Mechanistic Simulation of Normal-Tissue Damage in Radiotherapy

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Radiobiological modelling is essential to the progress of clinical radiotherapy. The use of robust normal-tissue complication probability (NTCP) models has the potential to allow truly individualised treatment plans where the tumour control probability is not limited unnecessarily by the sometimes conservative application of techniques based on the response of a population.

In this thesis NTCP models and methods for analysing clinical data are tested on data simulated by a 3D mechanistic model of normal-tissue damage. This mechanistic model was developed to represent local tissue damage by functional subunit inactivation, and the overall organ response by a critical functioning volume (CFV). The size of the CFV varies between organs and depends on the volume effect, i.e. how large volumes of tissue damage are necessary to cause a complication.

The model complexity was guided by the degree of information available about the pathogenesis of radiation-induced side-effects. The model was used to generate pseudo-clinical datasets, which typically consisted of dose-volume histograms (DVHs) and binary complication information, for a large number of simulated treatments. Because all dataset characteristics and the 'biology' of the organs were known, studies on the simulated data could give insights into data analysis methodology.

It was demonstrated that correlation analyses between dose-volume parameters and outcome are strongly influenced by dataset characteristics, but that information about the volume effect of the organ can be gained if care is taken to identify all factors influencing the observed correlations.

The relative performance of several DVH-based NTCP models was explored for different levels of confounding factors, and it was found that model performance was influenced more by confounding factors than by the choice of model.

The 3D mechanistic model of normal-tissue damage, developed in this thesis, is a powerful tool for studying data analysis methodology and is also useful as a framework for summarising the radiobiological knowledgebase of normal-tissue effects in radiotherapy.

There is great potential to develop the model further to include e.g. non-local effects of irradiation, time effects, and several FSU populations, related to different endpoints, co-existing in one organ.