USI Cancer Prostate Guidelines

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Material and Methods

Literature search was conducted in PubMed, Cochrane Central register of Controlled trials including randomized and quasi randomized trials from Embase and PubMed), Medley and Directory of Open Access of Journals. Each set of search was conducted twice, once for high level evidence (randomized trials and systematic reviews) and another time for all levels of evidence with geographical area restricted to ‘India’. Secondary evidence sources included citations from all published English language guidelines and reviews. Level of evidence was evaluated by the center for evidence-based medicine method. (1) References were collated on the Zotero reference manager and irrelevant and duplicate references were eliminated. Each search was assessed by two individuals with reconciliation of any discordance.

The guidelines panel based its final recommendations on the best available global evidence, Indian data as well as the socioeconomics of health care in India. Grades of recommendation (strong/moderate/weak) are the strength of mandate based on the extent of risk benefit ratio of either taking or not taking an action. Clinical principle is a statement that is widely agreed upon

by clinicians for which there may or may not be evidence in the medical literature. Expert opinion is a statement agreed upon by the guidelines panel in the absence of evidence.

1. Epidemiology of prostate cancer in India

Prostate cancer is the fourth most common malignancy globally after lung, breast and colorectal cancers. It is the most common cancer diagnosed among men in 105 countries of the world. It is also the second most common cause of death in males worldwide, surpassed only by lung cancer. (2)

Recent reports from 25 population-based Indian cancer registries show an increase in the incidence of prostate cancer. This correlates with the recent widespread adaptation of PSA screening in the country. (3) As per the 2018 GLOBOCAN data, prostate cancer is the sixth most common cancer in the country, with an age-adjusted incidence rate of 10.2 per 100000 and age-adjusted mortality rate of 4.2 per 100000 population. (2)

1.1 Incidence and Mortality rates of prostate cancer

The prostate cancer, as recorded in the four metropolitan cities, is among the top three cancers diagnosed in men between 2009 - 2011. (3) Kolkata has a crude incidence rate of 7.6 per 100000 population, which is higher than the other three metropolitan cities of the country. However, the age-adjusted rate (ARR) is highest in New Delhi (10.7 per 100000 population) followed by Mumbai (7.8), Chennai (7.0) and Kolkata (6.9). Chennai (4.1) had the highest annual percentage change in age-adjusted incidence rate of prostate cancer followed by Bangalore (3.36) and New Delhi (3.33). On the other end of the spectrum, the incidence of prostate cancer is lowest in the north-eastern states of India, followed by Gujarat and Madhya Pradesh. (3) The global crude mortality rate of prostate cancer is 9.3 per 100000 population, whereas,(4) the registered crude mortality rate in India is 4.5 per 100000 population for the year 2018 as per the GLOBOCAN data.(2)

1.2 Future trends in incidence and mortality

Overall, there is a rising trend in the incidence of prostate cancer globally, with a projected leap from 1,276,106 in 2018 to 2,293,818 by 2040. (5) The increase in incidence has been projected to be as high as 100.9% in the Asian countries including India. The prostate cancer-related mortality is also expected to double at the global level, from 358,989 in 2018 to 737,994 in 2040. (5) Similarly, the number of prostate cancer deaths in India is also projected to double by 2040 compared to 2018.

1.3 Differences in prostate cancer disease status and mortality between the Indian and the western population

Indian men are diagnosed with prostate cancer at a higher serum PSA level (>10ng/ml) than their western counterparts.(7) They also tend to present with higher Gleason score (≥7) at the diagnosis($p<0.001$).(8) Among the Asian Indians who migrate to America, the possibility of finding a pT3 disease and seminal vesicle extension ($p=0.03$) is significantly greater, although the biochemical recurrence-free survival and the positive surgical margin rates are not statistically different from the Caucasians.(9) The incidence of metastases is also higher in Indian men than the western population ($p<0.001$).(7)

2. ETIOLOGICAL AND RISK FACTORS FOR PROSTATE CANCER

2.1 Genetic factors

Single Nucleotide Polymorphism (SNP) of the FDFT1 gene, which encodes a synthase enzyme, has a significant role in the aggressive phenotypes of prostate cancer among the Asian men.(4) BRCA 1 and 2 genes are also associated with aggressive forms of familial prostate cancers.(10) TMPRSS2-ERG and TMPRSS2-ETV1 fusion genes have been found to be associated with advanced stage and lymph nodal metastases.(11) The Cys allele of CYP19, Rr genotype of ER beta gene, -/- genotype of ER alpha gene and CYP19 TTTA genotype of Androgen Receptor (AR) gene have been implicated in carcinogenesis of the prostate among Indians.(12,13)

2.2 Family history

The risk of prostate cancer increases proportionately with the number and degree of related family members diagnosed with the disease. The relative risk (RR) is 2 when either the father or a brother is affected, 3 when father or a brother is affected at less than 60 years of age and 4 when both father and brother are affected. The RR is 5 in cases of hereditary prostate cancer. (14)

2.3 Age

Prostate cancer is predominantly a disease of the elderly and Indian men above 55 years of age are 18 times more prone to develop the disease, than those younger than 55 years. (15) There is a steep increase in the risk of prostate cancer in males beyond 70 years of age. (16)

2.4 Dietary factors

The dietary pattern in India is diverse and the 'westernization of Indian diet' is proposed as a reason for the rising incidence of prostate cancer in the country. While a vegetarian diet offers protection against prostate cancer, both the type and quantity of fat appear to be equally important in carcinogenesis. Omega 3 fatty acids are found to be protective against prostate cancer whereas omega 6 fatty acids are detrimental.(17,18,19) Processed meat increases the risk of prostate cancer and this risk is amplified when meat is grilled, due to the generation of mutagenic aromatic compounds.(18) Consumption of crucifers, green tea, soy, coffee and Vitamin-D is proven to be of benefit in reducing the risk of prostate cancer.(20,21) The effect of tomato, lycopene, folate and vitamin B12 is equivocal and further studies are required for stronger evidence to emerge.(22) There is no significant preventive role of Vitamin E and Selenium as evident from the results of the SELECT trial.(23)

2.5 Lifestyle and Obesity

Smoking has shown to increase cancer-related mortality and smokers are twice more likely to die of prostate cancer than non-smokers.(24) Heavy alcohol consumption (>15g ethanol/day) is also a risk factor promoting prostate cancer, although several studies have shown only a weak association.(25) Obesity is an important risk factor that perpetuates physical inactivity and also dilutes the PSA leading to delayed prostate biopsy and hence a late diagnosis.(26) One of the

modifiable risk factors is physical inactivity and men who exercise regularly have been found to have a significantly lower risk of prostate cancer.(27) Ejaculatory frequency of more than 21 per month confers 20% protection from low-risk prostate cancer, compared to less than 4-7 ejaculations per month.(28) There is no association of vasectomy with high grade or high stage prostate cancer.(29)

2.6 Sexually transmitted infections

Prostatic inflammation induces proliferative inflammatory atrophy (PIA) which leads to prostatic intraepithelial neoplasia (PIN) – a forerunner of prostate cancer (odds ratio 1.7).(30) Chronic bacterial infections induce prostatic inflammation. On the other hand, viruses like Herpes Simplex Virus (HSV-16) can cause transformation of genes and prostate carcinogenesis. (31,32,33,34)

2.7 Drugs and Environmental toxins

The use of Finasteride and Dutasteride did not prove to be of significant benefit in preventing high-grade prostate cancer in the PCPT and REDUCE trials.(33,35) Recent evidence points to the potential protective effect of Non-steroidal anti-inflammatory drugs and Aspirin in prostate cancer.(36) The use of statins in the chemoprevention of prostate cancer requires further evaluation.(11) Environmental toxins present in preserved food products such as Agent Orange, Chlordecone, Bisphenol-A have been implicated in prostate carcinogenesis.(37,38,39)

Key points

Key points	Level of evidence
The incidence of prostate cancer is increasing in the recent years due to westernization of lifestyle and the widespread adaptation of PSA screening.	
The incidence and mortality of prostate cancer in India are expected to double by 2040.	
Indian men tend to be diagnosed with higher PSA and higher Gleason scores and are more likely to harbor locally advanced and metastatic disease at presentation.	**3**

There is an urgent need for research to further define the epidemiology and risk factors of prostate cancer in Indian men.	

3. SCREENING AND EARLY DETECTION IN PROSTATE CANCER

Prostate cancer (PCa) is an indolent cancer and lacks specific symptoms in the early stages. (40) It is essential to formulate screening guidelines for early detection.

3.1 Burden of prostate cancer in India

Contrary to the western world, poor access to the health care services masks true burden of PCa in India. Data from various agencies show that the age standardized rates (ASR) for prostate cancer range from 4.7-10.2%. (41,42,43,44,45) Comparing the data from United States Vs India reveal a higher annual incidence rates in the US than in India (5.9/ 100000 people in India and 110 and 180/100000 people respectively in white and black men in the US). (46)

3.2 Screening benefits and harms: Western data vs Indian setup

Need for prostate cancer screening is a subject of global debate due to harms of over-diagnosis and the perceived benefits of early diagnosis. Screening has shown to increase the overall diagnosis of the prostate cancer (RR 1.3, 95CI 1.02-1.85) as well that of the localized disease (RR 1.79, 95CI 1.19-2.70), and decrease the incidence of advanced staged cancers (RR 0.80, 95CI 0.73-0.87).(47) The European randomized study of screening for prostate cancer (ERSPC) data showed a 27% reduction in the mortality in the screened men at 13 years but at a cost of 781 screened participants for the detection of one cancer.(48,49) United States Preventive services Task Force(USPSTF) study showed a small benefit of prostate cancer screening in individuals between 55-69 years with no benefit in patients beyond 70 years.(50,51,52) The western literature recommends a ‘Shared-Decision-Making’ approach where-in screening is offered to

asymptomatic men after discussion with the patient about the pros and the cons of screening. Screening data from India is non-existent. Systematic screening will add burden on our health-care system. Hence, systematic screening is not feasible. However, a case by case approach, depending on individual risk profile, can be considered after the age of 45 years in a man with a life expectancy >10 years.

3.3 Modalities for screening

The ideal screening tool must be highly sensitive & specific, reproducible and readily available.

Digital rectal Examination (DRE): An abnormal DRE is a definite indication for biopsy and predicts higher grade of disease but alone has low sensitivity and specificity. (53,54) Considering the ease and cost effectiveness of DRE, Indian council of medical research (ICMR) has recommended regular DRE after 50 years of age for the early detection of prostate cancer. (55)

Prostate Specific antigen (PSA): PSA is organ but not cancer specific thus can be elevated in other non-malignant conditions as well. (56) As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS) alone. (57) There are no standardized parameters for “normal” PSA. A lower cut-off is associated with higher detection rate at the cost of higher false positive results, while the higher cut-offs have higher chances of false negative results. (57) The panel could not find longitudinal Indian studies to recommend a specific PSA cut-off. Globally, 4ng/ml of PSA is taken as the cut-off and various nomograms are available for further evaluation. (58,59) Japanese guidelines (60,61) have different cut off of serum PSA for different age ranges; 3.0, 3.5, and 4.0 ng/ml for the age ranges of 50–64, 65–69, and ≥ 70 years. This cut-off of PSA may not be appropriate in India. A PSA cut-off of 5.4 ng/ml as a trigger to prostate biopsy has been proposed by some Indian studies.(62,63,64) Agarwal et al (65) observed that in 29.9% of the patients with prostate cancer, the serum PSA was less than 4ng/ml. Yii et al (66), showed that Asia falls into a low incidence region and most of the patients with PSA 4-10 ng/ml have report biopsy results, so apart from PSA, other adjuncts should be considered while

deciding for biopsy. These are Free PSA, PSA Density, PSA velocity, PSA doubling time and these PSA derivatives are beneficial when the PSA ranges between 4-10ng/ml. (65,67,68,69,70,71,72)

3.4 Early detection

Although screening is elusive, early detection of significant cancers is vital. DRE and PSA are the two common modalities for screening. Early detection requires other imaging modalities such as Multiparametric Magnetic resonance imaging (MP-MRI) and Transrectal Ultrasonography (TRUS).

