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Prostate Cancer Screening Methods and Its Management Along Its Precision Medicine Recent Approach in The Light of ESMO Guidelines, A Review Article

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Abstract

Risk of clinically significant prostate cancer is related to age, family history, PSA level, free and total PSA ratio as well as finding of digital rectal examination DRE, subclinical prostate cancer is common in men over 50 years of age, hence PSA (Prostate specific Antigen) testing Has been recommended in men over 60years of age if PSA level is more than 2ng/ml. The 5 - year survival rate for prostate cancer in India is 64%. Although many cancers deem fit for cancer screening but prostate cancer screening having limited role author will try described about current recommendation of prostate cancer screening, recent data of HBCR Hospital based cancer registry shall also be discussed in order to understand disease burden in Indian context, along with management of prostate cancer in depth. Recently precision medicine has opened its wings for prostate cancer as well what we achieve out of it shall further address in this review article.

Keywords: Screening test; Cancer registry in India; Precision medicine; Prostate cancer

Discussion

Prostate cancer is one among the top ten leading cancer in India. It usually affects men in the age group of 65+ years. However, recently there has been an increase in reports of cancer in younger men in the age group of 35 - 44 and 55 - 64 residing in metropolitan cities. Old age, obesity, improper diet, and genetic alterations have been identified as some of the main contributing factors towards an increased cause of prostate cancer. A study revealed that those patients who underwent prostate cancer treatment with surgery had a better survival rate (91%) [1-5]. These findings prove that while treatment may save a life or extend the number of survival years, awareness about and prevention of the disease has become crucial in today's day and age. Compared data available from various cancer registries and observed that the average annual cancer incidence rate for prostate cancer in India ranged 5.0 - 9.1 per 100, 000/year, whereas the comparative rate in the United States were 110.4 for whites and 180.9 for Blacks. The incidence rates of this cancer are constantly and rapidly increasing and the cancer projection data shows that the number of cases will double by 2020.

Recommendation for prostate cancer screening as per ESMO guidelines

i. Population based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of over diagnosis and over treatment thus it is not recommended.

ii. Early PSA testing can offer to men over 50 years of age with family history of prostate cancer and BRCA - 1/ BRACA - 2, genetic mutations.

iii. Testing for prostate cancer in asymptomatic men with life expectancy more than 10 years should not be done.

Diagnosis and Early detection of Prostate cancer

The risk of clinically significant prostate cancer is related to age, family history, PSA levels, free/total PSA level ratio and clinical finding of digital rectal examination. MPMRI (Multi parametric MRI) Can be explained as a method to obtain 3D Prostate image on MRI by combining T2 Weighted image with Diffusion weighted image combination of both images called as

MPMRI this very investigation is highly recommended before performing prostatic biopsy. Trans perennial biopsy results in high yield results so when MPMRI is positive than only prostatic biopsy is recommended since when MPMRI Imaging is negative clinical suspicion of prostate cancer is very low.

Staging and Risk Assessments for Prostate Cancer

MRI imaging provides T-Staging, MRI can help in surgery, especially for nerve sparing surgery as well as wide excision of areas of potential extra prostatic disease extension.

a) 1 Men with low-risk disease like Gleason score less than or equal to 6, and PSA<10ng/ml do not require further imaging.

b) 2 Men with high-risk disease should go for further workup like imaging for nodal and metastatic workup with MRI, Whole body PET scan, CECT for chest abdomen and pelvis.

