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INNOVATIONS IN

RADIATION ENGINEERED THERAPY

November 14 - 15, 2016

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Posters

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Niki Law, Azza Al-Mahrouki, Scott Mckay, Christine Tarapacki, Farah Hussein, Gregory Czarnota.	Effective Ultrasound Stimulated Microbubbles Therapy Used to Treat PC3 Xenografts in a Rabbit model
Daniel DiCenzo, Claire McCann, Carl Kumaradas.	An *In Vitro* Study of Radiation Dose Enhancement Using Gold Nanorods and Plasmonic Photothermal Therapy
Derek J Gillies, Lori Gardi, Ren Zhao, Aaron Fenster.	Real-Time Prostate Motion Compensation for 2D/3D Ultrasound-Guided Biopsy
Ezra Hahn, Sandi Bosnic, Nadiya Makhani, Hany Soliman, Danny Vesprini, Maureen Trudeau, Brian Keller, Claire McCann, Justin Lee.	Hypofractionated Partial Breast Irradiation for Unresected Locally Advanced Breast Cancer in Metastatic and Medically Inoperable Patients
Christianne Hoey, Jessica Ray, Samira Taeb, Xiaoyong Huang, Nancy Yu, Paul Boutros, Stanley K. Liu.	MicroRNA-106A Confers Radiotherapy Resistance and Tumour Aggression by Targeting LITAF in Prostate Cancer
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Anthony Kim, Shahad Al-Ward, Claire McCann, Patrick Cheung, Arjun Sahgal, Brian M. Keller.	Magnetic Field Effects on Dose Delivery Robustness of Lung Stereotactic Body Radiation Therapy
Jae. Lee, Eric D. Silva, Shun Wong, Claire McCann, Carl J. Kumaradas.	A Novel Dissolvable Seed for Brachytherapy
Lucas C. Mendez, Moti Paudel, Matt Wronski, Lisa Barbera, Ananth Ravi, Eric Leung.	Dosimetric Comparison of Interstitial Brachytherapy with Multi-Channel Vaginal Cylinder Plans in Patients with Vaginal Cancer
Geordi Pang.	Could α/β Ratio Change During MRI-Guided Brachytherapy?
Michael C Tjong, Salman Faruqi, Joelle Helou, Liying Zhang, Patrick Cheung, Darby Erler, Ian Poon.	Post-Stereotactic Body Radiation Therapy (SBRT) Tumor Response and Inflammatory Changes as Predictors of Non-Local Failure and Survival Outcomes in Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)
L. Chin, A. Dhillon, S. Lim-Reinders, J. Cifuentes Gaitan, T. Conrad, D. Brotherston, C. Caldwell, J. Lee, I. Karam, I. Poon.	Can Intratreatment PET CT Based Adaptive Radiotherapy Reduce Treatment Margins in Head and Neck Cancers ?

Posters

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Jessica Ray, Christianne Hoey, Samira Taeb, Xiaoyong Huang, Stanley K. Liu.	MicroRNA-198 Targets Wnt Signaling to Regulate Prostate Cancer Aggression
Jessica R. Rodgers, Kathleen Surry, David D'Souza, Eric Leung, Aaron Fenster.	360-Degree 3D Transvaginal Ultrasound Needle Guidance System for Interstitial Gynecologic Brachytherapy
Arman Sarfehnia, Niloufar Entezari, Humza Nusrat, James Renaud.	Accurate Dosimetry in MR-Linac and GammaKnife
Deepa Sharma, Anoja Giles, Amr Hashim, Jodi Yip, Juliana Sebastiani, Martin Stanisz, Scott Mckay, William Tyler Tran, Gregory J. Czarnota.	Ultrasound Microbubble Potentiated Enhancement of Hyperthermia in Tumours
Ekaterina Tchistiakova, Anthony Kim, William Y. Song, Geordi Pang.	Investigating effects of strong magnetic field on OSLD personal dosimeters

Itinerary

Innovations in Radiation Engineered Therapy
Monday, November 14th 2016

Presenter	Time	Title
BREAKFAST	**08:00 - 08:45**	
G. Czarnota & A. Sahgal	08:45	Welcome & Introduction
R. Kolesnick	09:00	The "New Biology" of Single Dose Radiotherapy
MRI BRACHYTHERAPY – Chaired by G, Stanisz		
E. Leung	09:30	Innovations in Interstitial Brachytherapy
N. Mayr	09:50	Functional Imaging and Integration of MR
W. Song	10:10	MRI-Guided Direction Modulated Brachytherapy for Cervical Cancer
A. Owrangi	10:30	Magnetic Resonance Imaging-Guided Brachytherapy
BREAK	**10:45 - 11:15**	
MRI IMAGING – Chaired by A. Sahgal		
L. Warner	11:15	MRI for Radiation Oncology: From Spatial Accuracy to MR-Only Radiation Therapy Planning Welcome & Introduction
G. Stanisz	11:30	Advanced MR Imaging and Radiation Response
C. Heyn	11:50	Evolution of Perfusion Parameters in Brain Metastases Treated with Stereotactic Radiosurgery in the First Month after Treatment: Comparison of Dynamic Contrast Enhanced MRI and Intravoxel Incoherence Motion
C. Cunningham	12:05	Acquisition & Reconstruction Strategies for ^{13}C MRI Integrated with Radiation Therapy
B. Chugh	12:20	Development of Realistic Phantoms for MR-Guided Radiotherapy
LUNCH	**12:35 - 14:00**	
ULTRASOUND & RADIATION- Chaired by G. Stanisz		
M. Kolios	14:00	Ultrasound Tissue Characterization at Multiple Scales to Inform Tissue Characterization Approaches for Treatment Monitoring
W. Tome	14:20	Development of Animal Models for Radiation Engineered Oncology- Experiences and Potential Pitfalls
G. Czarnota	14:40	*A Priori* Prediction of Neoadjuvant Chemotherapy Response and Survival in Breast Cancer Patients Using Quantitative Ultrasound
P. Kupelian	15:00	Trends in Radiotherapy
BREAK	**15:15 - 15:45**	
ADVANCED & PARTICLE RADIATION - Chaired by A. Sahgal		
J. Jachinowski	15:45	Addressing the Limitations of Conventional Proton Pencil Beam Scanning
J. Capala	16:00	Particle Beam Therapy in the United States
L. Ma	16:20	Sharpening a Knife with Precision Dose Sculpting
A. Nicolae	16:50	Evaluation of a Machine-Learning Algorithm for Treatment Planning in Prostate Low-Dose-Rate Brachytherapy
POSTER SESSION & HORS D'OEUVRES	**17:15 - 18:45**	
DINNER	**18:45 - 20:30**	

Innovations in Radiation Engineered Therapy

Tuesday, November 15th 2016

Presenter	Time	Title
BREAKFAST	**08:00 – 09:00**	
MRI-BASED RADIOTHERAPY -Chaired by G. Czarnota		
B. Raaymakers	09:00	The Promise of the MRI Linac: Simultaneous MRI and Irradiation
A. Li	09:20	MRI-Guided Adaptation: From Anatomy to Biology
J. Goldwein	09:40	Prospects of MR-guided Radiotherapy
B. Keller	10:10	The MRI Linac Program at Sunnybrook Health Sciences Centre
E. Tseng	10:25	Dosimetric Feasibility of the Hybrid Magnetic Resonance Imaging (MRI)-LINAC System for Brain Metastases: The Impact of the Magnetic Field
BREAK	**10:40 - 11:10**	
RADIOTHERAPY ENHANCEMENT – Chaired by A. Sahgal		
S. Krishnan	11:10	The Current Landscape of Radiosensitization Strategies using Gold Nanoparticles
C. Guha	11:30	Immune Priming Ablation (IPA) for *in situ* Vaccines
G. Czarnota	11:50	Ultrasound-Stimulated Microbubble Enhancement of Radiation Responses
LUNCH	**12:10 - 14:00**	
HYPOFRACTONATION & RADIOSURGERY – Chaired by S. Liu		
A. Sahgal	14:00	Brain Hypofractionated Radiosurgery for Metastases: Rationale and Outcomes
D. Schaal	14:20	Facing the Future of Radiation Oncology
J. Kirkpatrick	14:35	Understanding and Optimizing Clinical Outcomes in Stereotactic Radiosurgery
D. Prasad	14:55	Gamma Knife Icon: Early North American Experience
B. Valcu	15:10	Technology Solutions for Modern Management of Cerebral Metastatic Disease
BREAK	**15:25 - 16:00**	
BIOPHYSICS OF RADIATION – Chaired by A. Sahgal		
S. Liu	16:00	Unravelling the Biology of Recurrent Radioresistant Cancer
D. Vesprini	16:15	Using Genetics to Tailor Prostate Cancer Care: The Male Oncology Research and Education (MORE) Program
J. Michael	16:30	Development of Three-Dimensional Ultrasound Scanner and Needle Template Localizing Arm for Guidance of Permanent Seed Breast Brachytherapy
CLOSING REMARKS	**16:45 - 16:55**	

Speaker Abstracts

Particle Beam Therapy in the U.S.

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ABSTRACT

The U.S. National Cancer Institute (NCI) and Department of Energy (DOE) have a long tradition of supporting research and development (R&D) efforts to apply accelerator technology for radiation therapy (RT) of cancer. Many preclinical studies investigating the effects of particle beams on tumor and normal tissues have been funded over the last five decades. In the 1970s and 1980s, NCI supported clinical trials using a variety of particle beams, many of them at the U.S. Department of Energy (DOE) facilities. Renewed interest in particle therapy led to a 2013 joint NCI/DOE workshop on particle RT-related R&D questions. Currently, clinical trials involving protons are being carried out by NCI-funded National Clinical Trials Network and under a collaborative agreement between NCI, MD Anderson Cancer Center, and Massachusetts General Hospital. To encourage establishment of a research center adjunct to a planned, independently created and funded clinical facility for hadron RT, two exploratory project grants have been awarded. In addition, NCI has issued a contract to conduct a randomized phase III clinical trial of carbon ion vs. 3D conformal RT for unresectable pancreatic cancer. DOE has supported accelerator technology development and facility use for RT for decades, having operated the Bevalac for ion beam cancer therapy trials and played a key role in the construction of the proton therapy machine at Loma Linda. Accelerator technology has advanced considerably since these early machines, and DOE is investing in use-inspired basic R&D to translate the latest accelerator technologies into a new generation of lower cost, higher performance RT machines.

Keywords: Cancer, Particle Beam Radiotherapy, Accelerators

Development of Realistic Phantoms for MR-Guided Radiotherapy

Brige Chugh (1,2), Abraam Soliman (1), Levi Burns (1), Shahad Al-Ward (1), Young Lee (1,2), Chia-Lin Tseng (1,2), Arman Sarfehnia (1,2), Amir Owrangi (1,2), Anthony Kim (1,2), Alex Karotki (1), Lee Chin (1,2), Claire McCann (1,2), Mark Ruschin (1,2), Collins Yeboah (1,2), Adam Gladwish (1,2), Brian Keller (1,2), William Song (1,2), Arjun Sahgal (1,2), Greg Stanisz (1,3)

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ABSTRACT

Introduction: Novel phantoms will play an important role in MR-guided radiation therapy (RT). In this field, MR-only workflows base treatment planning on MR information alone. 4D MRI can accurately define treatment margins and provide real-time tracking of moving tumors and organs-at-risk. The goal of this multidisciplinary project is to develop realistic phantoms for technique validation, QA and commissioning to ensure that MR-only and 4D-MRI workflows are consistent and reproducible.

Materials and Methods: Two realistic phantoms were developed and evaluated:

1. Phantom to test MR-only workflow (Fig.1): To accurately represent MRI properties of skull and brain tissue, a human skull was immersed in liquid contrast solution ($GdCl_3$ in bovine milk). Imaging included CT and MR (T_1-w, T_2-w, Ultra-short TE (UTE), T_1 and T_2 maps).

2. Phantom to test 4D-MRI workflow (Fig.2): For end-to-end testing, a 4D-MRI prototype (by Modus QA) was modified to include four Optically Stimulated Luminescent Dosimeters (OSLDs) in the motion insert. Imaging included CT and MR at eight equally spaced phases to simulate realistic breathing motion.

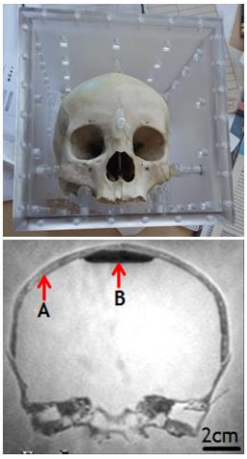

Fig.1: Top: MR-only phantom prior to adding $GdCl_3$ solution. Bottom: UTE coronal. Arrows: A= bone signal; B= air bubble

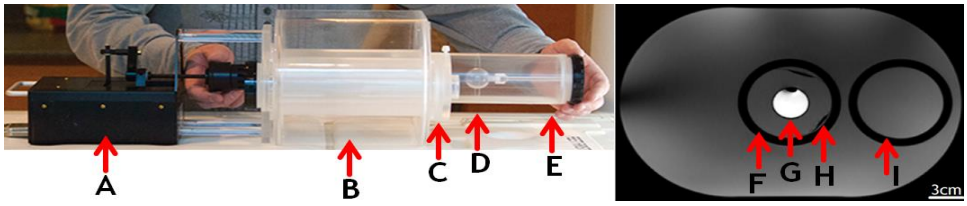

Fig.2: Left: 4D-MRI phantom prototype; Right: axial T_1-w MR for a single phase, positioned at level of arrow B. Arrows: A=piezoelectric motor; B= phantom body; C= dummy insert; D=spherical tumor model; E= motion insert (retracted); F= motion insert; G=tumor model; H=void for detector; I=dummy insert.

Results and Discussion: The UTE image of the human skull was able to differentiate bone from air (Fig. 1). Air bubbles formed during preparation of the MR-only phantom may help model air/bone interfaces, but are unstable in liquid and do not represent geometry of realistic air spaces; this area requires further development. The 4D MRI resolved Gross Tumor Volume (GTV) and detectors suitable for planning (Fig.2); brighter signal in GTV was expected since it corresponded to higher concentration of $GdCl_3$ than surrounding compartments. Small air bubbles, as seen in MR of tumor model need to be eliminated for accurate delineation. The signal void corresponding to the detectors was expected since they are solid state. This is a novel approach to development of phantoms that are uniquely suited to advance the field of MR-guided RT.

Keywords: MR-guided Radiotherapy, Radiation Therapy, Phantom, 4D-MRI, MR-only

Acquisition & Reconstruction Strategies for ^{13}C MRI Integrated with Radiation Therapy

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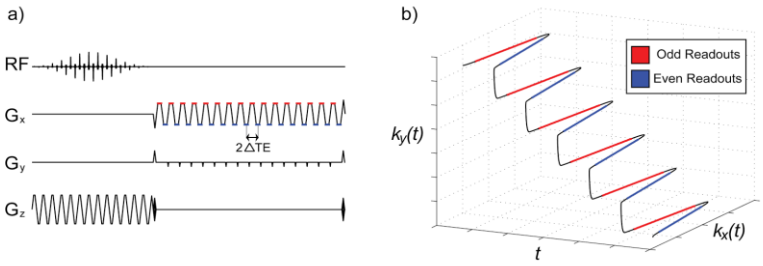
ABSTRACT

Introduction: The advent of hyperpolarized liquids as an MR contrast agent has opened up many new possibilities for metabolic imaging and created much excitement in the field. However, the unique properties of this contrast agent creates many challenges for the pulse-sequence designer. The biggest concern, of course, is that the polarization is not replenished by T1 recovery, so careful tipping of the magnetization by a limited number of RF pulses is essential. Furthermore, the particular T1 and metabolic conversion rates of interest must be taken into account when considering the details of an acquisition scheme. For radiotherapy applications, the goal is to spatially map the metabolic conversion of [1-^{13}C]pyruvate to [1-^{13}C]lactate.

Materials and Methods: When the particular frequencies that will be in the spectrum are known a priori, which is often the case, there are many other options for acquiring the spectral information in a more efficient manner. The longest duration per k-space traversal is possible with the use of spectrally-selective RF pulses to excite single metabolites. This results in a single spectral component (e.g. [1-^{13}C]lactate) that can be imaged with conventional fast imaging methods such as a single-shot k-space trajectory. With a dominant long-T2 component observed from in vivo signals, these long-duration readouts can result in high SNR efficiency.