3.4.1 Multiparametric Magnetic resonance imaging (MP-MRI)

MP-MRI includes T2 weighted, Dynamic contrast enhancement and the Diffusion weighted images. (73) The lesions are graded as per the PIRAD V2 system. PIRADS IV or V lesions have a higher likelihood of harboring significant prostate cancer.(74) However, it may have a limited role in evaluating transition zone cancers because of the heterogenous appearance and enhancement secondary to the benign prostatic hyperplasia.(75) Availability, cost, expertise, duration of the procedure etc. are the other limiting factors for its use.(75) However, if the serum PSA is high and the DRE is normal, MP-MRI should be considered for the detection of hidden prostate cancer.

3.4.2 Transrectal Utrasonography (TRUS):

Utility of greyscale transrectal probe (5-10 Hz) to detect the cancer bearing lesion in the prostate is low, with up to 39% of the cancers being not visible. (76,77) Moreover, TRUS is observer dependent. Although handy during the biopsy, it is inconvenient for the early detection. (77)

3.4.3 Prostate biopsy – finger vs TRUS vs mpMRI Fusion

Finger guided prostatic biopsy of the non-palpable disease is sparingly practiced because of the availability of better techniques, fear of injury to the surgeon's finger and under-sampling. Limited literature shows comparable results with TRUS guided biopsy except in patients with very low PSA. (78) TRUS guided 12-core systematic biopsy allows maximal cancer detection. (79) Increasing the number of biopsy cores marginally increases the yield.(80) Upcoming elastography

and contrast-enhanced ultrasound are being investigated for “targeted” biopsies.(81) The yield of TRUS-guided biopsy in Indian patients is low as compared to the western men.(77,82)

Three methods of fusing MRI for targeted biopsy have been described; MRI–ultrasound fusion, MRI–MRI fusion (‘in-bore’ biopsy) and cognitive fusion .(83) MRI–ultrasound fusion for lesion targeting is likely to result in fewer and more accurate prostate biopsies than the TRUS guided systematic biopsy alone.(84,85) Cognitive fusion is simple, quick and requires no additional equipment beyond the MRI and a conventional transrectal ultrasound (TRUS) facility.(86) It has been shown to yield improved accuracy over TRUS biopsy.(86) One Indian study found that MRI-TRUS fusion biopsy has a limited value in normal DRE with PSA range 4-10 ng/ml.(85) Considering the two key aspects, availability and cost, the use of MRI with TRUS has a definite role in repeat biopsies.(87)

Recommendations:

Recommendations	Level of evidence	Strength rating
A personalized risk-stratification may be undertaken for early detection on a case to case basis after the age of 50, when the life expectancy is > 10-15yrs and at risk men must undergo both, serum PSA and DRE.	**1**	**Strong**
No recommendation can be made on the PSA cut-off of PSA values for considering the prostate biopsy. However, a PSA cut-off of 4 ng/ml can be considered for further evaluation.	**3**	**Strong**
PSA derivatives should be considered only when the PSA is between 4-10ng/ml.	**1**	**Strong**
MP-MRI should be considered in a patient with elevated PSA and negative DRE.	**1**	**Strong**
Age specific PSA values and PSA density are important concepts to be developed for the Indian setup for screening and early detection as a future direction.		

4. STAGING ANG HISTOLOGY

The idea of classification and staging is to group together patients with potentially similar characteristics, so as to define evaluation, treatment options, predict outcomes and even use the subsets to generate data in the study settings.

Staging evaluation includes – assessment of tumor, nodes, metastases, histopathology and prostate specific antigen (PSA) levels. The extent of prostate cancer is evaluated by digital rectal examination (DRE) and PSA, and may be supplemented with multiparametric magnetic resonance imaging (mpMRI), bone scanning and computed tomography (CT). However, in the AJCC 8th edition, the clinical T staging is based on DRE alone.

4.1 Staging –

4.1.1 Trans-rectal Ultrasonography – is no better than DRE for predicting organ confined disease. (88)

4.1.2 Contrast Enhanced Computed Tomography/ Magnetic resonance imaging –

CECT – the role of CECT is limited, due to its poor sensitivity and specificity and accuracy in local staging. The only clinical application would be in the assessment of lymph nodes. A short axis diameter of >8 mm in pelvic nodes and >10 mm in retroperitoneal nodes signifies involvement by prostate cancer.

MRI – T2 weighted imaging in mp MRI is the current standard for local staging. As compared to 1.5 T MRI, a 3T MRI has higher specificity with good sensitivity. (89) Currently, in India, 1.5 T MRI

machines are used with software updated to give better and 3T comparable images. MRI may not be so useful in local staging in low risk ca prostate, as its sensitivity for focal EPE is poor. However, it is still being used in planning the treatment. As with CECT, mpMRI can also help in detecting positive lymph nodes. A diffusion weighted image assessment would help, but a normal scan does not rule out metastases.

4.1.3 Bone scan – 99mTcMDP is the most used bone scan utilized for metastatic staging. Its sensitivity increases with increasing PSA, ISUP grade and increasing T stage. It should also be performed in patients with bone related complaints.
A Diffusion-weighted whole-body and axial MRI has higher accuracy than Bone scan and CT scan combined for the detection of bone metastases. (90)

4.1.4 PET scan –
18F-sodium fluoride (18F-NaF) PET or PET/CT is good for detecting bone metastasis and shows superior sensitivity than 99Tc-mdp scan. (91,92) In India, currently there are no facilities offering choline PET/CT. The Choline PETCT is slightly superior to 18F-NaF PET CT, as it detects lesions in bone and lymph nodes as well as other visceral metastases. (93,94,95)
PSMA PET CT is Prostate-specific membrane antigen-based PET evaluation and has higher PPV and NPV than most of the available investigations utilized for the initial evaluation of prostate cancer. As compared to conventional imaging, PSMA PET CT was able to detect 25% more lymph nodes and 6% more bone/visceral lesions in a prospective multicenter study and led to a change in the management decision of 21% of the patients. (96)

In the initial evaluation of men with suspected prostate cancer and PSA levels between 4-20 ng/ml, a study showed that Ga-PSMA PET had higher NPV and accuracy in predicting the cancer as compared to mpMRI and percentage free PSA. Also, cognitive fusion directed biopsies directed by the PSMA images might be more useful than MRI guided biopsies. (97)
In the evaluation of biochemical recurrence post definitive therapy PSMA PET, with its high NPV, high specificity and sensitivity, has proved to be a good investigation. The detection rates of 15-

58%, 25-73% and 69-100%, 71-100% have been reported with PSA ranges of 0.2-0.5 ng/mL, 0.5-1 ng/mL, 1-2 ng/mL and > 2 ng/mL, respectively. (98,99,100) For PSA levels as low as 0.2 ng/ml, PSMA PET has been shown to identify lesions. In patients with suspected metastatic ca prostate, PSMA PET CT, if available, is widely used and is a “one stop test”. Where not available, the option of axial imaging with bone scan should be considered.

4.2 Histology

4.2.1 Histological variants and incidence

Histological examination of prostate cancer is performed under low power microscopy. Most common is acinar adenocarcinoma, around 98%. Abnormal architectural glandular pattern secondary to disturbance of benign epithelial–stromal relationships are graded from 1 to 5, as per the International Society of Urological Pathology (ISUP) 2015 modified Gleason grading schematic diagram. These form the Gleason score, with the most prevalent as the first pattern and the highest pattern found as the second pattern.

The WHO scheme of classification 2016 has further histological variants of acinar adenocarcinoma prostate cancer - atrophic, pseudo hyperplastic, microcystic, and foamy [which are like benign] and signet ring-like cell, pleomorphic giant cell, and sarcomatoid [which are prognostically worse]. The non-acinar variants [1-2%] are - ductal adenocarcinoma, urothelial carcinoma, squamous neoplasms, basal cell carcinoma, and neuroendocrine tumors.(101)

4.2.2 Prognostication of prostate cancer

National cancer care network and the European urological association prostate cancer Risk stratification are shown in Appendix 1&2(102,103). The International Society of Urological Pathology 2014 grades (104) is shown in Appendix 3.

4.2.3 Staging algorithm for Prostate cancer

The 8th AJCC Cancer Prostate Staging is shown in Appendix 4. (105) No data was found on the Indian variants of prostate cancer or the Indian version of staging and classification.

Recommendations

Recommendation	Level of evidence	Strength rating
AJCC recommends DRE for cT staging.		
CECT or TRUS should not to be used for local staging.	**2**	**Strong**
Pre-biopsy mpMRI is not recommended for local staging but definitely for pre-treatment T-assessment.		
For patients stratified as intermediate risk with ISUP 3 grade group or high-risk localized ca prostate, metastatic work up is recommended.	**2**	**Strong**
Metastatic work up, is best obtained with a PSMA PET CECT. Where facilities are not available, clinicians should obtain a Bone scan and CECT Thorax, Abdomen and Pelvis as a means of cross-sectional imaging.	**1**	**Weak**
Histological reporting should follow recommendations by International Society of Urological Pathology 2014 and WHO 2016 classification. Apart from the Gleason score, grade grouping is a prognostic pathological indicator.		**Strong**

5. RISK STRATIFICATION

Multiple risk stratification systems are currently available, majority of them being based on the D`Amico's classification system. The systems, based on the pre-treatment clinical stage, PSA,

Gleason score and other factors, club the patients with similar likelihood of biochemical relapse and thus play an important role in treatment planning and prognostication. The National cancer care network and the European urological association prostate cancer Risk stratification are shown in Appendix 1&2. (102,103)

6. TREATMENT OF LOW RISK PROSTATE CANCER

6.1. Deferred treatment

In patients with ISUP grade 1 or 2, risk of dying from malignancy is 7% at 15 years follow up. (106) Patients with an expected lifespan of more than 10 years benefit the most from the curative interventions. There are two methods of conservative management: Active surveillance and watchful waiting.

6.1.1 Active surveillance (AS) : AS aims to prevent unnecessary treatment & treatment related side effects to a man with low risk disease (LRD) who has a high chance of cancer specific survival despite of deferred treatment. However, if patient progresses during AS & if he has life expectancy > 10 years, he is offered treatment with curative intent with a comparable oncological outcome. No prospective randomized data is available comparing active surveillance to standard modality. The strongest evidence for AS comes from ProtecT Trial which finds no difference in CSS and OS at 10 years for patients who underwent either active monitoring or active treatment. (107) However, it showed higher chances of metastatic progression. A recent, prospective series showed CSS of 99.9% & MFS 99.4% at follow up of 15 years for men with LRD kept on AS. (108) One interesting outcome of this study is the 8.5 years of median treatment free survival.

