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INDIAN COUNCIL OF MEDICAL RESEARCH

Consensus Document for Management of Prostate Cancer

Prepared as an outcome of ICMR's Subcommittee on Prostate Cancer

INDIAN COUNCIL OF MEDICAL RESEARCH
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Indian Council of Medical Research
New Delhi - 110029
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Division of Non Communicable Diseases

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Disclaimer

This consensus document represents the current thinking of experts on the topic based on available evidence. This document has been developed by national experts in the field and does not in any way bind a clinician to follow this guideline verbatim. One can use an alternative mode of therapy on the basis of discussions with the patient and institution and national or international guidelines. The mention of pharmaceutical drugs for therapy does not constitute endorsement or recommendation for use but serves as a guide for clinicians in complex decision-making processes.

Dr. Rajiv Bahl
Secretary,
Department of Health Research
and Director General, ICMR

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Foreword

I am glad to write this foreword for Consensus Document for Management of Prostate Cancer. The ICMR had constituted sub-committees to prepare consensus document for management of various cancer sites with a focus on patient management specifically in Indian context. This document is the result of inputs given by various experts across the country working in the area of oncology.

Prostate cancer features amongst the top 10 cancers in males in urban registries of Bangalore, Delhi, Bhopal and Mumbai while it is less of a menace in rural areas. This document tries to summarize the available evidences pertaining to available diagnostic modalities, multimodal treatment approaches, supportive and palliative care tailor made to patients in Indian context. Moreover, information and utility of upcoming molecular markers and possible future research questions have been incorporated. It also interweaves clinical, biochemical and epidemiological studies.

It is understood that this document represents the current thinking of national experts on subject based on available evidence. Mention of drugs and clinical tests for therapy do not imply endorsement or recommendation for their use, these are examples to guide clinicians in complex decision making. We are confident that this edition of Consensus Document on Management of Prostate Cancer would serve the desired purpose.

Rajiv Bahl

(Dr. Rajiv Bahl)
Secretary, Department of Health Research
and Director General, ICMR

Message

I take this opportunity to thank Indian Council of Medical Research and all the expert members of the subcommittees for having faith and considering me as chairperson of ICMR Task Force project on guidelines for management of cancer. The Task Force on management of cancers has been constituted to plan various research projects. In phase-I; 20 documents were published in selected cancer sites viz: lung, breast, oesophagus, cervix, uterus, stomach, gall bladder, soft tissue sarcoma and osteo-sarcoma, tongue, acute myeloid leukemia, acute lymphoblastic leukaemia, CLL, Non-Hodgkin's Lymphoma-high grade, Non Hodgkin's Lymphoma-low grade, Hodgkin's Disease, Multiple Myeloma, Myelodysplastic Syndrome, Pediatric Lymphoma, Pancreatic Cancer, Hepatocellular Carcinoma and Neuroendocrine Tumours. All aspects related to management were considered including, specific anti-cancer treatment, supportive care, palliative care, molecular markers, epidemiological and clinical aspects. The theme behind designing of the consensus document for management of cancers associated with various sites of body is to encourage all the eminent scientists and clinicians to actively participate in the diagnosis and treatment of cancers and provide educational information and support services to the patients and researchers. In phase-II; it is planned to formulate guidelines for 18 cancer sites. The assessment of the public-health importance of the disease has been hampered by the lack of common methods to investigate the overall worldwide burden. ICMR's National Cancer Registry Programme (NCRP) routinely collects data on cancer incidence, mortality and morbidity in India through its coordinating activities across the country since 1982 by Population Based and Hospital Based Cancer Registries and witnessed the rise in cancer cases. Based upon NCRP's three-year report of PBCR's (2016-2018) and time trends on Cancer Incidence rates report, the burden of cancer in the country has increased many fold.

In summary, the consensus document for management of various cancer sites integrates diagnostic and prognostic criteria with supportive and palliative care that serve our three-part mission of clinical service, education and research. Widespread use of the consensus documents will further help us to improve the document in future and thus overall optimizing the outcome of patients. I thank all the eminent faculties and scientists for the excellent work and urge all the practicing oncologists to use the document and give us valuable inputs.

(Dr. G.K. Rath)
Chairperson,
ICMR Task Force Project

Preface

Incidence of prostate cancer is increasing in various parts of India. Increasing life expectancy, changes in diagnostic modalities, increased awareness among the public, and changing lifestyle may be responsible for much of the observed change. The treatment of localized prostate cancer is either radical surgery or radical radiotherapy with androgen deprivation therapy, whereas, for advanced stages the treatment remains as androgen deprivation therapy with other systemic therapies. There has been several advances and refinement in the treatment modalities for treatment of prostate cancer in past few years. The management of prostate cancer should be well defined and accomplished. It has been noticed that there are variations in the treatment pattern across the country.

It is an admirable initiative of the ICMR for setting-up task force to bring out the consensus document for the management of cancer of the prostate. These guidelines will be useful to the practicing clinicians and students to optimize the treatment of their patients. This will also bring the uniformity in the management across the country and establish collaborative studies. This will also help in bringing out Indian data related to outcome and toxicity of the treatment and further refinement of management and research in this area.

I am grateful to all members of the task group, who have been expert in their field, for devoting their valuable time from their busy schedule and remaining committed to their assigned task. I would like to thank Dr GK Rath for his untiring support, inspiration and guidance and Dr Tanvir Kaur for her continuous efforts and support in all meetings and invaluable suggestions. The ICMR deserves special thanks for these consensus documents. The consensus on the management of cancers is a dynamic process in view of emerging evidence, and these will also be updated regularly as the evidence evolves with newer knowledge. We would be happy to receive constructive feedback to further improve this document for the benefit of our patients.

(Dr Prashanth Giridhar)
Chairperson
Subcommittee on Prostate Cancer

Preface

Cancer is a leading cause of death worldwide. Globally cancer of various types affect millions of population and leads to loss of lives. According to the available data through our comprehensive nationwide registries on cancer incidence, prevalence and mortality in India among males cancers of lung, mouth, oesophagus and stomach are leading sites of cancer and among females cancer of breast, cervix are leading sites. Literature on management and treatment of various cancers in west is widely available but data in Indian context is sparse. Cancer of gallbladder and oesophagus followed by cancer of breast marks as leading site in North-Eastern states. Therefore, cancer research and management practices become one of the crucial tasks of importance for effective management and clinical care for patient in any country. Hence, the need to develop a nationwide consensus for clinical management and treatment for various cancers was felt.

