Review Article

A Comprehensive Review on Prostate Cancer

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ABSTRACT

India is about set to leave behind all other countries with the highest number of Prostate Cancer (PCa) cases. Prostate cancer incidence is increasing in India by 1% every year. It is the second most common cause of male cancer deaths. This will create untold human agony, causing severe ordeal on an already struggling public health system and have a catastrophic financial blow on families. With growing life expectancy, the overall prevalence of cancer has increased. Environmental and geographical factors also play some role. High consumption of dietary fats, deficiency of selenium and low levels of Vitamin D_3 and E are also the risk factors. About 10-15% of patients have positive family history. With the goal to achieve a healthy aging society, early detection of urological malignancies is of vital importance. This ensures curative treatment strategy and cure. The absolute number of prostate cancer deaths has increased in the past 5 years. This has been attributed by some to the widespread use of PSA-based detection strategies. The tremendous research progress made in recent years, and underscore the challenges that lie ahead.

Keywords: Prostate Cancer, PSA, dietary fats, malignancies.

INTRODUCTION

The prostate is a small walnut-size gland in men that is part of the reproductive system. It helps produce seminal fluid, the fluid that carries semen out of the body during ejaculation. The nerves that control erection and ejaculation are also found in the prostate. Prostate cancer is the most frequently diagnosed cancer other than skin cancer and the second leading cause of death from cancer in men in the United States[1]. Among men in the United States, prostate cancer accounts for more than 200,000 new cancer cases and 32,000 deaths annually[2]. Prostate cancer (PCa) is initially regulated by androgens, such as testosterone and dihydrotestosterone, which regulates cell proliferation and survival by activating the androgen receptor (AR), but later progresses to an aggressive, metastatic, androgen-independent stage for which, currently, there is no cure. Here, we argue that prevention of PCa progression is a better strategy compared to trying to cure the disease once it has already progressed[3].The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. Prostate-specific antigen testing increases cancer detection but does not decrease mortality. Management strategies for prostate cancer should be guided by the severity of the disease. Many low-risk tumors can be safely followed with active surveillance. Curative treatment generally involves surgery, various forms of radiation therapy, or, less commonly, cryosurgery; hormonal therapy and chemotherapy are generally reserved for cases of advanced disease (although hormonal therapy may be given with radiation in some cases). Several studies suggest that masturbation reduces the risk of prostate cancer.

Classification[4,5]

Table 1: Tumour Node Metastasis (TNM) classification of PCa

T - Primary tumour
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically in apparent tumour not palpable or visible by imaging
T1a Tumour incidental histological finding in 5% or less of tissue resected
T1b Tumour incidental histological finding in more than 5% of tissue resected
T1c Tumour identified by needle biopsy
T2 Tumour confined within the prostate(1)
T2a Tumour involves one half of one lobe or less
T2b Tumour involves more than half of one lobe, but not both lobes
T2c Tumour involves both lobes
T3 Tumour extends through the prostatic capsule(2)
T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement

T3b Tumour invades seminal vesicle(s) T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes(3)
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis
M - Distant metastasis(4)
MX Distant metastasis cannot be assessed M0 No distant metastasis M1 Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other site(s)
1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c. *2. Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.* *3. Metastasis no larger than 0.2 cm can be designated pN1 mi.* *4. When more than one site of metastasis is present, the most advanced category should be used*

Signs and symptoms

Early prostate cancer usually causes no symptoms. Sometimes, however, prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine), and dysuria (painful urination). About a third of patients diagnosed with prostate cancer have one or more such symptoms, while two thirds have no symptoms. Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Because the vas deferens deposits seminal fluid into the prostatic urethra, and secretions from the prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erectionor painful ejaculation[6].