The criteria for active surveillance include (108):

a. ISUP grade 1, when specified, 2 or less cores with < 50% cancer involvement in each positive core.

b. A clinical stage T1c or T2a

c. A PSA < 10 ng/mL

d. PSA density < 0.15 ng/mL/cc

Drawbacks of AS include repeated DRE, PSA, Biopsy & MRI and the associated cost. It is also important for the patient to understand that 50% patients on AS, may require curative intervention at 10 years. (108)

6.1.2 Watchful waiting (WW)

It refers to conservative approach offered to the patients who are otherwise unfit (life expectancy less than 10 years & presence of co-morbidities) for curative interventions. It offers a minimalistic approach to the patients until they develop progression, either local or systemic and are then provided with palliative treatments in order to improve their quality of life (QOL). A Swedish study about WW showed that CSS was more than 80% at 10 years for men with low & intermediate risk disease. (109) The PIVOT study also supports a similar conclusion. (110) Considering the long & favorable natural history of LRD, WW offers prevention of treatment related harm & functional decline in QOL without significant disease progression & death.

6.2. Active treatment

While the Protect-T trial gives us encouraging results with the deferred treatment, the resultant risk of metastases in patients under the same were significantly higher than active treatment groups of Radical Prostatectomy and Radiation Therapy. The quality of life scores of patients in

the trial were quite encouraging with a very low risk of toxicity after either of the active treatments. Therefore, we recommend that active treatment be carefully considered in patients with life expectancy of more than 10 years.

6.2.1 Radical prostatectomy (RP):

Total surgical removal in the form of RP provides high chances of cure for the localized prostate cancer with the possible preservation of potency and continence. It also provides accurate pathological staging, as pathological upgrading & upstaging is very common and affects prognostication & further treatment options. The available literature indicates around 30-50% chances of pathological upgrading & 10% chances of pathological upstaging in low & intermediate risk disease. (111,112)

6.2.1a Approach:

RP can be performed by open, laparoscopic or robot-assisted (RARP) approaches. However, a recent Cochrane review comparing minimally invasive (MIS) RP vs. open RP found no significant differences in the oncological, urinary function and sexual function outcomes, although MIS resulted in statistically significant improvements in the hospital stay and the blood transfusion rates over open RP. (113)

6.2.1b Pelvic lymph node dissection (PLND):

Extended PLND (ePLND) provides important information for staging & prognosis but fails to improve the oncological outcomes including survival. (114) Based on the various western cohorts, the chances of lymph node involvement (LNI) in LRD is very low, which suggests that ePLND can be avoided. Various nomograms like Briganti nomogram can be used to predict the LNI and ePLND can be offered accordingly. (115)

6.2.1c Nerve sparing RP:

Nerve-sparing RP can be performed safely in most men with LRD. The benefits of nerve preservation include early recovery of erection & continence. (116) The decision to perform nerve sparing should be based on the pre-operative IIEF scores, patient's preference, clinical T stage & the MRI findings. However, if any doubt remains regarding the residual tumor, the surgeon should remove the neurovascular bundle (NVB).

6.2.2 Curative Radiation Therapy

Similar to radical prostatectomy, radiotherapy represents one of the recommended treatment options for all intermediate-risk patients with life expectancy >10yr. An external radiotherapy to the dose of no less than 74 Gy in conventional fractionation of 1.8-2 Gy per fraction is recommended. The modality of brachytherapy may also be considered after suitable assessment.

6.2.2a External Radiation therapy in conventional fractions:

Conventional fractionation is when 1.8-2 Gy per fraction is delivered. An external radiotherapy to the dose of no less than 74 Gy is recommended in said fractionation. (117,118,119) We recommend that such high doses of radiation therapy be always done with highly conformal techniques like IMRT (intensity modulated radiation therapy) preferably assisted by image guidance (Image guided IMRT or IGRT).

6.2.2b Hypofractionated radiation therapy:

Moderately hypofractionated IGRT regimens (2.4-4Gy per fraction in 4-6 weeks) have been tested in randomized trials for non-inferiority. While most results established non-inferiority, the difference in the biological effectiveness of some regimens may have led to a varied efficacy. Overall, toxicity results were also similar in both the conventional and moderately hypofractionated radiotherapy regimens. (120,121,122,123,124) Therefore, we recommend that the same should be considered for the patients due to the convenience of fewer hospital visits.

Recommendation for low risk prostate cancer

Recommendation	Level of evidence	Strength rating
AS can be offered to suitable candidates. Suitability must include patient's financial condition & access to health care facility.	1	Strong
Accurate staging includes pre-biopsy mpMRI & systemic & targeted biopsies.	1	Strong
Follow up protocol should include DRE, PSA, Re-staging biopsy & MRI as per clinician's decision.	3	Strong
Counsel patients about the possibility of requiring further treatment in the future.	3	Strong
WW can be offered to elderly, asymptomatic men with co-morbidities whose life expectancy is less than 10 years.	1	Strong
Offer RP to a suitable candidate who understands & accepts long term oncological outcomes & side effects of the procedure.	1	Strong
Avoid ePLND in LRD.	3	Strong
Perform nerve sparing RP with informed patient consent.	3	Strong
Offer radiotherapy to a suitable candidate who understands & accepts long term oncological outcomes & side effects of the procedure.	1	Strong

A dose of no less than 74 Gy should be delivered either as conventional or moderately hypofractionated regimen.	**1**	**Strong**

7. TREATMENT OF INTERMEDIATE RISK PROSTATE CANCER

When managed with a non-curative intent, intermediate-risk prostate cancer is associated with ten-year and fifteen-year prostate cancer specific mortality rates of 13.0% and 19.6%, respectively. (125)

7.1. Active Surveillance

A recent prospective study concluded that AS is a valid option for the intermediate risk disease (IRD) without Gleason pattern 4.(126) A recent review also suggests comparable oncological outcomes of AS in IRD for those who are classified as IRD due to the PSA between 10-20 ng% and have a small percentage of Gleason pattern 4 & a negative MRI or negative biopsy from the region of interest.(127) In future, genomic markers may play role in selection of the candidates.

7.2 Radical prostatectomy

Patients with intermediate-risk PCa should be informed about the benefits from surgery i.e. reduced chances of distant metastasis and death from prostate cancer compared to the conservative approaches. In the SPCG-4 study comparing radical prostatectomy with watchful waiting, death from any cause (RR: 0.71; 95% CI:0.53-0.95), death from PCa (RR: 0.38; 95% CI: 0.23-0.62) and distant metastases (RR: 0.49; 95% CI: 0.32- 0.74) were significantly reduced in intermediate-risk prostate cancer undergoing surgery at 18 years. (128) The risk of having positive lymph nodes in intermediate-risk PCa is between 3.7-20.1%. (129)

7.3 Radiation Therapy

Patients with Intermediate risk prostate cancer must be counselled about radiation therapy since the cancer specific and overall survival has been similar for both surgery and radiation therapy, with each having their own advantages and disadvantages. A favorable intermediate risk patient is defined as one with only one intermediate risk factor (T2b-T2c, Gleason grade group 2 or 3, and PSA 10–20 ng/ml), with only Gleason grade group 1 or 2, and <50% biopsy cores positive. A favorable intermediate risk patient need not receive prophylactic nodal radiation of the pelvic lymph nodal stations, whereas, the same can be considered in an unfavorable intermediate risk patient (two or three intermediate-risk factors, Gleason grade group 3, and/or > 50% positive cores). Radiation therapy can be delivered as conventionally fractionated or moderately hypofractionated manner (see above for details). We recommend that such a high dose of radiation be planned for by volumetric imaging using a CT scan, boosted by an MRI image if required. The treatment delivery should be offered in a highly conformal technique to spare the surrounding organs of morbidity.

7.3.1 Use of Androgen deprivation therapy (ADT) with Radiation therapy:

A short term (4–6 months) ADT is recommended along with radiation therapy, since it has a survival benefit in the unfavorable intermediate-risk patients (defined above). The answer, however, is not so clear for the favorable intermediate risk patients. (130,131,132,133,134,135,136,137) Therefore, we recommend the use of ADT for 4-6 months in the latter group as well, if any additional tumor risk assessment is unfavorable.

Recommendation for the treatment of intermediate risk prostate cancer:

Recommendation	Level of evidence	Strength rating
Offer AS in selected patients with IRD with a clear explanation for the increased chances of metastases.	**3**	**Strong**

Offer RP with ePLND as a local treatment in IRD.	**2**	**Strong**
Nerve sparing RP can be offered if the chances of extracapsular spread is low.	**3**	**Strong**

8. TREATMENT OF HIGH RISK LOCALIZED PROSTATE CANCER

The panel includes [PSA > 20 ng/ml or GS > 7 (ISUP grade 4/5) or cT2c] under high risk localized category of prostate carcinoma.

8.1 Radical prostatectomy

A recent international literature review involving radical prostatectomy (RP) in patients with high risk prostate cancer reported the biochemical recurrence free survival (BRFS) ranging from 40-94% at 5 years and 27-68% at 10 years. The overall survival (OS) and the cancer specific survival (CSS) were 55.2%-98.6% and 89.8% – 100% at 5 years, respectively. At 10 years, the OS and CSS were 58%-84% and 65%-96%, respectively. The 12-month continence rate was 32%-96.6% and the erectile function recovery was 60%-64% among the patients who were potent before the surgery. (138)

At 7 and 10 years, prostate cancer-specific survival (PCSS) was found to be 79.7% and 65%, respectively, BRFS was 42.4% and 36.7%, respectively and the metastasis free survival (MFS) was 71.1% and 64.4% respectively in the Indian population after RP. (139)

LRP (Laparoscopic radical prostatectomy) also provides adequate outcomes in Indian patients with 58%, 5-year BRFS in high-risk prostate cancers. (140,141)

In an Indian study, RARP (Robot assisted radical prostatectomy) provided equivalent results. Overall, the 2-year and 5-year BRFS was 45% and 35%, respectively. (142)

Based on the literature discussed above this panel also recommends RP as a treatment option for the management of localized high-risk prostate cancer.

