IRRS 2024 Annual Meeting

School of Pharmacy

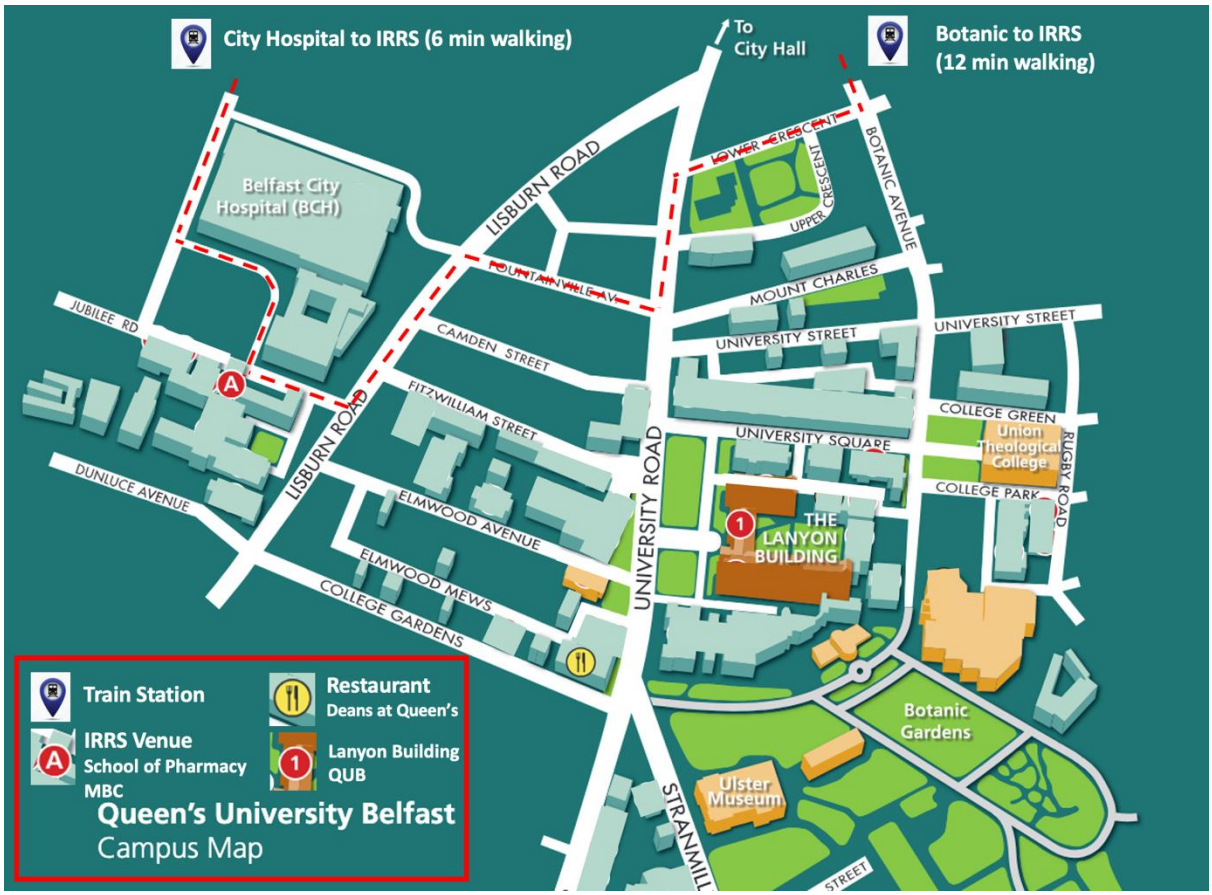
Queen's University Belfast

21st & 22nd March 2024

Programme & Abstract Book

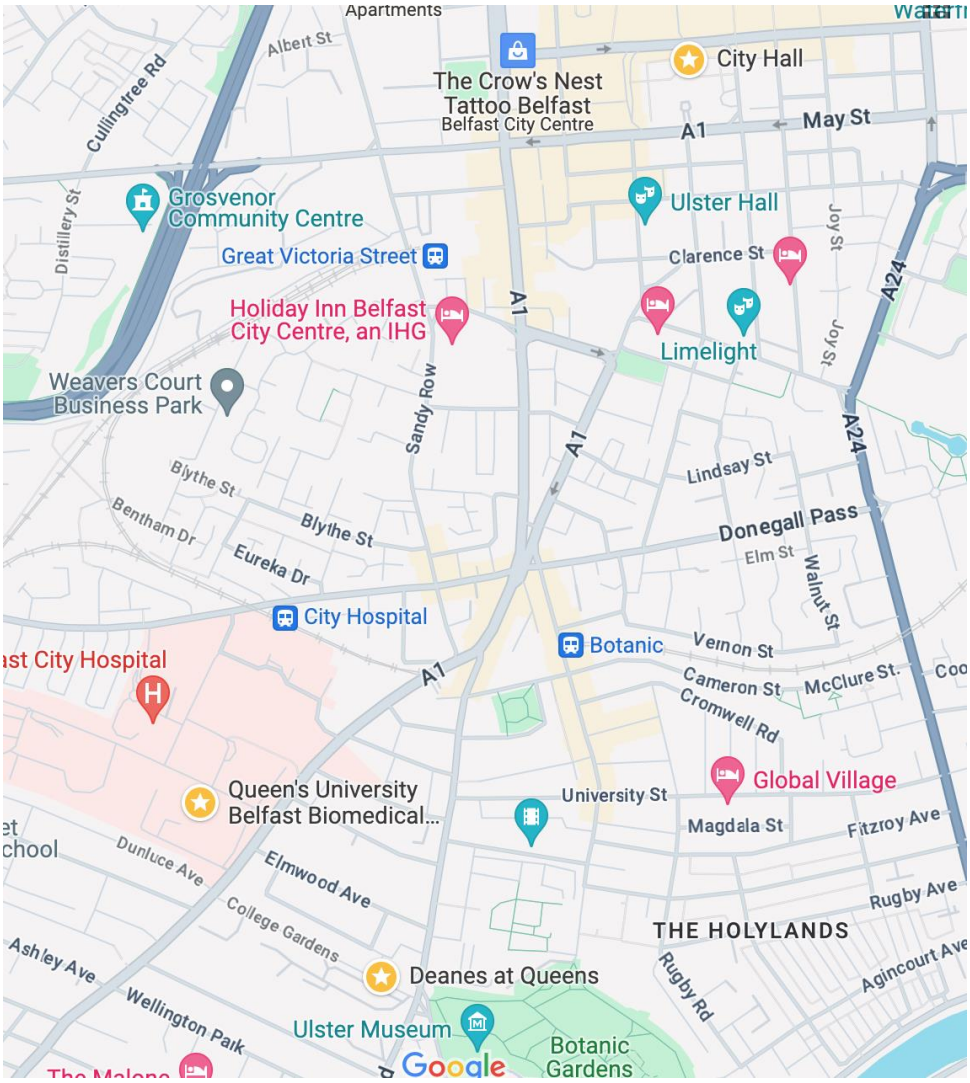
Travelling to School of Pharmacy – MBC

The School of Pharmacy at Queen's is acknowledged as a leading centre for Pharmacy teaching and research in the UK. The School of Pharmacy's strategic location on the Queen's University MBC (Medical Biology Centre) makes it an ideal location for the IRRS annual meeting. Situated at 71 Jubilee Road, Belfast at a short walking distance from two train stops, City Hospital (6 min) and Botanic (12 min).



Conference Dinner – Deanes At Queens

A stylish restaurant overlooking Methodist College. Deans at Queens brings a continental-style eating experience, serving local, seasonal, and simple food, prepared to perfection by Great British Menu Chef Chris Fearon. Its location, 1 College Gardens, Belfast, is less than a 10-minute walk from the IRRS Annual Meeting venue.



