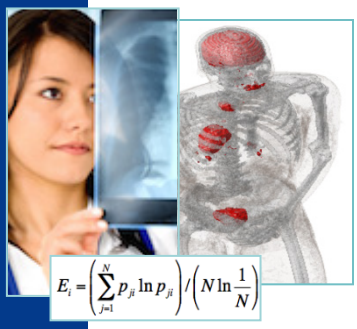
A Quantitative Framework to Identify Radiation Targets for Cancer Treatment that Synergize with Immunotherapy



As 90% of cancer morbidity is due to metastasis, maximizing systemic response with limited toxicity will play a role in almost all cancer therapy. Local irradiation of immunogenic metastases may cause a systemic (abscopal) regression of unirradiated metastases. This technology is a decision support tool for clinicians that uses a mathematical model to determine which tumor(s) to irradiate. The inputs include: patient-specific distribution and volumes of metastases, blood flow to each affected organ, and immune cell homing to the irradiated and unirradiated tumor sites. This model focuses on which irradiated site(s) will produce the greatest systemic immune response, and concurrent immunotherapy will enhance the likelihood of an abscopal effect.

COMMERCIAL OPPORTUNITY

- At diagnosis, 40% of lung cancers, 30% of colorectal cancers, and 15% of melanomas will already be metastatic. This represents a significant challenge to the management of disease. Currently, clinicians treat individual metastatic site(s) to ease local burden in patients that fail systemic therapy, and, while the irradiated tumor shrinks, other metastases may continue to grow.
- Cases have been reported of patients undergoing an abscopal effect, whereby local radiation, usually in combination with immunotherapy (mainly high dose IL-2), has caused systemic immunoeradication of tumor burden. The synergy between radiation and immunotherapy stems from radiation-induced cell death locally exposing tumor antigens to dendritic cells. Subsequent immunotherapy can stimulate rapid growth and differentiation of T cells for a targeted elimination of antigen-presenting tumor cells throughout the body.
- This mathematical model framework can increase the metastatic cancer patient's the likelihood of responding with an abscopal effect post radiation therapy, by assigning each metastasis a global impact score which informs clinicians to specifically choose the site(s) where localized radiation will maximize a systemic response.

TECHNOLOGY

This is a mathematical model framework of systemic T cell trafficking after activation by local cancer therapy. The framework takes into account patient-specific geographic distribution of metastatic sites (using PET/CT scans), the physiologic blood flow fractions to tumor bearing organs, tumor burden and distribution in each tissue, and T cells' homing cues (based on site of activation via localized therapy) Utilizing an existing model of local tumor-immune system interactions, then simulating development of metastatic sites under the dynamic patterns of T cell trafficking, the algorithm predicts which irradiated site(s) will illicit the greatest systemic anti-tumor response. When the algorithm was tested on 40 virtual patients with multiple tumors randomized in both size and organ distribution, it conclusively showed that the best target was not always obvious simply based on size and organ function. Currently, the model is being validated in three cohorts of metastatic melanoma, breast and lung cancer patients treated with radiotherapy and different types of immunotherapy.

PUBLICATION/PATENT

- Abscopal benefits of localized radiotherapy depend on activated T-cell trafficking and distribution between metastatic lesions, Cancer Research, *in press*, doi: 10.1158/0008-5472.CAN-15-1423
- A PCT application was filed for Dr. Enderling on 4/4/2015.

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