Dual echo EPI pulse sequence for robust C13 pyruvate/lactate imaging (a) and k-space trajectory (b). Odd (red) and even (blue) echoes are separated by ΔTE = 0.892 ms, allowing for the extraction of field-map information from the phase difference between the odd and even readouts.

Discussion: In this presentation, the constraints on pulse sequence duration and timing (T1, T2, T2* and metabolic conversion rates) will be used as a framework for the discussion of the data acquisition schemes designed for radiotherapy applications. The design and application of efficient k-space trajectories such as spiral and EPI, as well as the use of variable tip-angle approaches will be discussed.

Keywords: Metabolism, DNP, MRI, Lactate, Warburg

Ultrasound-Stimulated Microbubble Enhancement of Radiation Responses

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ABSTRACT

Introduction: We have recently demonstrated that ultrasound-stimulated microbubble treatment may be used to enhance radiation responses. Recent analyses in vitro and in vivo have demonstrated that this is related to the production of Asmase-induced ceramide in response to radiation-induced cell membrane damage. Here we further investigate the importance of the Asmase pathway.

Materials and Methods: Experiments were carried out in wild-type (C57BL/6) or *asmase*-knockout animals, implanted with fibrosarcoma xenografts (MCA-129). A cohort of wild-type animals received the endothelial ASMase-ceramide pathway inhibitor sphingosince-1-phosphate (S1P). Animals were treated with radiation doses of 0-8 Gy with or without *a priori* USMB exposure at varying microbubble concentrations. Treatment response was assessed with high-frequency 3D Doppler ultrasound acquired at baseline, and at 3, 24 and 72 hours after treatment and the vascular index (VI) was used to quantify imaging. Immunohistochemistry (ISEL, ceramide and CD31) of
tumour sections served to complement imaging and further assess treatment response.

Results and Discussion: Results confirmed a dose-dependent synergistic decrease in VI of greater than 40% by 3 hours following radiation and USMB. This peaked at 24 hours following treatment, persisting for up to 72 hours, and was accompanied by extensive tumour cell death. In contrast, minimal decreases in tumour perfusion (power Doppler/CD31) or cell death (ISEL) were noted in S1P-treated and *asmase* knockout animals for all treatments. Results are the first to demonstrate the importance of the ASMase-ceramide pathway in mechanotransductive vascular targeting using USMB radiation enhancement. These further confirm that an acute vascular effect is necessary for rapid tumour cell death, and that a vascular effect can be elicited at low radiation doses (< 8 Gy) by *a priori* USMB exposure.

Keywords: ASMase, Sphingomyelinase, radiation therapy, endothelial cells, ceramide, radiosensitization, microbubbles, mechanotransduction

A Priori Prediction of Neoadjuvant Chemotherapy Response and Survival in Breast Cancer Patients using Quantitative Ultrasound

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ABSTRACT

Introduction: Quantitative ultrasound (QUS) can probe tissue structure and analyze tumour characteristics. We have used it previously to monitor the early effects of chemotherapy with results indicating imaging-outcomes obtained one week after therapy initiation can predict ultimate clinical outcomes of patients.

Materials and Methods: Using a 6-MHz ultrasound system, radiofrequency data were acquired from 56 locally advanced breast cancer patients prior to their NAC and QUS texture features were computed from regions of interest in tumour cores and their margins as potential predictive and prognostic indicators. Breast tumor molecular features were also collected and used for analysis.

Results and Discussion: A multiparametric QUS model was constructed, which demonstrated a response prediction accuracy of 88% and ability to predict patient 5-year survival rates ($p=0.01$). QUS features demonstrated superior performance in comparison to molecular markers and the combination of QUS and molecular markers did not improve response prediction. This study demonstrates for the first time, that non-invasive QUS features in the core and margin of breast tumours can indicate breast cancer response to neoadjuvant chemotherapy (NAC) and predict five-year recurrence-free survival.

Keywords: Quantitative Ultrasound, Ultrasound Spectroscopy, Tumour Response Assessment, Prognostic Biomarker

Prospects of MR-Guided Radiotherapy

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ABSTRACT

Historically, radiotherapy has been characterized by increasingly sophisticated imaging and image guidance systems linked more and more closely to actual treatment delivery systems. Current state-of–the-art radiotherapy employs linac-integrated cone-beam computerized tomography (CBCT) to assure proper treatment guidance and plan adaptation before, after and to some degree during RT delivery. This paradigm is representative of the most common Image Guided Radiation Therapy (IGRT) systems used today, but still has limitations that prevent optimal radiation delivery.

The limitations of current IGRT systems can potentially be overcome using high field Magnetic Resonance Imaging that is fully integrated into linac delivery systems, effectively providing the basis for MR-Guided Radiotherapy (MRGRT). However, while MRGRT may have great promise for improving care, the evidence for such improvement, at this time, remains largely theoretical. This presentation outlines the hypothetical bases for anticipated outcome improvements, the evidence available to date, and outlines the plan for developing high level evidence of value in the near and long term. The presentation will highlight a unique Industry-Academia partnership and framework that is geared towards establishment of an infrastructure intended to lead to the evidence development as well as to change the paradigm of how radiotherapy technology is introduced to the Market.

Keywords: MR Guided Radiotherapy, Cone Beam CT, CBCT

Immune Priming Ablation (IPA) for *In Situ* Vaccines

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ABSTRACT

Reports from multiple groups suggest that local application of physical energy (e.g., ionizing radiation, thermal, ultrasound and photodynamic therapy) to tumors alone or in combination with local/systemic administration of immuno-therapeutics has the potential to induce systemic immune response and improve survival in murine cancer models by promoting both primary tumor control and suppressing metastatic progression. The immunosurveillance network eliminates cells harboring oncogenic mutations. With tumor progression, the immunosuppressive tumor microenvironment over-rides the surveillance network to anergize anti-tumoral T cells via tolerogenic dendritic cells.

Furthermore, tumor cells display new mutations and epigenetic modifications suppress the antigen presentation machinery within tumor cells, resulting in immune escape and tumor progression. In order to restore the balance towards tumor immunity and achieve consistent and sustainable systemic response after local ablative procedures, we are designing a sequential immune priming therapy followed by ablation to generate anti-tumoral systemic immunity after local tumor ablation.

Several examples will be provided for IPA therapy towards developing *in situ* tumor vaccines in mouse models of solid tumors. We will also describe the development of a novel class of protein therapeutics, which relies on a unique design that covalently links single chain peptide-MHC (sc-pMHC) constructs to a variety of costimulatory and coinhibitory molecules for clonally specific T cell modulation. This will serve as foundations to develop energy-based precision immunotherapeutics.

Keywords: Immuno-therapies, Tumor Ablation

Evolution of Perfusion Parameters in Brain Metastases Treated with Stereotactic Radiosurgery in the First Month after Treatment: Comparison of Dynamic Contrast Enhanced MRI and Intravoxel Incoherent Motion

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ABSTRACT

Introduction: Stereotactic radiosurgery (SRS) of brain metastases results in injury to tumour endothelium and profound reduction in blood flow occurring hours to days after treatment. This reduction in blood flow and ensuing tumour ischemia is hypothesized to play an important role in the therapeutic response of metastases to SRS. While this radiobiology has been extensively studied in animal models, there is little human data examining changes in tumour blood flow early after SRS. The purpose of this study was to characterize changes in tumour blood flow using two different MRI techniques: dynamic contrast enhanced (DCE)-MRI and intravoxel incoherent motion (IVIM) in the first week and month after SRS of brain metastases.

Materials and Methods: Seventeen patients with a total of 21 brain metastases were scanned prior to treatment, and at 1 week and 1 month after SRS. Tumour blood volume was measured using DCE-MRI and IVIM which provide measurements of plasma volume fraction (v_p) and perfusion fraction (f) respectively. Changes in DCE-MRI and IVIM parameters were evaluated by paired t-test or Wilcoxon signed-rank test. Linear regression between blood volume measured using DCE-MRI and IVIM was performed and the Pearson correlation coefficient was calculated.

Results and Discussion: No significant change in blood volume measured using DCE-MRI or IVIM was observed at 1 week. DCE-MRI measurement of blood volume (v_p) showed a statistically significant decrease at 1 month. IVIM measurement of blood volume (f) showed an opposite trend with a statistically significant increase at 1 month. DCE-MRI and IVIM measurements of blood volume appeared poorly correlated at baseline (r=0.33) and this correlation worsened after treatment (r=0.14 and 0.3 at 1 week and 1 month respectively).

In summary, MRI measurements of tumour perfusion fail to show significant change at 1 week post SRS. Significant changes in blood volume were found at 1 month for both MRI techniques with DCE-MRI agreeing with expected radiobiology and IVIM showing contradictory behaviour. These results support the use of DCE-MRI for studying changes in tumour perfusion after SRS and raise questions about the validity of the IVIM methodology.

Keywords: Brain Metastases, Magnetic Resonance Imaging, Perfusion

Addressing the Limitations of Conventional Proton Pencil Beam Scanning

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ABSTRACT

The transition from double-scatter delivery to pencil beam scanning (PBS) in proton therapy is gaining momentum. Although the majority of patients treated today are still treated with double-scatter systems, it is a near certainty that PBS will be the favored approach five years from now. PBS is attractive for a number of reasons: lower proximal dose, lower neutron generation, improved conformality and the elimination of physical apertures and compensators.

First generation PBS systems however, suffer from some significant limitations including: slow energy layer switching, poor lateral penumbra and a high quality assurance burden. This talk will present HYPERSCAN, Mevion's novel approach to PBS that eliminates these drawbacks

Keywords: Mevion, Proton Beam Scanning, Proton Therapy

The MRI Linac Program at the Sunnybrook Health Sciences Centre

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ABSTRACT

Introduction: In 2013, the Sunnybrook Health Sciences Centre joined the Elekta MRI-Linac Consortium, which today consists of seven academic centres in combination with the companies Elekta and Philips. Since that time Sunnybrook has built and continues to build an infrastructure geared towards more MRI guided radiation therapy. The purpose of this abstract is to give an overview of the current MRI-linac physics research and infrastructure development taking place in preparation for the MRI-linac. Prior to the actual installation of the treatment machine, initial studies have focused on the treatment planning system that will be used with the MRI-linac. Such studies have been grouped into a number of categories A) evaluation of the integrity of the Elekta Monte Carlo treatment planning algorithm and its ability to model the magnetic field effects particularly at inhomogeneity boundaries B) the dosimetric effects of irradiating through higher atomic number materials (such as dental fillings, spinal rods, hip prosthesis) and the ability of the planning system to model the dose appropriately C) establishing a method to accurately model contrast agents in the planning system as this will be relevant for a number of disease sites such as brain. We spent some time establishing a 4D treatment planning methodology and applied this methodology to central lung tumors to determine the impact of tracking a tumor within the magnetic field and the impact of the electron return effect when motion is considered. These motion studies will be experimentally verified with a 4D MRI compatible phantom that is currently being developed in collaboration with a vendor. This phantom will serve the dual purpose of evaluating 4D MRI sequences and experimentally testing our 4D treatment planning methodology.

Materials and Methods: Treatment planning studies were done using a research version of the Monaco treatment planning system which models dose in a magnetic field using the GPUMCD Monte Carlo dose calculation algorithm (Elekta, AB, Stockholm, Sweden). A stand-alone version of the GPUMCD algorithm was also obtained from Elekta in order to independently evaluate it against another Monte Carlo dose calculation algorithm (Geant4 v10.1). For the motion studies, deformable image registration was done using the software ADMIRE (Elekta, AB, Stockholm, Sweden).

Results and Discussion: The GPUMCD algorithm, capable of modeling dose in a magnetic field, showed good agreement against Geant4 for a number of clinical scenarios. Interface effects for various heterogeneities (including prosthesis and contrast agents), in the presence of a 1.5 T magnetic field, are quite interesting and involved and depend on the composition of the heterogeneities. The effects of tracking a central lung tumor in a magnetic field (using the MRI-linac beam model with its 7.2 mm MLC leaf width) had a beneficial impact on organ-at-risk doses and depended not only on the tumor motion but the relative motion between the tumor and the organ-at-risk. General updates regarding MRI-Linac preparation details will be discussed.

Keywords: MRI-Linac, Monte Carlo Dosimetry, Treatment Planning, Motion Management

Understanding and Optimizing Clinical Outcomes in Stereotactic Radiosurgery

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ABSTRACT

Introduction: Over the past twenty-five years, stereotactic radiosurgery (SRS) has evolved to be the treatment of choice for many patients with small, discrete brain lesions, due to its high efficacy, low toxicity and logistical advantages compared to surgical resection, conventional large-field radiotherapy, systemic chemotherapy and immune/targeted therapies. Nevertheless, the need to optimize the practice of SRS remains, particularly in regard to improving the balance of efficacy and toxicity via selection of optimal target volumes, total doses, (hypo)fractionation and the use of agents that augment tumor kill and mitigate normal tissue damage. Moreover, the "environment" of SRS is changing, as new agents are introduced that modulate the immune response, possibly enhancing tumor kill but definitely confounding the image response to radiation. We will present the results of our institutional studies on SRS that frame these issues and illustrate approaches to understanding and optimizing outcome in patients with primary and metastatic brain lesions.

Materials and Methods: IRB-approved retrospective and prospective studies of SRS in the treatment of 1-3 and 4+ brain metastases and recurrent malignant gliomas, conducted using an image-guided, linear-accelerator-based radiosurgery system at our institution from 2008-2015, are presented. Key outcomes include rates of local and distant recurrence, overall survival, incidence of adverse radiation effects, neurocognitive changes and quality of life. Results from complementary computational studies of tumor control and normal tissue damage, using model target volumes, tumor cell distributions and tumor/normal tissue radiation responses are presented.

Results and Discussion: The randomized study of margin about the GTV in 39 patients with 1-3 brain metastases revealed a very high rate of local control whether a 1mm or 3mm margin was utilized, as biopsy was used distinguish true local recurrence from RN. Rates of RN trended higher with the larger margin and our practice is now to use the 1mm margin in intact lesions. In the setting of immune modulation, a measured approach to an "enlarging lesion" is essential as inflammation is often more pronounced but associated with improved response. Retrospective analysis of 59 patients with 4+ brain metastases treated with a single-isocenter technique, show a strong dependence of overall survival on the total volume, rather than the number, of lesions (HR=3.34 for total volume $\geq$10ml; CI 1.74, 6.43; p=0.0003.) A (re)planning study in this patient population also showed that the hippocampus can be spared with modest changes in a volumetric-modulated SRS plan. Prospective and retrospective studies of SRS with and without the anti-angiogenic agent bevacizumab in patients with recurrent glioma s/p standard chemoradiation show that the combined approach offers reasonable local control with low toxicity (median OS 8.5 months in 210 GBM patients.) However, patients who had been treated with BVZ more than 3 weeks before SRS exhibited poorer survival than those patients only treated with BVZ during or after SRS (5.1 vs 12.6 months.) A simple computational model informed by a patterns of failure analysis suggests that the addition of agents that control "distant" brain disease are essential complements to SRS in optimizing long-term control.

Keywords: Stereotactic Radiosurgery (SRS), Brain Metastases, Recurrent Malignant Gliomas, Tumor Response, Normal Tissue Damage, Radiobiologic Modelling

The "New Biology" of Single Dose Radiotherapy

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ABSTRACT

Introduction: Single dose radiotherapy (SDRT), facilitated by image guidance and intensity modulation technologies that improve precision in tumor targeting to reduce risk of normal tissue toxicity, has revolutionized cancer treatment with local control rates ≥90%, even in tumors resistant to conventional fractionation. While classic radiobiology focuses on response of tumor cells rather than non-tumor microenvironmental cells, initial pre-clinical studies in our lab found disruption of tumor vasculature obligate for SDRT cure.

