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Review

Boosting the Immune Response – Combining the Local and Immune Therapy for Prostate Cancer Treatment

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Abstract: Due to slow progression and susceptibility to radical forms of treatment low-grade PC is associated with high overall survival (OS). With the clinical progression of PC the therapy is getting more complex. The immunosuppressive tumor microenvironment (TME) makes PC a difficult target for most immunotherapeutics. Its general immune resistance is established by i.e. immune evasion through Treg cells, synthesis of immunosuppressive mediators, and defective expression of surface neoantigens. The success of sipuleucel-T in clinical trials initiated several other clinical studies that specifically target the immune escape of the tumor and eliminate the immunosuppressive properties of TME. In the settings of PC treatment, this can be commonly achieved with radiation therapy (RT). Also, focal therapies usually applied for localized PC, such as high-intensity focused ultrasound (HIFU) therapy, cryotherapy, photodynamic therapy (PDT), or irreversible electroporation (IRE) were shown to boost anti-cancer response. Nevertheless, the present guidelines restrict their application to localized and low-grade PC. This review explains how RT and focal therapies enhance the immune response. We also provide data supporting the combination of RT and focal treatments with immune therapies.

Keywords: metastatic castration-resistant prostate cancer; cancer vaccines; immunotherapy; focal therapy; combination immunotherapy; tumor immune microenvironment; in vivo vaccination

1. Introduction

In 2020, prostate cancer (PC) was the second most frequent cancer and the fifth cause of cancer-related death among men. In more than half of the countries of the world it was the most frequently diagnosed cancer in men [1]. While mortality rates are relatively low in comparison to other malignancies, metastatic castration-resistant prostate cancer (mCRPC) remains an incurable condition, with few treatment strategies providing any clinical benefit [2].

Focal therapies are minimally invasive treatment strategies used in the management of PC to provide a local control of the disease, minimalizing the risk of possible complications. Despite their limitations, these strategies show some promising oncological results, especially from a short-term perspective [3]. Immunological impact of focal therapies, as well as immunotherapy of PC itself, have been addressed by academic research for years now. Thus, it was a substantial breakthrough when sipuleucel-T became the first therapeutic vaccine for patients with mCRPC approved by the United States Food and Drug Administration (FDA), and the first autologous cellular therapeutic

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vaccine in oncology [4,5]. Nevertheless, the clinical benefit of immunotherapy alone remains limited due to low-grade inflammation in the tumor microenvironment (TME). However, both radiotherapy (RT), and various focal therapies have the potential for activating the anti-tumor immune response, and, therefore, enhance efficacy of immunotherapy [6–8].

The purpose of this review is to identify the immune properties of RT, and focal therapies, including high-intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy (PDT), and irreversible electroporation (IRE). Furthermore, we attempted to compile available knowledge on different combinational therapies including both a focal and an immunotherapeutic component.

2. Immunological Background of Prostate Cancer

2.1. PC Microenvironment

Microenvironment of PC consists of numerous elements, including both neoplastic cells, and diverse host cells. The host component comprises stromal cells and extracellular matrix, endothelial and vascular cells, immune cells, and various soluble factors [9]. The tumor microenvironment (TME) in PC plays an ambiguous role in carcinogenesis. Particularly, the impact of the immune system is highly complex, as both innate and adaptive immune response mechanisms can provide anti-neoplastic activity, as well as propagate carcinogenesis [10]. For example, cytotoxic T-lymphocytes (CTLs), which are one of the most important cancer cell killers, are also able to secrete transforming growth factor-beta (TGF-β), which both supports tumor growth, and induces immune suppression [11].

There is a multitude of mechanisms affecting the TME in PC, including inhibition of neoantigens expression and instability of rapid cell division, DNA damage response (DDR) genes defects, decreased human leucocyte antigens (HLA) expression, phosphatase and tensin homolog (PTEN) protein loss, and dysfunction of in interferon (IFN) type I signalling [12].

2.2. T-cell Infiltration

Many immune cell types play a role in TME functionality, although one considered most vital, is the T-cell population, especially CTLs [13]. They are the key elements of the physiological cancer immunity cycle, which is briefly summarized in Figure 1 [14]. T-cells are recruited from peripheral blood after antigen-presenting cells (APCs), specifically dendritic cells (DCs) and macrophages, capture neoantigens released by the tumor. Presenting the abovementioned antigens to CTLs using a major histocompatibility complex (MHC) is called priming, and takes place in the local lymph nodes. This results in recruiting and stimulating more T-cells, including $CD4^+$ cells. CTLs infiltrate the tumor, recognize cancer cells and kill them. Neoantigens are then released and the process comes full circle [14]. Localization and density of tumor infiltrating lymphocytes (TILs) and memory T-cells within the center of the tumor and its margins were the foundation for creating the “immunoscore”. It divides tumors into two groups: T-cell inflamed (“hot”) and non-T-cell inflamed (“cold”) [15]. This immune contexture is significant in efficacy of the therapy in the variety of cancers. Many publications indicate that a high level of TILs shows a positive prognostic value [16–21]. PC is primarily described as a “cold” tumor, with a low inflammation burden and immune activation [22]. However, the impact of TME on PC oncological outcomes is unclear [12]. Some studies show that the high intratumoral density of CTLs is associated with improved cancer-specific survival (CSS) in PC patients undergoing RP [23,24]. Others show that the higher the level of CTLs infiltration in PC, the greater the risk of distant metastases and biochemical recurrence [10,25]. Although the connection between inflammation and tumorigenesis remains unclear, one of the main goals of various local pre-immunotherapy technics is to propagate inflammation of TME, converting it to inflamed and susceptible to immunotherapy [26].

