UTDRO 2020
Annual Research Day

Book of Submitted Abstracts

Contents

Radiation Oncology
UNIVERSITY OF TORONTO

Message from Co-Chairs

Dear colleagues,

Despite the many challenges due to the global pandemic that have impacted research programs across the University of Toronto, UTDRO continues to demonstrate resilience and our faculty have pulled together to carry on with practice-changing and high-impact research. This reflects the ongoing dedication to our exceptional training program, patients, and the community.

On behalf of the UTDRO Research Day Organizing Committee, we are proud to showcase the outstanding research of our faculty and trainees in this report for the 2019-2020 academic year. Although this year's format is unconventional due to the cancellation of the planned in person event, it nevertheless highlights the extraordinary work of UTDRO researchers across several academic areas including education, basic science, clinical science, and the physical sciences. Importantly, despite the many challenges in past months, we continue to collaborate and innovate.

Here, we recognize the remarkable efforts of our trainees in radiation oncology, therapy, physics, as well as graduate students in our affiliate programs. The projects are indeed a reflection of expertise across all UTDRO clinical and academic sites. The emerging work on ***radiomics, clinical epidemiology, and molecular medicine*** are some of the highlighted research themes in this year's report. We hope this will spark more discussions, albeit even if done virtually.

We are optimistic that the coming months will bring forward new perspectives, and exciting research priorities for UTDRO. In reflection, it is clear that among these priorities will be to continue on with building a strong and unified department across all of the clinical and academic sites. As well, emerging research by UTDRO is leveraging the current momentum to enhance our knowledge in the context of COVID-based research. We are looking forward to learning about these results and its impact on radiation oncology.

In closing, please join us in celebrating our accomplishments presented in this report. We look forward to celebrating in-person in the coming months.

Sincerely,

Mike and William

Michael Milosevic

Michael Milosevic, MD, FRCPC
Professor and Vice-Chair, Research

William T. Tran, MRT(T), MSc, PhD
Assistant Professor

2020 Award Winners

R. S. Bush Award - Academic Excellence in Research by a Radiation Oncology Fellow: **Dr. Shivakumar Gudi**

J. R. Cunningham Award - Academic Excellence in Research by a Physics Resident: **Dr. Lee MacDonald**

Richard P. Hill Award - Academic Excellence in Research by a Graduate Student: **Drs. Mary Shi and Michael Sandhu**

W. J. Simpson Award - Academic Excellence in Research by a Radiation Oncology Resident: **Drs. Jennifer Kwan and Kang Liang Zeng**

Chair's Award for Academic Excellence in Research: **Dr. Meetakshi Gupta**

Abstract Number	Abstract Title	Award Winner
AW1	Clinical Presentation and Outcomes of East-Indian versus Non-Indian ethnicity with oral cavity cancer treated with Postoperative Radiotherapy in a Western Institution	Shivakumar Gudi
AW2	Personalized Treatment Gating Thresholds in Frameless Stereotactic Radiosurgery using Predictions of Dosimetric Fidelity and Treatment Interruption	Lee MacDonald
AW3	A Custom EpiDrug CRISPR Screen Identifies RGFP966 (HDAC3 Inhibitor) as a Radiosensitizer of Small Cell Lung Cancer	Mary Shi
AW4	MRI-radiomic signature for differentiating low grade glioma from peritumoral region of glioblastoma	Michael Sandhu
AW5	The Role of Cytokine Signaling in the Reversal of Chronic Lymphedema	Jennifer Kwan
AW6	Imaging-Based Local Control Rates for “Radioresistant” Spinal Metastases Following Spine Stereotactic Body Radiotherapy Using Prostate Cancer as the “Radiosensitive” Reference	Kang Liang Zeng
AW7	Radiation-Induced upregulation of CXCL12/CXCR4 signaling in cancer – Understanding the mechanism to guide biomarker development	Meetakshi Gupta

AW1

Clinical Presentation and Outcomes of East-Indian versus Non-Indian ethnicity with oral cavity cancer treated with Postoperative Radiotherapy in a Western Institution

Shivakumar Gudi, Ali Hosni, Jie Su, Andrew Hope, David Goldstein, John de Almeida, Aaron Hansen, John Waldron, Brian O'Sullivan, Andrew Bayley, Scott Bratman, John Cho, Meredith Giuliani, John Kim, Jolie Ringash, Li Tong, Katrina Hueniken, Geoffrey Liu, Wei Xu, Shao Hui Huang

Purpose

Oral cavity squamous cancers (OSCC) with East-Indians is reported to have inferior outcomes, potentially related to ethnicity, socio-economic status or access to health care. We compare clinical presentation and outcome of East-Indian and non-Indian patients with OSCC treated in a Western Institution within a universal health care system.

Method

All OSCC treated with postoperative radiotherapy/chemoradiotherapy (PORT/POCRT) in our institution between 2005-2015 were reviewed. Ethnicity determination was based on a questionnaire completed by patients and supplemented by clinician's documentation. Uncertain ethnicity patients were excluded. To control for potential confounding effect on disease control due to imbalance of baseline characteristics, a propensity-matched-cohort (control) of non-Indian patients was generated with 2:1 ratio for outcome comparison using the variables: stage, subsite, tobacco consumption, and chemotherapy use. Overall survival (OS), disease-free survival (DFS), locoregional control (LRC) and distant control (DC) were compared between Indian vs control cohort.

Results

A total of 38 East-Indian and 479 non-Indian were identified (427 Caucasians, 52 other ethnicities). Compared to the non-Indians, the East-Indian cohort had a higher proportion of non-smokers (68% vs 29%, $p<0.001$), non-drinkers (81% vs 58%, $p=0.008$), but with more betel nut chewing habits (13% vs 0.4%, $p<0.001$). Tumor was more likely from buccal mucosa (BM) (24% vs 8%) and retromolar trigone (RMT) (13% vs 6%) ($p=0.01$). There was no difference in the distribution of T & N categories. Chemotherapy use was also similar (34% vs 25%, $p=0.24$). A matched control cohort of 76 non-Indians (63 [83%] Caucasians, 13 [17%] other ethnicities) was selected from the initial 479 non-Indian group. Baseline characteristics of Indian and control cohorts were similar in terms of age ($p=0.08$), gender ($p=0.16$), ECOG performance status ($p=0.42$), smoking pack-years ($p=0.42$), subsite ($p=0.41$), T ($p=0.68$) & N category ($p=0.53$), and chemotherapy usage ($p>0.99$). Median follow-up was 5.5 years. Indian and propensity-matched control cohorts had similar 5-year OS (65% vs. 54%, $p= 0.53$), DFS (55% vs 53%, $p= 0.85$), LRC (73% vs 75%, $p= 0.84$), and DC (82% vs 83%, $p=0.93$).

Conclusion

This study of OSCC patients treated in a Western institution under universal health care shows that East-Indian patients have less smoking and alcohol consumption but more likely to have betel nut chewing habits and with a higher proportion of BM & RMT primaries compared to non-Indian counterparts. Oncologic outcomes are similar between Indian and non-Indian ethnicity groups after matching baseline characteristics. The literature reports of inferior outcome in Indian patients may not be completely explained by ethnicity.

AW2

Personalized Treatment Gating Thresholds in Frameless Stereotactic Radiosurgery using Predictions of Dosimetric Fidelity and Treatment Interruption

R Lee MacDonald, Young Lee, Jannie Schasfoort, Hany Soliman, Arjun Sahgal, Mark Ruschin

Purpose

Gamma Knife Icon (GKI) enables user-defined gating threshold for intra-fraction motion tracking during stereotactic radiosurgery (SRS). An optimal threshold ensures dosimetric fidelity of the planned distribution and minimizes prolonged treatment time as caused by gating events. A prediction of motion performance can be made based on a database of traces and a short acquisition of motion to help define an optimal threshold selection for a given patient.

Method

A database of 2,490 motion traces (717 individuals) was analyzed using previously published methods [1] to characterize patient intra-fraction motion performance on the GKI. A 600 second sample of motion was used to classify a patient's motion and identify cases in the database with similar metrics. These motion traces were used to perform a predictive reconstruction of that patient's actual delivered dose distribution for a range of motion thresholds. The remaining patient's fractions were then reconstructed and compared to prediction. Four patient cases (16 fractions) were used to predict number of interruptions (n=16), change in target coverage (n=16), and change in brainstem maximum dose (n=10). The difference between mean predicted value and reconstructed value were compared for accuracy.

Results

The difference between mean prediction and reconstructed values were 0.83 ±1.39 interruptions, 0.42 ±0.44 % target coverage change, and 32.3 ± 41.9 cGy for brainstem maximum dose. Thirty-five of the Fourty-two predictions were within one standard deviation of the predicted mean.

Conclusion

Large databases of motion traces can be used to characterize patient performance and predict motion performance. Dosimetric deterioration due to motion and extension to treatment duration can be accurately predicted in some cases using only a short acquisition of motion and the treatment plan. This reconstruction may provide benefit in generating a patient-specific motion threshold which balances dosimetric accuracy and treatment duration.

AW3

A Custom EpiDrug CRISPR Screen Identifies RGFP966 (HDAC3 Inhibitor) as a Radiosensitizer of Small Cell Lung Cancer

Mary Shi, Mansi Aparnathi, Safa Majeed, Lifang Song, Ratheesh Subramaniam, Richard Marcellus, Rima Al-awar, Troy Ketela, Hansen He, Benjamin Lok

Purpose

Small cell lung cancer (SCLC) is a highly malignant type of lung cancer. Most patients are diagnosed with extensive-stage SCLC, which is characterized by widespread metastases. Consolidative thoracic radiotherapy (TRT) after chemotherapy has improved overall survival in some of these patients but high tumor relapse in intra- and extrathoracic regions remains a therapeutic challenge that needs to be addressed. One promising strategy to improve local tumor control in the thorax is the combination of radiosensitizers to improve the efficacy of TRT. This study aims to identify epigenetic and druggable targets that could sensitize SCLC cells to ionizing radiation (IR) and understand the mechanisms underlying these targets.

Method

A CRISPR knockout screen was conducted on the SBC-5 SCLC cell line using a custom EpiDrug CRISPR sgRNA library targeting ~1,000 genes: 657 genes with FDA approved drugs and 334 genes involved in epigenetic pathways. The DrugZ and MAGeCK algorithms were used to analyze the results. Candidate genes with a statistically significant false discovery rate adjusted p-value were orthogonally validated using shRNA knockdown, CRISPR sgRNA knockout, and pharmacological approaches with chemical probes depending on availability. Resazurin conversion assays and clonogenic assays were performed to quantify cell viability and clonogenicity, respectively. Dose modification factor (DMF; defined as the ratio of radiation doses in the radiation alone group to the radiation plus drug group at an equivalent cell survival fraction) was calculated at 37% survival for the clonogenic assays.

Results

The screen identified several known radiosensitizing genes, including ATM and BRCA2, along with novel candidates such as HDAC3. The HDAC3-specific inhibitor, RGFP966, was used to validate this screen hit. The monotherapy effect of RGFP966 was quantified by a resazurin conversion assay in 8 SCLC cell lines and 1 ex vivo derived patient-derived xenograft cell line. RGFP966 exhibited an anti-proliferative effect on all cell lines with an IC50 value ranging from 2–9.5 μM. Clonogenic assays confirmed the radiosensitizing effect of RGFP966 with a DMF of 1.3 in SBC-5 cells. Additional resazurin conversion assays, clonogenic assays, and functional genetic experiments are ongoing and will be reported.

Conclusion

RGFP966 has been identified using a custom EpiDrug CRISPR screen as a potential novel radiosensitizer in SCLC in vitro. Future work will examine this novel combination in vivo, including patient-derived xenograft mouse models, to assess clinical-translation potential.

AW4

MRI-radiomic signature for differentiating low grade glioma from peritumoral region of glioblastoma

Michael Sandhu, Archya Dasgupta, Benjamin Geraghty, Nauman Malik, Pejman Maralani, Jay Detsky, Arjun Sahgal, Gregory Czarnota

Purpose

Low grade glioma (LGG) and the peritumoral region (PTR) of glioblastoma (GBM) can have an indistinguishable appearance on conventional MRI sequences. The PTR is identified as areas of T2W hyperintensity/ T1W hypointensity considered as the region of interest (ROI) in this study. The ROI in LGG usually represents tumor component, while in GBM, it is a combination of infiltrative tumor and edema. We explored the utility of MRI-radiomics in distinguishing the two groups.

Method

T1W post-contrast, T2-FLAIR, and apparent diffusion coefficient (ADC) scans were obtained using a 1.5T MR scanner with the ROI segmented manually guided by the areas of T2W hyperintensity. Images were resampled to 1x1x1 mm3, skull stripped, rigidly registered, and bias-field corrected. A total of 3612 features, including first-order, texture, wavelets, were extracted. Three classifiers (Support Vector Machine (SVM), K-Nearest Neighbours and Linear Discriminant Analysis), and three feature selection algorithms (Univariate T-test, Minimum Redundancy Maximum Relevance and Recursive Feature Elimination (RFE)) were applied to the extracted features. Nested 3-fold cross-validation was used to evaluate model performance using the best 10 selected features.

Results

A total of 73 patients (41 IDH-wild GBM and 32 grade 2 LGG) were included in this study. The best results were obtained using SVM-RFE with sensitivity, specificity, accuracy, F1-score, area under curve being 93%, 94%, 93%, 93%, 0.98, respectively. On analysis of features from individual T1, T2, and ADC sequences, the accuracy was 78%, 88%, and 93%, respectively, suggesting ADC can provide the most crucial information regarding tissue characteristics and organization.

Conclusion

This study suggests MRI-radiomics can differentiate the ROI between GBM and LGG with high accuracy. Future research can be undertaken to apply the radiomic signatures differentiating tumor from a combination of edema and tumor that can be used in mapping target areas for LGG and GBM.

AW5

The Role of Cytokine Signaling in the Reversal of Chronic Lymphedema

Jennifer Yin Yee Kwan, Wenxi Xu, Vandana Sandhu, Valentin Demidov, Willa Shi, Justin Williams, Alex Vitkin, Jennifer Jones, Siba Haykal, Benjamin Haibe-Kains, David G. Brooks, Kenneth W. Yip, Fei-Fei Liu

Purpose

Lymphedema is a condition of obstructed lymphatic vasculature commonly caused by infection or as a side effect of cancer therapies, such as radiation or surgery. It is characterized by a build-up of lymphatic fluid in the interstitium, which leads to swelling and scarring of tissues with chronic, progressive fibroadipose deposition. In addition to functional debilitation, it is associated with a >70-fold increased risk of infection and rare risk of developing a lethal lymphangiosarcoma. Despite affecting >5 million North Americans and a growing number of cancer survivors, there are no curative treatments. This research aims to identify sustained molecular alterations in chronic lymphedema and reverse the pathological changes using a pharmacologic approach.

Method

A lymphedema mouse model was generated in C57Bl6 mice and validated for clinical features consistent with human disease (i.e. inflammatory edema, fibroadipose deposition) by histology and by intravital imaging. To characterize the etiology of lymphedema and identify novel therapies, this research employed: (1) a temporal, systems-level analysis of biological changes of bulk lymphedematous tissues using RNA-sequencing, (2) targeted profiling of lymphedematous cellular infiltrate using single-cell RNA sequencing and mass cytometry (CyTOF), and (3) pharmacogenomics analysis to identify candidate drugs targeting the reversal of lymphedema pathology.

Results

RNA-sequencing of bulk lymphedematous tissues revealed systems-level changes in biological processes altered in this disease acutely and chronically. A T cell effector cytokine signaling pathway was identified as a top, sustained, upregulated pathway on functional enrichment analysis (FDR<0.01). CyTOF and single-cell RNA-sequencing analysis corroborated the importance of cytokine signaling by confirming the identities and gene expression activities of immune subpopulations in the interstitium. Candidate drugs neutralizing the gene expression changes present in lymphedema were identified using pharmacogenomics analysis and validated in vitro and in vivo with reduction in inflammatory edema and fibroadipose deposition ($p<0.05$).

Conclusion

Overall, cytokine signaling was identified to be an important, modifiable target for lymphedema therapy.

AW6

Imaging-Based Local Control Rates for "Radioresistant" Spinal Metastases Following Spine Stereotactic Body Radiotherapy Using Prostate Cancer as the "Radiosensitive" Reference

Kang Liang Zeng, Zain A. Husain, Hany Soliman, Sten Myrehaug, Chia-Lin Tseng, Jay Detsky, Young Lee, Mikki Campbell, Monica Foster, Eshetu Atenafu, Pejman Maralani, Arjun Sahgal

Purpose

It is thought that stereotactic body radiotherapy (SBRT) challenges the notion of a radioresistant phenotype given the high rates of local control. To determine the impact on local control for those classically considered radioresistant spinal metastases, we compared outcomes following spine SBRT using prostate cancer metastases as the radiosensitive comparator.

Method

We retrospectively reviewed a prospectively maintained database of 1394 spinal segments in 605 patients treated with SBRT between January 2009 to December 2018, and identified renal cell carcinoma (RCC), melanoma, sarcoma, colon cancer, and thyroid cancer metastases as the radioresistant cohort and prostate cancer metastases as the radiosensitive cohort. All patients were serially followed with a clinic visit and full spine MRI every 2 to 3 months. The primary endpoint was imaging-based local control using the prostate cancer cohort as the comparator, and secondary endpoints included overall survival (OS) and vertebral compression fracture (VCF).

Results

173 patients/395 radioresistant spinal segments were compared to 94 patients/185 prostate cancer spinal segments and the median follow-up was 15.5 months (range: 1.4-84.2 months). For the entire cohort, the majority had an ECOG of 0-1 (87.3%), were treated with 24-28 Gy in 2 fractions (71.9%), and half had oligometastatic disease (53.9%). 1- and 2-year local control (LC) rates for the radioresistant cohort were 80.8% and 77.6%, as compared to 96.8% and 91.6% for the prostate cancer cohort. Variation amongst radioresistant histologies was observed with 1-year LC rates of 76.2% for melanoma (41/395), 76.3% for colon cancer (85/395), 81.1% for renal cell carcinoma (225/395), 86.2% for thyroid cancer (29/395), and 100% for sarcoma (15/395). Local failure was associated with presence of epidural disease (HR 2.481, 95% CI: 1.652-3.724, $p<0.0001$), radioresistant histology (HR 2.318, 95% CI: 1.397-3.848, $p=0.0011$), and a lower CTV V90 ($p<0.0001$). For the radioresistant and prostate cancer cohorts the median OS was 17.4 and 61.0 months and the 2-year OS rates were 37.4% and 81.4%, respectively. Presence of lung, liver and brain metastases, widespread (non-oligometastatic) disease, epidural disease and an ECOG ≥ 2 were prognostic for worse OS. Non-significant differences in the 1- and 2-year VCF rates at 9.8% and 14.1%, and 5.1% and 12.7%, were observed in the radioresistant and prostate cancer cohorts, respectively. Coverage of CTV V95 by > 0.87 (HR 2.32, 95% CI: 1.29-4.18, $p=0.005$), no-prior radiotherapy at index lesion (HR 1.963, 95% CI: 1.086-3.546, $p=0.0254$), and higher SINS score ($p=0.0125$) predicted for VCF on multivariable analyses.

