Combining Immunotherapy and Radiation for Prostate Cancer

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Abstract

Radiotherapy has conventionally been viewed as immunosuppressive, which has precluded its use in combination with immunotherapy for prostate and other cancers. However, the relationship between ionizing radiation and immune reactivity is now known to be more complex than was previously thought, and data on the use of radiotherapy and immunotherapy are accumulating. Herein, we review this topic in the light of recently available data in the prostate cancer setting. Recent research has shown no significant lymphopenia in patients undergoing radiotherapy for high-risk adenocarcinoma of the prostate. In addition, emerging evidence suggests that radiotherapy can have immunostimulatory effects, and that tumor cell death, coupled with related changes in antigen availability and inflammatory signals, can affect lymphocyte and dendritic cell activation. Initial studies have focused on combinations of tumor irradiation and immunotherapy, such as the autologous cellular immunotherapy sipuleucel-T and the monoclonal antibody ipilimumab, in metastatic castration-resistant prostate cancer. These combinations appear to have clinical promise, and further investigation of the potentially synergistic combination of radiotherapy and immunotherapy is continuing in clinical trials.

Introduction

Radiotherapy has historically been thought of as immunosuppressive and therefore not appropriate for combination with treatments that act on the immune system. However, this view of radiotherapy might be overly simplistic, and a growing body of evidence suggests that ionizing radiation can be immunostimulatory. This opens up opportunities for combining radiotherapy with cancer immunotherapies, which are approved or under investigation for various malignancies including prostate cancer. Clinical data on the use of radiotherapy with immunotherapy, both together and sequentially, are accumulating. In this review we consider recent advances that challenge widely held views, not only on the effects of radiotherapy but also the potential synergy between radio- and immunotherapeutic approaches.

Effects of Radiotherapy on the Immune System

The accepted rationale for using radiotherapy in cancer is underpinned by tumor cell death and effects on tumor-associated stroma caused by DNA damage.1 The conventional view is that rapidly dividing cancer cells are more sensitive to ionizing radiation than normal tissue, and therapeutic radiation is therefore applied to induce apoptosis and other forms of cell death within a defined area while minimizing toxic effects on normal tissue around the treatment field.1,2

Inevitably, irradiation of living tissue involves damage to that tissue, whether it is tumor tissue, normal host stroma, normal host parenchyma, or leukocytes.1 The attenuation of lymphocyte numbers by radiotherapy, as previously reported in patients undergoing treatment for gynecologic3 or prostate4 malignancies, might therefore be viewed as an adverse effect. The ultimate manifestation of this is seen in patients who undergo total body irradiation (as widely used in conditioning regimens for hematologic malignancies), who experience prolonged pancytopenia.5 Studies have described reductions in numbers of T, B, and
natural killer (NK) cells, apoptosis or alteration of antigen-presenting cells (APCs), including dendritic cells (DCs) and macrophages, apoptosis of lymphocytes, and changes to antigen expression on tumor cells after radiotherapy with doses from approximately 50 to 70 Gy.\(^3\) Localized radiotherapy has reportedly resulted in significant reductions in lymphocyte levels in stage I to II prostate cancer or locally advanced gynecologic neoplasms.\(^3\) Similarly, studies on radiotherapy in patients with stage I to III breast cancer have shown lymphopenia, low functional activity of NK cells, decreased monocyte phagocytosis, and decreased tumor necrosis factor (TNF)-\(\alpha\) production.\(^3\)

Observations such as these have contributed to the conventional view of radiation therapy as immunosuppressive, and it has therefore not been used with cancer immunotherapy. However, emerging data suggest that standard radiotherapy in high-risk prostate adenocarcinoma might not be as immunosuppressive as previously thought, nor the relationship between radiation and immune responses as straightforward.\(^1\) The relative contributions and reactions of systemic and locoregional cell populations and the differing effects of dose and delivery methods might influence immune responses via a range of cellular mechanisms (Figure 1).\(^7\)

Radiotherapy can cause tumor cell apoptosis by inducing DNA damage, upregulating the p53 tumor suppressor gene, and through damage to the cellular lipid membrane. This in turn can lead to ceramide formation and activation of the stress-activated protein kinases/Jun amino-terminal kinases (SAPK/JNK) signaling pathway. The resultant damage-associated molecular patterns (apoptotic and necrotic cellular debris) can generate antigen-specific immunity through DC maturation and presentation of DC-processed antigen to T cells.\(^9\)