PLND should be part of the procedure. (139,143) International studies also favors PLND as there is 15-40% risk of lymph node positivity in this subgroup of patients. (144)

8.2 Radiotherapy

A phase 3 RCT (randomized controlled trial) revealed that EBRT plus ADT was associated with better 5-year disease free survival (40% vs 73%) and 5-year overall survival (62% vs 78%) in comparison to EBRT only arm. (145)

In an Indian study involving high risk localized cancer 5-year DFS (disease free survival) and BRFS was 70.2% and 79.2%, respectively after sequential IMRT with 74 Gy and maximum androgen blockade. This was accompanied with grade 2 and 3 bladder toxicity and rectal toxicity in 12% and 20% respectively. (146)

Moderately hypofractionated IMRT (intensity modulated radiotherapy) is also well tolerated with manageable acute side effects. (147)

From a dosimetric point of view HDR (high dose rate) brachytherapy may be better than IMRT for prostate cancer. (148)

Various retrospective studies and meta-analyses comparing RP and RT suggested lower risk of metastasis and survival advantage in the favor of RP. (149,150) But these studies cannot prove superiority of RP over RT considering their retrospective design, lack of randomization and probability of selection bias. Only a RCT (currently ongoing) can answer this important question (http://www.spcginfo.org/)

8.3 Androgen Deprivation Therapy

8.3.1 Neoadjuvant ADT before RP

Several phase 3 RCT have revealed that neoadjuvant ADT prior to RP leads to an improvement in the extracapsular extension, positive surgical margin and the lymph node status when compared with RP alone in high risk prostate cancer. However, none of the trial demonstrate a significant improvement in the BRFS or OS. (151,152,153,154,155,156,157,158,159,160,161)

Kumar et al performed systemic review and meta-analyses of randomized trials comparing neoadjuvant ADT prior to RP and RP alone. (162,163) The pooled analysis revealed that surgical margin positivity, extra prostatic extension and the lymph-node positivity were significantly lower in-patient group who received neoadjuvant ADT ($p<0.001$, $p<0.001$ and $p=0.02$ respectively). (151,152,153,154,156,159)

In contrast to this the BRFS and OS did not improve significantly ($p=0.48$ and $p=0.95$ respectively). (151,153,159,161)

The only phase 3 trial comparing docetaxel and leuprolide vs goserelin in high risk prostate cancer patients prior to RP is ongoing (NCT00430183) and its results are currently immature. (164)

As per the available evidence the panel does not recommend ADT prior to RP. This is in concordance with other previously published literature. (165,166)

8.3.2 Neoadjuvant ADT before RT

Four phase 3 RCT have evaluated the role of ADT before RT in high risk prostate cancer. Out of these, three concluded that neoadjuvant ADT leads to a significantly higher BCR (biochemical recurrence), DM (distal metastases) and CSM (cancer specific mortality) free survival after 10 years in comparison to RT alone (all $p\leq0.04$).(167,128,127) Fourth RCT reported only 7 year BCR (which was significantly lower in neoadjuvant ADT arm) so it cannot be compared with the other RCT.(168)

All these studies were unanimous about the survival benefit of neoadjuvant ADT. Two phase 3 RCT suggested that 2-3 months of neoadjuvant ADT is appropriate. (169,170)

8.3.3 Adjuvant ADT after RP

Three phase 3 RCT have evaluated the role of ADT after RP. (171,172,173) All three suggested statistically significant ($p\leq0.004$) increase in disease progression free survival (DFS) in the ADT arm as compared to the placebo arm. But conflicting results were found when OS was compared between adjuvant ADT vs. RP alone. Based on these results the panel doesn't recommend

adjuvant ADT, adjuvant ADT should be considered for patients with lymph node positive patients (pN1). (165,172)

8.3.4 Adjuvant ADT after RT

Several phase 3 RCT were performed to evaluate the role of adjuvant ADT after RT in high risk prostate cancer patients. Among them, the EORTC 22863 (171), RTOG 85-31(174,175,176) and the DFCI 95-096 (125,126) trials were the most important ones, which revealed that risk of death from prostate cancer was similar to the general population in adjuvant ADT arm after 10-15 years.

Several RCT concluded in the favor of prolong duration of ADT ranging from 2-3 years. (129,177,178,179,180)

Recommendations for the treatment of high risk localized prostate cancer

Recommendation	Level of evidence	Strength rating
Radical prostatectomy (RP) alone or as a part of multimodality approach is a reasonable option for high risk localized prostate cancer.	**2**	**Strong**
Pelvic lymph node dissection (PLND) should be part of RP.	**3**	**Strong**
Radiotherapy (RT) along with long term Androgen deprivation therapy (ADT) is a recommended therapeutic option.	**2**	**Strong**
Neoadjuvant ADT (androgen deprived therapy) is not recommended before RP.	**1**	**Strong**
Neoadjuvant ADT for 2-3 month prior to RT is recommended.	**1**	**Strong**
Adjuvant ADT after RP is not recommended routinely. It is recommended only in lymph node positive patients (pN1)	**3**	**Strong**
Adjuvant ADT after RT for 2-3 years is recommended.	**1**	**Strong**

9. TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

The panel includes cT3-T4, N0, M0 or any T, cN1, M0; with any Gleason score and any prostate specific antigen (PSA) in the definition of locally advanced prostate cancer (LAPC).

9.1 Radical prostatectomy

The literature supports RP as part of multimodal therapy for LAPC. (181,182,183) The panel could not find a head to head comparison of RP in a multimodality treatment strategy vs. upfront EBRT with ADT for LAPC. However, a phase III prospective randomized trial (RCT) (SPCG-15), including cT3 prostate cancer patients, comparing RP with or without the combination of external radiation versus primary radiation and hormonal treatment, for the impact on cancer specific survival (CCS) is underway.(184) The 2018 Asia Pacific Advanced Prostate Cancer Consensus Conference panelists noted that the recommendation of RP with or without RT and ADT for high-risk LAPC depends on multiple factors, including age, co-morbidities, the risk of local complications, performance status, access to appropriate expertise and contemporary RT technology.(185)

Retrospective studies for cT3 prostate cancer reported 15 years CSS rate of 76-84%, 10 years overall survival (OS) rate of 74-77%, 10 years biochemical recurrence (BCR) free survival rate of 15-51%.(186,187,188,189,190,191) Few cohort studies for cT3b-4 prostate cancer reported 10 years CCS and OS of 87-92% and 68-71%.(192,193,194) In a retrospective review, Moschini et al found that the clinical node positive status is not a significant predictor of outcomes compared to the pN+ status following RP with pelvic lymph node dissection.(195) Whenever possible, ePLND is recommended for high risk prostate cancer as it improves the nodal staging and also, a higher CSS was reported with higher number of nodes removed in pN1 patients.(196,197,198) Hsu et al studied the impact of neoadjuvant hormonal therapy among cT3 tumor and found no impact on the positive surgical margin and OS.(199) Pan J et al in a retrospective analysis including 177 patients found that the neoadjuvant docetaxel based chemo hormonal therapy resulted into

a significantly better biochemical progression free survival (PFS) compared to those with neoadjuvant hormonal therapy and immediate RP, despite the poorer prognostic factors.(200)

9.2 Radiotherapy

Several phase III RCT have proven the superiority of RT with ADT compared to RT with deferred ADT.(126,176,201) Also, phase III RCTs have proven the superiority of long term (2-3years) ADT following RT for LAPC in terms of CSS, local progression, distant metastasis and BCR free survival.(179,202) In a retrospective analysis of 138 Indian high-risk prostate cancer patients, of which 93 patients received hormonal manipulation, mostly in the neo-adjuvant settings, found significantly higher CSS with higher radiation dose and significantly higher CSS and OS with 3D conformal RT compared to whole pelvis RT.(203) In a recent study 46 newly diagnosed lymph node positive prostate cancer patients were treated with prostate specific membrane antigen positron emission tomography (PSMA-PET) guided dose-escalated intensity-modulated radiation therapy (DE-IMRT) and achieved 2 years failure free survival of 100% and OS of 95.7% with acceptable toxicity.(204)

9.3 Multimodality treatment

In a Surveillance, Epidemiology, and End Results (SEER)-Medicare database analysis, RP + RT was found to have superior CSS and OS compared to that of RT + ADT for T3-4, N0-1 M0 prostate cancer, however RP + RT was associated with higher rate of erectile dysfunction (28 vs 20%) and urinary incontinence (49 vs 19%).(205) In an instrumental variable analysis of population database including 2967 cN1 patients, significant OS benefit with RP + ADT and RT + ADT compared to ADT alone, with no significant difference between RP + ADT and RT + ADT.(206) Analysis of outcome of EORTC trail 30891, which compared immediate versus deferred ADT alone among T0-4, N0-2 and M0 prostate cancer patients unfit or unwilling for local curative treatment, concluded that patients with baseline PSA >50ng/ml and/ or PSA doubling time <12 months may benefit from the immediate ADT due to high risk of prostate cancer related death.(137)

9.4 Adjuvant treatment

Definition of adjuvant treatment includes treatments in addition to primary treatment aimed at reducing the risk of relapse. The factors predicting risk of relapse following RP include number of involved nodes (>2), size of the largest positive node, extranodal extension, positive surgical margins and seminal vesical invasion.(198,207,208) In a RCT, adjuvant Bicalutamide was found to be associated with significant improvement in PFS but not in the OS after RP for LAPC.(209) In a RCT of adjuvant RT following RP in pT3-4pN0 patients with undetectable PSA, 10 years PFS (56 vs 35%) was significantly better with RT compared to wait and see policy. However, there was no significant impact on metastasis free survival or OS with RT. (210)

Early ADT following RP in pTxN+ disease has been found to be associated with significant improvement in CSS, OS and PFS.(211) Adjuvant RT with ADT resulted in favorable CSS and OS in cases of low to intermediate volume non-organ confined node positive disease compared to the adjuvant hormonal therapy alone.(212) Presence of one positive lymph node following RP+PLND was found to be associated with 10 years CSS of 75% and PFS of 20% even in absence of adjuvant therapy.(213)

In RP + PLND patients with post-operative detectable PSA of 0.2-4ng/ml, addition of 24 months of ADT with Bicalutamide to salvage RT resulted in significantly higher CSS and OS compared to salvage RT plus placebo. (214) In a study of salvage RT without ADT after biochemical relapse following RP, 3.5 years biochemical relapse rate of 54% was achieved with long term cure among the patients with lower PSA post salvage RT. (215)

Recommendations for the treatment of locally advanced prostate cancer (LAPC)

Recommendation	Level of evidence	Strength rating
Radical prostatectomy (RP) along with extended pelvic lymph node dissection (ePLND) is a reasonable option for selected patients with LAPC as part of multimodal therapy.	**2**	**Strong**
Radiotherapy (RT) along with two to three years of androgen deprivation therapy (ADT) is a reasonable option for patients with LAPC.	**2**	**Strong**

ADT monotherapy should only be offered to patients unwilling or unfit for local treatment who are either symptomatic or, have asymptomatic disease with a high or rapidly rising PSA level.	**2**	**Strong**
Adjuvant treatment can be considered in men with with undetectable post operative PSA who are at high risk of biochemical relapse.	**2**	**Strong**
Adjuvant ADT should not be offered to patients with N0 disease.	**2**	**Strong**
Adjuvant external-beam radiation therapy (EBRT) to the surgical field can be offered to patients who are at increased risk of local relapse: pT3 pN0 with positive margins and/or invasion of the seminal vesicles.	**2**	**Strong**
Patients with pN+ disease after an e-PLND, can be offered: Adjuvant ADT; Adjuvant ADT with additional RT; Observation if < 2 nodes with microscopic involvement, and a PSA < 0.1 ng/mL and absence of extranodal extension.	**2**	**Strong**
ADT monotherapy can be deferred in M0 asymptomatic patients unwilling or unfit for any form of local treatment if they have a well differentiated tumor, a PSA doubling time >12months, a PSA < 50 ng/mL.	**2**	**Strong**

10. DEFINITION AND TREATMENT OF BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY/RADIATION THERAPY

10.1 Definition of Biochemical recurrence

10.1.1 Biochemical recurrence after Radical Prostatectomy

PSA ≥0.2ng/mL represents a sensitive threshold to PSA progression. The current consensus defines biochemical recurrence (BCR) as a serum PSA ≥0.2ng/mL followed by a second confirmatory reading.

10.1.2 Biochemical recurrence after Radiation therapy

Following RT, PSA levels may not decrease to the undetectable levels. Further, PSA fluctuations (the so called "PSA bounce") are common in the first 2 years after RT. Finally, concomitant use of androgen deprivation therapy (ADT) either prior to or along with RT complicates the interpretation of BCR.

At the 2006 RTOG-ASTRO Consensus Conference, the Phoenix definition of radiation failure was proposed as an increase of 2 ng/mL above the post-treatment PSA nadir. This definition also applies to patients who received HT.

