Royal College of Radiologists: CRUK Strategic Review of Radiation Biology and Oncology

1. What are the key discovery science questions in the field of radiation biology and physics?

Advances in precision cancer radiotherapy, particularly proton beam therapy, and image-guided radiotherapy can be combined with biological therapies and targeted small molecule therapy to improve cure rates for cancer. Significant advances are more likely to be made in academic radiation oncology departments embedded in multidisciplinary universities with collaboration between researchers and the following disciplines: physics, computational imaging, artificial intelligence, state-of-the-art imaging, biostatistics, drug discovery and cancer biology.

In this context, the key discovery science questions for radiation biology and physics are:

- How should the rapid advances in immunotherapy and targeted small molecule approaches for cancer be combined with the technical advances in photon and proton radiotherapy delivery and image-guided therapy?

- How does photon and proton radiotherapy affect immune recognition of tumours in preclinical models and in patients with cancer? This fundamental understanding will lead to broader knowledge of the immune landscape and its dynamics during and after radiotherapy, facilitating biologically-informed development of potent combinations of radiotherapy with immunotherapies.

- What are the biological factors that promote a cancer's resistance to ionising radiation?

- Protons offer superior dose distributions and potentially higher delivery dose rates compared to traditional photon radiotherapy. As cure rates increase with advances in proton radiotherapy, what is the best approach using proton beam therapy to minimise the long-term adverse effects of therapy for difficult-to-treat child and adult cancers? Survivorship issues include neuro-cognitive sequelae for children and adults with brain tumours and growth problems/secondary cancers for children with cancer.

- How should the large clinical datasets available from radiotherapy imaging and dosimetry be analysed with long-term outcome data as “big data” which can improve cure rates for cancer?

- What somatic mutations occur during and after radiotherapy that lead to resistance to therapy? Can circulating tumour DNA and single cell analysis be used to improve our understanding of this fundamental phenomenon?

- Which functional imaging modalities and computational imaging platforms should be used for adaptive radiotherapy? The vision is that adaptation of radiotherapy during treatment will be computed from MRI and PET scans based on biological understanding of the cancer and how it evolves during therapy.

- How to predict intrinsic radiosensitivity in vivo?

- How to measure normal tissue repair accurately?

2. What are the major challenges and research questions in clinical and translational radiation oncology?

A “one size fits all” radiotherapy approach is no longer acceptable. Research is needed to develop initially risk-adapted stratification and ultimately a true personalised approach based on genetic information regarding both tumour and surrounding normal tissues. Vastly improved patient selection for adjuvant radiotherapy is required, to ensure treatment for those who will benefit and avoidance for those who will not. Validated biomarkers are also required for early detection of disease relapse following radiotherapy, so that rapid and individualised treatment can be initiated.

In addition, better imaging strategies for truly adaptive radiation therapy, including improved MR imaging workflows, image registration and adaptive dose recalculation are needed. Also, as radiation treatment becomes more personalised, based on molecular subtypes, and relapse rates fall across many tumour sites, the pragmatic A versus B phase III randomised trial becomes less relevant. There is a further challenge with early phase radiation and novel drug combination designs given that late (permanent) normal tissue toxicity can occur many months and years following treatment. Therefore, innovative trial methodology is needed including development of adaptive platform studies and novel early phase study strategies.

- To ensure there is sufficient capacity and resource to develop and launch and support relevant trials
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- Service pressure reducing available clinician time to undertake local PI work to open and recruit to trials

- The need for a defined supported career structure to attract bright junior clinicians and scientists into radiation research and a pathway including post doctoral support to enable more to obtain clinician scientist fellowships.

- Development of a radiosensitiser for tumour tissue alone

- Development of an isolated normal tissue radiation protector

- Personalisation of therapy based on biological and genotypic characteristics

- The need for structured referral networks for complex proton therapy and immuno-radio-oncology clinical trials to succeed for common and rare cancers. Collaboration between Clinical Trials Units with a track record in successfully running radiotherapy

clinical trials, and CRUK infrastructure funding in to CTRad and the CRUK ART-NET accelerator grant, can help facilitate the development of these critical networks.

- The pharmaceutical industry may prioritise certain cancers, such as malignant melanoma, lung cancer and breast cancer, for the development of expensive immuno-radio-oncology clinical trials. How do we ensure that rare tumours and paediatric/adolescent tumour types are prioritised in academic studies of the most promising combination treatments? For example, interstitial brachytherapy research, which has not been prioritised by the commercial/industrial sector for over a decade, has not made any significant research advances during that time.

- How should we harness the cross disciplinary power of physics, computational imaging, artificial intelligence, state-of-the-art imaging, biostatistics, drug discovery and cancer biology which underpins the unprecedented progress that could be made for photon radiotherapy and proton beam therapy within one decade?

- The clinical success of novel immunotherapies has driven the development of a growing pipeline of biotherapeutics and novel combination approaches in the clinical and pre-clinical settings. How should we rapidly translate the most exciting approaches to radiotherapy science, including new clinical trials of stereotactic radiotherapy and proton beam therapy, from preclinical models to clinical trials?

- How should we collect reliable long-term response and toxicity data to allow radiation oncology to successfully utilise its potential to benefit from the “big data” imaging and dosimetry datasets that exist for radiation oncology

3. What are the emerging technologies and methodologies likely to have major impact the field over the next 10 years?

- Proton beam therapy will demonstrate superior dose distributions and potentially higher delivery dose rates compared to traditional photon radiotherapy, resulting in higher cure rates reduction of long-term toxicities for cancer survivors. Research will be performed on treatment with heavy ions (e.g. carbon ions, helium ions) to see if they add any further clinical advantages to proton beam therapy.