Conclusion

Our results confirm a significant difference in local control rates amongst those histologies classically considered radioresistant compared to radiosensitive. Although local control rates are still high, optimization strategies may include dose escalation and more aggressive management of epidural disease.

AW7

Radiation-Induced upregulation of CXCL12/CXCR4 signaling in cancer – Understanding the mechanism to guide biomarker development

Meetakshi Gupta, Naz Chaudary, Marissa Chow, Rob Cairns, Meegan Larsen, Richard Hill, Michael Milosevic

Purpose

Radiotherapy (RT) plays a central role in the treatment of a large number of malignancies. It is increasingly recognized that RT has important effects on cancer immunity, which in turn influences treatment response. RT upregulates CXCL12/CXCR4 chemokine signalling leading to the accumulation of immune cells in the tumor microenvironment and treatment resistance, which can be reversed with a CXCR4 inhibitor. Tumor hypoxia has been implicated in the regulation of CXCL12/CXCR4 expression in tumor cells and cancer associate fibroblasts (CAFs). This study explored the cell types involved in CXCL12/CXCR4 signalling and the effects of RT and hypoxia on CXCL12/CXCR4 upregulation, with the aim of identifying new biomarkers for future clinical trials.

Method

ME180 cervical cancer cells and CAFs in vitro were exposed to either hypoxia (0.2% for 24 h) or a single dose of radiation (10 Gy). CXCL12 and CXCR4 gene expression were quantified 24 h later using qRT-PCR. In a series of in vivo experiments, orthotopically implanted cervical cancer xenografts were irradiated to cumulative doses of 10 Gy, 20 Gy and 30 Gy in 2 Gy daily fractions. Mice were injected with the hypoxia markers pimonidazole and EF5 2 hours apart immediately prior to euthanasia. Immunofluorescence (IF) staining of excised tumor tissue was performed to look for acute and chronic hypoxia and its co-localization with the phosphorylated (activated) CXCR4 receptor (pCXCR4). Tumor CXCL12 was measured using qRT-PCR and circulating CXCL12 was measured using ELISA.

Results

In vitro, a significant increase in CXCL12 was observed in CAFs but not in ME180 cells following either RT or exposure to hypoxia. In contrast, CXCR4 expression increased in ME180 cells but not in CAFs. This implies cooperation between these cell types in CXCL12/CXCR4 signaling. In vivo, RT reduced total and chronic tumor hypoxia in a dose-dependent manner. The acute component of tumor hypoxia was greater than the chronic component at all timepoints. Despite reductions in hypoxia, tumor CXCL12 gene expression increased progressively with increasing doses of RT. Changes in tumor CXCL12 correlated with changes in circulating CXCL12 protein levels, suggesting that the later may be a relevant and practical biomarker of CXCL12 upregulation in future trials. Analysis of the IF images revealed greater pCXCR4 in irradiated tumors compared to controls, and variable co-localization with regions of total hypoxia.

Conclusion

CXCL12 and CXCR4 expression is influenced in a cooperative manner by tumor cells and CAFs and modulated by both RT and hypoxia. RT related CXCL12 upregulation is at least partially independent of changes in hypoxia. Future analyses will evaluate the relationship between acute vs. chronic hypoxia and CXCL12 upregulation, the role of paracrine signalling between tumor cells and CAFs and the influence of other, hypoxia-independent regulatory mechanisms, including the cellular response to DNA damage.

Abstract List

Abstract Number	Abstract Title	Submitted By
A1	Simultaneous integrated boost during postoperative radiotherapy in extremity soft tissue sarcoma	Lulwah Abduljabbar
A2	Imaging-Based Local Control Outcomes Specific to Spine Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Metastases	Ahmed Abugharib
A3	High Dose-Rate Brachytherapy Monotherapy (HDR-M) Versus Boost (HDR-B) In Intermediate Risk Prostate Cancer: Propensity Score Matched Analysis of Canadian Data	Saad Alrashidi
A4	Application of circulating tumor cells (CTCs) to assess tumor heterogeneity, therapeutic efficacy and generation of patient-derived xenograft (PDX) models in small cell lung cancer (SCLC)	Mansi Aparnathi
A5	Reduction in Cardiac Radiation Dose Among Children Receiving Mediastinal RT: Comparison of Involved-Site vs Involved-Field RT Delivered in Three Children's Oncology Group Trials.	Samuel Bergeron Gravel
A6	Prediction of neoadjuvant therapy treatment response in patients with locally advanced breast cancer using Quantitative Ultrasound higher-order texture derivatives	Divya Bhardwaj
A7	Practical considerations for the implementation of a stereotactic body radiotherapy program for oligo-metastases	Matthew Chan
A8	Reduction in Normal Tissue Complication Probability by Stereotactic Magnetic Resonance-Guided Ablative Radiotherapy for Adrenal Lesions	Hanbo Chen
A9	Customizable metallo-nanotexaphyrins for cancer imaging and therapy	Miffy Hok Yan Cheng
A10	A Retrospective Study of Plan Modifications Resulting from Peer Review of Palliative and Radical Radiation Treatment Plans	Adrian Cozma
A11	Quantitative Ultrasound Radiomics for LABC Therapy Response Monitoring: Multi-Institutional Study Results	Archya Dasgupta
A12	Exploration of Epigenetic Profiles in Circulating Tumor DNA to Identify Predictive Cancer Biomarkers	Steven De Michino
A13	Quantitative Ultrasound Radiomics In Predicting Response to Neoadjuvant Chemotherapy in Patients with Locally Advanced Breast Cancer: Results from Multi-Institutional Study	Daniel DiCenzo
A14	Development of risk score model for locoregional recurrence following upfront surgery for resectable pancreatic adenocarcinoma: therapeutic implication on adjuvant therapy for pancreatic cancer	Ahmed Elamir
A15	Predicting recurrence for patients with head-neck squamous cell carcinoma using quantitative ultrasound-based radiomic signatures integrated with machine learning	Kashuf Fatima
A16	Quantitative mapping of the peritumoral region to demarcate areas of tumor infiltration from vasogenic edema in radiation planning MRI of glioblastoma through extrapolation of a 10-feature radiomic signature	Benjamin Geraghty
A17	Primary analysis of a phase II study of metastasis-directed ablative therapy to PSMA (18F-DCFPyL) PET-MR/CT defined oligorecurrent prostate cancer	Rachel Glicksman
A18	Stereotactic Ablative Radiotherapy for the Management of Liver Metastases from Neuroendocrine Neoplasms	John Hudson

Abstract Number	Abstract Title	Submitted By
A19	Pan-Canadian Survey of Radiation Oncology Professional Involvement in Cancer Control Projects in Low-Income and Middle-Income Countries	Viktor Iakovenko
A20	Vulvar carcinoma: patterns of practice and clinical outcomes from a large academic cancer centre	Lama Khoja
A21	Patient-reported outcomes of adolescents and young adults with breast cancer treated with curative intent	Revathy Krishnamurthy
A22	Protein Secretion Rates of Vascular Endothelial Growth Factor and Carbonic Anhydrase 9 in Normoxia and Hypoxia	Sandy Che-Eun Lee
A23	Rates of radionecrosis in re-irradiation of brain metastases using hypofractionated stereotactic radiotherapy.	Minha Lee
A24	Long term biochemical control of a prospective cohort of prostate cancer patients treated with interstial brachytherapy versus radical prostatecomy	Gordon Locke
A25	A Prognostic Gene Expression Signature for Women With Cervical Cancer Receiving Curative Intent Treatment	Jelena Lukovic
A26	TAK-243 combined with radiation and other DNA damaging agents as a novel therapeutic strategy for small cell lung cancer	Safa Majeed
A27	SBRT for Primary Head and Neck Cancers: A Systematic Review and Meta-Analysis	Nauman Malik
A28	Elekta Unity MR-Linac daily automated end-to-end quality control	Victor Malkov
A29	MRI-guided Ultrasound Stimulated Microbubble Therapy in PC3 Xenografts in Rabbits	Evan McNabb
A30	Quality Control of Automated CBCT Dose Reconstruction using Statistical Process Control	Kelly McPhee
A31	A Machine Learning Based Priori Chemotherapy Response Prediction in Breast Cancer Patients Using Textural and Second Derivative of Textural CT Biomarkers	Hadi Moghadas Dastjerdi
A32	Incidence, Severity and Management of Pneumonitis in Stage III Lung Cancer Patients on Adjuvant Durvalumab	Richard Moore
A33	Designing Tools to Identify Causality of Treatment Failure in Glioblastoma	Marina Nikolopoulos
A34	Clinical Optimization of Diffusion Weighted Imaging on an MR-Linac	Humza Nusrat
A35	Breast Lesion Characterization using Quantitative Ultrasound (QUS) and Derivative Texture Methods	Laurentius Osapoetra
A36	RNF168 confers synthetic lethality in BRCA-deficient tumors through impairment of R-loop resolution	Parasvi Patel
A37	Impact of hypoxia-mediated regulation of DICER on treatment outcome in cervical cancer	Aesha Patel
A38	Validating and Refining the 8 th Edition TNM N-Classification for HPV Negative Oropharyngeal Cancer.	Avinash Pilar
A39	Stereotactic Ablative Radiotherapy in T1-2N0M0 Small Cell Lung Cancer: A Systematic Review and Meta-Analysis	Amir Safavi

Abstract Number	Abstract Title	Submitted By
A40	Stereotactic Body Radiation Therapy for Mediastinal and Hilar Lymph Node Metastases: A Single-Institutional Review of Clinical Outcomes	Jeevin Shahi
A41	Alignment of Regulatory Examinations and Public Health Priorities: Exploring the representation of Cancer in the MCCQE-1.	Marissa Sherwood
A42	Estimation of transport parameters employing Tofts Model and a novel advanced Cross-Voxel Exchange Model	Noha Sinno
A43	Outcomes of Spinal Metastases Treated with Stereotactic Ablative Radiotherapy of 24 Gy in 2 Fractions	Michael Tjong
A44	Deformable Registration for Accurate Re-Contouring and Total Planned Dose Records for Patients Undergoing Adaptive Re-Planning	Joshua Torchia
A45	Developing Epigenetic Biomarkers in Small Cell Lung Cancer using the Methylome	Sami Ul Haq
A46	Neutron dose for 10 MV flattening filter free and its clinical context	Jason Vickress
A47	Role and Outcome of Repeat Whole Brain Radiation (WBRT) for Leukemia and Lymphoma after Prior WBRT	Conrad Josef Villafuerte
A48	SBRT For Head and Neck Skin Cancer: An Initial Experience in 106 Medically Unfit Patients	Indu Voruganti
A49	Investigating the immune response as an approach to improve treatment of radiorecurrent prostate cancer	Hanzhi (Eric) Wang
A50	Limited-Stage Small Cell Lung Cancer: Outcomes Associated with Prophylactic Cranial Irradiation Over a 20-year Period at a Single Institution	Michael Yan
A51	Computational Staining of Tumour Hypoxia from H&E Images using Convolutional Neural Networks	Mark Zaidi

A1

Simultaneous integrated boost during postoperative radiotherapy in extremity soft tissue sarcoma

Lulwah Abduljabbar, Anthony Griffin, Zhihui Amy Liu, Charles Catton, David Shultz, Philip Wong, Kim Tsoi, Peter Ferguson, Jay Wunder, Peter Chung

Purpose

Intensity modulated radiotherapy (IMRT) has allowed the use of simultaneous integrated boost (SIB) volumes. We compared the outcomes of extremity soft tissue sarcoma (eSTS) patients treated with postoperative RT with either a sequential or integrated boost.

Method

We retrospectively reviewed a prospectively maintained institutional database of eSTS patients. All patients underwent assessment by both a surgical and radiation oncologist and surgical resection prior to definitive treatment. The majority underwent preoperative radiation followed by surgery as that was the preferred option. When chosen, postoperative RT consisted of either a 2 phase plan with 50 Gy in 25 fractions followed by 16 Gy in 8 fraction boost (total 66 Gy in 33 fractions) to a reduced volume or a single phase delivering 56 Gy in 33 fractions to the larger volume and 66 Gy in 33 fractions (SIB) to the reduced volume. The change from 3D-conformal RT (3DCRT) to IMRT facilitated the use of SIB. Functional outcomes were collected using Toronto Extremity Salvage Score (TESS) and Musculoskeletal Society Score (MSTS). Multivariable logistic regression was used to compare major wound healing complications (MWC) between the two groups. Cumulative incidence of local recurrence considering death as a competing risk was calculated. T-test was used to compare functional outcomes at each follow up time between the groups.

Results

Between January 2001 and December 2017, 112 patients were treated with surgery and RT of whom 104 were treated with post-operative radiation for eSTS excluding patients with angiosarcoma and desmoid tumor. Median age of patients was 64 years (range 17-95). Median tumor size was 9 cm, 61% had high grade tumor, 32% had upper and 68% had lower eSTS. The margin status was negative in 66% and positive in 35%. The median follow up was 45 months (range 3-194). There was no significant difference in MWC between the SIB group (18%) and the sequential boost group (16%) adjusting for lower vs upper extremities and tumor size, OR (95%CI) was 1.23 (0.39, 3.86), p=0.72. The 5-year cumulative incidence of local recurrence was 3.6% and 2.2% for the sequential and SIB groups, respectively, p=0.35. For the entire group the 5-year local recurrence (LR) was 3.4% (0-7.3), 5-yr metastasis-free rate was: 64.3% (55.-73.8) and 5-year OS: 68.7% (60.0-78.8). There was no difference in the functional outcome scores using TESS, MSTS87.

Conclusion

Postoperative RT in eSTS resulted in excellent local control rates. No differences were found in local control and functional outcomes between sequential or simultaneous boost techniques, although the analysis was limited by the relatively small sample size.

A2

Imaging-Based Local Control Outcomes Specific to Spine Stereotactic Body Radiotherapy (SBRT) for Prostate Cancer Metastases

Ahmed Abugharib, K. Liang Zeng, Arjun Sahgal, Chia-Lin Tseng, Hany Soliman, Sten Myrehaug, Zain A. Husain, Young Lee, Pejman Maralani, Jay Detsky

Purpose

We report the first dedicated series of spine SBRT specific to prostate cancer metastases.

Method

A prospective database was retrospectively reviewed identifying 183 spinal segments in 93 prostate cancer patients treated with SBRT. All patients were followed regularly post-SBRT with both a clinical exam and full spine MRI. The primary endpoint was imaging-based local control rates and secondary outcomes included overall survival (OS) and vertebral compression fracture (VCF).

Results

Of the 183 treated spine segments, 130 (71%) had no prior radiation, 18 (10%) were post-operative, and 35 (19%) were re-irradiated after conventional RT. The median follow-up was 16 months (range 2-70 months). 67 patients were oligometasatic (<5 metastases) of which 36 had a solitary spinal metastases. 44 patients (47%) had castrate resistant disease at the time of SBRT, while 10 of the 49 patients with hormone sensitive disease at the time of SBRT developed castrate resistance during follow up at a median time of 15 months after SBRT (range 7 – 37 months). Of the 183 spinal lesions, 120 (65%) were sclerotic, 32 (18%) were lytic, and 31 (17%) were mixed. The median spinal instability neoplastic score (SINS) was 5 (range 0-13). The majority of spinal segments (75%) were treated with 24-28 Gy/2 fractions while the rest (25%) were treated with 25-30 Gy/4-5 fractions. Actuarial local control (LC) rates at 1 and 2 years were 97% and 92%, respectively. The median OS was 61 months (range 43-77 months) and the 1 and 2 year OS rates were 91% and 81%, respectively. The cumulative risk of VCF was 5% at 1-year and 13% at 2 years.

Conclusion

Excellent local control rates were observed in this cohort of patients with spinal metastases from prostate cancer with an acceptable risk of VCF. The high rate of OS in prostate cancer supports the need for excellent LC of spinal disease. Whether similar rates could be observed with conventional palliative radiation remains to be proven. Further work will identify predictive factors for local control and fracture rate after SBRT.

A3

High Dose-Rate Brachytherapy Monotherapy (HDR-M) Versus Boost (HDR-B) In Intermediate Risk Prostate Cancer: Propensity Score Matched Analysis of Canadian Data

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Purpose

To compare outcomes in patients receiving HDR as monotherapy (HDR-M) or with EBRT (HDR Boost, HDR-B) in Intermediate Risk Prostate Cancer.

Method

66 patients with HDR monotherapy who received (13.5Gy x 2 fractions) were matched to 66 patients treated with HDR boost by Propensity score using retrospective database. Baseline characteristics including age, pre-treatment PSAs, clinical stages, Gleason scores, % of positive cores and PNI were well balanced. The median age was 66 years for both cohorts. Biochemical disease-free survival (bDFS) was assessed.

Results

In both cohorts, the 5-year bDFS was 92.4%. HDR-M had 91% bDFS, compared to 94% in HDR-B. At a 5-year follow-up, overall survival was 97%. Favorable intermediate risk represents 69% and 56% in HDR-M and HDR-B respectively. 5-year bDFS was 95% in unfavorable and 93% in Favorable intermediate risk HDR-M cohort. For HDR-B group, 5-year bDFS was 96.2% (in FIR and 90.1%. Within the HDR-M group, no grade 3 or higher GU or GI toxicity was recorded. In contrast, the HDR-B group encountered a grade 3 GU toxicity in 6%. No grade 3 or higher GI toxicity in either cohort.

Conclusion

Both groups within this paired cohort of patients with intermediate-risk prostate cancer, HDR-M and HDR-B demonstrated equally favourable oncological outcomes. Given the effectiveness of high-dose-rate monotherapy, shorter treatment course is convenient to the patients, more cost effective and less burden on health care.

A4

Application of circulating tumor cells (CTCs) to assess tumor heterogeneity, therapeutic efficacy and generation of patient-derived xenograft (PDX) models in small cell lung cancer (SCLC)

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Purpose

CTCs shed into peripheral blood circulation act as a surrogate to the tumor tissue and can grow into patient-derived xenograft models in mice closely recapitulating the characteristics of primary patient (pt) tumor. Since blood is non-invasive, readily available source of patient tumor cells, heterogeneity of SCLC tumor and its evolution in response to therapy or during metastasis can be better understood by serial longitudinal interrogation of CTCs. Here, we've employed a novel platform - magnetic ranking cytometry (MagRC) to enumerate and profile CTCs based on the expression of EpCAM protein epitope and assessed its correlation with demographics, therapeutic outcome and PDX models derived from these CTCs.

