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Radiotherapy plus immune checkpoint inhibitor in prostate cancer

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The immune checkpoint inhibitor (ICI) is a promising strategy for treating cancer. However, the efficiency of ICI monotherapy is limited, which could be mainly attributed to the tumor microenvironment of the "cold" tumor. Prostate cancer, a type of "cold" cancer, is the most common cancer affecting men's health. Radiotherapy is regarded as one of the most effective prostate cancer treatments. In the era of immune therapy, the enhanced antigen presentation and immune cell infiltration caused by radiotherapy might boost the therapeutic efficacy of ICI. Here, the rationale of radiotherapy combined with ICI was reviewed. Also, the scheme of radiotherapy combined with immune checkpoint blockades was suggested as a potential option to improve the outcome of patients with prostate cancer.

KEYWORDS

radiotherapy, immune checkpoint inhibitor, prostate cancer, cold tumor, toxicity

Introduction

The immune checkpoint inhibitor (ICI) is believed to be promising for tumor patients (1). It could restore the antitumor function of cytotoxic T cells by blocking immune checkpoints, like PD-1 and CTLA-4 (2). However, ICI monotherapy is approved and useful for some cancers (e.g., breast, lung, kidney, bladder) (3) but has a very limited role in other cancers, with an ORR rate of around 3%–5% in prostate cancer (4), around 10%–13% in pancreatic cancer (5, 6), etc. Several clinical trials have explored the use of single-agent immune checkpoint inhibitors for the treatment of metastatic castration-resistant prostate cancer (mCRPC). The benefit seems to be restricted to a subset of patients (7). In a retrospective series of 11 patients with mCRPC characterized by MSI-H/dMMR who were treated with anti–PD-1/PD-L1 inhibitors alone or in combination with another CPI, the ORR was 50%; 54.5% of the patients demonstrated a PSA drop of higher than 50%, and four of these patients had a PSA decline of more than 99% (8). In 2017, the FDA approved

pembrolizumab for the treatment of unresectable and metastatic tumors with an MSI-high (MSI-H) status or dMMR after progression on standard lines of treatment (9). Low incidence of TMB is one of the most important factors for ICI therapy failure (10). Behind this perspective, the true mechanism of ICI therapy is based on the antitumor function of CD8+ cytotoxic T lymphocytes. To fight against tumor, the human immune system must first recognize tumor cells with neo-antigens; then, T cells need to move to the tumor sight and contact with tumor cells to provide their antitumor effect. However, in the meantime, tumors would develop multiple mechanisms (mainly including T-cell priming dysfunction and T-cell homing dysfunction) to escape the hunt from tumor-reactive T cells (11). These tumors are called "Cold" tumors, tumors with a specific tumor microenvironment which causes the failure of ICI therapy (12).

"Cold" tumors have a limited infiltration of cytotoxic T lymphocytes (CTLs), a high activity of suppressor immune cells, and a poor response to ICI therapy. "Hot" tumors, on the opposite, are tumors that respond better to ICI therapy due to high infiltration of T cells and low activity of suppressor immune cells (Figure 1). "Cold" tumors are also called infiltrated excluded, non-inflamed, or non-immune reactive tumors (13). It is considered that prostate cancer is one of the "Cold" tumors (14).

Prostate cancer is the second most common cancers among men, after melanoma (15, 16). After definitive therapy, high-risk prostate tumors may have a recurrence and metastatic rate of around 30% (17). Although androgen deprivation therapy (ADT) is a standard therapy for prostate cancer in advanced stages, the tumor would still progress eventually. Around 70%–80% of prostate cancer would metastasize into the bone, which worsens the prognosis for prostate cancer patients (16). The immunologic landscapes of prostate cancer allow limited infiltration of immune cells into the tumor microenvironment (TME). The dysfunction of the immune system prevents it from initiating an effective response against tumors (18). Consequently, prostate cancer has a poor rate of response to ICI therapy (19).