The consensus document is based on review of available evidence about effective management and treatment of cancers in Indian setting by an expert multidisciplinary team of oncologists whose endless efforts, comments, reviews and discussions helped in shaping this document to its current form. This document also represents as first leading step towards development of guidelines for various other cancer specific sites in future ahead. Development of these guidelines will ensure significant contribution in successful management and treatment of cancer and best care made available to patients.

I hope this document would help practicing doctors, clinicians, researchers and patients in complex decision making process in management of the disease. However, constant revision of the document forms another crucial task in future. With this, I would like to acknowledge the valuable contributions of all members of the Expert Committee in formulating, drafting and finalizing these national comprehensive guidelines which would bring uniformity in management and treatment of disease across the length and breadth of our country.

(Dr. R.S. Dhaliwal)
Head, NCD Division

Acknowledgement

Consensus Document on Management of Prostate Cancer is a concerted outcome of efforts made by experts of varied disciplines of oncology across the nation and it is my pleasure to acknowledge the dedication and determination of each member who worked tirelessly in completion of the document.

I would like to take this opportunity to thank Dr. G.K. Rath, chairperson, ICMR Task Force on Guidelines for Management of Cancer for his constant guidance and review in drafting the consensus document. The chairperson of subcommittee, Dr Prashanth Giridhar is specially acknowledged in getting the members together, organizing the meetings and drafting the document.

I would like to express gratitude to Dr. Rajiv Bahl, Secretary, Department of Health Research and Director General, Indian Council of Medical Research, for taking his special interest and understanding the need of formulating the guidelines which are expected to help the cancer patients in India. I would like to thank Dr Bhawna Sirohi for her help and guidance in this entire effort.

I would like to thank Dr RS Dhaliwal, head, Division of NCD for his support and coordination in finalizing this document. I acknowledge the assistance provided by administrative staff of ICMR. This document is the result of the deliberations by subcommittees constituted for this purpose. The guidelines were further ratified by circulation to extended group of researchers and practitioners drawn from all over the country. It is hoped that these guidelines will help the practicing doctors to treat cancer patients effectively and thus help them to lead a better life.

The ICMR appreciatively acknowledges the valuable contribution of the members for extending their support in formulating these guidelines.

Tanvir Kaur

(Dr.Tanvir Kaur)
Programme Officer & Coordinator

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Categories of Evidence

Levels of Evidence

Level 1: High quality randomized controlled trials (RCTs) showing (a) a statistically significant difference or (b) no statistically significant difference with narrow confidence intervals; systematic reviews of Level I RCTs

Level 2: Lesser quality RCTs (e.g. <80% follow-up, no blinding, or improper randomization); prospective comparative studies; systematic reviews of Level II studies or of Level I studies with inconsistent results

Level 3: Case control studies; retrospective comparative studies; systematic reviews of Level III studies; retrospective studies

Level 4: Case series

Level 5: Expert opinions

The set of recommendations can be divided into 2 categories:

Desirable/Ideal: Tests and treatments that may not be available at all centres but the centres should aspire to have them in the near future.

Essential: Bare minimum that should be offered to all patients by all centres treating patients with cancer.

Contents

1 Epidemiology and Risk Factors

Prostate cancer appears to be a growing problem in males in India. The incidence of prostate cancer has been steadily increasing in recent years [1]. As per the NCDIR database, prostate cancer features amongst the top 10 cancers in urban cancer registries of Bangalore, Delhi, Bhopal and Mumbai [1]. Prostate cancer seems to be less of a menace in rural areas. It does not feature in the top 10 cancer in the rural Barshi registry. Prostate cancer has moved from being the eighth most common cancer in males in 1990s to being the third most common cancer in Delhi and Mumbai by 2014. Similarly, in Bangalore, it has become the third most common cancer from being seventh in 1990s. There were 37416 reported prostate cancer cases in 2016 in India which has increased to 41532 in 2020.Prostate cancer incidence is expected to increase to over 47000 cases by 2025 [1]. This figure constitutes about 3% of total cancer cases in the country. Mean age of incidence of prostate cancer in India is 69.7 years [2]. Metabolic syndrome has been linked to prostate cancer but the evidence is weak [3]. Testosterone supplements do not increase the risk of prostate cancer in hypo gonadal male [4]. No specific life style and dietary modifications are recommended for prostate cancer [5].

Screening

As per the available evidence population based screening cannot be recommended in Indian population in any age group (Level 1) [5]. There has been no improvement in prostate cancer specific survival and overall survival by routine population based screening [6].A person with known BRCA 2 mutation needs to be explained about increased risk of developing clinically significant prostate cancer. However, in view of limited evidence (Level 3) [7] routine screening with serum PSA cannot be recommended even for persons carrying BRCA2 mutation.

2 Diagnosis and Staging

Diagnosis

Patients presenting with clinical suspicion of prostate cancer are recommended to undergo a total serum PSA estimation.

If serum PSA <4 ng/ ml and digital rectal examination (DRE) is not suspicious: Evaluate for other causes like benign prostatic hyperplasia, prostatitis etc.

If serum PSA is 4-10 ng/mL and DRE is not suspicious: Antibiotic for 1 week with fluoroquinolones followed by repeat PSA may be considered though advantage of this practice is doubtful [8].

If serum PSA >10 or DRE is suspicious: Proceed for evaluation of prostate cancer diagnosis.

Role of mpMRI- Ideally a multi-parametric MRI (mp-MRI) of prostate is to be done prior to a systematic biopsy. If PIRADS≥3 targeted biopsies along with systematic biopsy is to be done. If mp-MRI not available or PIRADS≤2 only systematic biopsies is recommended [9, 10].

Biopsy

1st choice - Systematic 12 core biopsy by Trans-perineal route (low infection rates) [11]

2nd choice - Systematic 12 core biopsy by Trans-rectal route

In patients with strong clinical suspicion but negative biopsy -

To be kept on close follow up. Biopsy is to be repeated on rising PSA or persistently elevated PSA, only intra-ductal carcinoma in previous biopsy and positive mp-MRI findings.