Activation of the SAPK/JNK signaling pathway and the presence of damage-associated molecular patterns might also be partly responsible for other immunological effects seen after radiotherapy.\(^1\) Studies in a variety of tumors have shown that radiation induces chemokines Chemokine (C-X-C motif) ligand, CXCL10, and CXCL16, which in turn promote recruitment of effector CD8 and T-helper 1 CD4 T cells.\(^10\) Radiation has also been shown to induce a number of different proinflammatory cytokines, including interleukin (IL) 1\(\beta\), TNF-\(\alpha\) and type 1 and 2 interferons.\(^10\) Additionally, in several cancer models, tumor cells exposed to radiation have been shown to have enhanced expression of major histocompatibility complex (MHC) class 1 molecules, co-stimulatory molecules, adhesion molecules (such as intercellular

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**Figure 1** Radiation Effects on Immune Cells and Consequent Modulation by Radiotherapy. Apoptosis Can Be Initiated by Radiation-Induced DNA Damage and Upregulation of the p53 Tumor Suppressor Gene, and by Damage to the Cellular Lipid Membrane, Which Can Induce Ceramide Formation and Activate the SAPK/JNK Signaling Pathway. SAPK/JNK Can Upregulate PKR Expression, Which in Turn Induces MHC and Cytokines via NF-\(\kappa\)B. Radiation Treatment Induces Cellular Expression of MHC Class I, Adhesion Molecules, Co-Stimulatory Molecules, Heat Shock Proteins, Inflammatory Mediators, Immunomodulatory Cytokines, and Death Receptors.

Abbreviations: ATM = Ataxia Telangiectasia Mutated; CD = Cluster of Differentiation; DNA-PK = DNA-Dependent Protein Kinase; MHC = Major Histocompatibility Complex; NF-\(\kappa\)B = Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; PKR = Protein Kinase R; SAPK/JNK = Stress-Activated Protein Kinases/Jun Amino-Terminal Kinases.
adhesion molecule 1 (ICAM-1), and stress-induced ligands (including NK Group 2D ligands on NK cells). Furthermore, radiation can upregulate expression of the Fas death receptor on tumor cells, which induces sensitivity of the tumor cells to T-cell receptor independent, Fas-mediated killing. Finally, a direct effect of radiation on tumors has been reported, in which radiotherapy modifies the phenotype of tumor cells to render them more susceptible to vaccine-mediated T-cell killing. As a combined result of these mechanisms, radiotherapy can engage both the innate and adaptive arms of the immune system, thereby converting the irradiated tumor into an in-situ "vaccine" that elicits a tumor-specific T-cell response, and the infiltration of leukocytes.

A more detailed summary of the effects of radiotherapy on some of the components of the immune system is described in the following sections.

### Effects of Radiation Therapy on White Blood Cell Counts in High-Risk Adenocarcinoma of the Prostate

In contrast to observations discussed previously, our group has demonstrated no significant lymphopenia in 26 patients aged 62 to 86 years (median 73 years) undergoing radiotherapy for high-risk prostate adenocarcinoma. In this study, complete blood counts (CBCs) were retrospectively analyzed with differential data on prospectively collected blood samples. CBC data were collected before radiotherapy and at up to 4 time points thereafter (1-90 days, 91-180 days, 181-360 days, and > 360 days), and were compared with normal ranges from an outside laboratory reference (white blood cell [WBC] count, 3800-10,700 cells/μL; absolute lymphocyte count [ALC], 910-4280 cells/μL).

Patients received conventional external beam radiotherapy (EBRT) from 64.8 to 81.0 Gy in 1.8-Gy fractions, with a small number receiving brachytherapy. Sixteen patients also received androgen deprivation therapy. Baseline cell counts were within normal ranges (Table 1). Counts decreased in the 3 months after radiotherapy, although median values remained within the normal range. Thereafter, median WBC and then ALC increased gradually to 5800 and 1250 cells/μL, respectively, approximately 6 to 12 months after radiotherapy (Figure 2). Thus, median WBC and ALC remained within normal limits for the full follow-up period. These results challenge the view that standard radiotherapy in high-risk prostate adenocarcinoma is immunosuppressive. To be successful, immunotherapy requires an active immune system, and the stability of cell

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Normal reference ranges were 3800 to 10,700 cells/μL for WBC and 910 to 4280 cells/μL for ALC.

