Implications of the Bystander and Abscopal Effects of Radiation Therapy

Vivek Verma M.D.¹ and Steven H. Lin M.D. Ph.D.²

¹Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA
²Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Running Head: Bystander and Abscopal Effects of Radiotherapy

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*Corresponding Author:
Steven H. Lin, MD PhD
Department of Radiation Oncology
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Blvd, Unit 097
Houston, TX 77030
Phone: 713-563-8490
Fax: 713-563-2366
Email: shlin@mdanderson.org
SUMMARY

Siva and colleagues have demonstrated that localized thoracic radiation resulted in DNA damage at out-of-field sites. Though these interesting findings require validation, we discuss the important clinical implications of this data, especially in the era of immune therapies.
In this issue of *Clinical Cancer Research*, Siva and colleagues describe evidence of DNA damage to not only peripheral blood lymphocytes coursing through the irradiated thorax, but sustained DNA damage repair as showed by γH2AX foci within eye brow hair follicles far outside of the irradiated area (1). Several cytokines are implicated to at least partially mediate these apparent bystander effects. While the finding is an elegant portrayal of this phenomenon, it may have profound implications for both normal tissue toxicity prevention and cancer therapy.

Cases of the out-of-field “systemic effects” of radiation therapy exerting tumoricidal control at distant sites, known as the “abscopal phenomena”, have been sporadically described for decades (2) and are likely contributed by complex interactions of the immune system with localized inflammation induced by radiotherapy, including through both T-cell and cytokine signaling (3). The proposed mechanisms, likely similar to what is responsible for the bystander effect on normal tissue, are likely overly simplistic (Figure 1), but generally involve local tumor ablation, antigen presentation, and inflammatory mediators. The resultant systemic effect may produce generalized symptoms that patients often experience during protracted course of radiotherapy (e.g. fatigue, anorexia). In the current study (1), it is still uncertain how DNA damage as measured by γH2Ax foci in hair follicle cells is generated. However, unlike peripheral blood lymphocytes (PBL) which developed measurable γH2Ax foci at 1 hour that mostly disappears at 24 hours, eye brow hair follicle cells developed DNA damage starting at 24 hours after the first fraction, and persisted even 4 weeks into radiotherapy, and nearly recovered to basal levels by 3 months after radiation therapy. The initial delay and sustained time course suggests systemic inflammatory effects possibly mediated in part by cytokines and/or inflammatory cells gathering at distant sites away from the irradiated zones, although the authors didn’t comment on whether these inflammatory cells could be seen in the vicinity of the hair follicle. MicroRNA and exosomal signaling may also be involved, though the authors couldn’t find evidence to support the latter. It is known that certain inflammatory cytokines can mediate DNA damage response through elicitation of nitric oxide (NO) generation by inducible NO synthase (iNOS) (4). Interestingly, iNOS is an enzyme induced in activated monocytes and macrophages, and the authors discovered that CCL3 was significantly upregulated at 4 weeks that was dose-independent, much like the γH2Ax foci in the hair follicles. It is known that CCL3 and iNOS are coexpressed in activated macrophages, and CCL3 plays a role in inflammatory responses through binding CCR1 and 5 in mediating radiation induced lung injury (5). Whether this is the mechanism mediating this response in distal sites in the hair follicles is uncertain; possible future studies could explore the role of activated macrophages or iNOS expression in distant unirradiated areas.

While it is known that an intact immune system is important for radiation killing effect on tumors (6), it could very well be that indirect damage to normal tissues by the immunologic and inflammatory response may manifest as “silent” toxicities that could result in an increased risk of secondary malignancy in the appropriate patient populations, since the level of inflammation produced could be related to genetic susceptibility of individuals. We acknowledge that it may be questionable that such small numerical increases in DNA damage foci may portend to clinically evident increase in toxicity or radiation-induced neoplasms, especially with the 3-month time course as seen in the data. However, the “silent” toxicities experienced by highly radiation-sensitive tissues such as the bone marrow and gonads may very well have stochastic and long term implications. Inflammatory mediators may modify gene expression via transcriptional and/or epigenetic mechanisms. Importantly, these
alterations can occur in “bystander” germ cells, potentially creating a major conduit for predisposition of radiation-induced malignancies in future generations (7).