Radiotherapy increases the levels of immune checkpoints (PD-1, CTLA-4) locally in the tumor by enhancing the activation and infiltration of immune cells into the TME and the level of PD-L1 expression on the surface of tumor cells (20). Moreover, immune check inhibitors can restore the antitumor activity of T cells by binding PD-1, CTLA, and PD-L1 and lower the immune escape of tumor cells (21). Consequently, radiotherapy and immune checkpoint inhibitor therapy are mechanistically complementary, and their combination may provide favorable outcomes in "Cold" tumor treatments. To improve the therapeutic effect of immune checkpoint blockade in prostate cancer, in this paper, radiotherapy is suggested as a preferable option for combined immune checkpoint inhibitor therapy to achieve a better therapeutic effect in patients with prostate cancer.
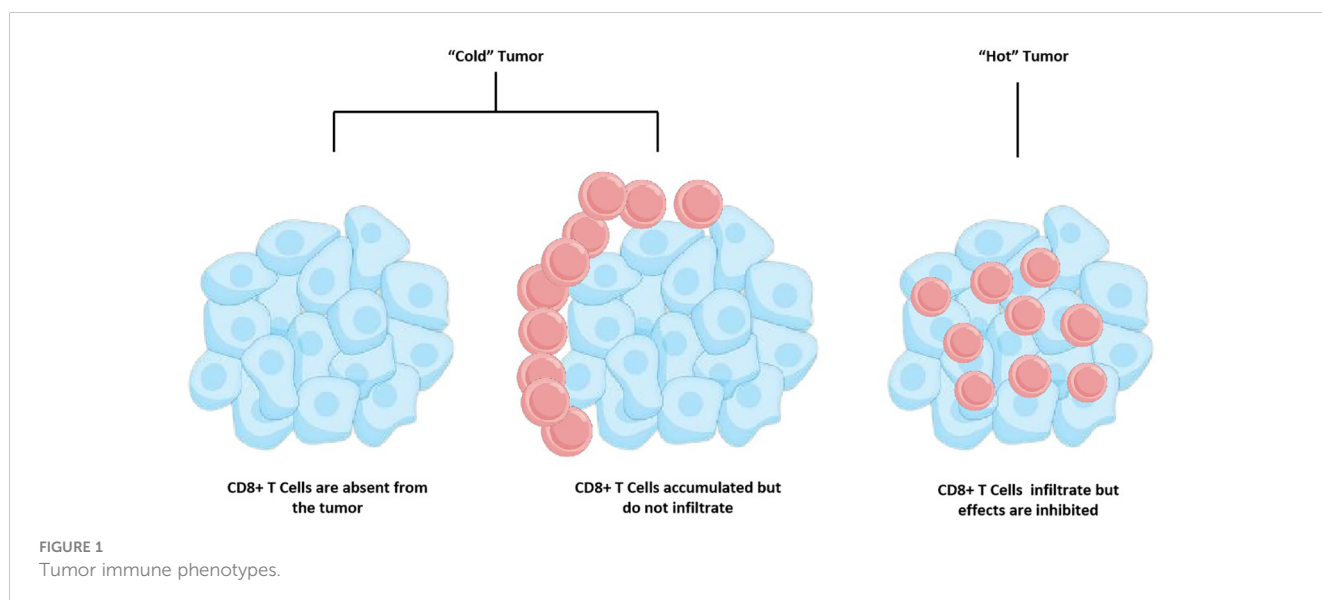
Mechanisms of the "cold" tumor resisting ICI

The primary characteristic of a "cold" tumor is the absence of T-cell infiltration, which leads to low response rates of ICI therapy. Either defective T-cell priming or defective T-cell homing to the tumor bed is the reason for the failure of T-cell infiltration.

T-cell priming dysfunction

Lack of tumor antigens and defects in tumor antigen presentation machinery are two main reasons for defective T-cell priming.