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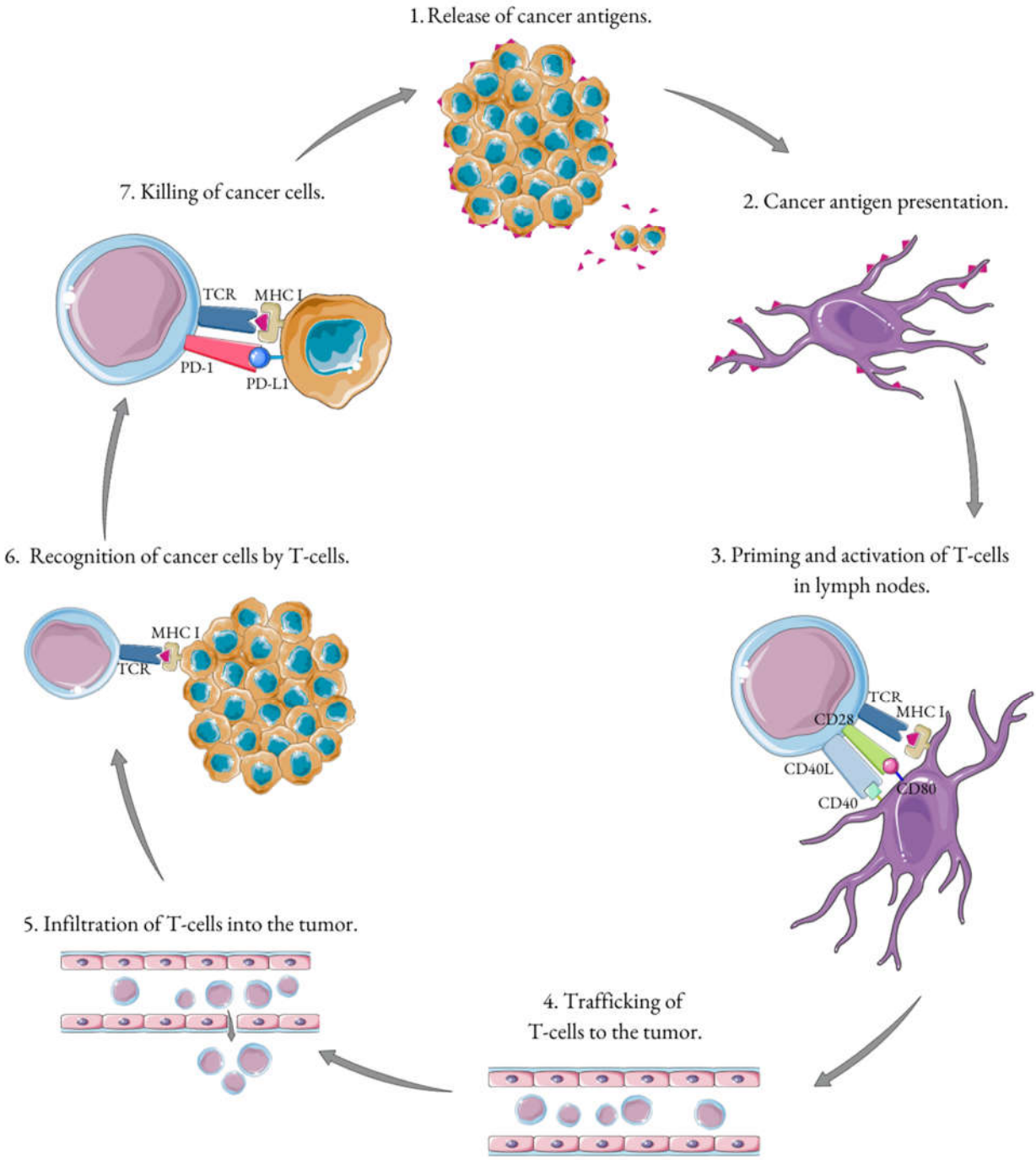

Figure 1. Schematic overview of cancer immunity cycle.

2.3. Regulation of the T-cell Response

After a T-cell is initially activated during priming, the second step of activation takes place: binding of costimulatory molecules, CD80 (B7-1) or CD86 (B7-2), which serve as ligands on APCs, and CD28, a receptor expressed on T-cells [27–29]. Cytotoxic T-lymphocyte antigen 4 (CTLA-4, or CD152) is a coinhibitory glycoprotein receptor expressed on the surface of the T-cell, competing with CD28 for B7 ligands. CTLA-4 is induced after T-cell activation (except for regulatory T cells [Tregs], which express it continuously), and because of its higher affinity for B7 molecules, it successfully outcompetes CD28 receptor [30–33]. The B7:CTLA4 interaction leads to inhibition of cell cycle progression through IL-2 accumulation [34,35]. Programmed death receptor 1 (PD-1) is another co-inhibitory receptor on the surface of T and B-cells. PD-1 ligand 1 (PD-L1

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or CD274) and PD-1 ligand 2 (PD-L2 or CD273) are two known ligangs for PD-1 receptor, expressed on macrophages, DCs and other immune cells [36]. Although the interaction of PD-L2 and PD-1 has an immunosuppressive outcome, it is the PD-L1:PD-1 binding, that induces the conversion of naïve T-cells into Tregs [37–40]. CTLA-4, PD-1 and its ligands are parts of B7 superfamily molecules and are the most vital immune checkpoints (ICPs) [41].

