Prostate Cancer - What's New?

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Abstract

Research has shown that prostate specific antigen (PSA) is a tumour marker for diagnosis of cancer prostate with significant prognostic value. Screening studies in North America and Europe have revealed that carcinoma prostate is common. Early detection and treatment improves the quality of life besides preventing deaths due to metastatic prostate cancer. Radical prostatectomy and laparoscopic radical prostatectomy has become the standard treatment for localized prostate cancer in all major uro-oncological centres resulting in reduced mortality. Magnetic resonance imaging and positron emission tomography have helped in detecting local and distant spread of cancer prostate. Revised approach to reduce occurrence of prostate cancer by the use of 5 alpha reductase inhibitors like finasteride and dietary supplements has been instituted. The World Health Organisation (WHO) has recommended lifestyle changes to promote men's health and reduce the incidence of prostate cancer.

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Introduction

Prior to the discovery of prostate specific antigen (PSA) in 1980, most cases of prostate cancer were diagnosed in an advanced stage and the usual treatment would be androgen ablation in the form of bilateral orchidectomy or administration of modified oestrogens. The discovery of PSA and its relation to prostate cancer enhanced its importance as a tumour marker both for diagnosis and prognosis. Early prostate cancer could be diagnosed by needle biopsy in those with elevated PSA, resulting in improved outcome [1]. Radical prostatectomy (RP) became the standard of care. Subsequently Walsh also stressed upon the importance of nerve sparing (the cavernous nerves from the pelvic plexus) radical prostatectomy which preserves potency and thus more patients started accepting RP when diagnosed with early prostate cancer. Following the advent of laparoscopic RP, few centres have excelled in performing robotic laparoscopic RP and have recently published their results. New molecular markers are being discovered for targeted therapies. Novel therapies in the form of vector vaccines and cryotherapy are being evolved.

Incidence

Carcinoma of the prostate (Ca P) is the third commonest cancer in males in the western countries. In United States, Ca P has the highest incidence (177 cases/lac population). It is the sixth commonest cause of death and the second most common cause of

carcinoma deaths after bronchogenic carcinoma. There is a 4% rise annually in its incidence and 35000 deaths were projected to occur due to Ca P in 2005 [2]. However the current incidence is the same as that of the pre PSA era but more number of cases are detected and treated at an early stage. Autopsy studies in asymptomatic individuals have revealed an incidence of 50% in those aged 50 years and 70% in those 65-80 years of age. Only about 29-44% of occult tumours are detected by screening. The lifetime risk of asymptomatic Ca P is about 35% (clinical Ca 9%).

Risk Factors

Though prostate cancer is universal, the incidence is highest in Caucasian and least in Asian men. Obesity resulting in an increased body mass index (BMI) is associated with higher risk of prostate cancer [3]. These patients usually have increased levels of low density lipoproteins (LDL), cholesterol and IGF (insulin like growth factor). These patients may have lower PSA levels but the increased risk of Ca P remains. Positive family history is a definite risk for Ca P, with increase incidence of five to eleven times as per the number of generations having Ca P.

Chronic prostatitis may be a risk factor or probably leads patients to seek medical attention earlier and hence early diagnosis. Definite proof of chronic prostatitis leading to Ca P is not yet available.

Anti inflammatory drugs like COX2 inhibitors have protective effect against Ca P. Studies have eliminated

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vasectomy as a risk factor. Deficiency of antioxidants could be a risk factor. Trials to prove their role in prevention of Ca P are being conducted.

Diagnostics Modalities

The discovery of new tumour markers is important, since these may be future targets for Ca P therapy [4].

PTEN is a tumour suppressor gene, a homologue of tensin, a contractile protein (hence the name Pten or PTEN) deleted on chromosome 10 [5]. It is a lipid phosphatase whose primary function is to negatively regulate P13 kinase /Akt signaling and is mutated frequently in advanced prostate cancer and cell lines. Loss of PTEN therefore provides a cellular environment for activation of the P13-kinase/akt survival pathway. PTEN is inactivated in several types of cancers, including those from prostate, brain, breast, endometrium and kidney. Loss of PTEN expression is an important factor in progression towards metastatic disease and could potentially serve as an early prognostic marker for prostate cancer metastasis. In an experimental study a combination of adenoviral vector-expressed PTEN (AdPTEN) and radiation (5 Gy) significantly inhibited xenograft tumour growth.

