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Abscopal but desirable

The contribution of immune responses to the efficacy of radiotherapy

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Radiotherapy applies ionizing irradiation to selected areas of the body with the scope of destroying cancer cells, either as part of curative therapies to remove a primary malignant tumor and to prevent tumor recurrence after surgery, or as part of palliative measures to avoid local advancement of bone and brain metastases. Intriguingly, radiotherapy does not only have local effects but may lead to the delayed regression of distant non-irradiated lesions. Most likely, these "abscopal" effects are mediated by the immune system.

Radiation oncologists have been reporting for a long time the so-called "abscopal" effect, denoting the impact that irradiation of a tissue has on remote non-irradiated tissues.[1] Beyond unwarranted side effects of radiotherapy, this "abscopal" effect may also be therapeutic, at least in some peculiar cases. Thus, occasionally, distant metastases, which have not been irradiated, exhibit a delayed therapeutic response, as this has been documented for example for melanoma,[2] lymphoma,[3] adenocarcinoma,[4] hepatocellular carcinoma[5] or Merkel cell carcinoma.[6] Clinicians initially attempted to explain the abscopal effect by a radiation-induced increase in the circulating levels of cytokines such as tumor necrosis factor[5] or interleukin-18.[7] However, recent evidence suggests that local radiotherapy can elicit an immune response whose effectors, most likely T lymphocytes, then migrate to distant lesions provoking their regression.

Indeed, there is convincing evidence that the therapeutic abscopal effect is mediated by an anticancer immune response, at least in mice. First, the abscopal effect can be increased by injecting bone marrow-derived dendritic cells into the irradiated lesion, after radiotherapy,[8] or by administering immunostimulatory factors such as MIP-1α,[9] toll-like receptor-9 agonists[10] or anti-CTLA antibody.[11] The abscopal effect correlated with the induction of IFNγ-producing T cells[11] and was abolished by depletion of $CD4^+$ or $CD8^+$ T lymphocytes.[9] Moreover, irradiation can induce immunogenic cell death, thus converting dying cancer cells into a therapeutic vaccine,[12] and that radiotherapy is more efficient in immunocompetent mice than in mice lacking TLR4 that are unable to mount an immune response against dying tumor cells.[13] Hence, the abscopal effect may be mediated by an anticancer immune response that is triggered by radiation-induced immunogenic cell death. Accordingly, both external-beam radiotherapy and brachytherapy can induce anticancer immune responses in patients with prostate cancer or colorectal cancer.[14,15]

In the March 8 issue of the *New England Journal of Medicine*,[16] a team of researchers at Memorial Sloan Kettering Cancer Center report the case of a patient with NY-ESO-1+ melanoma treated by local radiotherapy and systemic injections of the anti-CTLA antibody, ipilimumab, both before and after radiation. In this patient, palliative irradiation of a paraspinal thoracic mass led to the regression of distant lesions, in particular a hilar lymphadenopathy and splenic lesion. This response temporarily correlated with signs of anti-melanoma immune response, namely an increase in NY-ESO-1-specific antibodies, as well as a raise in the frequency of circulating $CD4^+$ T cells expressing the activation marker ICOS, NY-ESO-1-specific interferon-γ–producing $CD4^+$ cells, and HLA-DR-expressing $CD14^+$ monocytes.[16] These data plead in favor of the interpretation that abscopal effects of radiotherapy are indeed mediated by specific anticancer immune responses.

The aforementioned results may have far-reaching implications for the future amelioration of radiotherapies. How can this new knowledge be rendered useful? First, it remains to be determined which dose and which fractionation schedule[11] can induce an optimal combination of immunogenic cancer cell death and depletion of local immunosuppressive cells without destroying essential positive immune effectors at the irradiation site. Second, it will be important to determine which regimen of (local or systemic?) immunostimulation would facilitate post-radiation anticancer immune responses. We anticipate that an optimal combination of radiotherapy and immunotherapy will elevate abscopal effects to a systematically achievable rather than anecdotic therapeutic goal.

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