The most logical extension to the present work is to ask the question to what extent similar DNA damage occurs in other locations and organs. Radiation modality, tumor histology and volume, location, timing of immunotherapy with radiotherapy, and the patient’s immune microenvironment may play a role, among numerous other factors (8). Furthermore, it has been recently reported using mathematical modeling that different tumor locations may be more “immunogenic” than others (9). The model encompasses several factors, not limited to physiologic blood flow and imprinting of T cells by antigen-presenting cells. Despite the virtual nature of the work, the prominent theme remains that factors increasing T-cell trafficking to metastatic sites may be most associated with likelihood of observing an induced abscopal response. Similarly, it remains to be deduced whether particular “bystander” sites have greater proclivities to receive DNA damage from inflammatory mediators. Moreover, studies have shown that these phenomena may occur with large, ablative doses (10); albeit in different treatment conditions, others have not validated this notion (11). While many tumors are radiotherapeutically treated using hypofractionated regimens, it would be of great importance to assess whether these regimens produce altered levels of post-irradiation inflammation as compared to conventional fractionation.

Furthermore, the exploding field of immunotherapies has generated feverish interests in whether abscopal responses could be harnessed for cancer therapy, with ever burgeoning numbers of combination radiation-immunotherapy trials. The historically unreliability of a “systemic anti-cancer effect of radiotherapy” appears to be more reproducible with the combination of immunotherapies such as the immune checkpoint inhibitors. A seminal study by Golden et al. illustrated the most consistent detection of the abscopal phenomenon to date, in 11/41 (27%) prospectively-treated patients with various metastatic cancers (12). One of at least three actively metastatic lesions was irradiated (35 Gy/10 fractions), and granulocyte-macrophage colony stimulating factor (GM-CSF) was co-administered. GM-CSF by itself is not expected to generate any tumor response; however, the median survival of patients demonstrating an abscopal response (defined as ≥30% size reduction) experienced nearly threefold increased survival (21 vs. 8 months). This is the strong rationale to use when similar approaches are being considered for oligometastatic cancers, as well as high risk non-metastatic cancers, to enhance “cures”. However, we must proceed cautiously, as immune activation that works great for the abscopal effect will likely also exacerbate the bystander effect, to exert degrees of systemic normal tissue toxicities beyond what immunotherapies are causing by themselves.

In summary, Siva et al. have demonstrated the radiation bystander phenomenon manifested as persistent DNA damage foci in the hair follicles well outside the irradiated zone in the thorax. While this may be understood as the end result of the systemic inflammation that is induced by localized radiotherapy, much needs to be learned about the mechanism and long term consequence of this effect. The present study is a demonstration that systemic normal tissue injury likely occurs alongside the “abscopal effect”, with ablative radiotherapy as the “fire starter” in the presence of cancer immunotherapies. The clinical implications of this interesting work for both oncogenic treatments and normal tissue toxicities, especially in this era of immune-stimulation therapies, cannot be overstated.
REFERENCES


Figure legend

Figure 1. Simplified mechanism of how local radiation may induce a bystander or abscopal effect to cause DNA damage at distal sites. Radiation induces a number of changes during the cell killing process that can elicit a number of inflammatory mediators from the dying cancer cell that either attract or activate immune-related cells with the tumor microenvironment. These cells can generate additional cytokines that act locally and circulate systemically or propagate either hematogenously or lymphatically to act on normal tissues and tumor cells located at distant sites apart from the irradiated primary tumor.
Figure 1:

- **DNA damage to distant tumor cells**
- **DNA damage to “bystander” cells**
- **Systemic propagation**
- **Production of cytokines**
- **Coordination of tumoricidal immune response**

**Radiation**

**Cancer cell**

**Cellular damage**

**Elicit inflammatory mediators**

**Activation of DCs/Macs**
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