10.2. Treatment of Biochemical Recurrence After Radical Prostatectomy/Radiation Therapy

10.2.1 Salvage radiotherapy [SRT] for PSA-only recurrence after radical prostatectomy

In a comparative study, a 75% reduced risk of systemic progression was seen in patients receiving SRT versus no SRT. SRT is most likely to be effective when the rising PSA level is still low. (216) Salvage RT after primary RP has been associated with a 4-year progression-free probability of 45%. (217) For men with a greater than 10-year life expectancy with BCR, the focus should be on delivering "early" (PSA < 0.5 ng/mL), and potentially "very early" salvage RT (PSA < 0.2 ng/mL) (218,219). More than 60% of patients who are treated before the PSA level rises to > 0.5 ng/mL will achieve an undetectable PSA level corresponding to a ~80% chance of being progression-free five years later. (220,221,222,223,224)

In a retrospective study of men with BCR after RP, at a median follow-up of 6 years after BCR, SRT (alone or with ADT) was associated with a threefold improvement in prostate cancer-specific survival compared to observation, although only in men with a PSA-DT of <6 months (HR 0.32; 95% CI 0.19–0.54; $p < 0.001$).(225) However, if initiated more than 2 years after BCR, SRT provided no significant increase in cancer-specific survival, regardless of the PSA-DT. In another

retrospective study, at a median follow-up of 11.3 years, early (within 1 year of BCR) SRT led to a significant reduction in all-cause mortality both in men with a PSA-DT of <6 months (HR 0.53; 95% CI 0.31–0.90; *p* = 0.02) and PSA-DT of 6 months or longer (HR 0.52; 95% CI 0.34–0.80; *p* = 0.003). (226)

Patients with Gleason score 8–10, pre-RT PSA >2.0 ng/ml, positive surgical margins, seminal vesicle involvement (SVI) and/or PSA-DT ≤10 months had a higher risk of recurrence after salvage RT and may be spared toxicity of salvage RT. A salvage RT nomogram that calculates the 6-year BCR-free probability may help identify patients who may best benefit from salvage RT. (227)

Currently, there is no definitive recommendation on the relative merits of adjuvant RT (aRT) versus early SRT. One study suggested that early SRT was similar to adjuvant RT in improving BCR-free survival in most patients with pT3pN0, R0–R1 PCa previously treated with RP. This study therefore suggests that early SRT, when given at a low PSA level (≤0.5 ng/mL), can significantly reduce overtreatment associated with aRT.(228) Another study reported no significant difference in OS between aRT given within 9 months of RP and delayed sRT (≥12 months post-RP).(229)

Recently, two randomized phase III trials (RTOG 9601 AND GETUG-16) of salvage RT with or without androgen pathway inhibition have reported their results.(214,230) Men undergoing late salvage RT (PSA > 0.7 ng/mL) with high-risk features (Gleason score 8–10, T3 disease, and/or positive margins) appear to derive a metastasis and survival benefit from the addition of long-term hormonal therapy on the basis of RTOG 9601.(214) Men who undergo early salvage RT have yet to demonstrate clinically meaningful benefits.

The optimal SRT dose should be at least 66 Gy to the prostatic fossa (plus/minus the base of the seminal vesicles, depending on the pathological stage after RP).(221,231) In a SRT, the pre-SRT PSA level and SRT dose both correlated with BCR, showing that relapse-free survival decreased by 2.4% per 0.1 ng/mL PSA and improved by 2.6% per Gy, suggesting that a treatment dose above 70 Gy should be administered at the lowest possible PSA level.(232) The combination of pT stage, margin status and ISUP grade and the PSA at SRT seems to define the risk of biochemical progression, metastasis and overall mortality.(219,233,234)

10.2.2 Brachytherapy

The chance of cure using salvage brachytherapy following local recurrence post RT is low, as the total dose is limited. For carefully selected patients, high- or low-dose rate brachytherapy may be an effective treatment option with an acceptable toxicity profile. (235,236,237)

10.2.3 High-Intensity Focused Ultrasound

HIFU is a more recent option for post-radiation recurrent PCa; available data are therefore from shorter-term studies. (238,239,240,241,242) These studies have shown DFS rates of between 25 and 54% mean follow-up between 3 and 39 months. (241,243,244)

Recommendations for the definition and treatment of BCR

Recommendation	Level of evidence	Strength rating
After radical prostatectomy rising serum prostate-specific antigen (PSA) level is considered a biochemical recurrence (BCR).		**Strong**
After radiotherapy, an increase in PSA > 2 ng/mL above the nadir, rather than a specific cutoff value, is considered as BCR.		**Strong**
Offer possibly delayed salvage radiotherapy (SRT) to patients with biochemical recurrence who are classified as low-risk at relapse and may not benefit from intervention.	**2**	**Strong**
Treat patients with a PSA rise from the undetectable range with SRT. At least 66 Gy of RT should be given as soon as possible after the decision for SRT has been made.	**2**	**Strong**

Offer hormonal therapy (with bicalutamide 150 mg for two years, or LHRH agonists for up to two years) to patients with aggressive disease characteristics undergoing SRT.	**2**	**Strong**
Do not offer salvage brachytherapy to patients with proven local recurrence as it is still in experimental stages.	**3**	**Strong**
Do not offer high intensity focused ultrasound to patients with proven local recurrence since it is still in experimental stages.	**3**	**Strong**

11. FIRST LINE THERAPY IN METASTATIC PROSTATE CANCER

11.1 Introduction

Metastatic prostate cancer (mPCa) develops in a third of the men with prostate cancer (PCa), with bone (84%) being the most common site followed by distant lymph nodes (10.6%). (245) The estimated 5-year survival rate of mPCa is about 30%. (246). These rates have ever improved.

11.2 Prognostic factors

"Volume" of the metastatic disease was introduced as a prognostic factor in the recent CHAARTED trial. Men with mPCa were stratified as 'high volume' if there were ≥ 4 bone metastasis including ≥ 1 outside the vertebral column or the presence of visceral metastasis. (247) In the LATITUDE trial, presence of ≥ 2 of the factors such as the presence of ≥ 3 bone metastasis, visceral metastasis or ISUP grade ≥4 were considered as 'high-risk'. (248)

11.3 Therapeutic options

The various therapeutic options in the first-line therapy of mPCa are

Androgen deprivation therapy (ADT) ± anti-androgens

ADT + Docetaxel

ADT + Abiraterone + Prednisone

ADT + Enzalutamide

ADT + Apalutamide

ADT + EBRT to the prostate

Combination of above in sequence

11.3.1 ADT ± anti-androgen

All symptomatic patients with mPCa should be treated with ADT, which is the standard of care. Studies have shown that ADT should be instituted early as it significantly reduces the risk of disease progression. (249) Continuous ADT should be considered as the intermittent ADT was unable to achieve non-inferiority in the largest SWOG trial.(250) In a well-informed compliant men, intermittent ADT may be an option. Nonsteroidal anti-androgen (NSAA) monotherapy is found to be less effective in terms of survival, disease progression, treatment failure and discontinuation and should not be offered. (251)

11.3.2 Role of chemotherapy in mHSPC

Three RCTs evaluated the role of docetaxel in metastatic hormone sensitive prostate cancer (mHSPC). The CHAARTED trial compared docetaxel combined with ADT to continuous ADT alone in mHSPC. At a median follow-up of 29 months, the researchers showed that the chemo-hormonal group had a significantly better OS than ADT alone (57.6 vs 44 months, HR 0.61; 95% CI 0.47-0.80). While the median OS was not reached in the subgroup analysis of low-volume disease, a survival advantage of 17 months (HR 0.60; 95% CI 0.45-0.81) was noted in the combination group in men with high-volume disease. (247)

In the GETUG-AFU 15 trial, at a median follow-up of 50 months the combination of docetaxel with ADT had a higher median OS as compared to the ADT alone group, however the difference was not statistically significant (58.9 vs 54.2 months; HR 1.01; 95% CI 0.75-1.36). (252)

In the multi-arm, multi-stage STAMPEDE trial, the combination of docetaxel and ADT (standard of care) was compared with ADT alone. The trial included 2962 men with high-risk, locally

advanced, metastatic or recurrent PCa. They were randomized into four arms in 2:1:1:1 allocation to ADT alone, ADT + docetaxel, ADT + zoledronic acid and ADT + zoledronic acid + docetaxel. At a median follow-up of 43 months, ADT + docetaxel arm had a better OS than ADT alone (81 vs 71 months, HR 0.78; 95% CI 0.66-0.93). In the subgroup analysis of men with high volume mPCa, the survival benefit favored the ADT + docetaxel arm (60 vs 45 months, HR 0.76; 95% CI 0.62-0.92). (253)

A systematic review and meta-analysis of 2992 men with mHSPC including the above trials, showed a 9% absolute improvement in survival at 4 years with ADT plus docetaxel arm compared to ADT alone. (254)

11.3.3 Role of Abiraterone in mHSPC

The two landmark trials favoring the role of addition of abiraterone plus prednisone to the standard ADT established the newer anti-androgen in the list of first line therapeutic agents of mHSPC. The LATITUDE trial showed better median OS at 30-months in the abiraterone group compared to the ADT plus placebo group (median OS not reached vs 34.7 months; HR 0.62; 95% CI 0.51-0.76). The median length of radiographic PFS was significantly higher in the abiraterone group (33 vs 14.8 months, HR 0.47, 95% CI 0.39-0.55). Abiraterone was also found to be superior to placebo in other secondary endpoints such as time to pain development, initiation of chemotherapy, PSA progression, and the occurrence of a symptomatic skeletal related event (SRE). (248)

In the STAMPEDE trial, the combination of abiraterone plus prednisone with ADT showed significantly better OS (83% vs 76%) compared to ADT monotherapy. The study population included locally advanced and mPCa and at a median follow-up of 40 months, 184 deaths were noted in the abiraterone group as compared to 262 in the ADT arm (HR 0.63; 95% CI 0.52–0.76). Based on these trials, abiraterone plus prednisone combined with ADT should be considered as a standard in men with mHSPC, provided they are fit to receive the regimen. (255)

Role of Enzalutamide in mHSPC

Enzalutamide, a second-generation antiandrogen with dual inhibition of androgen biosynthesis pathway, has been evaluated by two recent RCTs in mHSPC setting. The first study – ARCHES trial, showed enzalutamide with ADT had a reduced risk of disease progression or death than placebo plus ADT (median not reached vs 19 months, HR 0.39; 95% CI 0.3–0.5) in men with mHSPC. The difference was regardless of disease volume and/or previous docetaxel therapy. Also, enzalutamide significantly reduced the risk of PSA and pain progression, initiation of new antineoplastic therapy, first symptomatic SRE and development of CRPC ($p<0.001$). Similar superior results were reported in all pre-specified subgroups stratified by disease volume and prior docetaxel therapy. (256)

In the ENZAMET trial, men with mHSPC who received ADT with or without prior docetaxel were randomized to receive either enzalutamide plus ADT or NSAA plus ADT. The combination of enzalutamide and ADT showed a favorable result compared to the NSAA plus ADT in terms of OS (HR 0.67; 95% CI, 0.52–0.86), PSA-PFS (HR 0.39; 95% CI, 0.33–0.47), clinical PFS (HR 0.40; 95% CI, 0.33–0.49). In the subgroup analysis based on receipt of docetaxel, enzalutamide significantly improved the time to clinical progression (HR 0.48, 95%CI 0.37-0.62), but did not improve the OS (HR 0.90, 95%CI 0.62-1.31) among men who have received prior docetaxel therapy. However, in chemotherapy naïve setting, enzalutamide improved both the clinical progression (HR 0.34, 95%CI 0.26-0.44) and the OS (HR 0.53, 95%CI 0.37-0.75). Serious adverse events were higher in the enzalutamide arm (42% vs 34%) compared to the NSAA arm and enzalutamide should be avoided in patients with pre-existing neurological disorders or seizure as it is associated with a significant risk of seizures. (257)

