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Institutionen för Onkologi - Patologi

From cell survival to dose response - Modeling biological effects in radiation therapy

AKADEMISK AVHANDLING

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ABSTRACT

The main goal in curative radiation therapy is to eradicate the tumor while minimizing radiation-induced damage to normal tissue. Ions, including protons and carbon ions, are increasingly being used for cancer treatment. They allow for a more focused dose to the tumor and exhibit higher effectiveness in cell killing compared to conventional radiation therapy using photons. The aim of this thesis is to develop and evaluate mathematical models for biological effect estimation with the focus on proton and light ion irradiation.

Two radiobiological models for ions were developed. Firstly, the repairable-conditionally repairable damage (RCR) cell survival model was extended to account for the linear energy transfer (LET). Secondly, a model that estimates the relative biological effectiveness (RBE) of protons based on dose, LET, and cell type was derived. The LET-parameterized RCR model provides an adequate fit to experimental cell survival data derived from irradiation with carbon ions and helium ions. The RBE model predicts a cell-dependent relation between RBE and LET determined by the cell-specific parameter α/β of the linear-quadratic model of photons.

In a separate study, the effect of accounting for variable RBE in treatment plan comparison was investigated using the proposed RBE model. Lower RBE was predicted in the tumor and higher RBE in adjacent organs than the commonly assumed RBE equal to 1.1. Disregarding this variation and instead assuming RBE equal to 1.1 in treatment plan optimization may lead to optimistic estimates for the proton plan and thereby biases treatment plan comparison in its favor.

Derived dose response relations of normal tissue toxicity are uncertain because they are based on limited numbers of patients. A bootstrap method was proposed to assess the uncertainty in clinical outcome data due to sampling variability, and translate this into an uncertainty in the dose-response relation. The method provides confidence intervals of the dose-response relation, suggests model parameter values with confidence intervals and their interrelation, and can be used for model selection.

Keywords: Radiobiological models, proton radiation therapy, carbon ion radiation therapy, relative biological effectiveness, linear energy transfer, bootstrap.