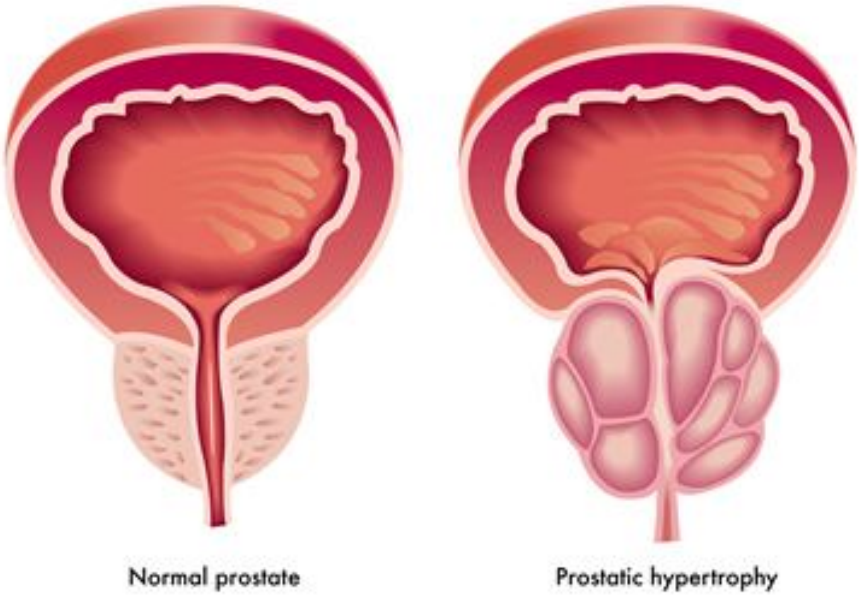

Fig. 1:

Risk factors

A complete understanding of the causes of prostate cancer remains elusive. The primary risk factors are obesity, age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70. However, many men

never know they have prostate cancer. Autopsy studies of Chinese, German, Israeli, Jamaican, Swedish, and Ugandan men who died of other causes have found prostate cancer in thirty percent of men in their 50s, and in eighty percent of men in their 70s. Men who have first-degree family members with prostate cancer appear to have double the risk of getting the disease compared to men without prostate cancer in the family. There is a small increased risk of prostate cancer associated with lack of exercise.

i. Genetic

Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants. Men who have a first-degree relative (father or brother) with prostate cancer have twice the risk of developing prostate cancer, and those with two first-degree relatives affected have a fivefold greater risk compared with men with no family history. In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men. In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. Studies of twinsin Scandinavia suggest that 40% of prostate cancer risk can be explained by inherited factors. No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in BRCA1 and BRCA2, important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate cancer. Other linked genes include the Hereditary Prostate cancer gene 1 (HPC1), the androgen receptor, and the vitamin D receptor. TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer cell growth.

Loss of cancer suppressor genes, early in the prostatic carcinogenesis, have been localized to chromosomes 8p, 10q, 13q, and 16q. P53 mutations in the primary prostate cancer are relatively low and are more frequently seen in metastatic settings, hence, p53 mutations are late event in pathology of prostate cancer. Other tumor suppressor genes that are thought to play a role in prostate cancer include PTEN (gene) and KAI1. "Up to 70 percent of men with prostate cancer have lost one copy of the PTEN gene at the time of diagnosis" Relative frequency of loss of E-cadherin and CD44 has also been observed. Two large genome-wide association studies linking single nucleotide polymorphisms (SNPs) to prostate cancer were published in 2008. These studies identified several SNPs which substantially affect the risk of prostate cancer. For example, individuals with TT allele pair at SNP rs10993994 were reported to be at 1.6 times higher risk of prostate cancer than those with the CC allele pair. This SNP explains part of the increased prostate cancer risk of African American men as compared to American men of European descent, since the C allele is much more prevalent in the latter; this SNP is located in the promoter region of the MSMB gene, thus affects the amount of MSMB protein synthesized and secreted by epithelial cells of the prostate.

