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REVIEW

Which Therapeutic Treatment Option is Best for Prostate Cancer?

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ABSTRACT

Prostate cancer (PC) is the second most common cancer among men in the developed world. PC spreads very slowly and is often detected late, so it requires much more rigorous treatment options than if it had been detected early. As with most cancer treatments, all these treatment options have their fair share of advantages and disadvantages. After a prostate cancer diagnosis, an assigned oncologist and multi-disciplinary team (MDT) come up with a treatment option that gives the patient a fighting chance considering the stage of the cancer. However, there is no go-to treatment option, and it is important to consider what the patient wants; if there are certain side effects, such as incontinence, that the patient is steadfastly against, it's important for the MDT to honour this as much as possible.

Keywords: Androgen receptors, chemotherapy, metastatic-castration-resistant, prostate cancer.

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1. Introduction

Prostate cancer (PC) is a complex malignancy cancer that affects many men worldwide. It is influenced by both inherited genetic factors and the environment. Key genes like ELAC2, RNASEL, NSB1, and CHEK2 can increase the risk of prostate cancer [1]. However, it can also occur without a family history, often due to hormones. Androgens, hormones that help the prostate grow, can raise the risk if there are mutations in androgen receptors.

One startling aspect of prostate cancer is that it can go undetected for many years. This makes early detection difficult. A study by Johansson et al. [2] found that after 15 years, many men experienced a rapid decline in how long they could stay cancer-free, and their cancer often spread. However, this study was conducted nearly 20 years ago with a small group of Swedish patients, so it may not reflect the situation for all men.

Androgen receptors (ARs) are crucial because they help regulate cell functions, such as growth and death. In metastatic castration-resistant prostate cancer (mCRPC), problems with these receptors are common, affecting about 62.7% of patients. A significant issue arises when there are too many receptors, leading to increased androgens that promote tumour growth. Unfortunately, treatments designed to lower androgen levels, known as androgen deprivation therapy, often do not work effectively for these patients since small amounts of androgen may still be present.

This paper demonstrates how genes can cause prostate cancer and look at different ways to help affected people, sharing new ideas for treatment options and improving understanding of what we know now and what we can do in the future to help with this common illness, hence strengthening current knowledge and improving future directions in managing this prevalent disease.

2. Pathophysiology of Prostate Cancer

The prostate is a glandular tissue with androgens controlling the growth and life span of the cells in this tissue. The prostate gland is made up of 4 zones: the peripheral, central, transitional and periurethral zones; the majority of prostate cancers develop in the peripheral zone [3]. Pathogenesis of PC is affected by both genetic and lifestyle factors such as smoking, diet, and age. Genes such as ELAC2, RNASEL, NSB1 and CHEK2 are hereditary prostate cancer genes and have been shown to increase susceptibility to developing prostate cancer. However, PC can also be sporadic as well as hereditary. For example, as mentioned before, prostate gland growth is controlled by androgens; mutations in the androgen receptors can increase the risk of developing PC [4]. As seen in Fig. 1, prostate cancer develops like many other cancers. It's virtually undetectable for the first few years before it grows and begins to spread.