Abbreviation: n = number of observations in an interval.

![Image of Figure 2](https://example.com/figure2.png)

**Figure 2** Median Baseline and Subsequent Cell Counts After Radiation Therapy. (A) White Blood Cell (WBC) Counts; (B) Absolute Lymphocyte Counts (ALC)

Abbreviation: AUC = Area Under the Curve.
counts in these patients therefore underlines the feasibility of combining radiation and immunotherapy.

**Radiotherapy and Antitumor Immune Responses**

Evidence shows that, in addition to treating a localized tumor, radiotherapy can influence immune responses. For example, tumor-specific immune responses have been reported after radiotherapy in patients with prostate cancer.14,15 Nesslinger et al examined serum samples before and after radiotherapy from men with localized disease and found treatment-associated autoantibody responses in 4 of 29 (13.8%) who had undergone radiotherapy and 3 of 10 (30%) who had received brachytherapy, which included autoantibody responses to serologically defined colon cancer antigen 1, outer dense fiber of sperm tails 2, and poly [ADP-ribose] polymerase family, member 1.14 In another study, Schaeue et al found the expression of survivin-specific cluster of differentiation (CD)8-positive (CD8+) T cells in peripheral blood to increase with radiotherapy in 7 of 11 (63.6%) prostate cancer patients.15 Increases in survivin-specific CD8+ T cells were also seen in patients with colorectal cancer in this study. Significantly, the observed lack of immune tolerance to survivin made immunotherapy combined with radiotherapy feasible in these patients.15

**Effects of Radiation Therapy That Might Influence Immune Responses**

When considering how radiotherapy could stimulate anticancer immune responses, there is now known to be interplay between tumor cell death, antigen expression, and inflammatory signals that affect lymphocyte and DC activation.16,17 Indeed, numerous studies have shown that targeted radiation can induce cellular expression of a wide variety of immune factors with effects on different cell types, as discussed in the following sections (see also Figure 1).

**Major Histocompatibility Complex Class I.** Major histocompatibility complex I molecules bind cytosol-derived peptides and present them at the cell surface, allowing CD8+ T cells to recognize and potentially destroy transformed or virus-infected cells.18 Localized irradiation of a wide variety of human tumor cell lines can result in increased expression of MHC class I, Fas, and ICAM-1.19 Upregulation of these cell surface molecules was accompanied by significantly enhanced tumor cell killing by CD8+ cytotoxic T lymphocytes (CTLs). Furthermore, in vivo cell surface expression of MHC class I molecules was shown in murine adenocarcinoma cells to be dose-dependently increased for several days after irradiation.18

**Death Receptors.** Fas is expressed at the cell surface in certain circumstances and induces apoptosis within the cell when engaged by the Fas ligand, which is present on activated T cell subsets.16 Therefore induction of Fas expression by tumor cells can facilitate tumor cell killing by immune effectors. In a murine carcinoma embryonic antigen-specific CD8+ CTL tumor model, localized irradiation of tumors caused upregulation of Fas and potentiated tumor rejection.19 In another study, sublethal irradiation of colorectal carcinoma cell lines resulted in sensitization of tumor cells to Fas- and TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis.20

**Immunomodulatory Cytokines Such as IL and TNF-α.** Expression of the proinflammatory cytokine TNF-α was increased after radiation exposure in a study of human sarcoma cells, with enhancement of radiation lethality in TNF-α–producing and —nonproducing cells.21 Radiation exposure has also been linked to expression of IL-1β (involved in T cell and macrophage activation) and TNF-α in mouse studies.22,23 Similarly, increased heat shock protein 72 expression has been linked to increases in circulating levels of IL-6 (involved in the acute phase response and antibody responses) and TNF-α after irradiation in patients with prostate cancer.24

**Adhesion Molecules.** Intercellular adhesion molecule 1 (also known as CD54) is an endothelial membrane protein that contributes to leukocyte adherence to, and migration through, blood vessel endothelia.16 This process, termed extravasation, is essential for immune effector cells to exit the blood into the tissues to reach the site of solid tumors. Irradiation of human dermal microvascular endothelial cells caused dose-dependent increases in surface expression and mRNA of ICAM-1.22