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Programme

Day 1 – Thursday 21st March 2024

1:00 PM	**Arrival & Lunch**	
2:00 PM	**Welcome**	Stephen McMahon
	Session 1 - Medical Physics & Modelling **Chair: Stephen McMahon**	
2:05 PM	Evaluation of an optical fibre sensor system for high dose rate brachytherapy using a 3D printed semi-anthropomorphic phantom	Owen McLaughlin
2:20 PM	Estimation of the Relative Biological Effectiveness of Clinical Kilovoltage Beams using TOPAS-nBio	Oran McElligott
2:35 PM	Performance Evaluation of An Inorganic Optical Fibre Dosimeter For Use In External Beam Radiotherapy	Carla McDonnell
2:50 PM	Clinical treatment planning for kilovoltage radiotherapy using EGSnrc and Python	Mihails Nikandrovs
3:00 PM	Modelling Intrinsic Radiosensitivity and Relative Biological Effectiveness in Clinical Radiotherapy Plans	Mohammed Dakheel
3:10 PM	Single-pulse Gy-scale irradiation of biological cells at average dose-rates above 10^{13} Gy/s from a laser-wakefield accelerator	Conor McAnespie
3:20 PM	Building predictive models to help further individualise radiation therapy	Shannon Thompson
3:30 PM	**Coffee Break**	
	Session 2 - Mechanisms of response in tumour and normal tissues **Chair: Kathryn Brown**	
4:00 PM	Preclinical development of physical and biological strategies to reduce radiation-induced cardiac toxicity	Karl Butterworth
4:15 PM	Dose-dependent changes in cardiac function, deformation and remodelling in a preclinical model of heart base irradiation	Mihaela Pettigrew
4:30 PM	The influence of hedgehog (Hh) signaling in modulating the radiosensitivity of Glioblastoma tumour models	Bayan Ahmed A Alkhaldi
4:45 PM	Increased FKBPL expression is associated with a radioresistant phenotype in oesophageal adenocarcinoma	Aisling Heeran
4:55 PM	Characterising the role of single strand break repair pathways in response to low and high LET radiation	Lydia Gardner
5:05 PM	Design and optimisation of an in vitro system to assess radiation responses at ultra-high dose rates using the FLASH small animal radiotherapy research platform (FLASH-SARRP)	Malachy McIvor
5:15 PM	Polonium-210 activity concentration in twelve seaweed species from the Irish coastline.	Angus Collison
5:30 PM	**Invited Speaker - Christophe Badie, UK Health Security Agency**	
7:30 PM	**Conference Dinner - Deane's at Queen's**	

Day 2 – Friday 22nd March 2024

9:00 AM	**Arrival & Coffee**	
9:30 AM	**Invited Speaker - Aidan McCormick, Chair of the NI Cancer Research Consumer Forum**	
	Session 3 - Enhancing Treatment Response **Chair: Niamh Lynam-Lennon**	
10:00 AM	Synergistic activity of DNA damage response inhibitors in combination with radium-223 in prostate cancer	Victoria Dunne
10:15 AM	Boosting Oxygen Diffusion in the Radioresistant Oesophageal Tumour Microenvironment to Improve Radiation Response.	Maitiú Ó Murchú
10:30 AM	Sensitising prostate tumour models to radiation using novel RALA/AuNPs nanocomplexes	Rayhanul Islam
10:40 AM	The Impact of CXCR2 Antagonism on the Radiation-Induced Bystander Effect	Lydia McQuoid
10:50 AM	Evaluation of the association between sex-linked genes and treatment response in lung cancer	Laure Marignol
11:00 AM	**Coffee Break**	
11:30 AM	**Inviter Speaker - Jonathan Coulter, School of Pharmacy, QUB**	
	Session 4 - Imaging & Spectral Biomarkers **Chair: Shannon Thompson**	
12:00 PM	Raman spectroscopy with machine-learning classification predicts stereotactic radiotherapy induced treatment toxicity in high-risk localised prostate cancer	Aidan Meade
12:15 PM	Characterisation of quantitative imaging biomarkers for inflammatory and fibrotic radiation-induced lung injuries using preclinical radiomics	Kathryn Brown
12:30 PM	Analysis of Computed Tomography (CT) Imaging Biomarkers using Radiomics to Assess Radiotherapy Response in a Colorectal Cancer Model.	Mark McDowell
12:40 PM	Spectral biomarkers of normal tissue toxicity in prostate cancer patients following radiotherapy	Fiona Lyng
12:50 PM	A comparative analysis of preclinical computed tomography radiomics using cone-beam and micro-CT scanners	Brianna Kerr
1:00 PM	**Lunch & IRRS AGM**	
2:00 PM	Close	

Abstracts

Session 1 - Medical Physics & Modelling

Evaluation of an optical fibre sensor system for high dose rate brachytherapy using a 3D printed semi-anthropomorphic phantom

Owen McLaughlin [1,*], Geraldine Workman [1,2], Monica Byrne[2], Sergio Esteve[2], Sinead O'Keeffe[3], Kevin M Prise[1], Conor K McGarry [1,2]

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Introduction
Brachytherapy is a radiotherapy treatment involving the positioning of radioactive sources inside or near the radiotherapy target. In-vivo dosimetry provides a means to verify the correctness of a delivered plan [1]. This work demonstrates an optical fibre dosimetry system for high dose rate brachytherapy (HDR) to measure dose and calculate source positions.

Methods
A male pelvic phantom was 3D printed to mimic a prostate patient. Bladder, rectum and prostate structures were printed with radiological properties to match patient tissue. The phantom included channels to insert HDR needles; thirteen source carrying needles and two sensors were used in the planning target volume (PTV) and nine sensors were placed in positions around the rectum.

A treatment plan was designed on Oncentra Prostate Treatment Planning System (TPS) based on computed tomography (CT) scans of the phantom. The treatment plan was delivered using an Iridium-192 HDR source to deliver 15 Gy to the PTV. Analysis involved the comparison of sensor doses to the TPS, and trilateration of source positions and comparison to planned dwell positions.

Results
Seven out of eleven sensors measured dose within 5% of the TPS dose, 5% being the dosimetric uncertainty for a HDR prostate treatment [2]. Errors up to 18% were measured with sensors positioned in regions of high dose in the PTV. When compared to the TPS dwell positions, the median error in source position was found to be 2.85 mm, with a maximum and minimum distance to agreement of 4.49 mm and 1.18 mm, respectively.

Discussion
Errors in dose measurement suggest the movement of optical fibre sensors between imaging and delivery of the treatment plan, this may be reduced with the inclusion of a live tracking system in clinic. The measurement of dose and use of sensor readings to localise HDR source locations in 3-dimensions is feasible with careful sensor management.

References
[1] Houlihan et al, Br J Radiol (2022) DOI: 10.1259/bjr.20220046.
[2] Kirisits et al, Radiother Oncol (2014) DOI: 10.1016/j.radonc.2013.11.002

Estimation of the Relative Biological Effectiveness of Clinical Kilovoltage Beams using TOPAS-nBio

Oran McElligott*[1,3], Mihails Nikandrovs[1,3], Patrick McCavana[2,3], Brendan McClean[2,3], Luis León Vintró[1,2,3]

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2 - Centre for Physics in Health and Medicine, University College Dublin, Belfield, Dublin 4, Ireland,
3 - St. Luke's Radiation Oncology Network, Dublin, Ireland

Introduction:
Modern advances in radiotherapy have led to improved survival rates for cancer patients and, therefore, an increase in the frequency of re-irradiations, which can involve the use of different modalities. When a recurring or a secondary cancer develops in the vicinity of a previously treated primary site, accurate dosimetric assessment is required to ensure normal tissue tolerances are not exceeded. Of particular concern is the variation in biological effectiveness with beam energy. The Relative Biological Effectiveness (RBE) of kV photon beams has been previously investigated in vitro and in silico, using analytical methods. The estimated values range from 1.03 to 1.82, depending on the methodology and beam energies examined. The focus of this work was to independently estimate RBE values for a range of clinical kV beams, while exploring the opportunities and limitations of the TOPAS-nBio program for the simulation of such radiobiological experiments.
Methods:
Previously validated clinical beam spectra were used to generate secondary electron spectra at several depths in a water tank phantom, via TOPAS Monte Carlo (MC) simulations. A cell geometry then was irradiated with the secondary electrons in TOPAS-nBio. An in-house Python algorithm was developed to estimate indirect DNA damage. The deposited dose and the calculated number of DNA double strand breaks were used to estimate RBE values of the kV photon beams relative to a 6MV photon beam.
Results and Conclusions:
Monoenergetic secondary electron simulations revealed the highest direct and indirect DSB yield at approximately 20 keV. The average RBE for 70-200 kVp photons was calculated to be 1.14 (1.10-1.19). TOPAS-nBio was successfully used to estimate the RBE values for a range of clinical radiotherapy beams. The calculated value was in agreement with previous estimates, providing confidence in its clinical use in the future.

