Can risk of radiotherapy-induced normal tissue complications be predicted from genetic profiles?

Christian Nicolaj Andreassen

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Official opponents: Lise Lotte Hansen, Niel G. Burn, England, Ulla B. Vogel, and Jens Overgaard.

Supervisors: Jens Overgaard and Jan Alsner.

Correspondence: Nicolaj Andreassen, Department of Experimental Clinical Oncology, Aarhus University Hospital, Nørrebrogade 44, 8000 Aarhus C, Denmark.

E-mail: nicolaj@oncology.dk

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ABSTRACT

Cancer patients exhibit substantial variation as to the severity of normal tissue reactions after radiotherapy. Various observations suggest that the individual risk of radiotherapy-induced treatment complications is influenced by genetic factors. However, only limited knowledge exists about the sequence alterations that may underlie differences in clinical normal tissue radiosensitivity among unselected cancer patients. The working hypothesis of this project is that radiosensitivity is influenced by single nucleotide polymorphisms in genes related to the biological response to ionizing radiation.

The project was based on a historic cohort of 319 breast cancer patients who have been given post-mastectomy radiotherapy during 1978-1982. The patients had been scored in detail with regard to several different normal tissue reactions. From a subset of 41 patients, fibroblast culture had earlier been established. From the remaining individuals, formalin fixed paraffin embedded tissue samples were the only available source of biological material for genotyping. In addition to these patients, an investigation was applied to a set of 52 British patients given radiotherapy after breast conserving surgery.

Within the 41 patients, seven SNPs in the genes *TGFB1*, *SOD2*, *XRCC1*, *XRCC3* and *APEX* were assessed. This investigation provided significant associations with enhanced risk of subcutaneous fibrosis for the *TGFB1* position -509 T, codon 10 Pro, *XRCC1* codon 399 Arg, *XRCC3* codon 241 Thr and *SOD2* codon 16 Ala alleles. In addition a complete screening of the *ATM* gene in the same patients provided indications that the *ATM* codon 1853 Asn allele may also increase fibrosis risk. The above-mentioned SNPs were assessed in another 120 patients from the historical cohort. In this study, the initial findings could not be replicated. In the cohort of 52 British breast cancer patients, the same set of SNPs were investigated. This study demonstrated significant associations with enhanced risk of altered breast appearance after post-lumpectomy radiotherapy for the *TGFB1* position -509 and codon 10 Pro alleles.

Overall, the present thesis, in conjunction with other studies carried out in the field, suggests that normal tissue radiosensitivity is under genetic influence and that SNPs in *TGFB1* and *ATM* may interfere with risk of particularly late toxicity. However, additional scientific work is needed to confirm this. These findings should encourage further efforts to unravel the genetics of radiosensitivity utilising novel high-throughput technologies in large well-powered clinical studies. The ultimate aim is to establish gene based predictive assays for normal tissue radiosensitivity and to develop pharmacological strategies against radiotherapy-induced morbidity.