Results and Discussion: SDRT-induced endothelial cell dysfunction results from activation of acid sphingomyelinase (ASMase), converting sphingomyelin to the second messenger ceramide in endothelial plasma membranes, events inhibitable by VEGF-121 or VEGF-165. Conversely, precisely timed delivery of anti-angiogenic agents, such as anti-VEGFR2 Ab DC101 (Imclone), de-represses ASMase activity, synergistically increasing SDRT-induced ceramide elevation, enhancing endothelial dysfunction. That ceramide is critical for anti-angiogenic radiosensitization is evidenced by □nti-ceramide Ab inhibition of DC101-enhanced endothelial damage and radiosensitization. These results translate *in vivo*, as anti-VEGFR2 DC101 or anti-VEGF G6-31 (Genentech) synergistically increase SDRT-induced endothelial injury in numerous solid tumor types, only if delivery timed to maximally enhance ASMase signaling. In contrast, tumors in *asmase*$^{-/-}$ mice, which provide damage-resistant vasculature, are radioresistant and unaffected by either anti-angiogenic agent. This presentation will review fundamentals of this "New Biology" and present unpublished data that define a mechanism coupling ceramide-driven endothelial dysfunction to DNA repair in tumor cells.

Keywords: Single Dose Radiotherapy, Acid Sphingomyelinase, Ceramide, Anti-angiogenic, Microvasculature

Ultrasound Tissue Characterization at Multiple Scales to Inform Tissue Characterization Approaches for Treatment Monitoring

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ABSTRACT

Ultrasound (US) imaging is predominantly used in B-mode, were changes in tissue echogenicity are displayed on a monitor. This typically provides information about anatomical structures that can be resolved. However, US can be used to infer the structure of sub-resolution tissue scatterers by quantitative analysis of the US backscatter data. The analysis is typically based on "raw" radiofrequency (RF) data that is collected by the ultrasound transducer, and subsequently normalized a reference to make the measurement system independent. The RF data can be analysed to make inferences about the tissue microstructures that modify the frequency dependence of the backscatter and other characteristics of the scattered signal. By collecting data from specimens at different frequencies, sub-resolution scattering sources and tissues can be probed at different length scales.

In this presentation and overview will be provided of the insights gained from the analysis of ultrasound scattering at different length scales, with an emphasis on detecting the changes in tissue / cellular structure that occur during cell death as a result of cancer therapeutics. Data have been collected with clinical instrumentation (Ultrasonix and Versonics between 1-15 MHz), high-frequency ultrasound instrumentation (VisualSonics VEVO-770/LaZR, between 20-60MHz) and acoustic microscopy (above 100MHz). Ultrasound backscatter was collected from different model systems, ranging from cell pellets to tissue engineered constructs and in-vivo tissues.

An overview of the work of the last 15 years will be presented, with an emphasis on recent results using acoustic microscopy. Changes in cellular structure result in concomitant changes in the ultrasound backscatter and its frequency dependence, that can be correlated to changes in particular cellular structures, such as the cell nucleus. This correlation is stronger when the interrogation frequency has a wavelength similar to that of the size of the nucleus. The important role of the spatial organization of the scattering sources, or what is known as the structure factor, will be emphasized. Recent results using co-registered ultrasound and photoacoustic imaging to better understand ultrasound scattering will be presented.

In summary, ultrasound can be used to generate imaging biomarkers of tumor treatment response, without the need for external contrast agents. Correlations of changes in ultrasound scattering with tumor treatment response indicate that for highly cellular tumors, changes in nuclear structure cause the changes in ultrasound backscatter detected.

Keywords: Tissue Characterization, Ultrasound Imaging

The Current Landscape of Radiosensitization Strategies using Gold Nanoparticles

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ABSTRACT

Introduction: Radiation therapy is a long-established component of modern therapy for localized cancers. However, its ultimate utility is limited by the inherent resistance of some cancer cells to ionizing radiation. To circumvent this problem, radiation dose escalation, targeting resistance pathways or resistant cells with novel agents, or image-guided tumor-targeted therapy are currently being investigated. Emerging evidence from an explosion of knowledge and research regarding oncologic uses of gold nanoparticles suggests that unique solutions to each of these problems of radiation resistance can be formulated via the use of gold nanoparticles.

Materials and Methods: Gold nanoparticles can be used to augment the efficacy of radiation therapy via physical dose enhancement based on an increase in photoelectric absorption due to the high atomic number (Z) of gold that accumulates preferentially within the tumor due to passive extravasation of nanoparticles through "leaky" tumor vasculature. This radiation dose enhancement can be heightened via biological targeting.

Enhancement of radiation therapy efficacy can also be achieved via extrinsic actuation of tumor-homing nanoparticles to generate mild temperature hyperthermia which enhances vascular perfusion and reduces hypoxia initially and causes vascular disruption subsequently to improve radioresponse. The extrinsic energy source is light for colloidal gold nanoparticles with a large absorption cross section that absorb and scatter light strongly at a characteristic wavelength (their plasmon resonance) and have a high thermal conductivity to couple this heat to the surrounding tissue.

Results and Discussion: This talk will review the current understanding of the use of metallic nanoparticles as radiosensitizers, and outline a path to potential clinical translation of these concepts of radiation sensitization. The interface between nanotechnology and radiation oncology warrants continued investigation by interdisciplinary teams of physicists, chemists, biologists, clinicians, and engineers in industry and academia.

Keywords: Radiation, Gold Nanoparticles, Dose Enhancement, Hyperthermia

Trends In Radiation Therapy: An Industry Perspective

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ABSTRACT

Introduction-Title*:* *"Trends in Radiotherapy: An Industry Perspective"*

Text:

The following are trends in radiation therapy (RT) that seem important:

1. High Definition Radiotherapy: The implications of expanding indications for SRS/SBRT have resulted in ushering an era of High Definition Radiotherapy where modern delivery devices have increasing capabilities of compacting delivered RT doses combined with improving guidance. This enables the use of ever increasing doses per fraction.
2. Multidisciplinary Care in Oncology: From a patient-centric point of view, the journey of cancer care is still a disjointed and difficult one. From diagnosis to survivorship, better tools have to be provided to enable better decision making, improved coordination and constructive patient engagement.
3. Immunotherapy: One of the most exciting breakthroughs in cancer care in recent years, immunotherapy is particularly well suited to be combined with radiation therapy, to improve outcomes after therapy for a multitude of cancers. This potentially opens the door for radiotherapy (in combination with immune drugs) to play an increased role in the management of metastatic cancers. In the coming years, understanding the optimal combination of RT with immunotherapy in different clinical contexts should be a primary objective.
4. Access to High-Value Care: Access to care, particularly to cost-effective quality care, is a priority to all. Global expansion of quality radiotherapy will require increased automation, reliability and simplicity of delivery devices and associated workflows. Evidence-based, cost-effective solutions that can be adaptated to resource-deprived will be needed.
5. Radiation Medicine: RT application outside oncology should be investigated. Preliminary results on the use of SBRT for the treatment of Ventricular Tachycardia are promising.

Keywords: High Definition Radiotherapy, Multidisciplanary Care in Oncology, Immunotherapy, Access to High-Value Care, Radiation Medicine.

Innovations in Interstitial Brachytherapy

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ABSTRACT

Introduction: Locally advanced gynecological cancers are complex diseases as the invasive nature of these tumours make conformal radiation treatment dose delivery challenging. Interstitial brachytherapy enables the delivery of targeted radiation through source channels that are embedded within the tumour by catheter needle insertion. In the past, this technique has not had widespread adoption due to lack to expertise and image-guidance.

Materials and Methods: This presentation will review novel imaging research in gynecological and interstitial brachytherapy to enhance and optimize this technique to help improve patient treatment.

Results and Discussion: With the introduction of 3D image-guidance and planning in brachytherapy, there is an increasing adoption of interstitial brachytherapy. Furthermore, there is an opportunity to optimize this technique through new imaging modalities
and 3D image guidance techniques.

Keywords: Gynecology, Brachytherapy, Interstitial

MRI-Guided Adaptation: From Anatomy to Biology

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ABSTRACT

Introduction: Adaptive Radiation Therapy (ART) is a state-of-the-art approach that uses a treatment feedback process to account for patient-specific anatomic and/or biological changes, thus, delivering highly individualized radiation therapy for cancer patients. ART is being enhanced with the recent introduction of MRI in radiation therapy. MRI offers superior soft tissue contrast and a wide array of physiological information, improving ART planning and delivery. The potentials and applications of MRI-guided ART will be discussed.

Materials and Methods: Basic components of ART include: (1) detection of anatomic and biological changes, often facilitated by multi-modality images before and during the treatment course; (2) adaptive planning optimization to account for the patient-specific spatial morphological and biological changes with consideration of radiation responses, and (3) technologies to precisely deliver the optimized plan to the patient. Strategies for ART include on-line and off-line approaches. The introduction of MRI-guided RT allows adaptation based on the tumor and/or normal tissue anatomy and biological information. In this presentation, anatomic and physiological MRI guided ART for pancreatic cancer will be discussed.

Results and Discussion: Recent advances in MRI in RT, deformable image registration for contour generation and dose tracking, fast and efficient plan optimization, and fast quality assurance method have enabled the implementation of ART in the clinic. MRI significantly improves target and normal structure delineation, allowing ART to be accurately practiced. Data obtained recently on MRI-guided ART will be presented.

Keywords: Adaptive Radiation Therapy, MRI in RT, RT for Pancreatic Cancer

Unraveling the Biology of Recurrent Radioresistant Cancer

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ABSTRACT

Introduction: Recurrent tumours tend to display an aggressive phenotype including increased proliferation and acquisition of a higher tumour grade, which clinically manifests as larger tumours that are typically associated with lymph node metastases, and a worse prognosis. To investigate the biological basis for this, we treated prostate cells with a clinical conventional fractionated (CFRT) schedule, and noted that the surviving cells became radioresistant and acquired an aggressive phenotype which mimics the clinical situation. In a similar manner, we treated cells with a clinical hypofractionated (HFRT) schedule, and discovered that, surprisingly, the surviving cells do not display an aggressive phenotype. To our knowledge, there have been no reports directly comparing the CFRT and HFRT phenotype, despite the clinical importance of treatment shift from CFRT to HFRT. We performed gene array (mRNA) and bioinformatics analysis to identify molecular determinants of radioresistance.

Materials and Methods: CFRT and HFRT resistant cancer cells were subjected to gene array analyses (Affymetrix), and bioinformatics analyses performed. Genes with significant differential mRNA abundance were identified. Real-time PCR was used to validate the findings. Cellular assays for radiation survival, proliferation, invasion and activation of survival pathways were performed on DU145 and PC3 cells treated with shRNA to knockdown genes of interest.

Results and Discussion: We discovered that BCHE (Butyrylcholinesterase) abundance was significantly reduced in both prostate cancer relative to normal prostate tissue. Similarly, it was also reduced in CFRT and HFRT cells compared to parental controls. Knockdown of BCHE in parental controls resulted in increased clonogenic survival, and proliferation following irradiation. Additionally, we noted increased activation of the pro-survival Akt pathway, and enhanced invasive capacity. We believe that low expression of BCHE may be a marker of aggressive and radioresistant prostate cancer. Ongoing studies are investigating its influence on *in vivo* tumor xenograft growth and radiation response. Future studies will evaluate its role as a predictive biomarker for tumor radiation response in patients.

Keywords: Radioresistance, mRNA, BCHE

Sharpening a Knife with Precision Dose Sculpting

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ABSTRACT

Introduction: Multiple studies have reported apparatus-dependent capabilities in sparing normal tissue sparing for intracranial stereotactic radiosurgery (SRS). Such studies included Gamma Knife, CyberKnife, and Linear accelerator-based X-ray knife. One major apparatus-dependent characteristic was the dose fall-off gradient surrounding a treatment volume, i.e., "sharpness of a knife". Despite multiple empirical estimates, the maximum knife sharpness that can be physically achieved remains unclear. In this project, we approached this challenge by investigating means of creating the sharpest knife possible via precision dose sculpting for ultra precise intracranial SRS treatments.

Materials and Methods: Three US patents co-developed by the lead author on techniques and implementations of precision dose sculpting are described. As proof of concept studies, prototype implementations of the dynamic dose painting have been tested for (1) the latest Leksell Gamma Knife Perfexion (PFX) treatment for large or complex intracranial lesions, (2) rotational volumetric arc beam treatments (VMAT) i.e. X-ray knife for multiple brain metastases. For PFX, peripheral dose sharpening was executed by augmenting the total number of beams (for example, by a factor of 3 to 20) via patient head tilt and/or sector beam intensity modulation. This technique was implemented on 20 clinical cases treated with the standard technique. For VMAT, a broad-range optimization approach (BROOMBA) was developed via selecting and connecting 20-30 beams from all possible beam directions surrounding a patient's cranium. The method was tested on a simulated multiple brain metastases case with 3 to 12 brain lesions. Finally, comparisons between the sharpened dose result and the standard treatments were carried out for both PFX and VMAT delivery

Results and Discussion: For PFX delivery, the beam-on time for beam number enhancement (BNE) treatment plans was found to be comparable with standard treatment. The composite dose gradient index and the low-level spillage isodose volumes were found significantly improved (by as much as 20%) for BNE treatment plans versus the conventional treatment plans. For VMAT delivery, BROOMBA treatment plans consistently surpassed conventional VMAT treatment plan quality, especially in terms of dose to normal brain and inter-lesion dose interference effects (by as much as 65% reduction for low-level isodose volumes). In summary, precision dose sculpting with a large number of confocal radiation beams and case-specific beam-path optimizations is promising to advance brain SRS by maximally sparing normal tissue and by targeting complex tumor burden patterns and distributions within a treatment volume.

Keywords: Stereotactic Radiosurgery, Dose Painting, Gamma Knife, CyberKnife, VMAT

Functional Imaging and Integration of MR

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ABSTRACT

Image guidance has made large advances as cross-sectional imaging has been fully integrated into radiation therapy planning and anatomical imaging has increasingly become part of the radiation treatment delivery. In parallel, imaging sciences have advanced beyond high-spatial/temporal resolution anatomical imaging to molecular and functional imaging, including functional MRI and PET that can assess heterogeneous biological tumor properties. A growing body of data shows promise for the therapeutic impact of advanced molecular and functional imaging biomarkers for tumor response and treatment cancer outcome.

Intra-treatment imaging (rather than pre- and post-treatment) is being increasingly explored, and the concept of adaptive therapy, guided by intra-treatment imaging, has been demonstrated not only of radiotherapeutic but also for systemic therapy approaches. Parallel advances in image-guided radiation therapy delivery and in the diagnostic capabilities continue to converge. Practical integration of functional imaging into radiation therapy is the new frontier.

Functional imaging integration has been well demonstrated in radiation therapy for CNS tumors. Gynecologic cancer is a prime example of shifts in the current paradigm, where the initially observed diagnostic benefits of MRI in tumor delineation are now becoming deeply integrated into the therapeutic approach. In MRI-guided brachytherapy for cervical cancer favorable outcome results are emerging and this concept is increasingly moving into practice while challenging logistics of its implementation are being overcome. MRI-guided adaptive external beam radiation planning and delivery offer personalization of treatment as well. Similarly PET imaging can provide critical diagnostic (pre-/post-therapy) information that correlates with treatment response and survival. Future opportunities for a comprehensive adaptive planning paradigm, that spans the continuum of combined modality therapies, based on functional MRI and molecular imaging, are exciting and need further validation studies.

While technologic capabilities are evolving rapidly, the seamless integration of functional imaging into the radiation therapy course and delivery remains challenged by efficient workflows and standardized approaches that require development, and by insurance approvals in a declining health care economic environment.

Approaches to the integration of functional imaging in various tumors, strategies, challenges and opportunities will be discussed.