Staging (AJCC Eighth edition)

Primary Tumor	
Tx T0	Primary tumor cannot be assessed No evidence of primary tumor
T1	Clinically inapparent tumor not palpable not visible by imaging
T1a	Incidental tumor in < 5% of TUR tissue
T1b	Incidental tumor in > 5% of TUR tissue
T1c	Needle biopsy prompted by elevated PSA

T2	Organ confined
T3	Tumor extends beyond the prostatic capsule
T3a	Extracapsular, unilateral and bilateral or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicles (s)
T4	Tumor invades external sphincter, rectum, pelvic side wall
Lymph Nodes	
Nx N0	Regional nodes were not assessed No regional (below level of bifurcation of common iliac arteries) nodes
N1	Regional node metastases – including pelvic, hypogastric, obturator, iliac, sacral
Distant Metastases	
Mx M0	Regional nodes not assessed No Metastases
M1 M1a M1b M1c	No distant Non-regional lymph nodes (outside true pelvis) Bone(s) Other site(s) with or without bone disease

Risk grouping (Adapted from NCCN risk stratification)

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**

International society of urologic pathology grade (group) system

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

Staging investigations

Staging recommendations: Staging is performed as per risk groups

Low risk prostate cancer: For treatment planning

Ideal: mpMRI Pelvis (Accurate for surgical/ radiotherapy planning)

Essential: CECT Pelvis (not as accurate for surgical planning)

Intermediate risk prostate cancer: Metastatic work up essential

Ideal: PSMA PET/CT, ± mpMRI Pelvis (If being planned for radical treatment)

Essential: CECT TAP ± Bone scan

High risk prostate cancer: Metastatic work up essential

Ideal: PSMA PET/CT ± mpMRI Pelvis (If being planned for radical treatment)

Essential: CECT TAP + Bone scan

Imaging in biochemical relapse: Metastatic work up essential

Ideal: PSMA PET/CT

Essential: mpMRI Pelvis

Summary of evidence for staging in prostate cancer

Initial Staging:

Choice of staging options depends on the availability of different diagnostic modalities and the course of treatment planned. With multiple novel and well established diagnostic options available it is imperative to understand pros and cons of each so that a well informed decision can be made for the right diagnostic test.

T-staging:

Trans-rectal ultrasound (TRUS):

Even though some single-centre studies reported good results using 3D TRUS or colour Doppler for local staging, these have not been confirmed by large scale studies [12, 13]. Thus, TRUS is no more accurate at predicting organ-confined disease than DRE [14] and NOT recommended for initial T staging.

MRI:

MRI has proven to be the most useful for local staging of prostate cancer, with T2-weighted imaging being the most reliable. For T3 stage prostate cancers, MRI has good specificity but low sensitivity for assessment of extra prostatic extension and seminal vesicle involvement as shown in a pooled data from a meta-analysis with overall sensitivity and specificity of 0.61 (95% CI: 0.54-0.67) and 0.88 (95% CI: 0.85-0.91) respectively [15] [Level 2 evidence]. In low-risk patients MRI is not recommended because of its low sensitivity in detection of focal (microscopic) extra prostatic extension. Addition of a 3T MRI or functional imaging along with T2-weighted imaging improves sensitivity for detection of extra prostatic extension and seminal vesicle involvement, but there is potentially large inter-reader variability [16]. MRI even though cannot be recommended for local staging in low-risk patients, still has a useful role in treatment planning [17-19].

N category:

CT and MRI:

Anatomical imaging modalities such as CT and MRI assess nodes based on their size and morphology. Nodes with short axis diameter >8mm in pelvis and >10mm outside pelvis are considered to be involved

with a sensitivity of less than 40 [20, 21]. Diffusion weighted MRI (DW-MRI) may detect metastases in normal sized nodes, but a negative DW-MRI cannot rule out nodal metastases [22, 23].

Choline PET/CT:

For identification of pelvic nodal metastases with choline PET/CT a meta-analysis of 609 patients revealed pooled sensitivity and specificity to be 62% (95% CI: 51-66%) and 92% (95% CI: 89-94%) respectively. The sensitivity of choline PET/CT increases to 50% in patients at high risk and to 71% in patients at very high risk, in both cases performing better than CECT [24] [Level 2 evidence]. When comparing choline PET/CT with DW-MRI, studies yielded contradictory results with sensitivity of PET/CT reported to be inferior [24], superior [25] and similar [26, 27] than that of DW-MRI. Due to its low sensitivity and poor widespread availability choline PET/CT role in regular patient workup need to be evaluated further.

PSMA PET/CT:

Prostate-specific membrane antigen (PSMA) PET/CT uses different radio-isotopes such as ^{68}Ga, ^{18}F and ^{64}Cu (including Tc99m PSMA SPECT/CT) most common being ^{68}Ga and ^{18}F. In a recent systematic review and meta-analysis no significant difference in terms of detection rate was noted among the most commonly used PSMA-radiotracers (^{68}Ga PSMA-11, ^{18}F-PSMA-1007, ^{18}F-DCFPyL), but a clear superiority to choline and fluciclovine was demonstrated [28]. In a meta-analysis comprising of 10 studies overall sensitivity and specificity was 0.84 (95% CI 0.55-0.95), specificity of 0.95 (95% CI 0.87-0.98) [29]. In a meta-analysis, the pooled sensitivity and specificity of PSMA PET/CT for nodal staging in a per node analysis was 75% and 99% respectively [30] [Level 2 evidence]. In a prospective multi-centric validation study in patients with newly diagnosed prostate cancer with a negative bone scan per patient-based sensitivity and specificity was 41.5% (95% CI: 26.7-57.8) and 91% (95% CI: 79.3-96.6) respectively, with treatment change occurring in 12.6% patients [31][Level 2 evidence]. According to a systematic review, with compared to mpMRI, ^{68}Ga PSMA PET/CT was found to have higher sensitivity 0.65 (95% CI: 0.49-0.79) compared to mpMRI sensitivity of 0.41 (95% CI: 0.26-0.57) with a comparable specificity 0.94 (95% CI: 0.88-0.97) of ^{68}Ga PSMA and 0.92 (95% CI: 0.86-0.95) [Level 2 evidence].

PET-MRI

PSMA PET/MRI has a new evolving role in work up and follow up of prostate cancer. A recent meta-analysis evaluating the role of PET/MRI for evaluation of prostate cancer revealed pooled sensitivity and specificity for primary tumour (per lesion) as 61.5% and 90.9% respectively and for lymph node metastatic (per lesion) as 64.3% and 97.4% sensitivity and specificity respectively [32] [Level 2 evidence]. Impact of better diagnosis using PET MRI on treatment and survival needs to evaluated further.

M Category:

Bone scan:

Bone scan has been the most widely used method of evaluation of bone metastases of Prostate cancer. A meta-analysis shows combined sensitivity and specificity of 79% (95% CI: 73-83%) and 82% (95% CI: 78-85%) respectively [Level 2 evidence]. ^{18}F-NaF PET/CT has superior sensitivity with a similar specificity for detecting skeletal metastases in newly diagnosed high risk prostate cancer [33, 34]. But in a prospective study, ^{18}F -NaF showed no added value over bone scintigraphy in newly diagnosed intermediate/high risk prostate cancer patients with negative bone scintigraphy [35].