Method

Patient blood samples incubated with anti-EpCAM antibody-conjugated magnetic nanoparticles were processed through the MagRC platform. CTCs were sorted into zones 1-8 in descending order of their EpCAM expression levels. Samples were processed at 2 different flow rates: 7 pts at 1mL/hr, 8 pts at 0.5mL/hr and 15 pts at both flow rates. For generating PDX models, CTCs were enriched from whole blood using RosetteSep and injected in flanks of immunocompromised mice.

Results

Among 29 pts, 17 were extensive stage (ES) and 12 with limited stage (LS). Median age at diagnosis was 71, 68% were male, 97% had a history of smoking and 69% had a family history of cancer. CTCs were detectable in 79% (23/29) of the patients. MagRC enumeration was done pre- and post- treatment in 4 patients, all of which showed reduced number of CTCs post-first cycle of chemotherapy. Number of CTCs captured in earlier zones was higher at 0.5ml/hr as compared to 1ml/hr (median zone 4.37 vs 6.50 p=<0.01). PDX models were attempted from 19 patients, of which 5 have engrafted and 5 are within latency window. All 5 patients from whom PDXs were derived had detectable CTCs. EpCAM heterogeneity observed in the MagRC chip correlated with the immunohistochemistry of these PDXs. Four of these patients relapsed within a year and one patient progressed and eventually died. These findings suggest that SCLC PDX engraftment is associated with aggressiveness of the tumor.

Conclusion

The MagRC platform enables quantitative estimation of EpCAM expression levels of CTCs from SCLC pts. CTC enumeration can be used as a tool to evaluate therapeutic efficacy. CTC generated PDXs recapitulate EpCAM heterogeneity as seen on MagRC and their engraftment might be related to disease aggressiveness. This is an ongoing study and these observations will be further validated in a larger dataset.

A5

Reduction in Cardiac Radiation Dose Among Children Receiving Mediastinal RT: Comparison of Involved-Site vs Involved-Field RT Delivered in Three Children's Oncology Group Trials.

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Purpose

Delayed cardiac toxicity is a potential complication of treatment among survivors of pediatric Hodgkin Lymphoma (HL) treated with mediastinal radiation therapy (RT). The transition from involved-field RT (IFRT) to more conformal involved-site RT (ISRT) was intended to reduce normal tissue exposure among patients treated on Children's Oncology Group (COG) trials. We evaluated the cardiac dose received by patients treated on three COG trials to determine whether ISRT had achieved this goal.

Method

Cardiac radiation dose was determined for patients with available RT-DICOM data submitted to IROC for patients treated with mediastinal RT on COG trials AHOD 0031(treated with IFRT to all involved sites, N=87 with evaluable DICOM RT plans), AHOD 0831 (IFRT to sites of bulk or slow response; N=121) and AHOD 1331 (treated with ISRT to large mediastinal adenopathy (LMA) or slow early response; N=227). For each patient we calculated the mean heart dose and percent volume of heart receiving ≥20Gy (V20), both of which have been shown previously to be correlated with delayed cardiotoxicity, and compared heart doses between AHOD 1331 (ISRT) and AHOD 0831 and AHOD 0031 (IFRT).

Results

There was a significant decline in the percentage of patients who received protocol directed RT in more recent studies: 93.8%, 75.8% and 45.8% respectively in AHOD 0031 (standard arm), AHOD 0831 and AHOD 1331. The heart doses among patients getting mediastinal ISRT on AHOD 1331 were significantly lower (median of mean heart doses = 10.1Gy) compared to IFRT used on AHOD 0831 (13.8Gy) and AHOD 0031 (14.5Gy), $p<0.05$. Similarly, the cardiac V20 was also significantly lower with ISRT on AHOD 1331. Patients receiving mediastinal ISRT on AHOD 1331 for LMA had a lower mean heart doses (median value = 10.1Gy) than those with LMA on the older studies (15.2Gy on AHOD 0031 and 14.1Gy on AHOD 0831).

Conclusion

The transition to ISRT on COG AHOD 1331 was associated with a significant decrease in cardiac heart dose compared to prior trials that used IFRT. Based on dose-risk data from the Childhood Cancer Survivor Study, these results suggest that compared to chemotherapy alone, mediastinal ISRT as used on AHOD 1331 could increase the 30-year cumulative incidence of heart disease by approximately 0.5-2% for all patients on the trial and 1-4% for those getting mediastinal RT.

A6

Prediction of neoadjuvant therapy treatment response in patients with locally advanced breast cancer using Quantitative Ultrasound higher-order texture derivatives

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Purpose

In this study, we aim to investigate the effectiveness of quantitative ultrasound (QUS) based higher-order texture derivatives in predicting the response of patients with locally advanced breast cancer (LABC) to neoadjuvant chemotherapy (NAC) with the help of advanced machine learning models.

Method

Using a 6-MHz ultrasound system, radiofrequency (RF) data were acquired from a total of 100 patients with locally advanced breast cancer before receiving NAC. From the RF data, five QUS parametric image-maps were produced within tumor regions of interest. From every QUS-image map, using a sliding window approach, four different gray-level co-occurrence matrices (GLCM) based texture images were derived (contrast, correlation, energy, and homogeneity). In order to obtain texture derivatives, further texture analysis was performed on each QUS image (QUS-Texture1) obtained in previous step to generate QUS-Texture1-Texture2. Patients were classified into two groups based on clinical/pathological responses; responders and non-responders. Three machine learning algorithms based on linear discriminant (FLD), k-nearest-neighbors (k-NN), and support vector machine (SVM) were developed to compare the parameters.

Results

Among the three classifier model used for analysis, the k-NN was the best classifier with sensitivity, specificity, accuracy, and area under the curve (AUC) of 91%, 83%, 87%, and 0.73 respectively. The texture derivatives (QUS-Tex1-Tex2) from scatterer size and acoustic concentration-related parametric images were found to be the most significant features in separating the two response group. Based on a QUS-Tex1-Tex2 model, the 5-year recurrence-free survival was calculated for responder and non-responding patients and the results were comparable to those based on the clinical-pathological outcomes.

Conclusion

This is the first study to use texture derivatives which represent higher order statistics to develop a machine learning model that can predict responses of NAC in LABC.

A7

Practical considerations for the implementation of a stereotactic body radiotherapy program for oligo-metastases

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Purpose

With multiple phase II trials supporting the use of stereotactic body radiotherapy (SBRT) in oligo-metastatic disease, we evaluated practices that could inform effective implementation of an oligo-metastasis SBRT program.

Method

Using a context-focused realist methodology, an advisory committee of inter-professional clinicians met over a series of semi-structured teleconference meetings to identify challenges in implementing an oligo-metastasis SBRT program. Recommendations were made within the context of two models of care: a sub-specialist anatomic expertise model versus a single-practitioner 'quarterback' model.

Results

The advisory committee concluded that during patient work-up, a single practitioner would arrange the minimum number of necessary tests, with case presentation at an appropriate multidisciplinary tumor board, including careful review of all previous treatments, and enrollment on a clinical trial when possible. At simulation, common patient positions/immobilization on a single simulation scan for multiple sites would be optimal, which may include a single radiation plan accounting for overlapping dose. During radiation planning, dose-fractionation regimens should safely facilitate cumulative doses, a single isocentre should be considered for multiple close targets to reduce treatment time, and adherence to strict quality assurance protocols is strongly recommended. Treatment duration should be minimized by treating multiple sites on the same day or choosing shorter dose-fractionations (e.g. single fraction for lung). Team communication and thorough documentation may reduce system errors. Follow-up should aim to minimize redundant clinical appointments and imaging scans. Expert radiology review may be required to interpret post-SBRT imaging challenges.

Conclusion

Using a realist approach, we identified practical considerations for the implementation of an oligo-metastasis SBRT program. Iterations of this approach could be further expanded based on local contexts.

A8

Reduction in Normal Tissue Complication Probability by Stereotactic Magnetic Resonance-Guided Ablative Radiotherapy for Adrenal Lesions

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Purpose

Adaptive radiotherapy using a magnetic resonance linear accelerator (MR-Linac) is a novel radiotherapy technique that can increase the therapeutic ratio of radiotherapy through daily visualization of the anatomy and adaptive re-planning. Data on daily-adaptive radiotherapy's ability to reduce organ-at-risk (OAR) toxicity are currently limited. We hypothesize that daily-adaptive stereotactic magnetic resonance (MR)-guided ablative radiotherapy (SMART) using an MR-linear accelerator (MR-Linac) for adrenal lesions can result in significant normal tissue complication probability (NTCP) reductions for upper abdominal organs-at-risk (OARs).

Method

All patients treated with adrenal SMART using an MR-Linac at a single institution up to December 2019 were reviewed. Doses used were 60 Gy in 8 fractions, 50 Gy in 5 fractions, or 24 Gy in 3 fractions, delivered every other day. An onboard MR scan was acquired before each fraction, and the plan was fully re-optimized using automatically deformed and manually re-adjusted contours. Using these pre-treatment MR scans, all OARs were manually re-contoured and dose-volume histogram data were acquired for all pre- and post-adaptation plans. Contours were randomly verified by a second author. Lyman-Kutcher-Burman models using published parameters were used to calculate the NTCP of upper abdominal OARs before and after daily adaptation. Doses were converted to equivalent doses in 2 Gy fractions for NTCP modelling using an alpha/beta ratio of 2.5 Gy. Differences in OAR NTCP were tested using paired t-tests.

Results

Forty-eight patients underwent SMART for 52 adrenal lesions (29 left-sided) between 2016 to 2019. For left-sided adrenal lesions, the mean predicted NTCP for the stomach was 18.1% (95% confidence interval: 9.7-26.6%) pre-adaptation. After adaptation, the mean stomach NTCP was 5.2% (2.9-7.6%), representing an absolute risk reduction (ARR) of 12.9% and relative risk reduction (RRR) of 71.2% ($p < 0.001$). Similarly, the mean predicted NTCP for bowel in left-sided lesions was 6.7% (0.9-12.3%), compared to 2.1% (0.6-3.5%) post-adaptation ($p = 0.086$), representing an ARR of 4.5% and RRR of 67.2%. No benefit of adaptation was seen for the duodenum, ipsilateral/contralateral kidneys or liver for left-sided adrenal lesions. Adaptation did not significantly change the NTCP of any OAR for right-sided lesions. The minimum number needed to treat to prevent one predicted stomach or bowel-related adverse event for left-sided adrenal lesions is 5.9.

Conclusion

SMART using daily adaptation decreased the NTCP for stomach and bowel in left-sided adrenal lesions. The low baseline NTCP for right-sided adrenal lesions have led us to adopt shorter (1-3 fraction) SABR schemes for this indication.

A9

Customizable metallo-nanotexaphyrins for cancer imaging and therapy

Miffy H. Y. Cheng, Marta Overchuk, Maneesha Rajora, Juan Chen, and Gang Zheng

Purpose

Oligometastatic prostate cancer affects over 260,000 people worldwide and is potentially curable with surgery and external beam radiation therapy if diagnosed and treated appropriately. However, ablative therapies are currently hindered by the lack of precision imaging and low treatment efficacy, leading to poor prognosis for patients and cancer recurrence. To overcome these challenges, we propose a multifunctional nanoparticle as a non-invasive tool for radionuclide imaging and focal photodynamic therapy. Multifunctional nanoparticles can add both diagnostic and therapeutic value in the management of oligometastatic cancer. The “one for-all” approach was developed, in which nanoparticle is composed of a single building block that when self-assembled, offers a multitude of intrinsic functions while minimizing formulation complexity.

Method

We developed a theranostics liposomal nanoparticle known as Lu-nanotexaphyrin. Lu-nanotexaphyrin is formed through the self-assembly of texaphyrin-phospholipid building block that has been chelated with a Lu metal ion. We utilized a post insertion method to quantitively chelate the ‘cold’ 175Lu and the ‘hot’ 177Lu. The use of different isotopies will enable us to use a single metal to evaluate both the in vivo pharmacokinetic profiles of 177Lu chelated nanotexaphyrin with SPECT imaging while assessing the image-guided photodynamic efficacy in prostate cancer as a PDT agent.

Results

The Lu-nanotexaphyrin formulation was optimized for both a structural and optical stability in different serum conditions. Subsequently, Lu-nanotexaphyrin showed excellent photostability in its intact form and as it disrupts, high level of singlet oxygen can be produced under light irradiation. Fluorescence microscopy and ICP-MS also revealed excellent cellular uptake of Lu-nanotexaphyrin. To further investigate the therapeutic effect of Lu-nanotexaphyrin, we performed in vitro PDT with PC3-luc-6 cells to find the combination of nanoparticles with laser treatment resulted in potent PDT effects. In vivo fluorescence imaging using a subcutaneous prostate tumour model also demonstrated tumour accumulations at 24 h post intravenous administration of Lu-nanotexaphyrins. Further studies will investigate the radiolabelling of 177 Lu and its in vivo disposition and pharmacokinetic profiles. In addition, we will evaluate SPECT imaging sensitivity and specificity of Lu-nanotexaphyrins as a imaged-guided PDT agent.

Conclusion

These results highlight the utility of metallo-nanotexaphyrins as a potential theranostics agent with good stability and therapeutic capability for prostate cancers. This work aims to demonstrate the metallo-nanotexaphyrins as a customizable and multifunctional nanomedicine platform for non-invasive SPECT imaging and image-guided photodynamic therapy

A10

A Retrospective Study of Plan Modifications Resulting from Peer Review of Palliative and Radical Radiation Treatment Plans

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Purpose

Multidisciplinary peer review of radiation treatment plans is recognized as an integral component to improving radiotherapy quality and safety. Peer review rates have steadily increased in Ontario over the last decade, aided by the introduction of performance targets by Cancer Care Ontario. In 2019, 88% of radical and 62% of palliative plans in Ontario underwent peer review. Our institution consistently approaches 100% peer review for all plans, irrespective of treatment intent. The primary objective of this study was to assess whether treatment intent influences the rate of plan modifications (PM) arising from peer review recommendations. The secondary objective was to identify whether the protocol status and target site affected the PM rate.

Method

All treatment plans peer reviewed between November 2015 and November 2016 were included in the analysis. Peer review primarily focused on target volumes, dose and/or fractionation. Pertinent clinical and treatment plan characteristics were extracted, including intent (palliative/non-palliative), whether the treatment plan followed institutional protocol or not, and anatomical target site. The primary endpoint was PM rate, defined as any change implemented following recommendations from peer review. Logistic regression analysis was used to analyze a causal model that included palliative intent as an exposure variable, plan modification as the outcome variable and both pre-existing protocol and target site as confounding variables.

Results

A total of 1740 treatment plans in 1195 patients were included in the analysis. We observed that plans with palliative intent were 35% less likely to have a PM (OR = 0.65, CI = 0.50 - 0.84). There was effect modification by pre-existing protocol status. Sensitivity analysis adjusted for patient clustering did not alter the results.

Conclusion

We found a higher proportion of PM for non-protocol plans of non-palliative intent compared to other types of plans. This may be due to a greater perceived risk of not optimizing plans with non-palliative intent. Additionally, the absence of standardized protocols may result in greater heterogeneity in opinion regarding the plan target volume and/or dose/fractionation. An expanded cohort is currently under analysis to elucidate these factors further, nonetheless, we advocate that all radiotherapy treatment plans undergo multidisciplinary peer review.

A11

Quantitative Ultrasound Radiomics for LABC Therapy Response Monitoring: Multi-Institutional Study Results

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Purpose

Neoadjuvant chemotherapy (NAC) is the standard of care for patients with locally advanced breast cancer (LABC). The study was conducted to investigate the utility of quantitative ultrasound (QUS) carried out during NAC to predict the final tumour response in a multi-institutional setting.

Method

Fifty-nine patients with LABC were enrolled from three institutions in North America (Sunnybrook Health Sciences Centre (Toronto, Canada), MD Anderson Cancer Centre (Texas, USA), and Princess Margaret Cancer Centre (Toronto, Canada)). QUS Data were collected before starting NAC and subsequently at weeks 1 and 4 during chemotherapy. Spectral tumour parametric maps were generated, and textural features determined using grey-level co-occurrence matrices. Patients were divided into two groups based on their pathological outcomes following surgery: responders and non-responders. Machine learning algorithms using Fisher's linear discriminant (FLD), K-nearest neighbour (K-NN), and support vector machine (SVM-RBF) were used to generate response classification models.

Results

Thirty-six patients were classified as responders and twenty-three as non-responders. Among all the models, SVM-RBF had the highest accuracy of 81% at both week 1 and week 4 with area under curve (AUC) values of 0.87 each. The inclusion of week 1 and 4 features led to an improvement of the classifier models, with the accuracy and AUC from baseline features only being 76% and 0.68, respectively.

Conclusion

QUS -radiomics obtained during NAC reflect the ongoing treatment-related changes during chemotherapy and can lead to better classifier performances in predicting the ultimate pathologic response to treatment compared to baseline features alone.

A12

Exploration of Epigenetic Profiles in Circulating Tumor DNA to Identify Predictive Cancer Biomarkers

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Purpose

Liquid biopsy has recently garnered interest due to technological advances that enable noninvasive molecular diagnosis and cancer monitoring. There is precedent for using predictive information from liquid biopsies to guide treatment decisions. For instance, EGFR mutations in non-small cell lung cancer (NSCLC) can be detected within ctDNA to guide use of tyrosine kinase inhibitors. Unlike mutations, epigenetic alterations in ctDNA have not yet been utilized as predictive biomarkers. Catalogues of drugs against histone modifying enzymes are undergoing clinical evaluation, however evaluation of the mechanistic activity of these drugs requires a tissue biopsy, so non-invasive approaches must be established. We hypothesize that specific profiles of histone modifications are detectable in ctDNA and can be used as non-invasive biomarkers for the activity of drugs against histone modifying enzymes.

Method

To address our hypothesis, we developed a preclinical model that simulated ctDNA/nucleosome shed from cancer cells. Cancer cell lines were grown in tissue culture, and conditioned media was collected for downstream processing of cell-free nucleosomes. Micrococcal nuclease was added to conditioned media and incubated for 30 minutes at 37ºC. Next, cell-free DNA fragments were purified using the QIAamp Ciruclating Nucleic Acids kit, quantified using Qubit and quantitative PCR, and profiled using Agilent BioAnalyzer.

Results

We applied the ctDNA/nucleosome simulation to the following cancer cell lines: HCT116 (colorectal cancer), MCF7 (breast cancer), A549 (NSCLC), SUDHL-6 and OCI-LY19 (diffuse large B-cell lymphoma). Conditioned media was collected from cell lines in log-phase growth. Without micrococcal nuclease treatment, cell-free DNA fragments were primarily >600 bp in length (35% - 97% of fragments). Micrococcal nuclease treatment resulted in predominantly nucleosomal ctDNA fragments (90% - 95% of fragments). This represents a considerable increase in the abundance of nucleosome-sized fragments which are suitable for ctDNA epigenome profiling.

