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The significant role of radiation therapy in the management of cancer requires a better understanding of this powerful therapeutic modality. The advances in imaging and radiation delivery technology promise to make this intervention more patient-specific with design of therapy based upon biological images and, furthermore, routine design of therapy progress. This complex interplay between the radiotherapeutic insult and the evolving biological processes will stress current models of RT effect and, ultimately, the current weak models will limit the potential for full exploitation of RT. The developments in small animal irradiators represent an important initiative to improve our understanding of RT. These developments also occur in the basic cancer research field challenging *in-vitro* and non-orthotopic assessments of radio-effect. Furthermore, image-based methods of evaluating the micro-environment are being recognized as necessary input to normalize the results of RT intervention. These trends suggest that animal irradiation systems are likely to play a central role in the development of robust models for radiotherapy effect.