Management of locoregional disease

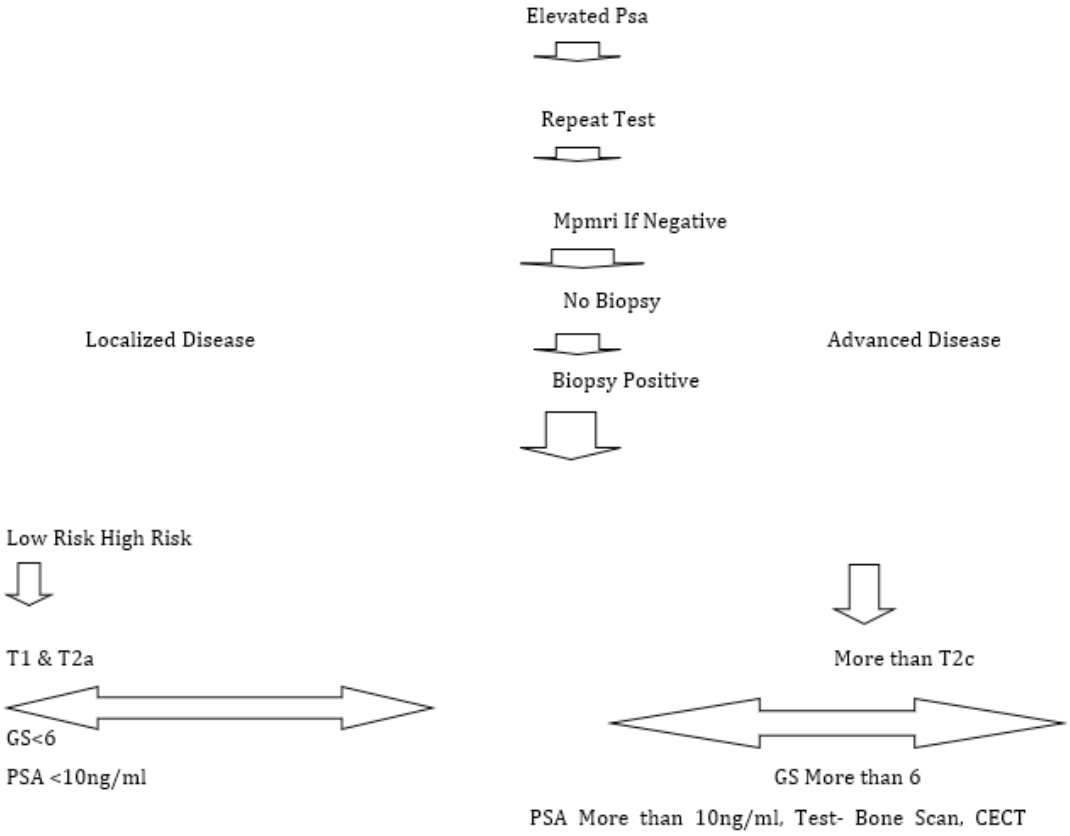
i. 1 Patients must be informed about the benefits and side effects of the treatment like they might have sexual dysfunction, infertility, bladder, and bowel problems.

ii. 2 Watchful waiting with delayed hormone therapy is an option for the men those who are not suitable or unwilling to have treatment with curative intent. Surveillance is a choice strategy with PSA monitoring.

iii.

iv. 3 Curative treatment options are Radical Prostectomy, External beam Radiotherapy.

Diagnostic Workup and Staging for Prostate Cancer



Stage wise treatment options

A-Localized and Low Risk Disease

a) Active surveillance

b) Radical Proctectomy

c) Radical Radiotherapy

B- High Risk Disease

i. Long Term ADT

ii. Radical RT +/– Docetaxil.

iii. Radical Prostectomy

Metastatic Disease

Hormone Naïve Disease Options Are

a) ADT+ Abiraterone

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b) ADT + Docetaxil

c) ADT+ Benzylamide

d) Radiotherapy for low volume disease

Castrations Resistant Prostate Cancer

i. Abiraterone

ii. Docetaxil

iii. Enzalutamide

Post Docetaxil Second Line

a) Abiraterone

b) Cabazitaxil

c) Enzalutamide

Localized Prostate Cancer Relapsed After Radical Radiotherapy Options Are

i. Radical Proctectomy

ii. Observation with Delayed ADT Therapy

iii. HIFU

Localized Prostate Cancer Relapsed After Radical Proctectomy Options Are

Radical radiotherapy to prostate bed and pelvic nodes followed by ADT (androgen deprivation therapy) for 6 months to 2 years.