Conclusion

We have successfully implemented a preclinical model to simulate ctDNA/nucleosome shed from cancer cells. This model opens avenues for discovering epigenetic signatures of drug resistance or to validate the epigenetic mechanisms of various drugs. Next steps are to build cancer-specific ctDNA epigenetic profiles for specific histone modifications, with and without exposure to epigenetic modifying drugs. We will then extend these methods to tumor xenograft models and finally to cancer patient plasma samples. The potential future impact of this project includes early cancer detection, monitoring for recurrence, as well as prediction of patient tumor drug response to aid in treatment decisions, contributing to the field of personalized cancer medicine.

A13

Quantitative Ultrasound Radiomics In Predicting Response to Neoadjuvant Chemotherapy in Patients with Locally Advanced Breast Cancer: Results from Multi-Institutional Study

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Purpose

This study was conducted in order to develop a model for predicting response to neoadjuvant chemotherapy (NAC) in patients with locally advanced breast cancer (LABC) using pre-treatment quantitative ultrasound (QUS) radiomics.

Method

This was a multicenter study involving four sites across North America, and appropriate approval was obtained from the individual ethics committees. Eighty-two patients with LABC were included for final analysis. Primary tumours were scanned using a clinical ultrasound system before NAC was started. The tumour were contoured, and radiofrequency data were acquired and processed from whole tumour regions of interest (ROI). QUS Spectral parameters were derived from the normalized power spectrum, and texture analysis was performed based on six QUS features using a gray level co-occurrence matrix. Patients were divided into responder or non-responder classes based on their clinical-pathological response. Classification analysis was performed using machine learning algorithms, which were trained to optimize classification accuracy. Cross-validation was performed using a leave-one-out cross-validation method.

Results

Based on the clinical outcomes of NAC treatment, there were 48 responders and 34 non-responders. A K-nearest neighbours (K-NN) approach resulted in the best classifier performance, with a sensitivity of 91%, a specificity of 83%, and an accuracy of 87%.

Conclusion

QUS-based Radiomics can predict response to NAC based on pre-treatment features with acceptable accuracy.

A14

Development of risk score model for locoregional recurrence following upfront surgery for resectable pancreatic adenocarcinoma: therapeutic implication on adjuvant therapy for pancreatic cancer

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Purpose

The aims of the study were: (1) to identify predictors of locoregional failure (LRF) following surgical resection for localized pancreatic adenocarcinoma (PA) (2) development of a prediction risk score model of LRF, and (3) evaluation of the impact of postoperative radiation therapy (PORT)

Method

A retrospective review was conducted on patients with stages I-III PA who underwent surgery at our institution between 2005-2016. 1) Univariable analysis (UVA) was used to evaluate clinical and pathological factors associated with LRF for patients who did not receive PORT. All variables with p-value <0.1 in UVA were entered into multivariable analysis (MVA) and <0.05 to stay in the model. 2) The risk score was calculated based on the sum of coefficients of the predictors of LRF. 3) The developed model was applied to the entire cohort to identify high and low-risk groups for LRF

Results

A total of 469 patients were identified, with a median follow up of 22 months. Two yr-LRF for the entire cohort was 41% (95% CI 35-46 %). Predictors of LRF were lymphovascular invasion (LVI), pN+, grade 2-3, and involved or close ≤ 1mm margins. Two yr-LRF for high-risk patients (n=264) who received PORT vs patients who did not receive PORT were 32% (95% CI 34-52) and 57% (95% CI 48-65) respectively.

Conclusion

The high-risk features (LVI, pN+, Grade 2-3, and involved or close margins) could be used to identify PA patients with a higher risk of LRF who may benefit from PORT

A15

Predicting recurrence for patients with head-neck squamous cell carcinoma using quantitative ultrasound-based radiomic signatures integrated with machine learning

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Purpose

We have demonstrated the ability of quantitative ultrasound (QUS) in characterizing tumour biology in previous in vitro and in vivo studies. This aim of this project was to investigate the clinical utility of QUS as a biomarker for predicting recurrence in patients with node-positive head-neck squamous cell carcinoma (HNSCC) treated with radical radiotherapy (RT).

Method

Fifty patients with HNSCC were treated with RT (70 Gy/33 fractions) (+/- concomitant chemotherapy) were included in the current analysis. QUS data acquisition involved scanning nodes with a conventional-frequency device having a central frequency of ~7 MHz. Data were collected at the following time intervals relative to the start of treatment: week 0 (baseline), after week 1, and week 4. Acoustic backscatter features were quantified using spectral analysis of the radiofrequency data within a region of interest. Second-order features included a set of 41 QUS radiomic features from a grey-level co-occurrence matrix. Radiological imaging (MRI, CT) was acquired as part of the usual standard-of-care at 3 months after completing RT. Subsequently, patients were followed every 3 months for the initial two years and then every 6 months with clinical examination supplemented with imaging as indicated. Patients were categorized into two groups based on clinical outcomes (recurrence vs. no recurrence). Results were compared from 3 classifications algorithms-Fisher linear discriminant, k-nearest-neighbours, and support vector machine (SVM). Three features used in each model were selected using a forward sequential selection method and validated using leave-one-out cross-validation.

Results

The median follow up for the entire group was 18 months. The most common primary site was oropharynx in 34 patients, followed by hypopharynx (7), larynx (4), unknown primary (4), and oral cavity (1). There were 16 complete responders (CR) and 34 partial responders (PR) at 3 months following completion of RT. Fourteen patients had recurrences: isolated regional (2), regional-distant (3), isolated distant (7), local-regional-distant (2), all belonging to the cohort of PR. The SVM classifier resulted in the best predictive performance (sensitivity, specificity, accuracy, and area under the curve values of 92%, 71%, 86%, and 71%, respectively, for week 0). There was an improvement in classification accuracy at week 1 and week 4 using the SVM classifier (Table 1). Most of the features selected for the recurrence classification were second-order QUS-texture features.

Conclusion

Our preliminary results demonstrate encouraging results for QUS radiomic features as a potential biomarker for predicting patients at higher risk of disease recurrence. This is the first clinical report showing the ability of ultrasound to predict the outcomes even before the initiation of treatment in HNSCC.

A16

Quantitative mapping of the peritumoral region to demarcate areas of tumor infiltration from vasogenic edema in radiation planning MRI of glioblastoma through extrapolation of a 10-feature radiomic signature

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Purpose

The peritumoral region (PTR) is known to represent distinct micro-environment for brain metastases (BM) composed of vasogenic edema as opposed to glioblastoma multiforme (GBM) which is a combination of infiltrative tumor and edema. We explored the utility of MRI-radiomics in distinguishing the PTR between the two groups and generate a radiomic model for quantitative mapping in radiation planning scans.

Method

Pre-treatment T1W post-contrast, T2-FLAIR, and apparent diffusion coefficient (ADC) scans were obtained using a 1.5T MR scanner. The PTR was segmented manually, which corresponded to the areas of T2W hyperintensity/ T1W hypointensity surrounding the tumor core. Images were resampled to 1x1x1 mm3, skull stripped, rigidly registered, and bias-field corrected. A total of 3612 features including first order, texture, wavelets, were extracted from the entire PTR for BM and central 1 cm rim of GBM PTR (as it has a higher likelihood of having infiltrative tumor). Three classifiers (Support Vector Machine (SVM), K-Nearest Neighbours and Linear Discriminant Analysis), and three feature selection algorithms (Univariate T-test, Minimum Redundancy Maximum Relevance and Recursive Feature Elimination (RFE)) were applied to the extracted features. Nested 3-fold cross-validation was used to evaluate model performance using the best 10 selected features. All patients were subsequently pooled into a single training set to train a final classifier. The final 10 features selected we then used to generate spatial feature maps on the radiation planning scans from 11 post-operative GBM patients and the classifier was applied on each pixel of the post-operative edema regions. The classifier output was calibrated to output classification probability for either GBM-like or BM-like edema.

Results

A total of 87 segments (42 GBM and 45 segments from 23 patients with BM) were included in this study. The best results were obtained using SVM-RFE with all of sensitivity, specificity, accuracy, F1-score being 91% with area under curve (AUC) of 0.97. On analysis of features from individual T1, T2, ADC sequences, the accuracy was 85%, 91%, 87%, respectively. The 10-feature radiomic signature was applied to the clinical target volume (CTV) in the radiotherapy (RT) planning MRI for 11 patients with GBM to create a color-coded map representing the probabilities of infiltrative tumor vs. edema. The follow-up MRI showing recurrent disease were compared and showed a good correlation in 7 patients, with the most obvious recurrences occurring in the areas indicated to harbor higher infiltrative tumor.

Conclusion

This study suggests MRI-radiomics can demarcate the PTR between GBM and BM with excellent accuracy, and a 10-feature signature can be effectively employed in the mapping of CTV on RT planning scans. Further research has the potential to explore such a radiomic-signature for personalized radiotherapy (individualized CTV and dose painting).

A17

Primary analysis of a phase II study of metastasis-directed ablative therapy to PSMA (18F-DCFPyL) PET-MR/CT defined oligorecurrent prostate cancer

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Purpose

Despite maximal local therapies (MLT) (radical prostatectomy followed by radiotherapy [RT]), 20-30% of men will progress to incurable prostate cancer (PCa). Most recurrences in this scenario are characterized by rise in PSA with negative bone scan (BS) and computed tomography (CT). We conducted a phase II trial for men with rising PSA after MLT using 18F-DCFPyL (PSMA) PET-MR/CT followed by metastasis-directed therapy (MDT) to PET positive foci. We report the results of our primary analysis.

Method

Patients with rising PSA (0.4-3.0 ng/mL) after MLT, negative BS/CT and no prior salvage ADT were eligible. All patients underwent PSMA PET-MR followed by immediate PET-CT acquisition. Those with limited disease burden amenable to MDT underwent either stereotactic ablative RT (SABR) or surgery (lymph node dissection). No ADT was used. The primary endpoint was biochemical response rate (complete [undetectable PSA] or partial [PSA decline ≥50% from baseline]) following MDT. A Simon's two stage study design was employed. Estimated time of delay in salvage ADT was calculated using the Kaplan-Meier method. Toxicity was prospectively recorded according to CTCAE v4.0.

Results

After a median of 63 months (range 3-180) post MLT, 72 patients underwent PSMA PET-MR/CT. Median PSA at enrollment was 0.98 ng/mL (range 0.4-3.1). Sixteen patients had negative and 56 had positive PET-MR/CT scans, of which 37 (51%) were amenable to MDT. The median number of treated lesions was 2 (range 1-5). Of the treated patients, 30 (81%) had miT0N1M0 disease, 2 (5.5%) had miT0N1M1a disease, 2 (5.5%) had miT0N0M1a and 3 (8%) had miT0N0M1b disease. Twenty-seven patients underwent SABR (median 30 Gy in 3 fractions) and 10 had surgery. At a median of 11 months (range 1-29) post MDT, 8 patients (22%) had complete and 14 (38%) had partial responses. Amongst the 8 complete responders, 5 had surgery and 3 had SABR; of the 14 partial responders, 2 had surgery and 12 had SABR. The estimated median delay in salvage ADT for the entire cohort, partial and complete responder subgroups were 13 months (IQR 8-20), 16 months (IQR 13-20), and 30 months (IQR not reached), respectively. Two grade 2+ toxicities were observed, both in surgical patients: deep venous thrombosis and ureteric injury requiring stent placement.

Conclusion

18F-DCFPyL (PSMA) PET-MR/CT has high detection rates (78%) in men with rising PSA after MLT. We observed a favorable therapeutic index with MDT (60% response rate) for patients with metachronous PSMA-unveiled oligometastatic PCa following MLT. Phase III studies using validated intermediate clinical endpoints are needed before integration into routine clinical practice.

A18

Stereotactic Ablative Radiotherapy for the Management of Liver Metastases from Neuroendocrine Neoplasms

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Purpose

Liver metastases are common in patients with metastatic well-differentiated neuroendocrine neoplasms (WD-NEN). Given the potentially indolent clinical course of WD-NEN, patients may have a prolonged survival even in the setting of metastatic disease; therefore, treatments must maximize tumour control and minimize treatment side effects in order to maintain quality of life. The role of stereotactic ablative radiotherapy (SABR) is not well understood in this unique patient population. The purpose of this study is to evaluate the safety and efficacy of SABR in treating well-differentiated neuroendocrine liver metastases (WD-NELM).

Method

An institutional REB approved retrospective review of patients with WD-NELM treated with SABR was performed spanning January 2015 to July 2019. Demographic, treatment details and clinical/radiographic follow-up data were abstracted from the patients' clinical and radiation planning records. RECIST 1.0 criteria were applied to each individual target to evaluate the overall response rate to treatment. Local control and progression free survival was determined using Kaplan-Meier methodology. Toxicity was reported as per CTCAE v 5.0 criteria.

Results

Twenty-five patients with a total of 53 individual liver metastases treated with SABR were identified. The median number of liver metastases treated per patient was 2 (range: 1-4) with a median size of 2.5 cm (range 0.7-9.7 cm). The median radiation dose delivered was 50Gy/5 fractions (range 25Gy/5 - 60 Gy/3) with a median biologically effective dose (BED10) of 100 (range 39-180). The median follow-up was 14 months (range 2-54 months). Twenty-four of the 25 patients were still alive at time of data analysis. Most patients (68%) had midgut tumors (small bowel, pancreas), were Grade II (80%) and had high volume intrahepatic and/or extrahepatic disease (76%). Almost all patients (96%) remained on systemic somatostatin analogues despite having radiographic disease progression. Six targets underwent pseudoprogression. The best treatment response according to changes in axial diameter was -100% (median: -16%, range: -100% to 47%). The objective response rate was 32%, with initial disease improvement or stability in 96% of all lesions treated. The median time to best response was 9 months (range: 3-16 mos). The 1-year local control and PFS were 92% (CI 85-99.9%) and 44% (CI 28-70.1%) respectively. No Grade III/IV acute or late toxicity was identified.

Conclusion

Liver SABR is a safe and effective means of providing local control for WD-NELM. This treatment modality should be considered a care option in select patients in concert with strategies to manage systemic disease.

A19

Pan-Canadian Survey of Radiation Oncology Professional Involvement in Cancer Control Projects in Low-Income and Middle-Income Countries

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Purpose

The global cancer burden has risen to 18.1 million cases and 9.7 million deaths in 2018. The disease burden is the greatest in low- and middle-income countries (LMICs), where 75% of cancer deaths occur and the number of cancer cases is rising most rapidly. The purpose of this survey was to determine the current level of involvement and engagement of Canadian radiation oncology professionals in global oncology initiatives in LMICs.

Method

A CARO subcommittee, in partnership with medical physicists across Canada, initiated a national survey, which was distributed via CARO and COMP mailing lists in March 2019. The survey included questions to assess the participant's awareness of ongoing global oncology initiatives in the domains of a project's region, objectives, and multi-disciplinary involvement. Regional representatives were assigned in each province to ensure multidisciplinary response from radiation oncologists (ROs) and medical physicists (MPs).

Results

A response was received from 86 professionals (44 ROs and 42 MPs), across 37 cancer centres in Canada. From 25 cancer centres a feedback was received from both RO and MP. Respondents reported that 20% are currently involved in projects and 21% were involved in the past. Project regions currently span 20 countries: Algeria, Armenia, Chile, China, Ecuador, Ethiopia, Egypt, Ghana, India, Iraq, Jordan, Kenya, Kuwait, Malawi, Morocco, Nigeria, Pakistan, Qatar, South Africa, Sudan. Typically RO professionals' involvement was in quality improvement (19%: MPs (7%) vs ROs (12%)), capacity building (14%: MPs (6%) vs ROs (8%)), clinical care (12%: MPs (2%) vs ROs (10%)) and research (11%: MPs (5%) vs ROs (6%)). Fraction of interested professionals with no experience (32%) in global oncology initiatives was significant (MPs (23%) vs ROs (9%)), suggesting a potential resource to increase Canadian impact in moving forward projects in LMICs.

Conclusion

A positive response was received from the radiation oncology community regarding the survey initiative. The results of the survey have provided aggregated data on the current involvement and will help coordinate the efforts of Canadian RO professionals in LMICs in the future.

A20

Vulvar carcinoma: patterns of practice and clinical outcomes from a large academic cancer centre

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Purpose

Vulvar cancer is a rare malignancy. Unfortunately, prospective randomized trials are limited. Our objective was to evaluate patterns of practice and clinical outcomes for vulvar cancer patients treated at a large, academic cancer centre.

Method

Between January 2008 and December 2017, vulvar cancer patients treated at our institution were identified. Patient demographics, treatment characteristics and clinical outcomes were extracted from medical records. Variables were summarized using descriptive statistics. Disease free survival (DFS) and overall survival (OS) rates were calculated using the Kaplan-Meier method. Factors associated with receipt of adjuvant (chemo)-radiotherapy were tested using the Mann-Whitney (continuous) and Fisher's exact (categorical) tests. Multivariable analysis (MVA) for survival was performed using Cox regression.

Results

A total of 248 patients were identified, 36 patients were diagnosed with vulvar melanoma and were excluded, leaving 212 patients for analysis. Median follow-up was 2.0 years. Median age at diagnosis was 69 years (range: 20-95). Primary surgery was performed in 151 patients: 35 received adjuvant radiotherapy (23%) and 11 received concurrent chemotherapy (31%). Larger tumor size, lymphovascular invasion, close/positive margins, higher depth of invasion and higher grade were associated with receipt of adjuvant radiation ($p<0.05$). Younger age was associated with receipt of concurrent chemotherapy ($p=0.0025$). There were no differences in DFS for patients treated with surgery alone compared to patients receiving adjuvant (chemo)-radiation (2-year: 81% vs. 68% and 5-year: 67% vs. 50%, respectively; log rank p-value 0.21). However, OS was significantly higher for patients treated with surgery alone compared to patients receiving adjuvant chemo-radiation (2-year: 97% vs. 88% and 5-year: 95% vs. 79%, respectively; log rank p-value 0.03). Sixty-one patients were inoperable at diagnosis: 30 underwent definitive radiation, 10 underwent neoadjuvant radiation and 21 underwent palliative radiation. Concurrent chemotherapy was given in 52%. Two-year and 5-year DFS were 58% and 43%, respectively, and 2-year and 5-year OS were 81% and 72%, respectively. On MVA, systemic therapy and depth of invasion were associated with poor DFS (HR 3.23, 95% CI 1.2-8.66, $p=0.02$; HR 1.06, 95% CI 1.02, 1.1, $p=0.005$, respectively). There were too few deaths to perform MVA for OS.

Conclusion

Vulvar carcinoma is a rare malignancy and optimal patient management requires multi-disciplinary management. Opportunities exist to improve clinical outcomes for those receiving adjuvant (chemo)-radiation. Our results will be used to develop clinical care pathways to ensure multi-disciplinary, harmonized practice.

