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

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BACKGROUND

PELVIC RADIATION

•Pelvic malignancy accounts for a third of new cancer cases and up to half receive radiation. (Siegel RL, 2015)

•Radiotherapy: vascular compromise, obliterative endarteritis, ischemic fibrosis. (Rajaganapathy BR, 2014)

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

AIMS

RAT MODEL OF CHRONIC RADIATION CYSTITIS

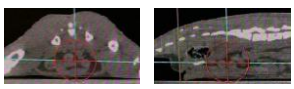
•Evaluate changes in ambulatory and cystometric lower urinary tract function during the chronic phase of radiation cystitis (at least 50 days after radiation injury)

METHODS

BLADDER IRRADIATION

•36 female SD rats. Bladder identified by CT and irradiated (PXi X-Rad SmART)

•0 Gy (n=7)
•20 Gy (n=25)
•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 cage cycles and 16 time points.
•Bladders assessed by terminal anesthetized cystometry.
•Data analyzed in SAS (Students t-test, Spearman correlation, Mixed effects model over time)

METABOLIC CAGE

•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 and weekly following radiation.

CMG / EMG

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

RESULTS

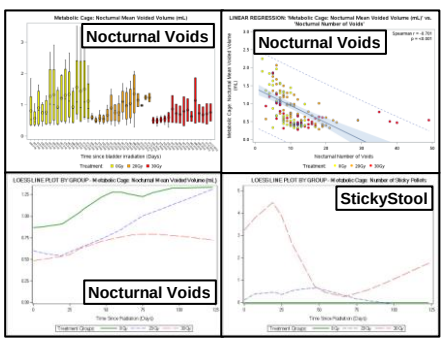


Figure 1. METABOLIC CAGE:

•Void volume inversely correlated to # of voids (r=-0.70, p<0.01)
•Urine output (r=0.05, p=0.54) and water intake (r=0.03, p=0.74) independent of void volume

Void volume correlated with:
•Food intake (r=-0.41, p<0.01)
•Rat weight (r=0.27, p<0.01)
•Stool output (r=-0.58, p<0.01)

Mixed effects model:
•Decrease in mean void volume after 20 Gy (p=0.014)
•Recovery of void volume only after 20 Gy (3 mo)
•50% mortality (30 Gy), radiation proctitis associated with sticky stool

RESULTS

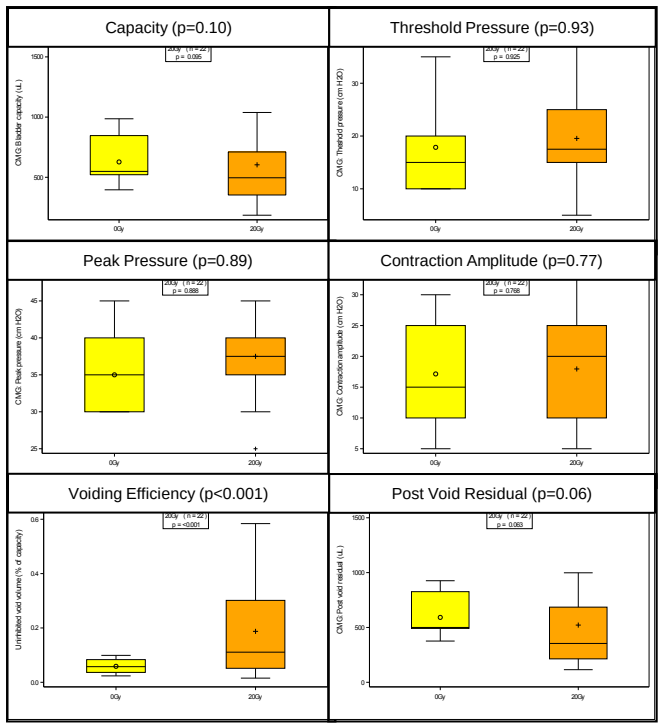


Figure 2. BLADDER CYSTOMETRY:

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

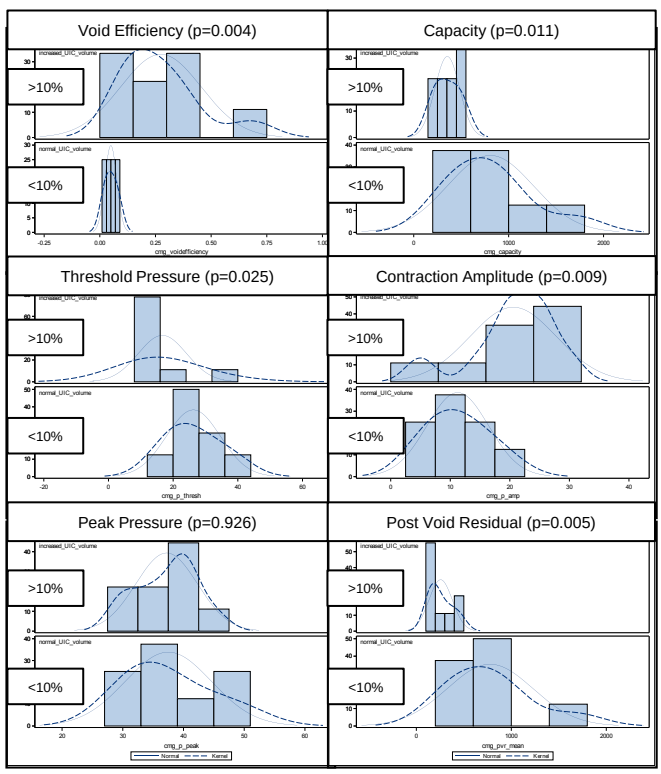


Figure 3. 10 % VOIDING EFFICIENCY THRESHOLD ANALYSIS:

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 end-stage bladders (>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

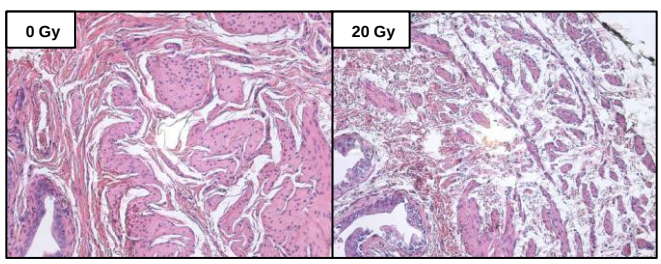


Figure 4. HISTOLOGY:

Irradiated bladder (day 50)
•Sloughing urothelium
•Smooth muscle atrophy
•Interstitial 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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