Mini-review of conventional and hypofractionated radiation therapy combined with immunotherapy for non-small cell lung cancer

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Abstract: A successful antitumoral response requires immunological activation as well as an antigenic pool capable of stimulating both the innate and the adaptive immune system. Recent advances in immunotherapy have been aimed at boosting the activation status of the innate and adaptive immune system, including cytokine administration, monoclonal antibodies engineered to target high yield elements in oncogenic signaling pathways, cancer vaccines, and checkpoint inhibitors. Herein, we examine the ways that radiation therapy induced cell death provides a pool of stimulus antigen, and draw parallels from the immunobiology of autoimmunity to explore how the immunogenicity of antigen derived from radiation-induced cell death might augment the antitumoral response. We also review basic research into the ability of different radiation dose fractionation schedules to induce an antitumoral response. After a discussion of basic immunotherapeutic principles, we review the published literature in the field of non-small cell lung cancer (NSCLC) and examine the ways that combining radiation and immunotherapy have begun to change the therapeutic terrain. We provide a summary of ongoing clinical trials aimed at combining immunotherapy and radiation therapy in NSCLC while emphasizing the need for identification of biomarkers with predictive power and the assessment of efficacy as a function of fractionation strategy.

Keywords: Radiotherapy; immunotherapy; non-small cell lung cancer (NSCLC); checkpoint inhibition

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Immunotherapy and radiotherapy: theoretical and practical synergy

The intuitive appeal of perturbing the immune system to generate an effective anti-tumor response is so profound that the idea emerged contemporaneously with the field of cellular immunology itself. In 1884, Elie Metchnikoff discovered macrophages (1) and Anton Chekov noted a connection between erysipelas and cancer remission (2). Less than a decade later, William Coley was injecting patients with a cocktail of Streptococcus pyogenes and Serratia marcescens (3-5). Over a century of subsequent empirical inquiry has uncovered a plethora of interacting signal transduction cascades within a multitude of interacting cell types. We are faced with not only understanding this system, but with purposefully manipulating it for the advancement of human health. Despite formidable immunological complexity, immunotherapy has yielded recent gains in overall survival and disease-free progression in a variety of cancers, most notably: melanoma (6-10), non-small cell lung cancer (NSCLC) (11-14), and renal cell carcinoma (RCC) (15-17). These therapies are designed to work by increasing the activation levels of the immune system.
system in response to the antigenic load generated by the tumor in question.

At the most reductive level, harnessing the immune system to attack a tumor consists of two components that are amenable to manipulation: the stimulus and the subsequent response. The word and concept of “immunotherapy” invites a particular focus on the latter, but manipulation of the stimulus (in this case, the antigenic load provided by the tumor) may be equally powerful. The most obvious way to influence the quality or quantity of antigenic load is by inducing preferential killing of tumor cells, either systemically with chemotherapy, or locally with radiation therapy. Increasing the antigenic load and facilitating immune activation with optimal kinetics may achieve a synergistic anti-tumor response, producing an effect on the immune system more definitive and durable than either approach alone. In this review we will provide a brief overview of the conceptual and empirical underpinnings that make radiotherapy and immunotherapy such promising therapeutic partners before turning our attention specifically to oligometastatic lung cancer and summarizing current experience with the combined approach of radiotherapy and immunotherapy in this particular patient population.

**Augmented immunological activation**

Like the brain, the immune system generates complex output in response to input that varies in character from the simple to the multiplex. Every fate choice, line of cellular communication, and metabolic activation state becomes a branch point in an intricate effector response that might be modified to produce an improved clinical outcome. Over the past several decades, we have attempted to influence the cytokine milieu, kick-start the innate and adaptive arms of the immune system with vaccines and their adjuvants, and prevent T cell exhaustion with immune checkpoint inhibitors (as depicted in Figure 1). A full discussion of the history, breadth, and efficacy of these approaches is beyond the scope of this review, though we will touch on relevant highlights here, with particular attention paid to NSCLC.