**Co-Stimulatory Molecules.** Expression of co-stimulatory B7 molecules by APCs contributes to T cell activation, and engagement of T cells in the absence of co-stimulation can lead to immune regulation and dampening of immune responses.16 Therefore, B7 expression is particularly relevant in the context of myeloid leukemias, because key APCs are derived from the myeloid lineage. Gamma irradiation of human acute myeloid leukemia (AML) cells has been shown to result in induction of B7.1 expression, and might therefore be capable of stimulating an anti-AML immune response.25

The described molecular effects combine with other local effects to influence immune responses. For example, radiation can induce a proinflammatory microenvironment within tumors that provide DCs with maturation-inducing stimuli.26 Cell death caused by irradiation also results in extensive exposure of the lymphatic system to tumor antigens through necrosis or apoptosis of tumor cells and the subsequent release of cellular debris.27,28 Furthermore, irradiation of DCs has been shown to inhibit endogenous antigen processing while enhancing antigenic peptide presentation.29,30 DCs that had acquired antigen from apoptotic tumor cells were in turn able to induce MHC class I–restricted T cells and confer antitumor immunity in a murine model.27 Molecular pathways specifically activated during irradiation-induced cell death can also be immunostimulatory.31 For example, dying tumor cells secrete the high-mobility group box 1 (HMGB1) alarmin protein that acts on toll-like receptor 4 expressed by DCs, thereby promoting efficient processing and presentation of antigens.32 HMGB1 effects on DCs also include maturation changes and creation of a chronic inflammatory state.33 In addition, the adhesion molecule effects on stromal cells described previously increase the permeability of the local vasculature that allows circulating leukocytes to infiltrate the surrounding tissues.25 Remodeling of the vasculature in a proinflammatory environment can permit T lymphocytes to extravasate
and destroy tumor cells. In addition, tumor cells can be phenotypically modulated by radiation, which increases their susceptibility to cell-killing. Taken together, these immunostimulatory effects of radiation might at least partly explain the abscopal effect, in which localized treatment with ionizing radiation can result in reduction of tumor masses distant from the primary site. This effect has been reported in 2 recent cases of metastatic melanoma treated with radiotherapy and immunotherapy, demonstrating that the combination of these 2 therapeutic approaches might support the host immune response to tumor antigens.

Finally, when reviewing data on this subject it is important to remember that there is a balance between suppressant and stimulant effects on the immune system that depends on the dose, fractionation, and targeting of radiotherapy. In addition to providing a radiation-induced proinflammatory environment that facilitates antigen presentation and other positive immunologic effects, radiation can also promote the development of myeloid cells, which facilitate tumor growth, and regulatory T cells, which dampen or prevent immune responses. Thus, radiation can be an immunoadjuvant in the right circumstances, but the response reportedly varies with dose and fractionation. This offers possibilities for refining radiotherapy techniques so that they favor stimulant effects.

**Combination of Radiotherapy and Immunotherapy for Prostate Cancer**

Discovery of the variety of immunostimulant effects resulting from radiation treatment has increased interest in combining immunotherapy with tumor irradiation to produce synergistic benefit in a range of cancers. The preclinical evidence for synergy between radiotherapy and immunotherapy has been reviewed recently by Kwilas et al and we therefore focus herein on recent clinical data.

**Immunotherapy in Prostate Cancer**

New findings are constantly being made in animal models of oncology immunotherapy, and these often have important implications for furthering immunotherapy research in humans. Currently, a variety of immunotherapeutic treatments are available or in development for use in prostate cancer. These include sipuleucel-T, an autologous, APC-based immunotherapy that targets the immune response toward a defined prostate antigen (prostatic acid phosphatase [PAP]). Sipuleucel-T was the first cancer immunotherapy approved by the United States Food and Drug Administration for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC) and by the European Medicines Agency for asymptomatic or minimally symptomatic metastatic (nonvisceral) castration-resistant prostate cancer in male adults in whom chemotherapy was not yet clinically indicated. Approval was primarily based on the phase III IMPACT (IMmunotherapy Prostate AdenoCarcinoma Treatment) trial, which showed a 4.1-month improvement in median survival over placebo (25.8 vs. 21.7 months). The relative reduction in risk of death was 22% with sipuleucel-T (hazard ratio, 0.78; 95% confidence interval, 0.61-0.98; \( P = .03 \)). T cell and humoral immune responses to the prostate antigen were observed in patients receiving sipuleucel-T and correlated with survival. These results and subsequent approval are reflected in recent updates to National Comprehensive Cancer Network guidelines for prostate cancer treatment, which include the option of first-line immunotherapy with sipuleucel-T in men with mCRPC and good performance status (category 1; Figure 3). The guidelines also emphasize the importance of radiotherapy for patients with high-risk localized tumors, and clinical practice has shown the value of EBRT and stereotactic body radiation therapy, also known as stereotactic ablative radiotherapy, for bone metastases.