ii. Dietary

While some dietary factors have been associated with prostate cancer the evidence is still tentative. Evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence. Red meat and processed meat also appear to have little effect in human studies. Higher meat consumption has been associated with a higher risk in some studies. Lower blood levels of vitamin D may increase the risk of developing prostate cancer. Taking multivitamins more than seven times a week may increase the risk of developing the disease. A study on folic acid supplements showed an association with an increased risk of developing prostate cancer.

iii. Medication exposure

There are also some links between prostate cancer and medications, medical procedures, and medical conditions. Use of the cholesterol-lowering drugs known as the statins may also decrease prostate cancer risk. Infection or inflammation of the prostate (prostatitis) may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In particular, infection with the sexually transmitted infections chlamydia, gonorrhea, or syphilis seems to increase risk. Finally, obesity and elevated blood levels of testosterone may increase the risk for prostate cancer. There is an association between vasectomy and prostate cancer however more research is needed to determine if this is a causative relationship. Research released in May 2007, found that US war veterans who had been exposed to Agent Orange had a 48% increased risk of prostate cancer recurrence following surgery.

Pathophysiology

The prostate is a part of the male reproductive system that helps make and store seminal fluid. In adult men, a typical prostate is about three centimeters long and weighs about twenty grams. It is located in the pelvis, under the urinary bladder and in front of the rectum. The prostate surrounds part of the urethra, the tube that carries urine from the bladder during urination and semen during ejaculation. Because of its location, prostate diseases often affect urination, ejaculation, and rarely defecation. The prostate contains many small glands which make about twenty percent of the fluid constituting semen. In prostate cancer, the cells of these prostate glands mutate into cancer cells. The prostate glands require male hormones, known as androgens, to work properly. Androgens include testosterone, which is made in the testes; dehydroepiandrosterone, made in the adrenal glands; and dihydrotestosterone, which is converted from testosterone within the prostate itself. When normal cells are damaged beyond repair, they are eliminated by apoptosis. Cancer cells avoid apoptosis and continue to multiply in an unregulated manner.

The prostate is a zinc accumulating, citrate producing organ. The protein ZIP1 is responsible for the active transport of zinc into prostate cells. One of zinc's important roles is to change the metabolism of the cell in order to produce citrate, an important component of semen. The process of zinc accumulation, alteration of metabolism, and citrate production is energy inefficient, and prostate cells sacrifice enormous amounts of energy (ATP) in order to accomplish this task. Prostate cancer cells are generally devoid of zinc. This allows prostate cancer cells to save energy not making citrate, and utilize the new abundance of energy to grow and spread. The absence of zinc is thought to occur via a silencing of the gene that produces the transporter protein ZIP1. ZIP1 is now called a tumor suppressor gene product for the geneSLC39A1. The cause of the epigenetic silencing is unknown. Strategies which transport zinc into transformed prostate cells effectively eliminate these cells in animals. Zinc inhibits NF-κB pathways, is anti-proliferative, and induces apoptosis in abnormal cells. Unfortunately, oral ingestion of zinc is ineffective since high concentrations of zinc into prostate cells is not possible without the active transporter, ZIP1[7].

Screening and early detection

The rationale for screening is that early detection and treatment of asymptomatic cancers could extend life, as compared with treatment at the time of clinical diagnosis. Effective cancer screening requires an accurate, reliable, and easy-to-administer test that detects clinically important cancers at a preclinical stage and the availability of effective treatment that results in better outcomes when administered early, rather than after signs or symptoms of disease have developed[9].

For many years, the digital rectal examination was the primary screening test for prostate cancer. However, this test has considerable interexaminer variability, and the majority of cancers detected by means of digital rectal examination are at an advanced stage. In the late 1980s, PSA testing, which was initially developed for prostate-cancer surveillance, was rapidly and widely adopted for screening; by 2001, a population-based survey in the United States showed that 75% of men 50 years of age or older had undergone PSA testing[8].The widespread use of PSA testing was based on its increased detection of early-stage cancer, as compared with digital rectal examination; there was no evidence that testing reduced the risk of death from prostate cancer[9].