**Cytokines**

Administration of purified cytokines began in the 1980s with IL-2 (18). Dramatic clinical responses in a modest percentage of patients with melanoma (19) and RCC (20) led to FDA approval of IL-2 for the treatment of these diseases, though unfortunately, IL-2—monotherapy did not provide a significant benefit in patients with NSCLC (21). Other gamma-chain cytokines, such as IL-7, IL-15, and IL-21 have theoretical promise in stimulating antitumoral T-cell activation (22), though they have yet to fulfill their bench promise of bedside clinical gains. Cytokines that are major players in innate responses have also been shown to augment the antitumoral response. IL-12 is a particularly attractive immunomodulator due to its ability to activate cytocidal innate and adaptive responses, but its efficacy in early clinical trials was disappointing and it carried attendant toxicities (23). Interest in IL-12 continues with alternative administration strategies designed to increase intratumoral levels while circumventing systemic exposure (24). GM-CSF has shown promise in murine models of melanoma, and it has consequently been evaluated as a monotherapy and as part of multipronged approaches, with
mixed results (25).

**Vaccination**

Cancer vaccination is a strategy with attractive theoretical underpinnings, and many ongoing trials are using peptide vaccines, cellular vaccines, or viral-based approaches to stimulate the adaptive immune system to identify and attack tumor cells (26). Of particular relevance to NSCLC was the Phase III MAGRIT trial, which evaluated a peptide vaccine containing MAGE-A3, an antigen expressed in 35% of lung cancers. Unfortunately, vaccination failed to confer any benefit to overall survival (27). Cellular vaccines, composed of cancer cell lines, are intended to provide a selection of antigen that is broad as well as a more authentic stimulus, which allows for cross-presentation by dendritic cells, though in NSCLC there have yet to be any significant improvements in overall survival (28). A viral-based vaccine designed to stimulate an immune response against the antigen Mucin 1 (MUC1), expressed in NSCLC, has shown an improvement in progression-free survival, but has not yet demonstrated a difference in overall survival, though final results from the phase III trial have not yet been published (29).

**Checkpoint inhibitors**

The most promising immunotherapeutic interventions have come in the form of checkpoint inhibitors, so called because they remove the biochemical brakes on immunological activation. Two such inhibitory pathways have been targeted in T cells: the signaling cascade initiated by cytotoxic T lymphocyte antigen 4 (CTLA-4), and the signaling cascade initiated by the receptor known as programmed death 1 (PD-1) and its ligand, PD-L1, both of which function in T cells. CTLA-4 was first identified as a homolog to CD28, another member of the Ig superfamily known to be essential to the two-signal model of T cell activation (30). Mice deficient in CTLA-4 had a dramatically proinflammatory phenotype (31) and blockade of this pathway enhanced antitumoral immunity in murine tumor models (32). Two monoclonal antibodies have been developed that serve as CTLA-4 antagonists: ipilimumab and tremelimumab. The first success with CTLA-4 blockade came in a trial of ipilimumab used as a second-line agent in melanoma, which showed an advantage in overall survival (7). The beneficial effects of ipilimumab extended to other cancers, including NSCLC, where a regimen of ipilimumab and paclitaxel increased overall survival when compared with paclitaxel alone (11). As of yet, tremelimumab has not been approved by the FDA for use in treating any cancer as initial trials in melanoma failed to demonstrate significant survival benefit (33).

PD-1 and PD-L1, a receptor and ligand respectively, control T cell exhaustion, maintain tissue tolerance, and initiate resolution of inflammation (34,35). Mice deficient in PD-1 do not spontaneously develop flagrant autoimmune disease, though they have a predisposition toward developing spontaneous glomerulonephritis on the B6 background and dilated cardiomyopathy on the BALB/c background (36). Two monoclonal antibodies that target PD-1 have been approved by the FDA for NSCLC: nivolumab and pembrolizumab. Nivolumab has been approved for use in second-line NSCLC based on the results of a phase III trial comparing nivolumab to docetaxel which showed a benefit in overall survival (12,13). Pembrolizumab was also found to confer an overall survival benefit in NSCLC patients who failed other therapies and whose tumors expressed PD-L1 (37). Atezolimumab and durvalumab are two of several antibodies under development that target PD-L1 rather than its receptor. Atezolimumab was initially approved by the FDA for its promise in bladder cancer (38), and a recently completed phase II study has demonstrated an increase in overall survival in patients with previously treated NSCLC (39).