2.4. Immune Evasion Mechanisms

Cancer cells have developed several immune evasion mechanisms associated with TME components. Immune evasion may be described as the entirety of biochemical interactions leading to the suppression of the natural immune response to tumor cells. The spectrum of possible "back doors" can be generally divided into a few mechanisms. These include 1) immune evasion through immune cells (most notably Tregs), 2) synthesis of immune-suppressive mediators, and 3) defective expression of surface neoantigens [42].

2.4.1. The Role of Specific Immune Cells

One of the cancer immune evasion mechanisms is CD4+ CD25+ FOXP3+ Tregs activity, as their physiological role is to modulate effector T-cells to support immunological tolerance to self-antigens (self-Ags) [43–45]. Tregs drawn by the tumor have higher suppressive properties compared to circulating Tregs, and are able to inhibit anti-tumor activity of other immune cells directly by cell-cell interactions or indirectly through synthesis and secretion of mediators, e.g. TGF-β, interleukin 10 (IL-10) [46,47]. Many tumor-associated Ags are expressed by host cells and can therefore act like self-Ags, which further emphasizes the Tregs role in immune evasion [48,49].

MDSCs are another heterogeneous group comprising immature DCs, granulocytes, and macrophages. Overproduction and concentration of these cell types in an inflammatory environment are correlated with the immunosuppressive qualities of TME [50,51]. Their functions include the inhibition of CLTs through various mechanisms (e.g. producing reactive oxygen species (ROS) or interactions with T-cell receptor [TCR]), suppressing natural killer (NK) cells, and Tregs induction [52–56]. MDSCs level correlate with the stage of PC, applied treatment, as well as with serum levels of crucial inflammatory mediators – IL-6 and IL-8 [57–59].

DCs are the most professional and efficient APCs, but their functionality is mutilated due to tumor's modulatory activity. Impaired DCs have lower levels of CD80, CD86, and CD40, thus they cannot present antigens and activate T-cells effectively enough [42,60]. The role of CD40 is highly complex, as it connects the T and B-cell responses. Namely, when DCs remain active and secrete IL-12, they may interact with CD40L on both T-cells and B-cells [61–64]. The first interaction induces the Th1 and IFN-γ secretion by the T-cells and the latter induces the class switching between IgG and IgA in B cells [65–67]. Also, the reciprocal expression of CD40 and CD40L on DCs, T cells and B cells links the humoral and cellular immune response, thus the reduced level of CD40 might lead to the impairments in both responses [67].

Tumor-associated macrophages (TAMs) are another important group contributing to PC TME. TAMs, especially M2 type, can stimulate tumor growth through the secretion of various mediators such as TGF-β, IL-10 and vascular endothelial growth factor (VEGF) [42,68–70]. Overexpression of TAMs in PC is correlated with unfavorable oncological outcomes in patients with PC, including biochemical recurrence (BCR), or worse distant metastasis-free survival [71–73].

The role of B-cells in immune evasion is not well understood in the case of PC. However, B-cells infiltration has prognostic significance in different cancers like breast cancer and melanoma [74]. B-cell TILs secrete a significant member of the TNF family, the lymphotoxin (LT), which promotes survival and proliferation of androgen-deprived cells, therefore encouraging castration-resistant PC (CRPC) development [75].

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2.4.2. Immunosuppressive Mediators

There are many immunosuppressive cytokines, which aid tumor in the immune evasion through the promotion of tumor proliferation, chemoresistance, angiogenesis, or migration, and these are most notably TGF-β, VEGF, IL-6, RANKL, or CXCL family [76]. TGF-β is one of the most vital mediators, acting both as a direct growth-promoting factor, as well as a stimulator of CD4+ T-cells-Tregs transformation [77–79]. Its other roles include promoting angiogenesis, and downregulating HLA-1 expression, thus inducing epithelial-mesenchymal transition (EMT) [76,80–83]. Another important cytokine is VEGF, which also contributes to tumor growth, as well as inhibits DCs differentiation. A similar role is performed by cancer-associated ganglioside antigens, which conduct an immunosuppressive activity through impairing CTLs and DCs [42,84,85].

2.4.3. Dysfunctional Expression of Surface Neoantigens

MHC Class I proteins are found on nucleated cells and platelet surfaces and their role is to be recognized by CD8+ T cells, which trigger the immune response against certain antigens by activating T cells and leading to target cell destruction [5,86,87]. Decreased MHC I presentation of tumor-associated antigens in one of the immune evasion mechanisms of PC [88,89].

2.5. Immune Check-Point Inhibitors

Immune checkpoint inhibitors (ICIs) are novel treatment options gaining more and more interest, as they already appeared to be successful strategies in cancers such as melanoma or lung cancer [90–96]. Among CTLA-4 inhibitors there are ipilimumab and tremelimumab, while the most pivotal PD-1 inhibitors comprise nivolumab and pembrolizumab; atezolizumab belongs to PD-L1 inhibitors [97].

Immune checkpoint blockade in PC remains a poor monotherapeutic tool [98,99]. Among the reasons for this state there are the low level of T-cell infiltration, "cold" immunogenic profile of the tumor, mutational burden, and immune evasion mechanisms [100–102].