Lack of tumor antigens is the most direct cause of T-cell priming disorders. There are two categories of targeted tumor antigens: non-mutated self-antigens and neoantigens (22). Self-antigens, such as tumor-associated antigens (TAAs) and cancer/testis antigens (CTAs), are overexpressed non-mutated proteins in

FIGURE 1
Tumor immune phenotypes.

"Cold" Tumor

"Hot" Tumor

CD8+ T Cells are absent from the tumor

CD8+ T Cells accumulated but do not infiltrate

CD8+ T Cells infiltrate but effects are inhibited

tumor cells. Neoantigens, also called tumor-specific antigens (TSAs), are specific mutated proteins in tumor cells. The recognition of tumor neoantigens by the immune system might promote T-cell priming and infiltration to the tumor region, which may result in antitumor responses (23).

This leads to tumor mutation burden (TMB), the total amount of non-synonymous single-nucleotide mutations in a tumor, a potential predictor for the response of ICI therapy. It is generally believed that tumors with a higher TMB would carry a higher neoantigen load that could be recognized by the immune system, making greater T-cell infiltration (24). Multiomics network analysis has further proved that higher mutation or neoantigen burden was positively correlated with higher CTL infiltration in various solid tumors, whereas lower mutational or neoantigen burden might be correlated with the lack of CTL infiltration and the failure of ICI therapy (25). However, kidney cancer presents with low TMB incidence, which showed 40% of response rate to ICI therapy (26). In gastric cancer, no difference in response rate was observed between TMB-H (16.7%) and TMB-L (16.2%) tumors treated with ICI (27). This evidence suggests that there are many other factors determining ICI response or resistance.

Damage to the machinery responsible for processing and presenting tumor antigens is another important cause of T-cell priming or homing defects in the tumor bed (APM). Normally, antigen-presenting cells (APCs) could express the tumor neoantigen peptide–MHC class I complex on its surface after recognition. However, impairs in the APM pathway, like downregulation of MHC-I molecule expression, could lead to the failure in presenting antigen peptide-MHC class I complexes even though tumor-specific antigens were present. During antigen processing and presentation, transporters associated with antigen processing (TAP) transport cytosolic cleaved antigens to the endoplasmic reticulum to bind with MHC molecules. Therefore, the deletion of TAP could also cause antigen presentation process failure, which further affects the priming of T cells (28). Beta-2-microglobulin (B2M), the invariant chain of the MHC, is critical for the successful folding and transport of MHC-I to the cell surface (29). Knocking down the B2M gene in human carcinoma cell lines led to the absence of MHC-I molecules expressed on their surface and the failure of tumor-specific T-cell recognition and cytotoxicity (30). These findings suggest that defects in the APM pathway would interfere with T-cell priming and the effectiveness of ICI therapy despite the presence of tumor antigens.

Dysfunction of dendritic cells (DCs) could also impair T-cell priming. DC activation requires pattern recognition receptors (PRRs), which are found on the surface of DCs and include pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (31). This activation enables DCs to present a tumor antigen peptide-MHC class I complex to T cells when contracting with them. DCs could also express secondary signaling necessary for T-cell activation, such as B7 (32). Tumor cells could impair the function of DCs by trapping "danger signals". For example, stanniocalcin 1 (STC1) could trap DAMPs, leading to the failure of DC activation and T-cell activation. This eventually contributes to tumor immune escape (33). Furthermore, BATF3 DCs are the primary source of CXC-chemokine ligand 9 and 10 (CXCL9 and CXCL10), two key chemokines required for the recruitment of CD8+ T cells to tumors. In the absence of BATF3 DCs, CD8+ T cells would not migrate to the tumor region (34). However, a number of tumor types, including prostate cancer, did not express CXCL9 and CXCL10, which prevented CD8+ effector T cells from activating (35).