**Biomarkers**

Checkpoint inhibitors have been notable for the durability and magnitude of the clinical responses they effect in certain subpopulations of patients. There is consequently a great deal of interest in identifying biomarkers that, used as screening tools, would signify a higher pre-test probability of response in a given patient. The B7 family of cell surface proteins consists of related ligands for CTLA-4 that are expressed by many different cancers, including NSCLC (40). Perhaps because of the wide variety of B7 family members that are expressed on host antigen presenting cells at baseline, no surface marker has yet been identified capable of predicting response to ipilimumab (41).

Significantly more progress has been made in predicting responses to PD-1 blockade. PD-1 transduces an inhibitory signal after binding its ligand; therefore, patients with tumors expressing PD-L1 would potentially be good candidates for therapy with nivolumab, pembrolizumab, atezolimumab and durvalumab. PD-L2, which leads to inhibitory signaling through PD-1 (42), is also expressed by tumor cells. Tumoral overexpression of PD-L2 may
render these cancers particularly sensitive to nivolumab and pembrolizumab, while anti-PD-L1 antibodies might fail to provide significant clinical benefit. PD-L1 and PD-L2 status have been determined as part of several trials, and some data is beginning to emerge on the utility of these two molecules as predictive markers. A trial evaluating the use of PD-1 blockade in NSCLC demonstrated that patients with PD-L1 expressing tumors responded to treatment while those without PD-L1 expressing tumors did not (43).

The picture has been complicated by subsequent studies, which have revealed a subset of PD-1 negative tumors that respond to PD-1 blockade (44). Alternative predictive strategies are therefore needed. Venturing beyond surface markers, genetic analysis of the mutational burden in tumors from patients with NSCLC has demonstrated that a high mutational load predicts a positive response to PD-1 blockade (45). Immunohistological characteristics of pre-treatment tumors in melanoma have demonstrated that a preponderance of CD8+, PD-1+ T cells near or within the tumor correlates with robust T cell infiltration and response to anti-PD-1 therapy (46).

**Augmented antigenic immunogenicity**

When it comes to tumor cells, the manner of death may be as important as death itself when immunological activation is on the line. Recent insights into cellular death pathways have transformed the idea of a binary live/dead fate into interacting signal cascades influenced by cell intrinsic and extrinsic factors. The baseline burden of dying cells is estimated to be on the order of billions of events per day (47,48), and any defect in clearance of this material—whether from deficiencies in complement (49), mutations in Fcγ receptors (50), disruption of phagocytosis (51,52), inability to break down DNA (53)—leads to autoimmunity. Insights into aberrant immune activation and the pathogenesis of autoimmune disease are directly responsible for the development of checkpoint inhibitors. The potential synergy between antigen load and immunological activation is illustrated in **Figure 1**. Proinflammatory cell death triggers the innate immune system to stimulate an adaptive antitumoral response while checkpoint inhibitors sustain that activation by preventing T cell exhaustion.

**Forms of cell death and their relative immunogenicity**

Here we will describe three forms of cell death in the order of putative increasing immunogenicity: apoptosis, necrosis/ necroptosis, and pyroptosis. Apoptosis is an intrinsically or extrinsically mediated proteolytic cascade that transforms a dying cell into consumable packets that fall away like so many leaves. Dendritic cells take up the debris and present it to T cells. In the absence of costimulatory innate signals, this process promotes and maintains peripheral tolerance (54,55). The canonical contrast to apoptosis is necrosis, a disaster of cytoplasmic swelling, plasma membrane rupture, and organelle degradation that was originally thought to proceed in the absence of intracellular signaling (56). While there is little ambiguity in the fatal mechanical disruption, if necrotic death takes place over the course of hours, there seems to be some room for cellular preparation for the inevitable in the form of a signaling cascade dependent on RIP kinases that is known as necroptosis (57). Pyroptosis is a form of proinflammatory cell death in which pores in the plasma membrane, created by the activity of caspase-1, achieve membrane lysis in seconds and allow undegraded DNA and bioactive cytoplasmic enzymes to spill into the extracellular space (58). This form of cell death has been described in macrophages and other professional phagocytic cells. Our understanding of cellular death pathways is far from complete, and it is worth noting that a binary conceptualization—immunogenic or not—is unlikely to reflect in vivo reality. Immunogenic potential of tumor antigen is perhaps better described as a spectrum determined by the load, kinetics, and manner of cellular death. As we move away from morphology-based descriptions and toward biochemical characterization of cellular demise, the hope is that our ability to predict the relative immunogenicity of tumor antigen liberated by chemotherapy and radiation therapy will improve.

