Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Second cancer risk after intensity-modulated and conventional radiotherapy in a small animal model

Autor: Kaga Gomarteli
Institut / Klinik: Klinik für Strahlentherapie und Radioonkologie
Doktorvater: Prof. Dr. F. Wenz

Introduction: Intensity-modulated radiotherapy (IMRT) involves exposure of large volumes of healthy tissue to a low-dose. This is thought to increase the risk of a radiation-induced second cancer (SC) compared to 3D-conformal radiotherapy (3D-CRT). As a consequence, patients with radiotherapy curable diseases such as pediatric and juvenile Hodgkin's Lymphoma (HL) are not treated with IMRT techniques thereby accepting high(er) doses to the heart and breast. The purpose was to test this dogma in cancer-susceptible rats irradiated either with a highly conformal volumetric-modulated arc therapy (VMAT, a rotational IMRT) or a conventional 3D-CRT in form of two opposite anterior-posterior / posterior-anterior (AP/PA) technique.
Methods: Heterozygous *Tumor protein 53* knockout rats belonging to four treatment groups of $n = 15$ animals each were irradiated with either 3×5 Gy or 3×8 Gy doses delivered with VMAT or AP/PA to a mediastinal planning target volume (PTV). Two control groups were given anesthesia only (AN, $n = 15$) or anesthesia with additional cone-beam computed tomography (CBCT) scanning (CBCT, $n = 15$). Animals were followed up to tumor detection using high-resolution CT. Tumors were scored according to the volume in which they occurred: low dose volume (LDV, receiving lower than 50% of target doses), bordering high dose volume (BHDV, 50% - 90%), high dose volume (HDV, > 90%) or non-irradiated volume (NIRV). Tumor and healthy tissues were characterized by histology. The analysis of loss of heterozygosity (LOH) of *Tp53*, were performed using Polymerase Chain Reaction (PCR) and sequencing. Tumor development after VMAT vs. AP/PA compared using Fisher's exact test, Kaplan-Meier analysis, and the Mann-Whitney test ($\alpha < 0.05$).
Results: In 84/90 animals, at least one tumor was detected, while six were lost due to other causes. In AN- and CBCT- control groups, all tumors were found in the body volumes corresponding to the NIRV of irradiated animals. By contrast ($p = 0.0001$), in the irradiated groups, 17/29 (after 3×5 Gy) and 16/28 (after 3×8 Gy) of all tumors were found in the volumes exposed to doses 0.75 – 24 Gy. The majority (23/33) of these irradiated volume-associated tumors were found inside the HDV, whereas only $n = 3$ tumors were detected in the BHDV and $n = 7$ in the LDV (combined 3×5 Gy and 3×8 Gy groups). Notably, no increased tumor induction was observed in the volume irradiated with VMAT compared to AP/PA (14/28 vs. 19/29, $p = 0.44$). The attained age from birth, for control rat groups and groups treated with 3×5 Gy were similar, while decreased significantly in 3×8 Gy VMAT ($p = 0.02$) and AP/PA ($p = 0.0005$) due to earlier tumor appearance compared to controls. A maximum decrease in time to tumor (TTT), from treatment to appearance, compared to AN/CBCT revealed for tumors within the BHDV/HDV after 3×8 Gy treatment ($p < 0.0001$). All lymphomas and most soft tissue sarcomas were specifically developed in the irradiated volume without regard to radiation doses and techniques. LOH was not significantly specific for tumors in the irradiated volume or for the shortening of the TTT, and no inflammatory background in irradiated rat lungs was observed.
Conclusions: The present results do not support the hypothesis that the enlarged low-dose volume generated in highly conformal radiotherapy techniques is associated with a higher SC risk. In contrast, the results show that higher local doses to normal tissue can accelerate the development of radiation-associated lymphoma and sarcoma, regardless of the RT technique used, LOH in tumors, or an inflammatory background in the lungs.