A21

Patient-reported outcomes of adolescents and young adults with breast cancer treated with curative intent

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Purpose

To evaluate patient-reported outcomes of adolescents and young adults (AYAs) with breast cancer treated with curative intent.

Method

AYA Stage 0-IV breast cancer patients (age at diagnosis between 18 to 39 years) treated at our institution with curative intent between January 2014 and December 2016 were identified. Patient, clinical and treatment characteristics were extracted from medical records. Edmonton Symptom Assessment System-revised (ESAS-r) scores up to 2 years post-diagnosis were obtained from our internal database. Summary statistics were used to describe patient, clinical and treatment characteristics, as well as ESAS-r scores. Elevated ESAS-r scores were defined as > 4 for each individual symptom. Time to recurrence was calculated from diagnosis to local or regional recurrence, distant metastasis or death (whichever occurred first). Kaplan-Meier survival analysis and log-rank tests were used to compare time to recurrence between women with vs. without elevated symptom scores. Chi-squared test was used to evaluate the change in symptom scores over time. Multivariable logistic regression was used to assess factors associated with elevated ESAS-r psychosocial symptoms (depression, anxiety and well-being). Univariable logistic regression was fitted to assess the association between elevated psychosocial symptoms and referral to Psychosocial Oncology and/or Survivorship clinics.

Results

Among 258 patients identified, 212 (82%) had accompanying ESAS-r and were eligible for analysis. Median follow-up was 3.6 years (range: 0.2-5.8 years). Median age at diagnosis was 35 (20-39), most were clinical stage 2/3 (63%), 20% had triple negative disease, 76% received chemotherapy and 81% received radiotherapy. All patients except one underwent surgery, with 55% undergoing lumpectomy and 51% undergoing sentinel lymph node assessment. The most common elevated patient-reported symptoms were worse well-being (52%), tiredness (48%) and anxiety (44%). The above symptoms were persistently elevated at 2 years post-treatment in 43%, 38% and 33% of patients, respectively. All patient-reported symptoms significantly decreased over time, with the exception of nausea, shortness of breath and appetite, which remained stable. Multivariable analysis found that receipt of chemotherapy was significantly associated with elevated anxiety (p=0.01). Elevated depression and anxiety and worse well-being were significantly associated with referral to Psychosocial Oncology (p=0.0095, p=0.035 and p=0.0021, respectively), whereas worse well-being was also associated with referral to Survivorship Clinic (p=0.0032). However, rates of referral were much lower than symptom prevalence. There was no association between elevated symptoms and time to recurrence.

Conclusion

AYAs diagnosed with breast cancer report high levels of symptoms that persist at 2 years post-diagnosis. Patients with elevated psychosocial distress are more likely to be referred to Psychosocial Oncology and Survivorship clinics, indicating that the ESAS-r is a useful screening tool in a real-world setting. However, a gap between symptom burden and intervention exists, providing opportunities for future research.

A22

Protein Secretion Rates of Vascular Endothelial Growth Factor and Carbonic Anhydrase 9 in Normoxia and Hypoxia

Sandy Che-Eun Serena Lee, Stephanie Hulme, Fiana Levitin, Ryan A. Rumantir, Jenna Sykes, Marianne Koritzinsky

Purpose

Tumor hypoxia results in poor patient outcome due to treatment resistance as well as biological changes that stimulate angiogenesis, vasculogenesis, migration, invasion and immune suppression. These hypoxia-induced adverse biological changes are often mediated by membrane bound or secreted proteins through transcriptional and translational upregulation. Thus, understanding the regulation of how secreted proteins in hypoxia can therefore reveal novel therapeutic targets. Proteins that traverse through the secretory pathway form disulfide bonds in the endoplasmic reticulum (ER). Recent data from our lab have demonstrated that disulfide bond formation remains incomplete in ER cargo proteins like LDLR and Flu-HA in the absence of oxygen.

Method

To address whether hypoxia-induced proteins were likewise impaired, radioactive pulse chase assays were performed to measure disulfide bond formation and secretion capacity under both normoxic and hypoxic conditions.

Results

Here, we demonstrate that both hypoxia induced proteins carbonic anhydrase 9 (CA9) and vascular endothelial growth factor (VEGF) complete disulfide bond formation and are secreted with equal kinetics under hypoxia and normoxia. These proteins hence have a superior ability to be expressed in the absence of oxygen. Additionally, in a global in silico analysis of all proteins that traverse through the ER, we discovered that hypoxia-induced proteins on average contain fewer free cysteines and shorter-range disulfide bonds in comparison to other proteins.

Conclusion

These traits may contribute to their superior ability to form correct disulfide bonds in hypoxia. These data show that the ability of proteins to form native disulfide bonds in hypoxia varies widely which can ultimately contribute to their expression in the extracellular space.

A23

Rates of radionecrosis in re-irradiation of brain metastases using hypofractionated stereotactic radiotherapy.

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Purpose

Improved overall survival rates among brain metastases (BM) patients have led to higher rates of salvage re-irradiation in patients with local failure. Hypofractionated stereotactic regimens are an attractive option due to the possibility of lower rates of radionecrosis (RN). This study aims to determine the incidence and risk factors of RN following re-irradiation with hypofractionated stereotactic radiotherapy (hSRT) and compares the results to the incidence of RN following re-irradiation with single fraction SRS reported in literature.

Method

Retrospective chart review was conducted on patients from a single institution who received re-irradiation using hSRT to BMs that previously received stereotactic radiotherapy. Patients who received additional whole brain radiation (WBRT), prior to, or after stereotactic radiotherapy were included. Patient, tumor, treatment characteristics, and follow-up data were collected. MRI and pathology of any lesions resected post-radiotherapy were reviewed to assess for the development of RN and the response to treatment. RN was confirmed through MRI or by surgical resection. Associations between RN and target volume, as well as number of months between stereotactic treatments were examined using logistic regression. Association between RN and use of additional WBRT was examined using relative risk and chi-square tests.

Results

A total of 110 metastatic brain lesions in 90 patients received hSRT reirradiation between August 2010 and December 2019. 26.7% (n=24) of patients also received additional WBRT. The most common histologies were breast (n=31), NSCLC (n=30), and melanoma (n=29). The median volume of lesions was 12.25cc (IQR 4.97 – 25.07cc). The most common fractionation scheme was 25 Gy in 5 fractions (72 lesions). The incidence of local failure was 11.6% and 17.4% at 6 and 12 months, respectively. Incidence of symptomatic RN was 6.15% and 15% at 6 and 12 months, respectively. There was no statistically significant association between symptomatic RN at 12-months and radiation dose (p=0.40), target volume (p=0.96), use of additional WBRT(p=0.74), or number of months between SRT(p=0.99).

Conclusion

The incidence of symptomatic RN following re-irradiation with hSRT is lower compared to re-irradiation with single fraction SRS as reported in literature. hSRT provides an alternative salvage option for treating local failure of BMs to reduce risk of RN while achieving local control.

A24

Long term biochemical control of a prospective cohort of prostate cancer patients treated with interstial brachytherapy versus radical prostatecomy

Gordon Locke, Juanita Crook, Charles Catton, Zhihui Lui, Srinivas Raman, Peter Chung, Alejandro Berlin, Neil Fleshner, Joelle Helou

Purpose

Management strategies for localized prostate cancer include radical prostatectomy (RP) and low dose rate brachytherapy (LDR-BT) however there is a lack of randomized evidence directly comparing LDR-BT to RP. The American College of Surgeons Oncology Group Phase III Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial (SPIRIT) suffered from poor accrual and was closed early. We report on the long-term biochemical control rates of men treated prospectively as part of SPIRIT at our institution.

Method

Patients approached for SPIRIT between 2003 and 2004 at our institution who either chose or were randomly assigned to RP or LDR-BT following a multidisciplinary educational session, were included in this analysis. Biochemical failure (BF) after RP was defined as a PSA level ≥ 0.2 ng/ml and the phoenix definition of PSA of ≥ 2 ng/ml above the nadir was used to define BF after LDR-BT. A sensitivity analysis using a PSA > 0.5 ng/mL to define BF after LDR-BT was performed to test the robustness of the results. To account for the competing risk of death, Gray's test was used to test the equality of the cumulative incidence function (CIF) of BF between treatment groups. The Kaplan-Meier method was used to estimate prostate cancer specific survival (PCSS). A two-tailed p-value ≤0.05 was considered statistically significant.

Results

Of 156 patients, 100 received LDR-BT and 56 underwent RP. Median follow-up was 12.5 (9.2- 15.8) and 14.2 (IQR: 8.3-15.9) years for LDR-BT and RP cohorts respectively (p=0.633). Median age was 60 (IQR: 56-65) years, median pre-treatment PSA was 5.51 (IQR: 4.32-7.12). 151 patients had Gleason Score 6. 55 patients were clinically staged as T2a and 101 patients had T1c disease. No statistically significant differences in patient characteristics were found between groups. Two patients received adjuvant external beam RT after RP. Two patients had a BF in the LDR-BT cohort versus 10 patients in the RP arm. The latter received salvage external beam RT. 85% of patients treated with LDR-BT had a PSA ≤ 0.05 at last follow-up. The CIF of BF was 0.0% and 1.1% (CI: 0.09-5.34) at 5 and 10 years respectively in the LDR-BT arm versus 8.5% (CI:2.6-18.7) and 15.8% (CI:6.8-28.2) in the RP cohort (p <0.001). These results were robust when varying the definition of BF; The CIF of BF at 10 years after LDR-BT was 2.5 % (0.4-7.9), p=0.009. There was no statistically significant difference in PCSS between interventions.

Conclusion

This analysis was undertaken on a cohort of men with similar patient and tumor characteristics who were prospectively enrolled and were candidates for both RP and LDR-BT. Excellent oncologic outcomes were found in both arms, suggesting that LDR-BT is non inferior to RP in this relatively young population, in addition to the previously suggested advantage for LDR-BT in urinary and sexual quality of life domains and patient satisfaction.

A25

A Prognostic Gene Expression Signature for Women With Cervical Cancer Receiving Curative Intent Treatment

Jelena Lukovic, Melania Pintilie, Jeffrey Bruce, Kathy Han, Rob Cairns, Trevor Pugh, Michael Milosevic

Purpose

Cervical cancer is a global health problem. Despite scale up of prevention programs, there is an important need to improve the effectiveness of treatment for women with established disease, including identifying those who may benefit from treatment intensification and/or the addition of new targeted treatments. To this end, we developed and validated a prognostic gene expression signature and risk score (RS) for women with cervical cancer.

Method

Tumor biopsies were obtained from 81 women with locally advanced cervical cancer prior to curative-intent radiotherapy and concurrent cisplatin followed by brachytherapy (RTCT) (median follow-up 6.8 years). Whole genome RNA sequencing was performed using the Illumina NextSeq (80M reads per sample). Using a 2-fold cross validation, 69 genes were selected. Principal component (PC) analysis was applied and 4 PCs were found to be associated with disease-free survival (DFS) using a Cox proportional hazards model (Cox PHM). The RS was calculated as the product of the coefficients from the Cox PHM, the rotation coefficients that determined the PCs and the expression levels of the genes. The RS was internally validated in subsets of 20 patients selected at random from the entire cohort of 81 patients. The RS was externally validated using an independent cohort of 206 cervical cancer patients from TCGA who received curative intent treatment with RTCT or surgery +/- adjuvant RTCT (median follow-up 2.2 years).

Results

The 5-year DFS was 60% in the PM cohort and 58% in TCGA cohort. The 69 gene RS was strongly associated with DFS in the PM cohort (HR 2.72, 95% CI 2.06-3.59, $p<0.0001$) and remained significant after adjusting for known clinical prognostic factors. The C-index was 0.61 (95% CI: 0.51-0.70) when only clinical factors were included in the Cox PHM and increased to 0.87 (95% CI: 0.82-0.92) when the RS was added. The 5-year DFS results for patients with RSs above and below the median value were 22% and 95%, respectively. The RS was similarly associated with DFS in TCGA cohort (HR 1.56, 95% CI 1.23-1.97, $p=0.03$). Functional enrichment analysis showed a strong association between the 69 genes in the signature and the immune state of the tumor, suggesting that the immune microenvironment may be an important determinant of outcome in these patients.

Conclusion

This validated 69 gene signature and RS may be used to identify cervical cancer patients at increased risk of recurrence following standard treatment and who may benefit from treatment intensification or possibly novel immune targeting strategies alone or in combination with surgery or RTCT. Prospective validation of the signature and RS in future clinical trials is required.

A26

TAK-243 combined with radiation and other DNA damaging agents as a novel therapeutic strategy for small cell lung cancer

Safa Majeed, Mansi Aparnathi, Lifang Song, Jessica Weiss, Aaron Schimmer, Ming Tsao, Geoffrey Liu, and Benjamin Lok

Purpose

Small cell lung cancer (SCLC) (~15-17% of lung cancer) is an aggressive disease, with a dismal overall five-year survival of 7%. The current first-line therapy consisting of cisplatin and etoposide chemotherapy (C/E) +/- radiation (RT), has changed minimally in >30 years. TAK-243, an E1 ubiquitin-activating enzyme (UAE) inhibitor, is a promising novel SCLC therapy. TAK-243 limits the formation of ubiquitin conjugates that mediate many cellular processes including DNA repair signalling. By dysregulating cancer-specific dependencies of UAE, TAK-243 may induce malignant cell death and potentiate DNA damage induced by RT and chemotherapeutic agents. Initial findings show TAK-243 is particularly effective for 2 SCLC cell-lines (EC50 of 0.006 - 0.011□M), compared to other cancers and normal tissues (n=29, EC50 ranging from 0.012 to 1.31□M; Hyer et al., 2018). However, TAK-243 has not been comprehensively evaluated as a single agent or in combination with C/E and RT for SCLC.

Method

SCLC cell-lines were treated with incremental doses of TAK-243 (0-1uM) and viability was determined by a resazurin conversion assay after 6 days. EC50 values were compared. To evaluate combination effects, C/E were administered (1:1 ratio, 0-1uM) to cell-lines together with a fixed cell-line specific TAK-243 dose (EC30). Area under the curve (AUC) was compared between TAK-243+C/E and C/E-alone groups. TAK-243 (0-1uM) was administered with RT (2-8 Gy) in a similar manner and cell viability was measured after 9 days. Dose modification factor (DMF), the ratio of RT dose required between control and drug-treated groups, was calculated at survival fraction 37. TAK-243 single-agent therapy (20mg/kg, BIW) was evaluated in a patient-derived xenograft (PDX) SCLC model (SCRX-Lu149). Subcutaneous tumours were established, and tumour volumes were compared between experimental and control conditions. Kaplan-Meier survival analysis and significance testing using the Log-Rank Test were completed.

Results

Single-agent therapy: EC50 values of SCLC cell-lines (n=11) ranged from 0.003-0.12uM in vitro. TAK-243-treated animals experienced significantly increased freedom from volumetric endpoint (p-value = 0.028) when evaluated in vivo. TAK-243+Chemotherapy: treatment revealed a positive combination effect for the majority of SCLC cell-lines (n=5, ΔAUC from -13-47 units), suggesting potential chemosensitivity. TAK-243+Radiotherapy: potential radiosensitization was observed in all SCLC cell-lines (n=5) as tested by the resazurin assay (DMF from 1.25-1.35).

Conclusion

Cell-line and PDX models of SCLC are sensitive to TAK-243. With TAK-243, lower doses of C/E and RT are required for most cell-lines. Use of TAK-243 may be a novel strategy to improve SCLC therapies. These findings will be validated using clonogenic survival assays and interrogated in vivo, which may provide a basis to move TAK-243 to the clinic.

A27

SBRT for Primary Head and Neck Cancers: A Systematic Review and Meta-Analysis

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Purpose

Stereotactic ablative radiotherapy (SBRT) is a well-established treatment modality for various medically-inoperable tumours. However, there is limited data examining the use of SBRT as a primary treatment strategy in head and neck cancers (HNC). The purpose of this study was to perform a systematic review and meta-analysis of outcomes and toxicities of SBRT for primary HNC.

Method

A systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered on PROSPERO, was conducted using MEDLINE® (PubMed®), EMBASE and Cochrane Library databases from inception until October 2019. Two reviewers (NM, MK) independently analyzed records, with discrepancies settled by a third (IK). Studies in the English language that reported treatment-related toxicity and outcomes post-SBRT for patients with primary HNC were included and those with fewer than 5 patients were excluded from the meta-analysis. Inverse variance-weighted linear mixed-effects models were used to summarize overall survival (OS) and local control (LC) curves over time. Inverse variance-weighted random effects meta-analyses of proportions were used to summarize crude late toxicity rates (>6 months from treatment).

Results

The initial search strategy identified 2763 records. After removing duplicates, screening, and full article review, 8 studies with n=109 patients met inclusion criteria. There were 2 prospective larynx studies (n= 13 and 29, respectively), with the remainder being retrospective in design, and most included mixed subsites. Radiotherapy dose and fractionation ranged from 18 – 59.5 Gy in 1 – 17 fractions, with biologically effective doses (BED10) ranging from 43 – 83 Gy10. LC rates at 1 year with 95% confidence intervals (CI) was 94% (95% CI: 80-98%), and 86% at 2 years (95% CI: 62-95%). OS rates at 1, 2, 3 and 4 years were as follows: 79% (95% CI: 78-81%), 65% (95% CI: 63-67%), 54% (95% CI: 51-57%), and 45% (95% CI: 41-50%), respectively. Late grade 3-4 toxicity was 3% (95% CI: 0.0-12.6%), with late grade 5 toxicity 0.1% (95% CI: 0.0-1.6%). Late toxicities included 1 case each of the following:grade 3 vocal cord ulcer requiring laryngomicrosurgery biopsy; grade 3 arytenoid cartilage necrosis requiring supraglottic laryngectomy, grade 4 laryngeal edema requiring tracheostomy, gastrostomy, and hyperbaric oxygen; grade 3 radionecrosis of vocal cord requiring gastrostomy; grade 3 facial pain, grade 3 cataracts; grade 5 sepsis secondary to aspiration pnuemonia six days after initiating treatment.

Conclusion

SBRT for primary HNC shows acceptable LC and survival with relatively low late toxicities and is a feasible alternative in medically-inoperable patients. Given the paucity of data and variability in reporting, prospective studies are necessary to further define the optimal doses, volumes, normal tissue tolerances, impact on quality of life, and refine the patient population that could benefit the most from SBRT.

A28

Elekta Unity MR-Linac daily automated end-to-end quality control

Victor Malkov, Jeff Winter, and Daniel Letourneau

Purpose

On the Elekta Unity MR-Linac, beam apertures are adapted daily based on patient position and anatomy variations. This poses a unique challenge to standard machine and patient-specific quality control (QC) measurement to verify machine performance and plan delivery as conventional QC tests cannot be easily applied to such workflows. In this work we developed a QC test to evaluate the Elekta Unity's end-to-end (E2E) MR-guided plan adaptation and delivery performance using automated analysis.