Differentiation and recruitment of DCs require various factors like Fms-like tyrosine kinase 3 ligand (FLT3L) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (36). Deficiency of these factors could result in a reduced number of DCs in secondary lymphoid organs and attenuated T-cell immune responses (37). To sum up, impaired DC activation, a lack of DCs, and the overexpression of co-suppressive signals could all lead to T-cell activation failure as DC-T cell crosstalk plays a vital role in naïve T-cell priming.

T-cell homing dysfunction

Recent evidence has shown that the activation of tumor cell oncogenic pathways is associated with the immune-suppressive TME of "cold tumor", which causes the potential for ICI therapy resistance. When the WNT pathway was activated, CCL4 expression is downregulated, resulting in decreased recruitment of BATF3 DCs to the TME (38). Also, the WNT pathway activation would cause decreased expression of CXCL9 and CXCL10, making CTLs not being able to recruit to the tumor region. Furthermore, Spranger et al. have found a negative correlation between CD8A expression and activation of the WNT signaling pathway *via* human metastatic carcinoma sample analysis (25). Direct injection of BATF3 DCs into the tumor region restored CXCL9 and CXCL10 expression and T-cell infiltration in WNT signaling pathway-positive tumors (39). Activation of the PI3K/AKT pathway could decrease autophagic activity by reducing the lipidation of the autophagosome protein LC3, which inhibits T-cell homing to the cancer site (40). A TCGA dataset analysis also revealed that the expression of T-cell effector molecules (like IFN-γ, granzyme B) was negatively correlated with the activation of the PI3K/AKT pathway in various carcinomas (40). Oncogenic K-RAS mutations might also contribute to tumor-promoting inflammation through the production of inhibitory cytokines (IL-6, IL-8, etc.), the activation of NLRP3 inflammasome, and the release of chemokines (CCL5, CCL9, etc.) (41). In addition, oncogenic MYC signaling could overexpress CD47 and PD-L1 on tumor cells. As a immune checkpoint, CD47 can attach to signal regulatory proteins α(SIRPα) on the surface of macrophages in the tumor microenvironment and deliver "don't eat me" messages in order to evade immune surveillance (42, 43). Consequently, CD47 becomes an attractive target for immunotherapy. PD-L1 and CD47 are both highly expressed in tumor cells and can be simultaneously regulated by MYC. A high expression of MYC in tumor cells can regulate the tumor microenvironment by acting on innate immune cells and adaptive immune cells as well as cytokines,

and activation of MYC can upregulate the expression of CD47 and PD-L1 leading to immunosuppression and tumor proliferation (MYC can directly act on the promoters of CD47 and PD-L1 and then regulate their mRNA and protein expression levels) (44).

The immunosuppressive cells at tumor sites could also prevent T-cell homing in "cold tumors". For example, CXCL12, generated by cancer-associated fibroblasts (CAF), could inhibit T-cell infiltration in the tumor region (45). Moreover, CTLs could not reach the edge of "cold" tumors because they could be trapped within the stroma of the tumor or in the peri-tumoral tissue because of the unique immunosuppressive structure built by immunosuppressive cells, like tumor-associated macrophages (TAM), cancer-associated fibroblasts (CAF), regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs) (45) (Supplementary Figure S1).

Immune landscape of prostate cancer

Prostate cancer is considered to be a "cold" tumor as the tumor mutation burden is low, causing a lower number of T-cell infiltrations (46). Prostate cancer also presents a lot of hypoxic zones, which seriously affect the antitumor function of T cells by a variety of mechanisms including the depletion of essential nutrients, abnormal angiogenesis, increased expression of adenosine, acidic pH, immunosuppressive transforming growth factor β (TGF β), and upregulation of PD-L1 (47, 48). Moreover, hypoxic zones could attract immature myeloid cells into the tumor region and turn into myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages, making the TME of prostate cancer even more immunosuppressed (47). In fact, the immune cells that are part of the prostate tumor microenvironment are frequently characterized by an anergic and immunosuppressive phenotype and include regulatory T cells (Tregs), M2-polarized tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs) (49).

