

STRIKING DOSE- AND TIME-DEPENDENCY OF RADIATION CYSTITIS IN THE RAT: REPEAT CYSTOMETRIC EVALUATION WITH SALINE ALONE AND POTASSIUM CHLORIDE CHALLENGE

Hypothesis / aims of study

Radiation therapy is the first choice for treatment of many pelvic visceral cancers. Two forms are currently employed, external beam radiation and brachytherapy. In the case of the former, ionizing radiation is directed at the afflicted organ and, in the latter, pellets of radioactive material are implanted at cancer lesion sites. The therapeutic mechanism of action is indirect (via reactive oxygen species) and direct damage to DNA of cancer cells. In non-replicating cells, this is not necessarily a lethal event, and DNA repair mechanisms may be utilized to repair the damaged DNA and maintain the terminally differentiated cells. In the case of cancers, where the cells are rapidly replicating and doing so before DNA repair mechanisms are able to correct the radiation-induced damage, this damage results in death of the cells during mitosis and thus elimination of the cancer.

Try as we might, it is very difficult to confine the effects of the radiation therapy only to cancer cells. Not only are other cells of the afflicted organ affected, but also cells from neighbouring organs. Unfortunately, cells which are required to replicate often in order to maintain function, such as epithelial basal cells, may also incur DNA damage. In the case of the mammalian urinary bladder, this leads to an imbalance of the urothelial turnover such that lost luminal "umbrella" cells which provide barrier function are no longer replaced by dividing basal cells at the same rate in which they are lost.

As one might predict, the disruption in epithelial turnover by radiation treatment results in a breakdown in urothelial barrier function. This breakdown in barrier function allows the high potassium and hydrogen ion levels normally found in urine to breach the barrier and gain access to the underlying non-luminal epithelial cells, as well as sentinel nociceptor afferent neuronal terminals and other submucosal cell types, such as resident mast cells and myofibroblasts. All of these cell types are known to release neurotransmitters, neuroeffectors, cytokines and other paracrine factors which result in inflammation. Once initiated, the condition may progress in a positive feedback fashion until finally resolved.

Post-radiation cystitis arising from pelvic cancer radiotherapy occurs frequently and is characteristically expressed in two phases. The first phase arises soon after treatment and is likely due to free radical formation during irradiation. This phase resolves within a few months and is followed by a much later cystitis, often haemorrhagic, occurring many months following resolution of the acute phase.

As a first step toward developing therapies to prevent or treat radiation cystitis, we are developing a rodent model

Study design, materials and methods

Female Sprague Dawley rats (250-275 g BW) received chronic bladder catheters via surgical implantation [1]. Briefly, the bladder was exposed via a midline laparotomy and a PE50 flame-flared catheter tip was inserted into the dome and secured using a silk tie. The catheter tubing was then tunnelled subcutaneously, and exited through a small incision at the base of the neck. The catheter was flushed with antibiotic solution (1 mg/ml gentamicin sulphate), flame sealed, and placed in a subcutaneous pocket for future access. All incisions were closed with surgical clips.

One week after catheter implant, the animals received single dose bladder irradiation with 0, 5, 10 or 20 Gy using a cone-beam CT image guided irradiator. Every week for 4 weeks thereafter, bladder function was evaluated by conscious restrained cystometry with infusion of normal saline, and 300 and 500 mM potassium chloride (KCl). Two days following the final cystometry, bladders were harvested and banked for histology and proteomics. Our primary outcome measure is cystometric functional bladder capacity (FBC or intermicturition interval) during each infusate at each weekly post-irradiation time point. Data was analysed using 2-Way ANOVA, $p < 0.05$ was considered significant.

Results

Statistical analysis reveals a marked and significant inverse relationship between radiation dose and FBC. The 5 Gy dose was without effect on FBC. The 10 Gy dose was also without effect until week 4, when FBC was reduced by ~30% under saline infusion. The 20 Gy dose resulted in a ~50% reduction in FBC under saline by Week 1 that further evolved to a ~60% reduction by Week 4. Furthermore, KCl sensitivity was evident by Week 1 following 20 Gy exposure. By week 4, KCl reduced FBC to ~50 and 25% of control in the 10 and 20 Gy groups, respectively.

The greater effect of higher doses (10 and 20 Gy) of radiation on bladder function was qualitatively reflected by the effect of these doses on body weight gain over the course of the experiment.

Interpretation of results

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The greater effect of higher doses (10 and 20 Gy) of radiation on bladder function was also qualitatively reflected by the effect of these doses on body weight gain over the course of the experiment.

Concluding message

We have provided the first longitudinal cystometric study of the effects of pelvic radiation on lower urinary tract function and, in so doing, have demonstrated a dose- and time-dependent effect of single dose irradiation. Future studies will be directed toward further validation of the model, the testing of potential prophylactic and therapeutic treatments, and the extension of post-irradiation survival into the second, chronic phase of radiation cystitis.

References

1. Yaksh TL, Durant PA, Brent CR. 1986. Micturition in rats: a chronic model for study of bladder function and effect of anesthetics. Am J Physiol. 251:R1177-85.

Disclosures

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