

# Endocrine manipulations in cancer prostate: A review

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### ABSTRACT

Prostate cancer is an androgen dependent condition where Dihydrotestosterone promotes the growth of the neoplastic tissue. Androgen deprivation has been the mainstay of therapy for this condition. This can be achieved by surgical or medical means. Types of medical regimens are intermittent maximal or sequential androgen blockade.

**Key words:** Prostate cancer, androgen deprivation therapy, endocrine manipulation

## INTRODUCTION

The pedigree of endocrine manipulation of cancer prostate dates back to 1941 when the American surgeon Charles Brenton Huggins with his classic work introduced hormonal therapy for cancer prostate.<sup>[1]</sup> Since then, androgen deprivation therapy (ADT) has become the mainstay of therapy for locally advanced and metastatic cancer prostate.

In men, testosterone derived from testicular secretion is the primary circulating androgen, and 3 to 10 mg of it is secreted daily from the testes. Another 500 µg of it is collectively generated by both direct secretion and the peripheral conversion of androstenedione secreted by the adrenal.<sup>[2]</sup> However, the main androgen active in the prostate is dihydrotestosterone (DHT), which is derived from circulating androgens by the action of intracellular enzyme 5 $\alpha$ -reductase. Two isoforms of this enzyme are known- type I and type II.<sup>[2]</sup> The latter isoform is the most prevalent type within the normal prostate and is also

elevated in benign prostatic hyperplasia (BPH). However, it is the expression of type 1 5 $\alpha$ -reductase that is increased in prostate cancer.

The underlying principle of hormonal treatment of cancer prostate is to deprive the malignant cells of androgens. This can be achieved either by elimination of testosterone production by the testes i.e. castration or by the blockade of androgen receptors (AR) of the prostate. Castration can be surgical orchiectomy or with hormonal therapy with estrogen agonists, gonadotropin hormone-releasing (GnRH) agonists and GnRH antagonists. All of these treatment modalities have specific adverse effects and affect the quality of life (QOL) of the patient, and their proper use and timing remain controversial.

As many as 94% of cancer prostate patients do respond to androgen deprivation.<sup>[3]</sup> However, such effects are ill sustained and after initial responses to blockade of androgen secretion or action, tumors re-grow. The cellular mechanisms behind this suggest that the tumors that were previously thought to be androgen-independent are actually androgen-hypersensitive and are thus called castration-resistant prostate cancers (CRPC). This has led to a paradigm shift in thinking and provided the rationale for secondary endocrine therapies that further reduce androgen concentrations or interact with the AR. Currently, novel drugs are being developed such as the new anti-androgen MDV3100 and inhibitor of androgen synthesis abiraterone. They have already shown efficacy in phase II and III trials.<sup>[4,5]</sup>

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The use of prostate-specific antigen (PSA) as a monitoring tool in patients undergoing treatment of localized cancer prostate leads to early detection of recurrence. But, the hormonal treatment of such patients remains a matter of debate. The life expectancy of those who have recurrence after local therapy is still 10-15 years in contrast to those with metastatic disease where it is only 3 years. Substantial ambiguity prevails in whether treatment should be initiated early in those with long life expectancy and whether treatment should be continuous. This is crucial keeping in mind the side-effects of ADT and the detriments it imposes on the QOL of the individual patient.