Neoadjuvant And Adjuvant Hormone Treatment

_Role of Neo adjuvant and adjuvant ADT Hormone treatment in men with high risk localized prostate cancer has been well established by multiple randomized control trails study shows the use of ADT therapy for six months significantly improve overall survival as well as mortality rate in compression to Radiotherapy alone. In young men with high-risk prostate cancer with localized disease docetaxel-based chemotherapy is an reasonable option.

Post Operative Radiotherapy

Post operative radiotherapy followed by Radical Proctectomy may be given as adjuvant treatment in case of persistent high PSA level or rising PSA level after surgery this is at present "Standard of Care."

Approach for Relapse After Radical Treatment in Prostate Cancer

The natural history of PSA recurrences after primary treatment is usually long and life expectancy must be taken into account when considering treatment, MPMRI is useful in detection of local recurrences and can guide targeted biopsy in case biopsy is positive, but no metastasis has been found available options are salvage radical proctectomy if primary treatment was radical radiotherapy or HIFU / Brachytherapy.

Metastasis Directed Therapy

Its technically possible to selectively abate metastasis this could slow down the progress of disease and improve overall survival in this situation SBRT can be very good option to looked upon.

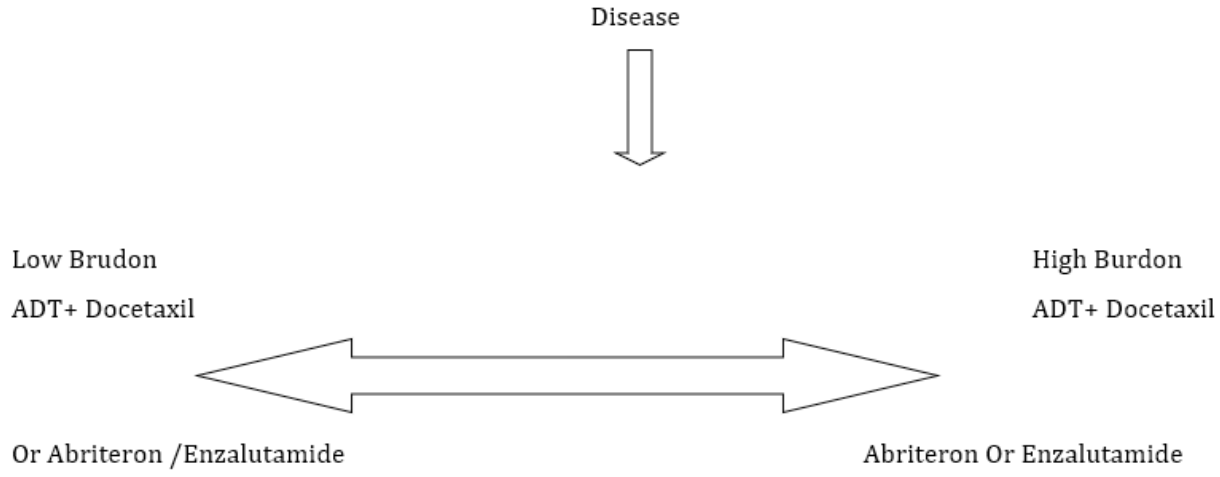
Systemic Therapy for Prostate Cancer

The study suggests no survival advantages with early start of Androgen deprivation therapy ADT rather early start of ADT Therapy had adverse effects on quality of life, especially in terms of sexual dysfunction hot flashes.

Metastasis Hormone Naïve Prostate Cancer

Prostatic cancer patients those having PSA recurrences without metastasis known as hormone naïve prostate cancer, ADT therapy improve overall survival in MHNPC

Hormone Naïve Prostate Cancer



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The benefits of docetaxil for MHNPC was established by phase-3 trail namely CHAARTED trail and STAMPEDE trail, Addition of to ADT d Abiraterone demonstrated to improve overall survival in comparison to ADT therapy alone henceforth recommended ADT along Abiraterone 1000mg plus 5 mg prednisolone daily until disease progression.