Whole Body-MRI (WB MRI):

In a prospective study with 100 patients comparing diffusion weighted WB-MRI (DW-WB MRI) with conventional imaging including bone scan revealed that DW-WB MRI is more sensitive than bone scan in detecting bone metastases in high risk patients [36] [Level 2 evidence]. WB MRI is also more sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT [37]. Compared to choline PET/CT WB-MRI is more sensitive while choline PET/CT shows higher specificity [38]

PSMA PET/CT:

A recent systematic review consisting of 12 studies with a total of 332 patients evaluating the role of ^{68}Ga PSMA PET in primary staging of prostate cancer revealed high variation in sensitivity (median sensitivity on per lesion analysis of 33–92% and on per-patient analysis of 66– 91%) with good specificity (per lesion 82–100% and per patient 67–99%), with most studies demonstrating increased detection rates with respect to conventional imaging modalities (bone scan and CT) [Level 2 evidence]. A prospective multi-centric randomized study comparing Ga^{68} PSMA PET/CT to conventional imaging in 302 high risk prostate cancer patients, PSMA had higher accuracy (92% of PSMA v/s 65% of conventional imaging) and led to change in management in higher number of patients (27% with PSMA v/s 5% with conventional imaging) [39] [Level 1 evidence]. However, it is unclear if the stage shifts with more sensitive modalities (e.g. PSMA) adds to any clinical benefit and whether patients with metastases detectable only with MRI or PET/CT should be managed with systemic therapies or they should be subjected to aggressive local treatment with metastases directed therapies.

Role of imaging in relapsing and metastatic prostate cancer:

Biochemical relapse (BCR) after radical prostatectomy (RP) and radiotherapy (RT) precedes clinical metastases by 7-8 yrs. Therefore, accuracy of conventional imaging techniques (bone scans, CT and MRI) is poor in asymptomatic patients especially with low PSA. Usually in men with PSA only relapse after RP, salvage radiotherapy is offered to the patient on the basis of biochemical relapse without confirming with imaging.

A meta-analysis revealed that choline PET/CT is strongly influenced by PSA level and kinetics [40] Sensitivity is only 5-24% when the PSA level is <1ng/mL [41]. PSMA PET/CT is more sensitive than other imaging modalities especially for PSA level <1ng/mL [40, 42]. Scan positivity rate of Ga^{68} PSMA PET/CT for PSA level <1ng/mL are 33% (95%CI: 16-51), for 0.0 to 0.19ng/mL PSA, 45% (95%CI: 39-52) for 0.2-0.49ng/mL PSA, and 59% (95%CI: 50-68) for 0.5-0.99ng/mL PSA respectively.

In patients with BCR after RT, there is high morbidity of local salvage options hence its necessary to obtain a histological proof for local recurrence before offering treatment [43]. MpMRI has shown excellent results in detecting local recurrences [43]. PET has poor spatial resolution compared to MRI, a study for evaluation of a combination of PET/MR in setting of biochemical relapse could be worthwhile.

3 Management of Low Risk Prostate Cancer

Options include :

Active surveillance

Surgery

Radiotherapy

Patients with low risk are particularly at increased risk of over-treatment

Management - Active surveillance should be considered for all patients. Presently, it remains unclear if regular repeat mpMRI should be performed in the absence of any triggers (i.e. protocol-mandated). Similarly, it remains unclear if protocol-mandated, untriggered repeat prostate biopsies should be performed at regular intervals. As such, no recommendations can be made at this time regarding these issues.

Active surveillance/ watchful waiting in low risk prostate cancers:

Active surveillance - Aims to avoid unnecessary treatment in men with clinically localized prostate cancer who do not require immediate treatment, but at the same time achieve the correct timing for curative treatment in those who eventually do [44]. Patients remain under close surveillance through structured surveillance programs with regular follow-up consisting of PSA testing, clinical examination, mpMRI imaging and repeat prostate biopsies, with curative treatment being prompted by pre-defined thresholds indicative of potentially life-threatening disease which is still potentially curable, while considering individual life expectancy.

Watchful waiting - Refers to conservative management for patients deemed unsuitable for curative treatment from the outset, and patients are clinically 'watched' for the development of local or systemic progression with (imminent) disease-related complaints, at which stage they are then treated palliative according to their symptoms in order to maintain QoL.

	Active surveillance	**Watchful waiting**
Treatment intent	Curative	Palliative
Follow-up	Pre-defined schedule	Patient-specific
Assessment/markers used	DRE, PSA, mpMRI, re-biopsy	Not pre-defined, but dependent on development of symptoms of progression
Life expectancy	> 10 years	< 10 years

	Active surveillance	Watchful waiting
Aim	Minimize treatment-related toxicity without compromising survival	Minimize treatment-related toxicity
Comments	Low-risk patients	Can apply to patients with all stages

Recommendations for active surveillance

Inclusion criteria

1. For inclusion, patients must have a life expectancy of 10 years, but there is no lower or upper age limit for inclusion.
2. Evaluate life expectancy using a combination of performance status, co morbidity index, and health status screening.
3. Patients of low risk prostate cancer (NCCN criteria) to be considered. Patients with low-risk localized disease should be excluded if the extent and/or stage of disease is high based on mpMRI.
4. Patients with Gleason 3+4=7(ISUPgrade2) may be considered, if favorable characteristics are present, including PSA (<10), clinical stage (cT2a), and biopsy characteristics (low core positivity).
5. Patients with intra-ductal and cribriform histology on biopsy should be excluded automatically.

Monitoring and follow-up criteria

1. During active surveillance, men should have their PSA checked every 6 months.
2. During active surveillance, men should have a DRE every 12 months.
3. During active surveillance, repeat biopsy should be performed if there is a change in mpMRI (ie, increase in PI-RADS score, lesion volume, or radiological T stage), or by DRE progression or PSA progression.
4. If repeat biopsies are needed, they should be performed by mpMRI guided targeted biopsies (including in-bore, cognitive guidance, or mpMRI fusion) with systematic biopsies. However, it remains unclear when mpMRI should be performed during monitoring, and whether it should be performed routinely or triggered (Eg: by PSA or DRE changes)
5. Active surveillance should only be continued in patients if their life expectancy continues to be 10 years.

Reclassification criteria (i.e., leaving active surveillance for an active treatment)

1. Re-classification should apply only to patients with life expectancy of 10 years at the time of assessment.
2. Consider reclassifying patients if they develop anxiety or depression due to prostate cancer.
3. Consider reclassifying patients if they are reluctant to undergo repeat biopsies or repeat imaging.