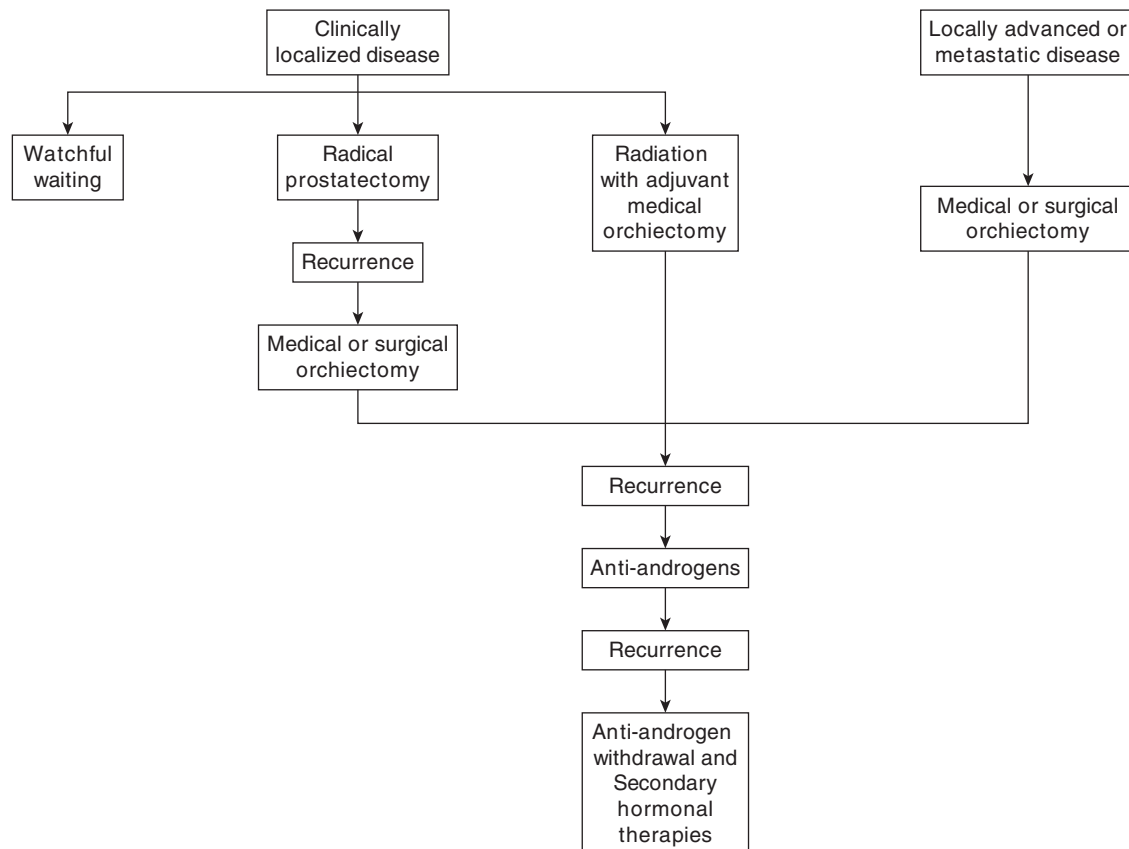
This review discusses the available endocrine options in cancer prostate prevention and management, the controversies abutting them, and the future perspectives in sight.

**Endocrine manipulation as prevention of cancer prostate [Figure 1]**

5 $\alpha$ -reductase inhibitors (ARI) are the drugs that have been evaluated for prevention of cancer prostate. Two ARIs are currently available- finasteride and dutasteride. Finasteride, which is a specific inhibitor of type-2 5 $\alpha$ -reductase, was tested in Prostate Cancer Prevention Trial (PCPT). It

resulted in a 24.8% reduction in the prevalence of prostate cancer. There was, however, an increase in the detection of high-grade prostate cancer (HGPC) in the finasteride-treated population compared with the placebo group.<sup>[6]</sup> The plausible explanation given was that more detection of HGPC was because of shrinkage of size of prostate, leading to more accurate biopsy. The PCPT trial data thus suggested that finasteride does not reduce the chances of HGPC as effectively as in low-grade disease. Dutasteride is the drug that inhibits both isoforms of 5 $\alpha$ -reductase and thus could be a better chemo-preventive agent against cancer prostate. It was tested in Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, which observed that it significantly reduced the rate of biopsy-detectable prostate cancers compared with placebo. The detection rate of HGPC was, however, comparable.<sup>[7]</sup>

It can thus be interpreted that ARIs, by suppressing PSA from indolent cancers, enhance the ability of rising PSA level to recognize those men who are at increased risk of clinically significant prostate cancer. For chemoprevention, ARIs reduce but do not eliminate the risk of being diagnosed with cancer prostate. However, current clinical guidelines are reluctant to give recommendations for prostate cancer



**Figure 1:** Endocrine manipulation as treatment of cancer prostate

chemoprevention, reflecting the insufficiency of available data.

The pathologist assigns a grade to the most common tumor pattern and a second grade to the next most common tumor pattern [Table 1]. The two grades are added together to get a Gleason Score [Table 2].