Keywords: MR, Functional Imaging, Radiotherapeutics

Development of Three-Dimensional Ultrasound Scanner and Needle Template Localizing Arm for Guidance of Permanent Seed Breast Brachytherapy

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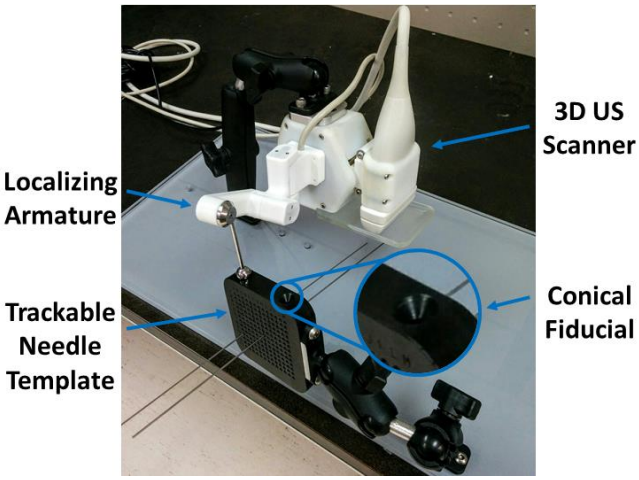
ABSTRACT

Introduction: Permanent breast seed implantation (PBSI) is a type of low dose-rate brachytherapy used in breast conserving therapy of early stage breast cancer that reduces radiation treatment time to a single visit. PBSI uses needles to implant 'seeds' of radioactive Pd-103 under 2D ultrasound guidance. A limiting factor to wider adoption of PBSI is operator dependence, caused primarily by limitations of 2D ultrasound. Our goal is to develop a guidance system that uses 3D ultrasound (3D US) and an instrumented mechanical arm for localizing the needle template in order to reduce operator dependence and procedure time while increasing implantation accuracy.

Materials and Methods: A 3D US system was constructed consisting of a mechanically moved and tracked 2D ultrasound transducer. Images are captured using a laptop and commercial screen-grabber and reconstructed into a 3D volume. Additionally, a mechanical arm with 3 encoded joints was constructed and mounted to the scanner. The spherical tip of the arm fits into conical fiducials on the needle template so that it can be localized relative to the imaging volume. 3D reconstruction was validated, 1) geometrically, using distance measurements of strings with 10 mm spacing in three directions, and 2) volumetrically, using volume measurements of patient specific agar phantoms compared to water displacement measurements. Volunteer scans were conducted to demonstrate clinical proof of concept. Arm measurements were validated using a testing jig of 45 divots with 4 mounting positions for the scanner, creating 180 known positions. Each position was measured 3 times, with parameters for calculating point measurements from arm encoders tuned using 60 positions and accuracy validated using the remaining 120. 95% confidence intervals are reported for distance and volume measurements (median; Wilcoxon signed rank test and mean; unpaired student's t-test, respectively). Median and interquartile range of the validation error (mm) is reported for localizing arm point measurements.



Results and Discussion: Geometric validation showed 95% confidence intervals within ± 2% of nominal and volumetric validation showed differences of <5.3% between 3D US and water displacement measurements (95% confidence intervals <10% difference). Volunteer scans produced clinical quality images with positive user feedback. Arm validation measurements showed median (interquartile range) errors of 0.475 mm (0.150 mm). A 3D US scanner tailored to the needs of PBSI has been developed and validated for geometric and volumetric accuracy, as well as clinical proof of concept. A localizing arm has been constructed and its 3D accuracy validated to approximately ¼ mm. Future work includes validating localization of the needle template from point measurements and integration of the localized needle template with a 3D US volume into a common coordinate system for 3D visualization.

Keywords: Image Guided Therapy, Brachytherapy, Breast Cancer, Radiation Therapy, Ultrasound

Evaluation of a Machine-Learning Algorithm for Treatment Planning in Prostate Low-Dose-Rate Brachytherapy

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ABSTRACT

Introduction: This work presents the first known incorporation of machine learning (ML) to automatically generate high-quality, prostate Low-Dose-Rate (LDR) brachytherapy treatment plans. The ML algorithm has the ability to mimic implant characteristics of expert brachytherapists. The planning efficiency, dosimetric and clinical quality of plans generated using an ML planning approach was evaluated in this study.

Methods & Materials: Pre- and post-implant treatment plans were extracted from 100 high-quality LDR treatments and stored within a training database. The ML algorithm matches similar features from a new LDR case to those within the training database to rapidly obtain an initial seed distribution; plans were then further fine-tuned using a stochastic local search algorithm. Pre-implant treatment plans generated by the ML algorithm were compared to brachytherapist (BT) treatment plans in terms of planning time (Wilcoxon rank sum, $\alpha = 0.05$) and dosimetry (one-way ANOVA, $\alpha = 0.05$). Qualitative clinical implant quality was evaluated by expert LDR radiation oncologists using a Likert scale questionnaire.

Results & Discussion: The average planning time for the ML algorithm was 0.84 ± 0.57 min compared to 17.88 ± 8.76 min for the expert planner ($p=0.020$). Treatment plans were dosimetrically equivalent to the BT plans; the average prostate V150% was 4% lower for ML plans ($p=0.002$); although, not clinically significant. Respondents ranked the ML generated plans as equivalent to expert BT treatment plans in terms of target coverage, normal tissue avoidance, implant confidence, and the need for plan modifications. Respondents had difficulty differentiating between plans generated by a human or the ML algorithm.

Prostate LDR treatment plans that have equivalent clinical and dosimetric quality to plans created by brachytherapists can be rapidly generated using ML. The adoption of ML in the brachytherapy workflow is expected to produce high quality LDR treatment plans uniformly, while dramatically reducing planning time and resources.

Keywords: Brachytherapy, Machine Learning, Treatment Planning, Low-Dose-Rate, Optimization

Magnetic Resonance Imaging-Guided Brachytherapy

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ABSTRACT

Introduction: With the increased accessibility of magnetic resonance imaging (MRI) and its superior soft tissue contrast, there has been an increase in its usage for brachytherapy treatment planning and treatment response evaluation. There is growing evidence to suggest that improvements in accuracy of target delineation in MRI-guided brachytherapy may improve clinical outcomes in cervical cancer.

Materials and Methods: Detection of residual tumour volume during radiotherapy has been accomplished using repeated MRI, which is shown to improve clinical outcomes in brachytherapy of cervical cancer and prostate cancer. These benefits start to change the clinical practice toward individualizing treatments which helps maximize the dose received by a specific region of interest while minimizing the dose to the surrounding normal structures.

Results and Discussion: To implement a high quality image guided brachytherapy program, a multidisciplinary team is required with appropriate expertise as well as an adequate patient load to ensure a sustainable program. It is imperative to know that the most important source of uncertainty in the treatment process is related to target delineation and therefore, the necessity of training and expertise as well as quality assurance should be emphasized.

Keywords: MRI, Brachytherapy, Cervical Cancer, Prostate Cancer

Gamma Knife Icon: Early North American Experience

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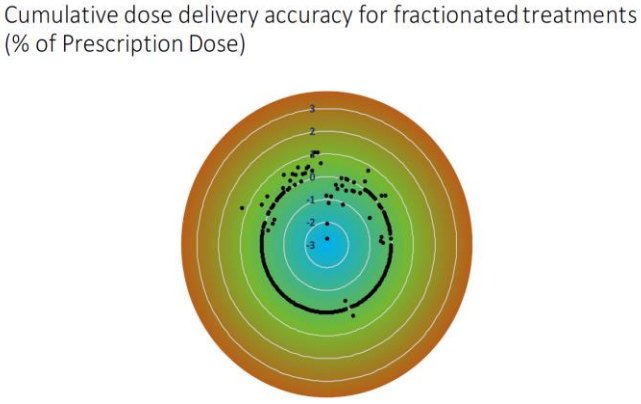
ABSTRACT

Introduction: Gamma Knife Icon represents a major change in both fixation options and image based on set verification of patient position, and raises interesting questions regarding fractionation of treatments for different pathologies. This study aims to report the early experience with this technique and the unique questions it raises to serve as the launch point for the design of clinical trials for our patients.

Materials and Methods: 360 patients were treated with the ICON for different pathologies till September 2016. 100 of these were immobilized with a mask. Delivery reproducibility data and intra-fraction motion data was collected and is reported. Impact of these motions was analyzed in dosimetric terms
Two different mask materials were compared for their thermal annealing and pressure characteristics on a humanoid phantom.

Results and Discussion: Variations in dose delivery based on inter fraction repositioning was less than 1% plus minus of the prescribed dose. Variations in intra-fraction motion yielded negligible alteration in delivered dose to target. These findings can guide patient selection by indication for the appropriate fixation technique.
Thermoplastic masks used with the ICON have long curing curves, making them best suited to prefabrication at least 1 day prior to treatment delivery for minimizing intra-fraction motion
Clinical outcomes over the short term are comparable to frame based patients.



Keywords: Gamma Knife Icon, Radiosurgery, CBCT, Image Guidance, Thermoplastic Mask

The Promise of the MRI LINAC: Simultaneous MRI and Irradiation

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ABSTRACT

Introduction: Image guidance during radiotherapy is widely applied in the current clinic. Prior to treatment a variety of imaging modalities is used to localize and characterize the tumour and the surrounding organs at risk. These data are used to optimize the treatment plan, i.e. optimize the radiation dose delivery. Still, during the course of radiotherapy many sources of geometrical uncertainties exist, leading to treatment margins and with that to unwanted involvement of healthy tissues in the targetted volume. By integrating 1.5 T MRI functionality with a radiotherapy linear accelerator (linac), the anatomy can be visualized during irradiation and thus decreasing the geometrical uncertainties and improve the targetting.

Materials and Methods: Together with Elekta (Stockholm, Sweden) and Philips (Best, The Netherlands) a 1.5 T MRI system is integrated with a 7.2 MV linac. The active shielding of the MRI as well as the layout of the linac is modified to mitigate the magnetic interference. A dedicated cage of Faraday was designed to mitigate the RF interference and a beam window in the MRI was created to allow beam passage.
In parallel with the hardware developments a pipeline for daily online and ultimately real-time plan adaptation has been set-up. This enables to adapt the plan as soon as an anatomical change is detected. The pipeline can re-optimize the treatment plan for the latest state of the anatomy while taken into account the dose delivered so far. This loop can be run daily but also on an intra-fraction time scale.

Results and Discussion: The first prototype MRI linac gave the proof of concept for simultaneous irradiation and MRI. The second prototype showed MRI guided IMRT. The third prototype in Utrecht is the pre-production MR linac and currently the fourth MR linac is installed, this is the pre-clinical MR linac that will be introduced in the clinic.
The adaptive treatment pipeline has been shown to converge for regular clinical plans. Also for changing anatomies over the course of days and for changes during a single fraction the dose distribution converges to a clinically acceptable dose distribution. Currently the loop is fast enough, in the order minutes, for daily plan adaptation. We are working on speed optimization for the intra-fraction applications.

In summary, the 1.5 T MRI linac is operational in a research setting and work on the clinical introduction is ongoing. The advent of on-line MRI directly from the treatment table enables true on-line adaptive radiotherapy.

Keywords: MRI, Radiotherapy, Hybrid, Simultaneous, Online Adaptive Radiotherapy

Brain Hypofractionated Radiosurgery for Metastases: Rationale and Outcomes

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ABSTRACT

Introduction: Stereotactic radiosurgery has traditionally been a single fraction invasive head frame procedure delivering doses in the order of 15-24 Gy. The treatment is limited to smaller tumors and ones in non-eloquent brain locations. For tumors greater than 2 cm, or in eloquent areas, single fraction radiosurgery is associated with compromised local tumor control secondary to a dose de-escalation required to satisfy normal tissue safety constraints. The development of hypofractionated radiosurgery is increasingly practiced and refers to the delivery of >5 Gy per fraction stereotactically over 3 to 5 days, and total doses typically ranging from 24 to 40 Gy.

Materials and Methods: A review of the clinical literature to support the clinical rationale and radiobiological rationale. Data from the Sunnybrook Odette Cancer Center will also be presented.

Results and Discussion: Outcomes suggest superior efficacy and safety profiles for metastases >2 cm treated with hypofractionated radiosurgery as compared to single fraction radiosurgery. The use of hypofractionation for surgical cavities will also be discussed as an area of development and one where the rationale supports hypofractionation as compared to single fraction practice. Future trials in need will also be discussed.

Keywords: Brain Metastases, Hypofractionation, Radiosurgery

Facing the Future of Radiation Oncology

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ABSTRACT

Introduction: There is a clear trend in radiation oncology toward hypofractionated treatment (including stereotactic body radiotherapy, or SBRT, and stereotactic radiosurgery, or SRS). For many patients with lesions of the brain, lung, liver, kidney, pancreas, prostate, spine, etc., treatment with a few high-dose fractions will eventually be the standard of care. Accuray is committed to developing technologies that exceed the demands of this changing landscape.

Results and Discussion: In this presentation three major developments in Accuray technology will be presented; the CyberKnife M6 System with the Incise MLC, the Radixact System (the next generation TomoTherapy System), and the integrated Accuray Precision treatment planning software. The unique approaches they enable to the treatment of cancer in the primary and recurrent setting, for reirradiation and treatment plan adaptation, will be highlighted. Excellent treatment plan quality, dose placement accuracy, and adaptive flexibility enable these Accuray systems to meet the unique demands of cancer treatment for each patient through the entire course of their disease.

Keywords: Accuray, Adaptive Radiotherapy, CyberKnife, Hypofractionation, Radixact, Stereotactic Body Radiotherapy, Stereotactic Radiosurgery, TomoTherapy

MRI-Guided Direction Modulated Brachytherapy for Cervical Cancer

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ABSTRACT

Introduction: A novel, MRI-compatible, intrauterine tandem design that is capable of creating *anisotropic* ^{192}Ir radiation profiles is proposed. Our intention is, in combination with inverse planning optimization, to achieve improved dose conformality for HDR treatment of cervical cancer. This treatment concept is termed Direction Modulated Brachytherapy (DMBT).

Materials and Methods: The proposed DMBT tandem applicator has 6 peripheral grooves of 1.3mm width, along a 5.4mm thick nonmagnetic tungsten alloy rod of density 18.0g/cm^3, capable of generating directional dose profiles. We performed a comparative planning study with 45 cervical cancer patients enrolled consecutively in the prospective observational EMBRACE study. In all patients, MRI-based planning was performed while utilizing various tandem-ring (27 patients) and tandem-ring-needles (18 patients) applicators, in accordance with the GEC-ESTRO recommendations. For unbiased comparisons, all cases were replanned with an in-house developed inverse optimization code while enforcing a uniform set of constraints that are reflective of the clinical practice. All plans were normalized to the same CTV_{HR} D90 values achieved in the original clinical plans.

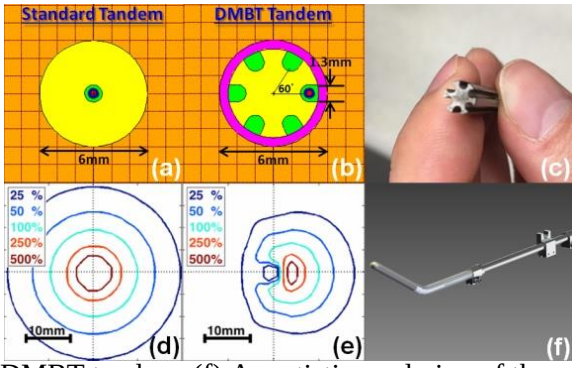

Figure 1. The proposed DMBT-concept tandem applicator design. A (a) standard plastic tandem and (b) DMBT tandem cross-section with 6 peripheral holes carved out of a nonmagnetic tungsten alloy rod of 5.4-mm diameter, housed by a thin plastic sheath with 0.3mm wall thickness. (c) A successfully machined-to-specifications tungsten alloy piece to demonstrate the manufacturability of the applicator. The Monte Carlo simulated isodose distributions of an ^{192}Ir source inside a (d) standard tandem and a (e) DMBT tandem. (f) An artistic rendering of the concept applicator in full assembly.

Results and Discussion: In general, if the standard tandem is replaced with the DMBT tandem whilst maintaining all other planning conditions the same, there was consistent improvement in the plan quality. For example, amongst the 18 tandem-ring-needles cases, the average D2cm^3 reductions achieved were -2.48±11.03%, -4.45±5.24%, and -5.66±6.43% for the bladder, rectum, and sigmoid, respectively. An opportunity may also exist in avoiding use of needles altogether for when the total number of needles required are small (about 2-3 needles or less), if DMBT tandem is used.
Integrating the novel DMBT tandem onto both intracavitary and intracavitary-interstitial applicator assembly enabled consistent improvement in the sparing of the OARs, over a standard "single-channel" tandem, though individual variations in benefit were considerable. While at early stage of development, the DMBT concept design is demonstrated to be useful and pragmatic for potential clinical translation.

