Editorial

The abscopal effect and its implications for radiotherapy-immunotherapy combinations

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Abscopal effects (from "ab" "scopus" meaning away from target) have grown from being a mere curiosity to providing an insight into more complex and previously unrecognised effects of radiotherapy (RT) that can be exploited alongside synergistic effects of immunotherapy, particularly immune checkpoint inhibitors (ICI), that counteract the actions of tumours to suppress an immune response against them.

The report by Aoyama *et al.* in this issue (1) is one of a long line of case reports of the abscopal effect, although in this instance the first time this has been reported in a solitary extramedullary plasmacytoma of the thyroid. First described by Mole in 1953 (2), the typical occurrence is in a patient with widespread disease where one site of involvement is irradiated, and clinical responses are observed at other sites also. Two systematic reviews have collated well over 50 case reports (3,4). A wide range of RT fractionation was used, though mostly representative of the range of doses and fractionation used for palliative (i.e., non-curative) RT. In both reviews, the median total dose delivered was 31–32 Gy (with a wide range) and the median dose per fraction 3 Gy (range, 0.15–26 Gy). In 2 of 46 cases this was delivered with brachytherapy and in 8 with stereotactic radiotherapy (SRT) (3). In general, abscopal effects were first apparent within weeks of completing RT and the median time to confirmation of an abscopal response was 2–4 months (range, 0.5–24 months) (3,4) with a median time to progression at these sites of 6 months (range, 0.7–14 months) (3). At 5-year, overall survival was 63% and distant progression-free survival 45% (4), suggesting that these responses might result in better outcomes, or perhaps more likely, that cancers open to immune-manipulation might carry a better than average prognosis. However, these systematic reviews do show that abscopal effects are seen more commonly with some cancer types than others. In fact, two-thirds of all reports are in patients with non-small cell lung cancer, renal cancer, melanoma, lymphoma or hepatocellular carcinoma (4). Even allowing for a degree of under-reporting, given the number of patients who have received RT for metastatic disease over the same time-period, abscopal effects are very rare. However, in a series of 28 patients with renal cell cancer receiving SRT to inoperable primary tumours or to metastatic sites, there were four patients (14%) in whom non-irradiated metastases had regressed at least temporarily (5).

The main conclusions to be drawn from this collection of case reports are that abscopal effects are more frequently observed with certain cancer types, and that these responses can be quite prolonged. There are no clear markers that might predict for abscopal effects, although a review of possible biomarkers did identify a raised absolute lymphocyte count following initiation of ICI or following RT, a higher pre-treatment neutrophil to lymphocyte ratio, or the presence of tumour infiltrating lymphocytes in biopsy material as having some predictive value (6).

Abscopal effects have not been observed following

surgery, though there are reports of regression of lung metastases lasting at least four years following hepatic artery embolization and radiofrequency ablation for a hepatocellular carcinoma (7) and following cryotherapy for melanoma skin metastases (8), the common feature being that cell death is required to trigger an abscopal effect.

The question therefore is whether the processes underlying abscopal effects reflect a series of immune events that commonly occur following RT, in certain cancer types, and whether these can be turned to therapeutic advantage, particularly where it is possible to exploit a synergism with immunotherapy.

Classical radiobiology teaches that the cytotoxic effects of RT are due entirely to DNA damage and these are proportional to the radiation dose delivered. However, it is now clear that DNA damage also triggers a range of local effects that can have cytotoxic effects on immediately adjacent non-irradiated cells (bystander effects) and on tissues in other parts of the body (abscopal effects). DNA damage produces a range of by-products, loosely described as damage-associated molecular patterns (DAMPs) (9). These "neoantigens" activate cross-primed dendritic cells within tumours by stimulating toll-like receptor 4 (TRL4) and type-1 interferon signalling (10,11). Activated dendritic cells then migrate to the draining lymph nodes where they activate $CD8^+$ cancer-specific cytotoxic T-lymphocytes (CTL). These activated T-cells travel to distant sites where they are responsible for abscopal effects (12). Radiation also triggers release of high mobility group B1 (HMGB1) which promotes antigen presentation (13), expression of surface-exposed calreticulin which serves as an "eat me" signal to macrophages (14), and release of heat shock proteins which further promote immune tumour cell death (15).

