Scientific Abstract

SU2C-CRUK Pediatric Cancer New Discoveries Challenge:

"BRAINatomy: A Validated Anatomical Atlas of Childhood Neuroradiation Damage"

Background and rationale: Over 70% of children with brain tumours survive long term. Radiotherapy is a key component of curative treatment but cognitive and endocrine toxicity in survivors is life-changing and impacts on educational attainment, employment, independence and quality of life. Although the clinical phenotype is well known, the functional brain units that contribute most to late toxicity are poorly described, and accurate risk prediction models are lacking. The knowledge gap is a major limitation in efforts to improve radiotherapy and to maximize patient benefits from recent advances such as proton bean therapy.

Hypothesis: Damage to functional brain subunits is responsible for observed changes in brain function in children treated with radiation therapy. These subunits can be identified using image-based data mining (IBDM) methods and used to develop prediction models for future interventions. **Aims:** We aim to identify the brain regions responsible for observed cognitive and endocrine phenotypes in childhood brain tumour survivors using IBDM in a large, clinically annotated cohort of childhood brain tumour survivors, and to validate our findings in an independent patient cohort and in an animal brain irradiation model.

Study design: Two independent, well annotated patient cohorts treated at the St Jude Children's Research Hospital, USA (n=200, test cohort) and the Christie Hospital, UK (n=200, validation cohort) will be studied. The pre-morbid imaging data for each dataset will be semi-quantitatively analysed to take account of variation in pre-treatment imaging appearances. IBDM involves morphing the pre-radiation MR images to a standardized reference anatomy, overlaying each patient's radiotherapy dose distribution and correlating the radiotherapy dose in each MRI voxel to specific outcomes. The primary outcomes for this study are processing speed and working memory. IBDM will first be applied to a test cohort and modelled, using Cox regression with relevant clinical and treatment variables and appropriate multiple testing correction, to identify the anatomical regions that explain most variation in outcomes. A risk prediction model will be built and validated in the validation cohort. In parallel, we will compare the functional and radiobiological effects of cranial radiation with X-ray photons and high energy protons in a three-week old rat model. Neurocognitive function will be assessed by a panel of behavioural tests and RNA sequencing of tissues sampled from different brain regions performed to identify structure- and radiation modality-specific genes and pathways associated with neurocognitive decline and radiation toxicity.

Clinical significance: Current radiotherapy planning is hampered by the absence of information about which brain structures should be avoided to reduce late toxicity, nor pre-morbid features that may be significant for long term outcome. This project's primary significance is its potential to identify

the brain regions that should be avoided and to change how cranial radiotherapy is planned. A secondary outcome is to identify pre-morbid imaging metrics that may inform longer term outcome. Additionally, better understanding of the cell biological effects of proton and photon radiation on immature brain components has the potential to deliver future therapeutic impact through intervening in the underlying biological pathways.