Other markers found in cancer prostate cells include MSR1 mutations (macrophage scavenger receptor) and HoGG1 mutations (protects against oxidative damage). The loss of GSPT1 CpG island (PIN hypermethylation) is found in 90% of Ca P cases. Amethylacyl coenzyme A racemase is an immunohistochemical marker which is over expressed in Ca P and positive in 80% of prostate cancers. Heat shock protein 70(Hsp 70), an apoptosis inhibitor in conjunction with PSA may be useful in detecting early prostate cancer.

Novel therapies with antibodies to target EGFR and IGF levels are under development. Targeted antibodies against TGF beta, ET1B, ET1A (which is anti apoptotic), CDKs (cyclin dependant kinases) and aurorakinases (important for mitosis) are also being developed. Monoclonal antibodies against VEGF may be one of the novel therapies available in future.

New therapies like dendritic cell vaccine therapy, adenovirus linked IL2, GM-CSF are still in the experimental stage. Other therapies include anti EGFR monoclonal antibodies VEGF or MMP(matrix metalloproteinases) inhibitors [6].

Diagnosis

Prostate cancer is diagnosed by digital rectal examination (DRE), PSA estimation and trans rectal ultrasound (TRUS) or a combination of all three. However for screening, PSA estimation is being followed worldwide. The individuals at high risk also

undergo DRE. If PSA is high, a TRUS guided trucut biopsy is advised. The sextant biopsy has been replaced by a minimum of 11 cores (range 8-22 biopsies) from different areas of the prostate including the lateral borders of both lobes [6]. Gleason score is considered an optimal method of grading biopsies because it takes the inherent heterogeneity of prostate cancer into account and has a prognostic value. Patients who are initially negative for Ca P, but are considered at risk are advised repeat biopsy after four to six weeks [7].

Prostate Specific Antigen

Prostate specific antigen is a serum protease and it liquefies semen. Normally PSA is not detectable in the serum because of the blood prostate barrier. It is produced by the glandular cells of the prostate and is abundant in the semen. Only when these cells are disrupted as in Ca P, the levels of PSA become detectable in the serum. Prostate cancer releases 10 times more PSA into the circulation per gram of tissue than does normal epithelium or epithelium associated with benign prostatic hypertrophy (BPH).

Levels of total PSA above 2.5ng/ml are now considered an indication for biopsy [8]. In such cases, the free PSA should be below 19%. Catalona et al [1], report that using these parameters, 83% of cancers diagnosed were clinically significant and 81% of those who underwent surgery had organ-confined disease. The ratio of free PSA to total PSA improves detection at levels 4-10 ng/ml. As the levels of free PSA decreases (below 20%) the risk of Ca P rises. PSA density (PSAD) of more than 0.15 ng/ml has also been suggested as an excellent tool to diagnose cancer when levels are between 4- 10 ng/ml. However an accurate estimate of prostate volume will be required [9].

Pre pro PSA is a precursor form of PSA which is broken down to 7pro PSA which is further converted to complexed mature PSA and inactive free PSA by unknown enzymes. There are other forms of cleaved PSA or zymogen forms, the role of which is still unclear. Free PSA (fPSA) is associated with BPH and its ratio to PanProPSA (total of all zymogen forms) in the range of 2.5-4 ng/ml correlated well with the presence of CaP. The evaluation of PSA-DT or PSA doubling time is useful in predicting progression and survival. If PSA-DT is less than three months an early androgen ablation is advised.

Human kallikrein:2(hK2) has a amino acid sequence similar to PSA and is expressed in various tissues but the highest levels are found in prostate tissue [10]. Human kallikrein 2 by itself has not been found to outperform PSA.

Mass spectrometry [10], also known as surfaced

enhanced laser desorption and ionization time-of-flight mass spectrometry (SELDI-TOF) has been used to identify prostate cancer specific serum patterns and tissue derived cancer specific proteins. The test uses protein chips and laser desorption and ionization to detect abnormal proteins. Three studies have shown a sensitivity of 95-100% and a sensitivity of 78-100%. The practical applicability of this test appears remote.

In a recent Japanese study, researchers found power doppler imaging (PDI) of the prostate useful in those with intermediate levels of PSA (3-10 ng/ml) [10]. PDI showed hypervascular lesions which were hypoechoic on TRUS. Biopsy of these lesions revealed that unnecessary biopsies can be avoided if PDI was negative (in almost 60% of patients) and missed only 8-14% of cancers.