Keywords: DMBT, MRI-guided Adaptive Brachytherapy, Tandem Applicator, Cervical Cancer

Advanced MR Imaging and Radiation Response

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ABSTRACT

Introduction: The use of *radiation therapy* for the treatment of patients with solid tumours has been a standard clinical practice. Reliable biomarkers which allow for expeditious assessment of tumour response to radiation therapy are highly sought-after. Multiple treatment options are available, however, they require an early assessment of tumour response in order to switch the treatment while still within an effective time window. Current clinical practice is subjective, and relies heavily on the RECIST criteria which judge response by the largest intra-tumoral distance. This is inadequate for describing early apoptotic changes in cell structure which precede changes in tumour dimension that may not stabilize until weeks or months after treatment. Tumour biopsy may be informative, but is often too invasive, especially in the brain, and not completely descriptive of a heterogeneous tumour with a heterogeneous response. Managing radiation-induced late effects is also challenging, as high radiation doses increase the likelihood of developing necrosis which occurs months after treatment. It is difficult to differentiate radiation-induced changes from tumour progression using conventional MRI since they both appear as an enlarging enhancing region on post-Gadolinium (Gd) T1-weighted MRI, and as increased vasogenic edema on T2w-FLAIR.

Materials and Methods: We discuss the use of two quantitative MRI methods: Chemical Exchange Saturation Transfer (CEST) to assess tumour metabolism and Dynamic-Contrast-Enhanced MRI (DCE-MRI) to evaluate vascular and intra-extracellular cellular structure. The study was performed on a clinical 3T MRI system (Phillips) in 30 patients undergoing stereotactic radiosurgery (SRS) for brain metastasis. The patients were scanned before the SRS treatment and one and four weeks after.

Results and Discussion:
We were able to show that:

1. Quantitative assessment of changes in tumour metabolism (using CEST), and changes in tumour cellular microstructure as measured by intra-extracellular water exchange, were able to **separate responders from non-responders** one-week post treatment.
2. Quantitative MRI (qMRI) could also **predict, one week after treatment,** how much shrinkage of the original tumour mass may occur after one month.
3. Certain quantitative features of CEST (most notably Nuclear Overhauser Effect) could predict the tumour response **before treatment was administered**. This has significant implications, as the current model of "one size fits all", where tumours are given the same dose of radiation, can be changed to a radiation dosing scheme based on pretreatment CEST features of the tumour (Appendix 1).
4. CEST was capable of differentiating radiation necrosis from tumor progression in brain metastases.

Keywords: Chemical Exchange Saturation Transfer, SRS, Tumour Response, Brain Metastasis

Development of Animal Models for Radiation Engineered Oncology - Experiences and Potential Pitfalls

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ABSTRACT

Introduction: Pre-clinical experiments involving focused ultrasound and therapeutic radiation oncology are becoming increasingly advanced and technically challenging. Because variations in biological effects can be considerable when using small animal systems, any variations in treatment delivery must be kept to a minimum, or else the interpretation of experimental results may be jeopardized.

Materials and Methods: To this end we have compiled a summary of important factors to consider when setting up quality assurance programs for animal models, as well as potential pitfalls that may not be obvious but can be quite problematic. This includes our own experiences form the last few years of research involving tumor treatments with focused ultrasound, normal tissue radiation injury, and radiation-induced immunotherapy using animal models.

Results and Discussion: Some of the key examples include the use of imaging modalities for targeted hepatic irradiation, thermal and spatial phantom studies for focused ultrasound localization, and the importance of systematic animal handling procedures. We will share our experiences with issues such as unwanted and unexpected morbidity and mortality, uncertainty related to whether the correct dose was delivered to the intended target, and how to implement precise and accurate targeted treatment models. The importance of systematic quality assurance procedures will be discussed for the various examples and how we chose to implement these in order to ensure the reliability of experimental results.

Keywords: Animal Models, Quality Assurance Programs, Image-guided Therapy, Normal Tissue Injury, Precision Delivery

Dosimetric Feasibility of the Hybrid Magnetic Resonance Imaging (MRI)-LINAC System for Brain Metastases: The Impact of the Magnetic Field

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ABSTRACT

Introduction: The hybrid MRI-LINAC (MRL) system consists of an integrated diagnostic-quality 1.5 T MRI and a 6-MV LINAC to allow for on-line position verification, treatment monitoring, and potential real-time MR imaging during irradiation. We aimed to investigate the feasibility of delivering stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy with the MRL for patients with single brain metastases, and to characterize the dosimetric impact at tissue-air interfaces resulting from the electron return effect (ERE).

Materials and Methods: 24 patients treated for intact single brain metastases between January and October 2015 were selected for analysis. Three radiotherapy plans with the same prescribed dose were generated for each case: 1) standard noncoplanar volumetric modulated arc therapy (VMAT) as per institutional protocol, 2) coplanar step-and-shoot intensity modulated radiotherapy (IMRT) on the MRL in the absence (MRL_B=0), and 3) in the presence of the transverse magnetic field (MRL_B=1.5). All plans were optimized to achieve at least 98% coverage of the planning target volume (PTV) with 100% of the prescription dose (V100% > 98%) while meeting all organs-at-risk (OARs) constraints. The plans were evaluated using cumulative dose-volume histograms (DVHs) and by calculation of Paddick conformity index (PCI), V100%, V12Gy minus gross tumor volume (V12Gy – GTV), and V2Gy. The dosimetric impact of ERE to the skin and air cavities was quantified using a 5 mm rim of tissue around tissue-air boundaries.

Results and Discussion: All plans met the objectives with respective to target coverage and OAR constraints. The mean PTV was 10.05 cm3 (range 0.13-63.05 cm3). Differences between all investigated dosimetric parameters significantly favored the VMAT plans as compared to the MRL_B=0 and MRL_B=1.5 plans, except for V2Gy. The VMAT plans showed a higher mean (± standard deviation) PCI compared to the MRL_B=0 and MRL_B=1.5 plans (0.85 ± 0.08 vs. 0.79 ± 0.09 vs. 0.78 ± 0.11). The mean V12Gy – GTV and V2Gy marginally favored the MRL_B=0 plans compared to the MRL_B=1.5 plans (mean difference: 0.45 cm3, $p = 0.0019$ and 16.46 cm3, $p = < 0.0001$, respectively). In the presence of the magnetic field, ERE resulted in a statistically significant but small increase in mean dose and D2cc in the skin (0.08 Gy, $p < 0.0001$ and 0.66 Gy, $p < 0.0001$, respectively) and around air cavities (0.07 Gy, $p = 0.0092$ and 0.25 Gy, $p = 0.0004$, respectively). In conclusion, stereotactic radiation to single brain metastases is feasible using the MRL Monaco treatment planning system; however, in its current iteration, application to small targets deserve careful consideration given the technical limitations resulting in less favorable plan quality compared to that of a noncoplanar standard VMAT technique. The dosimetric impact of ERE at tissue-air boundaries is minor and does not compromise target conformity or dose gradient.

Keywords: MRI-Linac, Electron Return Effect, Brain Metastases, Stereotactic Radiosurgery, Stereotactic Radiation

Technology Solutions for Modern Management of Cerebral Metastatic Disease

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ABSTRACT

Introduction: Improved systemic therapies are transforming management of patients with secondary brain metastasis as overall survival has dramatically amplified across all histologies. A wide scale change in clinical decision making continues to increase utilization of focal therapies with curative intent, and we are observing a paradigm change toward avoidance or delay of WBRT. As quality of life and neurocognitive preservation become major considerarions for a growing population of patients with improved survival prognosis, better tools are necessary to assess treatment response and provide timely inputs for addressing therapy change.

Results and Discussion: The presentation focuses on modern requirements for mutli-disciplinary programs to better integrate surgical and radiosurgerical practices in the upfront setting; tools for longitudinal patient monitoring, and new metrics for better trcking and reporting of outcomes and QoL parameters. New software solutions from Brainlab will be presented together with a clinical review (courtesy of Novalis Circle) of treatment response challeges for patients who survive radiosurgery treatments beyond year one. The role of patient registries, data collection efrorts and potential for big data enrichment will also be addressed.

Keywords: Brainlab, Novalis Circle, Surgery, Radiosurgery, Neurocognitive Testing

Using Genetics to Tailor Prostate Cancer Care: The Male Oncology Research and Education (MORE) Program

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ABSTRACT

Introduction: Men with a known BRCA1/2 mutation are known to have a higher risk of developing prostate cancer at an earlier age and with a more aggressive phenotype which results in a very poor prognosis. Several studies now suggest that the median survival of men with BRCA-associated prostate cancer to be less than 5 years, which is in stark contrast to that seen in the general population which is measured in decades. Despite this male BRCA1/2 mutation carriers are still screened and treated as per standard of care, or not at all given the recent recommendations by some regulatory groups that are against PSA screening. For those men that do develop BRCA-associated prostate cancer, the optimal management options are unknown, and to date there has been no evidence to support personalizing the treatment to take advantage of the known genetic trait these men share. The Male Oncology Research and Education (MORE) program at the Sunnybrook Odette Cancer Centre is a clinical and academic platform for men at high risk of developing aggressive prostate cancer. To date we have accrued and regularly follow over 120 men with a BRCA1 or BRCA2 mutation for clinical prostate cancer screening and contribution to our biobank. Research foci include determining which patients need early or enhanced prostate cancer screening, what other genetic or epigenetic factors influence their increased risk, and what are the optimal treatment strategies in these groups.

Methods/Objectives: The MORE program follows men at a high risk of developing aggressive prostate cancer including men with a known BRCA1 or BRCA2 mutation, those of Western-African/Caribbean ancestry and those with a strong family history of early onset disease. To date we have accrued over 200 men, of which 127 have are BRCA1/2 carriers. Men are seen every 6-12 months for clinical examination and PSA screening. All men are invited to contribute to our biobank including blood (DNA, serum/plasma) and tissue (where applicable). Men aged 50 or over are also invited to participate in our ongoing multiparametric prostate MRI-biopsy trial. Molecular characterization of prostate tissue from men that undergo biopsy will be compared to sporadic cases to help elucidate the etiology of aggressiveness in BRCA-associated disease. Those BRCA1/2 carriers diagnosed with aggressive prostate cancer may be candidates for pending trials exploring the use of targeted therapies (e.g. PARP inhibitors).

Discussion: Men with a known BRCA1 and BRCA2 mutation that develop prostate cancer do so at an earlier age with a poor prognosis. It is unclear if standard prostate cancer screening and management is appropriate for this group of men. Enhanced screening using multiparametric MRI as well as identification of biomarkers that predict both prognosis and response to treatment may help improve the long-term outcomes in this genetically distinct group of men. The MORE program is a clinical and academic program that will further our understanding of prostate cancer in high risk individuals and families.

Keywords: Hereditary Prostate Cancer; Genetics; BRCA; MRI Screening

MRI for Radiation Oncology: From Spatial Accuracy to MR only Radiation Therapy Planning and Beyond

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ABSTRACT

Over the past few years, cancer care has evolved to deliver more advanced treatments and technologies that do not always integrate seamlessly, thus complicating the workflow. While, the treatment plan plays a big role in determining the quality of the treatment itself, most patients wait a week or more after their simulation scan to start their treatment, which can lead to poor survival rates.
The Philips Ingenia MR-RT is a dedicated MR simulation platform designed to integrate MR simulation into Radiation Therapy workflows with superior spatial and temporal integrity. The MR-only simulation for prostate treatment planning(510k) generates a CT-Dicom from a 3D mDixon FFE sequence ($TR/TE_1/TE_2$, voxel size, flip angle, imaging time = 3.3ms/1.1/2.1ms, 1.7x1.7x2.5mm, 10°, 2:30min).

Philips aims to further streamline the often repetitive and time-consuming process from imaging to treatment planning with intelligent workflow automation. The goal is to further accelerate the time to treatment and to enhance consistency through automated contouring on MR-only based datasets.

Keywords: MRgRT, MRSim, MR only simulation, Radiation Therapy, intelligent workflow

Poster Abstracts

The Dosimetric Impact of Gadolinium-Based Contrast Media in GBM Brain Patient Plans using the Monaco TPS for the MRI-Linac

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ABSTRACT

Introduction: We evaluated the dosimetric effects of gadolinium based contrast media (GdCM) on the radiotherapy of a Glioblastoma (GBM) patient for the Elekta MRI-Linac using the Monaco treatment planning system (TPS) (Elekta). Monaco has a fast, integrated Monte Carlo dose calculation algorithm, GPUMCD, which allows for the assignment of a foreign material such as GdCM to the patient volume.

Materials and Methods: A GBM patient treated with a 7-field IMRT beam arrangement was used. Plans were optimized and calculated both in the presence ($\overrightarrow{B_0} - On$) and absence ($\overrightarrow{B_0} - Off$) of a 1.5 T orthogonal magnetic field. These plans were then recalculated with manual density override for GdCM in the CTV using the same MUs/Fx. A custom material specification table (CMT) for Monaco was defined to specify the relative electron density of the GdCM. Both the custom material specification table and the default material specification table (DMT) were used for dose calculations. Comparisons were drawn in terms of the dose difference maps and DVH analysis. Aside from Monaco, a cubical phantom (20x20x20 cm) was also built, in a stand-alone version of GPUMCD, in order to investigate the dose perturbation effects of GdCM for a single beam.

Results and Discussion: Dose calculations using the stand-alone version of GPUMCD showed a dose enhancement of 5% for the $\overrightarrow{B_0} - Off$ case and no dose enhancement for the $\overrightarrow{B_0} - On$ case at the tissue-GdCM interface for a concentration of 15 mg/ml of Gd in the CTV. In order to model these effects accurately in the TPS, a CMT is required with correct relative electron density for the GdCM. For a patient with no GdCM, the use of the CMT or DMT gave statistically insignificant dose differences suggesting there was no error in electron density / material assignment when implementing the CMT. However, with density override for GdCM, the CTV V100 changed from 99% when using the CMT to 95% when using the DMT indicating that Monaco can model GdCM (Fig A). The plans calculated using a CMT with and without density override showed that the V100 dropped from 99% to 92% ($\overrightarrow{B_0} - On$) (Fig B) and from 99% to 86% ($\overrightarrow{B_0} - Off$). This indicates that accurate modelling of GdCM, for the concentration used here, is necessary for the MRI-Linac.

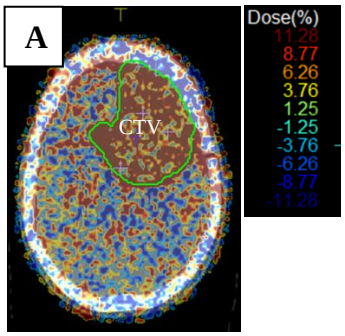
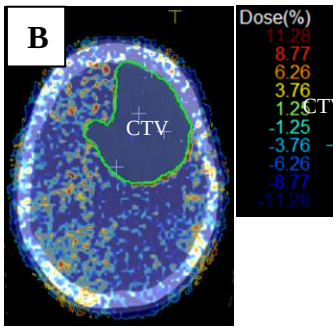


Fig A: Difference between doses calculated with density override for GdCM using CMT and DMT with magnetic field.
$Dose_{CMT,GdCM} - Dose_{DMT,GdCM}$

Fig B: Difference between doses calculated with and without density overrides in CTV using CMT with magnetic field.
$Dose_{CMT,GdCM} - Dose_{CMT,0}$



Keywords:MRI-Linac, Contrast dose enhancement, Gadolinium based contrast, GPUMCD, Monaco TPS

Effective Ultrasound Stimulated Microbubbles Therapy Used to Treat PC3 Xenografts in a Rabbit Model

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ABSTRACT

Introduction: Ultrasound activated microbubbles (US/MB) is a promising new adjuvant therapy in the treatment of cancer which has been thoroughly investigated by our group *in vitro* and *in vivo* in murine models. The *in vivo* experimental outcome revealed an enhanced tumour cell death of up to 60% when combining US/MB with ionized radiation (XRT) compared to single treatments. Recent work was done using xenografts of human prostate cancer (PC3) in mice. Treatment with US/MB/XRT primarily affects the tumor stroma and vasculature and thus influenced by the physiology of the mouse model. In order to proceed to clinical trials, this treatment need to be optimized in a large animal model.