Table 2: Prostate-Cancer Screening Guidelines

Prostate-Cancer Screening Guidelines[9].*			
Recommendation	**American Urological Association**	**American Cancer Society**	**U.S. Preventive Services Task Force**
Shared decision making between patient and clinician	Yes	Yes(consider use of decision aid)	Yes(when patient requests screening)
Age to begin offering screening			
Average-risk patients	40	50	Not applicable
High-risk patients (black patients and those with first-degree relative with prostate cancer)	40	40-45	Not applicable
Discontinuation of screening	Life expectancy <10 yr	Life expectancy <10 yr	Not applicable
Screening tests	PSA, digital rectal examination	PSA, optional digital rectal examination	Not applicable
Frequency of screening	Annual (possibly less often for men in their 40s)	Annual (every other year when PSA <2.5 ng/ml)	Not applicable

Criteria for biopsy referral	Age, family history, race or ethnic group, findings on digital rectal examination, total PSA, free PSA, PSA velocity, PSA density, previous biopsy findings, coexisting conditions	PSA ≥4.0 ng/ml, abnormal digital rectal examination; individualized risk assessment if PSA is 2.5–4.0 ng/ml	Not applicable

* The sources for the guidelines are as follows: the American Urological Association, the American Cancer Society and draft guidelines from the U.S. Preventive Services Task Force.

Diagnosis

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS). Its definite diagnosis depends on the presence of adenocarcinoma in prostate biopsy cores or operative specimens. Histopathological examination also allows grading and determination of the extent of the tumour.

a) Digital rectal examination (DRE)

Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. A suspect DRE is an absolute indication for prostate biopsy. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level[10]. A suspect DRE in patients with a PSA level of up to 2 ng/mL has a positive predictive value of 5-30%.

b) Prostate-specific antigen (PSA)

The measurement of PSA level has revolutionised the diagnosis of PCa . Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS[11].

Treatment

i. Radical prostatectomy

The surgical treatment of prostate cancer (PCa) consists of radical prostatectomy (RP), which involves the removal of the entire prostate gland between the urethra and the bladder, and resection of both seminal vesicles along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by a bilateral pelvic lymph node dissection. In men with localised PCa and a life expectancy > 10 years, the goal of an RP by any approach must be eradication of disease[12].

ii. Radiation therapy

There are no randomised studies comparing radical prostatectomy (RP) with either external beam radiation therapy (EBRT) or brachytherapy for localised prostate cancer. However, the National Institutes of Health (NIH) consensus set up in 1988[13] remains available: external irradiation offers the same long-term survival results as surgery; moreover, EBRT provides a quality of life at least as good as that provided by surgery.

Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard and, at the beginning of the third millennium, intensity modulated radiotherapy (IMRT), an optimised form of 3D-CRT, is gradually gaining ground in centres of excellence.

a) Hormonal therapy

Prostate cells are physiologically dependent on androgens to stimulate growth, function and proliferation. Testosterone, although not tumorigenic, is essential for the growth and perpetuation of tumour cells. The testes are the source of most of the androgens, with only 5-10% (androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulphate) being derived from adrenal biosynthesis.

Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis. The hypothalamic luteinising hormone-releasing hormone (LHRH) stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH). Luteinising hormone stimulates the Leydig cells of the testes to secrete testosterone. Within the prostate cells, testosterone is converted by the enzyme 5-α-reductase into 5-α-dihydrotestosterone (DHT), which is an androgenic stimulant about 10 times more powerful than the parent molecule. Circulating testosterone is peripherally aromatised and converted into oestrogens, which together with circulating androgens, exert a negative feedback control on hypothalamic LH secretion.

If prostate cells are deprived of androgenic stimulation, they undergo apoptosis (programmed cell death). Any treatment that

results ultimately in suppression of androgen activity is referred to as androgen deprivation therapy (ADT).