3. Cancer Vaccines

3.1. Dendritic Cell Vaccines – Sipuleucel-T, DCvac/PCa, and others

As mentioned above, DCs are one of the most important features of the immune system; they are the most efficient APCs, not only able to activate T-cells (both Tregs and CTLs), but also NK cells. DC vaccines require blood-derived DCs, pulsing them ex vivo with the tumor-associated antigen and activating them by the specific adjuvant, and then reinjecting them to the patient [103]. The first DC vaccine approved by the U.S. Food and Drug Administration (FDA) was sipuleucel-T (Provenge®), and so far it remains the only DC vaccine for mCRPC [104,105]. Sipuleucel-T promotes the immune response against tumor cells using prostatic acid phosphatase (PAP) antigen-activated DCs [41]. A double-blind, placebo-controlled, multicenter phase III trial compared this DC vaccine to the placebo group, with the results of a 22% reduction in the risk of death and more than 4 months of improvement in overall survival (OS) [4]. Another trial showed even greater improvement in OS (up to 8.1 months), if sipuleucel-T therapy is extended by the APC8015F, a variant of the DC vaccine prepared from cryopreserved cells, which were frozen for future use [106].

DC vaccines are a very promising therapeutic tool, although requiring further clinical trials, and more attempts of combining them with different approaches [107]. There is only one ongoing trial assessing the combination of sipuleucel-T and other therapies: sipuleucel-T plus stereotactic ablative body radiation (SABR) (NCT01818986, phase II). Different phase III trial evaluates the efficiency of sipuleucel-T in reducing the progression of CRPC. The study includes active surveillance patients (the ProVent Study; NCT03686683).

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DCvac/PCa is an autologous DC-based vaccine, in which case DCs are pulsed with killed lymph node carcinoma of the prostate (LNCaP) cells. Several clinical trials have investigated its efficacy in PC. Podrazil et al. researched the combination of DCvac/PCa and docetaxel in phase I/II clinical trial in mCRPC, concluding this strategy is characterized by longer OS [108]. A similar study was conducted by Kongsted et al., which compared the same combination with docetaxel alone. PFS and disease-specific survival were comparable in both arms [109]. Fucikova et al. assessed the DCvac/PCa impact on PSA in patients with rising PSA after RP or salvage RT. PSA doubling time was elongated significantly in this variant [110]. Although DCvac/PCa immunological impact is quite well documented by now, translation to clinical benefits is needed and further clinical trials are required, especially concerning different combinations of therapies. A recent clinical phase III trial (the Viable) by Vogelzang et al. investigated DCvac/PCa combination with docetaxel and prednisone. The therapy failed to improve OS in patients with mCRPC [111].

Other DC-based vaccines that have been tested in the last decade in PC patients are prostate-specific membrane antigen (PSMA) and survivin loaded DC vaccine, mucin 1 (MUC1) vaccine, or T-cell receptor ɣ alternate reading frame protein (TARP) vaccine [112–115].

3.2. PROSTVAC – a PSA-Based Viral Vector Vaccine

One of the trailblazing PC vaccines is PROSTVAC (PSA-TRICOM), which comprises two recombinant poxvirus vectors containing transgenes for PSA and three costimulatory molecules: B7.1, ICAM-1, and LFA-3 [116,117]. A phase II trial analyzing neoadjuvant PROSTVAC in patients awaiting RP showed an increase in CD4+ and CD8+ T-cell infiltration of the tumor, as well as the peripheral immune response to neoantigens in 13 of 25 patients [118]. This promising immune response doesn't yet translate into a clinical advantage, however. In a phase III trial Gulley et al. concluded that despite the therapy was well-tolerated and safe for patients, treatment had no impact on median OS and alive without events (AWE) in patients with mCRPC, disappointingly [119]. Parsons et al. evaluated the preventive value of PROSTVAC in patients with localized PC which is managed by an active surveillance strategy. Although some initial data on the immunological effect of the vaccine is already available, we are looking forward to the summary of this phase II trial in the future (NCT02326805) [120]. Madan et al. revealed that the addition of PROSTVAC to enzalutamide doesn't affect PSA levels. The authors concluded that in this particular combination PROSTVAC effect may get lost and remain unseen due to patients' response to enzalutamide [121].

Several ongoing clinical trials are investigating different combinational management strategies including PROSTVAC. These are evaluating, among others, combination with nivolumab (NCT02933255, phase I/II) or nivolumab and ipilimumab (NCT03532217, phase I), with CV301 (a poxviral vaccine) and M7824 (a protein targeting PD-L1 and TGF-β) (NCT03315871, phase II), docetaxel (NCT02649855, phase II), or enzalutamide (NCT01867333, phase II).

TroVax is another viral vector, 5T4 (oncofoeatal glycoprotein) targeting vaccination. It's characterized by the good immune response in mCRPC and the potential to efficiently combine with docetaxel [122,123].

3.3. Peptide-Based Vaccines

Among peptide-based vaccines, one of the most interesting is GX301, consisting of four telomerase peptides and two adjuvants – Montanide ISA-51 and Imiquimod. Fenoglio et al. assessed its potential in phase I/II clinical trial, revealing its immunological response in PC and renal cell cancer (RCC). An increase in PFS and OS were observed as well [124]. Filaci et al. evaluated GX301 efficiency and immunological impact in mCRPC. The therapy didn't increase OS, though they observed that higher numbers of drug administration were correlated with increased immunological response [125].

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Cell division associated 1 (CDCA1) peptide vaccination was a topic of research in phase I clinical trial by Obara et al. CDCA1 is a peptide overexpressed in a few malignancies, including PC. Authors indicated that the vaccine is well-tolerated, and it boosts immunological response in patients with CRPC. Additionally, they pointed out that CDCA1 vaccine therapy might increase survival rates and aid to maintain the quality of life of CRPC patients, but further clinical trials are required to prove that [126,127].