Furthermore, the expression of major histocompatibility complex (MHC) class I, a molecule presenting antigenic protein fragments to cytotoxic T cells, is lost or diminished in prostate cancer (50, 51). Also, PTEN, whose existence could improve the immunosuppressive tumor microenvironment, is frequently downregulated (52), leading to a decrease in the response to immunotherapy in prostate cancer. Single-cell analysis revealed that CD4+ FOXP3+ CD25+ T cells and CD8+ FOXP3+ CD25+ T cells are the main T-cell types in prostate cancer. However, FOXP3+ T cells are immunosuppressive regulatory T cells that both inhibit naïve T-cell proliferation and produce inhibitory cytokines, like IL-6 and IL-8 (53, 54).

Radiotherapy in prostate cancer

Radiotherapy is considered to be one of the most effective therapies for prostate cancer. There are mainly two techniques applied to deliver radiations to the prostate cancer area, namely, brachytherapy (the use of seeds placed in the body) and external beam (projecting energy through the skin) (55).

Brachytherapy means the direct placement of radioactive sources into the prostate gland under the guidance of transrectal ultrasound. There are two dose rates, low dose rate and high dose rate. The low dose rate refers to the permanent implantation of seeds in the prostate tissue so that the seeds project radioactivity gradually. This dose is mainly used in clinics (56). The high dose rate refers to a radiation therapy whose dosage is high enough to possibly lead to leakage to surrounding organs from the prostate tissues. As a result, the high dose rates are rarely applied in the clinic. The advantage of brachytherapy is that the whole process is convenient for patients as it only takes a day or less and no further intervention is needed (57). In addition, the erectile function would not be affected due to brachytherapy (58).

External beam radiation therapy (EBRT) is a commonly used local treatment of tumors in which strong X-ray would emit specifically targeting the prostate tissues (59). Its radiation dose is high (higher than brachytherapy), whereas its radiation would emit less to the surrounding tissues. Radiotherapy could be used in not only patients with localized prostate cancer but also patients with bone metastasis or with metastatic castration-resistant disease (60).

Combination therapy of radiation therapy and androgen deprivation therapy (ADT) is considered to be effective for patients with prostate cancer (61). It is reported that this combination has more advantages than surgical therapy. There are lower risks, such as hemorrhage, myocardial infarction, pulmonary embolism, urine incontinence, and erectile dysfunction, when treating prostate cancer in its early stages (62). This evidence also proved the concept that radiation therapy could be used in company with other therapy in patients with prostate cancer.

Radiotherapy could "heat" prostate cancer

The conventional goal of radiation in the treatment of cancer is to use high-energy particles to cause deadly DNA damage in tumor cells, causing the cancer cells to eventually perish (63). Recently, the ability of radiotherapy to cause an antitumor immune response has drawn large attention as cancer immune therapy has achieved great success in clinics (64). Studies have proved that radiotherapy could cause immunogenic cell death and cellular stress, which could increase the exposure of tumor-associated antigens and damage-associated molecular patterns (DAMPs) (65). Elevated tumor-associated antigens and DAMPs could activate DCs. Furthermore, DCs could present tumor-associated antigens to CD8+ T cells and help recruit CD8+ T cells into the TME to enhance the antitumor responses (66).

Furthermore, the interferon genes (STING) pathway would be activated in the presence of DAMPs. Production of interferon gene pathways, including type I interferons (IFN-α and IFN-β), could further activate antitumor immune responses (67). Both preclinical and clinical studies validated that radiotherapy could increase antitumor immune cells such as CD4+, CD8+ T, cytotoxic NK, and CD8+CD56+ natural killer T (NKT) cells infiltrating into the

TME (68, 69). All of these data imply that radiotherapy may transform "cold" cancers with low immunogenicity and immune cell infiltration into "hot" tumors with dense immune cell infiltration.