❖ Different types of hormonal therapy

a) Testosterone-lowering therapy

i. Castration level

Surgical castration is still considered the 'gold standard' for ADT against which all other treatments are rated. Removal of the testicular source of androgens leads to a considerable decline in testosterone levels and induces a hypogonadal status, although a very low level of testosterone (known as the 'castration level') persists.

The standard castrate level is < 50 ng/dL. It was defined more than 40 years ago, when testosterone level testing was limited. However, according to current testing methods using chemiluminescence, the mean value of testosterone after surgical castration is 15ng/dL. This has led to a revisiting of the current definition of castration, with some authors suggesting a more appropriate level to be < 20 ng/dL.

ii. Bilateral orchiectomy

Bilateral orchiectomy, either total or by means of a subcapsular technique (i.e. with preservation of tunica albuginea and epididymis), is a simple and virtually complication-free surgical procedure easily performed under local anesthesia. It is the quickest way to achieve a castration level, usually within less than 12 hours.The main drawback of orchiectomy is that it may have a negative psychological effect: some men consider it to be an unacceptable assault on their manhood. In addition, it is irreversible and does not allow for intermittent treatment. The use of bilateral orchiectomy has declined recently, probably because of stage migration towards earlier disease and the introduction of equally effective pharmacological modalities of castration[14].

b) Oestrogens

Oestrogens have several mechanisms of action

- down-regulation of LHRH secretion;
- androgen inactivation;
- direct suppression of Leydig cell function;
- direct cytotoxicity to the prostate epithelium (in-vitro evidence only) Eg: Diethylstilboesterol (DES).

c) LHRH agonists

Long-acting LHRH agonists (busereline, gosereline, leuproreline and triptoreline) have been used in advanced PCa for more than 15 years and are currently the main forms of ADT .They are synthetic analogues of LHRH, generally delivered as depot injections on a 1-, 2-, 3-, or 6-monthly basis by initially stimulating pituitary LHRH receptors, inducing a transient rise in LH and FSH release. This then elevates testosterone production (known as the 'testosterone surge' or 'flare up' phenomenon), which begins within approximately 2-3 days of the first injection and lasts through approximately the first week of therapy.

d) LHRH antagonists

In contrast to LHRH agonists, LHRH antagonists bind immediately and competitively to LHRH receptors in the pituitary gland. The effect is a rapid decrease in LH, FSH and testosterone levels without any flare. This seemingly more desirable mechanism of action has made LHRH antagonists very attractive. However, practical shortcomings have limited clinical studies. Many LHRH antagonists have been associated with serious and lifethreatening histamine-mediated side-effects and, until recently, no depot formulation was available.

e) Anti-androgens

Anti-androgens compete with testosterone and DHT at the receptor level in the prostate cell nucleus, thus promoting apoptosis and inhibiting PCa growth[15]. These oral compounds are classified according to their chemical structure as steroidal, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate, and non-steroidal or pure, e.g. nilutamide, flutamide and bicalutamide. Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal anti-androgens. However, in addition, steroidal anti-androgens have progestational properties due to central inhibition of the pituitary gland. As a consequence, non-steroidal antiandrogens do not lower testosterone levels, which remain normal or, conversely, slightly elevated.

Table 3: Contraindications for various therapies

Therapy	Contraindications
Bilateral orchiectomy	Psychological reluctance to undergo surgical castration
Oestrogens	Known cardiovascular disease
LHRH agonists alone	Patients with metastatic disease at high risk for clinical 'flare up' phenomenon
Anti-androgens	Localised PCa as primary therapy

CONCLUSION

By observing the above description, Cancer survival tends to be poorer in developing countries, most likely because of a combination of late diagnosis and limited access to standard treatment. A substantial proportion of cancer burden can be prevented by implementing programs, early detection and treatment, and majorly public health check-up camps promoting investigations. Clinicians, health professionals, and policy makers can play an active role in the application of such interventions. Yet, rigorous studies has to be made to find out the most opt combination for the treatment of Prostate Cancer.

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