Recent Advances in the Management of Prostate Cancer

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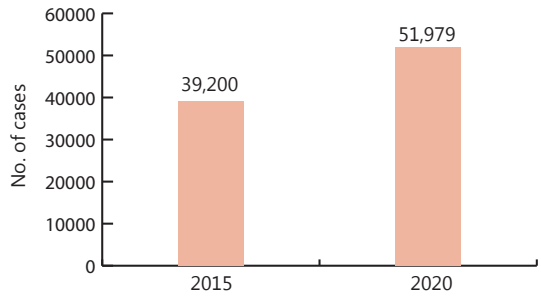
Prostate cancer: Rising burden

Prostate cancer (PC) is the second most common malignancy and the fifth leading cause of cancer-related death in men worldwide.[1] It is primarily a disease of the elderly with majority of the cases occurring in men above 65 years of age.[2] Growing age alone is presumed to increase the number of new cases and new deaths to 1.7 million and 4,99,000, respectively by 2030.[3] However, the projected cases of prostate cancer all over India for 2020 is estimated as 30,185.[4] Jain *et al*. reported a wide variation in annual percentage change of prostate cancer in various population-based cancer registries of India, ranging from 3.4% in Bangalore to 11.6% in Kamrup District in Assam.[3] Projected cases of prostate cancer in India are shown in Figure 1.[3] The high incidence and mortality rates thus indicate the public health significance of this disorder. Prostate cancers have substantial economic impact, and utilize significant proportion of healthcare resources.[5]

Risk stratification in prostate cancer

Prostate cancer risk factors includes older age, positive family history, increased height, obesity, hypertension, lack of exercise, persistently elevated testosterone levels, and ethnicity.[6] Risk stratification is important in determining the timing and treatment regimens for patients with prostate cancer.[7] D'Amico and colleagues presented a risk stratification nomogram for clinically localized prostate cancer as shown in Table 1. It is important to realize that significantly changing paradigms in different aspects of advanced prostate cancer may not only contribute to increased burden of the disease but also influence clinical decisions.[8]

Figure 1: Projected cases of prostate cancer in India



Source: Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. *Meta Gene.* 2014; 2:596-605.

Table 1 D'Amico and colleagues presented a risk stratification nomogram for clinically localized prostate cancer

Risk group	Clinical stage	PSA (ng/mL)	Gleason score	Biopsy criteria
Low	T1a or T1c	<10	2-6	Unilateral or <50% of core involved
Intermediate	T1b, T1c, or T2a	<10	3 + 4 = 7	Bilateral
High	T1b, T1c, T2b, or T3	10-20	4 + 3 = 7	>50% of core involved or perineural invasion or ductal differentiation
Very High	T4	>20	8-10	Lymphovascular invasion or neuroendocrine differentiation

Source: D'Amico AV, Moul J, Sun L, et al. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol.* 2003; 21:2163–2171.

Table 2: Characteristics of selected clinically validated prostate cancer biomarkers

Biomarker	FDA-approved	Recommended by EAU guidelines
PSA, fPSA and pro2PSA – protein-based test	Yes	Yes
tPSA, fPSA, iPSA and hK2 – protein-based test	No	Yes
PCA3 – qRT-PCR	Yes	Yes
8 proteins prostate expression	No	No
17 (12 + 5) genes – qRT-PCR	Yes	Yes
46 (31+15) genes – qRT-PCR	Yes	No
22 RNA biomarkers prostate expression	No	No
GSTP1, APC and RASSF1 – methylation assay	No	Yes
4 metabolites (aminoacids) LC-MS assay	No	No
Immuno-PCR (IPCR) for pg/mL PSA levels	Yes	No
NGS in cfDNA	No	No
2 mRNA biomarkers combined with clinical variables	No	No
SChLAP1 expression (ISH or qRT-PCR)	No	No
PCA3 and ERG exosome-derived gene expression (qRT – PCR)	Yes	No

FDA - Food and Drug Administration; EAU - European Association of Urology; tPSA - total PSA; f PSA - free PSA; iPSA - intact PSA; qRT-PCR - quantitative reverse transcription polymerase chaining reaction; AS - active surveillance; LC-MS - liquid chromatography–mass spectrometry; NGS - next generation sequencing; cf DNA - cell-free DNA; ISH - in situ hybridization.