Performance Evaluation Of An Inorganic Optical Fibre Dosimeter For Use In External Beam Radiotherapy

C. McDonnell[1,*], O. McLaughlin[1], C. K. McGarry[1,2], A. R. Hounsell[1,2], S. O'Keeffe[3], K. M Prise[1]

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Introduction

One of the main objectives to improve treatment delivery in radiotherapy is to have the ability to perform real-time dosimetry during treatments with adequate spatial resolution. This information would allow treatment plans to be monitored and, if needed, altered during delivery thus reducing the likelihood of over- or under-dosing. Optical fibre dosimeters (OFDs) are recognised as excellent candidates for meeting these requirements.

Materials and Methods

The OFD used in this work was primarily designed for dosimetry in high-dose-rate brachytherapy as part of the EU Origin project. However, it is evaluated here using a Varian Truebeam Linac. The optical fibre is equipped with an inorganic scintillating tip which scintillates upon radiation exposure. The light yield is detected by a silicone photomultiplier and readout via CITIROC-1A ASIC which is integrated into a CAEN FERS board.

Results

The response of the OFD showed excellent short-term dose repeatability represented by a very small coefficient of variation of 0.2 %. The response also demonstrated linearity with increasing dose in the explored interval of 1-10 Gy, producing an $R^2 > 0.9997$ for all Linac beam energies. By testing all available dose rates at each beam energy, a minor dose rate dependence was identified of 0.96 %, 2.44 %, 2.49 %, and 0.53 %, for 6, 6 (FFF), 10 (FFF) and 15 MV respectively. Due to some of the properties of the OFD, an undesirable dose-per-pulse dependence was identified which stemmed from an absorbed dose and intrinsic energy dependence.

Conclusion

As a consequence of this dependence, several different correction factors are in principle needed depending on the beam quality for accurate dosimetry measurements to be made. Therefore, the OFD is not an ideal candidate for dosimetry in external beam radiotherapy treatments, however, it could still be of use for quality control measurements where standard configurations are often used.

Clinical treatment planning for kilovoltage radiotherapy using EGSnrc and Python

Mihails Nikandrovs*[1,2], Brendan McClean[1,2], Laura Shields[1], Patrick McCavana[1], Luis Leon Vintro[2]

1 - St. Lukes Radiation Oncology Network, Dublin, Ireland
2 – Centre for Physics in Health and Medicine, University College Dublin, Ireland

Introduction:
Kilovoltage radiotherapy is often used to treat inoperable skin cancers. Current treatment planning approach involves manual point dose calculations in rectangular water geometry. Limitations of this method include inability to accurately account for tissue inhomogeneity, beam-shaping lead cutouts, surface geometry heterogeneity, and 3D dose distribution assessment. The aim of this work was to develop a Monte Carlo (MC) based treatment planning system for kilovoltage radiotherapy to address these limitations.

Methods:
EGSnrc Monte Carlo code was used to model Xstrahl 200 kilovoltage unit for all 49 possible clinical setups. The models were validated against measured beam characteristics including percentage depth dose (PDD) curves, beam profiles, half-value layers (HVL), backscatter factors (BSF) and output factors. A Python based treatment planning system (TPS) was developed to aid in simulation setup and result analysis. Its main functionality allows for inclusion of lead shields and cutouts in the simulations, cropping of the dose grid for simulation time optimisation, tissue segmentation, 3D interactive treatment planning, dose distribution evaluation and conversion to DICOM format. End to end testing was performed using heterogeneous phantoms and custom lead cutouts.

Results & Discussion:
MC models agreed well with measured beam characteristics. PDDs and profiles agreed to within 2%, HVLs agreed to within 0.5mm Al, BSF agreed to within 3% and output factors were within 2%. Gamma passing rate for end to end testing was over 85% (3%/2mm 50% threshold) and over 80% (3%/2mm 20% threshold). Sample profiles of lead cutout shaped fields agreed to within 3% and dose to medium estimations were within 7%. TPS allows medical physicists without MC experience to setup and run patient simulations. 3D dose distribution evaluation for kilovoltage treatments is clinically significant for complex setups and re-irradiation cases.

Modelling Intrinsic Radiosensitivity and Relative Biological Effectiveness in Clinical Radiotherapy Plans

Mohammed Dakheel*, Kevin M Prise, Stephen J McMahon

Patrick G. Johnston Centre for Cancer Research, Queen's University Belfast, Belfast, United Kingdom

Background
Proton therapy is believed to achieve superior clinical outcomes to conventional radiotherapy due to its better physical dose distribution and its greater Relative Biological Effectiveness (RBE). However, incorporating RBE variability and individual radiosensitivity into treatment planning remains a challenge. This study aims to address these issues by integrating and benchmarking various RBE models and incorporating predictions of individual radiosensitivity into treatment plans. The impact of these changes on clinically relevant predictions will be evaluated by integrating models of tumour response and normal tissue toxicity.
Methods
Our study examines the behaviour of different RBE models across various cancer types, including prostate, head and neck, and liver cancer, utilizing clinical data as the basis of analysis. The Dose-Volume Histograms (DVHs) and Normal Tissue Complication Probabilities (NTCPs) for Organs at Risk (OARs) were obtained using MATLAB and CERR (Computational Environment for Radiotherapy Research). MATLAB was used for data analysis and processing, while CERR provided a platform for generating DVHs and NTCPs based on clinical cases in these cancer types.
Results
Initial findings reveal a dependence of RBE on parameters such as dose, dose-averaged Linear Energy Transfer (LET), dose fraction, and α/β values. Notably, certain models exhibit significant variability based on dose fraction, as observed in the Frese, Jones, a Wilkens and Oelfek models. Furthermore, RBE models suggest that LET emerges as a significant determinant in NTCP for OAR.
Conclusions
This study investigates the use of RBE models and radiosensitivity predictions in proton therapy. Initial results demonstrate that RBE depends on dose and LET, with substantial variation across models and dose fractions. This research offers vital insights for using RBE models and radiosensitivity predictions to personalise and optimise radiotherapy, which could enhance clinical outcomes.

Single-pulse Gy-scale irradiation of biological cells at average dose-rates above 10^{13} Gy/s from a laser-wakefield accelerator

C.A. McAnespie, P. Chaudhary, M.J.V. Streeter, S.W. Botchway, N. Bourgeois, L. Calvin, N. Cavanagh, K. Fleck, D. Jaroszynski, B. Kettle, A.M. Lupu, S.P.D. Mangles, S. J. McMahon, J. Mill, S. R. Needham, P. P. Rajeey, K. M. Prise and G. Sarri.

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We report on the first experimental characterization of a laser-wakefield accelerator able to deliver, in a single pulse, doses in excess of 1 Gy on timescales of the order of tens of femtoseconds, reaching unprecedented average dose-rates above 10^{13} Gy/s. The irradiator is demonstrated to deliver doses tuneable up to 2.2 Gy in a cm^2 area and with a high degree of longitudinal and transverse uniformity. In this irradiation regime, proof-of-principle irradiation of patient-derived glioblastoma stem-like and human skin fibroblast cells show indications of a differential cellular response, when compared to similar irradiations at conventional dose-rates. These include a statistically significant increase in relative biological effectiveness (1.40 ± 0.08 at 50% survival for both cell lines) and a significant reduction of the relative radio resistance of tumour cells. Data analysis suggests that these effects might not be related to the oxygen tension in the cells but may be instead linked to novel phenomena triggered by the ultra-high density of ionising tracks of femtosecond-scale radiation pulses.

