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Radiotherapy to convert the tumor into an *in situ* vaccine

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Over the past several months new examples of abscopal effects of radiotherapy have added to the existing literature on this subject, and demonstrated an association with an anti-tumor immune response (1–3). Initially met by understandable scepticism, our original hypothesis that the rare but repeatedly observed abscopal effect of radiation is, at least in part, immune-mediated is acquiring increasing support (4). Importantly, this new role of radiotherapy brings radiation oncology to the table of the "systemic disease modifiers", a place it is generally excluded from.

In 2004 we introduced the concept that danger signals associated with the effects of ionizing radiation could convert the irradiated tumor into an immunogenic hub, and in some patients, become a very efficient individualized *in situ* vaccine (4). Once vaccinated, the host's immune response both contributes to the local response to radiotherapy as well as to a systemic rejection of metastases (5). This model has important implications for two distinct and often overlapping fields of research.

The first one focuses on the "in field" consequences of ionizing radiotherapy according to the host's immune system. The classical damage response of irradiated tissues and the derived types of cell death, are revisited in the context of the host's immunity. In this regard, more than 30 years ago seminal work from Helen Stone and colleagues did already demonstrate how the degree of integrity of the host's immune system determines the radiosensitivity of a tumor (6). The average TCD_{50} of a mouse fibrosarcoma was increased from 30 to 64.5 Gy in syngeneic mice that were T cell competent versus deficient, respectively. Interestingly, immune-suppressed hosts were also more likely to develop metastatic spread, linking immune status, local response to radiation and systemic progression in a close association. This paper provided the very first, albeit indirect, insight about the contribution of the immune-mediated component of cell killing by ionizing radiation.

Over the years more and more independent evidence has stressed the impact of radiotherapy on the survival of most cancer patients. In breast cancer, for instance, two consecutive meta-

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analyses have reported a statistically significant increment on survival when radiotherapy is added in patients who have undergone either post-mastectomy or post breast conservation surgery. The degree of this effect is similar to that conferred by adjuvant chemotherapy in similar patient populations. In these clinical setting the irradiated target is often comprised of microscopic residual disease and its has been extrapolated that for every four local recurrences prevented by radiotherapy an additional patient is alive at ten years of follow-up. Traditionally, the association of local control with better survival has been explained as the result of a reduction in metastatic seeding from the primary tumor, once it is successfully ablated by radiotherapy. However, an additional interpretation could be considered (7).

It can be hypothesized that, in some cases, radiotherapy may successfully immunize the patient against the cancer, converting the irradiated tissue into an *in situ vaccine* and endowing the host with a set of new and powerful tools to master systemic disease, as it emergences from dormancy, over time. The success of this process depends on many variables including the immune status of the host, his/her immmunogenetic profile, the intrinsic radiosensitivity of the tumor and its degree of genomic instability, the type of cell death achieved, etc. This variability is reflected by the clinical heterogeneity of outcomes demonstrated by our patients, often despite the fact that they carry tumors of similar histology and stage. What observed in the clinic can be easily explained by the variable contribution of the immune system to a clinical response. After treatment, in some successful cases the irradiated tumor is converted in a vaccine and the derived effective immunological memory provides protection for the lifetime of the host. In others, an initially successful vaccination despite having contributed to the initial local response, reveals ineffective at recurrence. In these cases it is likely that genetic instability and immunoediting during dormancy and subclinical growth have enabled immune-escape, as manifested by clinically recurrent or metastatic disease (8).

The concept of standard treatments potentially converting the tumor into a vaccine can also be applied to explain the frequent success of concurrent chemo-radiation compared to the same two modalities used sequentially. Characteristically, concurrent chemo-radiation results in enhanced local and systemic control, in many different cancer types and clinical settings. It is conceivable that the concurrent use of the two modalities induces a more efficient form of immunogenic cell death, enhancing their respective potential as “cryptic vaccines” (9).

The second area of research regards the concept that radiotherapy can be applied as a more general “immune response modifier”, a novel tool to add to the arsenal of immunotherapy agents. In this context, the pro-immunogenic effects of radiotherapy can be harnessed in concert with strategies to correct the immunosuppressive networks that are in place once tumors have established (8). Modern immunotherapy is gradually taking on the challenge of defeating the established tolerance toward the cancer, to recover an effective tumor-specific immune response.

This partnership between radiotherapy and immunotherapy is finding clinical confirmation in recent reports. Even in patients who are at advanced stages of metastatic disease and have already failed immunotherapy, the addition of radiotherapy can recover a cancer-specific immune response (1). These preliminary examples of success suggest that radiotherapy may be gaining a new role in metastatic cancer, in addition to that of simply palliating symptoms.

Finally, the three recent reports of abscopal effects in patients treated with radiotherapy in combination with different immunotherapy agents represent an exquisite translation of preclinical work, another confirmation of the importance of supporting laboratory research in our field. Experimental work done in a syngeneic mouse model of carcinoma, testing

radiotherapy with Flt-3 ligand (a growth factor for dendritic cells), demonstrated the induction of an immune response that reduced tumor growth outside the field of radiation (4). The findings inspired a trial testing the combination of s.c. GM-CSF (125 micrograms/m^2) with standard radiotherapy to a metastatic site in patients with metastatic solid tumors. GM-CSF increases the percentage of dendritic cells and their maturation, facilitating cross-presentation of newly released antigens after cell death at the site of radiotherapy. An abscopal response was detected in 30% of the patients accrued to the trial (5). Abscopal responses were also detected among 15 patients with low-grade B-cell lymphoma treated by low-dose radiotherapy to a single tumor site that was injected with the C-G enriched, synthetic oligodeoxynucleotide (also referred to as CpG) TLR9 agonist PF-3512676. These compounds can activate both lymphoma B-cells as well as nearby antigen-presenting cells, as previously demonstrated in a murine lymphoma model (3). T cells reactive to autologous tumor cells treated in vitro with CpG were detected in the peripheral blood and a temporal correlation of immune and clinical response was noted in some but not all patients. In some patients, CpG-treated lymphoma cells induced regulatory T cells in vitro, and this ability correlated with worse clinical response, suggesting that the balance of positive and negative immune mechanisms triggered determined the response.

Another combination strategy to overcome immune-tolerance consists of the blockade of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), a checkpoint receptor that inhibits T cell activation. We previously showed in a syngeneic model of poorly immunogenic, metastatic, mammary carcinoma that local radiation in combination with anti-CTLA-4 antibody elicited an anti-tumor CD8+ T cell response able to inhibit lung metastases as well as the subcutaneous irradiated tumor, extending survival and curing a small percentage of mice (10). A case report of a melanoma patient with disease progression while receiving ipilimumab, a monoclonal antibody that targets human CTLA-4, demonstrated response in multiple metastases outside the field after radiotherapy to a pleural-based paraspinal metastasis. Importantly, monitoring for several markers of anti-tumor immunity showed an anti-tumor response that paralleled the clinical course (1).

In summary, although still anecdotal, evidence is emerging to support the concept that local radiotherapy and immunotherapy can successfully synergize and produce a therapeutically effective anti-tumor immune response, even in metastatic cancer. It is the very beginning of a novel field, with much research warranted to better define the many mechanisms that characterize the cross talk with the immune system and to establish how to best harness ionizing radiation in this new role.

Whether as a direct inducer of immunogenic cell death or in its application as a simple adjuvant to more complex immunotherapy manipulations, radiotherapy is once again playing a central role in the management of the cancer patient at any stage, and in the everlasting quest for cancer “cure”.

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