Other peptide-based vaccinations include personalized peptide vaccination (PPV), which includes administration of different HLA-matched peptides, multi-peptide vaccines, and a vaccine targeting Ras homolog gene family member C (RhoC) [128–130]. Their clinical use requires further phase II and III trials in the future.

3.4. Whole-Tumor-Cell Vaccines

GVAX is a vaccine consisting of genetically modified PC cells, which undergone radiation. Studies suggest that this vaccination induces the immune response by activation of DCs and MDSCs [131]. A combinational therapy with ipilimumab has been investigated in a phase I trial by van den Eertwegh et al., which showed that GVAX is well-tolerated and safe for patients with mCRPC [132]. Once again, further clinical trials are required [133].

4. Focal Ablation and Immune Therapy Combination

4.1. High-Intensity Focused Ultrasound

Lately, HIFU appeared as a potential neoadjuvant-like therapy, serving as the first step of immunotherapeutic treatment. HIFU itself has already made an appearance in guidelines, concerning PC treatment options, although only as an investigational therapeutic tool, or as salvage therapy [134]. The most important benefit of HIFU is that it is minimally invasive when compared to surgical treatment, and it is devoid of systemic toxicity in comparison with androgen deprivation therapy (ADT) or chemotherapy, nevertheless possible adverse effects may occur quite frequently, and they include erectile dysfunction, urinary tract infections, rectal injuries, and more [135,136]. Properties of HIFU can be divided into a few groups – ablative and non-ablative (mechanical), immune, and biological effects; induced activity depends on a multitude of factors including frequency, pressure, duty cycle, and treatment time, achieved temperature, tissue susceptibility, and more. This allows to distinguish several possible technique variants, such as thermal ablation, thermal stress and hyperthermia, mechanical perturbation, or histotripsy [137]. However, first and foremost effect of HIFU is thermal ablation (by heating tumor tissue above approximately 55°C), resulting in coagulative necrosis, combined with additional cavitation formation, the most captivating secondary effect is anti-tumor immunity induction [138,139].

HIFU immunotherapeutic effect has lately been investigated in many kinds of malignancies. Hu et al. confirmed HIFU promotes DCs infiltration and activation in mice bearing colon adenocarcinoma and indicated that the mechanical components of this procedure may be successfully combined with other types of therapy [140]. Ran et al. showed that HIFU increases peripheral blood CD3+, CD4+ levels and CD4+/CD8+ ratio, enhances CTLs cytotoxicity against murine hepatocarcinoma, and inhibits tumor growth and progression in mice [141]. The impact on the CD4+/CD8+ ratio has been observed in the past by Rosberger et al. [142]. Activation of anti-tumor immunity promoted by HIFU can be partially explained by tumor debris "left-over" antigens immunogenicity, which was demonstrated by Zhang et al. in the murine hepatocellular carcinoma model [143]. Similar investigations have been conducted with other malignancies, such as melanoma, neuroblastoma, or pancreatic cancer [144–149]. Wu et al. researched tumor debris immunogenic properties in 23 patients with breast cancer. Using HIFU, they ablated primary tumors, and evaluated the expression of tumor antigens and heat-shock protein 70 (HSP-70), also pointing out the immunogenic potential of neoplastic debris [150].

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Sonodynamic therapy (SDT) is another promising strategy concerning the usage of ultrasound. It is based on the application of sonosensitizers, which is followed by their activation with the ultrasound. Activated particles then transfer the energy to oxygen accumulated in TME, creating ROS, which kill or damage tumor cells [151,152]. HIFU, and the spectrum of ultrasound-based therapies in general, is still a very modern approach used for enhancing the immune response. Further investigation is required, especially concerning PC.

4.2. Cryotherapy

Cryoablation or cryotherapy performed either as a focal therapy, or as the whole-gland procedure, is an ablation technique using extremely low temperatures to induce both necrosis and apoptosis of tumor cells. With the use of special cryoprobes, liquid nitrogen or argon, passaging from high pressure to an atmospheric pressure revealing its cooling effect, is implemented inside a prostate gland. Although it may be used as monotherapy, for this review we will only focus on its immunomodulatory activity and its synergy with immunotherapy.

Cryotherapy has a great enhancing potential to enhance the immune response, due to its significant preservation of tumor antigens and cytokines, compared to other ablation techniques based on high temperatures rather than hypothermia [153]. It is believed to leave tumor's intracellular molecules intact and, through attracting the immune system by these factors, stimulate tumor-specific immunity. However, cryotherapy can prompt both immunostimulatory and immunosuppressive response, which is strongly dependent on the type of induced cell death; studies suggest that necrosis, occurring mainly in the inner zone of the tissue, causes tumor cells to release danger-associated molecular patterns, which boost the immune response through the maturation of DCs, and consequently T-cells activation. However, apoptosis occurring primarily in the peripheral margin of the ablated organ leads to a lack of secretion of danger signals, therefore caring immunosuppressive impact [154]. The cryoimmunological effect is further described by the term "abscopal effect". This rare phenomenon refers to the systemic immunological impact a focal therapy has, and primarily refers to the reduction of a metastasis preceded by a localized treatment in a different location [155]. This process was proved to be mediated by CD8+ T-cells and correlated with a low level of CD4+CD5+ Tregs, as well as an increased level of IFN-ɣ [156,157].