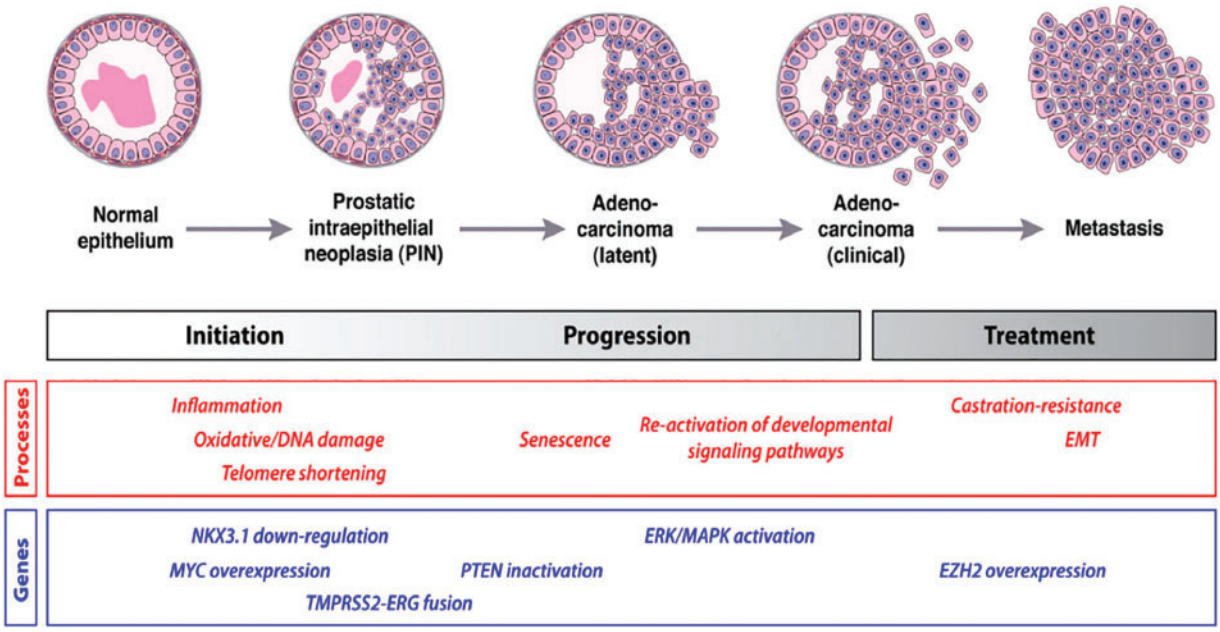

Fig. 1. Diagram illustrating the development of cancer in the epithelium. Source: Sekhoacha et al. [5].

PC can go undiagnosed and relatively asymptomatic for as long as 15 years. Johansson et al. [2] found that after 15 years (from their early-stage PC diagnosis), there was a rapid decrease in cumulative progression-free survival and an increase in metastases. However, it is important to note that this study was conducted over 21 years and ended almost 2 decades ago, so treatments have changed significantly since then. This study also used an incredibly small sample size of 223 patients, all based in Sweden, so the data may not be illustrative of all men at risk of PC globally.

Androgen receptors (ARs) are responsible for transcription regulation, proliferation and programmed cell death under normal conditions. These receptors are the most common gene abnormality in metastatic castration-resistant prostate cancer (mCRPC); it is present in 62.7% of patients [6]. One of these abnormalities may be androgen amplification; this is the overexpression of the AR and, therefore, the increase of androgen concentration and facilitation of tumour cell growth. Androgen deprivation therapy as a treatment form doesn't work in patients with androgen receptor amplification as there are always trace amounts of androgen left functioning [7].

3. Existing Treatment Options

Treatment plans are created by oncologists, MDTs and patients based on their Gleason grading system score, their PSA levels and the wants and needs of the patient. The Gleason system is a measure of the severity of PC by assigning histological patterns 1–5 to the two most common patterns and adding them, which provides Gleason scores like 7 (4 + 3) [8]. The higher the Gleason score, the direr the patient's prognosis. The PSA levels are elevated in patients with PC. These tests allow us to identify how advanced and widespread the cancer is when diagnosed and how intensive the treatment plan will have to be.

The most radical approach would be a prostatectomy, the surgical removal of the prostate gland. This treatment option works very well if the cancer has yet to metastasize; however, it can have undesirable side effects such as erectile dysfunction, infertility and incontinence [9]. As well as this, the cancer can come back if the patient has particularly high PSA levels or is in a later stage of cancer.

The most common form of treatment is chemotherapy, especially for metastatic PC. Unlike prostatectomy, it doesn't get rid of the cancerous tumour(s); it instead interrupts the metastatic process and slows the multiplication of the cancer cells. It will increase the life expectancy of the patient; however, it causes nausea, hair loss, fatigue and other unpleasant effects.

As the name suggests, mCRPC is metastasized prostate cancer that has developed a resistance to androgen hormone therapy over time. Therapy that is reliant on androgen sensitivity no longer works to shrink the tumour(s) or slow growth. In such cases, combination therapies and targeted treatment plans, such as PARP inhibitors and ARATs alongside chemotherapy, are most effective [10].

In most early-stage localized (non-metastasized) PC patients, prostatectomy is a successful treatment option. However, it can result in recurrence up to 1/3 of the time [11].

There has been a rising case of neoadjuvant chemotherapy treatments before prostatectomies to reduce the risk of recurrent tumours. Neoadjuvant therapy shrinks the tumour before the main therapy is administered. A study done of high-risk localized prostate cancer patients with this treatment option showed recurrence in 63% of the men [12]. However, it is difficult to draw conclusions from this study as there was no control group who were treated with just a prostatectomy, so we can't say for certain whether neoadjuvant chemotherapy improves prostatectomy treatment in the long-term or not. The sample size was also very small, making it difficult to extrapolate any results.