**Surgical castration: Bilateral orchiectomy**

The idea of performing orchiectomy is to bring down testosterone levels quickly to castrate levels, which is defined as < 20 ng/ml.<sup>[8]</sup> Despite having a better side-effect profile than ADT, fewer patients resort to orchiectomy because of the attendant psychological ill-effects.

**Medical Castration**

The various hormonal therapies available for medical castration are depicted in Table 3.

**Estrogens**

DES was one of the first means of medical treatment of cancer prostate used, and observational studies demonstrated its efficacy. But, this came at the cost of

significant cardiovascular and thrombo-embolic side-effects. Its use was thus abandoned in the 1970s. Currently, estrogens are no longer recommended as first-line means of medical castration.

**GnRH agonists**

Physiologically, the polypeptide hormone GnRH is secreted into the hypophyseal-portal blood circulation in a pulsatile manner, and it stimulates the secretion of the gonadotropins LH and FSH from the anterior pituitary.<sup>[2]</sup> The pharmacologic basis of administering GnRH agonists to cancer prostate patients is to produce continuous stimulation of the gonadotrophs and thereby bring about GnRH receptor de-sensitization. This decreases LH secretion and hence testosterone production falls down to castrate levels. Today, synthetically produced GnRH agonists (goserelin, leuprorelin, buserelin, and tritorelin) are administered as depot preparations and suppress testosterone level to < 50 ng/ml in about 95% of the patients.<sup>[9]</sup> But, this effect is not immediate. Rather, the initial response is an increase in testosterone production for a period of 1-2 weeks. This is responsible for the tumor flare effect. The raised levels of testosterone not only stimulate tumor growth but also increase the size of bony metastases and can lead to malignant spinal cord compression. To avert this, anti-androgens are co-administered along with GnRH agonists for a period of 3-4 weeks, and the said adverse effect is rarely seen now-a-days.

The choice between orchiectomy and GnRH agonists

**Table 1: National comprehensive cancer network (nccn) risk stratification for cancer prostate**

**CLINICALLY LOCALIZED**

**Low Risk**

- T1-2
- Gleason score 2-6
- PSA < 10 mg/mL

**Intermediate Risk**

- T2b to Tc *or*
- Gleason score 7 *or*
- PSA 10-20

**High Risk**

- T3a *or*
- Gleason score 8-10 *or*
- PSA > 20 mg/mL

**LOCALLY ADVANCED**

- T3b-T4

**METASTATIC**

**Lower Risk**

- Any T, N1

**Higher Risk**

- Any T, any N, M1

- T1a: Incidental tumor ≤ 5%
- T1b: Incidental tumor > 5%
- T1c: Identified by biopsy/ PSA screening
- T2a: Palpable or screen on TRUS- one lobe
- T2b: Palpable or screen on TRUS- two lobes
- T3a: Extra-capsular extension
- T3b: Seminal vesicle involvement
- T4: Bladder neck, external sphincter, rectal levator, or pelvic wall involvement
- N1: Regional nodes
- M1: Non-regional nodes
- M1b: Bone
- M1c: Other sites.

**Table 2 Gleason scoring**

- Pattern 1 - The cancerous prostate closely resembles normal prostate tissue. The glands are small, well-formed, and closely packed.
- Pattern 2 - The tissue still has well-formed glands, but they are larger and have more tissue between them.
- Pattern 3 - The tissue still has recognizable glands, but the cells are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.
- Pattern 4 - The tissue has few recognizable glands. Many cells are invading the surrounding tissue.
- Pattern 5 - The tissue does not have recognizable glands. There are often just sheets of cells. throughout the surrounding tissue.

**Table 3: Drugs**

| GnRH Agonists | GnRH Antagonists | Anti-Androgens | Adrenal androgen inhibitors | Estrogens               |
|---------------|------------------|----------------|-----------------------------|-------------------------|
| Leuprorelin   | Abarelix         | Flutamide      | Ketoconazole                | DES                     |
| Goserelin     | Degarelix        | Bicalutamide   | Corticosteroids             | Estradiol               |
| Triptorelin   |                  | Nilutamide     | Aminoglutethimide           | Polyestradiol phosphate |
| Histrelin     |                  |                |                             | Premarin                |

represents a major question. Surgical orchiectomy assures the clinician of several benefits- it produces a rapid and assured decrease in serum androgen levels, does not require patient compliance long term, and is effective in inducing tumor regression in nearly 90% of patients. Despite these advantages, majority of men opt for medical castration to avoid surgery and the psychological effects associated with orchiectomy.

