seven patients (78%) received twice daily PBT. Three (33%) received concurrent chemotherapy with DHT and PBT. Forty-two treatments were completed with the following averages (ranges): 5 (1-8) treatments per patient, therapeutic time of 33 min (0-65 min), and net power of 597 W (408-856 W). Temperatures were recorded in target (tumor/surrogate) and normal tissue using 1-3 and 5-7 sensors, respectively. The target Tmax achieved on average 40.9°C (38.3-43.7°C) which corresponded to a TDmax average of 3.2 CEM43 (0-25.5 CEM43). Healthy tissue Tmax ranged from 38.6°C to 42.2°C and the correspondent TDmax varied from 0 to 9 CEM43. Toxicities during treatment were generally mild and included grade 1-2 pain (n=7), diarrhea (n=4) and dermatitis (n=3). There was one patient with transient lymphedema due to tumoral edema and compression on iliac vessels that resolved during treatment. With a median follow up of 2 months (range, 1-3 months) there have been no reported local failures or deaths to date. Updated outcomes and toxicities will be presented.

Conclusions: Initial combination of DHT with PBT is well tolerated and toxicities during treatment have been mild. Continued follow up is required to assess late toxicities and treatment related outcomes.

THUR 24

TOXICITY AND EFFICACY OUTCOMES OF CONCURRENT RADIATION AND HYPERTHERMIA IN SOFT TISSUE SARCOMA

Cristina DeCesaris1, Osman Siddiqui1, Santanu Samanta1, Emily Kowalski1, Stephanie Rice1, Jason Molitoris2, Dario Rodrigues2, James W. Snider III2, Zeljko Vujaskovic2

1University of Maryland Medical Center Department of Radiation Oncology, Baltimore, MD, USA. 2University of Maryland School of Medicine Department of Radiation Oncology, Baltimore, MD, USA

Abstract

Background: Soft tissue sarcomas (STS) represent a heterogeneous group of malignancies with a high propensity for both local and distant recurrence. External thermal therapy (ETT) delivered concurrently with external-beam radiation therapy (EBRT) acts as a radiosensitizer to improve outcomes, particularly for recidivistic disease. We present an update to our single-institution clinical experienced utilizing concurrent ETT and EBRT for the management of de novo, recurrent, and/or reirradiation STS.

Methods: All patients treated for STS with concurrent ETT and EBRT within a single institution were retrospectively reviewed. ETT was delivered using the BSD-500 microwave hyperthermia system, most commonly twice weekly with concurrent RT. Individual patient and tumor characteristics were analyzed. Local control (LC), freedom from overall progression (FFP) and overall survival (OS) were estimated using the Kaplan Meier method.

Results: Thirty-seven patients were treated for 40 lesions to a median total RT dose of 57Gy (range 27.5-74.4 Gy) per treatment course. One patient was treated simultaneously for two discrete lesions, and two patients underwent two courses of treatment to the same initial lesion. Four out of 40 lesions (10.0%) included a single-fraction GRID treatment of either 10 or 15Gy. ETT was delivered to a median of 43°C (range, 40-44°C) for 60 minutes (range 45-60). The majority of lesions were recurrent 21 (52.5%), and 15/40 (37.5%) had undergone previous radiation. Treatment was delivered to the lower extremity (n=10, 25.0%), breast/chest wall (n=9, 22.5%), upper extremity (n=8, 20.0%), thorax/back (n=7, 17.5%) abdomen (n=4,10.0%) and the H&N/scalp (n=2, 5.0%). Histologies included spindle cell (n=8, 20.0%), myxofibrosarcoma (n=7, 17.5%), angiosarcoma (n=6, 15.0%), pleomorphic (n=5, 12.5%), leiomyosarcoma (n=3, 7.5%), liposarcoma (n=3, 7.5%), and unclassified (n=8, 20%). Median follow up of all treatment courses was 23.4 months (range 1-67). At 18 months, LC of all lesions was 56% (95% CI 47-65); overall FFP was 50.6% (95% CI 40.6-60.6). Two-year survival was 69.5% (95% CI 59.5-79.5). There were no grade 4 toxicities, and lower grade acute/subacute toxicity was primarily limited to radiation dermatitis, pain, and hyperpigmentation.

Conclusions: The addition of ETT to EBRT in our advanced, predominately recurrent, very high-risk cohort showed promising LC and overall FFP for a challenging, heterogeneous disease subset with limited treatment options. Continued investigation and prospective validation is warranted.

THUR 25

THE EFFECT OF THE TIME INTERVAL BETWEEN RADIATION AND HYPERTHERMIA ON CLINICAL OUTCOME IN 400 LOCALLY ADVANCED CERVICAL CARCINOMA PATIENTS.

