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Different DNA Damage Repair Rates in Blood Lymphocytes after Peptide Receptor Radionuclide Therapy and Radioiodine Therapy of Thyroid Cancer

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Objectives: Radiation-induced DNA double strand breaks (DSBs) cause, in their vicinity, the phosphorylation of the histone H2AX (then called γ-H2AX) and the accumulation of the 53BP1 protein that binds to and signals damaged chromatin at a DSB site. This leads to the formation of microscopically visible nuclear foci containing both markers, which thus mark radiation-induced DSBs. The aim of the study is to describe the time course of DNA damage in blood lymphocytes in molecular radiotherapy after internal irradiation with I-131 and Lu-177. Methods: We investigated blood samples of patients either after their first peptide receptor radionuclide therapy (PRRT) or their first radioiodine therapy (RIT) of differentiated thyroid cancer (DTC). The average frequencies of radiation-induced foci (RIF) containing both γ-H2AX and 53BP1 fluorescence were determined in the nuclei of two-colour immunostained γ-H2AX/53BP1 lymphocytes isolated from peripheral blood samples of patients before and after molecular radiotherapy (MRT). The foci containing both DSB markers were scored manually in a fluorescence microscope equipped with a red/green double-band-pass filter by an experienced observer. The individual background focus rate was determined in a sample taken prior to therapy. The EANM SOP for DTC was followed to determine the absorbed dose to the blood. The number of RIF as a function of time was described by combining a linear dose-dependent increase with a multi-exponential function characterizing different rates of DNA repair. Results: 283 blood samples (at least 6 per patient) of 36 patients (PRRT: 16, RIT: 20) up to 168h after therapy were evaluated. At late time points (10-12h) after therapy the decay of the average RIF number per cell is best described by a mono-exponential decay function with a decay constant of 0.04h-1. When the absorbed dose to the blood exceeded 20mGy in the first hour, only seen in patients with DTC, we observed the on-set of a fast repair component with a fast decay rate of 0.33h-1 resulting in a bi-exponential decay function. Conclusions: This analysis provides a comprehensive description of the time course of the number of radiation-induced DNA damage foci after molecular radiotherapy of beta emitters. It furthermore reveals a threshold dose for the induction of a fast repair component after in vivo DSB induction by incorporated I-131.