### GnRH antagonists

GnRH antagonists offer several advantages over agonists. They bind directly to GnRH receptors in the pituitary and bring about a reduction in serum testosterone level as early as brought by orchiectomy. Moreover, the LH and testosterone surges associated with GnRH agonists are not seen. Abarelix and degarelix are the two GnRH antagonists available. The latter has been shown to be well-tolerated and as effective as GnRH agonists.<sup>[10]</sup> More so, it is not associated with immediate-onset systemic allergic reactions resulting from histamine release seen with Abarelix. The widespread use of GnRH antagonists awaits the test of time.

### Side-effects of ADT

ADT produces a multitude of adverse effects apart from just loss of libido and erectile dysfunction [Table 4].

### Non-steroidal anti-androgens

The non-steroidal anti-androgens bicalutamide, flutamide, and nilutamide interfere with the binding of testosterone and DHT to the AR. These drugs cross the blood-brain barrier, raise LH secretion and, therefore, testosterone secretion from the testes. Thus, they are the agents that can help avoid castration for the treatment of cancer prostate. Flutamide produces nausea, diarrhea, and liver toxicity. These side-effects are not seen with bicalutamide, which is the best tolerated drug in this group.<sup>[11]</sup> It even leads to an increase in bone density because of an increase in circulating estradiol. However, the same mechanism also leads to gynecomastia and breast pain in most men receiving it. Apart from this, all non-steroidal AR antagonists may have AR agonist activity, especially in association with CRPC. To circumvent this, MDV3100, a new anti-androgen, is being developed. It has 4-8-fold higher affinity for AR than bicalutamide and has reduced agonistic activity.<sup>[12]</sup> Phase 1 and 2 studies in CRPC with this drug have been promising, and larger phase 3 studies are underway.

Since these drugs provide the advantage of better QOL, there has been increasing interest in monotherapy with these drugs, especially bicalutamide which has been evaluated in doses of 50 mg and 150 mg daily. A meta-analysis of studies involving more than 2700 patients

suggested that recurrence was greater with anti-androgen monotherapy than with medical or surgical castration. Still, many men choose this option because of the QOL advantages. Currently, anti-androgen monotherapy can be discussed as an alternative to castration in young men with cancer prostate after duly informing them about higher recurrence rate.

### Approaches to endocrine manipulation: Intermittent androgen deprivation (IAD), maximal androgen blockade (MAB), and sequential androgen blockade (CAB)

The concept of IAD therapy involves the placement of the patient on androgen blockade for a period of 6-9 months. GnRH agonist is withheld once PSA nadir is reached. Serum PSA determinations provide an easy method for early detection of tumor growth during the period when treatment is withheld. Once PSA levels rise, treatment is re-instituted. The possible advantages include QOL improvement during off-treatment periods and postponement of hormonal resistance. Data is available that documents the effectiveness of IAD as much as continuous therapy in patients with locally advanced disease and relapse after curative treatment, but not in those with metastases.<sup>[13]</sup>

Since around 500 µg/day of testosterone secretion is of adrenal origin, and since 40% of prostatic DHT originates from steroids of adrenal origin, it has led to a belief that the development of CRPC was caused by adrenal androgens. Therefore, GnRH agonists have been used with anti-androgens in what is known as complete or combined or maximal androgen blockade (MAB). Contrary to the belief, however, randomized trials have not conclusively proven superiority of MAB over castration in patients with metastatic cancer, and a meta-analysis has showed only a minimal improvement in 5-year survival.<sup>[14]</sup>

**Table 4: Side-Effects of Androgen Deprivation Therapy**

|                                  |
|----------------------------------|
| Anemia (normochromic/normocytic) |
| Cholesterol/lipids               |
| Cognitive changes                |
| Depression                       |
| Edema                            |
| Erectile dysfunction             |
| Fatigue                          |
| Glucose/insulin changes          |
| Hair loss/gain                   |
| Hot flushes/chills               |
| Libido changes                   |
| Muscle/joint pain                |
| Muscle tone reduction            |
| Osteoporosis                     |
| Thyroid hormone levels reduced   |
| Weight gain (abdominal)          |



SAB refers to initial castration followed by anti-androgen upon relapse. For relapses after initial ADT, addition of an anti-androgen produces response in a third of patients though for short periods. However, if the initial therapy was MAB, clinical responses lasting 3-6 months are produced just by withholding the anti-androgen in as many as 30% of the patients. Other secondary hormonal agents include ketoconazole and hydrocortisone, which reduce adrenal androgens. Though these drugs bring about a reduction in PSA levels, none has shown survival advantage in patients with CRPC. The current guidelines favor the SAB strategy and use of anti-androgens only after relapse from medical or surgical orchiectomy.