- Molecular radiotherapy has made significant progress in the treatment of neuroendocrine tumours and metastatic prostate cancer. The prospect of combining molecular radiotherapy with understanding of immuno-radio-biology holds great potential for the future.

- Artificial intelligence will enhance and optimise treatment planning (outlining of critical organs, target definition, optimal plans, adaptation during therapy)

- New particles will be developed for therapy (protons, helium ions, carbon ions) for preclinical studies and clinical trials to allow more precise treatment delivery, sparing of normal tissues and lower integral dose to the body. Combinations of photons and particle therapy may be particularly valuable, and combinations of particle therapy with new cancer drugs, particularly immunotherapy.

- Computational imaging will improve our ability to track the target and ensure that photon and proton radiotherapy is delivered with minimal toxicity to normal tissues Image fusion for planning/verification.

- Combined modality therapy with new drug classes including immunomodulatory drugs

4. How will the research workforce in UK radiation oncology need to develop over the next 10 years to achieve the necessary critical mass to remain internationally competitive?

- Research capacity within clinical departments: research time on treatment machines and dedicated research staff (medical physics and treatment radiography)

- More multidisciplinary cooperation within each site, expanding the links between clinical oncology, medical oncology, radiology, immunotherapy, drug manufacturing, particle technology, computational imaging, artificial intelligence, maths, physics, bioengineering and cancer biology institutes.

- Access to international collaboration.

- Sufficient pipeline of young scientists to ensure significant critical mass at each career point. Expansion of numbers of clinical academic posts in the way that medical oncology and haematology have expanded in previous decades

- Access to sufficient IT infrastructure and computational power to support research projects

- Support for a critical mass of basic science research into the underpinning biology of radiation response: 'Radiobiology' and support for translational research from basic science to the clinic. Because of the multidisciplinary nature of radiation related research this warrants major investment in an Institute scale programme of funding.

- Opportunities for NHS clinicians to engage in research within specialist teams via academic research time.

- Physics will need to overlap more with computational imaging and machine learning: workforce training in this area should be increased.

- Develop staff at Clinical Trials Units and the central Radiotherapy Quality Assurance team for research trials, prioritising CTUs with a track record of delivering on complex, radiotherapy clinical trials with evolved referral pathways.

5. What are the critical infrastructure and capital investments necessary over the next 10 years in order for the UK to be/ continue to be world-leading in this field?

- Guaranteed upgrade of software / hardware with no machine more than five years old to allow rapid roll out of emerging treatment technologies. IT infrastructure and personnel to support comprehensive collection of outcomes data to be used for radiotherapy studies correlating imaging and dosimetry with clinical outcomes.

- Ability to harness artificial intelligence advances quickly to improve quality and safety and free spare capacity in clinicians and dosimetrists time.

- Computational imaging and artificial intelligence to address the areas that can significantly improve proton beam therapy and photon radiotherapy

- Power to harness and use national data to test hypotheses on quality and dose distribution

- Equality of access to advanced techniques regardless of geography

- Maintained access to radioisotopes used in therapy / diagnosis. Particularly in light of the negotiations to leave the EU and Euratom.

- Funding for Clinical Trials Units with a track record in radiotherapy clinical trials and developing referral pathways for high specialised treatments and rare cancers

- Investing in the leaders of the future. Researchers, clinicians and clinician scientists with the skills to work across disciplines will be attractive globally and to industry: retention of talent in the UK, particularly academia may be challenging.

- Thematic funding for specific areas of high importance in radiotherapy research, such as paediatric cancers and brain tumours, preferably in academic radiation oncology departments embedded in multidisciplinary universities with collaboration between radiation researchers and relevant disciplines such as physics, computational imaging, state-of-the-art imaging, biostatistics and cancer biology.

6. Where are the top radiation oncology centres internationally and what makes their programmes cutting-edge? What can the UK learn from these centres?

- MD Anderson Cancer Center: https://www.mdanderson.org/research/departments-labs-institutes/programs-centers/center-for-radiation-oncology-research.html
- Memorial Sloan Kettering Cancer Center - https://www.mskcc.org/departments/radiation-oncology
- Stanford: https://radonc.stanford.edu/
- Mayo Clinic - http://www.mayoclinic.org/departments-centers/radiation-oncology/home/orc-20188588
- UCLA Radiation Oncology - http://radonc.ucla.edu/research
- University of Wisconsin, Medical Radiation Research Center - https://uwmrrc.wisc.edu/
- St Jude's Children's Research Hospital - https://www.stjude.org/research/departments-divisions/radiation-oncology.html
- Princess Margaret Cancer Center - http://www.uhn.ca/PrincessMargaret/Health_Professionals/Programs_Departments/RMP
- Netherlands Cancer Institute - https://www.nki.nl/
- Maastricht - http://www.maastrolab.com/members
- Aarhus - http://www.en.auh.dk/departments/cancer-and-inflammation-centre/department-of-oncology/research/
- Heidelberg - https://www.nct-heidelberg.de/en/research.html

These centres have a research-focused culture, well developed research infrastructure, clear focus on specific areas of research and centralised funding structures. Some benefit from major charitable donations or government investment. Links with industry are important, particularly radiotherapy equipment manufacturers and pharmaceuticals.

Institutions that have led technical innovation (largely physics) include NIRS in Japan, PSI in Switzerland and the Harvard Cyclotron. These are examples of how basic science facilities need to collaborate with radiation oncology centres to innovate to improve clinical therapy.