Radiation-induced DNA damage classically produces double-strand breaks, which result in micronuclei formation which are sensed by cGAS, a pattern recognition receptor that triggers type-1 interferon production (the cGAS-STING pathway), a pathway common to responses to viral infection (16). Other changes in the tumour microenvironment (TME) due to radiation include the activation of local macrophages (17) but also other processes which serve to suppress this immune response, with activation of regulating T-lymphocytes (Tregs; a subset of $CD4^+$ T-lymphocytes) which also transform macrophages from an M1 mode (essentially cytotoxic) into an M2 mode (essentially a healing and recovery mode) (17,18). Radiation is directly toxic to lymphocytes of all types, although less so for Tregs, resulting in the lymphopenia that is commonly seen after radical RT (19). Radiation might also inhibit immune processes within draining lymph nodes when these are included within radiation fields (12).

All this is further complicated by the effects of RT being dose-dependent, with highest doses (>5 Gy per fraction and higher total doses) being immune-ablating whereas low doses (less than 1 Gy per fraction, and commonly around 0.5 Gy) have an immune-stimulating effect (20).

For curative RT, immune effects, either locally or at a distance may be less relevant in that lymphopenia does not seem to have any direct clinical consequence and in that lymph nodes need to be included in radiation treatment volumes where there is a risk that these might harbour cancer cells. It is only in the realms of non-curative RT, given for locally advanced or metastatic disease, that these immune effects need to be taken into account or can be exploited.

Yet this is only one half of the equation in that the TME of the distant sites needs to be responsive to CTL to achieve a true abscopal response. Accessibility of CTL to tumour tissue depends on vascular permeability which is restricted by abnormal tumour vasculature (21). The pro-inflammatory effects of low-dose RT can increase vascular permeability by production of the CTL attractant cytokine CXCL16 (22) and by upregulating ICAM-1 (23) thereby allowing extravasation of CTL into tumour tissue. Effective cell lysis in many cases is then blocked by inhibitory signals from PD-1, PD-L1 and CTLA-4 and it is here that the potential synergy of radiation and ICI can be realised.

In addition to the abscopal effects from RT alone, there are an increasing number of reports of abscopal responses in patients being treated with ICIs. Typically, these are in patients treated over a period of months (but with evidence of disease progression) either with a CTLA-4 inhibitor (ipilimumab) (24), a PD-1 inhibitor (nivolumab) (25) or a combination of the two (26). In a retrospective review of 47 consecutive patients with metastatic melanoma treated with ipilimumab, there were more responses in (unirradiated) index lesions in those patients who had subsequently received some form of RT (27). Responses were more frequently seen in those with radiation fractions ≤3 Gy, even after exclusion of those receiving some form of SRT. There are additional reports of striking responses where the RT and ICI were given in closer temporal proximity which, though consistent with an abscopal response, do not totally exclude the possibility of an extraordinary response just to the ICI component (28,29).

In order to assess the potential benefit from RT-

ICI combinations, a number of clinical trials have been undertaken. These include the PACIFIC trial, where patients with unresectable stage III non-small cell lung cancer (NSCLC), were randomised following chemoradiotherapy to receive the PD-L1 inhibitor, durvalumab, or placebo, there was a significant improvement in progression-free survival from 5.6 to 17.2 months with durvalumab (30). Similarly, in resected oesophageal cancer the addition of nivolumab (compared to placebo) to chemoradiotherapy resulted in a significant improvement in disease-free survival (31).