Method

Our E2E QC workflow employed the vendor supplied MR-to-MV phantom, which contains seven MR and MV detectable fiducials. To test the MR-guided online plan adaptation, we generated a 3D-CRT plan composed of four cardinal-angle radiation beams targeting two fiducials on a reference CT scan. During the daily QC, the phantom is setup in an offset position from the reference plan position by shifting the couch-index bar in the superior-inferior direction and by having a virtual isocenter shift in the lateral and vertical directions. We placed a separate index bar with an x-ray marker on the couch to evaluate positioning reproducibility. Plan adaptation was performed on a T1-weighted MR image that was rigidly fused with the planning CT. We generate a plan-of-the-day using the Adapt to Position workflow, delivered the beams and collected MV images. We exported the RT plan, MR image and MV images for offline automated processing with our in-house developed Python tool, which compares the phantom and plan isocenter shifts, planned and observed radiation field centers, couch position, and MR-to-MV shift.

Results

We analyzed 76 daily test instances. Couch positioning reproducibility was within 0.5 mm. Phantom and plan isocenter shifts were within ±0.5 mm in the lateral and vertical directions and ±1 mm in the longitudinal direction. We found the increased longitudinal variation was associated with the 0.9 mm MR-to-CT fusion variability. Planned and observed radiation field centers were within ±0.6 mm in the jaw and MLC directions. Calculated MR-to-MV isocenter shifts agreed within 0.1 mm of the vendor-provided test results.

Conclusion

We implemented a novel automated and sensitive E2E QC workflow capable of efficiently and accurately integrating numerous daily QC elements. The test informs on multiple system subcomponents required for online adaptation, including the MR-to-MV shift which is applied during each plan adaptation when transferring MR images to the Online re-planning tool. Further, by using the supplied MR-to-MV phantom, an independent software analysis tool, and a straightforward beam arrangement this test can be easily ported into any clinic using the Elekta Unity system.

A29

MRI-guided Ultrasound Stimulated Microbubble Therapy in PC3 Xenografts in Rabbits

Evan McNabb, Anoja Giles, Wenyi Yang, Zahra Jahed, Michael Sandhu, Justin Meneses and Gregory Czarnota

Purpose

The use of novel ultrasound-stimulation of microbubbles (USMB) in tumours have a radiation-enhancing effect. This extends the uses of microbubbles as vascular therapy agents by using focused ultrasound at energy levels lower than those used for ablation to create a biophysical response and perturb nearby endothelial cells. The purpose of this project is to utilize MRI-guidance in ultrasound-stimulated microbubble-enhanced radiation treatment in large animal models.

Method

PC-3 human prostate cancer cells were implanted on the hind legs of New Zealand White rabbits. Ultrasound-stimulated microbubble treatment (USMB) consisted of a 3 mL bolus injection of microbubbles (Definity), followed by seven minutes of sonication using an MRI-integrated FUS system (Sonalleve, Profound Medical). Sonication was delivered to a circular PTV, 10 – 20 mm in diameter, depending on the size of the tumours. This consisted of a modified hyperthermia protocol using 16-cycle pulses (7.5 W, 800 kHz). Tumour localization consisted of T1 and T2-weighed MRI on a 3T system (Achieva, Philips Healthcare). 8 Gy radiation (XRT) was delivered to the whole tumour either as a single treatment or immediately after USMB treatment.

Results

Tumours were extracted for immunohistochemistry analysis 24h post therapy. The mean and standard error of positive TUNEL staining relative to the total tumour area were: 2.94% +/- 1.26% for the control group, 5.72% +/- 2.53% for USMB-only treatment, 7.59% +/- 3.81% for the XRT-only treatment, and 17.90% +/- 5.67% for combined USMB+XRT treatments. Positive TUNEL staining was corroborated with blanched areas on respective H&E stains. In particular, combined treatments displayed larger and more diffuse areas of cell death in comparison to XRT- or USMB-only treatments.

Conclusion

Results indicate there is a radiation enhancement effect using ultrasound-stimulated microbubbles therapy in large tumour models. The percentage and range of cell kill increases with addition of USMB therapy prior to radiation in large PC3 tumour models.

A30

Quality Control of Automated CBCT Dose Reconstruction using Statistical Process Control

Kelly McPhee, Tirth Patel, Zhihui Liu, Beibei Zhang, Andrea McNiven, Tony Tadic

Purpose

Large-scale implementation of adaptive radiotherapy requires automated methods for reconstructing dose, including efficient quality control (QC) of dose calculation accuracy (DCA). The purpose of this work is to benchmark DCA on CBCT images and develop a QC framework using statistical process control (SPC) to monitor automated CBCT density assignments and daily reconstructions.

Method

Daily dose reconstructions were performed in RayStation (v6.1) for 30 oropharyngeal cancer (OPC) patients treated with daily CBCT using histogram-based intensity thresholding for bulk density assignment. All dose comparisons used planning CTs deformably registered to each fraction CBCT as the gold standard, and DCA was quantified as mean absolute dose difference in the high dose region, and near-max (99th percentile) absolute voxel-wise dose difference. Histogram thresholds for first-fraction CBCTs were defined manually (n=10, manual cohort) or using an automated RayStation algorithm (n=20, automated cohort). First-fraction thresholds were copied to subsequent CBCTs for each patient. Inter-patient control limits derived from the manual cohort were applied to monitor first-fraction errors in the automated cohort. Intra-patient control charts were generated for 10 patients with acceptable first-fraction DCA to detect errors on subsequent fractions (i.e. fractions 1-5, 10, 15, 20, 25, 30, 35).

Results

Manual and automated cohort averages for the first-fraction DCA were 0.4% and 1.1% mean voxel differences, and 2.4% and 3.7% near-max differences. That is, density thresholds computed automatically by RayStation result in greater errors for some patients, such as those with dental implants and CBCT artifacts that cause histogram aberrations. A method for automatically detecting which patients suffer from poorly-defined thresholds is required for complete automation of the dose reconstruction workflow. Applying the inter-patient control chart to the automated cohort detected first-fraction out-of-control signals in 16/20 patients. Manual intervention to redefine thresholds in the failing cases yielded acceptable DCA values, matching the manual cohort. Intra-patient control charts applied to serial CBCTs detected out-of-control signals in 2 out of 100 examined fractions, indicating excellent CBCT histogram stability.

Conclusion

We developed a framework for automated QC of CBCT dose reconstruction based on inter- and intra-patient SPC. Manually-defined thresholds for bulk density assignment are typically required for first-fraction CBCTs in our OPC cohort. However, DCA of subsequent fractions can be maintained and monitored effectively using SPC. We have therefore established a method to ensure accurate and automated CBCT dose reconstruction, which will help power large retrospective research studies and offline/online clinical adaptive radiotherapy workflows.

A31

A Machine Learning Based Priori Chemotherapy Response Prediction in Breast Cancer Patients Using Textural and Second Derivative of Textural CT Biomarkers

Hadi Moghadas-Dastjerdi, Hira. R. Shan-E-Tallat, Lakshmanan Sannachi, Ali Sadeghi-Naini, Gregory J. Czarnota

Purpose

To develop a data-driven machine learning method to differentiate benign nonresponders from responders to neoadjuvant chemotherapy in locally advanced breast cancer (LABC) patients using quantitative feature classification on texture patterns from pre-treatment contrast-enhanced computer tomography images.

Method

Textural and second derivative of textural (SDT) features were extracted from pre-treatment CT images acquired from 39 LABC patients using a grey-level co-occurrence matrix (GLCM) method. For each patient, eight textural features (and eight corresponding parametric maps) were derived from a CT image and eight textural (SDT) features were extracted from each textural parametric map. Consequently, 8 textural and 64 SDT features were extracted for each CT image. The best feature subsets were selected through a multi-step feature ranking and selection process and then used to train an ensemble machine learning algorithm using a decision tree (DT) as the weak learner classifier (AdaBoost-DT). The response prediction framework was evaluated using a leave-one-patient-out (LOPO) cross-validation scheme.

Results

It has been indicated that SDT features in conjunction with an adaptive-boosting decision tree classifier can be used to predict pathological response of LABC tumours to NAC before the start of the treatment with a sensitivity and specificity of 76% and 81%, respectively.

Conclusion

This study investigated the capability of qCT biomarkers to predict response to NAC in LABC patients prior to start of treatment. Patients were assessed prior to the initiation of treatment and were subsequently followed up during and after the course of chemotherapy. Results indicated that SDT features provided better performance with an accuracy, F1-score and AUC0.632+ of 81.25%, 80.85% and 86.45%, respectively. The higher discriminatory power of SDT features might be due to the fact that they could capture more local distribution variation of tumour texture characteristics. Although a large-cohort study is required to further investigate the efficiency of the proposed biomarkers, results obtained in this study are promising and motivate future studies towards adapting quantitative CT imaging in conjunction with machine learning techniques for chemotherapy response prediction in cancer patients.

A32

Incidence, Severity and Management of Pneumonitis in Stage III Lung Cancer Patients on Adjuvant Durvalumab

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Purpose

Adjuvant durvalumab is the standard of care after concurrent chemo-radiation (CRT) for stage III non-small cell lung cancer (NSCLC). Clinical trials data suggest that durvalumab does not significantly increase rates of grade (G) ≥3 pneumonitis. The purpose of this study was to describe the incidence, severity and management of pneumonitis and determine its impact on durvalumab delivery.

Method

Stage III NSCLC patients (pts) at a single cancer center were prospectively accrued onto a biomarker study (LIBERATE) and treated with CRT. Those treated with adjuvant durvalumab and at least 4 months (mo) follow up, underwent chart review, including radiation fields, radiology report and image review by two study investigators. Pneumonitis graded using CTCAE v5.0 was the primary endpoint. RT pneumonitis was defined as changes within RT field, within 6 mo of RT completion; radiological changes outside RT field were judged as infection or durvalumab pneumonitis through chart and radiology review by two co-authors. Timing of pneumonitis, and its impact on subsequent durvalumab were recorded along with demographic and treatment factors. The Kaplan-Meier method was used to estimate the median time to pneumonitis.

Results

From August 2018 to August 2019, 53 pts completed CRT. 39/53 pts proceeded with adjuvant durvalumab at a median of 1.3 mo from end of CRT (range 0.6-5.1). Median age was 69, treated with median RT dose 60Gy (58 - 85Gy), mean lung dose 14Gy (standard deviation SD 3.17Gy), average V20 25.7% (SD 5.9), all had concurrent CRT (36% platinum-etoposide, 33% platinum pemetrexed, 31% platinum-taxol). 33/39 (85%) developed evidence of pneumonitis on follow up, 11/39 pts (28%) had G1 as worst grade, 21/39 pts (54%) G2, and 1/39 (3%) had G3. All pneumonitis changes occurred in the RT field, and within a median of 3.1 mo from end of CRT (95%CI 2.6-5.0). 10/22 G≥2 pts had durvalumab interrupted and treated with steroids (durvalumab held in 9/10: median gap 2.1 mo, range: 0.9 – 4.5, and 1/10 had 5 mo delay to durvalumab start). Durvalumab was restarted in 6/10 pts, discontinued 2, and a decision pending at time of analysis in 2 pts. Durvalumab was held in 1/22 pts with G≥2 RT pneumonitis who did not require steroids.

Conclusion

G ≥2 pneumonitis after definitive CRT and adjuvant immunotherapy in our cohort was 56%, which is higher than clinical trials have previously suggested. Although CRT and durvalumab both can cause pneumonitis, our review suggests that all changes were in RT field. Whether steroids were used impacted on administration of durvalumab.

A33

Designing Tools to Identify Causality of Treatment Failure in Glioblastoma

Marina Nikolopoulos, Sunit Das, Arjun Sahgal

Purpose

Glioblastoma (GBM) is the most common and malignant form of brain tumour in adults. Despite aggressive therapy, prognosis for GBM patients remains poor, with an average life expectancy of 15 months following diagnosis. Unfortunately, standard of care has remained unchanged for GBM patients since 2005, with the implementation of the Stupp protocol: maximal safe surgical resection followed by radiation therapy (RT) and concomitant temozolomide (TMZ). Patients continue to experience high rates of recurrence, with approximately 30% experiencing tumour progression during RT. GBM remains difficult to treat due to a poor understanding of the biological mechanisms of treatment resistance, as well as a highly heterogeneous cell population within and between tumours. We have studied 104 newly diagnosed GBM patients at Sunnybrook Hospital using Chemical Exchange Saturation Transfer (CEST) MRI. Patients who experienced early tumour progression showed divergent radiographic signatures prior to RT initiation, which strongly predicted treatment resistance and early disease progression. We have archived tumour tissue and whole blood from this cohort of 104 patients in the St- Michael's Brain Tumour Biobank.

Method

Whole genome sequencing will be performed on the full cohort of patients (n = 104) to identify the genetic variants that contribute to treatment resistance. Bulk and single cell RNA-seq will be performed in a subset of both treatment resistant (n =12 bulk, n = 3 single cell) and treatment responsive patients (n =12 bulk, n = 3 single cell). CRISPR/Cas9 dropout screens will be performed to identify genes that confer TMZ/RT resistance in n = 3 glioma stem cells (GSC) generated from the tumour tissue harvested from treatment resistant patients.

Results

Data collection and analysis are on-going.

Conclusion

N/A

A34

Clinical Optimization of Diffusion Weighted Imaging on an MR-Linac

Humza Nusrat, Rachel W. Chan, Alyaa Elzibak, Brige Chugh, Angus Z. Lau, Arjun Sahgal, Brian Keller

Purpose

With the advent MR-linac technology, diffusion weighted imaging (DWI) during radiotherapy (RT) can be used to monitor treatment via functional changes in the tumor. Despite DWI being common in diagnostic imaging, the optimal scan parameters for DWI in an MR-linac are unknown and will be different due to its specialized hardware constraints. Several scan parameters require optimization along with validation and testing. In this work, DWI was examined in an MR-linac using a standardized phantom in order to examine and optimize DWI.

Method

Using the NIST-QIBA Phantom (High Precision Devices, Boulder, USA), DWI scans were run on a 1.5T Elekta Unity MR-linac (Elekta AB, Stockholm, Sweden) as well as a Philips Ingenia 1.5T MR system (Philips, Amsterdam, Netherlands) and scanner-reconstructed ADC maps were used for analysis. Twenty-four hours prior to measurement, the phantom was prepared with ice and water, ensuring a homogeneous temperature of 0°C(+/-0.3°). Both MR-linac and MR-simulator scans were validated by comparing the measured ADC values from the manufacturer recommended scan to their standard data. Four sequences were used on each machine: phantom (b-values: 4; range: 0-2000), brain (6; 0-1000), prostate (12; 0-1000), and head and neck (12; 0-800). Scans were conducted monthly; during each measurement, scans were repeated (n=3) to account for scanner and set-up variation.

Results

For the brain, head and neck, and phantom sequences, ADC values agreed within 72×10-6 mm2/s. For the prostate sequence, MR-linac consistently measured lower values ((933+/-5)×10-6 mm2/s vs. (1187+/-10)×10-6 mm2/s in MR-sim for the vials with highest ADC – 0%PVP).

Conclusion

DWI in the MR-linac was examined using several sequences. For certain sequences, ADC measurements were biased due to noise at high b-values. Results suggest that rigorous QA must be done when an MR-simulator image is used as a baseline for DWI-based plan adaptation on the MR-linac.

A35 Breast Lesion Characterization using Quantitative Ultrasound (QUS) and Derivative Texture Methods

Laurentius Osapoetra, Lakshamanan Sannachi, Daniel DiCenzo, Karina Quiaoit, Kashuf Fatima, Gregory Czarnota

Purpose

Accurate and timely diagnosis of breast cancer is extremely important because of its high incidence and high morbidity. Early detection of breast cancer results in an improved overall prognosis as better treatments can be provided to patients with disease detected at an earlier stage. Currently, biopsy remains as the gold standard for tumor pathological confirmation. Development of diagnostic imaging techniques for rapid and accurate characterization of breast lesions is required. Here, we demonstrate, for the first time, the clinical utility of texture-derivate features of QUS spectral parametric images in the non-invasive characterization of breast lesions.

Method

A total of 204 patients (99 benign and 105 malignant) with suspicious breast lesions was scanned with a 6.5MHz clinical ultrasound imaging system. QUS Spectroscopy was used to determine parametric images of mid-band-fit (MBF), spectral-slope (SS), spectral-intercept (SI), averaged scatterer diameter (ASD), and averaged acoustic concentration (AAC). Subsequently, texture analysis techniques were used to generate texture-encoded maps from parametric images to quantify heterogeneities of QUS parametric images. Further, a second-pass texture analysis was applied to obtain texture-derivate features. QUS parameters, texture-parameters and texture-derivate parameters were determined from both tumor core and a 5-mm tumor margin and were used in comparison to histopathological analysis in order to classify breast lesions as either benign or malignant. Three standard classification algorithms including a linear discriminant analysis (FLD), k-nearest neighbors (KNN), and support vector machines-radial basis function (SVM-RBF) were evaluated.

Results

Core and margin information using the SVM-RBF attained the best classification performance of 90% sensitivity, 92% specificity, 91% accuracy, and 0.93 AUC. The most relevant features that separate the two lesion groups were QUS parameters and their texture derivatives.

Conclusion

QUS-based framework and derivative texture methods enable accurate classification of breast lesions. Evaluation of the proposed technique on a large cohort demonstrates its robustness and its generalization. This work provides a foundation for the use of QUS in the characterization and differentiation of breast lesions.

A36

RNF168 confers synthetic lethality in BRCA-deficient tumors through impairment of R-loop resolution

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Purpose

Tumor suppressor BRCA1 and BRCA2 are involved in DNA double strand break (DSB) signaling and homologous recombination (HR) repair. As a result, women who inherit harmful BRCA mutations are at a higher risk of developing breast (≥60%) and ovarian (≥40%) cancers compared to those with wildtype BRCA (12%) genes. Similar to BRCA1, RNF168 is an E3 ubiquitin ligase, which orchestrates the recruitment of effector proteins to DSB sites, allowing their repair. While research has led to discovery of drugs like Olaparib to target BRCA- and HR-deficient tumors, optimal therapeutic targets have not been established for majority of patients carrying BRCA mutations.

Method

Using mouse models coupled with cell-based assays including proximity-dependent biotin identification (BioID), immunoprecipitation (IP), chromatin IP (ChIP), immunofluorescence, and western blotting, DNA-RNA IP (DRIP), we have examined the impact of RNF168 loss in a BRCA1-deficient setting. We have also utilized publicly available datasets on The Cancer Genome Atlas (TCGA) and collaborated with the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) to assess the essentiality of RNF168 in the absence of functional HR.

