A novel mouse model to study image-guided, radiation-induced intestinal injury and preclinical screening of radioprotectors
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Abstract
Radiation is an important treatment modality for gastrointestinal tumors, but intestinal injury is a common side effect. We developed a physiologically-relevant model for studying the molecular determinants of radiation-induced intestinal damage and testing novel radioprotectors. The model employs a radiopaque marker implanted onto the surface of the mouse jejunum serving as a fiducial marker for precise radiation targeting. Mice were imaged with Cone-Beam CT (CBCT) and irradiated to the marked area using the Small Animal Radiation Research Platform (SARRP©). Cohorts of mice were sacrificed at different timepoints post-RT and molecular markers of DNA damage and cell fate were analyzed to assess radiation damage. Intestinal lysates and plasma were also collected to assess inflammatory cytokine levels. Our results indicate that the IR-induced damage is acute but reversible and largely restricted to the area of the marker, leaving the surrounding tissues intact. Intriguingly, although whole gut irradiation with these doses causes lethal GI syndrome, focal (5mm) radiation of the intestine did not cause any weight loss or lethality. However, fibrosis and collagen deposition 4 months post-IR indicated chronic intestinal damage. A separate cohort of mice was treated daily with curcumin, a clinically-tested radioprotector, prior to and post-IR. Curcumin-treated mice showed significant decreases in both local and systemic inflammatory cytokine levels and in fibrosis suggesting it is effective as a radioprotector of the intestine. Our results indicate that this model, which emulates closely clinically relevant intestinal radiation-induced injury, can be used to assess radioprotectors prior to testing in the clinic.