**Immunological impacts of chemotherapy**

Chemotherapy preferentially affects rapidly dividing cells by inducing death or cell cycle arrest. While this is an effective strategy for killing tumor cells, it hampers the ability of the adaptive immune system to mount an effective response against tumor antigen. In the broadest terms, impaired proliferation in the presence of chemotherapy leads to subpar clonal selection, in turn blunting the specificity of the antitumoral response. Furthermore, the cytoidal action of chemotherapeutic agents has been primarily characterized as apoptotic by in vitro studies, which (given the caveats mentioned above) is primarily a tolerogenic form of cell death (59). The picture rapidly complicates when individual agents or classes of agents are considered,
with different drugs interacting to influence the immune system in unexpected ways. As a case in point, imatinib, famous for its specificity, has been shown to activate NK cells to produce IFN-γ in a manner that is independent of mutation status in KIT or PDGFRA when studied in a population of patients with GIST tumors. In these patients, IFN-γ levels correlated with prognosis, suggesting that imatinib-mediated activation of NK cells may be playing a clinically meaningful role (60,61).

**Radiation therapy as an immunomodulator**

As our understanding of cellular death pathways deepens, we will gain additional tools to assess the role these forms of cell death may play in the tissue response to radiation *in vivo*. The ability of ionizing radiation to induce apoptosis via the creation of double strand breaks has been studied the most, and is reviewed elsewhere (62). We are only beginning to explore the roles that necroptosis, and pyroptosis may play. Necroptosis has been demonstrated to occur in an anaplastic thyroid cell line exposed to radiation *in vitro* (63), but the extent to which this occurs *in vivo* is as yet unknown. Pyroptosis occurs in macrophages in response to multiple signals, including adenosine triphosphate (ATP) (64), which has been demonstrated to be released from cells exposed to ionizing radiation (65). Though it continues to be difficult to study cellular death pathways within the context of a living host, one might predict that if radiation-induced cell death *in vivo* is capable of providing a stimulatory signal to the immune system one might see anti-tumor effects that occur outside the radiation field. Such an “abscopal”, or “away from the target”, effect was first described in 1953 (66). In recent years there have been a small number of patients who, after receiving an immunotherapeutic agent followed by radiation therapy, have had responses outside the radiation field (67-69). The “abscopal effect” is a putative combination of augmented immunological activation with augmented availability of antigen, which gives it a satisfying theoretical appeal. There is little wonder it has so captured the excitement and attention of the oncology community, with the hope that predictable, reproducible, and durable responses in at least a subset of patients might be achieved.

**Immunological correlates of fractionation strategies**

In a murine model of melanoma it has been demonstrated that both single fraction and multi-fraction regimens increase the number of tumor-infiltrating lymphocytes that synthesized IFN-γ and lysed tumor cells (70). A subsequent series of experiments in a murine model of breast cancer assessed the ability of fractionated versus single-dose radiotherapy to activate CD8 T cells and elicit an anti-tumor response outside the radiation field found that a fractionated strategy was superior to a single dose. The fractionation regimen consisted of either 8 Gy × 3 fractions or 6 Gy × 5 fractions, both of which would be comparable to a hypofractionated, or stereotactic body radiation therapy (SBRT) regimen (71). A second study that compared an ablative to a conventionally fractionated regimen in a murine model of melanoma demonstrated that a hypofractionated regimen was superior to a conventional regimen in its ability to activate CD8 T cells and trigger the reduction or destruction of distant metastases (72). These findings were supported by a study assessing tumor control in a murine melanoma model as a function of dose and fractionation. The most effective strategy was a hypofractionated regimen. The less robust response in the conventionally fractionated regimen was associated with an increase in regulatory T cells (73). It is tempting to hypothesize that cell death induced by conventional fractionation may be more tolerogenic than death via hypofractionation, but ambiguity remains. A murine model examining tumor-associated macrophages exposed to radiation therapy found that high dose radiation caused impaired T-cell recruitment while low dose radiation led to effective T cell recruitment and tumoral killing (74). A follow-up study demonstrated that low-dose irradiation converted tumor-associated macrophages back to the M1 phenotype, which are better able to coordinate antitumoral T cell responses (75).