Materials and Methods: Here we demonstrate the effectiveness of this therapy in a large animal model using New Zealand rabbits. PC3 was used to form hind leg xenograft tumors. Rabbits were injected daily with the immunosuppressant cyclosporine in order to facilitate tumor growth. Developed tumors were treated when they reached a size of 12- 20 mm. Treatment consisted of US/MB, XRT (8Gy), or US/MB/XRT. The experimental outcome was evaluated using, histopathology, immunolabelling, and ultrasound imaging techniques.

Results and Discussion: A significant increase in the level of tumour cell death was observed with the use of the combined treatment (US/MB/XRT) compared to the control, which was validated by the labelling of fragmented DNA. Factor VII immunolabelling indicated significant vascular reduction 24 hours post treatment which was validated by a decrease in vascular index (VI) as measured by Power Doppler Imaging. Results obtained in the large animal model compare favourably to results obtained in the small animal study and support advancing this treatment to clinical trials.

Keywords: Ionized radiation, Microbubbles, Prostate Cancer, Rabbits, Ultrasound

An *In Vitro* Study of Radiation Dose Enhancement Using Gold Nanorods and Plasmonic Photothermal Therapy

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ABSTRACT

Introduction: Gold nanoparticles (GNP) have been shown to highly absorb ionizing radiation compared to tissue, resulting in a higher absorbed dose. GNPs have also been shown to be high absorbers of non-ionizing radiation with a peak absorbance at a wavelength dependent on their shape and size. This study investigated radiation dose enhancement in PC3 cells when exposed to gold nanorods (NR) and near infrared light (IR). This study also compared dose enhancement when using NRs with different coatings. Dose enhancement using an untargeted NR with polyethylene glycol (PEG) coating was compared to a targeted NR conjugated with both anti-prostate stem cell antigen (PSCA) antibodies and nuclear localization sequence (NLS) peptides.

Materials and Methods: The PC3 cells were incubated with either PEGylated NRs (PNR) or antiPSCA antibody + NLS peptide conjugated NRs (AbNR). Plasmonic photothermal therapy was applied via near infrared light at a wavelength of 810 nm to achieve hyperthermia treatment at a temperature of 42ºC to 43ºC for 60 min. They were also exposed to 160kVp x-rays at a dose of 0 Gy, 2 Gy, 4 Gy or 8 Gy. Cell survival was assessed using a colony forming assay and the data was fit to a linear quadratic curve. Dose enhancement factors for the combination therapies were determined by calculating the dose to achieve 10% cell survival using radiation alone and dividing it by the dose to achieve 10% cell survival using a combination therapy.

Results and Discussion: It was found that both targeted and non-targeted GNPs when exposed to radiation and hyperthermia synergistically enhanced radiation dose. The dose enhancement factors for the simultaneous delivery of x-rays and near infrared light with AbNRs and PNRs were 1.72 and 1.27 respectively. This shows that the combination of GNPs, IR light and 160kVp radiation provides synergistic radiation enhancement. This also shows that antiPSCA antibody + NLS peptide conjugated NRs provide greater dose enhancement than pegylated NRs.

Keywords: Gold Nanorods, Dose Enhancement, Hyperthermia, Plasmonic Photothermal Therapy, Radiation Therapy

Real-Time Prostate Motion Compensation for 2D/3D Ultrasound-Guided Biopsy

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ABSTRACT

Introduction: Of cancers tracked by Canadian registries, prostate cancer has the highest incidence in men and prostate biopsy is the current clinical standard for definitive diagnosis. These biopsies use needles to remove small tissue samples in the prostate and are guided by two-dimensional transrectal ultrasound (2D TRUS). We have previously proposed the use of 3D TRUS/MR fusion images during biopsies with the goal of more accurate needle guidance and improved diagnoses by augmenting the conventional 2D TRUS guidance. However, in aligning the 2D and 3D images, prostate motion can cause misalignment of the anatomical and planned targets identified using the 3D TRUS/MR fused images. Here we show a motion compensation algorithm with image reduction techniques to align 2D and 3D TRUS images, correcting for these misalignments real-time.

Materials and Methods: Rigid registration along six degrees-of-freedom (DoF) was performed using an intensity based normalized cross-correlation similarity metric optimized with the Powell method from the Insight Segmentation and Registration Toolkit (ITK). Previously acquired 3D US prostate images from seven biopsy patients were reconstructed into a matrix size of 448×448×350 pixels with voxel sizes of 0.18×0.18×0.19 mm^3 and registered to 14 2D US images taken from the same group of patients. Registration of these images was then accelerated using a graphics processing unit. Since the Powell method minimizes the similarity metric along one DoF at a time, the order of searching angular and translation components was investigated. The number of pixels used to compute the image similarity metric significantly affects registration speed and accuracy so this effect was examined by selecting and varying a region of interest in the 2D image passed to the registration algorithm. Image downsampling was also explored to check the influence on error and speed. Target registration errors (TRE) were used to quantify the error of the algorithm.

Results and Discussion: When downsampling the images by 2 and with an optimum 2D region of interest found at 356×290, a mean TRE in the algorithm for the 14 image pairs was 2.8 ± 2.3 mm with a mean registration time of 112 ± 34 ms per 2D image when searching by angle first. The TRE was reduced to 2.0 ± 1.6 mm when searching translations first with a marginal increase in computation time at 120 ± 48 ms. An optimum downsampling factor of 4 was found when searching translations first, resulting in a mean TRE and computation time of 1.6 ± 0.6 mm and 57 ± 20 ms respectively. The registration algorithm performed with a clinically acceptable error and had computation speeds close to a real-time implementation which is an improvement over our previous version. Current and future work involves validating this algorithm on a 3D TRUS system for real-time guidance on prostate phantoms and patients undergoing biopsy procedures for continuous background motion compensation.

Keywords: 2D-3D Transrectal Ultrasound-Guided ProstateB, Real-Time Image Registration, Prostate Motion Compensation, Prostate Cancer

Hypofractionated Partial Breast Irradiation for Unresected Locally Advanced Breast Cancer in Metastatic and Medically Inoperable Patients

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ABSTRACT

Introduction: In breast cancer patients who do not undergo surgery due to metastatic disease or severe medical comorbidities, the unresected primary tumor may cause symptoms such as pain, skin ulceration and bleeding. Hypofractionated partial breast irradiation (HPBI) is a treatment modality aimed at achieving local control (LC) and reducing symptom burden while minimizing the duration of radiation treatments.

Materials and Methods: This retrospective review included all patients treated with HPBI for unresected breast tumors at a large tertiary cancer center between August 2013 and December 2015. Primary outcome measures were LC (no progression of disease after treatment) and feasibility (no discontinuation of HPBI due to acute toxicity). Secondary outcomes included: response (categorized as complete, >50%, or <50%), change in symptoms, and acute toxicities.

Results and Discussion: Twenty patients (22 breast tumors) were evaluated. Median age was 83 (range: 46-100). Thirteen of 22 (59%) breast tumors were ER/PR positive and 60% of patients had prior endocrine therapy for a median duration of 10 months (range: 1-40). Eleven patients had comorbidities precluding surgery, 7 had metastatic disease, and 2 declined surgery. Eleven patients (55%) presented with skin ulceration, 4 (20%) with substantial bleeding requiring dressing changes, and 6 (30%) with pain not adequately controlled with analgesics. Average size of the primary lesion was 6.1cm (range: 2-14). HPBI was delivered as 5 fractions given once or twice per week; the prescribed dose was 35-40Gy to the primary lesion, 25-35Gy to the axilla, and 25Gy to the supraclavicular fossa/whole breast, as indicated. Eighteen (90%) patients completed HPBI and 2 stopped after 1 fraction (though not due to toxicity). Acute grade 1 (RTOG scale) skin toxicity was seen in twelve patients and grade 2 or 3 toxicity with moist desquamation in 7 patients (no grade 4 toxicities). Average follow up was 6.4 months (range: 1-23). At 3 months follow up (n=19), all had LC, with 16% having a complete response (CR), 37% a >50% response, and 47% a <50% response. Bleeding resolved in all and skin ulceration had a CR in 22% and partial response in 78%. At 1 year follow up (n=10), 9 had LC and 1 had progression (this patient declined completing HPBI after 1 fraction). CR was seen in 30%, >50% response in 40%, and <50% response in 10%. Skin ulceration had a CR in all 5 patients with documentation at this time point. One patient had 23 months follow up and had LC with complete resolution of pain, bleeding, and skin ulceration.
HPBI is a feasible treatment modality for LABC and is effective at achieving LC and reducing symptoms in the context of patients with metastatic disease or comorbidities precluding surgery. Longer follow up and prospective research is needed to further assess this approach.

Keywords: Breast Cancer, Altered Fractionation, Stereotactic Body Radiotherapy, Palliative Care

MicroRNA-106A Confers Radiotherapy Resistance and Tumour Aggression by Targeting LITAF in Prostate Cancer

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Introduction: Prostate cancer is the most prevalent cancer affecting Canadian men and a leading cause of cancer-related death. Prostate cancer recurrence is a major clinical problem with up to a 40% biochemical recurrence rate at five years after external beam radiotherapy. This significantly decreases patient outcomes and poses a serious burden on Canada's healthcare system. MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression and their expression is dysregulated in cancer. Specifically, miR-106a is overexpressed in many cancers, and we hypothesize that miR-106a confers a radiation-resistant and aggressive phenotype in prostate cancer.

Materials and Methods: To determine whether miR-106a is enriched in prostate cancer samples, bioinformatic analysis was performed using The Cancer Genome Atlas Data Portal in R statistical environment. Clonogenic survival assays were used to assess cancer cell survival following radiation treatment in PC3 and DU145 prostate cancer cell lines overexpressing miR-106a (by miR-106a mimic transfection). Proliferation assays were used to quantify number of viable cells with and without radiation between miR-106a overexpressing cells and normal control cells. Cell cycle analysis using flow cytometry was used to analyze miR-106a's effects on prostate cancer cell cycle distribution before and after ionizing radiation. Gene array analysis was used to identify possible targets of miR-106a. Cells were stained for β-galactosidase expression following radiation to assess cell senescence, as a mode of cell death following radiation treatment.

Results and Discussion: MiR-106a was significantly overexpressed in patient prostate cancer samples relative to normal prostate samples, suggesting that miR-106a is involved in prostate carcinogenesis. Clonogenic assays displayed increased survival after radiation treatment with cells overexpressing miR-106a compared to control cells. Proliferation assays showed that miR-106a-overexpressing cells had a higher proliferation rate than control cells in both unirradiated and ionizing radiation-treated cells. MiR-106a overexpression resulted in a greater proportion of cells in S phase, and allowed more cells to bypass the G2/M cell cycle checkpoint after ionizing radiation. We identified lipopolysaccharide-induced TNFα factor (LITAF) as a putative downstream target of miR-106a. LITAF knockdown lead to increased proliferation and clonogenic survival following IR. We assessed miR-106a and LITAF's effects on cellular senescence, as senescence is the predominant mode of cell death following radiation in prostate cancer. We found that both miR-106a overexpression and LITAF knockdown resulted in significantly fewer senescent cells post-IR. This suggests that miR-106a inhibits LITAF, which increases survival following IR by reducing senescence in PCa cells. Tumour xenograft experiments performed in athymic nude mice confirmed that miR-106a increases proliferation compared to control tumours. This trend was seen without radiation, in addition to following radiation treatment. Thus, these *in vitro* and *in vivo* experiments show that miR-106a is involved in PCa aggression and confers a radiation-resistant phenotype.

Keywords: Radiotherapy Resistance, MicroRNA, LITAF, Cellular Senescence

Consensus Statement from the International Stereotactic Body Radiotherapy Consortium for Head and Neck Carcinoma- Technical Factors

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Introduction: To provide a multi-institutional consensus statement for technical factors for stereotactic body radiotherapy (SBRT) for head and neck carcinoma. **Materials and Methods:** Fifteen international institutions with significant experience in head and neck SBRT were asked to complete a 70-item questionnaire covering simulation, treatment planning, dose prescription and image guidance. **Results:**CT simulation is performed using 1-3 mm slice thickness in all 15 centres.Twelve centres use IV contrast at time of simulation. Types of immobilization device include thermoplastic masks (n = 13), bite block (n = 7), thermoplastic open face mask (n = 3) and custom posterior head cushion (n = 1). Organ motion managementis carried out using 4DCT in 3 institutions, and robotic tracking in 10 institutions.Imaging modalities used for image fusion for gross tumor volume delineation include diagnostic CT ± contrast (n = 9), MRI of the neck (n = 15) and PET/CT (n = 12).Twelve institutions routinely perform CT fusion with treatment planning MRI and/or PET-CT obtained with patient immobilized in treatment position. Treatment delivery systems include Linac with CBCT (n = 11), robotic SBRT (n = 8), Co-60 SRS (n = 2) and proton systems (n = 3). Thirteeninstitutions use daily pre-treatment imaging and online correction. Most centres (n= 10) use robotic tracking as part of pre-treatment imaging verification and intra-fractional monitoring.The action level for correction of set-up errors is 1-3mm for 10 institutions and 5mm for 1 institution. Tencentresroutinely repeat imaging after couch adjustment prior to treatment delivery, and 3 institutions repeat imaging only if the shift was greater than 3-5mm. Nine institutions apply aclinical target volume expansion of 1-10 mm and 14institutions use a planning target volume margin of 1-5 mm.Fractionation and dose varied between 15-24 Gy in 1 fraction to 30-50 Gy in 5 or 6 fractions prescribed to an isodose line. Three institutions deliver treatment on consecutive days and 12 institutions every other day.**Discussion:**There is considerable heterogeneity in the techniques used by 15 high volume centres in head and neck cancer SBRT. Further study is needed to understand the impact of these variables on outcomes, which can provide an evidence base for a consensus statement.

Keywords: Ablation, Stereotactic, Radiotherapy, Head and Neck, Practice Patterns

Magnetic Field Effects on Dose Delivery Robustness of Lung Stereotactic Body Radiation Therapy

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ABSTRACT

Introduction: MRI-linac systems are promising new delivery solutions that aim to use the excellent soft tissue contrast of MRI to target disease in real-time or near real-time. Due to the ever-present magnetic field during dose delivery there are magnetic field effects on the dose distribution. This is especially evident at high-to-low density tissue interfaces such as in lung tissue where magnetic dose effects are driven by the Lorentz force, a phenomenon commonly referred to as the electron return effect (ERE). The objective of this work is to determine the effects of the magnetic field on the robustness of dose delivery of lung stereotactic body radiation therapy (SBRT) to small inter- or intra-fractional translational shifts. The prototype Elekta MRI-linac was considered in this study.

Materials and Methods: 5 NSCLC patients were selected. Patients were simulated with 4DCT with targets contoured by a staff oncologist. For this study, the max inhale phase was used for planning with the aim to demonstrate how translational shifts would affect the dose distribution in the GTV. A 5 mm PTV margin was added to the GTV. The Monaco treatment planning system and the Elekta MRI-linac beam model was used for planning. Each patient case was optimized with three beam geometries: IMRT, full arc VMAT, and half arc VMAT (placed on the ipsilateral side). For each of these beam geometries, one plan was optimized without the magnetic field and one plan was optimized with a B_0=1.5 T magnetic field transversely placed to the radiation beam (the Elekta MRI-linac configuration). Prescription dose was 52 Gy in 4 fractions. All plans were normalized such that the GTV V52 was >99% and the PTV V49.4 was >99%. In order to quantify robustness, a 3 mm translational shift of the beam isocenter was performed in 3 different directions: medial, posterior, and superior for each of these plans (i.e. the 3 beam geometries, with B_0 on and off). The GTV coverage and hot spots were evaluated to quantify robustness.

Results and Discussion: Preliminary results show that there are some spurious dosimetric effects due to translational shifts of the beam isocenter. These shifts represent daily positional setup inaccuracies or motion during treatment. Figure 1 shows DVH graphs for a single patient, and demonstrates that these shifts cause the plan DVHs to stray from optimality. The effect is most severe for the VMAT half arc and with the magnetic field turned on. The comprehensive set of results can inform what shifts are tolerable for a given beam geometry and magnetic field state, and can potentially be used to justify more sophisticated motion management techniques such as exception gating and MLC tracking methods.