4. Patients should not be reclassified automatically based on any one criteria of
    1. PSA progression alone in the absence of other factors.
    2. Histological changes alone (increased core positivity or % involvement of core) in absence of other factors
    3. Solely on DRE / mpMRI findings.

Consider reclassifying patients if they choose to undergo active treatment, independent of other factors.

Alternatives to active surveillance for the treatment of low-risk disease

If a patient is decided to be changed to an active treatment strategy due to any reason he may either, choose between Radical prostatectomy (RP) and radical radiotherapy. There has been no head on comparison between these 2 treatment modalities but as per the results of trials [45] both of them fare pretty similarly. The side effect profiles of both however differ. Hence it should be the patient's choice.

Surgery: Although AS should be the default management strategy in patients with low-risk disease and a life expectancy > 10 years, it would be reasonable to consider surgery as alternatives to AS in patients suitable for such treatments and who accept a trade-off between toxicity and prevention of disease progression if opting for AS.

Surgical approach in low risk prostate cancer: (Radical prostatectomy) RP can be performed via open, laparoscopic or robotic retro-pubic approach or by trans-perineal approach.

Ideal: Retro pubic RP should be performed for low risk prostate cancer. Minimal invasive techniques like robotic approach preferred where facilities and expertise available.

Essential: Open and laparoscopic RP can be performed with equally comparable outcomes.

Summary of evidence for surgery in low risk prostate cancer

The goal of radical prostatectomy (RP) is cancer control with preservation of organ function [46]. The procedure involves removal of the entire prostate with its capsule and seminal vesicles (SVs), followed by vesico-urethral anastomosis. The nerve sparing technique of RP is preferred in low risk disease [47]. Temporary urinary incontinence is common early after surgery. Pre-operative pelvic floor exercises (PFE) with, or without biofeedback may reduce the incidence of urinary incontinence. Prophylactic antibiotics should be used; however, no high-level evidence is available to recommend specific prophylactic antibiotics prior to RP.

Neoadjuvant androgen deprivation therapy

Neoadjuvant ADT is associated with a decreased rate of pT3 (i.e. down staging possible), decreased positive margins, and a lower incidence of positive lymph nodes. But neoadjuvant ADT is not associated with improvement in survival. So, it should not be considered as standard clinical practice. A small recent RCT comparing ADT vs ADT plus Abiraterone in the neo-adjuvant setting found significant reduction in tumour volume and lower biochemical relapse at > 4 years ($p = 0.0014$) [48]. Till level 1 evidences come, do not offer neoadjuvant androgen deprivation therapy before surgery.

Surgical techniques

Prostatectomy can be performed by open-, laparoscopic- or robot-assisted (RARP) approaches. The initial open technique of RP described by Young in 1904 was via the perineum [49]. The open retro-pubic approach was popularised by Walshin. It permitted a bilateral nerve-sparing procedure [50]. The first laparoscopic RP was reported in 1997 performed by trans-perineal route [51]. Most recently, robot assisted prostatectomy (RARP) was introduced using the da Vinci Surgical SystemR by Binder in 2002 [52].

In a randomised phase III trial, RARP was shown to reduce blood loss during surgery and duration of hospital stay, without improvement in early (12 weeks) or late functional or oncological outcomes compared to open RP [53, 54]. A recent Cochrane review comparing either RARP or LRP vs. open RP found no significant differences for oncological, urinary and sexual function outcomes, although RARP and LRP both resulted in statistically significant decrease in blood loss and duration of hospital stay [55]. Inform patients that no surgical approach (open-, laparoscopic- or robotic radical prostatectomy) has clearly shown superiority in terms of functional or oncological results.

A recent systematic review found with moderate certainty that retzius sparing (RS) RARP as compared to standard RARP improved continence at 1 month, 3 months as well as 12 months [56]. A single-surgeon propensity score matched analysis of 1,863 patients reached the same conclusion as the systematic review [57].

Pelvic lymph node dissection (PLND)

PLND during RP has so far failed to improve oncological outcomes, including survival [58]. It can be performed via extended (eLND) or limited approach however a RCT failed to show oncological benefit of an extended approach [59]. However, eLND provides important information for staging and prognosis [60, 61]. So, when a lymph node dissection (LND) is deemed necessary, perform an extended LND template for optimal staging. The patients with low risk disease usually do not require LND.

The individual risk of patients harbouring positive LNs can be estimated based on validated nomograms. The Briganti nomogram [62, 63], the Roach formula [64] or the Partin and MSKCC nomograms [65] have shown similar diagnostic accuracy in predicting LN invasion. These nomograms have all been developed in the pre-MRI setting based on systematic random biopsy. A risk of nodal metastases over 5% can be used to identify candidates for nodal sampling by eLND during RP [66, 67].

An updated nomogram has been externally validated in men diagnosed based on mpMRI followed by MRI targeted biopsy [68]. Based on this nomogram, patients can be spared an eLND if their risk of nodal involvement is less than 7%; which would result in missing only 1.5% of patients with nodal invasion [68].

Surgical techniques dilemmas

1. **Sentinel lymph node biopsy (SNB)** - There is insufficient high-quality evidence supporting oncological effectiveness of SNB [69, 70].
2. **Prostatic anterior fat pad (PAFP) excision** - The PAFP is always removed at RP for exposure of the endo-pelvic fascia and should be sent for histologic analysis as it contains metastatic PCa in up to 1.3% of intermediate- and high-risk patients [71, 72].

3. **Management of the dorsal venous complex** - Given the relatively small differences in outcomes, the surgeon's choice to ligate prior to transection or not, or whether to use sutures or a stapler, will depend on their familiarity with the technique and the equipment available [73, 74].

4. **Nerve-sparing surgery** - During prostatectomy, preservation of the neurovascular bundles with parasympathetic nerve branches of the pelvic plexus may spare erectile function [75, 76]. Extra-, inter-, and intra-fascial dissection planes can be planned, with those closer to the prostate and performed bilaterally associated with superior (early) functional outcomes [77 - 80]. Do not perform nerve-sparing surgery when there is a risk of ipsilateral extracapsular extension (based on cT stage, ISUP grade, nomogram, multi-parametric magnetic resonance imaging) [81, 82].

5. **Role of frozen section of lymph nodes during radical prostatectomy** - Although no RCTs are available, data from prospective cohort studies comparing survival of pN+ patients (as defined following pathological examination after RP) support that RP may have a survival benefit over abandonment of RP in node-positive cases [83]. As a consequence, there is no role for performing frozen section of suspicious LNs.