Indium(In)111 Prostascint (Capromab Pendetide) is indicated as a diagnostic imaging agent in newly diagnosed patients with biopsy proven prostate cancer, thought to be clinically localized after imaging studies especially in high risk cases of pelvic lymph node metastases. The overall sensitivity and specificity is about 68%. In recurrent disease the sensitivity and specificity is about 63%. It is available in few centres in the US and has not been accepted elsewhere. Since capromab pendetide is a murine monoclonal antibody it is contraindicated in those allergic to murine antigens.

Positron emission tomography (PET) using F-18 fluorodeoxyglucose (FDG) has been used to detect distant metastases in prostate and other cancers [11]. However this is excreted in bladder and it obscures local spread of prostate cancer. C11 acetate and C11 choline have been used with PET which are not excreted in the bladder and are useful in detecting local, regional and metastatic disease in prostate cancer. C11 choline PET is useful in detecting 5mm nodules and residual or recurrent disease after hormonal therapy in the prostate with a sensitivity of 83%. PET CT is however a poor tool to detect extra prostatic extension because of its limited spatial resolution. MR spectroscopy also uses the principle of imaging choline compounds in the prostate in detecting local spread.

Management

In stage T1a or 1b (T1a is when less than 5% of the chips are involved and T1b is when more than 5% of chips are involved), the patients are offered choice of watchful waiting or radical prostatectomy.

In stage T1c (Ca P detected by trucut needle biopsy), T2a-c (prostate cancer confined to one or both lobes but not extracapsular clinically or on imaging) a full metastatic workup including chest radiograph, bone scan, magnetic resonance imaging (MRI) is performed.

Endorectal coil MRI has better sensitivity and specificity to detect extracapsular extension or seminal vesical extension with an accuracy of 89%. Radical prostatectomy is indicated in these patients [12]. The other factors taken into consideration are PSA less than 20 ng/ml, a life expectancy more than 10 years, Gleason score less than 7, no lymph nodes and the choice of the patient. Radical prostatectomy reduces disease specific mortality, overall mortality, risk of metastases and local tumour progression. Recently a meta-analysis of 10737 patients who underwent radical prostatectomy revealed that the mortality was only 0.5% and major surgery related complications were 28.6 %. Of these, 28% had satisfactory erections, 6.7-14% had urinary leakage and 10-17% had positive margins. Since 1998 laparoscopic radical prostatectomy has become the procedure of choice. Introduction of the Da Vinci robot has enabled precise surgical manipulation and suturing of the vesicourethral anastomosis easier [13]. Table 1 shows the number of laparoscopic radical prostatectomies performed worldwide.

Various nomograms to predict biochemical failure after surgery, external beam radiotherapy (EBRT) and brachytherapy exist. None of them are perfect, but some can predict metastases and cancer specific death. Those with short PSA doubling times are at the greatest risk of death. Radical prostatectomy has decreased metastatic prostatic cancer and cancer specific death by 50%. Adjuvant therapy for those with positive margins or if PSA levels become detectable subsequently, is in the form of EBRT. If lymph nodes are positive, immediate androgen ablation is advised.

Brachytherapy [14] with radioiodine or palladium seeds is the choice in early (T2a-b) cancer prostate. The treatment is permanent and is available in select centres. Iridium needles can be used as a temporary option. Brachytherapy is usually combined with EBRT. Biochemical control rates of 66-88% have been achieved

Table 1
Number of laparoscopic and robotic laparoscopic prostatectomies performed at major centres

Author	Surgery	Period & Centre	Patients
Rassweiler et al	Lap RP	Mar 99-Jul 2004	5500
Partin et al	Lap RP	1998-1999 (JohnHopkins)	225
Guilloneau et al	Lap RP	Montsourris Center, France 2000-2002	311
Guilloneau et al	Lap RP	Jan 2003 to May 2004 (MSK center)	240
Germany	Lap RP	Mar 99 – Aug 2004	5585
Lepor and Taneja	Robotic Lap RP	Jan 1997 –Dec2000	906
Vatticutti Institute Menon et al, Detroit	Robotic Lap RP	2000 -2004	1500

with brachytherapy alone using a dosage of 140 Gy. Brachytherapy is contraindicated in those with prior transurethral resection of prostate, a very large prostate or bladder neck obstruction.