#### ADT in combination with surgery: Neo-adjuvant and adjuvant approaches

In clinically localized disease, many studies have shown that 3 months of neo-adjuvant therapy before radical prostatectomy reduces prostate size and the incidence of positive margins. However, this does not lead to any reduction in recurrence rate. Fewer studies are available for locally advanced T3 disease. They also do not put forward any evidence of beneficial role of neo-adjuvant ADT before surgery. Thus, no advantage of neo-adjuvant ADT, both in recurrence rate and in reduction of complications of radical prostatectomy, has been demonstrated so far.<sup>[15]</sup>

Similarly, for adjuvant ADT, benefit has been demonstrated only for those having metastatic disease. Thus, adjuvant ADT is recommended only for the patients who have evidence of metastatic disease in the form of early time to PSA recurrence, rapid PSA doubling time, and adverse pathologic features (Gleason score 8–10, positive lymph nodes, and seminal vesicle invasion).

#### ADT in combination with radiotherapy

The rationale behind this combination is multi-factorial.<sup>[16]</sup> ADT reduces the size of the prostate, the dose of radiation needed, and thereby reduces the RT-related adverse effects to the adjacent organs as bladder and rectum. Secondly, it inhibits repopulation during irradiation, thus reducing the chances of relapse. Thirdly, the occurrence of metastatic disease is reduced. And finally, it provides an additive effect and improves the effectiveness of radiation. The optimal duration of adjuvant hormone therapy has not been determined, but the available data points that in Gleason score 2-6 disease, survival benefit can be achieved by less than 6 months of adjuvant ADT, while a longer duration of treatment is necessary in patients with Gleason score 8–10 disease.

#### Timing of hormonal therapy: Immediate v/s delayed

Ambiguity prevails in the timing of initiation of hormonal

therapy despite its potential benefits in locally advanced disease after local therapy. The points favoring delayed ADT include the substantial side-effects and the fact that it is not curative. Moreover, the time lapse between PSA rise and symptomatic metastatic disease is prolonged. Contrary to this, early therapy prolongs overall and disease-free survival as shown in various studies in different populations. Thus, survival benefit offered by early therapy must be weighed against the QOL detriments that attend it. To summarize, the present data favors the use of early ADT in both-metastatic (M1) as well as locally advanced, high volume, high grade, or lymph node-positive disease.

## CONCLUSIONS

It is thus concluded that endocrine manipulation has an important role to play in cancer prostate despite many areas pertaining to it needing clarification. For prevention, ARIs reduce the risk but do not eliminate it. Moreover, their use augments the ability of raised PSA level to correctly identify patients having cancer prostate. But, current clinical guidelines are reluctant to give recommendations for prostate cancer chemoprevention, reflecting the insufficiency of available data. ADT in the form of surgical or medical castration (with estrogens, GnRH agonists, and antagonists) is an effective therapy for locally advanced and metastatic disease, but it brings along adverse effects and QOL issues. To circumvent this, anti-androgens especially bicalutamide have been tested as monotherapy but proven less effective. IAD is as effective as continuous therapy in patients with locally advanced disease and relapse after curative treatment. For MAB, studies and meta-analyses have not conclusively proven superiority over single agent ADT in patients with metastatic cancer. Adjuvant hormonal therapy with surgery delays disease progression, but provides no survival benefit. It, however, has a role when given with RT. For the timing of such therapy, the present data favors the use of early ADT in both-metastatic as well as locally advanced disease. Finally, the challenge for the future is to develop means to prevent and treat CRPC. Novel drugs such as the new anti-androgen MDV3100 and inhibitor of androgen synthesis abiraterone are already under development for this.

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