6. **Removal of seminal vesicles** - The more aggressive forms of PCa may spread directly into the seminal vesicles (SVs). For oncological clearance, the SVs have traditionally been removed intact with the prostate specimen. Whilst complete SV removal should be the default, preservation of the SV tips may be considered in cases of low risk of involvement [84, 85].

7. **Techniques of vesico-urethral anastomosis -** Several methods have been described. However, no clear recommendations are possible due to the lack of high-certainty evidence. In practice, the chosen method should be based on surgeon familiarity and preference [86, 87].

8. **Bladder neck management** - Some surgeons perform mucosal eversion of the bladder neck as its own step in open RP with the aim of securing a mucosa-to-mucosa vesico-urethral anastomosis and avoiding anastomotic stricture. A non-randomised study of 211 patients with and without bladder neck mucosal eversion showed no significant difference in anastomotic stricture rate [88]. Bladder neck preservation should be performed routinely when the cancer is distant from the base as it has shown to improve urinary continence post-operatively [89]. However, bladder neck preservation cannot be performed in the presence of a large median lobe or a previous TURP as it carries risk of margin positivity.

9. **Urethral length preservation -** The length of preserved membranous urethra is chiefly responsible for urinary continence. A systematic review and meta-analysis has found that every extra millimetre of membranous urethral length seen on MRI pre-operatively improves early return to continence post-RP [90].

10. **Cystography prior to catheter removal** - Cystogram to assess anastomotic leakage is not indicated as standard of care before catheter removal 8 to 10 days after surgery [91]. If a cystogram is used, men with LUTS, large prostate, previous TURP or bladder neck reconstruction, may benefit as these factors have been associated with leakage [92, 93]. Contrast-enhanced transrectal US is an alternative to assess leakage [94].

11. **Urinary catheter** - A urinary catheter is routinely placed during RP to enable bladder rest and drainage of urine while the vesico-urethral anastomosis heals. Compared to a traditional catheter duration of around 1 week, some centres remove the transurethral catheter early (post-operative day 2–3) [95, 96].

12. **Use of a pelvic drain** - A pelvic drain has traditionally been used in RP for potential drainage of urine leaking from the vesico-urethral anastomosis, blood, or lymphatic fluid when a PLND has been performed. Two RCTs in the robotic-assisted laparoscopic setting have been performed [97, 98]. Patients with urine leak at intra-operative anastomosis watertight testing were excluded. Both trials showed non-inferiority in complication rates when no drain was used. When the anastomosis is found to be watertight intra-operatively, it is reasonable to avoid inserting a pelvic drain. There is no evidence to guide usage of a pelvic drain in PLND.

Acute and chronic complications of surgery

Post-operative incontinence and erectile dysfunction are common problems following surgery for prostate cancer. At 1 year after surgery, approx. 20% patients have incontinence. Erectile dysfunction was observed in 70.4% after RALP and 74.7% after RRP. [99]. A RCT comparing RALP and RRP reported outcomes at 12 weeks in 326 patients and functional outcomes at 2 years [100]. Urinary function scores did not differ significantly between RRP vs. RALP at 6 and 12 weeks' post-surgery (p = 0.18). Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common adverse event [100]. Similar rates of lymphoceles have been observed in RALP series; however, in one subgroup analysis lymphoceles were more common with the extraperitoneal approach (19%) vs. the transperitoneal approach (0%) [101, 102].

Table: Intra-and peri-operative complications of retropubic RP and RALP

Predicted probability of event	RALP (%)	Laparoscopic RP (%)	RRP (%)
Bladder neck contracture	1.0	2.1	4.9
Anastomotic leak	1.0	4.4	3.3
Infection	0.8	1.1	4.8
Organ injury	0.4	2.9	0.8
Ileus	1.1	2.4	0.3
Deep vein thrombosis	0.6	0.2	1.4
Predicted rates of event	**RALP (%)**	**Laparoscopic RP (%)**	**RRP (%)**
Clavien I	2.1	4.1	4.2
Clavien II	3.9	7.2	17.5
Clavien IIIa	0.5	2.3	1.8
Clavien IIIb	0.9	3.6	2.5
Clavien IV	0.6	0.8	2.1
Clavien V	<0.1	0.2	0.2

RALP = robot-assisted laparoscopic prostatectomy; RP = radical prostatectomy; RRP = radical retro-pubic prostatectomy.

Non-surgical management of low risk prostate cancer:

External beam radiotherapy: Moderate hypofractionation has been shown to provide similar disease control in well conducted randomized controlled trials [103] in low risk prostate cancer. Dose fractionation of 70 Gy in 28 fractions over 5.5 weeks may be preferred (Level 1). No role of androgen deprivation therapy.

Stereotactic ablative body radiotherapy (SABR): SABR has been shown to provide similar biochemical control rates with very low gastro-intestinal and genito-urinary toxicity rates in low risk prostate cancer [104]. SABR to a dose of 36.25 Gy in 5 fractions over 1.5 weeks may be considered where in advanced radiation techniques are available (Level 2)

Role of brachytherapy: Brachytherapy may be performed with low dose rate (LDR) (Level 1) or high dose rate (HDR). The indications and proposed doses are indicated below

Indications and selection criteria for brachytherapy in low-risk prostate cancer	
Factors	Recommended (Do well)
PSA (ng/mL)	<10
Gleason score	5-6
Stage	T1c-T2a
IPSS	0-15
Prostate volume (g)	<60
Qmax (ml/s)	>15

Contraindications for brachytherapy in low risk prostate cancer	
Absolute	**Relative**
• Limited life expectancy • Unacceptable operative risks • Distant metastases • Absence of rectum, precluding the use of TRUS • Large TURP defects • Ataxia telangiectasia	• High IPSS >20 • History of prior pelvic radiotherapy • TURP defects • Large median lobes • Prostate gland >60 cm^3 at implantation • Inflammatory bowel disease

Proposed doses for brachytherapy	
^{125}I (Low dose rate)	145 Gy
^{103}Pd (Low dose rate)	125 Gy
3 – 4 fractions (HDR)	9.5 Gy to 10.5 Gy

4 Management of Intermediate Risk Prostate Cancer

When managed with non-curative intent, intermediate-risk prostate cancer is associated with 10-year and 15-year Prostate cancer specific mortality rates rate of 13.0% and 19.6%, respectively [105]

Active surveillance in favorable intermediate risk patients can be an option as explained earlier. (weak recommendation). Criteria for active surveillance - Intermediate risk ISUP grade 2 (GS -3+4) with PSA<10ng/ml and low core positivity.

