Acute reactions in IMRT treated H&N cancer patients: association with DVH and SNPs in DNA DSB repair genes

J. Werbrouck[a], K. De Ruyck[b], F. Duprez[c], K. Claes[d], M. Van Eijkeren[c], T. Boterberg[d], P. Willems[a], A. Vral[a], W. De Neve[c] and H. Thierens[a]

[a] *Dept Basic Medical Sciences, University Hospital Ghent, Building B3, De Pintelaan 185, 9000 Gent, Belgium;* [b] *Ghent University, Proeftuinstraat 86, 9000 Gent, Belgium;* [c] *Radiotherapy Dept, University Hospital Ghent, Building P7, De Pintelaan 185, 9000 Gent, Belgium;* [d] *Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium*

joke.werbrouck@ugent.be

The aim of present study was to investigate the relation between physical dose related parameters and single nucleotide polymorphisms (SNPs) in DNA DSB repair genes XRCC3 (c.-1843 A>G, c.562-14 A>G, c.722 C>T), Rad51 (c.-3429 G>C, c.-3392 G>T), Lig4 (c.26 C>T, c.1704 T>C), Ku70 (c.-1310 C>G) and Ku80 (c.2110-2804 G>A) and development of acute normal tissue RT reactions. The study population consisted of 89 head and neck cancer patients treated with IMRT. All RT reactions were scored using the CTCAE scale for mucositis, dermatitis and dysphagia. The population was subdivided in a group with low and moderate radiosensitivity (CTC0-2) and a group with high radiosensitivity (CTC3) for each acute normal tissue effect. The polymorphic regions were analysed by PCR- RFLP or single base extension analysis (PCR- Snapshot). Analyses showed that if we compare the CTC0-2 and the CTC3 group, the mean dose to the oral cavity is significantly associated with the development of mucositis (p= 0.042). For dysphagia a statistically significant relation was found with the dose of the upper, mid and lower constrictor pharyngeus (CP) muscles. These physical factors are considered as confounding factors in the radiogenomics analyses of this study. The SNPs in the coding region of the XRCC3 gene (c.722 C>T) and in the 5' UTR region of the Ku70 gene (c.-1310 C>G) were significantly associated with the risk of developing severe dysphagia (CTC3) and can therefore be considered as risk alleles. Heterozygous carriers of the variant allele had a respectively 4.47 (p= 0.033) and 4.17 (p=0.014) increased risk to develop acute swallowing problems. We developed a risk analysis model using logistic regression analysis to predict patients probability to suffer from severe dysphagia as a result of the RT treatment. In this model the CP dose and the information regarding XRCC3 c.722 C>T and Ku70 c.-1310 C>G genotypes were included. Using a cut off value of two times the median, the model provided us a sensitivity of 78.6% and a specificity of 77.6% for prediction of severe dysphagia. No association between the investigated polymorphisms and the development of mucositis or dermatitis was found. Considering the dose to the CP muscles as confounding factor in a logistic regression model, presence of the variant allele of XRCC3 c.722 and Ku70 c.-1310 is significantly associated with development of dysphagia. Using the paramount physical and biological parameters, we developed a risk model for prediction of patients risk for severe dysphagia.

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