Keywords: MRI-linac, Electron Return Effect, Isocentric Shifts, IMRT, VMAT

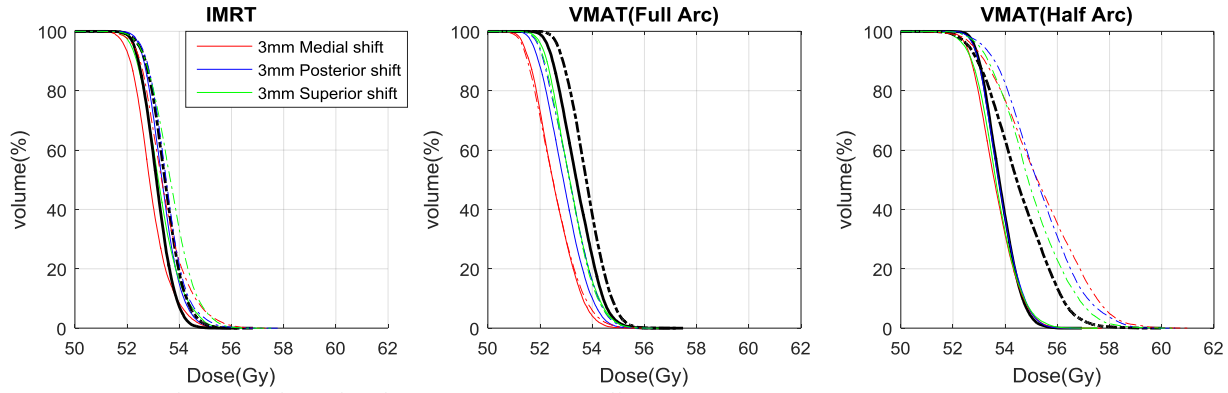

Figure (1): DVHs of the GTV of one of the five patients using three different beam geometries. Dashed lines represent plans with the magnetic field; solid lines indicate plans optimized without the magnetic field. Black lines represent the original, non-shifted plans.

A Novel Dissolvable Seed for Brachytherapy

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ABSTRACT

Introduction: In low dose rate brachytherapy, small permanent seeds (5mm) containing low-energy gamma photon emitters like Pd-103 delivers the dose during prolonged period of the time. However, there are limitations to this technique that give rise to inhomogeneous dose distribution, requirement for short range photon sources, and the possibility of seed miss positioning. Gold nanoparticle (AuNP) have been extensively studied as a radio-sensitizers for enhancing the effectiveness of the radiation treatment. High Z value of gold allows greater local photo-absorption followed by photoelectrons and Auger electron emission, in which, contributes to local dose enhancement. The Auger electrons emission is maximized when AuNp interacts with low energy x-ray source like palladium. It has been proposed that intratumoral injection of the AuNP combined with low energy x source may potentially enhance the dose uniformity and therapeutic dose compared to the conventional brachytherapy seeds. To test the possibility of constructing dissolvable brachytherapy seed, multi-metallic nanoparticles (Pd/AuNP) with a palladium core and a gold shell structure size of 50 nm has been created by using various stabilizing agents including CTAB, PVP, and PEG. Then prepared nanoparticles were embedded into the sodium alginate gel to form a dissolvable seed.

Materials and Methods: Na_2PdCl_4 solution was reduced with the ascorbic acid(AA) and different stabilizing agents including, Poly-Vinyl-Pyrrolidone (PVP), Cetrimoniumbromide (CTAB), and Polyethylene glycol (PEG) were mixed in to reduced palladium solution to produce mono-dispersed nanoparticle. Then palladium nanoparticle solution was mixed with AA and $HAuCl_4$ to form core-shell nanoparticle (Pd/Au NP) with palladium core and a gold shell structure. Same stabilizing agents used for palladium were tested to construct core-shell nanoparticle. Prepared nanoparticles were analyzed with TEM to observe different properties (size, shape, crystal structure, and size distribution). Then Pd-Au NP solution mixed with sodium alginate gel was poured into the brachytherapy seed mimicking mold and solidified by submerging into sodium chloride solution.

Results and Discussion: Cubic shaped palladium nanoparticles with monocrystalline structure of size 18±2 nm and 23±3 nm were produced with the use of PVP and CTAB, respectively. Given the known cytotoxicity of CTAB in biological system, PVP stabilized palladium nanoparticle were used to construct the core and shell structured nanoparticle (Pd/Au NP). Pd/Au NP were stabilized with PVP and further stabilized PEG. Final Pd/Au NP showed mono-dispersed size of 50±5 nm, smooth and equal thickness of gold layer and sphere shaped morphology. Then Pd-Au NP solution mixed with sodium alginate gel was poured into the brachytherapy seed mimicking mold and solidified by submerging into sodium chloride solution. This work demonstrates the feasibility of creating dissolvable seed with Pd/Au NP, however, further studies need to be done to test nanoparticle stability and cytotoxicity in biological system. Pd/Au NP release rate from the alginate seed and diffusion rate in to the tissue phantom also needs to be determined.

Keywords: Brachytherapy,Gold Nanoparticle, Palladium 103, LDR

Dosimetric Comparison of Interstitial Brachytherapy with Multi-Channel Vaginal Cylinder Plans in Patients with Vaginal Cancer

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ABSTRACT

Introduction: Brachytherapy plays an important role in the treatment of vaginal tumors. Traditionally vaginal cancers are boosted with single-channel cylinder or interstitial brachytherapy (ISBT). The American Brachytherapy Society suggests that lesion thicker than 5mm should have the interstitial approach favored. More recently a multi-channel vaginal cylinder (MCVC) was developed, but its role in this setting still yet not defined. Thus, this present study aims to evaluate the dosimetric performance of MCVC against ISBT in patients with vaginal cancer previously treated with ISBT

Materials and Methods: Patients with recurrent or primary vaginal carcinoma with target volumes ≤ 2cm of maximum thickness from the lateral vaginal wall and ≤ 1cm of thickness cranially from the vaginal vault were identified. All patients were previously treated with ISBT. For each ISBT treatment plan, a corresponding MCVC-BT plan was produced in Oncentra Brachy by rigid registration of the 35mm MCVC with the ISBT vaginal cylinder. This registration was performed by aligning cylinder central axes and tips, followed by translation of bladder and rectum anteriorly and posteriorly, respectively, to accommodate MCVC larger size. Organs at risk (OAR) were delineated in accordance to published guidelines and vaginal mucosa was achieved by a 3mm isometric expansion of the cylinder followed by gross tumor and cylinder volumes subtraction. Both the ISBT and MCVC-BT plans were optimized using the Inverse Planning Simulated Annealing optimization algorithm and target coverage was normalized at 700cGy. Dose to OAR and vaginal mucosa were evaluated and compared between plans. Paired t-test was used in statistical analysis and $p < 0.05$ was considered significant.

Results and Discussion: Six patients treated with ISBT met the inclusion criteria for this study. Four had vaginal primaries (2 T1 and 2 T2) and two, relapsed cancer to the vagina. In total, ten target volumes (5 HRCTVs and 5 IRCTVs) were planned using ISBT and MCVC techniques and subsequently compared. All volumes had a maximum lateral thickness between 10-20mm and a median volume of 37.5ml (7.8-57.6 mL). Overall, bladder and rectum received higher dose in the MCVC plans than in ISBT. The bladder D2cc mean values were 371 cGy (145-491cGy) and 545 cGy (348-654 cGy) for interstitial BT and MCVC BT, respectively ($p<0.001$). Rectum doses were also higher in MCVC plans. The mean rectum D2cc between ISBT and MCVC was 385cGy (316-455cGy) and 494cGy (432-555cGy), respectively ($p<0.009$). Higher doses to the bladder and rectum were also noticed when the target volumes (IRCTV or HRCTV) were analyzed separately ($p<0.05$). Dose to vaginal mucosa in HRCTV were significantly reduced with ISBT, however no statistical difference was seen in vaginal mucosa dose (D2cc, D1cc and D0.5cc) for IRCTV. In fact, a non-statistical reduction of dose to the vaginal mucosa was seen for plans based in MCVC.
Interstitial BT was dosimetrically superior to MCVC-BT in this series of vaginal cancers with ≤ 2cm of thickness from the lateral vaginal wall and ≤ 1cm of thickness cranially from the vaginal vault. Nevertheless, ISBT was not superior to MCVC in vaginal mucosa constraints for circumferential lesions (IRCTV). In fact, MCVC plans resulted in reduced dose to the vaginal mucosa. MCVC may be considered as a possible tool in the armamentarium against vaginal tumors ≤ 2cm of thickness.

Keywords: Vaginal Cancer; Interstitial Brachytherapy; Multichannel Vaginal Cylinder

Could α/β Ratio Change During MRI-Guided Brachytherapy?

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ABSTRACT

Introduction: Magnetic resonance imaging **(**MRI) is being integrated into radiotherapy delivery for MRI-guided brachytherapy. The presence of a strong magnetic field from a MRI machine during brachytherapy delivery presents a new challenge since the trajectories of electrons liberated by ionizing radiation in patients are strongly dependent on the applied magnetic field. The purpose of this work is to explore the potential effect of a strong magnetic field on the α/β ratio, an important radiobiological parameter in radiotherapy.

Materials and Methods: Based on the theory of dual radiation action, the α/β ratio can be expressed by an integral of the product of two microdosimetry quantities $\gamma(x)$ and $t(x)$, where $\gamma(x)$ is the probability that two energy transfers, a distance x apart, results in a lesion, and $t(x)$ is the proximity function, which is the energy-weighted point-pair distribution of distances between energy transfer points in a track. The quantity $t(x)$ depends on the applied magnetic field. An analytical approach has been used to derive a formula that can be used to calculate the α/β ratio in an extremely strong magnetic field.

Results and Discussion: The α/β ratio has been evaluated in the special case when the applied magnetic field is larger than a critical value B_c, at which the radius of the helix motion of electrons is comparable to the biological target size. This gives the upper limit of the potential change of the α/β ratio due to the presence of a strong magnetic field. For V79 Chinese hamster cells it has been shown that the α/β ratio could be increased by 2.90 times for Pd-103 and 2.97 times for I-125 sources when the applied magnetic field is larger than B_c.

Keywords: *α/β* ratio, Microdosimetry, Proximity Function, Magnetic Field, MRI-guided Radiotherapy

Post-Stereotactic Body Radiation Therapy (SBRT) Tumor Response and Inflammatory Changes as Predictors of Non-Local Failure and Survival Outcomes in Patients with Stage I Non-Small Cell Lung Cancer (NSCLC)

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ABSTRACT

Introduction: SBRT is an alternative treatment to surgery for stage I NSCLC. Intriguingly, NSCLC lesions post-SBRT rarely exhibit a complete response locally and yet yield excellent local control of around 95%. Unfortunately, alongside excellent tumor control, radiation-induced inflammation is a common sequela post-SBRT. The degrees of treatment response and radiation-induced inflammatory changes seem to have little effect in current clinical practice. This study hypothesized post-SBRT tumor response and inflammatory changes as disease control and survival predictors in stage I NSCLC patients.

Materials and Methods: Survival outcomes of 233 patients were reviewed retrospectively from Sunnybrook Electronic Patient Record. Tumor sizes were collected from radiologist's measurements based on CT-Scan pre and post-SBRT within 6, 12, and 18 month intervals. Each patient's maximum response within 18 months was calculated and grouped using RECIST 1.1 methodology: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Maximum post-SBRT inflammatory changes within 18 months was graded and grouped into three categories by radiation oncologists: no changes (NC), mild to moderate changes (MC), and severe changes (SC).

Results and Discussion: Median age of study population was 77.5 years. Median follow-up duration was 25 months. Local control (LC), overall survival (OS), and non-local control (NLC) for all patients at 2 years were: 92.5, 74.6, and 68.0% respectively. Of patients with available pre and post-SBRT tumor sizes (N=188), 11 (5.9%), 92 (48.9%), 79 (42.0%), and 6 (3.2%) patients were categorized CR, PR, SD, and PD respectively. LC were: CR (100%), PR (94.0%), SD (89.7%), and PD (66.7%) respectively after 2 years. OS were: CR (80.0%), PR (80.8%), SD (72.0%), and PD (44.4%) respectively. NLC were: CR (100%), PR (66.4%), SD (62.5%) and PD (16.7%) respectively. There is a statistically significant difference in NLC between groups (p=0.0009). Of patients with available pre and post-SBRT CT-Scans (N=212), 23 (10.8%), 123 (58.0%), and 66 (31.1%) were grouped NC, MC, and SC respectively. For these groups, LC were: 90.9%, 95.0%, and 91.2% respectively. OS were: 66.1%, 78.8%, and 75.3% for NC, MC, and SC respectively. NLC were: 80.1%, 69.5%, and 69.3% for NC, MC, and SC respectively. No statistically significant difference for LC, OS, and NLC between three groups.
The results indicated that stage I NSCLC patients with a lesser response post-SBRT are at higher risk of developing non-local recurrences. These patients may benefit from closer follow-up and adjuvant treatment post-SBRT. Post-SBRT inflammatory change was not shown to be a predictor of survival or recurrences.

Keywords: Non-Small Cell Lung Cancer, Stereotactic Radiotherapy, Tumor Response, Post-Radiation Changes, Survival Outcome

Can Intratreatment PET CT Based Adaptive Radiotherapy Reduce Treatment Margins in Head and Neck Cancers?

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ABSTRACT

Introduction: Traditionally, a high dose CTV of 5 mm is routinely added to the GTV to ensure proper coverage of microscopic disease. However, HN tumors often respond during RT, which suggests that the microscopic CTV through a significant portion of the treatment is shrinking to < 5 mm and could be reduced. This study intends to quantify the decrease in CTV margin in a series of HNC patients.

Materials and Methods: A prospective study in 2009 enrolled advanced HNC patients undergoing curative IMRT (70 Gy in 33 fractions, with or without chemotherapy) to receive a dynamic pre-treatment fluorodeoxyglucose (FDG) PET-CT simulator scan (with mask), which was also repeated during the 2nd-3rd week. 53 patients with different HNC were evaluated. Two radiation oncologists separately contoured GTVs in the pre- and intra-treatment scans to account for inter-observer variability. Rigid fusion of the planning CT to pre- and intra- treatment PET-CT scans was performed using the image fusion module. Margin expansions ranging from 1-25 mm were performed on the pre-treatment GTV to volumetrically match the original clinical target volume (CTV) (as defined by the treating radiation oncologist), based on optimal Dice Similarity Indices (DSI). A similar process took place with the intra-treatment scan, where the intra-treatment GTV was expanded to the original treatment CTV.

Results and Discussion: 53 patients were evaluated with a total of 152 targets (50 primaries and 102 LNs).Volume matching given by DSI showed that the pre-treatment GTV needed an average 7.22 ± 4.75 mm expansion to optimally match the clinical CTV while the 2nd-3rd week GTV required a margin of 8.27± 4.18 mm . On average, the radial size of the primary CTV decreased by 1.05 ± 3.59 mm between pre- and 2nd-3rd week scans. Primaries and LNs had similar outcome with a mean of 1.14 ± 3.99 mm and 0.67 ± 3.63 mm respectively (p=0.54). 40 targets (26.3%) had a shrinkage at 2 weeks over 5 mm.

Conclusion: Our results show that HNC tumor shrinkage during RT is highly variable with no difference between primaries and LNs. There seems to be a subset of patients that is highly responsive to treatment where adaptive radiotherapy could help minimizing normal tissue toxicities.

Keywords: Adaptive Radiotherapy, FDG PET, Tumour Shrinkage

MicroRNA-191 Promoting Prostate Cancer Radiation Therapy Resistance

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ABSTRACT

Introduction: microRNAs are small non-coding RNA molecules which act as repressors of gene function, and have been identified as having substantial roles in cancer as both tumour suppressors and oncogenes, as well as regulators of response to chemotherapy or radiation. By identifying and characterizing miRNAs promotingradiation resistance in prostate cancer, we can ultimately identify their pivotal targets and develop strategies to overcome therapy resistance. MicroRNA-191 (miR-191), is abnormally expressed in numerous cancer types including prostate, breast and lung; however no previous investigations have examined its role in tumor response to ionizing radiation. We aim to characterize how miR-191 promotes prostate cancer (PCa) radioresistance, and to discover and validate the miRNA targets responsible.