Various investigations have been conducted on the theme of cryoimmunological synergy, both in murine models and in clinical trials. For instance, Gaitanis and Bassukas researched the impact of immunocryosurgery on basal cell carcinomas (BCC). Their study indicated that cryoablation combined with TLR7 agonist, imiquimod, can be a very effective substitute for surgical treatment for BCC under 20 mm in diameter [158]. In another study, Lin et al. prospectively evaluated allogeneic NK cell immunotherapy combined with cryosurgery in renal cell carcinoma (RCC). They once again proved a synergistic effect of the two therapies [159]. The same group of researchers conducted similar investigations in patients with lung and hepatocellular cancers, with similarly favorable outcome results [160,161].

So far clinical trials including synergy of cryosurgery and immunotherapy in patients with PC are rarely conducted. One of them is a therapy using granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine regulating functions of granulocytes and macrophages, as well as promoting survival of DCs [162,163]. These investigations revealed that GM-CSF administration enhances INF-ɣ secretion by T-cells on the base of prior cryoablation procedures, as well as the fact that GM-CSF increases levels of prostate-specific and nonspecific antigens. Ross et al. examined cryosurgery combined with short term ADT and pembrolizumab, a PD-1 inhibitor, proving local disease control, but questioning its potential for management of systemic disease [164].

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4.3. Photodynamic Therapy

PDT is an example of another targeted treatment option, that has already been used as an alternative to radical therapies, with intention of reducing levels of side effects, while maintaining favorable oncological outcomes [165]. This focal therapy is based on the usage of a laser of a specific wavelength, which activates the photosensitizer (PS), administered systemically or locally, and therefore generates ROS resulting in necrosis of the tumor cells. Depending on the qualities of photoagents, different effects can be achieved. Photothermal therapy (PTT) is a subtype of phototherapy different from PDT, as it engages PS properties not to produce ROS, but to execute a thermal effect through the conversion of absorbed laser light into heat [166].

As for PDT in PC, researchers point out high efficacy and low level of adverse effects of vascular-targeted photodynamic therapy (VTP) in comparison to other therapies, while addressing the great need for long-term benefit evaluation in randomized clinical trials (RCT) [167]. Rastinehad et al. introduced the results of a clinical trial in which they used gold-silica nanoshells (AuroShells) to conduct PTT in 15 patients with PC. The study revealed high-profile feasibility of the procedure, and once again pointed out its low-rate adverse effects burden [168]. Another study by Azzouzi et al. compared padeliporfin VTP with active surveillance strategy in a phase III RCT. They evaluated VTP as a safe and effective treatment for low-risk, localized PC, with a longer time to progression and a higher proportion of negative biopsy results in comparison to active surveillance [169]. On the other hand, a review of this investigation, aroused by the Oncologic Drugs Advisory Committee within the FDA, resulted in voting against approval of this therapeutic strategy in the United States, which emphasizes that the topic requires more RCTs proving its safety and efficacy [170]. Besides, a lot more clinical trials have been conducted, evaluating different dozes of various PS, varying laser wavelengths, and manipulating other parameters [170].

Nevertheless, more and more papers these days have been turning its attention to immunological aspects of PDT, as it propagates inflammatory response, induces necrosis, and promotes recruitment of neutrophils, and other immune cells. Furthermore, PDT can promote immune cells and engage them to eradicate distant metastases [171]. Therefore, the term photoimmunotherapy (PIT) has been forged, and it may be described as a combination of immunogenic properties of PDT and immunotherapy treatment [172]. The immunological effect obtained by PDT is complex and multi-level. First of all, it affects immune cells directly through the recruitment of neutrophils, DCs maturation, and macrophage activation, as well as accumulation of CTLs and affecting them through regulation of NK cells migration [173,174]. Secretion of IL-1 α/β, IL-6, IL-8, IL-10 and IL-12 is boosted, as is the release of a few secondary inflammatory mediators, including thromboxane and prostaglandins [175]. Furthermore, a few strategies concerning the combination of PDT with different immunotherapeutic strategies have been conducted and their results are promising. Li et al. evaluated the synergistic effect of CTLA-4 antibodies and single-walled carbon natotube-glycated chitosan complex (SWNT-GC) in metastatic mammary tumors in mice. Local administration was then followed by PTT. The results showed that this strategy prolonged survival time, suppressed primary tumors, and inhibited metastases [176]. Huang et al. introduced a drug conjugate consisting of protoporphyrin IX and NLG919, a potent indoleamine-2,3-dioxygenase (IDO) inhibitor, which is applied to the cells through liposomal delivery (PpIX-NLG@Lipo). They showed its strong ability to generate ROS after phototherapeutic procedure, as well as its potential of increasing CD8+ T-cells infiltration [177]. Kim et al. investigated the impact of PDT with Ce6-embedded nanophotosensitizer (FIC-PDT) with rapasudil, a rho-kinase (ROCK) inhibitor on the immune response in mice with uveal melanoma. Their research indicated that this combination demonstrates vaccine-like function, leads to CD8+ T-cells accumulation in the primary tumor and, in further synergy with anti-PD-L1 antibody, to metastasis inhibition [178].

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Nagaya et al. presented the effects of near-infrared photoimmunotherapy (NIR-PIT) with prostate-specific membrane antigen (PSMA) antibody in the PC cell line. The anti-PSMA antibody was conjugated to the light-absorbing agent, IR700DX. This antibody-PS conglomerate was observed to bind cell-specifically and to effectively kill PC cells after activation using NIR-PIT, with over two-thirds of the investigated tumors cured [179]. Research on the same topic was conducted by Watanabe et al. and it pointed to the possibility of using only fragments of anti-PSMA antibodies instead of the full antibodies, which may clinically translate to a more thorough penetration of the tumor milieu. Using smaller parts of antibodies should also shorten the time gap between injection of the PS and NIR-PIT [180].

