A novel mouse model to study image-guided, radiation-induced gastrointestinal injury and its application to preclinical research

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Radiation is a major treatment modality in cancer, however the therapeutic dose is often limited by gastrointestinal toxicity. The prevailing animal models for studying the effects of radiation on the gastrointestinal tract are limited in their physiological relevance. As such, we propose a model in which a radiopaque marker is surgically placed onto the surface of the intestine. The animal is then imaged with a cone beam CT to identify the location of the marker. X-rays are then administered targeted to the marker site using the Small Animal Radiation Research Platform (SARRP®). In this study, C57Bl/6 mice were administered a single dose of 12, 18 or 24 Gy of x-rays before being sacrificed at designated time points to obtain samples for histology and cytokine analysis. γ-H2AX, EdU, and TUNEL immunofluorescence assays were conducted to assess damage in tissue samples taken from the marker site, proximal to the marker site and distal to the marker site. All three stainings indicated that radiation damage was localized to the marker site. Furthermore, H&E staining supported this result suggesting that the irradiation was able to be successfully targeted to the marker site. A cytokine panel showed increased inflammatory cytokines on the marker site when compared with the proximal and distal to the marker site. Overall, there was an 86% survival rate following the surgery and animals maintained weight well. Interestingly, in the 24 Gy group there were no deaths associated with the high radiation dose, thus indicating a potential volume effect of radiation damage to the small intestine. To test the efficacy of this model in studying radioprotectors, a cohort of mice was administered curcumin by oral gavage from three days prior to irradiation until seven days post-irradiation. These animals showed reduced acute damage and significant reduction in IL-6 levels soon after irradiation, as well as reduced fibrosis 4 months post-irradiation when compared with animals administered a control solution. This data indicates that this model may be a powerful tool in studying radiation response modifiers and radiation pathology in the gastrointestinal tract.