Materials and Methods: Current data was generated by transiently overexpressing miR-191 in the prostate cancer cell lines PC3 and DU145. To determine the effects of elevated miR-191, we performed the gold standard clonogenic survival assay to analyze ionizing radiation dose response. Additional *in vitro* analyses on the hallmarks of cancers were performed using standard protocols to assay proliferation, 3D colony formation, cell cycle profile, migration, and invasive potential. Pathway analysis, qPCR, western blotting, and siRNA knockdown experiments were used to investigate miR-191 downstream targets.

Results and Discussion: We have found that miR-191 is significantly elevated in tumor versus normal prostate tissue using patient data collected from The Cancer Genome Atlas. Subsequently, qPCR analysis from our laboratory confirmed higher miR-191 expression with increasing prostate cell line tumourigenicity, with the lowest expression in a normal prostate epithelial cell line.
Elevation ofmiR-191 resulted in significant resistance to ionizing radiation in multiple cell lines. Cell cycle analyses exhibited a reduction in the G2/M block after radiation of PCa cells overexpressing miR-191. The ability of miR-191 to circumvent this cell cycle block likely contributes to radiation resistance, however additional experiments will be conducted to examine additional survival mechanisms. This was also supported by results showing increased proliferation capacity post-radiation in miR-191 overexpressing PC3 and DU145 cells.
In order to narrow down potential miR-191 targets, we combined results from multiple *in silico* target predicting algorithms, an *in vitro* gene array, and *in vivo* patient miRNA-mRNA expression correlation data to create a higher probability target subset, which was then manually surveyed for genes contributing to cell cycle profile and proliferation post-radiation. Validation experiments for the refined subset of miR-191 targets are currently underway. Future experiments include studying the*in vivo*effect of miR-191 expression on tumor xenografts by monitoring tumour growth delay following radiation, as well as quantitating immunohistochemical changes (necrosis, proliferation, angiogenesis) in the tumours.
In response to ionizing radiation, elevated miR-191 results in increased proliferation, reduced cell cycle blocks, and radio-protection of the prostate tumor. By further characterizing this role of miR-191 in radiation resistant prostate cancer, we can ultimately identify targets and develop strategies to overcome therapy resistance.
Keywords: microRNA, Prostate Cancer, Radiation Resistance

MicroRNA-198 Targets Wnt Signaling to Regulate Prostate Cancer Aggression

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ABSTRACT

Introduction: microRNAs (miRNAs) are small non-coding RNA molecules which act as repressors of gene function, and have been identified as playing substantial roles in cancer as both tumour suppressors and oncogenes. microRNA-198 has been reported to be downregulated in several cancers, and has demonstrated tumor suppressor effects by altering the hallmarks of cancer including decreasing proliferation, invasion, and tumor formation. High expression of miR-198 has recently been associated with better overall survival in pancreatic, gastric, and colorectal cancers. Despite compelling evidence in other solid cancers, miR-198's role in prostate cancer progression has not yet been evaluated.

Materials and Methods: microRNA-198 was transiently overexpressed in three prostate cancer cell lines: DU145, LNCaP and 22RV1. To examine microRNA-198's effect on the hallmarks of cancer *in vitro*, we used standard protocols to assay proliferation, 3D colony formation, cell cycle profile, migration, and invasive potential. Pathway analysis, qPCR, western blotting, and siRNA knockdown experiments were used to establish microRNA-198 downstream targets. For i*n vivo* analysis, control and microRNA-198 LNCaP xenografts were generated to monitor tumour growth, as well as quantitate immunohistochemical changes (necrosis, proliferation, angiogenesis) between the tumours.

Results and Discussion: Overexpression of the candidate tumor suppressor microRNA-198 diminished proliferation in multiple prostate cancer cell lines and impaired colony formation in soft agar, an in vitro surrogate for tumourigenicity. In silico pathway analysis and target prediction identified the Wnt pathway members Wnt5a, Fzd3, and Fzd5 as potential targets of microRNA-198, and these were subsequently confirmed to be decreased at both the RNA and protein level with microRNA-198 overexpression. Inhibition of these Wnt pathway members with microRNA-198 reduced the levels of β-catenin, the essential element of Wnt signaling. A corresponding decrease in Wnt signaling activity was confirmed using a reporter assay for β-catenin dependent transcription. Knockdown of the target Fzd5 has recapitulated microRNA-198's effects on proliferation and colony formation, and further experiments are underway to demonstrate a direct binding relationship.
Over-activation of the Wnt pathway in prostate cancer has been reported to contribute to aggression, cancer cell 'self-renewal', and therapy resistance. We are currently investigating the *in vivo* consequences of microRNA-198 overexpression, and our pilot experiment indicates reduced ability to form tumours with elevated microRNA-198. Moving forward, we aim to assay how microRNA-198's inhibition of Wnt signaling may alter cancer cell 'stemness', and determine whether a clinically-available Wnt antagonist can potentiate the anti-tumor effects of microRNA-198.
In vitro evidence supports microRNA-198 as a tumor suppressor in prostate cancer, with elevated microRNA-198 expression suppressing proliferation, reducing colony formation, and impairing Wnt signaling. The effect of microRNA-198 on the Wnt pathway is particularly relevant as several Wnt antagonists are currently undergoing testing in clinical trials.

Keywords: microRNA, Prostate Cancer, Wnt signaling

360-Degree 3D Transvaginal Ultrasound Needle Guidance System for Interstitial Gynecological Brachytherapy

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ABSTRACT

Introduction: In high-dose-rate (HDR) interstitial gynecologic brachytherapy, brachytherapy needles are currently inserted through a template without a standard modality for intra-operative visualisation. Two-dimensional (2D) ultrasound (US) is sometimes used; however, 2D US is heavily operator dependent and can lead to inaccuracy and variability when localising needles. As precise needle placement is required to provide optimal treatment and avoid nearby organs, the addition of intra-operative guidance may allow for improved needle positioning. We have developed a three-dimensional (3D) transvaginal ultrasound (TVUS) system, using a clinical 2D side-fire transrectal US transducer and performing a 360-degree rotation to visualise all needles. As the template currently includes a cylinder placed in the vagina for stability, we have recreated this cylinder from acoustically translucent plastic with a hollow interior to accommodate the US probe. We propose the use the 360-degree 3D TVUS system for the improvement of intra-operative needle visualisation and positioning during HDR interstitial gynecologic brachytherapy.
Materials and Methods: The 3D TVUS system performs a 360-degree rotation in 24 seconds, using a motorized mover and reconstructing the 2D images into a 3D image as they are acquired. This system was validated using geometric phantoms and the visualisation of the needles under idealised conditions was evaluated by inserting 12 needles were into an agar pelvic phantom, including a model uterus, a model tumour, and rectal and vaginal canals. A 3D TVUS scan and MR image were manually, rigidly registered to compare the needle trajectories and tips between the modalities, as well as to their expected positions.
Results and Discussion: The mean linear measurement error was less than 1.7% in each direction and the mean measured volumetric error was 2.65% with the cylinder in place. Based on these results, the geometric reconstruction of the 3D US images was considered accurate. Figure 1 shows an image collected from the 3D TVUS phantom scan. The mean needle tip difference and mean trajectory difference between the modalities was 2.11 ± 0.73 mm and 1.07 ± 0.75 degrees respectively. The mean difference in the needle tip positions between the 3D US and expected values was 1.84 ± 0.42 mm and the mean difference in the trajectories was 0.40 ± 0.35 degrees. Based on this initial study, this 3D TVUS approach is a feasible method for visualising needles intra-operatively during this procedure and a proof-of-concept patient study will be performed.

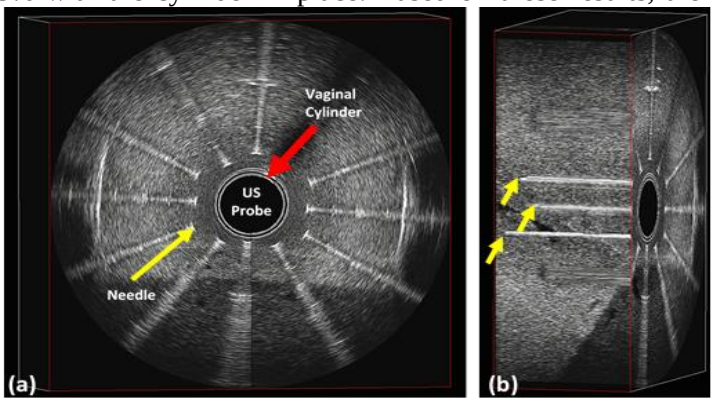

Figure 1. (a) 3D TVUS image of pelvic phantom, (b) second view of 3D TVUS image of the phantom with 3 needles

Keywords: Gynecologic Brachytherapy, 3D Ultrasound, Transvaginal Ultrasound, Interstitial Brachytherapy

Accurate Dosimetry in MR-Linac and GammaKnife

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ABSTRACT

Introduction: One of the most important considerations in radiotherapy is the accuracy of the absorbed dose delivered to patients. New radiotherapy delivery technologies are rapidly being developed that either make use of ever smaller radiation fields (CyberKnife, GammaKnife, etc.), or combine therapy with imaging (MR-Linac, etc.). However, despite our ability to deliver ever more complex radiation fields guided with online imaging, the dosimetry and dosimetric techniques have not kept up with such developments. The purpose of this work is to introduce and summarize some of the work that has been done to address such shortcomings in radiation dose measurement through development of novel technologies based on calorimetric principles.

Materials and Methods: In calorimetry, radiation energy absorbed in a sensitive volume is determined by measuring the radiation-induced temperature rises of the volume (the two are related by the medium specific heat capacity). Given the direct relationship, calorimetry is the only radiation detector that is theoretically independent of all irradiation conditions (i.e. beam type, energy, dose rate, presence of the magnetic field, etc.). However, in reality, a small heat transfer correction factor needs to be applied to compensate for heat gain/loss from the point of measurement due to conductive and convective effects. This correction is numerically calculated as the ratio of temperature rise in the absence of heat loss to that in the presence of heat loss.
A 4ºC stagnant water calorimeter (WC) was developed to directly measure the absolute dose in water. The design aim was to develop a WC appropriate for use in MRI-linac and small fields produced by GammaKnife. Constructed fully out of plastic, the WC should allow for direct measurement of absolute absorbed dose in MRI-Linac without being affected by the strong MRI-fields. The design also accommodates the device setup in the GammaKnife unit allowing to measure *absolute* absorbed dose in these machines for the first time. A commercial finite element software was used to guide the design and modeling phase, while several WC designs with different insulation materials and thicknesses were considered and numerically evaluated and compared. Optimization was based on a minimization of long term calorimeter drift (24h) as well as variation and magnitude of k_{ht}.
Furthermore, a miniaturized graphite probe calorimeter (GPC) designed and built for routine clinical dosimetry was also tested in MRI-Linac as well as conventional radiotherapy beams.

Results and Discussion: The final selected WC design reached a modest drift of <1E-5 K/s after 15h for the worst-case outside temperature variation. This design consists of coolant channels being encompassed on both sides by cryogel insulation. The construction of the WC based on this final design is nearly over and the device will be tested in a conventional radiotherapy beam shortly. Furthermore, the GPC prototype testing in Utrecht clearly showed a minimal dependence of the device on magnetic field. Given the anomalous effects of the magnetic field on ion chambers, calorimetric-based dose detectors such as WC and GPC constructed as part of this work will play a significant role in future dosimetry of advanced delivery units such as MR-Linac.

Keywords: Calorimetry, MR-Linac, GammaKnife, Absolute Dosimetry,

Ultrasound Microbubble Potentiated Enhancement of Hyperthermia in Tumours

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ABSTRACT

Introduction: Ultrasound-stimulated microbubbles (MBs) has proven to be more effective when combined with various treatments including radiation therapy or chemotherapy (Al-Mahrouki et al., 2012; Goertz et al., 2012; Tran et al., 2012). Hyperthermia is known to enhance cell kill when combined with ultrasound-mediated MBs *in vitro* (Ghoshal and Oelzea, 2015). In the current study we demonstrated the effect of ultrasound and MBs in combination with hyperthermia upon tumour response in a prostate cancer xenograft model.

Materials and Methods: For the experiments, tumour bearing mice (n=150, 30 conditions × 5 animals/condition) were injected with 0.08 mg/kg definity microbubbles. Later on the animals were exposed to ultrasound with peak negative pressure varied from 0 kPa, 126 kPa, 246 kPa, 570 kPa and 740 kPa followed by hyperthermia exposure at 43 °C in water bath for 0, 10, 20, 40 and 50 min. Cell death and vascularity was determined 24 hours after the treatments which included treatment of ultrasound-stimulated MBs only, hyperthermia alone and combined ultrasound-MBs and hyperthermia.

Results and Discussion: Tumour exposed to ultrasound-stimulated MBs in combination of hyperthermia resulted in enhanced cell death with 51% at 126 kPa, 55% at 246 kPa, 52% at 570 kPa and 53 % at 740 kPa) compared to untreated tumour or tumour treated with hyperthermia alone or ultrasound-stimulated MBs only with (< 20%) cell death. Furthermore a significant decreased in vasculature ($p < 0.01$) was observed with combined treatment compared to ultrasound-stimulated MBs only or hyperthermia alone treated tumours. Deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining was used to access cell death and cluster of differentiation 31 (CD31) labeling was used for confirmation of vascularity.

Our study revealed that combined treatment of ultrasound-mediated MBs with hyperthermia resulted in increased cell death and reduced vascularity. Combining hyperthermia with ultrasound-stimulated MBs might be a novel therapy approach to improve the efficacy of various treatments.

Keywords: Cell Death, Hyperthermia, Prostate Cancer, Ultrasound, Vasculature

Investigating Effects of Strong Magnetic Field on OSLD Personal Dosimeters

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ABSTRACT

Introduction: Increased interest in the application of magnetic resonance imaging (MRI) in radiation therapy prompts the need to investigate potential effects of strong magnetic fields on personal radiation dosimeters.

Materials and Methods:

A personal dosimeter badge containing 4 OSLDs was modified to remove all ferromagnetic material (Figure 1). The badge was then exposed to scattered/leakage radiation from 6MV beam (~1mSv). OSLD readings were taken before irradiation and 10min after irradiation, averaging over 5 readings for each OSLD.

Figure 3. Design of MRI compatible OSLD badge

Magnetic field effect on measurement reproducibility

Irradiated badge and a secondary, non-irradiated badge were placed in the 3T MRI scanner room (within 5 Gauss line). A third, control badge, was placed outside the MRI room in the patient preparation area. OSLD measurements were read weekly for 3 months (standard time for radiation badge cycle).

Magnetic field effect on radiation sensitivity

At the end of 3 month period, the irradiated badge and the control badge received an additional dose of 1mSv to compare the sensitivity of OSLDs to radiation post magnetic field exposure.

Results and Discussion:

Average change for OSLD measuremnts for all 3 badges was less than 0.005cGy/week (Figure 2). At the end of 3 month period the change is OSLD readings from baseline were: 0.004±0.002cGy, -0.011±0.006cGy and 0.004±0.002cGy, for MRI only, MRI + irradiation and control badges, respectively.

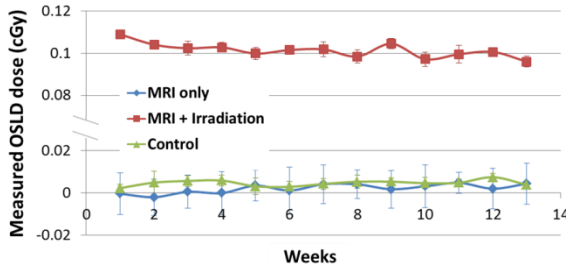

Figure 4. OSLD measurements over 3 months

Previous studies demonstrated that the repeated reading of OSLDs decreases the signal by 0.05% due to the partial discharge of trapped charges. Our results suggest that exposure of OSLDs to the magnetic field has minimal additional effect on OSLD measurements.

The difference in radiation sensitivity between control and the badge exposed to magnetic field was 5.2% which is consistent with expected OSLD-to-OSLD variability and is within the tolerances for radiation protection purposes.

Results of this work demonstrate that the effects of strong magnetic field are minimal on OSLD measurements when irradiation occurs before or after the exposure to strong magnetic field. Future work will investigate potential effects when radiation and magnetic field are applied simultaneously.

Keywords: Radiation Protection, Personal Dosimetry, MRI

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