Results

Our data indicates that mice with mammary-specific deletion of Rnf168 and Brca1 are significantly protected from mammary tumors when compared to mice with mammary-specific deletion of Brca1. Depletion of RNF168 results in accumulation of triple-stranded nucleic acid structure or R-loops which leads to compromised genomic integrity, replication fork instability, and senescence in BRCA1-deficient cells and tumours; thus, resulting in synthetic lethality and protection from BRCA1-associated mammary tumorigenesis. Furthermore, our data indicates that depletion of RNF168 in deficient human tumors impairs their in vivo and in vitro growth and increases their sensitivity to radiation and Olaparib. Mechanistically, we have discovered a novel role of RNF168 in regulating RNA:DNA helicase DHX9 through K63-linked ubiquitination. In the absence of RNF168, DHX9 is not recruited to R-loop prone genomic loci, leading to R-loop accumulation, genome instability, and synthetic lethality. Furthermore, analysis of the TCGA breast cancer (provisional) dataset indicates that homologous-recombination (HR) -deficient tumors express higher levels of RNF168 compared to other tumor types. Patients with HR-deficient tumors that express low levels of RNF168 have improved survival outcome compared to patients that express high levels of RNF168.

Conclusion

Collectively, our data supports targeting RNF168 for treatment of BRCA1-deficient cancers and potentially for other HR-deficient tumors, including tumors with mutations in BRCA2, RAD51, and FANCD2.

A37 Impact of hypoxia-mediated regulation of DICER on treatment outcome in cervical cancer

Aesha Patel, Rob Cairns, Brad Wouters

Purpose

The adaptive response of tumor cells to microenvironmental conditions, including hypoxia, affects patient response to radiotherapy. Recent data suggests that tumor hypoxia alters microRNA (miRNA) expression. This regulation of miRNA by a diverse and changing environment may contribute to the heterogeneity observed within and between tumors. The DICER protein globally regulates miRNA expression by cleaving precursor RNA to mature, functional miRNA, and can be affected by hypoxia. We hypothesize that hypoxia driven changes in miRNA expression, via DICER suppression, alter cellular phenotypes that contribute to radiotherapy resistance and tumor progression.

Method

DICER expression was measured by RT-qPCR in HeLa, ME-180, and SiHa cells after exposure to 21%, 5%, 1%, 0.2%, and 0% oxygen for 8, 16, and 24 hours. Cell proliferation and clonogenic survival were measured in control and DICER knockdown (shDICER) cell lines in response to hypoxic exposure and radiation. Control and shDICER xenograft tumors were used to measure response to fractionated radiotherapy.

Results

DICER expression was reduced under hypoxic conditions in an oxygen dependent manner. DICER knockdown did not alter proliferation under hypoxia or intrinsic radiosensitivity, but it did shorten growth delay following fractionated radiotherapy. Intriguingly, DICER knockdown tumors were less hypoxic as measured by EF5 at the time of treatment initiation.

Conclusion

The increased radioresistance of DICER knockdown tumors suggests a mechanism by which tumor hypoxia may impact treatment outcome. Like many cellular responses to hypoxia, it appears that regulation of miRNA by DICER may participate in a feedback loop that improves oxygenation. The previously described increase in stemness upon hypoxic DICER repression, especially in the post irradiation microenvironment, may be responsible for increased cell survival and tumor regrowth. Identifying mechanisms of treatment resistance in the dynamic tumor microenvironment during and following radiation therapy could provide novel opportunities for therapeutic intervention.

A38

Validating and Refining the 8 th Edition TNM N-Classification for HPV Negative Oropharyngeal Cancer

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Purpose

The 8th edition TNM (TNM-8) re-introduced "overt clinical extranodal extension (cENE)" as an N-classification (cN) modifier for HPV-negative (HPV –) oropharyngeal cancer (OPC), although independent validation of outcome prediction over TNM-7 is not yet available. Emerging data shows that radiologic ENE (rENE) has a high specificity to predict pathological ENE (pENE) with similar prognostic importance. This study evaluates the performance of the TNM-8 vs TNM-7 N-classifications and explores the potential role of rENE in future cN classification.

Method

All HPV– OPC patients (n=361) treated with definitive IMRT between 2005-2016 were included. cENE was retrospectively ascertained based on unambiguous "fixation" of neck mass or "skin involvement" detected by clinical examination. Pre-treatment CT/MR of cN+ cases were reviewed by a head-neck radiologist (EY) to determine rENE, defined as unequivocal evidence of tumor invading beyond the nodal capsule. Disease-free survival (DFS) and overall survival (OS) were compared between cENE-positive (cENE+) vs cENE-negative (cENE–) and rENE-positive (rENE+) vs rENE-negative (rENE–) patients. The prognostic value of cENE and rENE was confirmed by multivariable analyses (MVA). A refined cN-classification incorporating both cENE and rENE parameters was developed and then included in a revised TNM proposal. The performance of the revision was next compared to TNM-8 and TNM-7 using established criteria examining hazard consistency within each stage, hazard distinctiveness across stages, prognostic importance of the stage schema and sample size balance.

Results

A total of 48 cENE+ and 72 rENE+ cases were identified. Of cENE+ cases, 42 were rENE+ and 6 were rENE– due to excessive time lapse between CT and clinical evaluation, or subjectivity including primary tumor misinterpretation as nodal disease. The cENE+ and rENE+ proportion increased with higher N-category (N1/N2/N3: 2%/14%/87% and 7%/23%/100%, respectively $p < 0.001$). Median follow-up was 5.4 years. Compared to cENE–, cENE+ patients had lower 5-year OS (25% vs 42%, p=0.006) and DFS (17% vs 37%, $p <0.001$). Compared to rENE–, rENE+ patients had lower 5-year OS (30% vs 42%, p=0.037) and DFS (24% vs 36%,p=0.015). MVA confirmed a prognostic impact of cENE for OS (HR = 2.3, p= 0.001) and DFS (HR = 2.8, $p <0.001$). We propose a refined N-categorization that reclassifies any cENE– case with rENE+ to one N stratum higher while any cENE+ still occupies the most adverse cN3b category. The revised stage schema with the refined N-categorization, that included both cENE and rENE elements, outperformed TNM-8 and both outperformed TNM-7 in OS prediction.

Conclusion

We confirm the prognostic value of cENE and rENE. TNM-8 N-classification with the inclusion of cENE has improved outcome prediction compared to TNM-7 in HPV-negative OPC. rENE incorporation into TNM-8 appears to additionally augment the existing N classification to facilitate clinical trial design and decision making.

A39

Stereotactic Ablative Radiotherapy in T1-2N0M0 Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

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Purpose

Stereotactic ablative radiotherapy (SABR) is a treatment option for inoperable early stage, node-negative small cell lung cancer (SCLC). Data supporting this practice is limited and outcomes have not been synthesized. The purpose of this study was to systemically review the literature on SABR for T1-2N0M0 SCLC and meta-analytically summarize local control (LC), overall survival (OS), progression-free survival (PFS), failure pattern, prophylactic cranial irradiation (PCI) use, and toxicity.

Method

A PRISMA/MOOSE-based protocol was prospectively submitted to PROSPERO. An information scientist-supervised search of PubMED and EMBASE from inception to November 2019 was conducted. Two investigators (AHS and DYPM) independently reviewed abstracts and full-texts for inclusion, with discrepancies settled by a third (AVL). Eligible studies evaluated SABR (8 or fewer fractions) for pathologically-confirmed SCLC. Amongst studies utilizing the same institutional or national dataset, the most relevant one was chosen for meta-analysis based on recency of publication, number of patients, and outcomes reported. The primary outcome was LC. Secondary outcomes were OS, PFS, failure pattern, PCI use, and treatment-related toxicity reported per Common Terminology Criteria for Adverse Events (CTCAE). Inverse variance-weighted random effects meta-analysis was carried out to generate pooled estimates for survival, LC, failure pattern and toxicity proportions.

Results

From 173 articles screened, 11 studies were identified (8 multi-institutional/database, 3 single-institutional). Seven retrospective studies were selected for meta-analysis (n=399 mutually-exclusive patients). Inoperability was the most commonly reported indication for SABR (87.6% [range: 75-100%, n=160 in 6 studies]). Follow-up duration was 20.7 months (range: 0.1-114.6, n=378 in 6 studies). Mean tumor size was 21 mm (range: 5-72, n=370 in 5 studies). Dose-fractionation was variable, with 50 Gy in 5 fractions as the most common regimen. Chemotherapy use rate was 38.7% (range: 19-75%), of which 67.6% (range: 33-100%) was adjuvant. LC was 96.9% (95% CI: 92.0-99.6%) at 1 year, 94.6% (73.4-100.0%) at 2 years, and 93.3% (77.6-99.9%) at 3 years. OS was 86.2% (74.5-94.7%) at 1 year, 63.7% (45.7-79.9%) at 2 years, and 55.2% (43.5-66.6%) at 3 years. PFS was 70.2% (48.5-87.9%) at 1 year, 52.0% (29.5-74.1%) at 2 years, and 46.0% (11.9-82.4%) at 3 years. Nodal and distant failure rates were 17.8% (7.5-31.2%) and 26.9% (7.4-53.0%), respectively. PCI use rate was 20.9% (range: 0-66.7%, n=139 in 5 studies). The rates of Grade 1, Grade 2, and Grade 3 toxicity were 12.6% (6.7-19.9%), 6.7% (3.3-11.2%), and 1.4% (0.0-5.3%), respectively. No Grade 4/5 events were observed across the studies.

Conclusion

SABR for inoperable T1-2N0M0 SCLC is locally effective with limited toxicity. Prospective studies are required to further evaluate the role of SABR for patients at high risk of toxicity with surgery or combined chemoradiation.

A40

Stereotactic Body Radiation Therapy for Mediastinal and Hilar Lymph Node Metastases: A Single-Institutional Review of Clinical Outcomes

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Purpose

Stereotactic body radiation therapy (SBRT) to metastatic mediastinal and hilar lymphadenopathy (mMHL) is challenging due to the proximity of centrally located, thoracic organs-at-risk. As limited data exist on the safety and efficacy of SBRT for mMHL, a retrospective review of clinical outcomes was conducted. We hypothesize that SBRT to mMHL is well tolerated with high rates of local control (LC).

Method

Patients were identified from a prospectively maintained SBRT database at a large tertiary cancer centre. At our institution, mMHL SBRT is a strategy to delay the need to start or change systemic therapy (ST), and/or to prevent airway/great vessel compression. Eligible patients received SBRT to mMHL between 2014-2019 for the following indications: oligometastases (OM), oligoprogression (OP), or LC of a dominant area of progression (DAP). The primary endpoint was grade 3 or greater (G3+) toxicity (CTCAEv5.0). All G3+ toxicities were reviewed independently by four radiation oncologists, with final scoring and attribution achieved by consensus. Secondary endpoints were cumulative incidence (CIN) of local failure (LF), progression-free survival (PFS), overall survival (OS), and CIN of starting or changing systemic therapy (SCST). Kaplan-Meier estimates of PFS and OS (from SBRT completion date) were conducted.

Results

Fifty-two patients (84 lesions treated) were included. Median follow-up was 19.9 months. Common primary cancer sites were kidney (54%), lung (13%), and breast (8%). Indications for SBRT were OP (n=35; 67%), OM (n=10; 19%), or DAP (n=7; 14%). Thirty-two patients (62%) received ST prior to SBRT, and of these, most (n=29; 91%) temporarily stopped ST before and during SBRT. The majority (n=31; 60%) received SBRT to a single lymph node metastasis. Median maximum lesion size was 2.0 cm. Of the 84 metastatic lymph nodes, 53 (63%) were mediastinal and 31 (37%) were hilar. Median SBRT dose was 35 Gy (range: 30-50Gy) with a median BED10 of 59.5 Gy (range: 48-100 Gy). All treatments were delivered in 5 fractions, every other day. Seven G3+ toxicities were experienced by six patients (11.5%) and were mostly transient (5/7; 71%). One (1.9%) probable G5 event was found (radiation pneumonitis) in a patient who underwent synchronous SBRT to a parenchymal lung metastasis. The CIN of LF was 9.0% at 2 years. Median PFS was 4.0 months (95% CI: 2.8-7.3) and median OS was 31.7 months (95% CI: 23.8-87.5). The CIN of SCST was 33.2% and 57.1% at 1- and 2-years, respectively.

Conclusion

In one of the largest series of patients undergoing SBRT for mMHL, we found that treatment was generally well tolerated and provided excellent LC. A significant proportion of patients did not require a change in ST strategy following SBRT. Most G3+ toxicities were transient; however, given the potential risk for serious toxicity, prospective evaluation of SBRT for mMHL is warranted.

A41

Alignment of Regulatory Examinations and Public Health Priorities: Exploring the representation of Cancer in the MCCQE-1

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Purpose

Cancer is the leading cause of death in Canada - yet research has demonstrated that medical education in oncology is perceived as inadequate by learners, educators and generalist physicians. The Medical Council of Canada (MCC) conducts two examinations as Canada's national standard of assessment of medical graduates. Our study aimed to determine the representation of topics in the MCCQE-1 objectives with respect to leading public health priorities, including cancer.

Method

The Medical Council of Canada Qualifying Examination – Part 1 (MCCQE-1) lists roles in which medical graduates should be competent – the focus of this study was the "Medical Expert" role and its associated testable objectives. A deductive coding method, using NVivo 11 software, was used to map these objectives for the representation of leading Canadian health priorities – specifically oncology, cardiology, cerebrovascular disease and chronic lower respiratory disease. Two coders analyzed the data to increase objectivity and reduce bias.

Results

Mapping of the MCCQE-1 objectives found 190 discreet topics listed under the Medical Expert objectives section. Of those 190, oncology content was found in 57 (30%), cardiovascular diseases in 56 (29.5%), cerebrovascular diseases in 21 (11%) and chronic lower respiratory diseases in 7 (3.7%) respectively. Within the 57 objectives containing oncology content, the three most frequently mentioned cancer sites were gastrointestinal (16/57, 23%), followed by generalized/nonspecific indicators of cancer (7/57, 12%) and genitourinary/musculoskeletal cancers (6/57 each, or 10.5%). The mapping of each disease content by two coders had inter rater agreement greater than 99%, with Kappa values ranging from 0.73 – 1.00, indicating substantial agreement.

Conclusion

Our data suggests top public health concerns in Canada are highly represented in the MCCQE-1 examination. Further work is needed to understand the mismatch between content representation on the MCCQE-1 and perceptions of learners, educators and generalist physicians regarding inadequate education in cancer.

A42

Estimation of transport parameters employing Tofts Model and a novel advanced Cross-Voxel Exchange Model

Noha Sinno, Edward Taylor, Mike Milosevic, David Jaffray

Purpose

The quantification of tumor perfusion parameters is closely connected to tumor aggressiveness and treatment outcome. Tofts Model (TM) is the most widely used pharmacokinetic model allowing the estimation of perfusion properties of tumor tissues. It assumes that the perfusion of tumor tissue is achieved solely through the exchange of tracer between the capillaries and the tissue, ignoring the effects of extravascular diffusion and convection and through the tissue. This is often violated leading to the misinterpretation of derived perfusion parameters. An advanced Cross-Voxel Exchange Model (CVXM) is proposed for the quantification of cross-voxel tracer kinetics and the evaluation of Tofts' parameters.

Method

CVXM was proposed for the analysis of cross-voxel tracer kinetics. It includes the effects of extravascular diffusion and convection, in addition to the exchange of tracer between the capillary bed and tumor tissue. In silico datasets were generated to investigate the validity of Tofts' perfusion parameters. Transport parameters were derived from Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) of a TS-415 human cervical carcinoma xenograft by using TM and CVXM.

Results

The contribution of cross-voxel exchange to tracer transport and its effects on the interpretation of standard perfusion parameters are controlled by the diffusivity of tracer, the velocity of the fluid flow, the spatial distribution of blood vessels and the voxel dimensions. TM mostly results in high quality fits to concentration-time curves derived from a model that includes inter-voxel exchange, even though TM does not include these effects. The physiological interpretation of the parameters must be changed, however. An equation developed gives the correct physiological interpretation of Tofts' fitted parameters and predicts the deviations from the correct values. Preliminary fittings prove the effectiveness of the CVXM model in deriving more accurate perfusion parameters including measurements of diffusion, convection and extravasation compared to TM.

Conclusion

For treatment decisions, caution must be exerted when interpreting Tofts' perfusion parameters. The results support the need for utilizing CVXM to DCE-MRI in order to accurately determine metrics of tissue permeability and diffusivity of the tracer. This model promises a clearer understanding of the tumor microenvironment that can lead to enhanced personalized treatment planning.

A43

Outcomes of Spinal Metastases Treated with Stereotactic Ablative Radiotherapy of 24 Gy in 2 Fractions

Michael C. Tjong, Fabio Y Moraes, Jonathan So, and David. B. Shultz

Purpose

Stereotactic ablative radiotherapy (SAbR) is increasingly utilized for spinal metastases (SM), with reported 1-year local control (LC) and pain relief of >80% for de novo metastases. However, spine SAbR is associated with vertebral compression fracture (VCF), with reported rates as high as 42%. Previous reports have found that >20Gy per fraction is a predictor of VCF. Our institution uses a schedule of 24 Gy in 2 fractions for spine SAbR. We aimed to identify whether spine SAbR with a 24Gy/2 fraction schedule is associated with low VCF rates and high local control and pain relief. We also sought to explore predictors of LC and VCF.

Method

We retrospectively analyzed clinical outcomes of 123 de novo spine metastatic lesions from 113 patients treated with SAbR with 24 Gy in 2 fractions from January 2009 to October 2017 at a single institution. Baseline patient and disease characteristics were collected. Local failures (LF) and VCF were defined using follow-up MRI or CT scans. Outcomes were analyzed using the Kaplan-Meier method. Cox-Proportional Hazard multivariable analyses (MVA) were performed to identify independent predictors of LC and VCF.

Results

Median age was 61.0 years. Median follow-up and OS were 16.3 and 45.6 months, respectively. Non-small cell lung cancer was the most common histology (n=27, 22.0%). LC rates at 1 and 2 years were 88.9% and 87.3%, respectively, while VCF rates were 21.8% and 28.0%, respectively. Complete (CR) and partial (PR) pain responses were achieved in 52.6% and 35.1% of patients at 3 months, respectively, and in 57.3% and 32.0% of patients at 6 months, respectively. Gastrointestinal (GI) histology (Hazard Ratio [HR]: 7.3, 95% Confidence Interval [CI]: 1.6-33.4; p=0.011) was associated with LF, after adjustment for age, sex, ECOG performance score, and Spinal Instability Neoplastic Score (SINS). Median SINS was 6; after adjustment for age, sex, and ECOG performance score, SINS ≥ 7 (HR: 2.6, 95% CI: 1.2-5.7; p=0.015) predicted for VCF.

Conclusion

SAbR delivering 24 Gy in 2 fractions for metastatic spine lesions yielded excellent LC but was still associated with significant VCF risk of 21.8% at 1 year in our cohort. Despite ablative dose, GI primaries were still associated with poor LC.