Michiel Kroesen1,2, H. Tim Mulder1, Netteke (J.M.L) van Holthe1, Aleida A. Aangeenbrug1, JanWillem E. Mens1, Lena (H.C.) van Doorn3, Maarten M. Paulides1,4, Esther Oomen-de Hoop1, René M. Vernhout1, Ludy C. Lutgens5, Gerard C. van Rhoon1, Martine Franckena1

1Department of Radiation oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands. 2Holland Proton Therapy Center, Delft, Netherlands. 3Department of Obstetrics and Gynaecology, Erasmus MC Cancer Institute, Rotterdam, Netherlands. 4Department Center for Care & Cure. Technical University Eindhoven, Eindhoven, Netherlands. 5Department of Radiation oncology (MAASTRO), University Medical Centre Maastricht, Maastricht, Netherlands

Abstract

Background: Addition of deep hyperthermia to radiotherapy results in improved local control (LC) and overall survival compared to radiotherapy alone in advanced cervical carcinoma patients. Based on preclinical data, the time interval between radiotherapy and hyperthermia is expected to influence treatment outcome. Clinical studies addressing the effect of time interval are sparse. The repercussions for clinical applications are substantial, as the time between radiotherapy and hyperthermia should be kept as short as possible. In this study, we therefore investigated the effect of the time interval between radiotherapy and hyperthermia on treatment outcome.

Methods: We analyzed all primary cervical carcinoma patients treated between 1996 and 2016 with thermoradiotherapy at our institute. Data on patients, tumors and treatments were collected, including the thermal dose parameters TRISE and CEM43T90. Follow-up data on tumor status and survival as well as late toxicity were collected. Data was analyzed using Cox proportional hazards analysis and Kaplan Meier analysis.

Results: 400 patients were included. Kaplan Meier and univariate Cox analysis showed no effect of the time interval (range 30-230 minutes) on any clinical outcome measure. Besides known prognostic factors, thermal dose parameters TRISE and CEM43T90 had a significant effect on LC. In multivariate analysis, the thermal dose parameter TRISE (HR 0.649; 95% CI 0.501–0.840) and the use of image guided brachytherapy (HR 0.432; 95% CI 0.214–0.972), but not the time interval, were significant predictors of LC and disease specific survival.

Conclusions: In contrast to thermal dose, the time interval between radiotherapy and hyperthermia, up to 4 hours, has no effect on clinical outcome. These results are re-ensuring for our current practice of delivering hyperthermia within maximal 4 hours after radiotherapy.

THUR 26

CONCURRENT PENCIL BEAM SCANNING PROTON THERAPY AND EXTERNAL THERMAL THERAPY: GROWING CLINICAL EXPERIENCE WITH PROMISING RESULTS

James Snider1, Jason Molitoris1, Stephanie Rice2, Cristina Decesaris2, Osman Siddiqui2, Santanu Samanta2, Emily Kowalski2, Dario Rodrigues1, Zeljko Vujaskovic1

1University of Maryland School of Medicine, Baltimore, MD, USA. 2University of Maryland Medical Center, Baltimore, MD, USA

Abstract

Background: External Thermal Therapy (ETT) has been regularly used in clinical practice as an excellent adjunct to conventional radiotherapy (RT) in patients with superficial tumors in both the definitive and palliative settings. ETT is known to improve radiosensitivity through improved oxygenation and inhibition of RT-induced DNA damage repair, among other mechanisms. However, there is a paucity of safety and efficacy data for the concurrent use of proton therapy (PT) and ETT due to the relative lack of institutions with capabilities for both modalities. Despite initial concerns for higher grade toxicity with this combination, as it has been likened to high-LET RT techniques, our institutions initial reports have been encouraging. We report, herein, the largest, and growing, clinical experience with concurrent Pencil Beam Scanning Proton Therapy (PBS-PT) and ETT from a single institution.

Methods: At the Maryland Proton Treatment Center, PBS-PT has been utilized in over 1,400 patients, of which 30 courses/sites (25 curative, 5 palliative) have been delivered with concurrent ETT in 27 patients (2 patients retreated, 1 patient with 2 sites) at the University of Maryland Medical Center. These patients' malignancies include a wide range of histologies though sarcoma (n=11) and breast cancer (n=9) have been most common: vulvar (n=1), skin (n=1), mesothelioma (n=1), ovarian (n=1), head/neck (n=1), anal (n=1), and ureteral (n=1). PBS-PT doses ranged from 36 to 70.2 Gy(RBE) (median 57 Gy[RBE]) with some included altered/hypo-fractionation. The BSD-500 platform was utilized for all ETT administrations (median 8, range 4-28 ETT per course) with a bolus temperature between 39-40oC, target surface temperature 40-44oC, for 30-60 minutes (median 60) per treatment.