Intensity modulated or 3D conformal radiotherapy is an advanced method of irradiating the prostate with minimal damage to the surrounding tissues.

Cryotherapy using liquid nitrogen or argon has been used since the 1960s [15], especially for those patients who refuse surgery or they are unfit for other therapies. The technique involves placing 9-19, 17G cryoneedles in the prostate under transrectal ultrasound guidance. Freezing is done using liquid nitrogen or argon with transrectal temperature monitoring. The therapy is stopped once the rectal temperature reaches 15 degree Celsius. There is a high incidence of impotence after this therapy, with a smaller incidence of rectal fistula formation and incontinence. 72-77% of patients are free of cancer in subsequent TURP specimens. This therapy can also be performed in locally advanced (upto stage 3b) after antiandrogen or complete androgen blockade.

Treatment of Advanced Prostate Cancer

The treatment of advanced prostate cancer (Stage T3 and beyond) is in the form of androgen ablation. Bilateral orchidectomy is the most common treatment [16]. Alternatives are LHRH analogues like leuprolide, goserelin or buserelin, which have similar side effects like flushing, loss of libido, fatigue and osteoporosis as bilateral orchidectomy. Bicalutamide (a non steroidal anti androgen) 150 mg/day as monotherapy or in combination with LHRH analogues is administered to prevent flare effects (initial stimulation by LHRH analogues). The levels of PSA usually become undetectable or are very low after orchidectomy in hormone dependant Ca P. A similar but slow decrease is seen after LHRH analogue therapy. Abarelix, a new GnRH antagonist [17], but without the initial testosterone surge has also been introduced for therapeutic use. It decreases circulating FSH levels without affecting the already suppressed levels of testosterone.

Androgen Independent Prostate Cancer

When the levels of PSA start rising after bilateral orchidectomy and flutamide therapy, (or LHRH analogues), the options are withdrawal of antiandrogens or replacement with bicalutamide or nilutamide. Nilutamide has better response rate than bicalutamide [18]. Intermittent androgen therapy may be tried at this juncture but the long-term efficacy is unproven. The other options available are second line manipulation in the form of adrenal blockage using ketoconazole (200-400 mg/d), or aminoglutethimide, oestrogens (DES). All of these block adrenal function

and steroid supplementation is required.

Hormone Resistant Prostate Cancer

Hormone Resistant Prostate Cancer (HRPC) is defined as progressive disease in spite of first and second line hormonal manipulation [19-21]. It is usually incurable, but symptoms can be relieved. Multiple systems are usually involved in the form of lower urinary tract malfunction, haematuria, bladder outlet obstruction or incontinence; ureteric obstruction by prostate or lymph nodes; skeletal dysfunction like pathological fractures, spinal cord compression; bone marrow insufficiency; lymphoedema; rectal obstruction; pain due to bony metastases-treated by local radiotherapy, radiophosphorus, strontium 89 or biphosphonates and psychological dysfunction, mental impairment.

Systemic chemotherapy in the form of docetaxel with estramustine or mitoxantrone and prednisolone have been found effective in HRPC. For localized disease mitoxantrone 21mg/m² with prednisolone resulted in a median survival of 15 months. Single agent docitaxel also resulted in a median survival of 18 months. Docitaxel based regimens are now the standard for HRPC [22].

Treatment versus Watchful Waiting

In Sweden, where treatment of CaP is not pursued aggressively, patients with biopsy positive CaP are given a choice of watchful waiting (WW). In the Pre PSA era, CaP in Sweden was not treated with radical surgery. Only the complications were treated. Johansson [23], followed 200 men who had biopsy proven CaP for 20 years, out of which 31 died of metastatic disease, 27 died of complications due to CaP, 113 died of other causes and 27 are still alive. However progression was found to be three times faster after 15 years.

Bill-Axelson et al [24] in Scandinavia randomized 700 men to radical surgery and WW groups and followed them for a median of 8.2 years. The study concluded that 19% of WW patients had died of CaP versus 8.5% of those who underwent surgery after ten years. Watchful waiting refers to observation with no treatment. The term expectant management involves actively monitoring the course of the disease with the expectation to intervene if the cancer progresses or if symptoms become imminent. Expectant management is indicated in men with low or intermediate risk and a life expectancy of less than 10 years (serum PSA less than 20 ng/ml, Gleason score 7 and stage T2c) [25]. These patients are offered palliative treatment if they become symptomatic. The indications and follow up for expectant management is given in Table 2 [26].

