Pelvic Irradiation Induces Two Bladder Phenotypes Which are Dichotomized at the 10 Percent Voiding Efficiency Threshold - Small Capacity End Stage Overactive Bladder and Large Capacity Underactive Bladder

Amy D. Dobberfuhl MD, Mason A. Briggs BS, Jan Wen MD, Edward C. Diaz MD, Edward E. Graves PhD, Shoucheng Ning PhD, Susan J. Knox MD PhD, and Bertha Chen MD

Dept. of Urology, Dept. of Radiation Oncology, Dept. of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA

BACKGROUND

RADIATION

• Pelvic malignancy accounts for a third of new cancer cases and up to half receive radiation therapy. (Deap et al, 2015)

• Radiotherapy: vascular compromise, obliterator endarteritis, ischemic fibrosis. (Pogrel et al, 2014)

• Little is known about the time course of chronic radiation induced bladder dysfunction in rats.

AIMS

RAT MODEL OF CHRONIC RADIATION CYSTITIS

• Estimate changes in ambulatory and cystometric lower urinary tract function during the chronic phase of radiation cystitis (at least 50 days after radiation injury).

METHODS

BLADDER IRRADIATION

• 56 female 80 rats. Bladder identified by CT and irradiated (FX X-Ray SmartART).

• 0 Gy (n=7)

• 20 Gy(n=22)

• 30 Gy(n=4)

• Void frequency and volume recorded in 24hr intervals using metabolic cages weekly (day 0-123).

• There were 6,078 ambulatory voids, representing 362 individual single cycle and 16 time points.

• Bladders assessed by terminal anesthesia cystometry.

• Data analyzed in SAS (Students t-test, Spearman correlation, Mixed effects model over time)

METABOLIC CAGE

• Nocturnal amylloby (overnight, 12-hours per cycle) mucosal frequency and void volume were recorded using a 12-channel 100-gam blad cell array (sensitivity 50uL per void) and metabolic cages at baseline and weakly following radiation.

CMBG - EMG

• Bladder function was assessed using urethane anesthesia cystometry. Bladders were filled (3 times) at 50-100 uL/minute until three stable productive contractions were observed.

RESULTS

Figure 2. BLADDER CYSTOMETRY

• 0 Gy (n=7) versus 20 Gy (n=22)

• Heterogeneous response to radiation noted on cystometry

• Radiated bladders (20 Gy) tended to have:

• Smaller capacity (p=0.095)

• Higher threshold pressure (p=0.925)

• Higher peak pressures (p=0.888)

• Similar amplitude (p=0.768)

• Smaller PVR (p=0.063) with larger variability in residual

• Clear differences in void volume when expressed as a percent of bladder capacity (p=0.001)

• All 0 Gy rats had void volumes less than 10% of their capacity

• Voiding efficiency >10% associated with more severe irradiated phenotype

Figure 3. 10% VOIDING EFFICIENCY THRESHOLD ANALYSIS

• Radiation (20 Gy, Day 50, n=17) induced two distinct phenotypes, at a threshold of 10% voiding efficiency

• VE increased >10% (n=9)

• Smaller capacity and stage bladder phenotypes >10% VE

• Higher amplitude (>40 cmH2O) contractions

• VE Normal <10% (n=8)

• High threshold pressures (>20 cmH2O)

• Ref: 0 Gy < 20 cmH2O

• Weak amplitude (<10 cmH2O)

• Ref: 0 Gy > 15 cmH2O

• Increased PVR (>700 uL)

• ? underactive phenotype

• Heterogeneous response to radiation needs to be considered when assessing bladder response to therapy in future models

Figure 4. HISTOLOGY

• Irradiated bladder (day 50)

• Sloughing urothelium

• Smooth muscle atrophy

• Intestinal expansion

• Urothelial hemorrhage

CONCLUSIONS

• After bladder radiation (20 Gy), acute dysfunction subsided by 1 month

• There were two distinct phenotypes of chronic dysfunction noted at 50+ days, a small capacity end-stage overactive bladder and a large capacity underactive bladder

• Further investigation is needed to understand the mechanisms of heterogeneity following external beam bladder irradiation

DISCLOSURES

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• Autopspopous IPSC -based therapy for radiation induced bladder injury

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