Role of Apalutamide in mHSPC

Apalutamide is the most recent addition to the list with a similar mechanism of action of enzalutamide. The TITAN trial, included 1052 mHSPC men with the majority (63%) having high volume disease and 11% men with prior docetaxel therapy, randomized into ADT with or without

apalutamide. Apalutamide with ADT improved OS (HR 0.67; 95% CI, 0.51-0.89; p = 0.0053), with a 33% reduction in risk of death while median OS was not reached. The OS benefit was also consistent through all the subgroups. Median radiographic PFS was 22.1 months in the placebo group and not yet reached in the apalutamide group. (258)

Role of radiotherapy to the prostate in mHSPC

The role of radiotherapy (RT) to the prostate in patients with mHSPC was first reported by HORRAD trial. (259) In the trial, 432 men were randomized to ADT alone versus ADT plus EBRT to the prostate. The study results showed no difference in the OS between the group (HR 0.9; 95% CI 0.7-1.14). However, the median time to PSA progression was significantly improved in the RT group (HR 0.78; 95% CI 0.63-0.97). Similarly, in the STAMPEDE trial, RT to the prostate did not show significant difference in the OS as compared to ADT alone. However, after stratifying the patients into volume of disease as per CHAARTED trial, the authors found a significant benefit in the OS by the addition of RT to the prostate in low-volume mPCa. (260)

11.3.7 Role of combining more than one effective treatment in sequence

Recently the PEACE-1 trial was published in American Society of Clinical Oncology 2021. (261) The trial had 60% patients who received docetaxel prior to abiraterone acetate and were stratified in a hierarchical manner for statistical analysis to see impact of abiraterone post docetaxel. The study showed a rPFS difference of 2.5 years (2 years to 4.5 years) in favor of adding abiraterone even after docetaxel with hazard ratio of 0.5. Such remarkable clinical activity proves the efficacy of abiraterone irrespective of the previous exposure to docetaxel. These results are argued as practice changing.

11.4 Selection and sequence of treatment in mHSPC

Since 2015, several new agents have shown therapeutic benefits in mHSPC as compared to the standard ADT. However, the selection and sequence of the agents is still controversial. Also, there is no head-to-head comparison of the newer agents to suggest the optimum sequence. In a recent systematic review and meta-analysis comparing abiraterone and docetaxel therapy with ADT in 6067 men with high-risk and mHSPC, the pooled HR for OS demonstrated a benefit for docetaxel and abiraterone compared to ADT alone. However, the indirect comparison of both these treatment strategies demonstrated no significant difference in the OS (HR 0.84, 95% CI 0.67– 1.06). (262)

From the available data, docetaxel is preferred in men with high-volume metastatic disease. (247,253) However, the data is insufficient to suggest the selection and sequence of the other agents in mHSPC.

Recommendations for metastatic cancer prostate

Recommendation	Level of evidence	Strength rating
ADT should be instituted in all symptomatic men with mHSPC	**1**	**Strong**
Do not offer anti-androgen monotherapy	**1**	**Strong**
Surgical castration (orchidectomy) can be a cost-effective option in Indian scenario	**2**	**Strong**
ADT plus docetaxel therapy should be offered in mHSPC provided the patient is fit to receive the regimen	**1**	**Strong**

Abiraterone plus prednisone in combination with ADT is recommended in the first-line therapy of mHSPC provided the patient is fit to receive the regimen	**1**	**Strong**
Enzalutamide plus ADT is recommended in the first-line therapy of mHSPC provided the patient is fit to receive the regimen	**1**	**Strong**

12. CASTRATE RESISTANT PROSTATE CANCER

12.1 Definition:

12.1.1 CRPC is a state with disease progression despite castrate levels of testosterone. (Clinical principle)

12.1.2 Non-metastatic CRPC patients are diagnosed on the basis of rising PSA in the absence of visible metastasis. (Clinical principle)

Authenticating terminology:
We will follow PCWG (prostate cancer working group) criteria in this section for defining these aspects.

12.1.3 Disease progression is defined as any combination of three features – biochemical progression by rising PSA, radiological progression, and clinical progression. (Clinical principle)

12.1.4 Castration is defined as testosterone level <50ng/ml. (Strength rating - moderate)

Disease progression:

Biochemical progression:

12.1.5 Biochemical progression is defined as serial rise in serum PSA level identified with a minimal value of 2.0 ng/ml at least 1 week apart. (Strength rating - Strong)

12.1.6 Estimations of PSADT with at least 3 values measured ≥4 weeks apart has prognostic value especially when PSADT <10 months in nonmetastatic CRPC setting. (Level of evidence - 2; strength rating - Moderate)

Radiological progression:

12.1.7 Conventional imaging using a combination of computed tomography (CT), magnetic resonance imaging (MRI), and technetium-99m methylene diphosphonate (MDP) bone scan should be used for baseline radiological assessment and evaluation of treatment response. (Strength rating - Moderate)

12.1.8 The status of newer molecular scans (like PET scan) remains investigational at present due to lack of data of improved survival with treatment decisions based on their use. (Level of evidence - 2; strength rating - Strong)

12.1.9 For patients with mCRPC following initiation of ADT (with or without additional life-prolonging therapy) appearance of 2 or more new lesions on the bone scan qualifies as progression. (Strength rating - Strong)

12.1.10 Soft tissue progression should be evaluated using Response evaluation criteria in solid tumors (RECIST 1.1). (Strength rating - Strong)

12.1.11 Any new visceral lesion should be considered as radiological disease progression. (Strength rating - Strong)

12.1.12 Symptomatic progression in the first 12 weeks of starting ADT (GnRH agonist) could be due to flare or pseudo-progression and thus radiological evaluation to define progression should be delayed by 12 weeks following initiation of such treatment. (Strength rating - Moderate)

Clinical progression:

12.1.13 Clinical progression (like significant pain) may precede PSA or radiological progression and demand further evaluation. (Strength rating - Weak)

12.1.14 PSA progression and clinical progression in isolation may not mandate change in therapy without fulfilling one more additional criteria for progression. (Strength rating - Moderate)

12.2 Evaluation

Non metastatic CRPC

12.2.1 In nmCRPC patients, three- to six-monthly PSA measurements should be obtained, and PSADT should be calculated beginning from the time of development of CRPC. (Strength rating - Strong)

12.2.2 nmCRPC patients should be assessed for development of metastatic disease using conventional imaging at intervals of 6 to 12 months. (Strength rating - Strong)

Metastatic CRPC

12.2.3 In mCRPC patients, clinical evaluation for symptoms and performance status should be performed, lab parameters should be obtained, and conventional imaging should be used to confirm the mCRPC status and to assist in discussion of treatment decision as well as prognosis. (Strength rating - Strong)

Genetic testing

12.2.4 In patients with mCRPC, germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status should be offered. (Strength rating - Moderate)

12.3 Treatment of CRPC

Non metastatic CRPC

12.3.1 Offer enzalutamide, apalutamide, darolutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months). (Level of evidence - 1; strength rating - Strong) (Darolutamide and apalutamide are not available in India)

12.3.2 Secondary hormonal manipulation using abiraterone is an option in those unfit or unwilling for the above approved drugs. (Level of evidence - 3; Strength rating - Weak)

12.3.3 Observation with continued ADT may be recommended to nmCRPC patients who are at a lower risk (PSADT >10 months) of developing metastatic disease. (Level of evidence - 2; Strength rating - Weak)

12.3.4 Do not offer systemic chemotherapy or immunotherapy to nmCRPC patients outside the context of a clinical trial. (Strength rating - Weak)

12.3.5 Ketoconazole with steroid, first-generation anti-androgens (flutamide, bicalutamide, and nilutamide), estrogen, estrogen derivatives (fosfestrol) are the other less preferred options in this clinical setting. (Level of evidence - 3; Strength rating - Weak)

Metastatic CRPC

12.3.6 Continue ADT to maintain castrate levels of serum testosterone. (Strength rating - Strong)

12.3.7 In newly diagnosed mCRPC patients, offer abiraterone acetate plus prednisone, docetaxel, or enzalutamide along with continued ADT. (Level of evidence - 1; strength rating - Strong)

12.3.8 On the basis of current evidence, it is difficult to recommend one drug over the other as there is lack of head-to-head comparison in any of the published trials. (Strength rating - Weak)

12.3.9 In patients with high visceral metastatic burden and rapid progression on ADT and symptomatic bone metastases, docetaxel may be preferred agent over ARTA. (Level of evidence - 3; Strength rating - Moderate)

12.3.10 Docetaxel should be avoided in patients with poor performance status in view of high risk of adverse effects. (Strength rating - Strong)

12.3.11 Both abiraterone and enzalutamide have been found to be effective in chemo-naïve and post-chemo clinical settings. (Level of evidence - 1; strength rating - Strong)

12.3.12 Low dose abiraterone (250 mg) with fatty meal is non-inferior to standard dose abiraterone (1000 mg) and has a definite cost benefit. (Level of evidence 2; strength rating — Weak)

12.3.13 mCRPC patients with AR-V7 positivity have poor response to ART agents. (Level of evidence - 2; Strength rating - Moderate)

12.3.14 Sipuleucel-T can be offered to asymptomatic and minimally symptomatic mCRPC patients. It may not be justified in Indian scenario considering the exorbitant cost and minimal improvement in survival and availability of alternative inexpensive drugs. (Level of evidence - 2; strength rating - Moderate recommendation)

Neuroendocrine / small cell prostate cancer

De novo neuroendocrine prostate cancers are rare but are extremely aggressive. Treatment options include chemotherapy (cisplatin/etoposide, carboplatin/etoposide, docetaxel/carboplatin, atezolizumab/carboplatin) and best supportive care. Treatment is similar to that of small cell cancer of the lung.

12.3.15 Treatment emergent neuroendocrine prostate cancer should be suspected in mCRPC patients with rapid clinical and radiographic progression or visceral metastases with low PSA levels. (Strength rating - Moderate)

12.3.16 If there is suspicion of dedifferentiation of adenocarcinoma to other histologic variants like neuroendocrine cancer, metastatic lesion biopsy should be considered. (Strength rating - Strong)

12.3.17 Neuroendocrine prostate cancers should be treated aggressively with various chemotherapeutic agents and best supportive care. (Strength rating - Moderate)

Oligoprogression

Patients with oligoprogression or progression at one to three sites may be considered for metastases directed radiation therapy with high doses of ablative SBRT. Since there are only retrospective case reports to show benefit, we recommend that the cases best suited for this approach are the ones which have biologically indolent with a low Gleason score, vertebral/pelvic bone only metastases, good general medical condition and a long PSA doubling time. (263)

12.3.18 Ablative SBRT is recommended for oligoprogression in patients with biologically indolent mCRPC. (Level of evidence - 2; Strength rating - Weak)

12.4 Sequencing of therapy:

Sequencing of drugs should be based on prior treatment history, disease burden, and genetic alterations.