Meanwhile, elevated interferon activity *via* radiotherapy could upregulate exhaustion molecules such as PD-1 and PD-L1 (70, 71). Therefore, the combination of radiotherapy plus immune checkpoint inhibitor would be necessary to block the elevated exhaustion molecules, thus avoiding cancer immune escape and enhancing the therapeutic effect of radiotherapy (Supplementary Figure S2).

Clinical studies exploring radiotherapy plus immune checkpoint blockade

There are several clinical trials exploring the therapeutic effect of radiotherapy plus ICI in treating cancers.

A phase 1 study combined anti-PD-1/PD-L1 therapy with stereotactic body radiotherapy (SBRT); finding the combination could be well-tolerable by patients (72). There are five phase 1/2 studies that also showed that anti-PD-1/PD-L1 therapy plus radiotherapy was tolerable for patients with advanced non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and small cell lung cancer (SCLC) (73–77). These findings indicate that the combination of radiotherapy plus ICI is feasible for cancer treatment.

As this field is in its preliminary stages, most studies have shown encouraging efficiencies in patients treated with combination of radiotherapy and ICI. Most combinations of radiotherapy and ICI are based on stereotactic body radiotherapy (SBRT), which could precisely deliver ablative doses of radiation in image-guided and intensity-modulated manners (78). A phase 2 study in resectable non-small-cell lung cancer showed that patients who received 24-Gy SBRT before durvalumab (PD-1 antibody) treatment demonstrated a higher objective response rate (ORR) (53.5%) than patients who only received durvalumab or SBRT (6.7%) (79); however, long-term prognoses (such as OS, PFS) were not recorded in the study. A phase 3 study found that stage III NSCLC patients undergoing radiotherapy and durvalumab acquired a markedly improved progression-free survival (PFS) (17.2 *vs.* 5.6 months) and overall survival (OS) (The 12-month overall survival rate was 83.1% in the durvalumab group, as compared with 75.3% in the placebo group. The 24-month overall survival rate was 66.3% in the durvalumab group, as compared with 55.6% in the placebo group.) compared with those who only received radiotherapy (80). Tai et al. showed that combination of Y-90-RE with nivolumab had an optimistic ORR of 31% in patients with advanced hepatocellular carcinoma (HCC) (81). Chiang et al. reported an astonishing 100% ORR in five patients treated with SBRT followed by nivolumab for large unresectable HCC; another case report showed complete pathological response following Y-90-RE and nivolumab bridging therapy prior to partial hepatectomy (82, 83). Another phase I trial that evaluated liver/lung SBRT with ipilimumab reported that 23%

of patients experienced clinical benefit which corresponded to an increase in CD8+ T cells and CD8+/CD4+ ratios (84). Although these findings are promising, these trials only recruited limited patients in only one medical center.

There are also trials that have been carried out to investigate the interaction of radiation and ICI therapy in prostate cancer. Slovin et al. explored the combination of ipilimumab (anti-CTLA-4) and radiotherapy in patients with metastatic castration-resistant prostate cancer, finding that ipilimumab 10 mg/kg plus radiotherapy suggested clinical antitumor activity with disease control and manageable adverse events (85); in addition, the trial suggested that treatment with ipilimumab improved progression-free survival compared with placebo (median 4.0 *vs.* 3.1 months in the placebo group; p < 0.0001). Two phase 3 studies have evaluated the therapeutic effect of ipilimumab plus radiotherapy in patients with metastatic castration-resistant prostate cancer (86, 87). In a preplanned long-term analysis including 799 patients, ipilimumab plus radiotherapy improved the overall survival of these patients significantly. The OS rates at 3, 4, and 5 years were approximately two to three times higher than that of patients receiving only radiotherapy (87).