TABLE I: Different Treatment Options for Prostate Cancer in Order of Efficacy

Treatment option	How it works	Benefits	Side-effects
Prostatectomy	Surgical removal of the prostate gland	Removes the cancer completely with no follow-up treatment, provided it didn't metastasize.	Incontinence, Erectile Dysfunction, Infertility
Radiotherapy	Using radiation to kill cancer cells in early-diagnosed patients	Can cure the patient completely, provided the cancer hasn't spread far and they have a low PSA level [14].	Fatigue, Erectile dysfunction, Osteoporosis
Chemotherapy	Disturbs the multiplication of the cancer cells and kills them, slowing progression of the cancer.	Slows tumour growth, Prolongs life expectancy	Nausea, Hair loss, Fatigue
Hormone therapy	Slows the development of the cancer but doesn't cure it on its own. It can be used alongside other treatments.	Can shrink the tumour, Slows the growth	Fatigue, Erectile dysfunction, Reduced libido, Weight gain
Orchidectomy	Removal of the testicles in order to better control the cancer, as testosterone levels drop significantly [15].	Manages symptoms better, Slows cancer growth	Infertility, Reduced libido, Erectile dysfunction, Fatigue, Loss of muscle mass

A similar study was conducted, with one group receiving chemotherapy and prostatectomy and the control group only receiving the latter. Cancer-specific survival was 90% in the group receiving neoadjuvant chemotherapy and 60.9% in the control group [13]. While this study is a much clearer picture of how neoadjuvant chemotherapy benefits prostatectomy, it uses a sample size of 44 patients, all with a prostate-specific antigen (PSA) of over 10 ng/ml and a Gleason score of 7 or more. The results are promising, but the sample group is small and does not represent all PC patients receiving treatment.

Patients should be consulted about the side effects of different treatments and how they will affect their day-to-day. Of course, their health and survival should be the top priority, but if certain side effects that they're opposed to are avoidable, the MDT should do their best to avoid them. As seen in Table I, there are many different treatment options used for PC; it all depends on how far along the cancer is, how it's progressing and the needs of the patient.

Table I shows the main types of treatment available to Prostate cancer patients from most effective, meaning they are able to completely cure the cancer if caught early enough, to least effective, meaning it has no chance of curing the cancer, but it can lessen the symptoms and slow the growth and it can be used alongside other treatment options.

4. Future Treatment Options

Because PC is such a common cancer, there are several ongoing studies and trials to try and find new, more effective treatments, preferably with fewer complications. In May 2019, it was calculated that there were 1100 ongoing clinical trials for PC treatment, most of which were based on immunotherapy [16]. This means that instead of trying to remove the cancer, the treatment assists your immune system in fighting it.

One of the most popular immunotherapy approaches is DNA vaccines. This vaccine is capable of creating an antigen-specific immune response that works against the tumour; the vaccine has to be able to quash all the evasion techniques the cancer cells use [17]. However, in the clinical trials carried out so far for PC vaccines, the efficacy of the treatment has been disappointingly low [18]. Most ongoing trials have not yet gotten past phase I of the clinical trial. The sample size in this phase is very small, so whatever results are being collected right now are likely not representative of the global population susceptible to prostate cancer.

Another potential treatment option is immune checkpoint blockades (ICB); these are antibodies that block regulatory signalling molecules like CTLA-4 and activate T cells, which attack the tumour [19].

However, there has not been much clinical success with this treatment. A double-blind phase III trial using a placebo and ipilimumab (an ICB) found no significant difference in overall survival between the two groups [20]. ICB has been successfully developed for some other cancers; however, PC has been largely ineffective [21]. So, while there is clearly a desire to develop new, more effective treatments for PC, a lot of them have a long way to go before they become commonplace treatment options.

5. Conclusion

In conclusion, there is no go-to treatment option; PC treatment is mostly dependent on the stage and severity of the patient's cancer when they're diagnosed, as well as the wants and needs of the patient. The most effective treatment is undoubtedly a prostatectomy, and recurrence may be less likely if chemotherapy is also administered, but this only applies if the cancer is caught before metastatic processes have begun. They both also have unfavourable side effects; ideally, a treatment would be developed that is just as, if not more effective than a prostatectomy (for example, by diminishing the chances of recurrence), without the adverse effects—a treatment that worked on metastatic prostate cancer and mCRPC as well.

Conflict of Interest

The author declares that there is no conflict of interest.

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