Radiation therapy and the abscopal effect: a concept comes of age

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Submitted Jan 06, 2016. Accepted for publication Jan 18, 2016.
doi: 10.21037/atm.2016.01.32
View this article at: http://dx.doi.org/10.21037/atm.2016.01.32

The concept of utilizing localized radiation therapy to elicit out-of-target tumor responses—the abscopal effect—was proposed over 50 years ago (1,2). Over the past decades, the abscopal mechanism has been elucidated by the work of many investigators, including Formenti and Demaria, who showed that this process was likely mediated by the immune system leading to immunogenic tumor cell death, a process which involves dendritic cells, T regulatory cells, and suppressor cells as critical mediators (3-5). This research was inspired by the hypothesis that targeted radiotherapy in the proper setting can produce a consistent and robust abscopal effect, thus delivering clinically meaningful anti-tumor responses and disease control, if not eradicating distal disease in patients with metastatic cancer. The recent successes of several immune check point inhibitor clinical trials in various malignancies have demonstrated wide applicability and enormous therapeutic potential of immunomodulation and have galvanized keen interest in this field (6-10). An ambitious goal of combining radiotherapy and immunotherapy in the clinic would be long term remission for cancer patients with metastatic disease, perhaps through an approach analogous to delivering an *in-situ* anti-tumor vaccine (11-13).

In this proof-of-principle clinical trial, Golden and colleagues are the first to demonstrate that abscopal responses can be consistently detected in patients with confirmed solid metastatic cancer treated with radiation therapy and immunotherapy (14). All of the enrolled 41 patients had to have stable or progressing disease to standard systemic treatments and at least three distinct sites of measurable disease. These patients would then be maintained on their previous standard systemic regimen and receive granulocyte-macrophage colony-stimulating factor (GM-CSF) administered subcutaneously. The patients would receive fractionated irradiation (3.5 Gy × 10 daily fractions) to one of these measurable lesions. Non-irradiated lesions were then assessed either by physical examination or by CT scans 7–8 weeks from the start of treatment. An abscopal response was defined as an at least 30% reduction in size from baseline in any measurable non-irradiated lesion.

Golden *et al*. showed that 27% of the patients treated with this regimen demonstrated abscopal responses. Furthermore, those patients who developed an abscopal response had better overall survival (21 *vs*. 8 months). While there were a diverse set of solid tumor types in the study, the two best represented groups were non-small-cell lung cancer patients and breast cancer patients. The publication is the first reported study to date with long term results that validates the concept of synergistic interactions between radiotherapy, chemotherapy, and GM-CSF. One key interpretation of these results is that the concurrent use of GM-CSF and fractionated radiation, when combined with systemic treatment, can stimulate the patient's immune system to overcome immune tolerance. This study also showed that administering GM-CSF with the other modalities was safe and tolerable, and that further developing this combination treatment paradigm holds great promise. Building on this work and other studies, numerous centers worldwide are currently testing strategies that combine radiotherapy and immunotherapy (15,16).

A perplexing question is why the abscopal effect does not occur more frequently in patients receiving radiotherapy. A plausible explanation is that radiation treatments in different settings can be either immunosuppressive or immunostimulatory depending on tissue and tumor context, and the host anti-tumor immune response is often regulated through a tight network of opposing stimulatory and inhibitory signals (17,18). This study and other studies

suggest that a permissive tumor/host environment and an appropriate set of immunomodulatory events at the proper timing may be necessary to trigger an abscopal response (19,20). We are only beginning to realize the complexity of these pathways and their interactions and find ways to enhance the anti-tumor immune response. For example, several novel categories of targeted immunomodulators have recently been developed. They include TLR agonists, TGF-β antagonists and the immune checkpoint inhibitors, anti CTLA-4, anti PD-1, and anti PD-L1/L2 agents, which have re-kindled hope for successful cancer immunotherapy (21-24). There are numerous other potential immunomodulatory agents in the investigational pipeline. Some studies suggest that multiple immune mechanisms need to be targeted, and that dual immune checkpoint blockade together with radiotherapy might be necessary to elicit the optimal abscopal response (25). With a deeper understanding of mechanisms underlying tumor immune regulation, future strategies may be able to produce clinically meaningful abscopal responses more consistently.

The successful clinical demonstration of abscopal responses also shifts the treatment paradigm for radiation oncologists. The traditional goal of radiotherapy is to eradicate local disease by maximizing direct tumor cell killing while minimizing nearby normal tissue damage (26). Most of the research effort in radiation biology has been focused on understanding the mechanisms underlying DNA damage and repair pathways, cellular repopulation, and tissue re-oxygenation (27). In patients with metastatic disease, it has been widely accepted that the standard treatment for distant disease is from the administration of chemotherapy, hormonal therapy, or biologic targeted agents. Combining radiotherapy with immunotherapy shifts the focus from direct tumor kill to immunomodulation, which is at least in part due to broadened neoantigen exposure, thus memory T-cell repertoire expansion, T-cell infiltration into tumor and enhanced T-cell mediated tumor rejection (28-30). The optimal dosing, fractionation, and target volume determination could be quite different from classic radiotherapy paradigms.

In summary, this study by Golden and colleagues provides a foundation moving forward to explore a wider range of clinical strategies to be tested in clinical trials for metastatic cancer. Many important questions will need to be addressed. First, how can we best determine and monitor abscopal responses? Second, what impact do other modalities e.g., radioablation, electroporation, particle radiation such as protons or carbon ions, have on the abscopal effect? What systemic and immunomodulatory agents should be used and how should they be timed with the radiotherapy? What is the best disease site to irradiate in order to elicit the maximal abscopal response? Should short, large fractions of radiation be used or will longer, smaller fractions be better? These questions and others are actively being addressed in clinical studies. As the reviewed work and others in this rapidly moving field demonstrate, combination radiotherapy and immunotherapy represents an emerging treatment modality that may alter the natural history of solid malignancies.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by Section Editor Hongcheng Zhu, MD, PhD (Department of Radiation Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Ng J, Dai T. Radiation therapy and the abscopal effect: a concept comes of age. Ann Transl Med 2016;4(6):118. doi: 10.21037/atm.2016.01.32