4.4. Irreversible Electroporation

IRE is the permeabilization of cell membranes with electrical pulses, which affect membranous electrochemical potentials, creating pores in a lipid bilayer [181]. IRE has been already used in PC management, both as a focal therapy, and as the whole gland ablation. The procedure is based on needle electrodes, which are placed inside or nearby the targeted tissue. Then short electrical pulses are delivered, which induces apoptosis through a non-thermal mechanism [182]. Despite its role in the immune response is still unexplored, IRE seems to have immunomodulatory properties. The most pivotal immunological effect of IRE is a decrease of Tregs in TME; additionally, a decrease of MDSCs occurs as well [183].

The field of IRE-immunotherapy combinations in treating malignancies is still uninvestigated, though there are a few articles, especially on pancreatic cancer. Yang et al. for example revealed a connection between IRE and tumor-associated immune evasion in a mice model of pancreatic ductal adenocarcinoma (PDAC). They indicated that IRE combined with DC cancer vaccination increases the level of tumor-infiltrating cells including CD8+ T-cells and granzyme B+ cells in PDAC [184]. Similar investigations have been conducted by Zhao et al. and by He et al. Both studies showed promising results of the combination of IRE and PD-1 inhibitors in mice with PDAC [185,186].

A study by Burbach et al. examined the combination of IRE and ICI in mice with PC. Focal treatment using IRE combined with ICI led to the expansion of tumor-specific CD8+ T-cells in blood and TME [187].

5. Radiation and Immune Therapy Combination

RT has been used as a management strategy both in PC and in many other malignancies for years now. Its primary property exploited for the tumor treatment purposes was the effect on double-strand DNA, leading to its breakdown, and thus resulting in cell death, majorly through senescence, slightly less frequently through mitotic catastrophe, apoptosis, and necrosis [188]. Traditionally RT was considered to be a therapy of immunosuppressive qualities, therefore its combination with immunotherapy appeared to be irrational at first [189]. However, rapidly growing interest in TME affected the way RT is perceived, as its game with the immune system is far more complex and ambiguous [190,191].

Immune-stimulating effect of RT is generally achieved through induced cell death and modulating the composition of TME. One of the initial steps following tumor cell damage is enhanced release of damage-associated molecules, such as calreticulin, adenosine triphosphate (ATP), GM-CSF, high-mobility group box 1 (HMGB1), or heat shock proteins (HSPs) [192,193]. Afterwards, these damage signals activate DCs and APCs, which takes place in lymph nodes and leads to priming naïve T-cells in consequence [193]. Additionally, one of the radiation effects is the release of other inflammatory molecules, such as chemokines (e.g. CXCL10 or CXCL16) and other cytokines, including IL-1β, TNF-α, and type 1 and 2 interferons, which further contribute to increase inflammation in TME [194]. Finally, RT triggers upregulation of MHC I, NKG2D ligand, Fas/CD95, and other co-stimulatory molecules, resulting in cell death and further antigen exposure [193,194].

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Eckert et al. investigated the impact of RT on the immune system in 18 patients with localized PC. The study revealed the ambiguous effect of ionizing radiation, as RT resulted in a decrease in absolute leukocyte and lymphocyte counts, and an increase in Tregs and NK cells counts after over eight weeks since radiation. However, during RT an increase was observed in all immune cells counts excluding Tregs. Importantly, the percentage of CD8+ T-cells had its peak early during RT [195]. Nevertheless, Harris et al. researched a combination of RT and immunotherapy in a transgenic murine model and observed that the anti-tumor immune response occurred when immune therapy was administered 3 to 5 weeks after RT [19]. This further suggests the existence of a certain type of therapeutic time window, in which immunostimulatory properties of RT are emphasized, and the immunosuppressive component is partially inhibited. Nickols et al. researched the impact of stereotactic body radiotherapy (SBRT) on immunological homeostasis in a clinical trial evaluating resected prostate specimens of 16 patients. While prostates without SBRT were mainly lymphoid-diverse, specimens after SBRT were immunologically dominated by myeloid cells [196]. Keam et al. proved in their 24 patient clinical trial that high dose-rate brachytherapy (HDRBT) has a substantial potential in enhancing inflammation in prostate. In response to HDRBT an increase in CD4+ T-cells, macrophages and DCs counts was observed. Moreover, they evaluated tumor inflammation signature (TIS) and concluded that 80% of immunologically "cold" tumors were converted to "intermediate" or "hot" types [26].

Interestingly, RT is another management strategy with proven abscopal effect, hence resulting in regression of metastases, probably due to the outburst of tumor-associated antigens. This extremely rare effect is observed more often when RT is combined with immune therapy, particularly with checkpoint inhibitors [192]. Dudzinski et al. studied the combination of anti-PD-1 or anti-PD-L1 and radiation in mice, and they not only observed an increase in median survival in comparison to the drug alone (70% longer for anti-PD-1 and 130% for anti-PD-L1), but also detected the abscopal effect – a regression of unirradiated distant metastases [197].

In the research concerning the effects of RT and immunotherapy combination in mice, there have been a few distinguishing articles, including the paper from Wada et al. They assessed the efficacy of this therapy (immunotherapeutic component being GM-CSF) using an autochthonous model of PC. Improved OS and increase of the effector-to-regulatory TILs ratio, as well as treatment effect in both primary tumor and metastases, were observed [198]. Another investigation by Philippou et al. assayed the combination of anti-PD-L1 and RT and its impact on TME in PC. They observed macrophages and DCs counts increase, as well as upregulation of PD-1/PD-L1 in both arms of the study 7 days after RT. Radiation was observed to delay tumor growth and affect TME immunological composition. However, PD-L1 inhibition administered in one of the arms didn't affect tumor growth delay when compared to monotherapy [199]. Table 1 presents ongoing trials evaluating different combinations of RT and immunotherapy in PC management.