Results: With a median follow-up of 7.4 months (range 1-31 months), concurrent ETT and PBS-PT continues to be well tolerated. There were no acute/subacute grade 4-5 toxicities. Grade 3 toxicity arose in only 5 patients and primarily involved acute desquamation (n=3) or chronic lymphedema (n=2). Most common grade 1-2 toxicities included radiation dermatitis, pain, hyperpigmentation, and GI disturbance Although short follow-up, 22 patients (81.4%) remain alive, while 20 (74.1%) are locally controlled and 18 (66.7%) remain free of disease.

Conclusion: Concurrent PBS-PT and ETT continue to be well tolerated in the largest experience to date of this combination. While long-term follow-up and prospective data are needed, there remains no evidence of worsened toxicity over traditional RT+ETT.

THUR 27

SIMILAR RATES OF SKIN TOXICITY ASSOCIATED WITH CONCURRENT EXTERNAL THERMAL THERAPY WHEN DELIVERED WITH PENCIL BEAM SCANNING PROTON THERAPY OR PHOTON/ELECTRON TECHNIQUES

Santanu Samanta, J W Sinder, Osman Siddiqui, Christina DeCesaris, Emily Kowalski, Stephanie Rice, Dario Rodrigues, Jason Molitoris, Zeljko Vujaskovic

University of Maryland, Baltimore, MD, USA

Abstract

Introduction: External thermal therapy (ETT) is an excellent adjuvant to external beam radiation therapy (EBRT) for the treatment of patients with breast cancer, and especially chest wall recurrences. While the dose distributions of proton therapy (PT) are advantageous to reduce RT exposure to especially the heart and lungs, concerns have arisen regarding increased skin toxicity as PT lacks the "skin-sparing" build-up region associated with photon beams. It has been hypothesized that ETT would further enhance this divide. In this study we report the acute/subacute skin toxicities when ETT is combined with PT as compared to other forms of EBRT.

Methods: Since 2014 at the University of Maryland Medical Center, ETT-RT has been performed for treatment of breast cancer for 44 patients, out of which 42 patients (95.5%) had recurrent breast cancer. Median patient age was 61 years (range 33-90 years), while 20 patents had curative intent treatment. Ten patients underwent treatment with Pencil Beam Scanning Proton Therapy (PBS-PT), 12 patients with photon (3DCRT or IMRT), 16 patients with electron, and 6 patients with combined photon-electron. Patients received a median of 10 ETT treatments (range 2-18 treatments) median of 430C, duration of 45-60mins. Radiation dermatitis was reported based on CTCAE 4.0 criteria: Grade 2=Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema; Grade 3=Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion.

Results: Of 10 patients treated with PBS-PT/ETT, 20% (n=2/10) had grade 2+ and 20% (n=2/10) had grade 3 radiation dermatitis. Of 12 patients treated with Photon/ETT (3DCRT/IMRT) 25% (n=3/12) had grade 2+, 25% (n=3/12) had grade 3. Of 6 patients treated with combined Photon-Electron/ETT 33.3% (n=2/6) had Grade 2+ and 33.3% (n=2/6) grade 3. With electrons alone (n=16), 12.5% (n=2/16) experienced grade 2+ and 6.25% (n=1/16) grade 3 radiation dermatitis. There were no acute/subacute grade 4+ toxicities with any modality of RT+ETT. In summary, the rates of grade 2+ (20% [2/10] vs. 20.6% [7/34]) and grade 3 (20% [2/10] vs. 17.6% [6/34]) radiation dermatitis were not substantially higher with PBS-PT/ETT vs. Photon/Electron/ETT.

Conclusion: PBS-PT with ETT seems to have similar rates of acute/subacute skin toxicities when compared to treatment with photons/electrons and ETT. These initial results are encouraging, though longer follow-up and larger patient experience will be needed to evaluate this endpoint fully.

THUR 28

IMPROVED LOCAL CONTROL WITH HYPERTHERMIA (HT) PLUS PROTON BEAM THERAPY COMPARED TO ELECTRONS PLUS HYPERTHERMIA IN RECURRENT BREAST CANCER?

