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Modelling Late Toxicity in Hypofractionated Radiation Therapy

Development of Methods and Applications to Clinical Data

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Abstract

In hypofractionated radiation therapy (RT), the treatment is delivered by few fractions with high doses per fraction. This is in contrast to conventionally fractionated RT where the total dose is delivered in many fractions with low doses per fraction. Hypofractionation is increasingly used in RT for small tumour volumes, but knowledge about radiation-induced toxicity in healthy tissue (organs at risk, OARs) and suitable methods for modelling toxicity in this specific situation is limited. The aim of this thesis is to investigate radiation-induced toxicity in normal tissue caused by hypofractionated RT through the development of modelling methods and their applications to clinical data. Particular emphasis will be on the fractionation effect.

The thesis treats theoretical and practical aspects of normal tissue complication probability (NTCP) modelling such as radiobiologically consistent dose-response curves, how to estimate composite doses in combined radiation therapy with limited treatment information and how to manage situations where non-treatment-related factors contribute to a studied toxicity. The thesis also discusses how fractionation effects as described by the linear-quadratic model may affect the modelling procedure and the modelling results. The clinical applications involve two datasets with non-small-cell lung cancer (NSCLC) patients (n=26) or localized prostate cancer patients (n=874). Patients were consecutively treated at the Sahlgrenska University Hospital in Göteborg, Sweden, 1998-2005 and 1993-2006, respectively.

The first paper presents NTCP modelling results for radiation-induced rib fractures after hypofractionated SBRT for NSCLC. The results indicate that the high-dose region is more strongly associated with rib fracture than a low dose in a large volume.

The second paper presents a survey of 21 patient-reported genitourinary symptoms among prostate cancer survivors. The toxicity profile for survivors treated with the combination of conventionally fractionated external beam radiation therapy (EBRT) and hypofractionated brachytherapy (EBRT+BT) is similar to the toxicity profile for survivors treated with conventionally fractionated EBRT.

The third paper investigates urethral pain among prostate cancer survivors and finds that higher fractionation-corrected urethral dose corresponds to higher prevalence; no such relationship is seen for absorbed dose. Survivors with three years to follow-up report urethral pain more frequently than survivors with more than three years to follow-up.

The fourth paper suggests a method to estimate composite doses in pelvic OARs after prostate cancer EBRT+BT with limited treatment information. It was motivated by the lack of BT dose information in the prostate cancer dataset. The method produces robust estimations for OARs located far from the prostate, but estimations for OARs located close to the prostate may be less robust.

The fifth paper presents a relationship between mean urinary bladder dose (with or without fractionation correction) and urinary leakage for men treated with EBRT. Analyses are performed for survivors treated with EBRT and EBRT+BT separately as well as for the whole study population. Symptom background rates from non-irradiated controls were considered. Estimated composite urinary bladder doses by the method suggested in Paper IV are used for the EBRT+BT group.

Keywords: hypofractionation, normal tissue complication probability, modelling, linear-quadratic model, fractionation sensitivity, late toxicity, radiation-induced rib fracture, genitourinary toxicity, stereotactic body radiation therapy, high-dose-rate brachytherapy, multimodality radiation therapy, patient-reported outcomes, prostate cancer, NSCLC.