Prostate-specific antigen (PSA)-TRICOM (a recombinant viral vaccine mixture encoding PSA with B7.1, ICAM-1, and leukocyte functional antigen-3), ipilimumab (a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen [CTLA]-4), and various peptides, proteins, and tumor antigens alone or linked to viruses or co-stimulatory molecules are currently being investigated in prostate cancer.

**Recent Progress with Combination Therapy**

Notably, 2 recent studies have combined radiotherapy and immunotherapy to good effect in patients with prostate cancer. The first was a pilot study of intraprostatic injection of autologous DCs combined with EBRT and brachytherapy in 5 men with localized tumors without radiologically evident metastases but with high risk of recurrence (Table 2). In this study, serial prostate biopsies consistently showed limited levels of lymphocytic infiltration. No temporal infiltrate pattern linked to radiation or DC injection was evident. The theoretically optimal time to inject DCs into the tumor environment would be when apoptosis is proceeding maximally, which was assessed in this study. However, among tumor cores that were examined, there were up to 19% of cells showing apoptosis. This small proportion reflects the difficulty in targeting a tumor using biopsies (the organ rather than the tumor is targeted), and it therefore appears that the identification of time points at which radiation induces high rates of apoptosis is not straightforward.

Functional T-cell responses before, during, and after treatment were assessed by stimulating peripheral blood cells with prostate tumor cell-derived peptides and measuring the number of interferon-\( \gamma \)-producing cells by enzyme-linked immunosorbent spot. Tests showed a detectable increase from baseline in prostate-specific T-cell responses in 2 of the 5 men. However, there was no clear temporal pattern, baseline responses were detectable in some men, and in some cases, strong responses to control peptides were noted.

The technique used was feasible, well tolerated, and specific immune responses were observed. However, the coordination of apoptosis-inducing radiotherapy with autologous DC treatment requires further study. In fact, a randomized phase II trial (NCT01807065) is under way to assess the efficacy of sipuleucel-T in combination with radiotherapy in patients with mCRPC. It should be noted that the treatment described herein differed from sipuleucel-T therapy in the method of APC administration (intraprostatic injection vs. intravenous infusion), and also in a lack of a defined antigen (sipuleucel-T therapy directs the immune response toward PAP). Similar approaches combining
Intratumoral DC injection with radiotherapy or chemotherapy for sarcoma have shown promising preliminary results and warrant further study.\textsuperscript{61,62}

The second trial was a phase I/II study in men with mCRPC that compared ipilimumab as monotherapy and in combination with radiotherapy (Table 2).\textsuperscript{59} Ipilimumab is a fully human monoclonal antibody that specifically blocks the binding of the immunoregulatory molecule CTLA-4 to its ligands (CD80/CD86) and thereby augments T cell activation and proliferation.\textsuperscript{63} This combination therapy study was carried out after initial trials showed ipilimumab to have acceptable tolerability and antitumor activity in patients with mCRPC.\textsuperscript{64,65} Of the 41 patients who received combination therapy, 30, 8, and 3 had 1, 2, and 3 bone lesions irradiated, respectively. Among patients who received 10 mg/kg with or without EBRT (\(n = 34\)), 28 had evaluable tumors: 8 had PSA reductions of at least 50% ranging in duration from

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**Figure 3** Systemic Therapy for mCRPC. Abridged Summary of NCCN Guideline for Patients With Advanced Disease Who Test Positive for Metastases.