Treatment after prior ART agent (abiraterone or enzalutamide)

12.4.1 In principle, while sequencing treatments, two drugs with same mechanism of action should not be offered one after the other – it is advisable to sandwich ART agents with a chemotherapeutic agent (docetaxel / cabazitaxel) whenever feasible. (Strength rating - Weak)

12.4.2 While sequencing agents, prior treatment history and recommending therapy with an alternative mechanism of action should be considered. (Strength rating - Strong)

12.4.3 While sequencing agents, abiraterone plus prednisolone followed by enzalutamide should be favored over vice-versa as per the Canadian trial. (Level of evidence - 2; Strength rating - Weak)

Treatment after prior docetaxel therapy

12.4.4 In post-docetaxel setting, ART agent is preferred as second-line treatment. (Strength rating - Moderate)

In advanced or symptomatic mCRPC patients, cabazitaxel should be recommended as standard third-line treatment after docetaxel and one ART agent (abiraterone or enzalutamide) rather than an alternative ART agent. (Strength rating - Strong)

12.4.6 In mCRPC patients who received prior docetaxel chemotherapy without prior ARTA for the treatment of CRPC, cabazitaxel can be offered if ART agent is not affordable or available. (Strength rating - Weak)

12.4.7 In mCRPC patients, alternative ART agent may be a reasonable option as a third-line drug if they are asymptomatic or had long-term response to initial ART agent. (Strength rating - Weak)

12.4.8 In mCRPC patients, Docetaxel rechallenge may be considered in docetaxel responders with a progression free interval greater than 6 months, if cabazitaxel is not available/tolerable. (Level of evidence - 3; Strength rating - Weak)

12.4.9 Radium-223 can be offered to patients with symptoms from bony metastases from mCRPC and without known visceral disease or lymphadenopathy >3cm in the post-docetaxel setting and after using at least one ART agent. (Level of evidence - 2; Strength rating - Strong) (However, Ra-223 is not available in India)

Progression after cabazitaxel therapy

No chemotherapy regimen has demonstrated improved survival or QoL after progression on cabazitaxel.

Treatment based on genetic alteration

DNA defects occur in 30% mCRPC patients and such tumor cells depend on PARP-regulated DNA repair for survival. In PROFOUND trial, patients progressing on abiraterone or enzalutamide {all patients had a qualifying alteration in prespecified genes with role in HRR (homologous recombination repair)}, median PFS was higher in Olaparib group (7.4 months vs 3.6 months, HR=0.34, $p<0.001$). Overall survival was also better in the Olaparib group (18.5 months vs 15.1 months).(264) Olaparib has also been approved by Drug controller general of India recently. Rucaparib is also FDA approved mCRPC patients with BRCA2 mutation treated previously with ART and taxane-based chemotherapy based on the TRITON2 study, presently available only in abstract form.

Carboplatin has also been studied and found effective in mCRPC patients with BRCA2 mutations but in retrospective study design. (265)

Pembrolizumab was approved by FDA in 2017 for mismatch repair deficient or high microsatellite instability mCRPC with no suitable alternative treatment. A case series of 1033 patients showed >50% PSA decline in more than half of those receiving PD-1 therapy. (266)

12.4.9 A PARP inhibitor should be offered to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with ARTA, and/or a taxane-based chemotherapy. (Level of evidence - 2; Strength rating - Strong)

12.4.10 Platinum based chemotherapy (carboplatin) may be offered as an alternative for patients who cannot use or obtain a PARP inhibitor. (Strength rating - Weak)

12.4.11 In patients with mismatch repair deficient or high microsatellite instability mCRPC, pembrolizumab should be offered. (Level of evidence - 2; strength rating - Moderate)

Treatment monitoring

Baseline evaluation should include medical history, clinical examination, blood tests (PSA, LFT, complete blood counts, renal function tests), bone scan and CT of chest, abdomen, and pelvis. The use of PSMA/choline PET-CT scans for progressing CRPC is not clear and likely not as beneficial as for HSPC.

12.5 Palliative care

12.5.1 Clinician should incorporate multidisciplinary holistic palliative care as an integral part of CRPC management. (Strength rating - Strong)

Bone health:

Prevention of SRE and palliation of bone pain

Apart from bisphosphonates and RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitors, external beam radiotherapy is highly effective, even as a single fraction (267,268) for palliation of bone related significant pain. Various radiopharmaceuticals therapeutic options including newer PSMA (e.g Lutetium (Lu)-PSMA) based agents are effective for pain palliation.

12.5.2 Offer bone protective agents, radiation or radiopharmaceutical therapeutic options in isolation or combination to patients with mCRPC and skeletal metastases to reduce the risk of SRE and palliate the symptoms. (Level of evidence - 1; strength rating - Strong)

Bone protective agents (bisphosphonates & RANKL inhibitor)

Only zoledronic acid is found to be beneficial in terms of reducing SRE in the setting of CRPC. (269,270)

Denosumab: A non-inferiority randomized trial by Fizazi et al (271) conducted in patients with mCRPC demonstrated that denosumab was not only non- inferior to zoledronic acid in reducing SRE (20.7 vs 17.1 months, p= 0.0002) but also superior to zoledronic acid in improving time to first SRE in a secondary analysis. (p = 0.008)

The interval of zoledronic acid varies between 3 weeks to 3 months in different studies. (272,271,273)

The duration of treatment is not clearly defined, but all studies continued the treatment till trial end point.

12.5.3 A bone-protective agent should be offered (zoledronic acid or denosumab) to patients with mCRPC with bony metastases to prevent skeletal-related events. (Level of evidence - 1; strength rating - Strong)

12.5.4 Though denosumab may have a minor advantage over zoledronic acid in terms of preventing SRE and has a safety profile in renal impairment, however the latter appears more attractive in terms of cost, in Indian scenario. (Strength rating - Moderate)

12.5.5 Optimal scheduling of bone protective agents is not conclusively defined; hence it is recommended to follow the schedule as per trial design. (Strength rating - Weak)

Toxicity:

Osteonecrosis of the jaw and hypocalcaemia are two potential toxicities of these drugs and should be carefully monitored (274,275,276). Calcium and vitamin D repletion should be done prior to starting these agents along with maintenance. Daily calcium (> 500 mg) and vitamin D (> 400 IU equivalent) are recommended in all patients.

12.5.6 The patients should be educated regarding potential toxicities of bone protective agents and dental examination should be advised before initiation of treatment. (Strength rating - Strong)

12.5.7 Calcium monitoring should be started before initiation of treatment with bone protective agents, and calcium and vitamin D repletion as well as continuous supplementation is advised until toxicities appear. (Strength rating - Moderate)

Management of serious SRE

12.5.8 Impending spinal cord compression should be managed with immediate high dose corticosteroids by a multidisciplinary team approach in collaboration with neurosurgeon, orthopedic surgeon and radiation oncologist. (Strength rating - Strong)

Role of Radiation:

For symptomatic bone metastases, external beam radiation therapy (EBRT) provides important symptom palliation. (277) We recommend fractionated radiation therapy of 5 to 10 fractions as patients treated with single fractions have a higher need for retreatment. (278)

12.5.9 External beam radiation therapy (EBRT) can be recommended to palliate symptoms in patients with severe pain at one or more sites due to bone metastases. (Strength rating - Moderate)

Radiopharmaceutical:

Only radioisotope to demonstrate a survival benefit was radium-223, Lutetium (Lu)-PSMA and 177Lu-EDTMP.

177Lu-EDTMP has been studied in isolation or combination with Lu-PSMA and found to be safe and effective alternative for bone pain palliation and improves quality of life. (279,280)

12.5.10 Collaboration with nuclear physician should be sought for radiopharmaceutical based treatment such as Lu-PSMA-617 for palliation of severe bone related pain. (Strength rating - Weak)

12.6 Follow up

The follow up protocol should be based on clinical setting, type of treatment provided and symptomatology.

Statement

12.6.1 PSA based 3-6 monthly follow up is advisable in patients with CRPC. (Strength rating - Strong)

12.6.2 Routine imaging at six months intervals should be a part of nmCRPC follow up, however in mCRPC imaging should be individualized based on disease progression or annually (Strength rating - weak)

Suggested frequency of assessment in follow up of mCRPC patients as per APCCC 2015: Please see Appendix 5

The evaluation and treatment of CRPC is rapidly evolving. The above guidelines serve to guide the treating urologist to overcome the common challenges faced while treating CRPC patients. However, clinician should exercise discretion while treating individual CRPC patients.

Recommendations

Recommendation	Level of evidence	Strength rating
Biochemical progression is defined as serial rise in serum PSA level identified with a minimal value of 2.0 ng/ml at least 1 week apart.		**Strong**
Conventional imaging using a combination of computed tomography (CT), magnetic resonance imaging (MRI), and technetium-99m methylene diphosphonate (MDP) bone scan should be used for baseline radiological assessment and evaluation of treatment response		**Moderate**
The status of newer molecular scans (like PET scan) remains investigational at present due to lack of data of improved survival with treatment decisions based on their use.	**2**	**Strong**
Appearance of 2 or more new lesions on bone scan or any new visceral lesion qualifies as progression		**Strong**
In patients with mCRPC, germline and somatic tumor genetic testing to identify DNA repair deficiency mutations and microsatellite instability status should be offered.		**Strong**
Continue ADT to maintain castrate levels of serum testosterone.		**Strong**
Offer enzalutamide, apalutamide, darolutamide with continued ADT to nmCRPC patients at high risk for developing metastatic disease (PSADT ≤10 months).	**1**	**Strong**
In newly diagnosed mCRPC patients, offer abiraterone acetate plus prednisone, docetaxel, or enzalutamide along with continued ADT.	**1**	**Strong**

In principle, while sequencing treatments, two drugs with same mechanism of action should not be offered one after the other – it is advisable to sandwich ART agents with a chemotherapeutic agent (docetaxel / cabazitaxel) whenever feasible.		**Weak**
In post-docetaxel setting, ART agent is preferred as second-line treatment.		**Moderate**
A PARP inhibitor should be offered to patients with deleterious or suspected deleterious germline or somatic homologous recombination repair gene-mutated mCRPC following prior treatment with ARTA, and/or a taxane-based chemotherapy.	**2**	**Strong**
In patients with mismatch repair deficient or high microsatellite instability mCRPC, pembrolizumab should be offered.	**2**	**Moderate**
Offer bone protective agents, radiation or radiopharmaceutical therapeutic options in isolation or combination to patients with mCRPC and skeletal metastases to reduce the risk of SRE and palliate the symptoms.	**1**	**Strong**
Calcium monitoring should be started before initiation of treatment with bone protective agents, and calcium and vitamin D repletion as well as continuous supplementation is advised until toxicities appear.		**Moderate**

13. EMERGING MODALITIES/FUTURE TRENDS -THERANOSTICS – LUTETIUM & ACTINIUM PSMA

The term “theranostics” was coined to define the ongoing efforts in the clinics to develop specific, individualized therapies for various diseases, and to combine the diagnostic and the therapeutic capabilities into a single agent. Cancers are highly heterogeneous and hence the response to

therapies is variable in different subsets of patients and the therapeutic strategies may be effective at selective stages and only for a particular subset of the patients. Hence, the use of a combination of individual specific diagnosis and therapeutic strategy is likely to improve the prognoses. (281)

13.1 Lutetium PSMA radionuclide therapy for prostate cancer

Prostate-specific membrane antigen (PSMA) is a receptor on the surface of the prostate cancer cells. PSMA is a 750 amino acid type II transmembrane glycoprotein which is thought to have multiple cellular functions, including functioning as an enzyme involved in folate uptake. It also plays a role in cell migration, cell survival and proliferation.(282) While expressed at low levels in the normal human prostate epithelium, it is overexpressed (up to 1000 times higher than normal prostate cells) in virtually all the prostate cancers (5–10% of prostate cancers appear not to express the PSMA glycoprotein).(283) Depending on the Gleason score of prostate cancer, the density of PSMA increases, especially so in castration resistant prostate cancers. PSMA labelled radioisotopes bind to the PSMA and are internalized by endocytosis leading to its concentration within the cell and making it ideal for targeted radionucleide therapy in prostate cancer. (284) The higher density of PSMA in the prostate as compared to other organs largely spares the adverse effects to the non-target organs. However, these off-target effects may occur particularly on the salivary glands and the lacrimal glands which have been reported in the clinical trials. (285)

177Lu is a medium-energy b-emitter (490 keV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm. The shorter b-range of 177Lu provides better irradiation of the small tumors, in contrast to the longer b-range of 90Y. Also, 177Lu has a relatively long physical half-life of 6.73 days. These physical properties allow for the delivery of high activities of 177Lu PSMA to the prostate cancer cells.