Source: Zapała P, Dybowski B, Poletajew S, Radziszewski P. What Can Be Expected from Prostate Cancer Biomarkers A Clinical Perspective. *Urol Int.* 2018; 100(1):1-12.

Potential biomarkers for prostate cancer

Tumor biomarkers are substances present in or produced by a tumor or its microenvironment in response to tumorigenesis or progression processes. They can be used in early cancer diagnosis, anti-cancer therapy development, monitoring of treatment responses, and detecting individual risk for cancer development.[9]

Several serum, urinary, and tissue biomarkers have revealed favorable prognostic value. Prostate-specific antigen is an established biomarker used for diagnosis and treatment decisions in patients with prostate cancer. Nevertheless, with recent advances, a plethora of biomarkers have been identified, which may help in disease prognosis, predicting therapeutic response, and drug development. Various biomarkers for prostate cancer are summarized in Table 2.[10]

Management of prostatic cancer

Seven main phases on the care pathway for prostate cancer have been identified as diagnosis and treatment**,** recovery and readjustment, watchful waiting (WW), active surveillance (AS), monitoring – initial and ongoing, progressive care, and end of life.[11] The first decision is to determine if any treatment at all is needed, as low-grade tumors often grow slowly requiring no treatment.[6] Medical and surgical castration are the two most important aspects of therapy in prostate cancer.[7,12] Various therapies for the management of prostate cancer are elaborated in Table 3.[6,13,14]

Recommended treatment

Table 4 depicts the recommended treatment for patients with prostate cancer.

Advances in prostate cancer management

Advances in technology, including new imaging modalities, genomic tests, and biomarkers, have introduced practice-changing opportunities for the treatment of localized prostate cancer.[15] Newer chemotherapeutic agents, immunotherapies, bone microenvironment targeted agents, new androgen receptor blockers, antiangiogenic agents, endothelin receptor antagonists, growth factor inhibitors, radiotherapeutics and hormonal therapies are being added regularly. Some of the upcoming treatment strategies include:

Immunotherapeutic strategies (Sipuleucel-T): Sipuleucel-T is an autologous vaccine consisting of patients' autologous peripheral blood mononuclear cells (PBMCs) which aims at stimulating an effective immune response against human PAP, an antigen highly expressed in prostate cancer tissue.[16]

Novel chemotherapeutic agent (Cabazitaxel): Cabazitaxel is a novel semi-synthetic tubulin-binding taxane which has shown activity in docetaxel-resistant tumor cell lines. Studies have shown improved overall survival with combined cabazitaxel and prednisone in patients with metastatic castrate resistant prostate cancer (CRPC), whose disease had progressed during or after docetaxel-based therapy

Novel endocrine agents: Cytochrome P450 is a central enzyme in testosterone synthesis. New investigational agents for CRPC, specifically selective cytochrome p450 17 inhibitors and second-generation anti-androgens, are being evaluated in clinical trials. These include the novel androgen biosynthesis inhibitors abiraterone and AR antagonist enzulitamide.