PD-L1 expression was observed in serial biopsy samples in a phase 1 trial of nivolumab in combination with external beam radiation therapy and brachytherapy in patients with grade 5 prostate cancer and increased immune infiltration. A strong immune infiltrate was observed in the tissues, with an increase in CD8+ and FOXP3+/CD4+ T cells in the tissues and CD4+ effector T cells in the peripheral blood (88). Although a potentially T-cell-mediated antitumor effect of ipilimumab was observed in 13%–23% of men enrolled in the two trials, these data suggest that only a minority of men with mCRPC derive a benefit from the single-agent ipilimumab. Based on preclinical data showing that radiotherapy could improve the tumor microenvironment and the antitumor effect of CTLA-4, these studies used radiotherapy as a boost for ipilimumab. The long-term analysis shows that OS is improved with ipilimumab plus RT versus placebo plus RT in patients with post-docetaxel mCRPC, and treatment was associated with a fraction of patients with long-term survival. Although these findings might suggest that the combination of radiotherapy plus ICI would bring benefits to patients with advanced-stage prostate cancer, no definitive phase 3 studies are testing this combination of ICI plus radiotherapy in prostate cancer; more clinical trials should be conducted to confirm its therapeutic effect and other details such as dose, volume, fractionation, and sequence. The current research studies are listed in Table 1, which can further prove the efficacy of radiotherapy combined with ICI in prostate cancer. Those studies might also point out patients with which a specific prostate cancer stage could benefit most from using this combination. Furthermore, these studies might also show the association between radiotherapy plus ICI and conventional therapy such as androgen deprivation therapy, answering questions such as whether this strategy is better. Whether this strategy could be used on patients undergoing androgen deprivation therapy and so on.

TABLE 1   Trials of radiotherapy with ICI in prostate cancer.

Trials	Treatment plan			Status	Main outcome	Reference
	Experimental group A	Experimental group B	Experimental group C			
Karim F et al	Radiotherapy + ipilimumab	Ipilimumab	–	Finished	Radiotherapy with ICB improved OS in patients with post-docetaxel mCRPC	(84)
	SRT + pembrolizumab	Pembrolizumab	–	Recruiting	Not published	NCT04931979
	SRT + ipilimumab/nivolumab	Ipilimumab/ nivolumab	–	Recruiting	Not published	NCT05655715
	Nivolumab+ brachytherapy + external beam radiation therapy+ ADT	–	–	Recruiting	Nivolumab with brachytherapy is associated with evidence of increased immune infiltration and antitumor activity	NCT03543189
	SRT + REGN2810	SRT + ipilimumab	SRT + REGN2810 + ipilimumab	Recruiting	Not published	NCT03477864
	SRT + nivolumab CDX-301 + poly-ICLC	Nivolumab + CDX-301 + INO-5151	–	Finished	Not published	NCT03835533
	Pembrolizumab + SRT + ADT	–	–	Recruiting	Not published	NCT04569461

ICI, immune checkpoint inhibitor; OS, overall survival; SRT, stereotactic body radiation therapy; ADT, androgen deprivation therapy; REGN2810, anti-PD-1 monoclonal antibody; CDX-301, the dendritic cell growth factor fms-like tyrosine kinase 3 (FLT3) ligand, a dendritic cell mobilizer; Poly-ICLC, a TLR3 agonist; INO-5151, a combination of DNA plasmids encoding interleukin-12 (INO-9012 formulation) and prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSMA) (INO-5150 formulation) to activate a cytotoxic T-lymphocyte for an antitumor response.

Perspective

To sum up, radiotherapy combined with immune checkpoint blockade may be a more effective combination to enhance the efficacy of ICI monotherapy in the treatment of prostate cancers, since radiotherapy may boost tumor antigen presentation and CTL infiltration into the cancer region. However, there are currently only a few clinical trials focused on the combination of radiotherapy and immune checkpoint blockade for the treatment of prostate cancer. Further clinical trials are expected in the future to validate its efficiency in treating prostate cancer.

Author contributions

TL, XQ, XL, BX, and JXL conceptualized, wrote, and reviewed the manuscript. JYL, JY, FX, JL, and GY were involved in writing the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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