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Table 1. Ongoing trials assessing combination of radiotherapy and immunotherapy.

NCT Number	Phase	n	Setting	Immunotherapeutics	Radiotherapy
NCT03835533	I	45	mCRPC	NKTR-214, Nibolumab, CDX-301, Poly-ICLC, INO-5151	SBRT
NCT03795207	II	96	mPC	Durvalumab	SBRT
NCT03543189	I/II	44	PC	Nivolumab	Brachytherapy, EBRT
NCT03217747	I/II	173	mCRPC	Anti-OX40, Avelumab, Utomilumab	RT*
NCT03007732	II	42	PC	Pembrolizumab, SD-101	SBRT
NCT01818986	II	20	mCRPC	Sipuleucel-T	SBRT
NCT01436968	III	711	PC	Aglatimagene Besadenovec	EBRT

NCT: The National Clinical Trial; n: number of patients enrolled; PC: prostate cancer; mPC: metastatic prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; RT: radiotherapy; SBRT: stereotactic body radiation therapy; EBRT: external beam radiation therapy.

* The specific variant of radiation therapy wasn't specified.

The efficiency of radioimmunotherapy in patients with PC has been explored willingly in clinical trials for the last 10 years. Slovin et al. assessed the combination of anti-CTLA-4 antibody, ipilimumab, with external-beam radiotherapy (EBRT) in comparison to the drug alone. This phase I/II study on 50 patients evaluated adverse effects, defining them as manageable, and indicated anti-tumor activity [200]. In another investigation, a phase III trial concerning ipilimumab versus placebo after radiotherapy in patients with mCRPC that progressed after docetaxel chemotherapy has been conducted by Kwon et al. No notable difference in OS was found, though ipilimumab use was associated with a decrease in PSA levels and an increase in progression-free survival. Additionally, OS increase was observed in the ipilimumab subgroup without visceral metastases, with non-raised or mildly raised alkaline phosphatase, and without anaemia. Accordingly, the authors suggested that a specific constellation of prognostic features could potentially enhance clinical outcomes of radioimmunotherapy [201]. The final analysis of this phase III trial revealed that OS was two to three times higher at 3 years and beyond in favor of radiotherapy and ipilimumab combination [201]. Different clinical trials assessing nivolumab and brachytherapy or EBRT, as well as sipuleucel-T and EBRT combinations indicated that these therapies are safe and well-tolerated, though immunogenic effect and anti-tumor activity of radiation with nivolumab were observed, while radiation with sipuleucel-T showed no particular increase in the immune response [202,203]. Another phase II trial assessed the combination of sipuleucel-T and a radioisotope, radium-223, in patients with mCRPC. Despite paradoxically decreased the immune response in the combination arm, PSA levels were decreased and PFS and OS longer [204]. A case report by Han et al. presents a significant clinical response to pembrolizumab and radiation combination in patient heavily treated mCRPC with rectal involvement. After radiation and six cycles of the drug PSA was undetectable, prostate mass was decreased and rectal invasion was imperceptible in imaging studies [205].

Table 2 presents a comparison of the immunomodulatory impact of different local therapies on TME.

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Table 2. Immunomodulatory impact of local treatment strategies on TME.

Local Therapy	Immunomodulatory Effects	References
HIFU	▪ Promotion of DCs infiltration and activation. ▪ Increase of CD3+ and CD4+ levels cells, and CD4+/CD8+ ratio. ▪ Enhancement of CTLs cytotoxicity.	[140,141,150–152,142–149]
Cryotherapy	▪ Activation of T-cells. ▪ DCs maturation. ▪ The abscopal effect.	[154,155,164,156–163]
PDT	▪ Promotion of neutrophils recruitment. ▪ DCs maturation. ▪ Activation of macrophages. ▪ Regulation of CTLs and NK cells migration, increase of CD8+ T-cells infiltration. ▪ Secretion of IL-1, IL-6, IL-8, IL-10, IL-12, thromboxane and prostaglandins.	[171–180]
IRE	▪ Decrease of Tregs and MDSCs levels.	[183–187]
RT	▪ Enhancement of damage-associated molecules release. ▪ Activation of DCs and other APCs. ▪ Release of various cytokines (e.g. CXC10, CXCL16, IL-1, TNF-α, interferons). ▪ Upregulation of MHC I, NKG2D ligand and Fas/CD95. ▪ The abscopal effect.	[188,192,201–205,193–200]

HIFU: high-intensity focused ultrasound; PDT: photodynamic therapy; IRE: irreversible electroporation; RT: radiotherapy; DC: dendritic cell; CTL: cytotoxic T-lymphocyte; NK: natural killer; IL: interleukin; Treg: regulatory T cell; MDSC: myeloid-derived suppressor cell; APC: antigen-presenting cell; TNF: tumor necrosis factor; MHC: major histocompatibility complex.

6. Conclusions

The immunotherapy for PC remains an unexplored field, despite the initial success of sipuleucel-T. Further phase I/II clinical trials investigating combinations of focal and immune therapies are highly desirable. The RT and immunotherapy combo is an approach of the greatest potential to increase anti-tumor qualities of TME. Thus, it may be the most effective strategy stimulating the cancer-related immune response in PC.

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