Different PSMA peptides and antibodies labelled with 177Lu have been clinically user in trials in men with metastatic castrate-resistant prostate cancer (mCRPC) like PSMA–DKFZ-617, 177Lu PSMA-I&T, 177Lu-J591 etc. (286),(287)

13.1.1 Dosimetry of 177Lu PSMA Therapy

Doses used in the various studies have been variable. (288),(289),(290),(291),(292),(293) Injected doses have ranged from 3 to 8 GBq per single injections with up to six injections given to men, generally at a minimum 6-weekly intervals. Pre- and post-administration of 177Lu PSMA, 1–1.5 L of water may be given. Lu PSMA is administered by a slow intravenous injection (30–60 sec) in a volume of 5 mL (diluted with 0.9% sterile sodium chloride solution), followed by a flush of sterile 0.9% sodium chloride.

As dose related toxicity can occur due to susceptibility of organs like kidneys, salivary glands and lacrimal glands, it is ideal to use an accurate dose. This requires repeated imaging like 3D quantitative SPECT/CT over hours to days. 2D is less accurate due to overlap in the imaging. Such repeated imaging gives accurate dosimetry but is limited by patient comfort and a burden on the facilities. Alternatively, a planar approach of dosimetry may be more feasible. It uses geometric mean whole-body data with attenuation and scatter correction, combined with a whole organ MIRD approach (model-based estimate of absorbed dose). Another way is SPECT data which can avoid inaccuracies of overlapping activity as well as those due to metastasis in organs using hand-drawn VOIs (volumes of interest).

Kidney toxicity thresholds of 28 to 40Gray have been proposed but they need further evaluation. (294)

13.1.2 Radiation safety

General precautions for staff members are to follow the general radiation safety principle of ALARA (As Low As Reasonably Achievable). For patients, the ARPANSA (Australian radiation protection and nuclear safety agency) recommendation are followed which states, “when patient-specific dose estimates to family members and to members of the general public are not available, the ambient dose equivalent rate at a distance of 1 meter from a patient who is undergoing treatment with a radioactive substance should not exceed 25 lSv/h at the time of the patient’s discharge from hospital.”(295) Regulations regarding administration of the drug in outdoor or indoor setting differ across different countries; some allowing administration in indoor setting only while others allow both indoor and outdoor administration. Patients, staff

and families should be instructed regarding radioactive spills. 177Lu PSMA is excreted by the kidneys in the first 48 hours following injection. Given the rapid renal excretion of 177Lu PSMA, patients must be observed for up to 4 hours for measured radiation levels to decrease.

13.1.3 Clinical Evidence for Lu PSMA in Metastatic Prostate Cancer

As per the available literature, the patients who achieve a >50% reduction in the serum PSA (prostate specific antigen) levels ranges from 30% to 70%, which is comparable to the PSA response rates achieved by chemotherapy agents used in mCRPC (Cabazitaxel and Docetaxel). (296) Patients with progressive disease, who are unresponsive to 177Lu PSMA therapy range from 10% to 32%. Most published studies with 177Lu PSMA therapy in prostate cancer are retrospective, majorly single arm, using different treatment regimens with regard to dose given (ranging from 3.5 to 8.0 Gbq/injection of Lu PSMA) and the number of doses (ranges from a single injection up to 4–6 injections 6 weeks apart). (286,288,290,291,297,298,299,300,301) This makes the interpretation and generalizability of the efficacy of the treatment and the regime of treatment per se difficult at present. There is a consistent finding across the trials that the therapy is effective in a significant proportion of men with metastatic prostate cancer, who have no other treatment alternatives. Appropriately powered prospective randomized controlled trials comparing Lu PSMA with therapies of proven survival benefit are required to set evidence-based guidelines on the use of Lu PSMA in prostate cancer.

Certain factors determine the response to Lu PSMA therapy. One of them is the heterogeneity of tumor cell expression of PSMA. The exact cut off of intensity of activity of 68Ga-PSMA that determines good response is not known yet. A study found low platelet count and the need of analgesics for bone pain as indicators of bad prognosis in those with bone metastasis. (302)

Lu PSMA is well tolerated generally but adverse effects pertaining to off target effects have been reported, especially xerostomia. Other minor adverse effects like nausea and hypoguesia have been observed. Bone marrow toxicity is seen and may be related to the inherent long-range

radiation properties of Lu PSMA. However, it may also be a consequence of the metastasis itself as well.

13.2 Actinium PSMA

225Ac-PSMA-617 has also been reported to be effective in advanced prostate cancer. (303) Dosage used : initial administered activity was 8 MBq. Administered activity was de-escalated in subsequent treatment cycles to 7, 6 or 4 MBq based on the response to the earlier administered treatment. Treatment was repeated after every 8 weeks.

Lutetium-177 PSMA (177Lu-PSMA) is beta emitter and Actinium-225 PSMA (225Ac-PSMA) is an alpha-emitter. Similar radiation safety and dosing consideration apply to Actinium as well. Clemens Kratochwil, in a presentation to the annual congress of the EANM October 2017, documented this surrogate marker of response in seven reported studies of PSMA-radionuclide theranostic treatment of advanced mCRPC and compared them with published response data for approved, and non-approved, non-radionuclide molecular therapies. The pooled cohort of 160 patients treated with 177- lutetium-PSMA-617 achieved a mean decline in PSA greater than 50% in 42%, compared with 46% of the 92 patients who received 177-lutetium-PSMA-I&T. Theranostic alpha radionuclide treatment with 225-actinium-PSMA achieved the highest surrogate response of 63% in 38 patients.(304) In patients refractory to 177-lutetium-PSMA therapy, or for those who relapse early, dramatic response in end-stage mCRPC has been achieved with alpha radionuclide therapy with 225-actinium-PSMA.(305) However, more evidence is required before a definite superiority of one of the radionuclide over the other is established.

Germline testing

An increasing body of evidence supports genetic counselling and germ line testing in patients with prostate cancer. BRCA1 and BRCA 2 mutations are reported in 0.2-0.3% of the general population, and in up to 12% of patients with prostate cancer. In general population, mutations in these genes increases the risk of prostate cancer, however, in patients with prostate cancer, mutation in BRCA 1, BRCA 2, HOXB13 and other genes is associated with higher rates of having a high grade or lethal prostate cancer as these mutations are hypothesized to drive the

development of aggressive disease. Although still immature, the data supports germline testing in patients with localized high risk, locally advanced and metastatic cancer prostate. Testing should include BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6 and PSM2. Germline testing is available at a price around ten thousand rupees in the majority of the metropolitan cities across India. Further research, both in identifying other genes and to further evaluate the impact of germline testing is required till concrete evidence-based recommendations can be made.

Recommendations

Recommendation	Level of evidence	Strength rating
Lu PSMA and Ac PSMA have shown promising results in patients with mCRPC.	**3**	**Strong**
Lu PSMA can be offered to select patients with mCRPC under clinical trial settings.	**3**	**Strong**
Further trials are required to better establish the role of PSMA based therapeutic agents and the superiority of one over the other.		**Strong**
Consider germline testing in patients with localised high risk, locally advanced and metastatic prostate cancer	**3**	**Weak**

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Appendix 1: National cancer care network Risk stratification (102)

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk group	Clinical/pathologic features			Imaging[h,i]	Germline testing	Molecular and biomarker analysis of tumor[i]	Initial therapy
Very low[f]	• T1c AND • Grade Group 1 AND • PSA <10 ng/mL AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[g] AND • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Not indicated	See PROS-4
Low[f]	• T1-T2a AND • Grade Group 1 AND • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-5
Intermediate[f]	Has no high- or very-high-risk features and has one or more intermediate risk factors (IRF): • T2b-T2c • Grade Group 2 or 3 • PSA 10–20 ng/mL	Favorable intermediate	• 1 IRF and • Grade Group 1 or 2 and • <50% biopsy cores positive[g]	• Bone imaging[j]: not recommended for staging • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Consider if life expectancy ≥10y[m]	See PROS-6
		Unfavorable intermediate	• 2 or 3 IRFs and/or • Grade Group 3 and/or • ≥50% biopsy cores positive[g]	• Bone imaging[j]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended if family history positive or intraductal histology See PROS-1	Not routinely recommended	See PROS-7
High	• T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8
Very high	• T3b-T4 OR • Primary Gleason pattern 5 OR • >4 cores with Grade Group 4 or 5			• Bone imaging[j]: recommended • Pelvic ± abdominal imaging: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-9	Recommended[c,k]	Not routinely recommended	See PROS-8

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Appendix 2: the European urological association prostate cancer Risk stratification (103)

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)
and cT1-2a	or cT2b	or cT2c	cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen.

Appendix 3: The International Society of Urological Pathology 2014 grades (104)

Gleason score	ISUP grade
2 - 6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

Appendix 4:

Clinical Tumour Node Metastasis (TNM) classification of PCa

T - Primary Tumour (stage based on digital rectal examination [DRE] only)
TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
T1 Clinically inapparent tumour that is not palpable
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 (e.g. because of elevated prostate-specific antigen [PSA])
T2 Tumour that is palpable and confined within the prostate
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
T3a Extracapsular extension (unilateral or bilateral)
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 (pelvic) Lymph Nodes1
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Distant Metastasis2
M0 No distant metastasis
M1 Distant metastasis
M1a Non-regional lymph node(s)
M1b Bone(s)
M1c Other site(s)
1Metastasis no larger than 0.2 cm can be designated pNmi.
2 When more than one site of metastasis is present, the most advanced category is used. (p)M1c is the most advanced category.

Clinical T stage only refers to DRE findings;

AJCC 8th edition Pathological staging

T category	T criteria
pT2	Organ confined
pT3	Extra prostatic extension
pT3a	Extra prostatic extension (Unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Tumor invades seminal vesicle(s)
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles(SV) such as external sphincter, rectum, bladder, levator muscles, and /or pelvic wall
Note: There is no pathological T1 classification. Note: Positive surgical margin should be indicated by R1 descriptor indicating residual microscopic disease.	

Appendix 5

PSA	Three monthly and at progression
CBC,LFT, renal function tests	Three monthly and at progression
CT, bone scan	Annually and at progression