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## Modern approaches for antiandrogen-resistant prostate cancer therapy

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# Modern approaches for antiandrogen-resistant prostate cancer therapy

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## ABSTRACT



Prostate cancer represents the leading malignant tumor in men over 50 years of age with 400,000 new cases being diagnosed yearly in Europe. Even if the incidence rate is higher than the mortality rate, still there is an increasing trend when speaking of its mortality. The increasing incidence of the metabolic syndrome, the unhealthy lifestyle, the high lipid and Calcium intake, the high spread of infections with Human Papilloma Virus, Human Herpes Virus, the excess of androgen consumption and the longer life expectancy, are few of the main causes of prostate cancer increasing incidence. The new systemic therapies such as immunotherapy with Checkpoint Inhibitors or Poly, ADP-Ribose Polymerase inhibitors and local experimental procedures addressing tumor destruction, such as High-Intensity Focused Ultrasound, the Cryo and Focal Laser Ablation, provide good outcomes and become new promising tools for prostate cancer therapy. Physicians consider these methods worth using; the efficacy of some specific categories of patients being arguments for their use in the current protocols even though solid data regarding the improvement of global mortality rates are not yet published. The current article focuses on the newest systemic and local experimental treatment tools highlighting their benefits, especially for hormone-resistant prostate cancer.

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## Introduction

Prostate cancer represents the leading malignant tumor and the third cause of death in men over 50 years of age. Around 1.6 million new cases of prostate cancer are diagnosed worldwide, while 400,000 new cases are diagnosed yearly only in Europe [1-3]. The incidence looks to have an increasing pattern with a percentage between 2 to 8/ year, and it increases with age. Even if the incidence rate is higher than the mortality rate, still there is an increasing trend when speaking about prostate cancer mortality lately, especially in androgen resistant tumors. The increasing incidence of obesity, diabetes mellitus, hypercholesterolemia, the unhealthy lifestyle, alcohol abuse, the high lipid and Ca intake, the high spread of infections with Human Papilloma Virus (HPV), Human Herpes Virus (HHV) or other sexually transmitted

infections, the excess of androgen consumption and the longer life expectancy due to the decrease in mortality rates secondary to cardiovascular diseases, are few of the main causes for the increasing incidence of prostate cancer [4,5]. The stage of diagnosis changed during the last decade, the screening methods based on the widespread use of prostate specific antigen (PSA) testing have improved the mortality rates. The prolonged survival is related to the detection of prostate cancer in the early stages, secondary to screening global appliance. However, the difficulty in differentiating between clinically indolent prostate cancers, usually less symptomatic or even asymptomatic, and more aggressive types, with lethal potential still remaining a problem. On this background, the Gleason grading remains the best prognostic indicator, even if cases with morphologically similar structures can behave differently. New

approaches such as DNA microarray technology and the research results coming from the proteomics field made substantial discoveries for a better understanding of the pathogenesis of human cancer. Understanding the genetic changes underlying the onset, development, and progression of prostate malignant tumors made room for new therapeutic options. The discoveries of the prostate cancer molecular fingerprints will help physicians better classify patients according to the evolution pattern. The research resources are nowadays targeting cancers with poor prognoses [6-7]. The new systemic therapies such as immunotherapy with check point inhibitors (CPI) or Poly ADP-Ribose Polymerase inhibitors (PARPi) and local experimental procedures addressing tumor destruction provide good outcomes and are present in the current treatment protocols, even if some of these procedures are not yet considered gold standard. Besides the systemic therapies, the High-Intensity Focused Ultrasound (HIFU), the Cryo and Focal Laser Ablation are promising tools used in prostate cancer therapy. The following article presents the newest treatment options for prostate cancer, especially for cases of androgen-resistant tumors [8,9].

## Discussions

### *The Immune Checkpoint Inhibitor therapy (CPI) and Poly ADP-Ribose Polymerase inhibitors (PARPi)*

In the last few years, immunotherapy has been successful and proved to be a very effective treatment option in a variety of cancers [5]. Even though the efficacy of immune checkpoint blockade in the prostate cancer treatment looks promising, it still needs some clarifications. The latest clinical trials in the field support the theory according to which certain genetic mutations such as microsatellite instability/mismatch repair gene deficiency may increase the susceptibility to immune checkpoint blockade [10,11].

In general, the immune response acts against cancer occurrence by an active succession of immune events such as realization and presentation of tumor-associated antigens (TAA), activation and local infiltration with cytotoxic T-lymphocytes, and ultimately recognition and destruction of cancer cells. It seems that the loss of cancer-specific immune-dominant epitopes, the T cell priming and activation, the inefficient TAA processing and presentation, along with the local immunosuppressive microenvironment may produce immune tolerance to TAA [5,12]. Based on this evidence, the immune CPI therapy reactivates and enhances anticancer immunity by blocking negative co-stimulatory molecules such as programmed cell death-1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). The PD-1/PD-L1 blockade such as nivolumab or pembrolizumab downregulates glycolysis, the metabolism of amino acid and fatty acid oxidation, as well as cell proliferation. The anti-CTLA-4

class (ipilimumab) promotes the abundance of T lymphocytes in the microenvironment enhancing the immune response. Furthermore, the anticancer efficacy of the immune CPI can be boosted by synergic poly ADP-ribose polymerase (PARP) inhibition, the additive effects of this class inducing finally the synthetic lethal effect in cancer cells. Along with the immune CPI, numerous PARPis have been lately developed. Veliparib, rucaparib, olaparib, niraparib, and talazoparib are nowadays studied for their efficacy in ovarian, breast, pancreatic, lung and bladder cancer therapy based on their up-regulation of gene mutations, repairing the DNA damage accumulation and promoting the tumor cell death [13-16].