**Immunotherapy and radiation in oligometastatic and oligoprogressive NSCLC**

**Initial clinical experiences in the metastatic setting**

Given that checkpoint inhibitors have yielded promising results in NSCLC, there has been a great deal of interest in combining radiation therapy and immunotherapy in these patients. A case report documenting an abscopal effect in a patient with metastatic NSCLC who was receiving ipilimumab demonstrated a post-treatment immunological response in the form of infiltrating CD8 T cells within an affected supraclavicular node when compared to an adjacent pre-treatment node removed from the same
To date there have been no prospective studies combining checkpoint inhibition with radiation therapy for lung cancer. A proof-of-principle trial assessing local radiotherapy in conjunction with the cytokine GM-CSF enrolled 41 patients with metastatic solid tumors, which included 18 patients with NSCLC. An abscopal response was defined as: “a decrease in the longest diameter of at least 30% in any measurable non-irradiation lesion from baseline”. In patients with multiple tumors outside the radiation field, the best response was reported. According to these criteria, abscopal responses occurred in four patients with NSCLC (68). Further studies are being conducted using a combined approach of radiotherapy and immunotherapy in the metastatic setting, and in coming years we should have an improved idea of the magnitude of benefit a combined approach may provide.

**Immunotherapy in the oligometastatic and oligoprogressive settings**

While the abscopal effect has inspired intense interest, there are other ways in which immunotherapy and radiation might advantageously be combined. Oligometastatic disease has no consensus definition but is understood to represent a low disease burden, with limited spread. Immunotherapy, if used in this setting, may enhance the efficacy of local control by stimulating the immune system to respond more robustly within the radiation field, perhaps significantly prolonging survival and improving quality of life by giving a boost to the “three Es” of immunoediting—elimination, equilibrium, and escape. In the oligometastatic setting, several ongoing trials that combine immunotherapy with RT in metastatic NSCLC; these are listed in Table 1. The results of a phase Ib trial combining NHS-IL2 with radiotherapy in NSCLC patients who had received first-line palliative chemotherapy have recently been published. Thirteen patients were treated with varying doses of NHS-IL2. Though the trial was not designed to test efficacy, two patients achieved long-term survival, defined as >4 years from first chemotherapy (76).

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<tr>
<th>NCT#</th>
<th>Phase</th>
<th>Description</th>
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<tbody>
<tr>
<td>NCT02318771</td>
<td>I</td>
<td>Use of anti-PD-1 + RT in patients with metastatic or recurrent solid tumor</td>
</tr>
<tr>
<td>NCT02303990</td>
<td>I</td>
<td>RADVAX: use of pembrolizumab + hypofractionated RT in metastatic melanoma or NSCLC</td>
</tr>
<tr>
<td>NCT02400814</td>
<td>I</td>
<td>Use of MPDL3280A (anti-PD-1) with stereotactic ablative radiotherapy in patients with stage IV NSCLC</td>
</tr>
<tr>
<td>NCT0244741</td>
<td>II</td>
<td>Use of dose escalated ipilimumab and SBRT in patients with metastatic solid tumors</td>
</tr>
<tr>
<td>NCT0221739</td>
<td>II</td>
<td>Use of ipilimumab and RT in patients with metastatic NSCLC</td>
</tr>
<tr>
<td>NCT02831933</td>
<td>II</td>
<td>ENSIGN: use of SBRT and gene therapy prior to nivolumab in patients with metastatic NSCLC</td>
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<tr>
<td>NCT02658097</td>
<td>II</td>
<td>Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC</td>
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<tr>
<td>NCT02492568</td>
<td>II</td>
<td>Use of pembrolizumab following SBRT in patients with previously treated stage IV NSCLC</td>
</tr>
<tr>
<td>NCT02407171</td>
<td>II</td>
<td>Use of anti-PD1 MK-3475 (pembrolizumab) and stereotactic body radiotherapy in patients with metastatic melanoma or NSCLC</td>
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**Table 1 Ongoing trials combining immunotherapy with radiation in NSCLC**