Building predictive models to help further individualise radiation therapy

Shannon Thompson*, Kevin Prise, Ian Overton, Stephen McMahon

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Radiation therapy has been physically optimised to target tumours, while minimising exposure to the surrounding healthy tissue. However, radiation is typically delivered with X-rays with limited consideration for genetic differences in treatment populations, meaning a fraction of patients could be receiving suboptimal therapy. Ion therapy could offer an alternative treatment modality with superior tumour targeting and an increased biological effectiveness compared to X-rays. However, the exact magnitude of this increase remains poorly defined, alongside its potential implications in genetically heterogenous populations. Mechanistic models that simulate DNA damage and repair can be used to better quantify the relative biological effectiveness of ion therapies compared to X-rays. Through such investigations, evidence of the potential benefits of ion therapy can be gathered to further promote their clinical application. Recent studies undertaken at QUB have shown that when building radiation response models several simplifications can be made without compromising the predictive power of the model. Such simulations were validated against key experimental endpoints, linked to cell lethality. This work indicates that further model developments in the simulation of DNA damage would have limited impact on the predictive ability of the models in current datasets.
However, an alternative area of model development, currently under-explored, is the inclusion of cell-specific information which can affect biological responses after irradiation. Within the Medras biological response model, cellular phenotypic properties can be defined, which are considered in the prediction of biological outcome after irradiation. Current work is ongoing to incorporate cell specific information on different genetic mutations, by availing of mutational data involved in radiation response pathways and connecting their involvement to repair deficiencies accounted for within the model. From this, a translatable model could be built for more biologically personalised predictions, which if validated, could help separate genetically similar patients to further individualise and improve radiation treatments.

Session 2 – Mechanisms of response in tumour and normal tissues

Preclinical development of physical and biological strategies to reduce radiation-induced cardiac toxicity

Mihaela Ghita[1], Gerard M. Walls[1,2], Refik Kuburas[1], Kathryn H. Brown[1], Chris J. Watson[3], David Grieve[3], Alan McWilliam[4], Marcel van Herk[4], Kaye J. Williams[5], Karl T. Butterworth[1*].

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Purpose/Objective: Despite technological advances in radiotherapy (RT), radiation-induced cardiotoxicity (RICT) remains a common complication in patients with lung, oesophageal and breast cancers. In a preclinical model, we have recently recapitulated clinical observations showing the heart base as a radiosensitive subregion that could preferentially avoided reduced the risk of adverse events following treatment. Also, we are exploring the potential to repurpose clinically approved drugs to protect against RICT. In this study, we report recent data supporting heart base avoidance and responses to combined treatment with neprilysin/angiotensin inhibition (Entresto, ENT).
Materials/Methods: Studies were conducted using 12-week old C57BL/6J mice irradiated under CBCT image-guidance using the small animal radiotherapy research platform (SARRP, Xstrahl) targeting different regions of the heart. To assess cardioprotective function of ENT, mice were irradiated with a single fraction of 20 Gy to the superior 2/3 of the heart as a 90º arc field arrangement and ENT (100 mg/kg/day) was administered in the drinking water from one week prior to irradiation. Longitudinal transthoracic echocardiography (TTE) was performed at baseline and at 10-week intervals up to 50 weeks after irradiation. All animals were monitored by transthoracic echcardioghraphy (TTE) and global longitudinal strain (GLS) was assessed using two-dimensional speckle tracking (2D-STE).
Results: Heart base irradiation leads to BED-dependent changes in systolic and diastolic function at 50 weeks post-irradiation. GLS showed significant decreases in a BED-dependent manner as early as 10 weeks after irradiation. BED-independent increases were observed in the left ventricle (LV) mass and volume, and myocardial fibrosis. Treatment with ENT resulted in significant preservation of cardiac function for up to 30 weeks after treatment.
Conclusions: Our model of cardiac base irradiation accurately captures clinical observations of the heart base a radiosensitive subvolume with loss of cardiac function dependent on BED. Importantly, we show that GLS can accurately detect radiation-induced changes in cardiac strain at 10 weeks after treatment that are indicative of late functional loss at 50 weeks. We show that treatment with ENT can act to prevent radiation induced-cardiac disfunction and is a potential strategy for clinical exploration.

Dose-dependent changes in cardiac function, deformation and remodelling in a preclinical model of heart base irradiation

Mihaela Ghita [1]*, Kevin S. Edgar [2], Refik Kuburas [1], Kathryn H. Brown [1], Gerard M. Walls [1,3], Cecilia Facchi[4], David J. Grieve [2], Chris J. Watson [2], Alan McWilliam[5], Marcel van Herk[5], Kaye J. Williams[4], Karl T. Butterworth [1].

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Introduction: Radiation-induced cardiac toxicity (RICT) describes a range of adverse conditions that can manifest years or even decades after treatment. The heart has been assumed to be a uniformly radiosensitive organ and most preclinical studies have used whole heart or whole thorax irradiations for experimental purposes. In this study, we apply our model of cardiac regional radiosensitivity to assess the dose-dependent changes in cardiac function, deformation and remodelling Also, we aimed to demonstrate the predictive potential of global and segmental longitudinal strain as early biomarkers for late occurring RICT.
Materials & Methods: Female C57BL/6J mice were irradiated under image guidance using a small animal radiation research platform (SARRP) with a single fraction of 16 Gy or 20 Gy or with 3 consecutive fractions of 8.66 Gy targeting the heart base. The respective biologically equivalent doses (BEDs) were 101.3 Gy, 153.3 Gy and 101 Gy (α/β=3 Gy). Longitudinal transthoracic echocardiography (TTE) was performed at baseline and at 10-week intervals up to 50 weeks after irradiation. This was coupled with two-dimensional speckle tracking (2D-STE) to analyse early changes in global longitudinal strain (GLS).
Results: Irradiation of the heart base leads to BED-dependent changes in systolic and diastolic function 50 weeks post-irradiation. Systolic function measured by EF was significantly decreased in all groups compared to baseline and age-matched control animals with the largest decrease observed following 20 Gy irradiation. Diastolic function measured by the E/A ratio was decreased in all groups with the most significant changes observed following treatment with 20 Gy. BED-independent increases were observed in the left ventricle (LV) mass and volume, and myocardial fibrosis. GLS was significantly decreased in a BED-dependent manner for all irradiated animals, as early as 10 weeks after irradiation.
Conclusions: Our model of cardiac base irradiation accurately captures clinical observations of the heart base a radiosensitive subvolume with loss of cardiac function dependent on BED. We show that GLS can accurately detect changes in cardiac strain at 10 weeks after treatment that are indicative of late functional loss at 50 weeks. These data clearly demonstrate the potential use of GLS as an imaging biomarker of early radiation-induced cardiac dysfunction before detectable loss of systolic and diastolic function.

