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Introduction

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Technological advancements in Radiation Oncology have occurred at an impressive pace over the past few decades, fundamentally altering the practice of radiotherapy. The development of modern imaging modalities has enhanced our certainty of tumor location and extent. Simultaneously, radiation treatment delivery has undergone a revolution of conformality spurred by techniques such as intensity-modulated radiation therapy, image-guided radiation therapy, and proton therapy. The proliferation of these techniques into clinical practice has not only led to enhanced certainty of the accuracy of daily tumor targeting, but has also led to the capacity to more effectively exclude critical normal tissues from the high-dose region of treatment plans. This, in turn, has further encouraged interest in radiation dose escalation in some settings.

Although these changes have, on balance, reduced the rates of normal tissue injury in several clinical series reported across multiple tumor sites, normal tissue injury does indeed still occur as a consequence of treatment. The lack of capacity to accurately predict which patients are at highest risk of injury prospectively remains a deficiency. The ability to effectively manage and alleviate late toxicities of radiation therapy continues to be a source of frustration for practitioners and their patients. Despite our best attempts to treat tumor and exclude normal tissues, we cannot be blind to the reality that all tumors arise in a bed of normal tissue, and thus necessitate at least some normal tissue exposure. Normal tissue injury has important consequences to our patients and care providers, both in the short and long term. Acute toxicity limits treatment efficacy: treatment tolerance and treatment breaks due to toxicity are clearly tied to treatment outcome. Late injury from radiation, although thankfully rare, is often challenging to manage and frequently irreversible.

Improving outcomes for our patients relies on a continued concerted effort to understand, prevent, and alleviate radiation-induced normal tissue injury. It has become increasingly apparent that normal tissue complications of radiation share striking similarities to other chronic injury and inflammatory processes, and that understanding the underlying biology may not only lead to effective therapies, but also to an understanding of a number of diseases characterized by chronic inflammation. It has also become evident that understanding the risk of a given radiation exposure to an organ must consider the complexity of the tissue, not just in the hierarchy, but also in dose distribution relative to that hierarchy, a concept resulting from the use of techniques using extreme hypofractionation with rapid dose fall-off, such as stereotactic approaches.

This issue of *Seminars in Radiation Oncology* highlights recent advancements in the understanding and management of radiation-induced normal tissue injury. The intent of this

collection is to integrate multiple aspects of ongoing research with current best practices into a useful guide for clinicians, radiation biologists, physicists, and students of radiation oncology. In this issue, articles focusing on acute and late radiation toxicity observed in specific regions of the body are included that highlight common manifestations of injury and their management. In addition, an overview of radio-genomics reviews the promise and limitations of individual prediction based on genetic predilection to radiation injury. Additional nongenomic biomarkers of injury, including imaging of injury, are presented. Finally, recent advances in understanding the biology of radiation injury are highlighted.

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