- **Distant metastatic prostate cancer**
  - Maintain castrate serum levels of testosterone, along with denosumab or zoledronate if bone metastases are present

**Treatment options if asymptomatic**

- **Sipuleucel-T**\(^*\) (category 1)
  - Second-line HT:
    - Anti-androgen
    - Anti-androgen withdrawal
  - **Abiraterone acetate** (category 1)
    - Enzalutamide
    - Ketoconazole
    - Steroids
    - Diethylstilbestrol (or other estrogen)
  - *Docetaxel*\(^{1}\)
    - Clinical trial

**Treatment options if symptomatic**

- **Category 1**
  - *Docetaxel*
  - *Radium-223 for symptomatic bone metastases*\(^{2}\)
  - Mitoxantrone\(^{5}\)
  - Abiraterone acetate\(^{6}\)
  - Enzalutamide\(^{5}\)
  - Palliative RT/radionuclide (for symptomatic bone metastases)
  - Clinical trial
  - Best supportive care

- **Category 1 post-docetaxel:**
  - Abiraterone acetate or enzalutamide
  - Cabazitaxel
  - *Radium-223*\(^{2}\)
  - Docetaxel re-challenge
  - Mitoxantrone\(^{5}\)
  - Other second-line HT:
    - Anti-androgen
    - Anti-androgen withdrawal
    - Ketoconazole
    - Steroids
    - Diethylstilbestrol (or other estrogen)
  - *Sipuleucel-T*\(^*\)
    - Clinical trial

\(^{*}\)Sipuleucel-T Is Appropriate for Asymptomatic or Minimally Symptomatic Patients With Eastern Cooperative Oncology Group Performance Status 0 to 1, and Is Not Indicated for Patients With Hepatic Metastases or Life Expectancy < 6 Months.

\(^{1}\)Docetaxel Can Be Used To Treat Patients With Rapid Progression or Asymptomatic Hepatic Metastases, Because Asymptomatic and Symptomatic Patients Experience Survival Benefit With Docetaxel.

\(^{2}\)Radium-223 Is Not Approved for Use Combined With CT.

\(^{5}\)For Patients Unable to Receive Docetaxel, However, Although Mitoxantrone Is Included in the NCCN Guidelines, Some Physicians No Longer Consider This Agent As Standard First- or Second-Line CT.

Abbreviations: CT = Chemotherapy; HT = Hormonal Therapy; mCRPC = Metastatic Castration-Resistant Prostate Cancer; NCCN = National Comprehensive Cancer Network; RT = Radiotherapy.
3 to ≥ 13 months, there was 1 complete response (duration ≥ 11.3 months), and 6 had stable disease.69 PSA changes were seen irrespective of previous chemotherapy.69

However, a randomized phase III study (NCT00861614) in patients with mCRPC whose disease had progressed after docetaxel chemotherapy failed to show improved overall survival when ipilimumab was administered after radiotherapy compared with placebo (Table 2).60 Future studies might also consider the combination of radiotherapy and interferon, which has shown some promise in the treatment of melanoma.66

### Conclusion

The aim of cancer immunotherapy is to overcome the problem of weak immunogenicity of tumor-associated antigenic material and to provoke a robust immune response to cancer cells. Conventionally, radiation has been perceived as immunosuppressive, but recent experimental work shows that this is not necessarily the case and radiotherapy can in fact have a variety of immunostimulatory effects. Emerging data thus show the potential for radiotherapy to work synergistically with immunotherapy to enhance antitumor immune responses, inhibit immunosuppression, and/or alter tumor cell phenotype to increase their susceptibility to immune-mediated killing.45

The coordination of focal tumor irradiation and immunotherapy has the potential to maximize the benefit of both treatments in patients with prostate and other tumors. Augmentation of antitumor immune responses appears to be a logical and promising approach, and the small-scale studies of radiotherapy in combination with immunotherapy that have been carried out to date support this view. mCRPC is one of few tumor types in which immunotherapy is the current standard of care,57 and developments in combination therapy appear to be a logical route toward future improvements in outlook for affected patients.

Questions remain as to how best to exploit the full potential of combination therapy. There might be variations in tumor microenvironment, phenotype, and response brought about by differing types of radiotherapy, and certain dosages and courses of radiotherapy might be more beneficial than others.67 There is also a possibility that combination therapy might result in an increase in the local control rate of prostate cancer; however, further studies are required to clarify this. Optimization of the sequence and timing of treatments should also assist with maximizing the efficacy of radiation combined with immunotherapy.57 The results of ongoing studies investigating combinations of immunotherapies, such as sipuleucel-T or nivolumab, after radiotherapy for the treatment of prostate cancer are eagerly awaited.