Surgical management of intermediate risk:

These patients should be managed with RRP with bilateral eLND (if risk for pN+ exceeds 5%)

Ideal: A minimal invasive technique of RRP by robotics is preferred approach.

Essential: Open/laparoscopic RP with bilateral eLND can be performed with equally comparable outcomes.

Summary of evidence for surgery in intermediate risk prostate cancer

Surgery: Two RCTs [106, 107] had showed survival benefit in favor of RRP when RRP vs. WW was compared in localised PCa. The risk of having positive LNs in intermediate-risk PCa is between 3.7–20.1% [108]. An eLND should be performed in intermediate-risk PCa if the estimated risk for pN+ exceeds 5% or 7% if using the nomogram by Gandaglia *et al.*, which incorporates MRI-guided biopsies. One should offer RRP to patients with intermediate-risk PCa having life expectancy of > 10 years. The nerve-sparing surgery should be offered to patients with a low risk of extracapsular disease (based on cT stage, ISUP grade, nomogram, multi-parametric magnetic resonance imaging).

Non-surgical management:

Ideal: 4 – 6 months of androgen deprivation therapy (neo-adjuvant and concurrent) with intensity modulated radiation therapy to a dose of 76 – 78 Gy in conventional fractionation or equivalent doses in moderate hypo-fractionation (Eg: 60 Gy/ 20 fractions over 4 weeks) (Level 1)

Essential: 4 – 6 months' androgen deprivation therapy or orchidectomy (after explaining side effects to patients) with radiation therapy up to a dose of 70 Gy which may include brachytherapy boost after 45 – 50 Gy of pelvic radiotherapy

Summary of evidence for non-surgical management in intermediate risk prostate cancer

Radiotherapy - Patients suitable for androgen deprivation therapy (ADT) should be considered for combined

radiotherapy with external beam radiation (IMRT if feasible; 76–78 Gy conventional fractionation or equivalent doses Eg - 60Gy/20# in 4 weeks by moderate hypo-fractionation) with short-term ADT (4–6 months) [109 – 112]. For patients where in risk of radiation toxicity is expected to be higher a lower dose of 70 Gy may be considered [109]. For patients unsuitable for ADT (e.g., due to co-morbidities) or unwilling to accept ADT (e.g. to preserve their sexual health) the recommended treatment is IMRT (76–78 Gy or equivalent doses E.g - 60Gy/20# in 4 weeks) [113, 114].

Role of SABR in intermediate risk disease: Based on early results of randomized controlled trials, SABR appears well tolerated as well as equally effective in intermediate risk prostate cancer [115, 116]. Data on role of ADT with SABR is lacking. SABR should not be standard of care in intermediate risk patients till mature data (10-year and 15-year survival data becomes available)

Role of brachytherapy in intermediate risk disease: Brachytherapy boost after external beam radiation along with ADT has been shown to improve biochemical progression free survival without improvement in overall survival. The risks and benefits of brachytherapy boost have to be discussed with patients and may be considered in fit patients with minimal co-morbidities [117, 118]

Evidence for role of ADT along with radiotherapy in intermediate risk prostate cancer				
Trials	**Nabid et al[109]**	**Dubray et al[110]**	**D Amico et al[111]**	**Jones et al[112]**
Arms	**Phase III RCT** 3 Arms 1. Short term ADT + 70 Gy RT 2. Short term ADT + 76 Gy RT 3. 76 Gy RT alone	**Phase III RCT** 2 Arms 1. Dose escalated RT alone (80 Gy) 2. 4 months ADT + Dose escalated RT	**Phase III RCT** 2 Arms 1. RT 70 Gy alone 2. 6 months ADT + RT 70 Gy	**Phase III RCT** 2 Arms 1. RT 63.3 Gy alone 2. 4 months ADT + RT 63.3 Gy
End-points	Primary end-point: bPFS Secondary end- points: OS, Prostate Cancer specific mortality	Primary end-point: Freedom from failure (Combined clinical and biochemical)	Primary end-point: bPFS	Primary end-point: OS
Results	Biochemical failure was significantly lower in patients who received ADT No difference in OS Late GI toxicity higher in 76 Gy arm	Increased biochemical PFS, non-significant rise in freedom from failure (p=0 09)	Prolonged overall survival and decreased prostate cancer-specific mortality	Increased overall survival and biochemical progression-free survival, reduced prostate cancer-specific mortality and distant metastasis
Level of evidence	Level 1	Level 2 (Short follow up)	Level 1	Level 1
Remarks	Short term ADT + RT appears standard	Short term ADT improves bPFS in dose escalated RT	Short term ADT improves bPFS and possible OS if RT 70 Gy	Short term ADT improves bPFS and OS if RT dose lower

Evidence for role of hypo-fractionated radiotherapy in intermediate risk prostate cancer		
Trials	**Dearnaley et al[113]**	**Catton et al[114]**
Arms	3 Arms 1.RT 74 Gy/ 37 fractions (Conventional) 2.RT 60 Gy/ 20 fractions (Moderate hypo-fractionation) 3. RT 57 Gy/ 19 fractions (Moderate hypo-fractionation) 3 – 6 months ADT before and during RT in all arms	2 Arms 1.RT 60 Gy/ 20 fractions 2.RT 78 Gy/ 38 fractions No ADT
End-points	Primary end-point: Freedom from failure (Combined clinical and biochemical)	Primary end-point: Freedom from biochemical failure
Results	5-year biochemical failure free survival 85.9% (19 fractions) 90.6% (20 fractions) 88.3% (37 fractions)	5-year biochemical failure free survival Both arms 85% HR: 0.96 (NS)
Level of evidence	Level 1	Level 1
Remarks	Hypo-fractionated radiotherapy using 60 Gy in 20 fractions is non-inferior to conventional fractionation using 74 Gy in 37 fractions	Hypo-fractionated RT 60 Gy in 20 fractions not inferior to conventional RT and not associated with increased late toxicity