The influence of hedgehog (Hh) signaling in modulating the radiosensitivity of Glioblastoma tumour models

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Introduction: Ionizing radiation (IR) therapy is a primary treatment option for glioblastoma multiforme (GBM), a common and aggressive malignant human brain tumour. However, GBM radioresistance represents a major treatment barrier resulting in poor treatment outcomes. The hedgehog (Hh) signaling pathway is mainly active during embryogenesis, with aberrant activation associated with tumour development including GBM. Targeting and antagonising Hh signaling by blocking the smoothened (SMO) receptor, is one approach for interfering with this pro-survival pathway. The overall aim of this work is to establish the impact of inhibiting the SMO receptor, assessing the subsequent expression of the down-stream glioma-associated zinc finger transcription factors GLI-1, while determining the impact of pathway antagonism on GBM radiosensitivity.
Methods: For all *in vitro* studies U251MG, U87MG, and T98G human GBM tumour models were used. AuXSMO (SMO targeted gold nanoparticles) were synthesised and characterized confirming stability using DLS and subsequently functionality. Direct cytotoxicity of GDC-0449 (a small molecule SMO inhibitor), SMOi2-8 (a peptide-based antagonist) and AuXSMO were determined using a resazurin assay. Next using a non-toxic concentration of antagonist total RNA and protein samples were isolated at basal level and 24 h post treatment. Finally, the impact of SMO antagonism (drug/peptide/AuXSMO) combined with X-ray was established by clonogenic assay.
Results: Following conjugation of stabilising PEG polymer and SMOi2-8+C, AuXSMO exhibited and overall hydrodynamic size of 60.3 nm, with a good degree of sample heterogeneity (PDI 0.34). SMO and GLI-1 were expressed in all GBM cells, but at a significantly ($p < 0.001$) higher level in T98G cells, those positive for O^6-methylguanine DNA-methyltransferase (MGMT), and more resistant to temozolomide, expressed higher levels (16-fold) of SMO compared to U251 MG and U87 MG cells. No direct toxicity was reported from GDC-0449 and SMOi2-8 in all three GBM cells. However, pre-treatment with GDC-0449 antagonised GLI-1 expression by ~40% in T98G cells, minimally impacting GLI-1 in U251 or U87 cells. Interestingly, SMOi2-8 proved more effective than the small molecule inhibitor, suppressing T98G GLI-1 expression by ~75%. With respect to radiation modulation, antagonising SMO signaling additionally reduced survival fraction over radiation alone (4 Gy) in all cell lines tested, proving significant ($p<0.05$) in both U87 and T98G cells. Radiation failed to directly impact the expression of the SMO receptor; however, it did produce a potent but transient reduction in GLI-1 expression, returning to basal levels 24 h post radiation treatment.
Conclusion: Antagonising the SMO receptor using SMOi2-8 and our fully functionalised novel nanoparticle (AuXSMO) correlated with decreased GLI-1 expression, which acts as a major nuclear effector of Hh signaling by inhibiting the intracellular signal transduction cascades. Furthermore, combined Hh antagonism and radiotherapy resulted increased GMB cell death over radiation alone. AuXSMO targeting SMO could act as a radiosensitizer for the treatment of GBM. As such the Hh/SMO signalling axis may represent novel therapeutic target to help counteract GBM radioresistance. Further studies will be undertaken to expand the range of

radiation doses in addition to exploring the mechanisms contributing to drug mediated radiosensitisation.

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Increased FKBPL expression is associated with a radioresistant phenotype in oesophageal adenocarcinoma

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Introduction: Oesophageal adenocarcinoma (OAC) is the predominant subtype of oesophageal cancer in high-income regions. The standard of care for OAC is neoadjuvant chemotherapy or chemoradiation, followed by surgery. Rates of pathological complete response, an independent predictor of patient outcome, are as low as 30% in OAC, thus highlighting the need for improved therapeutic strategies to enhance radioresponse in OAC. FKBPL was originally discovered as a radioresponse gene, whereby downregulation of FKBPL enhanced DNA repair and radioresistance. We hypothesised that FKBPL would be differentially expressed in radiosensitive compared to radioresistant OAC cells and patient biopsies.
Methods: FKBPL was assessed basally and following a fraction of 2 Gy radiation at the gene and protein level in a novel isogenic model of radioresistant OAC cells by qPCR and Western blot. FKBPL gene expression was assessed in treatment naïve biopsies from OAC patients by qPCR. FKBPL protein levels were assessed in serum from treatment naïve OAC patients by ELISA.
Results: FKBPL protein levels were significantly higher in radioresistant OAC cells compared to radiosensitive OAC cells. In radiosensitive OAC cells, FKBPL protein levels increased following 2 Gy x-irradiation compared to the unirradiated cells. FKBPL gene expression was significantly higher in biopsies from patients that had a poor response to neoadjuvant treatment compared to those that had a good response to neoadjuvant treatment. There was no difference in serum FKBPL levels between good and poor responders.
Conclusion: FKBPL is increased in radioresistant OAC cells *in vitro* and radioresistant tumours from OAC patients. Further investigation into the functional role of FKBPL in radioresistant OAC may identify novel therapeutic strategies.

Characterising the role of single strand break repair pathways in response to low and high LET radiation

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The involvement of single strand break (SSB) repair pathways in radiation response has not been well characterised, as unlike double strand breaks (DSBs), radiation induced SSBs and base damages are not directly lethal to cells. However, mutations in SSB repair pathways are more common than in DSB repair pathways, therefore even small impacts on radiosensitivity may be clinically relevant. The aim of this work was to quantify the impact of SSB repair pathway disruption on cellular radiosensitivity.

A panel of SSB repair deficient cell lines was developed using CRISPR-Cas9 to knock out key genes in the base excision repair (BER) pathway: PARP1, XRCC1 and APE1, nucleotide excision repair (NER) pathway: XPC and ERCC1, and mismatch repair (MMR) pathway: MSH2. The impact of gene loss on radiosensitivity was assessed by measuring clonogenic survival and levels of DNA damage following exposure to low LET X-ray irradiation and high LET (129.3±15.2 keV/μm) alpha particle irradiation.

Small increases in radiosensitivity were observed in the SSB repair deficient cells following X-ray irradiation (SERs ranged from 0.96-1.36), with statistically significant increases in BER and NER deficient cells. Disrupting SSB repair pathways also resulted in increased residual DSB damage 24 hours following treatment with 2 Gy, with residual DSBs in knockout cells ranging from 4.11±1.54 to 7.18±1.52 compared to 1.27±0.92 in the parental cells. Significant increases in radiosensitivity were observed for all knockouts following alpha particle irradiation (SERs ranged from 1.16-1.31). These higher levels of residual damage and increased sensitivity to high LET radiation may be due to an increase in complex damage, resulting from unrepaired SSBs remaining within the cell.

The disruption of SSB repair pathways does therefore impact cellular radiosensitivity, and while this impact may not be as significant as DSB repair pathway disruption, the cumulative effect of mutations in these pathways may be clinically relevant, particularly for treatments using high LET radiation.

Design and optimisation of an *in vitro* system to assess radiation responses at ultra-high dose rates using the FLASH small animal radiotherapy research platform (FLASH-SARRP)

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FLASH radiotherapy (FLASH-RT) is emerging as a promising radiotherapy technique due to its potential to spare normal tissues whilst effectively damaging tumours. Most studies have demonstrated the FLASH effect using protons or electrons, but only a very small number of studies have used photons, the most widely used radiation in the clinic. Furthermore, previous *in vitro* studies of FLASH have reported inconsistent data. To address these challenges, our lab has recently installed the FLASH-SARRP, a unique, first of its kind technology for photon FLASH studies. As part of our emerging FLASH radiotherapy program, this project aims to develop a robust system for *in vitro* studies using the FLASH-SARRP in oxic and hypoxic conditions.

The FLASH-SARRP uses advanced photon technology to deliver photon beams at dose rates > 150 Gy/sec. Preliminary dosimetric measurements have evaluated dose-rate and beam flatness of the FLASH-SARRP. Conventional dose rate studies are being conducted in glioblastoma (GBM) cell models, U87-MG and U251, irradiated under oxic (21 % O_2) and hypoxic conditions (< 2 % O_2) using the nBIONIX-3 hypoxic cell culture kit.

Initial dosimetric measurements showed the FLASH-SARRP can deliver doses at ultra-high dose rates with adequate beam homogeneity. Radiobiological response of GBM cell lines were evaluated *in vitro* through clonogenic survival, cell cycle and DNA damage assays. Conventional irradiation of GBM cell lines under hypoxia showed increased cell survival and reduced DNA damage compared to oxic conditions. Following further beam characterisation, these studies will be repeated for FLASH exposures.

The results from this study will compare conventional and FLASH photons, representing one of the first reports of responses to *in vitro* photon FLASH-RT exposure. This work is supported by Brainwaves NI.

Polonium-210 activity concentration in twelve seaweed species from the Irish coastline.