**Oligometastatic/oligoprogressive disease**

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<tr>
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<td>I</td>
<td>Use of pembrolizumab with chemoradiation in stage II/III NSCLC</td>
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<tr>
<td>NCT00828009</td>
<td>II</td>
<td>Use of bevacizumab and BLP25 vaccine in patients with stage III NSCLC who have received chemoradiation</td>
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<tr>
<td>NCT02434081</td>
<td>II</td>
<td>NiCOLAS: use of nivolumab consolidation after standard first line chemoradiation in locally advanced NSCLC</td>
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<tr>
<td>NCT02125461</td>
<td>III</td>
<td>PACIFIC: use of anti-PD1 MEDI4736 (AstraZeneca) following chemoradiation in patients with unresectable stage III NSCLC</td>
</tr>
<tr>
<td>NCT02768558</td>
<td>III</td>
<td>RTOG 3505: use of chemoradiation with adjuvant nivolumab in patients with locally advanced NSCLC</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; PD-1, programmed death 1; SBRT, stereotactic body radiation therapy.
the first line use of radiation and immunotherapy may increase the magnitude of the initial round of tumoral elimination and prolong and enhance the amount of time the immune system is able to keep growth in check during the equilibrium phase. The combination of radiation and immunotherapy may also have a role in the oligoproggressive state where most sites of disease are responding to therapy but one or two continue to progress. It may be that the combined approach of immunotherapy and radiation directed at the progressing site is capable of preventing or slowing disease escape.

Ongoing trials and future efforts

Subgroup analyses of large trials have indicated a potential synergy between immunotherapy and select groups of patients who had received radiation therapy. In particular, the START trial, which examined the MUC1 liposomal vaccine, showed no significant difference between vaccine versus placebo, but a subgroup of patients who received concurrent radiation therapy did show a statistically significant benefit (77). Perhaps most promising are the trials combining checkpoint inhibitors with radiation therapy. The Phase III double-blinded PACIFIC trial is evaluating maintenance therapy with an anti-PD-1 agent MEDI4736 versus placebo in patients with stage III NSCLC (NCT02125461). We have provided a list of other ongoing trials in Table 1. Further inquiries into the safety and efficacy of combined immunotherapy and radiation therapy in NSCLC are needed, but based on the immunological principles and data reviewed above, there may be certain trajectories that are more fruitful than others. As future trials unfold, the following approaches may be of particularly high yield: (I) prospective investigation into combination therapy should include a gross evaluation of basic immunologic competence, including a quantitative assessment of circulating cellular compartments in the peripheral blood with a particular focus on the CD4 and CD8 T cell compartments, as the ability to mount an effective immune response may be at least correlative if not causative in the efficacy of any immunomodulatory agent; (II) investigation into the biomarkers PD-L1 and PD-L2 should continue, with tumoral expression of these ligands determined for patients receiving anti-PD-1 therapy; (III) given the lack of clarity regarding the immunological benefits of conventional versus hypofractionation, these two strategies should be prospectively compared in the presence of immunomodulatory agents.

Concluding remarks

The potential synergy of immunotherapy and radiation therapy has begun to blur the boundaries between systemic and local control. As synthesized in Figure 1, radiation releases and alters antigen as targeted tissue dies, influencing immunogenicity in ways we are only beginning to characterize, comprehend, and predict. The innate and adaptive immune systems work together to mount responses against tumor cells, aided by immunotherapeutic agents that provide stimulatory signals or circumvent checkpoints that prevent sustained T cell activation. Activated T cells act systemically, but also may play a potentially important role in augmenting radiation-induced local control in the oligometastatic or oligoprogressive setting. The confluence of basic science advances in immunology, radiobiology, and oncology have made this a particularly promising time for translational research. Anton Chekhov, one of the earliest physicians to point out the connection between infection and spontaneous cancer remission, said also: “If you say in the first chapter that there is a rifle hanging on the wall, in the second or third chapter it absolutely must go off.” This dictum is known as “Chekov’s Gun,” and is meant to be a tool of narrative fiction. But if immunotherapy is that rifle, we have been looking at it for a long time.

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Footnote

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