A44 Deformable Registration for Accurate Re-Contouring and Total Planned Dose Records for Patients Undergoing Adaptive Re-Planning

Joshua Torchia

Purpose

Some patients have significant anatomic changes during radiotherapy necessitating an adaptive repeat CT-simulation and re-planning intervention. This yields two unique planning datasets that introduces uncertainty into total dose records. This study quantified the impact of using deformable image registration (DIR) to spatially align repeat CT-simulation images and calculate total planned dose distributions.

Method

Data from 5 head-and-neck and 5 lung patients who had unanticipated re-planning during radiotherapy were analyzed in a treatment planning system (RayStation v6.1 RaySearch Laboratories). Total planned doses were calculated using two methods and the previously generated manual contours defined on each CT. The first method termed 'parameter addition' simply sums the relevant DVH metrics from the initial and re-planned distributions without registering the CTs. The second termed 'dose accumulation', uses a validated hybrid contour/intensity-based DIR to deform and sum the initial distribution and CT onto the re-planned distribution and repeat CT. DVH metrics from the summed distribution on the repeat CT are then calculated. Dose differences for organs-at-risk between parameter addition and dose accumulation >100 cGy were assumed to be clinically relevant. To elucidate whether relevant differences were due to registration accuracy or contouring variability between CTs, the analysis was repeated using contours on the first CT and the same contours deformed to the repeat CT with DIR.

Results

For all patients, high overall DIR accuracy was verified visually and quantitatively using image similarity and contour-based metrics. All 10 patients had dose differences between parameter addition and dose accumulation >100 cGy, with absolute mean differences of 175 cGy (range 101-409 cGy) seen in 40 of 184 total DVH criteria. In 21 of these 40 criteria, these differences were attributed to contouring variability between CTs. After correcting the contouring variations using DIR the mean absolute differences in 17 of the 21 DVH criteria was 78 cGy (range 2-502cGy). In only 4 DVH criteria (3 patients) the DIR mapped contours had higher variations than the original contours. One head-and-neck patient had a DVH criteria exceeding the acceptance constraint by 125 cGy with parameter addition, and with accurate DIR and dose accumulation the criteria was actually 97 cGy lower than the constraint.

Conclusion

The use of DIR to generate total planned dose records revealed substantial dose differences in most cases compared to commonly used clinical methods (i.e. parameter addition), and altered the planned acceptance criteria in a minority. DIR is recommended to be used for future adaptive re-plans to generate total dose records and facilitate accurate re-contouring. More accurate dose records may also improve our understanding of clinical outcomes.

A45

Developing Epigenetic Biomarkers in Small Cell Lung Cancer using the Methylome

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Purpose

Small cell lung cancer (SCLC) is one of the most aggressive types of cancer. Although patients are initially responsive to therapy, the vast majority of them develop recurrent disease and relapse. Currently, it is unclear how these mechanisms of resistance develop. Emerging evidence suggests epigenetic mechanisms might modulate such pathways. This project examines the role of DNA methylation, a type of epigenetic change, in mediating SCLC resistance mechanisms. We hypothesize that the SCLC methylome can 1) predict treatment response, and 2) identify molecular changes associated with relapse.

Method

Due to the aggressive nature of SCLC, tumor tissue is scarcely available. So, to examine DNA methylation, a novel technique called cell-free methylated DNA immunoprecipitation (cfMeDIP-seq) will be utilized to examine circulating-tumour DNA (ctDNA) in SCLC patients. cfMeDIP-seq will be done on peripheral blood samples collected from SCLC patients receiving chemoradiotherapy prior to receiving treatment (baseline). The blood samples were collected from patients undergoing treatment for SCLC at Princess Margaret Cancer Hospital, Toronto, Canada. Additionally, cfMeDIP-seq will be done on SCLC patient-derived xenograft (PDX) models before and after receiving fractionated radiotherapy. Subsequently, next-generation sequencing analysis will be used characterize and bioinformatics analyses will be done to examine changes in methylation patterns.

Results

Thus far, cfMeDIP-seq has been optimized for usage in SCLC cell lines NCI-H69, NCI-H82, and SBC-5 and on 2 different patient-derived xenografts. Based on the optimization for SCLC, the assay recovers >40% methylated DNA and <0.01% non-specific unmethylated DNA from peripheral blood samples. cfMeDIP libraries were subsequently sent for next-generation sequencing on the NovaSeq 6000 for shallow paired-end sequencing (2-3 million reads). Bioinformatic analysis on the sequenced libraries shows that the assay enriches for CpG sites (regions with high DNA methylation) at rates of greater than 3-fold compared to input control.

Conclusion

The results show that the cfMeDIP-seq assay has been adequately optimized for SCLC peripheral blood samples. In short, this project may change the SCLC treatment paradigm by laying the groundwork for development of a molecular predictor of patient treatment response and advance biomarker-informed clinical trials. This work may also identify biologic mechanisms of therapeutic resistance that will improve management of this aggressive and deadly disease.

A46

Neutron dose for 10 MV flattening filter free and its clinical context

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Purpose

Neutron generation in the treatment head of a linear accelerators starts to occur with 10 MV photon beams. Neutron dose is important because it can be deposited outside of the treatment field, and up to 20 times more damaging to healthy tissue than MV photons. With flattening filter free 10 MV (10FFF) being commissioned for highly modulated SBRT treatment, we measured the neutron dose per MU of 10FFF compared to 15MV to justify the clinical application.

Method

Neutron measurements were performed using a Ludlum Neutron meter (model 12-4) and two BD-PND bubble detectors from Bubble Technology Industries. All measurements were performed on a Varian TrueBeam. The jaws were set to 0.5cm x 0.5cm, dose rate 400 MU/min and gantry at 0 degrees. To test the neutron dose within the maze the neutron meter was placed at the inner entrance of the maze and measured the neutron dose per MU. Within the bunker the neutron dose was measured using bubble detectors at 2, 20 and 100 cm from iso along the treatment couch at 0 degrees.

Results

The neutron dose per MU from the inner entrance of the treatment maze was 0.019 uSv/MU for 10 MV FFF vs. 0.33 uSv/MU for 15X. The results within the treatment room were 0.63, 0.48, 0.4 uSv/MU for 10 MV FFF at 2, 20, 100 cm from iso respectively vs. 10.96, 7.3, 6.87 uSv/MU for 15X.

Conclusion

We have shown 10 MV FFF produces 17 times fewer neutrons per MU than 15 X. In clinical application, since 10FFF is widely used in SBRT treatment, one can infer that the neutron dose in one fraction SBRT treatment with 4000MU of 10MV FFF is about the same as that of conventional treatment with 250MU of 15MV.

A47

Role and Outcome of Repeat Whole Brain Radiation (WBRT) for Leukemia and Lymphoma after Prior WBRT

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Purpose

There is scarce literature on the feasibility of retreatment with whole brain radiation therapy (WBRT) for leukemia and lymphoma patients who have received prior WBRT. We reviewed the retreatment practice at Princess Margaret Cancer Centre to examine the efficacy and safety of a second course of WBRT. We aim to identify a subset of patients who may benefit from this treatment modality.

Method

Through a computerized database, a search was done to identify leukemia and lymphoma patients who underwent two courses of WBRT from January 1, 1997 to October 31, 2018. Twenty-one patients were found to have leukemia and lymphoma out of 462 cancer patients who received at least two WBRT courses and their records were reviewed and analyzed.

Results

Of the 21 patients, 7 had leukemia (ALL: 5; AML: 2) and 14 had lymphoma. For the lymphoma patients, 13 were diffuse large B-cell and 1 Burkitt. Lymphoma primary sites were: primary CNS lymphoma in 9, and systemic presentations in 5. The median age for all patients was 58 years. The most frequent dose used for the initial radiotherapy for leukemia was 12Gy in 8 fractions (4 cases with prophylactic intent), while it was 20Gy in 5 fractions for lymphoma. The most frequently used 2nd WBRT dose was 24Gy in 12 fractions for leukemia and 25Gy in 10 fractions for lymphoma. After re-irradiation, 38.1% of patients experienced a partial clinical response; 9.5% had stable disease; 23.8% had progressive disease and the remainder (28.6%) were non-evaluable. The median overall survival (OS) for all patients was 3.6 months. Lymphoma and leukemia patients have a median OS of 5.3 and 1.9 months, respectively. Patients with a lymphoma diagnosis were found to have better survival than leukemia patients on univariate analysis. None of the patients were found to develop any significant (grade 4/5) toxicity. However, one patient was reported to have dementia (grade 3) after the first WBRT course (50Gy in 25 fractions for primary CNS lymphoma).

Conclusion

In patients with hematologic malignancies developing a recurrence in the CNS, repeat WBRT may be a useful treatment modality in providing a transient clinical response. Our findings showed a longer median survival for those with lymphoma than with acute leukemia, however, the prognosis remains poor. Further investigations with a larger sample size and prospective research are required to identify patients who are more likely to benefit from a repeat WBRT approach.

A48

SBRT For Head and Neck Skin Cancer: An Initial Experience in 106 Medically Unfit Patients

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Purpose

To report outcomes of patients with head and neck skin cancer (HNSC) treated with Stereotactic Body Radiation Therapy (SBRT) at a high-volume institution.

Method

A retrospective review of patients who received SBRT from 2012-2019 was conducted. Kaplan-Meier method was used to estimate the one-year local control (LC), locoregional control (LRC) outside of SBRT field, overall survival (OS), progression-free survival (PFS) and late toxicity (LT) rates from time of SBRT completion. Univariate and multivariate Cox proportional hazard models were performed. Grade 3 and 4 toxicity were reported using Common Terminology Criteria for Adverse Events v4.0.

Results

A total of 106 patients were identified with 112 lesions treated. The cohort consisted of patients treated for primary (n=51), nodal (n=47) and both primary and nodal disease (n=8). The T and N categories prior to SBRT were Tx-2: n=78, T3-4: n=28; N0-1: n=67, N2-3: n=39. Median age at diagnosis was 84 years with median ECOG performance status of 2. HNSC histologies included cutaneous squamous cell carcinoma (n = 77), basal cell carcinoma (n = 14), melanoma (n = 8), merkel cell carcinoma (n = 6), and 1 unconfirmed. Fractionation schemes ranged from 32-50 Gy in 4-6 fractions, with the most common regimens being 45 Gy in 5 fractions [52% (n = 55)] and 40 Gy in 5 fractions [32% (n = 34)]. Median gross tumor volume (GTV) was 31 cm3 (17-56) and mean planning tumor volume (PTV) dose was 44 Gy. Median follow-up was 8 months and actuarial median overall survival was 14 months. The one-year LC, LRC outside of SBRT field, OS, PFS and LT rates were 78% (69-88), 72% (62-84), 53% (43-65), 52% (40-62), and 25% (16-38), respectively. Larger GTVs were associated with reduced PFS [HR 1.58, p=0.004] and OS [HR 1.37, p=0.039], and LRC outside of SBRT field [HR 1.83, p=0.006] but not LC [HR 0.87, p=0.50]. Multivariable models revealed that larger GTVs [HR 1.47, p=0.046] and higher biologically effective dose (BED10) [HR 1.05, p=0.03] were associated with a higher rate of late toxicity. There was no statistical difference between proportions of grade ≥3 acute (p = 0.22) and late toxicities (p=0.37) in patients treated with doses ≤40 Gy vs. >40 Gy. For acute toxicity, 41 patients had grade 3, and 1 had grade 4. The most common acute toxicity was dermatitis (n=39). Twenty-eight patients (26%) experienced ≥ late grade 3 toxicity, with fibrosis (n=19) and soft tissue ulceration (n=6) being most common. No grade 5 toxicity was observed.

Conclusion

SBRT in HNSC provides durable disease control with acceptable toxicity in medically unfit patients unable to undergo extended treatment. Predictive factors of response and toxicity include GTV and BED10. Prospective studies including quality of life measures and dosimetric correlations with larger cohorts are needed.

A49 Investigating the immune response as an approach to improve treatment of radiorecurrent prostate cancer

Hanzhi Wang, Xiaoyong Huang, Stanley K. Liu

Purpose

High grade prostate cancer (PCa) patients are at considerable risk of experiencing recurrence following radiotherapy. Local recurrences are challenging to salvage, thus the development of novel therapeutic approaches is of great clinical importance. PD-1 is an immune checkpoint receptor expressed on the surface of activated T-cells. The interaction of PD-1 with its ligands PD-L1 and PD-L2, both expressed by tumor cells, sends a downstream signal to inhibit T-cell activation and allows tumor tolerance. Immune checkpoint therapy promotes T-cell activation by blocking the checkpoint protein and/or its ligands and has shown success in some cancer types. This generated incentive to explore the synergistic effects of combining checkpoint therapy with other treatment modalities such as radiotherapy. Locally recurrent PCa may accumulate radiation-induced neoantigens and is hypothesized to be responsive to immune checkpoint inhibitors.

Method

To test this hypothesis, a mouse PCa cell line (TRAMP-C2) was treated with conventional fractionation (2 Gy x 38) or hypofractionation (10 Gy x 5) to generate radiorecurrent TRAMP-C2 CF and HF cells respectively. To determine the therapeutic potential of immune checkpoint therapy in radiorecurrent PCa, syngeneic mice will be transplanted with parental, CF, or HF cells to generate tumors and subsequently treated with anti-PD-L1 or anti-PD-L2 checkpoint inhibitors. Tumor growth delay will be determined, and tumors will be excised for histological studies. Gene signatures of tumor infiltrating immune cells in radiorecurrent and parental tumors will be determined using the NanoString PanCancer IO 360 Gene Expression Panel.

Results

In vitro, TRAMP-C2 CF and HF demonstrated increased radiation resistance, migration, and anchorage-independent colony formation in soft agar compared to parental. Additionally, TRAMP-C2 CF was found to be more proliferative than parental both in the presence and absence of radiation treatment. In vivo, CF and HF tumors grew significantly larger and quicker relative to parental tumors.

Conclusion

Overall, the radiorecurrent TRAMP-C2 model exhibits an aggressive phenotype akin to recurrent disease observed in clinic. This research may support new avenues for clinical trials investigating the use of immune checkpoint therapy as a novel approach to salvage radiorecurrent tumours.

A50

Limited-Stage Small Cell Lung Cancer: Outcomes Associated with Prophylactic Cranial Irradiation Over a 20-year Period at a Single Institution

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Purpose

Prophylactic cranial irradiation (PCI) is recommended for limited-stage small cell lung cancer (LS-SCLC) patients with good response to concurrent chemoradiation. However, not all patients receive this life-extending intervention; possible reasons include concern of toxicity, poor performance status, and other factors. We report our institution's 20-year experience with this patient population.

Method

A retrospective cohort of LS-SCLC patients treated with curative intent chemoradiation at our institution (1997-2018) was reviewed. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method, and significant covariates determined by the Cox proportional hazards model. Covariates predictive of PCI utilization were determined using the Chi-square test and the Mann-Whitney test.

Results

A total of 374 consecutive patients with LS-SCLC were included in this review. The median patient age was 66 years (32-91), with 57% of patients being male. Most patients were ECOG 0-1 (83%) at the time of diagnosis, and AJCC stage III (79%), with the remainder stage I or II. Chemotherapy and radiation were given concurrently in 85% of patients, with a median of 6 chemotherapy cycles. PCI was given in 59% of patients. Median follow-up was 20 months (range 1-236). The median OS and DFS was 23 months (95% CI, 21.0-25.0) and 14 months (95% CI, 12.9-17.3) respectively. On univariate analysis, stage, younger age, chemotherapy cycles ≥ 4, and PCI utilization were significantly associated with improved OS and DFS. Significant associations with receipt of PCI included treatment in 2007 or later ($p = 0.003$), younger age ($p = 0.002$), and cycles of chemotherapy ≥ 4 ($p = 0.004$). On multivariate analysis (MVA), PCI utilization and younger age retained significance for improved OS ($p < 0.001$). In addition, on MVA, lower stage ($p = 0.03$), PCI utilization ($p < 0.001$), younger age ($p < 0.001$), and receipt of ≥ 4 cycles of chemotherapy ($p = 0.05$) were significantly associated with improved DFS. The adjusted hazard ratio (HR) for OS for patients receiving PCI versus no PCI was 0.53 (95%CI, 0.40-0.71) with a median OS of 30.3 (95% CI, 23.6-39.1) months versus 17.6 (95% CI, 15.2-19.9) months, respectively. The adjusted HR for DFS for patients receiving PCI versus no PCI was 0.61 (95%CI, 0.49-0.77) with a median DFS of 17.8 (95% CI, 15.4-23.9) versus 12 (95% CI, 10.0-13.9) months, respectively.

Conclusion

PCI and younger age are significantly associated with improved OS and DFS. At our institution, PCI is more frequently utilized in younger patients, those that received ≥ 4 cycles of chemotherapy, and patients treated in 2007 or later. We confirm the OS and DFS benefit of PCI through this 20-year study period.

A51

Customizable metallo-nanotexaphyrins for cancer imaging and therapy Title of Abstract: Computational Staining of Tumour Hypoxia from H&E Images using Convolutional Neural Networks

Mark Zaidi, Haotian Cui, Trevor Mckee, Bo Wang, Bradley Wouters

Purpose

Heterogeneity in the tumour environment can be driven by multiple biochemical processes, such as immune infiltration, cell-to-cell genetic variation, and oxygenation gradients. Low oxygen, termed hypoxia, has been strongly correlated with metastasis, radiation resistance, and poor prognosis in preclinical models. One ongoing challenge is determining the magnitude of how hypoxia influences treatment response relative to other features, such as proliferation and micro vessel density. While it is possible to stain banked tissue for these markers, it is challenging to stain for endogenous markers of hypoxia. Exogenous probes have been developed to overcome this barrier; however, most clinical samples lack such probes. Previously, we have shown that spatial distributions of hypoxia correlate with morphological features of the tumour, such as necrosis and vasculature. Some of these features can be identified in H&E-stained sections, present for nearly all tumour samples. We hypothesize that a trained machine learning algorithm can be used to accurately predict hypoxia distributions given an H&E-stained section.

Method

Colorectal, pancreatic, and ovarian cancer cell line xenografts were cut and stained for markers of hypoxia, proliferation, perfusion, vasculature, and H&E. Binary masks of necrosis were generated, and together with the H&E and hypoxia images, were used to train a convolutional neural network.

Results

Once the model had been trained, a fairly precise prediction (MSE <0.012) had been obtained relative to the ground-truth hypoxia stained images.

Conclusion

We believe a model trained on clinical H&E and hypoxia sections can be used to accurately predict hypoxia distributions from a H&E section. This can be used to evaluate the influence of hypoxia on treatment outcome, by retroactively comparing a patient's prognosis with levels of hypoxia. This can serve as an invaluable tool in closing the gap between preclinical and clinical implementations of hypoxia-targeted therapies.