134

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THE NATURAL HISTORY OF ACUTE AND CHRONIC RADIATION INDUCED BLADDER DYSFUNCTION IN A RAT MODEL OF RADIATION CYSTITIS

Hypothesis / aims of study: Pelvic malignancies account for one-third of all new cancer diagnoses and up to half of all patients receive radiation therapy. Adverse effects include radiation cystitis, urothelial hemorrhage and ischemic bladder fibrosis. Little is known about the natural history of the acute and latent phases of radiation induced bladder dysfunction in conscious ambulatory rats. Our aim is to evaluate changes in lower urinary tract function over a 4-month period after a single dose of bladder radiation (0 Gy, 20 Gy, 30 Gy).

Study design, materials and methods: Twelve female adult Sprague Dawley (SD) rats were divided into three groups (n=4 per group). After institutional animal protocol approval, the bladder was identified by computed tomography and irradiated (0 Gy, 20 Gy, 30 Gy) using image-guided external beam radiotherapy. Nocturnal ambulatory (overnight, 12-hours per cage cycle) micturition frequency and voided volume were recorded using a 12-channel 100-gram load cell array (sensitivity 50 uL per void) and metabolic cages at baseline (day 0) and weekly following radiation (day 0 to day 123). Bladder function was assessed using urethane anesthetized cystometry at day 88 (two animals, 20 Gy), and the remaining animals at day 123. Data analysis was performed in SAS Studio (Cary, NC, USA) using ANOVA, Spearman correlation and generalized linear regression models to evaluate animals over time.

Results: There were 1,765 ambulatory voids recorded over the study time period, representing 162 animal cage cycles. Morbidity occurred in two animals in the 30 Gy group as a result of refractory radiation proctitis at day 32 and day 44, with high compensatory fluid intake and low body weight predictive of death. Ambulatory urinary frequency and mean voided volume demonstrated consistent trends in each treatment group over time. Each animal demonstrated a consistent voiding pattern at up to 16 metabolic cage time points. During the acute phase, radiation resulted in decreased mean voided volumes at day 19 (728 vs. 544 vs. 506 uL, ANOVA $p = 0.005$) and day 25 (701 vs. 515 vs. 542 uL, ANOVA $p = 0.007$) in the 0, 20 and 30 Gy groups respectively. Normalization of voided volume was noted in 20 Gy rats at day 32 after irradiation, with full recovery noted at 2 months. Ambulatory voided volume was reduced in all 30 Gy animals at all time points, and became significantly reduced after day 103, suggestive of the chronic phase of bladder dysfunction occurring at 3 to 4 months after bladder irradiation. Anesthetized cystometry at day 88 (3 months) in two 20 Gy rats demonstrated poor contractility, with elevated post void residual (range 709 to 1,139 uL), high threshold pressure and small volume voids noted. Cystometry at day 123 in the remaining two 20 Gy and two 30 Gy rats demonstrated a more pronounced weakly contractile bladder phenotype compared to day 88, with a consistently elevated post void residual noted in all radiated animals. On Spearman analysis, mean voided volume was significantly associated with food intake ($r = -0.41$, $p<0.001$), rat weight over time ($r = 0.27$, $p<0.001$) and stool output ($r = -0.58$, $p<0.001$); meanwhile overnight total volume of urine ($r = 0.05$, $p = 0.54$) and water intake ($r = 0.03$, $p = 0.74$) were independent from voided volume.

Interpretation of results: The acute phase of voiding dysfunction in rats occurs 3 to 4 weeks following 20 and 30 Gy of bladder radiation. At 30 Gy of bladder radiation, morbidity occurred in 50% of animals as a result of radiation proctitis. Recovery of bladder function is complete at 2 months in 20 Gy rats. At 3 to 4 months, chronic radiation bladder dysfunction occurs, with weakened bladder contractility and elevated post void residual noted in radiated animals.

Concluding message: Acute radiation induced bladder dysfunction subsided by 4 weeks post radiation. Chronic bladder dysfunction, with decreased contractility and elevated post void residual, developed at 3 to 4 months after both 20 and 30 Gy of bladder radiation.

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