Minimising radiotherapy toxicities in soft tissue sarcoma of the extremities by developing radiotherapy planning dose-volume constraints for limb normal tissue structures

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PhD **in progress** and funded by HEE/NIHR clinical doctoral fellowship award

Background:
Soft tissue sarcomas of the extremities (STSE) are uncommon, representing 1% of cancers diagnosed in adults. Localized disease is curable, with 5-year survival rates of 50%.
Radiotherapy improves local control rates, however STSE survivors often develop significant side-effects (defined as ≥ grade 2 RTOG; grade 2+), which can impact heavily on their quality-of-life. The CRUK VorteX trial, comparing standard against reduced post-operative radiotherapy target volumes, has recently reported grade 2+ toxicity rates of about 50%, including subcutaneous (47% in standard arm and 41% in the experimental arm), bone (11% versus 15%) and joint (18% for both arms) toxicities.
A radiotherapy plan is calculated on a computed tomography scan, ensuring that the target volume (either the tumour or the tumour bed) receives a therapeutic radiation dose, while limiting the volume of neighbouring healthy (defined as normal tissue) tissues receiving significant doses to minimise side-effects. These radiation dose limits, called dose-volume constraints, allow clinicians to predict the likelihood of a given patient developing severe side-effects. Dose-volume constraints for STSE are currently unknown.
Pre-defined dose-volume constraints for prostate and head and neck cancers have been shown to mitigate the incidence and severity (grade) of side-effects. My research hypothesis is that dose-volume constraints will allow better prediction of toxicity for STSE.

Objectives:
The primary objective is to identify specific dose-volume constraints for anatomical regions of interest within the normal limb tissues lying outside the target volume predicting for the frequency and intensity of side-effects induced by radiotherapy for STSE.

Secondary objectives are:
a. Identification of anatomical regions of interest within normal limb tissues where delivery of high dose radiotherapy may result in specific toxicities such as fibrosis and lymphoedema;
b. Quantification of differences in the frequency and intensity of side-effects between 3D-conformal radiotherapy and intensity-modulated radiotherapy (IMRT).

Methods:
A statistical model predicting radiotherapy side-effects will be generated using prospectively collected radiotherapy specific normal tissue dose volume histograms and patient and clinician-reported toxicity data from CRUK VorteX and IMRiS, two of the largest radiotherapy datasets for STSE. VorteX has completed accrual and outcomes presented recently, and IMRiS will have mature data for analysis in 2019. I will then test the validity of this model in an observational study, using a prospectively recruited cohort of patients with STSE.

Timelines for delivery: 5 years