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Polonium-210 is a naturally occurring radionuclide of particular interest due to its large dose coefficient and typically high activity concentration within marine biota. Although ^{210}Po has been identified as the largest contributor to dose from seafood consumption, few data exist on the accumulation of ^{210}Po by seaweeds. The Irish seaweed industry has expanded significantly in recent years, and this study aims to investigate the accumulation of ^{210}Po in a number of commercially important seaweed species from Ireland. Eight samples of seaweeds common to two locations, one on the east and one on the west coast of Ireland (Clogherhead, Co. Louth and Finavarra, Co. Clare) were collected. Three additional species were collected from Finavarra and one from Clogherhead. Seawater samples were collected from both locations for the determination of ^{210}Po concentration factors. The brown seaweed species collected were *Ascophyllum nodosum, Fucus vesiculosus, Fucus spiralis, Fucus serratus, Laminaria digitata, Halidrys siliquosa, Pelvetia canaliculata* and *Himanthalia elongata*, and the red seaweeds collected were *Osmundea pinnatifida, Palmaria palmata, Chondrus crispus* and *Corallina officinalis*. The ^{210}Po content was determined by radiochemical separation and the use of high-resolution alpha spectrometry. The ^{210}Po activity concentration was typically larger in red seaweed species compared to brown species. *Ascophyllum nodosum* from both sites had the lowest concentration of ^{210}Po , while *O. pinnatifida* from Clogherhead had the greatest concentration. Three species (*A. nodosum, F. serratus* and *P. palmata*) displayed similar concentration ranges at both sites. For the red seaweeds, ^{210}Po concentrations were consistently higher in Clogherhead than Finavarra. While the calculated concentrations factors ranged from 7×10^3 to 7×10^4, the levels of ^{210}Po in these seaweed species are of little radiological significance.

Session 3 – Enhancing Treatment Response

Synergistic activity of DNA damage response inhibitors in combination with radium-223 in prostate cancer

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Introduction

The Targeted radionuclide therapies (TRT), Radium-223 (^{223}Ra) and lutetium-177-labelled PSMA-617 (^{177}LuPSMA), are currently the only radiopharmaceutical treatments that prolong survival for patients with metastatic-castration resistant prostate cancer (mCRPC). Despite the clinical utility of these TRT, mCRPC remains an aggressive disease with poor survival.
To maintain genomic stability, cancer cells respond to radiation-induced DNA damage by activating a dynamic network of DNA damage response (DDR) signalling pathways and cell-cycle checkpoints. Selective inhibitors of key DDR components have demonstrated increased therapeutic efficacy when combined with X-rays, however, little is known regarding the potential of DDR inhibitors + TRT.
In this study, we aimed to determine the utility of combining the ATR-, ATM- and PARP-targeting DDR inhibitors (AZD6738, AZD0516 and AZD2281) inhibitors, to increase the therapeutic efficacy of X-rays or ^{223}Ra in prostate cancer models.

Methods

The radiobiological response of prostate cancer cells to isotoxic doses of X-rays (2 Gy) and ^{223}Ra (0.25 Gy) alone and in combination with DDR inhibitors were assessed. Cellular survival, DNA damage and cell cycle was examined using clonogenic assays, immunofluorescence staining of 53BP1 and flow cytometry. Further, apoptosis was assessed using western blotting for PARP-1 cleavage.

Results

Treatment with X-rays or ^{223}Ra alone significantly reduced cell survival compared to untreated controls ($p < 0.001$). ^{223}Ra was determined as the more potent radiosensitiser ($p < 0.05$), which was associated with a slower rate of DSB repair (< 0.01) and increased G2/M arrest ($p < 0.05$).
DDR inhibitors increased the therapeutic efficacy of both radiation qualities. The strongest synergistic drug-combination to enhance the efficacy of X-rays and ^{223}Ra was AZD6738 (CI= PC-3 0.73 ± 0.11 and 0.16 ± 0.54; LNCaP 0.45 ± 0.17 and 0.07 ± 0.32, respectively). Following 24 h, the number of 53BP1 foci after X-rays or ^{223}Ra + DDR inhibitors were significantly greater in comparison to individual radiation qualities ($p < 0.05$). Further, AZD0156 and AZD2281 + X-rays or ^{223}Ra induced a greater G2/M arrest whereas, AZD6738 abrogated the radiation induced G2/M phase with a significant accumulation of cells in G1.

Discussion

The next generation of TRT radiopharmaceuticals are gaining significant attraction as therapeutic options for mCRPC. Targeting the DDR pathway through inhibition of specific kinases remains an area of interest as a therapeutic strategy to enhance anti-tumour efficacy. The present study highlights the potential of exploiting DDR inhibitors, particularly AZD6738, as a mechanism of attenuating the therapeutic efficacy of X-rays and ^{223}Ra. Taken together, our findings support further pre-clinical evaluation *in vivo* to investigate the application of DDR inhibitors in combination with radiation qualities.

Boosting Oxygen Diffusion in the Radioresistant Oesophageal Tumour Microenvironment to Improve Radiation Response.

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Introduction

Oesophageal adenocarcinoma (OAC) is a poor prognosis cancer with a 20% survival rate [1]. OAC patients often receive neo-chemoradiotherapy prior to surgery [2]. Only 30% of patients achieve a pathological complete response [3]. Hypoxia is present in up to 50% of solid tumours and significantly contributes to treatment failure, in particular radiation treatment as oxygen is a potent radiosensitiser [4]. Increasing tumour oxygen level is a potential approach to improve radiosensitivity. Perfluorocarbons are chemically inert compounds which can assimilate large amounts of oxygen. This project aims to develop perfluorocarbon nanoemulsions (PFC-NEs) and assess their ability to radiosensitise an isogenic model of OAC radioresistance.

Methodology

PFC-NEs were produced using lipoid, phosphate-buffered saline, and perfluorocarbons. PFC-NE stability, imaging capacity, oxygen-carrying capacity and oxygen release profiles were measured. The toxicity of lead PFC-NEs were assessed using various in vitro and in vivo model systems (isogenic model of OAC radioresistance, 2D and 3D HepG2 models and zebrafish). Following treatment of an isogenic model of OAC with PFC-NEs, clonogenicity, DNA repair, metabolism, cytokines, and cysteinyl leukotriene receptor expression were assessed.

Results & Discussion

PFC-NEs are stable, can be visualised *ex vivo*, and can load a significant level of oxygen. Lead PFC-NEs do not induce toxicity *in vitro* using an isogenic model of OAC radioresistance and in 2D and 3D HepG2 models. Formulation B reduced zebrafish viability at higher concentrations. PFC-NEs significantly increase supernatant oxygen concentration and assimilate oxygen *in vitro.* PFC-NEs significantly reduce oxygen consumption rate and alter cytokine secretion in radioresistant OAC cells. PFC-NEs may reduce HIF-1a expression under hypoxic conditions and CysLTR1 expression in response to radiation in radioresistant OAC cells.

Conclusion

Hypoxia is a significant barrier to successful radiotherapy. These data suggest that PFC-NEs function as an oxygen delivery system with the potential to improve radiosensitivity in radioresistant OAC cells.

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Sensitising prostate tumour models to radiation using novel RALA/AuNPs nanocomplexes

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Introduction: Gold nanoparticles (AuNP) are effective radiosensitisers, however, successful clinical translation has been impeded by several limiting factors, notably, physiological instability and poor cellular internalisation efficiency. Previously, our group developed an AuNP formulation utilising a short cell penetrating peptide, RALA; (RALA-AuNP). RALA-AuNP showing efficient intracellular delivery, and a consequent radiosensitisation at low microgram AuNP concentrations in a range of prostate cancer cell models. However, creating a controlled release delivery implant for this formulation was challenging due to limited stability and issues relating to a requirement for hyper-concentration of the nanoparticle with the core implant material.