### Acknowledgments

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**Table 2** Overview of Clinical Trials Evaluating Immunotherapy Combined With Radiation for Prostate Cancer

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<th>Citation</th>
<th>Design</th>
<th>Treatment</th>
<th>Measurements</th>
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<tr>
<td>Finkelstein et al, 2012</td>
<td>Nonrandomized, open-label pilot study in 5 men with localized tumors without radiologically evident metastases but with high risk of recurrence</td>
<td>Twenty-eight months of androgen suppression, 45 Gy of EBRT, intraprostatic DC injection, and brachytherapy seed placement. Autologous DCs were obtained using single-treatment apheresis and frozen. Before reinfusion after radiation fractions 5, 15, and 25, cells were thawed and cultured in vitro for 4 days with GM-CSF and IL-4</td>
<td>PSA decline and tumor response</td>
<td>Biopsies showed some apoptosis (up to 19% in 11 tumor cores) and limited lymphocytic infiltrates, including CD8+ cells. Tests on circulating lymphocytes showed some instances of increased titers to the test peptides</td>
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<td>Slovin et al, 2013</td>
<td>Nonrandomized, open-label phase III trial in 71 men with mCRPC with disease progression after discontinuation of androgen therapy and who had received no more than 1 previous course of chemotherapy</td>
<td>Comparison of ipilimumab monotherapy (n = 29; 3, 5, or 10 mg/kg given every 3 weeks in a cycle of up to 4 doses) or ipilimumab (3 or 10 mg/kg) in combination with EBRT (n = 41). EBRT was given as a single dose of 8 Gy per target bone lesion for up to 3 lesions per patient, 24 to 48 hours before the first ipilimumab dose. Patients with disease progression after an initial response (or stable disease) could have up to 3 further ipilimumab cycles, but no further EBRT</td>
<td>Overall survival</td>
<td>Among patients who received ipilimumab 10 mg/kg with or without EBRT (n = 34), 28 had evaluable tumors. Of these, 8 had PSA reductions of at least 50% (duration: 3 to ≥13 months). There was 1 complete response (observed in the EBRT group; duration ≥11.3 months) and 6 patients had stable disease. PSA changes were seen irrespective of previous chemotherapy</td>
</tr>
<tr>
<td>Kwon et al, 2014</td>
<td>Multicenter, randomized, double-blind, phase III trial in men with mCRPC who had progressed after docetaxel treatment</td>
<td>Patients were randomized to receive bone-directed radiotherapy (8 Gy in 1 fraction) followed by either ipilimumab 10 mg/kg or placebo every 3 weeks for up to 4 doses</td>
<td>Interval biopsies and blood tests were used to assess immune reaction</td>
<td>Median overall survival was 11.2 months with ipilimumab and 10.0 months with placebo (HR, 0.85; 95% CI, 0.72-1.00; P = .033). Prespecified analyses suggested that ipilimumab might benefit some subgroups, particularly those with favorable prognostic features</td>
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Abbreviations: DC = dendritic cell; EBRT = external beam radiation therapy; GM-CSF = granulocyte-macrophage colony-stimulating factor; Gy = Gray; HR = hazard ratio; IL = interleukin; mCRPC = metastatic castration-resistant prostate cancer; PSA = prostate-specific antigen.
Immunotherapy and Radiotherapy for Prostate Cancer

United Kingdom) and was funded by Dendreon Corporation. The authors remain accountable for all aspects of the work and contributed to the conception/design of the report or the analysis/interpretation of data, critically revised the manuscript for important intellectual content, and approved the final version for submission.

Disclosure

Steven E. Finkelstein reports speaker bureau for Dendreon, Bayer, Algeta, and Spectrum, and advisory boards for Bayer, Algeta, Dendreon, and Spectrum. Neal D. Shore reports consultancy for Bayer, Janssen, Medivation, Astellas, Dendreon, Millennium, and Sanofi. Todd DeVries is an employee and shareholder at Dendreon. Robert Sims was an employee (during the drafting of this report) and is a shareholder at Dendreon. The remaining authors have stated that they have no conflicts of interest.

References