Editorial

The accelerating quest for optimal radiation and immunotherapy combinations for local and systemic tumor control

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Comment on: Zhang X, Niedermann G. Abscopal Effects With Hypofractionated Schedules Extending Into the Effector Phase of the Tumor-Specific T-Cell Response. Int J Radiat Oncol Biol Phys 2018;101:63-73.

Received: 19 July 2018; Accepted: 16 August 2018; Published: 24 August 2018.

doi: 10.21037/tro.2018.08.04

View this article at: http://dx.doi.org/10.21037/tro.2018.08.04

Current radiotherapy protocols have been empirically developed based on radiation-induced cell death and maximum tolerable dose concepts. Incremental improvements in radiotherapy protocols with each iteration of clinical trials have continued because they have produced reasonable outcomes. However, the concept of adaptive therapy allowing optimized novel treatments to achieve biological efficacy at significantly lower doses may be applicable to radiotherapy (1). As our biological knowledge has evolved, we have the opportunity and responsibility to challenge the very core of current practice. It is increasingly appreciated that radiation can induce robust antitumor immunity that provides a second wave of cell kill and tumor regression (2,3). Radiation increases the mutational burden and induces cell stress as well as immunogenic cell death, thereby exposing a wealth of *de novo* tumor-associated antigens, stress proteins, and danger-associated molecular patterns to the immune system (4,5). In this context, the role of radiotherapy is no longer simply confined to direct cell killing, and understanding the complex, non-linear cytotoxic and immunologic consequences of radiation is of pivotal importance to fully exploit the therapeutic efficacy of radiotherapy.

The concept of maximally tolerable dose to increase log cell kill to eradicate as many cancer cells as possible has been the prevailing dogma derived from numerous dose escalation studies. Increasing data suggest, however, that more radiation may not always be better (6). The effectiveness of radiotherapy in eliminating the cancer is likely a combination of the direct lethal effect of radiation on the tumor and, possibly more importantly, the subsequent indirect effect of stimulating a successful antitumor immune response. This has initiated the quest for the optimal radiation dose, dose fractionation, and sequencing with biological agents to maximize synergy with biological consequences of radiation (7). Pioneering studies by Dewan *et al.* have shown that hypofractionated radiation induces stronger immune responses than single dose radiation (8). This, however might not be generalizable and could be highly specific to the chosen cancer cell line and mouse model. Other studies have demonstrated that single ablative radiation doses best perturb immunosuppressive microenvironments to enable subsequent antitumor immunity (6). Previous studies suggest that radiation-induced infiltration of CD8+ cytotoxic T lymphocytes peaks at 5–8 days after hypofractionated doses (9). Protracted radiation has been assumed to be detrimental to antitumor immunity, as CD8+ T cells as well as most of other immune cells are highly radiosensitive.

The recent study by Zhang and Niedermann (10) demonstrates that hypofractionation protocols that extend into the immune response phases may not be as inferior to shorter treatments as previously thought. Biologically equivalent doses of 3×9.18 Gy given in three or five days as well as 5×6.43 Gy over 10 days in combination with anti-PD-L1 has showed comparable tumor-specific T cell infiltration into the radiation-targeted tumor as well as metastases outside the radiation field. While hypofractionated regimens are currently the mainstay of combining radiation with immunotherapy, there are clear

examples of clinical abscopal effect with a more protracted course of radiation therapy (11). Both local and systemic responses however were severely diminished with inhibition of T cell egression from the tumor draining lymph nodes. Lymph node sparing may thus offer a novel strategy to deliver radiation given with the intent to maximize synergy with the immune system, which is in direct contradiction to our current practice to irradiate the tumor draining lymph nodes which likely harbor metastatic tumor burden.

The fields of radiation biology, immunology, and radiation oncology are collecting a wealth of exciting data that both support and challenge our understanding of the biology underlying the responses seen in the clinic. Of utmost importance in the immediate future becomes the search for the optimal treatment combinations to eradicate the radiation-targeted tumor and induce robust systemic immunity to dwarf metastatic disease. Only few protocols have been modeled experimentally due to logistic limitations, and even fewer have been evaluated prospectively in the clinic. The study by Zhang and Niedermann demonstrates the acute need to further map out the vast unchartered territory of possible treatment combination, including those that have previously assumed to be non-synergistic. To exhaustively evaluate every possible (I) dose and (II) dose fractionation (III) with and (IV) without the growing number of immunotherapeutic agents in (V) different orders and (VI) at all possible timings (VII) *in vitro*, (VIII) *in vivo* and (IX) clinically is elusive. To fully decipher the complex dynamics of dose and time-dependent radiation-induced immunity, a concerted effort is needed that integrates disciplines that have not traditionally been consulted in experimental design and clinical studies. Mathematical modeling may provide the necessary tools to provide a mechanistic understanding of the many biological players and their interactions (12-16). The available preclinical data and outcomes from clinical studies are poised to help formulate, calibrate and validate purposely-built mechanistic mathematical models. Such models can then be used to simulate previously untested treatment protocols. Using machine learning and optimization theory concepts can then help identifying treatment approaches with the highest likelihood of success for subsequent experimental evaluation and validation.

Whilst truly exciting and necessary, the translatability of these approaches into precision radiation oncology is still afar. Zhang & Niedermann's results clearly demonstrate that tumor specific antigen presentation and generation of a robust antitumor immunity are required to successfully shrink tumors. Intrapatient heterogeneity in antigen presentation between the primary tumor and metastatic nodules as well as even higher interpatient heterogeneity may likely yield optimal protocols that must be specific not only to the targeted cancer but also specific to each patient. Hypofractionated protocols that further extend into the immune recruitment phases yet yield responses comparable to shorter protocols paves the way into investigation of many more combination of radiation and immunotherapy approaches to ultimately enrich the arsenal of available treatment options that may at some point become optimized for individual patients.

Acknowledgments

This work is supported in part by a 2017 Miles for Moffitt Award.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Hsin Hua Nien (Department of Radiation Oncology, Cathay General Hospital, Taipei).

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tro.2018.08.04
Cite this article as: Enderling H, Kim S, Pilon-Thomas S. The accelerating quest for optimal radiation and immunotherapy combinations for local and systemic tumor control. Ther Radiol Oncol 2018;2:33.