Elizabeth Nichols, Zeljko Vujaskovic

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

Abstract

Introduction: Hyperthermia (HT) reduces the oxygen enhancement ratio of low-linear energy transfer (LET) radiation (photon/proton) and increases relative biologic effectiveness (RBE), potentially mimicking high-LET particle therapy. Furthermore the distal part of the proton spread out Bragg peak has a higher LET and subsequently higher RBE in comparison to photons and electrons. Here we present a single case report of a woman with dermal lymphatic recurrence of a triple negative breast cancer who received both proton therapy plus HT in one treatment course and electron therapy and HT as part of a separate treatment course.

Materials and Methods: A 71 yo female developed a dermal lymphatic recurrence of a triple negative breast cancer 4 years after her initial diagnosis with no signs of metastatic disease. She was treated as per standard of care but ultimately developed 3 separate locoregional recurrences of disease resulting in additional surgeries and bilateral breast radiation. When she developed her dermal lymphatic recurrence, the disease was isolated to the bilateral breasts. She was treated with a combination of proton beam therapy and HT to a total dose of 60 Gy in 2 Gy fractions. HT was delivered using BSD-500 device with the 40-42oC target tumor temperature. She received 6 complete HT sessions. Two months following completion of therapy, the patient developed new nodules beginning at the field edge on the right back.This was biopsied and confirmed to be disease. She received electrons and HT (due to no prior radiation (RT) in this location) to a total dose of 50 Gy in 2.5 Gy fractions with 6 HTsessions. Two months after completion of the right back, new disease was noted in the right axilla, left back and on the upper abdomen bilaterally (all at prior proton field edges). She was again given 50 Gy in 2.5 Gy fractions without heat to these new areas.

Results: Three months following completion of her right back radiation, her disease recurred completely within the electron + HT field while the bilateral breast (proton + HT) continue to be free of disease on exam and imaging (7.5 months later).

Conclusions: The clinical findings seen in this case report of persistent local control with protons and hyperthermia compared to quick local failure with electrons and hyperthermia support the notion of a higher RBE of protons + HT regimen. At the present time, these findings are thought provoking and support further investigation of this concept.

THUR 29

OVERVIEW OF THE ASME STANDARDS DEVELOPMENT PROCESS & FRAMEWORK FOR VERIFICATION AND VALIDATION OF COMPUTATIONAL MODELING AND SIMULATION FOR MEDICAL DEVICES

Ryan Crane1, Christine Reilley2, Luis Pulgarin3

1Director, S&C Initiatives, ASME, New York, NY, USA. 2Director, Healthcare, ASME, New York, NY, USA. 3Project Engineering Advisor, Codes and Standards Initiatives, ASME, New York, NY, USA

Abstract

ASME (American Society of Mechanical Engineers) and Society of Thermal Medicine have an ongoing discussion in how both organizations can promulgate an open technical exchange of information, and sharing lessons learned and case studies, toward the development and application of standards specific to the thermal medicine industry. The purpose of these voluntary standards is to enhance public safety, health, and quality of life as well as facilitate innovation, trade, and competitiveness. ASME consensus committees are comprised of volunteer subject matter experts from a diverse range of interests, including manufacturers, testing laboratories, insurance, users, government and regulatory, academia, consultants, and general interest. ASME's consensus process ensures that all stakeholders – both direct participants and members of the general public – have the opportunity to submit comments and requires that the developing committees provide a formal response following due consideration.

An overview of the recently published ASME V&V 40-2018 "Assessing Credibility of Computational Modeling through Verification and Validation (V&V): Application to Medical Devices" will also be provided in this presentation. This Standard provides a framework for assessing the relevance and adequacy of completed V&V activities that establish credibility of a computational model. The credibility should be commensurate with the degree to which the computational model is relied on as evidence of device performance, functional characteristic, and/or safety to support a decision, and the consequences of that decision being incorrect. This Standard helps users communicate the value of the completed V&V activities and establish the associated credibility of the computational model to support a decision. It does not present a method for incorporating user expertise or modeler pedigree, nor does it describe the specific V&V activities and rigor that are needed to establish credibility for a particular application and/or device. Instead, this Standard presents a framework for the practitioner to make that assessment using sound engineering judgment. It is not a step-by-step guide, nor is it intended to present a quantitative method for establishing model credibility. While the framework was developed specifically for medical devices, the technical committee considers this Standard to be general enough to be applied to other disciplines.

PRESENTING AUTHOR INDEX

NOTES

NOTES

NOTES

NOTES

NOTES

NOTES


Congratulations to the University of Maryland School of Medicine.
World's First Combined Proton Therapy / Hyperthermia Center
Pyrexar MEDICAL
BSD-2000
Deep Regional Hyperthermia System
installed at the Maryland Proton Treatment Center
www.pyrexar.com