Finally, Recommendation Made As:

a) ADT is recommended as first line treatment of MHNPC in combination with Abiraterone / Docetaxil with Predenesolone or Enzalutamide

b) Radiotherapy to primary tumor in combination with systemic treatment is recommended for low volume MHNPC.

c) ADT alone recommended as first line of treatment of MHNPC in men who are unfit to Abiraterone or Docetaxil or Enzalutamide treatment.

Non-Metastatic Castration Resistant Prostate Cancer

Castration resistant prostate cancer (CRPC) is defined as a disease which progresses during ADT treatment despite serum testosterone being at castrated level. Absence of metastasis as traditional imaging (Bone scintigraphy and CT scan) has been used to identify Non metastatic castration resistant prostate cancer (MOCRPC) disease [6-15]. This state of disease exists because of early long-term use of ADT for men with Non metastatic prostate disease. Apalutamide significantly increases median metastatic disease-free survival as well as time to symptomatic progression.

i. Recommendations are: Aplutamide or Enzalutamide should be considered as options for men with non-metastatic castration resistant prostate cancer and especially those having high risk of disease progression.

Metastatic Castration Resistant Prostate Cancer

In men with metastatic CRPC both Bicalutamide and low dose corticosteroids shows benefits in terms of PSA and symptomatic response, but study demonstrated no benefits in terms of overall survival. Mildly symptomatic MCRPC Abiraterone significantly improves overall survival but along with side effects like, hypokalemia, hypertension, edema, and cardiac toxicity [16-20]. The role of chemotherapy in MCRPC was established with Docetaxil 75mg/m^2 three weeks along with prednisolone significantly increased over all survival in post docetaxel settings CABAZITAXIL Chemotherapy improve overall survival.

"There is strong evidence suggesting Cross resistance between Abriteron and Enzalutamide "

i. Recommendations are made:

a) Docetaxil is recommended for men with MCRPC.

b) Patients with MCRPC in post docetaxil setting Cabazitaxil or Enzalutamide are recommended options to use.

c) Patients with bone metastasis in CRPS are at risk of clinically significant Skeletal related events (pathological fractures) thus Bisphosphonates or Denusumab are recommended options to use.

Precision Medicine in Prostate cancer

In precision medicine various tissue based molecular test provide us prognostic as well as predictive information in many solid tumors and prostate cancer is not exception to that, in prostate cancer targets are identified in molecular test like immunohistochemistry (IHC), FISH test, etc, approximately 20% of metastatic prostate cancer harbors genetic abrasions like we look for BRACA 1/ BRACA2, mutations BRACA - 2 mutations are more commonly associated with prostate cancer, BRACA 2 mutant prostate cancer often having Gleason score more than 8 (GS»8) as well as commonly associated with pelvic lymph node involvement along distant metastasis at the time of diagnosis, henceforth mutation in BRACA2 associated with poor clinical outcome in these patients, men with prostate cancer should also be considered for genetic testing if at least two close blood relatives have been diagnosed with breast cancer /ovarian cancer/prostate cancer/ colorectal cancer, so far as prediction is concerned those who have been diagnosed to have BRACA2 mutations will very well response to platinum based chemotherapy as well as polymerase inhibitors example Pembrolizumab targeted drug [21-23].

i. Recommendations are made:

a) BRCA-2 & BRCA-1 (more commonly BRCA-2) Associated with prostate cancer predisposition henceforth in patients with positive family history of breast cancer / prostate cancer / colorectal cancers must be put under genetic screening test.

b) Olaparib can be use as new hormonal agents for MCRPS with alteration found positive in BRCA-1/ BRCA-2.

Palliative Care in Prostate Cancer

Fractionated verses single fraction Radiotherapy for bone pain has been compared in multiple randomized trials found single fraction 8Gy provides similar pain relief verses 20Gy in 5 fractions or 30Gy in 10 fractions, however it has been found multiple fraction radiotherapy were more effective when bone Mets were associated with nerve root compression or disease invading soft tissue along bone, Zoledronic acids shows to prolong skeletal related events.

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