However, this sequence does not preclude the possibility of this benefit simply being an effect of the ICI but the PEMBRO-RT study which randomised patients to pembrolizumab with or without SRT, demonstrated an improvement in median overall survival from 7.6 to 15.9 months (32). As survival in advanced NSCLC is increasingly dependent on distant failure, results of this trial are consistent with an abscopal effect. Interestingly, subgroup analysis showed that the largest benefit was in those whose tumours were PD-L1 negative (i.e., <1%). A further trial of similar design also showed prolongation of progression-free survival but with worse survival in those with low PD-L1 expression (defined as 1–49%) (33). A pooled analysis of both trials confirmed these benefits to be statistically significant (34). This latter review, conducted in 2021, lists seven ongoing trials of RT and ICI in early-stage NSCLC and a further 20 in locally advanced or metastatic NSCLC, many with use of SRT. Also, in castration-resistant prostate cancer previously treated with docetaxel, overall survival was improved by adding ipilimumab after a single fraction of 8 Gy to a site of bony involvement (compared to placebo in a randomised trial of 799 patients) (35). Conversely, a randomised trial of nivolumab with or without SRT in metastatic head and neck cancer showed no difference in response duration or progression-free survival between the treatment arms (36).

It is becoming clear that not all cancer types respond to immunotherapy in the same way, much as their responses to radiation and conventional chemotherapy differ. The concept of "hot" or "cold" tumours (from an immunological standpoint) serves to underline this. Those with high levels of infiltrating T-lymphocytes might be considered hot, while those without these or with low mutational burden or evidence of poor antigen presentation might be conserved low (37). Tumour hypoxia contributes to a "low" state by the presence of abnormal vasculature which encourages tumour immunosuppression by activating Tregs and MDSC (myeloid-derived suppressor cells) (38) as well as restricting access by CTL (21).

The idea of the abscopal effect being exploited by RT-immunotherapy combinations can be further extended by the combined use of SRT delivering a high (ablative) dose to one tumour site while utilising the low-dose volume surrounding this to provide immunomodulation to adjacent tumour sites in what would normally be regarded as out-of-field areas. This approach has the potential to maximise tumour response while minimising the risks of radiation-induced normal tissue damage. In a phase II trial of ipilimumab plus SRT in 106 patients with metastatic melanoma, utilising a combination of high- and low-dose areas, there were responses in non-irradiated sites in 26% overall, with higher rates of response in lung metastases compared to liver metastases, and in non-targeted lesions that received low-dose irradiation (31% compared to 5% in totally unirradiated areas) (39). In this study, sequential treatment with RT given 7–10 days after the second ipilimumab infusion appeared more effective that concurrent treatment where RT was delivered the day following the first ipilimumab infusion (31% versus 20%).

The same approach of low- and high-dose areas (but without immunotherapy) has been utilised in NSCLC where the hypoxic core of the tumour (accounting for just one-third of the gross tumour volume and avoiding any pathological lymph nodes) received 1–3 fractions of 10 Gy to the 70% isodose (Dmax 14.3 Gy). In a small prospective study of 23 patients, median bulk reduction was 70%, with 96% response rate (complete and partial responses) in irradiated sites and 52% response rate in unirradiated sites (although the actual dose received by these sites was not stated) (40). This approach, though promising, requires confirmation in a randomised trial setting.

It is now clear that there is clinical benefit from exploiting the abscopal effect, particularly in combination with immunotherapy. Although this so far has been seen mainly in melanoma and NSCLC, exploration of other cancer types is required in conjunction with further exploration of immune mechanisms in these cancers. The potential of intentionally including low-dose areas (delivering in the region of 0.5 Gy/fraction) adjacent to high-dose areas requires further exploration. Preclinical studies and early clinical studies investigating the use of multiple ICIs to achieve maximum immune blockade in conjunction with use of both high-dose ablative RT and low-dose immunomodulatory RT show that this approach is promising, although not without significant toxicity (20).

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