Result: To address these issues the RALA-AuNP complex was modified by incorporating 5 kDa polyethylene glycol into the AuNP-RALA nanocomplex. Optimised w:w ratios of RALA:AuNP:PEG yielded a positively charged nanocomplex sized <50 nm with PDI values <0.25 as measured by dynamic light scattering (DLS). This formulation was successfully lyophilised, and following reconstitution remained stable and functionally active within simulated physiological solutions for at least two weeks. Efficient cellular internalisation of lyophilised AuNP-RALA was observed in both PC-3 and DU145 prostate cancer cell models, treated at an ultralow dose of 3.5 µg/mL, confirmed by ICP-OES and enhanced dark field/hyperspectral microscopy. Significant radiation dose modulation (sensitivity enhancement ratio=1.9) using this novel formulation, a result further supported by significant increases in DNA double strand break damage.

Conclusions: Future work will ascertain the ability of this formation to act as a radiosensitiser following release from a biodegradable, sustained release implant.

The Impact of CXCR2 Antagonism on the Radiation-Induced Bystander Effect

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Introduction

Ionising Radiation (IR) is a widely used treatment modality against various forms of cancer, however off-target radiation induced damage is a common occurrence complicating therapeutic responses. Irradiated cells can release factors that propagate radiation damage to neighbouring unirradiated cells, an effect termed the radiation-induced bystander effect (RIBE) [1,2]. Manipulation of the RIBE has potential to greatly enhance the effects of IR. The chemokine receptor CXCR2 has been identified as a potential target to enhance RIBE due to its involvement in radiation triggered inflammatory processes[3]. Gold nanoparticles (GNPs) can also be used to radiosensitise tissues[4]. A chemokine-targeting GNP has been taken forward to first assess radiosensitisation properties before exploring potential impacts on RIBEs.

Methods

PC3, DU145 (prostate) and FaDu (head and neck) cancer cell lines were used following confirmation of CXCR2 expression by western blot. A clonogenic assay was used to quantify the radiosensitising ability of two CXCR2 antagonists: AZD5069 and the pepducin x1/2pal-i3. After radiation treatment, media was transferred to unirradiated bystander cells which were assessed for clonogenic survival. Physical properties of the GNPs were determined via DLS. A DCFDA assay was used to measure ROS production after 6 Gy irradiation in all cell lines following 24 h treatment with GNP.

Results

CXCR2 antagonism slightly, however not significantly, increased radiosensitisation. Basal bystander effects in all cell lines were inhibitory, however, CXCR2 antagonism alone had little effect on RIBE. The chemokine-targeting GNP was deemed to possess appropriate size, charge and PDI characteristics, increasing intracellular ROS levels immediately post-radiation.

Discussion

The lack of impact on RIBE suggests that CXCR2 targeting alone is not sufficient to alter this effect. The increase in ROS caused by a chemokine-targeting GNP suggests that this nanoparticle might radiosensitise cells more than CXCR2 targeting alone, and therefore should be taken forward for investigation into the RIBE.

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Evaluation of the association between sex-linked genes and treatment response in lung cancer

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Purpose/objective
Gender medicine is the next step in personalised medicine,[1] with lung cancer patients likely to benefit from these approaches owing to reports that male sex is linked to poorer survival outcomes.[2] There remains huge gaps in our understanding of the impact of biological sex on treatment response and patient outcomes. [3,4] Tumours arise from an individual that can identify to a gender but who are dichotomised into a male or female biological sex based on a pair of sex chromosomes. This study aimed to examine the relationship between sex-linked genes, DNA repair and senescence and survival in male and female lung cancer.
Methods
The lung adenocarcinoma (LUAD) whole genome mRNA expression dataset from The Cancer Genome Atlas (TCGA) PanCancer Atlas was accessed (N=275 female, N=239 male). A list of 874 X chromosome genes, 57 Y chromosome genes and 314 DNA damage response (DDR) genes was downloaded from Uniprot and approved in Human Genome Organisation (HUGO) database. A list of 279 cellular senescence genes was downloaded from https://genomics.senescence.info/cells/. The expression of the long coding RNA XIST was examined in A549 (male) and H1975 (female) lung cancer adenocarcinoma cell lines in response to radiation exposure and/or a senolytic drug (fisetin). Correlation analyses of mRNA expression between sex-linked genes and DDR/senescence genes were done using Spearman rank correlation method. The association between mRNA expression and patient overall survival analysis was measured using Kaplan-Meier.
Results
The tumour-specificity of X and Y-chromosome gene expression was examined using tumours and the adjacent normal tissues matched patient samples (N=32 female, N=24 male). The expression of 287 and 314 X-chromosome genes were significantly altered (FDR ≤ 0.05) in tumours compared to normal tissue in male patients and female patients, respectively. Of those 153 (males) and 256 (females) X chromosome genes were found to correlate with the expression of at least 1 DDR gene in tumour tissues (FDR of ≤0.05), respectively**.** In males, 11/44 Y-linked genes whose expression data was available were significantly altered between matched tumour and normal tissue. The X-linked genes CENPI and ECC6 were common to both males' and females most differentially expressed lists and were selected for further analysis. Low ERCC6L expression was associated with increased overall survival in both females ($p = 0.031$, Hazard ratio: 1.57) and males ($p = 0.029$, Hazard ratio: 1.65) patients. 15 cellular senescence genes were found to be correlated with ERCC6L in females, 13 in males. Similarly low CENPI expression was associated with increased overall survival in both male and female patients. In the male cell line A549, treatment with 4Gy radiation led to a significant reduction in both CENPI and ECC6 mRNA levels ($p<0.05$), whereas no change was seen in the female cell line. Treatment with the senolytic drug Fisetin (up to 90mM) resulted in a significant reduction in both CENPI and ECC6 mRNA levels in the female H1975 cell line,

but no effect was detected in the male A549 cell line. However, no link to a change in clonogenic survival could be established.

Conclusion

This study identifies that the expression of sex-linked genes is altered in tumour compared to normal lung tissue and that these genes can affect the expression levels DDR and senescence genes in tumours. In patient cohorts segregated according to recorded sex, statistically significant associations between expression levels in tours to overall survival could be detected. Further analysis of the biological and clinical relevance of these links to the radiation response and patient outcome is warranted.

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Session 4 – Imaging & Spectral Biomarkers

Raman spectroscopy with machine-learning classification predicts stereotactic radiotherapy induced treatment toxicity in high-risk localised prostate cancer

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Introduction
Following radiotherapy, patients can experience late toxicity, with variability in side effects experienced due to individual radiosensitivity. Predicting which patients will experience toxicity following radiotherapy is crucial, and Raman spectroscopy, an optical vibrational spectroscopic technique, offers a rapid, label-free, and non-destructive way to measure biochemical content in cells and biofluids.
Methods
High-risk localised prostate cancer patients were enrolled on to the SPORT (Stereotactic Prostate Radiotherapy in High-Risk Localised Prostate Cancer with or without Elective Nodal Irradiation; ClinicalTrials.gov study ID: NCT03253978) trial. Spectra of patient lymphocytes isolated from peripheral blood mononuclear cells (PBMCs) obtained at four treatment time points, i.e. baseline, post-hormone therapy, mid-treatment (4th fraction), and 3-month follow-up, were recorded and used to develop a machine-learning classifier to monitor the biological response to radiotherapy. Additionally, the lymphocyte and plasma spectra obtained at baseline were employed to create a machine-learning classifier for predicting toxicity. Model performance was assessed using the receiver-operator characteristic area-under-the-curve (ROC-AUC).
Results
A 10-fold cross-validated partial least squares discriminant analysis (PLSDA) for baseline / post-hormone therapy, baseline / mid-treatment (4th fraction) and baseline / 3-month follow-up returned mean AUC values of 0.93 (S.D. ±0.15), 0.92 (S.D. ±0.18) and 0.88 (S.D. ±0.14), respectively. Furthermore, PLS-DA of grade 0-1 and grade 2+ late toxicity returned mean AUC values of 0.89 (S.D. ±0.22) for lymphocytes, and 0.92 (S.D. ±0.23) for plasma. Classical least squares (CLS) fitting of lymphocyte spectra at baseline and mid-treatment (4th fraction) revealed changes in the cellular dynamics of L-valine, lectin, and histone 2A ($p < 0.001$), while the CLS toxicity models of lymphocyte and plasma spectra identified concentration differences in amino acids, phospholipids, and ceramides ($p < 0.001$).
Discussion
This study demonstrates the potential of Raman spectroscopy for predicting the development of late toxicity and monitoring the biological response to radiotherapy.