Screening

The incidence of CaP in Asia and India (4.8-8 cases

per lac population versus 140 per lac population) is more than ten times than that in USA or Europe. At present screening for CaP is not recommended in Asian men as a routine. Screening in USA and Europe has revealed that 70% patients are asymptomatic and 98% have abnormal PSA (>4ng/ml) and normal DRE. 78% are usually less than 59 years of age. Screening has produced an annual decrease in mortality of 4.3% since 1991 in USA.

The American Cancer Society Workshop on early prostate cancer detection has recommended that PSA test and digital rectal examination should be offered annually beginning at age 50 to men who have a life expectancy of at least 10 years. Indirect evidence based on decision models suggest that if screening and treatment prove beneficial, men who are 50-69 years of age will enjoy most of the benefit from screening. At present, the available data suggests that offering a screening programme to all men aged 50 to 70 would be prohibitively expensive.

The ESPRC trials of screening started in 1993 and has randomized 1,80,000 men over 10 years [26]. Their baseline PSA for biopsy was 3 ng/ml with a detection rate of 1.5-2.7%. An interim report published does not recommend generalized population screening for CaP.

Prevention

The PCPT (Prostate Cancer Prevention Trial) [27], randomized 18,800 men to finasteride (5mg daily) or placebo and followed them up for 10 years. The aim of 25% reduction in incidence of cancer prostate in 10 years was achieved three years earlier in the finasteride group and the study was terminated prematurely. During the study 1100 patients died of unrelated causes. The SELECT trial [28], involving about 33000 men in USA is in progress and aims at preventing prostate cancer

with Vit E and selenium. The results are awaited.

Toremifene, a selective estrogen receptor modulator, was tried by Price et al [29], in 514 patients with high grade PIN (prostate intraepithelial neoplasia) and was found to decrease the incidence of prostate cancer by 48.2%.

The other products likely to be beneficial are statins, soy products which contain phytoestrogens or isoflavonoids which have anti angiogenic effects and also act through the signal transduction pathway. COX2 inhibitors may have a protective effect. Finasteride reduces the risk of carcinoma by 25% at seven years as seen in the PCPT trial. Dutasteride, a dual 5 alpha reductase inhibitor may be better than finasteride. Lycopene is also considered protective.

Promotion of men's health has gained importance considering the various environmental factors having a deleterious effect on male physiology. The World Health Organisation recommended lifestyle changes for promotion of men's health are given in Table 3.

Prostate cancer is a major health problem in the Western world and Europe. However changing lifestyles and diet will probably lead to an increasing incidence in Asia also. At present few studies on the incidence in India are available. A small scale screening study of 908 symptomatic elderly men done in Pune in 2004 revealed an incidence of 0.8% incidence of prostate cancer. However for those volunteering for screening and early detection, surgery in the form of radical prostatectomy would reduce morbidity and mortality.

Conflicts of Interest

None identified

Table 3

Lifestyle changes recommended by WHO [30]

- Prevent risk factors for coronary artery disease
- Keep lipid profile optimum
- LDL levels < 130-160 mg%
- HDL levels > 40 mg%
- BP < 140/90 mmHg
- Know your PSA levels – starting at age 50 years
- Maintain healthy body weight
- BMI <25
- Low fat, Low carbohydrate diet
- Replace saturated fat and cholesterol with unsaturated fats
- Increase dietary fibre
- Increase fruit/vegetable consumption containing lycopene and carotenoids
- Encourage use of soy products
- Use of flaxseed oil, canola oil, soyabean oil
- Increase omega 3 fatty acid consumption, present in fish (except fried)
- Increase dietary Vit D, E and selenium
- Thirty minutes of physical activity every day
- Stop smoking, reduce alcohol

Table 2

Indications for watchful waiting (with intention to treat)

Low or Intermediate risk prostate cancer

- Age < 75 years, life expectancy > 10 years
- Stage T1-T2a, Gleason score < 6
- PSA < 8 ng/ml
- PSAD < 0.1 (amount of PSA per gram of prostate tissue)
- Free/total PSA > 19%
- Patient choice
- One core + with < 30% involvement

Expectant management - Follow up

- Every 3-6 months
- DRE +PSA or PSA-DT, creatinine
- TRUS and biopsy if indicated
- Or biopsy every year
- Treatment - if tumour progression is present
- Patient choice
- PSA-DT < 2 years or combination of above

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