However, prostate cancer seems to act a bit differently compared to other solid cancers, and only a minority of patients show sensitivity to the immune therapy. The “Immune Checkpoint Blockade for Prostate Cancer: Niche Role or Next Breakthrough?” session presented at the ASCO 2020, promotes the hypothesis according to which identifying specific biomarkers to predict the response to PD-1/PD-L1 blockade and combine CPI with other treatments seems a possible approach to optimize the outcomes in prostate cancer. Combining PARPi and immune CPI in prostate cancer patients looks rational due to their mechanisms of action. PARPi promote the release of damaged DNA into the cytosol, also promote the activation of the immune pathway called cGAS–STING and the release of TAA and, furthermore, as in breast cancer, PARP inhibition may upregulate PD-L1 [17-19].

The current evidence on this line is a phase II trial testing olaparib plus durvalumab in men castration-resistant prostate cancer which proved that 50% of the patients had an imaging and serologic response. Still, approximately 66% of the responders had microsatellite instability, indicating that this combination could be effective only in tumors with such defects [19,20]. More upcoming data will assure clinicians about the benefits of CPI and PRAPi combination common usage in specific categories of patients and will probably become standard approaches in prostate cancer therapy. In addition, the combinations of antiandrogen therapy with CPI, cytokine inhibitors, vaccines and specific T-cell engagers seem to provide new horizons for metastatic or non-metastatic castration resistant prostate cancers [19-22].

### *Local experimental procedures.*

In terms of local ablative procedures for prostate cancer, these methods are usually addressed to localized small tumors when radical prostatectomy is not applicable or as adjuvant or palliative treatments in case of recurrence or resistance to standard treatments. HIFU, cryotherapy and focal laser ablation are suitable methods to use as monotherapy or in combination with the current standardized treatments.

a) High-Intensity Focused Ultrasound (HIFU) designated to treat localized, locally advanced or recurrent prostate cancer uses high-intensity sound waves to heat up to 90 degrees C (194 degrees F) and destroy the prostate cancer cells. Under anesthesia, the US probe is fixed in the rectum and 2 crystals transmit the image to the computer and back to the gland in order to target the abnormal tissue. In this way, the normal prostate tissue is protected and HIFU seems to have greater success in studies, fewer side effects than reported in surgery or radiotherapy. Urinary incontinence, infection, prostate swelling and erectile dysfunction can occur in some cases. Clinical trials provide optimism in this direction [23-26].

b) Opposed to HIFU, cryotherapy freezes prostate cancer cells in order to destroy them and uses an argon-based machine. Its usage is reserved especially for disease recurrence or as an alternative to other options. The procedure is done under general or spinal anesthesia. Under US guidance, small tubular probes are inserted through the perineum into the prostate tissue and cold gases (nitrogen liquid, argon) are passed inside the gland. The US helps the physician avoid the normal tissue destruction. During the procedure, warm water is inserted through a urethral catheter to avoid its damage and it is left there for a few days [27-29]. Prostate targeted cryoablation (TCAP) is equal in efficacy or surpasses the morbidity produced by other standardized local procedures such as brachytherapy, external-beam radiation or three-dimensional beam radiation. Erectile dysfunction is present as a side effect in almost all cases (93%). Urinary incontinence (7.5%), and very rarely, the formation of rectal fistulae (0.5-1%) are observed [30-32]. TCAP provides a long-term, durable response with regard to disease control according to clinical trial results. Fewer positive biopsies were documented after cryoablation than after radiotherapy [33,34].

c) Focal Laser Ablation (FLA) is an alternative treatment for prostate cancer patients not yet standardized by guidelines. It is suitable for patients in whom radical prostatectomy or radiation are not considered as optimal therapy. The MRI guidance helps the physician fix the laser fiber into the tumor [34-36]. The energy flowed into the fiber will heat the tumor cells and will destroy them. The procedure is quick, safe, the patient's discomfort is minimal and the procedure itself does not require hospital admission. It is done under local anesthesia and mild sedation and can be repeated several times [35-37]. The procedure involves few side effects such as erectile dysfunction, urinary incontinence, or bowel problems, especially if the tumor is located in the proximity of the nerves responsible for the erectile function, innervate the urethra, or the rectal wall. Clinical trials have proven that the morbidity percentages are much lower than in other ablative procedures [36-38].

## Highlights

- ✓ Prostate cancer still poses difficulties in predicting the evolution pattern.
- ✓ Research focused on proteomics provides new therapy approaches on cancer in general and on prostate cancer, in particular.
- ✓ Immunotherapy with Immune Checkpoint Inhibitor therapy (CPI) and Poly ADP-Ribose Polymerase inhibitors (PARPi) seem to improve difficult-to-treat types of prostate cancer.
- ✓ Local ablative techniques using imaging guidance improve not only the outcome of patients, but positively influence their ECOG (Eastern Cooperative Oncology Group) performance status.

## Conclusions

The continuous and effervescent research in the field of oncology came with the development of new classes of drugs, such as immunotherapy, providing new horizons and better outcomes, especially for antiandrogen resistant prostate cancer patients. Along with the local ablative procedures such as HIFU, TCAP and FLA, immunotherapy with CPI and PRAPi, not only prolong life expectancy, but also improve the quality of life and reduce morbidity rates in prostate cancer patients.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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