Table 3: Therapeutic options for the management of prostate cancer

- **Active surveillance:** Patients are usually required to have periodic prostate-specific antigen (PSA) testing and at least one additional biopsy 12 to 18 months after the original diagnosis. It is considered appropriate for men with low-grade prostate cancer and limited sized cancers.
- **Watchful waiting:** It may be done in low to intermediate risk patients or for asymptomatic patients with high risk or locally advanced disease. According to this concept, patients are only treated when the disease has become symptomatic.
- **Focal Ablation Therapy:** It uses ablative energies such as microwave, cryotherapy, laser, high intensity focused ultrasound, etc. that can treat a localized malignant prostatic lesion. They are cost effective with substantially fewer side effects. It is optimal for those who show no evidence of extra prostatic or more widespread disease and have a single, isolated lesion.
- **Endocrine therapy:** Bilateral orchiectomy was originally used to produce castration levels of testosterone. Use of Luteinizing hormone-releasing hormone (LHRH) agonists such as leuprorelin, goserelin, triptorelin etc. is recommended as a first-line therapy for men with advanced prostate cancer. It lowers testosterone concentrations to castration level within a period of 3–4 weeks. Anti-androgens such as bicalutamide can be co-administered with LHRH agonists to prevent any clinical response to the temporary testosterone surge that often accompanies initiation of hormonal therapy with LHRH agonists. Additionally, gonadotropins releasing hormone (GnRH) antagonists such as abarelix and degarelix bind competitively to the receptor in the pituitary gland thereby blocking LH (luteinizing hormone) and FSH (follicle stimulating hormone) release and lowering testosterone concentration to castration level within 1-3 days.
- **Surgery:** Radical prostatectomy has been considered the cornerstone treatment for clinically localized prostate cancer. It has a survival advantage over radiotherapy. Additionally, lymhadenectomy may be done in high risk patients for more precise assessment of the stage of the disease. Furthermore, cryotherapy can be used as a salvage surgical treatment after radiation therapy has failed.
- **Radiotherapy:** The goal of radiation therapy is to provide a lethal dose of radiation to the tumor without harming the surrounding normal tissue of the bladder and rectum. It includes external beam radiation therapy (EBRT), low-dose-rate or high dose rate brachytherapy (LDR/HDR brachytherapy). The American College of Radiology recommends a total dose of 75 to 78 Gy for EBRT. Brachytherapy involves surgical implantation of tiny radioactive seeds into the prostate. Additionally, the use of hormonal therapy in combination with radiation or brachytherapy has demonstrated improved overall survival in intermediate and high-risk disease.

Table 4: Recommended treatment

Risk group	Life expectancy in years	Recommended treatment
Low	0-5	AS, HT
	5-10	AS, RT, HT, O
	>10	RP, RT, AS, O
Intermediate*	0-5	AS, HT, RT, O
	5-10	RT, HT, RP, O
	>10	RP, RT, O, HT
High*	0-5	AS, RT + HT, O
	5-10	RT + HT, HT, RP, O
	>10	RT + HT, RP + RT + HT, HT, ST, IT
Very high*	0-5	AS, RT + HT, O
	5-10	AS, RT + HT, O
	>10	RT + HT, RP + RT + HT, HT,ST, IT

*If there is more than a 20% probability of positive lymph nodes, AS, HT, ST + HT. AS, active surveillance; HT, hormone therapy; IT, investigational multimodal therapy; O, others; RP, radical prostatectomy; RT, radiation therapy; ST,systemic therapy. Courtesy : Campbell-Walsh Urology 11th Edition.

Apalutamide: Newly US-FDA approved, nonsteroidal antiandrogen for non-metastatic CRPC. It is a selective competitive silent antagonist of the androgen receptor. Among men with nonmetastatic castration-resistant prostate cancer, metastasis-free survival and time to symptomatic progression were significantly longer with apalutamide than with placebo.

Novel bone targeting agents: Bone metastases are the main cause of significant morbidity and poor quality of life, and may hasten death. The nuclear factor κB ligand (RANKL) inhibitor, denosumab, has been developed for the treatment of bone metastases and has shown significant reduction and delay in skeletal related events in comparison to bisphosphonate zoledronic acid. Alpharadin (radium-223 chloride) is another agent containing an alpha-particle-emitting nuclide that has shown significant improvement in overall survival & CSS in men with symptomatic bone metastatic CRPC[16]

Conclusion

Prostate cancer is the second most common form of cancer and the sixth leading cause of cancer-associated deaths among men worldwide. Progress in the field of diagnosis with novel biomarkers has been beneficially accompanied by advancements in the treatment modalities, such as hormone therapies, chemotherapies, bone targeting agents, vaccines and immunotherapies.

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Holmium Laser Enucleation of the Prostate

Holmium laser enucleation of the prostate (HoLEP) is a versatile and durable therapeutic option that has been the mainstay of treatment for lower urinary tract symptoms (LUTS) secondary to benign prostate hyperplasia (BPH) for nearly 20 years. The present study reviewed current and sentinel publications that provide outcomes data after HoLEP. Study results showed continued support for HoLEP as a resourceful surgical option for men with LUTS secondary to BPH. However, despite its proven efficacy for durable symptom relief beyond 10 years in large prostate glands, its extensive availability for treatment in patients is missing. This omission can be attributed to factors such as high rates of retrograde ejaculation and transient urinary incontinence. Concerns surrounding the learning curve of the procedure appear to persist and limit the adoption of HoLEP by established urologists and residency training programs.