Characterisation of quantitative imaging biomarkers for inflammatory and fibrotic radiation-induced lung injuries using preclinical radiomics

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Introduction: Radiomics is a rapidly evolving area of research that uses medical images to develop prognostic and predictive imaging biomarkers. In this study, we aimed to identify radiomics features correlated with longitudinal biomarkers in preclinical models of acute inflammatory and late fibrotic phenotypes following irradiation.

Methods: Female C3H/HeN and C57BL6 mice were irradiated with 20 Gy targeting the upper lobe of the right lung under cone-beam computed tomography (CBCT) image-guidance. Blood samples and lung tissue were collected at baseline, weeks 1, 10 & 30 to assess changes in serum cytokines and histological biomarkers. The right lung was segmented on longitudinal CBCT scans using ITK-SNAP. Unfiltered and filtered (wavelet) radiomics features (n=842) were extracted using PyRadiomics. Longitudinal changes were assessed by delta analysis and principal component analysis (PCA) was used to remove redundancy and identify clustering. Prediction of acute (week 1) and late responses (weeks 20 & 30) was performed through deep learning using the Random Forest Classifier (RFC) model.

Results: Radiomics features were identified that correlated with inflammatory and fibrotic phenotypes. Predictive features for fibrosis were detected from PCA at 10 weeks yet overt tissue density was not detectable until 30 weeks. RFC prediction models trained on 5 features were created for inflammation (AUC 0.88), early-detection of fibrosis (AUC 0.79) and established fibrosis (AUC 0.96).

Conclusions: This study demonstrates the application of deep learning radiomics to establish predictive models of acute and late lung injury. This approach supports the wider application of radiomics as a non-invasive tool for detection of radiation-induced lung complications.

Analysis of Computed Tomography (CT) Imaging Biomarkers using Radiomics to Assess Radiotherapy Response in a Colorectal Cancer Model.

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Introduction: Radiomics is an emerging field that translates medical images into quantitative data to determine the biological nature of tissues and tumours. This insight could lead to the development of imaging biomarkers in radiation oncology. In this study, we aimed to develop a radiomics signature for colorectal cancer (CRC) and determine if radiomics features are affected by radiation and the presence of a fiducial marker.

Methods: Retrospective CBCT scans acquired using the Small Animal Radiotherapy Research Platform (SARRP, Xstrahl) of a CRC xenograft tumour model (MC38) were analysed. Radiomics features were extracted using Pyradiomics (n=842) and reliability was measured using intra-class correlation coefficients (ICC), with ICC scores > 0.8 deemed reliable. Radiomics signatures were identified that correlated with the biological characteristics of an untreated CRC tumour and also in response to different fractionation schedules of radiotherapy (1 x 8 Gy or 3 x 4 Gy). The impact of a fiducial marker (BioXmark, Nanovi, A/S, Denmark) on these radiomics features was also evaluated. Reliable features were then used to build predictive models for CRC using random forest classifiers (RFC).

Results: For the control, 1 x 8 Gy and 3 x 4 Gy MC38 tumours, the most prominent reliable feature classes were wavelet first order, wavelet first order, and original GLSZM, respectively. A signature consisting of 64 features was identified for an unirradiated MC38 tumour. Five highly reliable features of an MC38 tumour were significantly different to those with BioXmark ($p < 0.0001$). A predictive model was developed to differentiate between an MC38 tumour before and after irradiation using 1 feature with an average AUC score of 1. A statistically significant difference ($p < 0.0001$) was observed between these radiomics features.

Discussion: We have developed a preclinical radiomics workflow to extract and analyse radiomics features in the MC38 CRC tumour model following fractionated irradiation and with and without the presence of a high contrast fiducial marker. We have created a radiomics signature for this tumour that could potentially aid clinical decision-making during patient diagnosis, alongside tumour biopsies. Preclinical models such as mice are essential tools to develop this database. This work is supported by the RadCoL project in collaboration with the Royal College of Surgeons in Ireland (RCSI) and funded by the Higher Education Authority (HEA) North-South Research Programme.

Spectral biomarkers of normal tissue toxicity in prostate cancer patients following radiotherapy

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Introduction
Late radiation toxicity can continue years after completion of radiotherapy and is generally irreversible. Known causes of radiation toxicity include dose volume parameters, co-morbidities such as diabetes, intrinsic radiosensitivity and concurrent chemotherapy, but there is a large patient-to-patient variability in response which is intrinsic to the patient. Currently, it is impossible to predict before treatment which patients will experience these long-term side effects. To date, no markers of tumour response to radiotherapy or predictors of normal tissue toxicity are in routine clinical use. Cell based predictive assays may not be easy to translate to routine clinical use due to intrinsic variability and labour intensive protocols and genomic assays can be expensive. A new approach based on optical spectroscopy has advantages in terms of minimal sample preparation, speed and cost. This study aims to develop an assay based on spectral biomarkers for the prediction of radiation toxicity.
Methods
Plasma samples were obtained from prostate cancer patients (n=143) enrolled on the EU funded REQUITE study (www.requite.eu) through a collaboration with the University of Leicester. The patients were followed up to 24 months following radiotherapy and toxicity was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grading system. Spectra were recorded from plasma samples using Raman spectroscopy and ATR-FTIR spectroscopy. Sphingolipidomic analysis was carried out using LC-MS/MS.
Results
After pre-processing and multivariate analysis, plasma samples from prostate cancer patients with no/minimal radiation toxicity (grade 0-1) could be differentiated from those with severe radiation toxicity (grade 2-3) with >85% sensitivity.
Discussion
Prediction of radiation toxicity could allow stratification of cancer patients according to risk and could guide the selection of treatment modality to reduce this risk in high-risk patients or allow dose escalation in low risk patients to improve tumour control.

A comparative analysis of preclinical computed tomography radiomics using cone-beam and micro-CT scanners

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Introduction: Radiomics is a novel field focusing on extracting quantitative data (features) from medical images that reflect the biological characteristics of tissues, including tumours and normal tissues. These radiomics features could potentially act as imaging biomarkers for precision medicine applications in radiation oncology. However, there is a lack of cross-comparison studies validating radiomics outputs which is paramount to achieving transferable results. In this study, we conducted a cross-centre comparison of reliable radiomics features derived from two computed tomography (CT)-based scanners to develop comprehensive preclinical radiomics signatures.
Methods: CBCT and µCT scans of a phantom and two mouse models were acquired using a SARRP (Xstrahl) and Quantum GX2 (Revvity, UK), respectively. Different volumes (phantom) and tissue densities (mouse) were segmented from the scans and the reliability of radiomics outputs was assessed using different imaging protocols and harmonisation of pre-processing parameters. Reliability was measured through intraclass correlation coefficient (ICC) analysis.
Results: The reliability of *in phantom* radiomics features differed across segmentation volumes, with first order and GLCM features being the most stable feature types identified across scanners and volumes. Overall, µCT imaging produced more reliable features compared to CBCT in mice with notable superiority in higher-density tissue (bone). Tissue density-specific preclinical radiomics signatures were developed for the lung (133 features), heart (35 features), and bone (15 features) that were shared across CBCT and µCT modalities. Variations in the reliability of radiomics features across scanners were observed yet normalisation steps including standardisation of imaging energy and pre-processing factors (voxel size) can be used to allow accurate comparisons across µCT and CBCT scans.
Discussion: µCT and CBCT scans can be used for radiomics analysis to gain a better understanding of the underlying biology of tumours and normal tissues. This study demonstrates the importance of standardisation and emphasises the need for multi-centre radiomics studies to assess feature reliability to aid widespread application and ultimately the clinical integration of radiomics.