To sum up, recent studies have persistently shown excellent short and long-term outcomes after HoLEP, specifically in the categories of voiding function and patient satisfaction. Moreover, continued attempts are being made by those performing HoLEP to demonstrate its equivalent efficacy and patient safety during the learning phase of HoLEP to other alternate-BPH surgical techniques for both mentored and self-directed surgical training.

Source: Large T, Krambeck AE. Evidence-based outcomes of holmium laser enucleation of the prostate. *Curr Opin Urol.* 2018 May;28(3):301-308.

Novel Investigational Procedures in Benign Prostatic Hypertrophy

The current study provides an overview of the most recently developed treatments for benign prostatic hypertrophy (BPH) along with available clinical data related to their application. BPH has increasingly become a common disease thereby causing a remarkable rise in the number of investigational procedures that are being developed to manage it. Study findings suggest that with a surge in the number of treatments available for BPH, improved diagnostic testing could be beneficial for guiding patient selection. Newer classification strategies and serum biomarkers are being identified specifically with MRI, to determine both the anatomy as well histologic distribution of BPH. Various novel outpatient procedures that are under development include the temporary implantable nitinol device and intraprostatic injections such as Botox and PRX302. Another novel technique that uses robotically guided high-pressured saline to ablate prostate tissue is aquablation, studies on which have shown non-inferiority compared with TURP. Lastly, application of robotics to BPH is in progress with the advent of a robotic transurethral platform that is designed for prostate enucleation.

In conclusion, numerous innovative techniques for detection and management of BPH are likely to be introduced over the coming years, specific detailed studies on which must be done to determine their roles in the management of patients with symptomatic disease.

Source: Acquaye J, Borofsky MS. Investigational procedures in benign prostatic hypertrophy. *Curr Opin Urol.* 2018 May;28(3):315-321.

Computer Vision Approach for Detecting Subtle Histological Effects of Dutasteride on Benign Prostate

The objective of the present study was to determine whether a computer vision-based approach applied to H&E prostate biopsy images can distinguish dutasteride-treated tissue from placebo. An additional objective was to identify features associated with degree of responsiveness to 5α-reductase inhibitor (5ARI) therapy. A total of 100 men from the REDUCE trial who were assigned to dutasteride or placebo group, were compliant to treatment, without prostate cancer, and had slides available from mandatory Year

4 biopsies were included in the study. 50 subjects also provided slides from a Year 2 biopsy. 20x whole slide images were obtained and specialized software was used to generate a library of 1,300 epithelial and stromal features from objects comprising superpixels and several types of nuclei, including spatial relations among objects between and within each hierarchical level. Additionally, optimal combinations of histological features in the Year 4 biopsies were determined using penalized logistic regression and 5-fold cross-validation. Finally, independent validation was done by fitting feature data from the Year 2 biopsies to a final model. Focal atrophy and histological features, previously linked to 5AR1 treatment, were scored for each image by two pathologists who were blinded to the treatment.

Results showed:

- Consensus classification by pathologists obtained a discrimination accuracy equivalent to chance
- A 21-feature computer vision model gave a cross-validation AUC 0.97 in the Year 4 biopsies and 0.79 in the set-aside Year 2 biopsies
- Histology scores did not correlate with changes in PSA, serum DHT or gland volume
- Key features associated with dutasteride treatment included greater shape and color uniformity in stroma, irregular clustering of epithelial nuclei, and greater variation in lumen shape

Overall, individual patient response in the context of BPH treatment or cancer chemoprevention can be predicted by a computer vision approach that can detect subtle histological effects attributable to dutasteride, resulting in a continuous measure of responsiveness to the drug

Source: Sethi A, Sha L, Kumar N, Macias V, Deaton RJ, Gann PH. Computer vision detects subtle histological effects of dutasteride on benign prostate. *BJU Int.* 2018 Feb 20.

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