Evidence for role of SABR in intermediate risk prostate cancer		
Trials	**Widmark et al[15]**	**Brand et al[116]**
Arms	Phase III RCT 2 Arms 1.78 Gy/ 38 fractions (Conventional) 2.42.7 Gy/ 7 fractions in 2.5 weeks SABR No ADT	Phase III RCT 2 Arms 1.78 Gy/ 38 fractions (Conventional) 2.36.25 Gy/ 5 fractions in 1-2 weeks SABR No ADT
End-points	Primary end-point: Freedom from failure (Combined clinical and biochemical)	Primary end-point: Freedom from failure (Combined clinical and biochemical)
Results	Failure free survival at 5 years 84% in both arms Grade 2 acute GU toxicity 23% vs 28% (p = 0.057) No difference in long-term toxicity	Grade 2 acute GI toxicity 12% vs 10 % (p = 0.38) Grade 2 acute GU toxicity 27% vs 23% (p = 0.16)
Level of evidence	Level 2 (Short follow up)	**Final results awaited**
Remarks	SABR appears non-inferior in terms of 5 year survival and toxicity	Results suggest that substantially shortening treatment courses with SABR does not increase either gastrointestinal or genitourinary acute toxicity

Evidence for role of brachytherapy in intermediate risk prostate cancer		
Trials	**Morris et al[117]**	**Hoskins et al[118]**
Arms	**Phase III RCT** 2 Arms 1. ADT for 12 months with pelvic RT 46 Gy/ 23 fractions followed by external beam boost to 78 Gy 2. ADT for 12 months with pelvic RT 46 Gy/ 23 fractions followed by LDR brachytherapy boost (Minimum peripheral dose 115 Gy)	**Phase III RCT** 2 Arms 1. External beam RT to prostate 55 Gy/ 20 fractions in 4 weeks 2. External beam RT 35.75 Gy/ 13 fractions followed by HDR brachytherapy boost 8.5 Gy for 2 fractions

End-points	Primary end-point: Freedom from biochemical failure	Primary end-point: Freedom from failure (Combined clinical and biochemical)
Results	In an intent-to-treat analysis, men randomized to EBRT were twice as likely to experience biochemical failure (multivariable analysis [MVA] hazard ratio [HR] 2.04; P=.004). No difference in OS	Recurrence free survival was significantly higher in patients treated with brachytherapy (log rank $p = 0.04$) No difference in OS No difference in late toxicity
Level of evidence	Level 1	Level 2
Remarks	The trial included both intermediate and high risk patients (Intermediate risk patients: 31%); Long term ADT used in all patients.	Dose in standard arm is lower than standard All risk groups of localized prostate cancer included No uniformity in ADT

5 Management of High Risk Prostate Cancer

Management of high risk disease

When managed with non-curative intent, high-risk prostate cancer is associated with 10-year and 15-year Prostate cancer specific mortality rates of 28.8 and 35.5%, respectively [119]

Surgical management of high risk prostate cancer

Surgery: RRP is a reasonable option for high risk disease. An eLND should be performed bilaterally. In follow up, patients may require multimodal treatment (ADT and/or RT) [120 - 122].

Adjuvant treatment after surgery:

After surgery, early salvage radiotherapy is preferred with regular PSA follow up. The threshold for salvage radiotherapy should be kept low i.e. PSA ≥0 1 ng/mL or three consecutive rises (Level 1). Adjuvant radiotherapy may be preferred if all three risk factors are present (Positive margins, extracapsular invasion and seminal vesicle invasion) (Level 1).

Summary of evidence for adjuvant treatment after surgery

Adjuvant RT Vs Salvage RT after prostatectomy: Based on earlier evidence [123 – 125], adjuvant radiotherapy to prostate bed +/- pelvic lymph nodes was delivered in patients with positive surgical margins, seminal vesicle invasion and extracapsular extension. A dose of 64 – 66 Gy was delivered by external beam radiotherapy. But the trials that contributed to this practice were from pre ultra-sensitive PSA assays. A recently published prospectively designed meta-analysis including the RADICALS-RT (time free of metastases), GETUG-AFU 17 (event-free survival), and RAVES (biochemical progression) trials stated that adjuvant radiotherapy does not improve event-free survival in men with localized or locally advanced prostate cancer and until data on long-term outcomes are available, early salvage treatment with radiotherapy to a dose of 64 – 66 Gy would seem the preferable treatment policy as it offers the opportunity to spare many men radiotherapy and its associated side-effects. 1 – 2 doses of GnRH antagonists may also be considered with salvage radiotherapy [125]. The threshold for early salvage RT must be low (Serum PSA 0.1 – 0.2 ng/mL)

Criteria for failure/recurrence after surgery

Serum PSA of more than 0.2 ng/mL that is confirmed by a second determination of more than 0.2 ng/mL after radical prostatectomy.

Non-surgical management

High risk disease non-surgical management

Ideal: 2 - 3 years of androgen deprivation therapy (4 – 6 months neo-adjuvant, concurrent, 1.5 – 2 years' adjuvant) with intensity modulated radiation therapy to a dose of 76 – 78 Gy in conventional fractionation or equivalent doses in moderate hypofractionation (Eg: 68 Gy/ 25 fractions over 5 weeks). Pelvic nodal irradiation to an equivalent dose of 50 Gy should be considered (Level 2).

Essential: 2 – 3 years of androgen deprivation therapy or orchidectomy (after explaining side effects to patients) with radiation therapy up to a dose of 70 Gy which may include brachytherapy boost after 45 – 50 Gy of pelvic radiotherapy

Summary of evidence for non-surgical management in high risk prostate cancer

Radiotherapy: A combined modality approach should be used consisting of external beam radiotherapy (preferably IMRT) plus long-term ADT (2-3 years) [126, 127]. A radiation dose of 76–78 Gy or equivalent doses Eg - 60Gy/ 20# in 4 weeks should be delivered [128, 129].

Lymph node Irradiation in cN0

Prophylactic lymph node irradiation should be considered in patients with expected lymph node involvement >20% calculated by Roach Formula because of benefits in terms of Biochemical failure free survival, disease free survival and distant metastasis free survival [130]. The dose of 68 Gy in 25 fractions in 5 weeks to prostate along with 50 Gy to pelvic nodes is preferred.

Role of SABR in high risk prostate cancer:

In the absence of level 1 evidence, SABR cannot be recommended in high risk patients.

Role of brachytherapy boost in high risk prostate cancer:

Brachytherapy boost after external beam radiation along with ADT has been shown to improve biochemical progression free survival without improvement in overall survival [131, 132]. The risks and benefits of brachytherapy boost have to be discussed with patients and may be considered in fit patients with minimal co-morbidities.

Evidence for role of ADT along with radiotherapy in high risk prostate cancer		
Trials	**Pilepich et al[126]**	**Bolla et al[127]**
Arms	**Phase III RCT** 2 Arms 1. RT plus adjuvant goserelin till progression 2. RT alone	**Phase III RCT** 2 Arms 1. RT plus 3 years of ADT 2. RT alone
End-points	End points Overall survival Local failure rates	Primary endpoint Clinical disease-free survival.
Results	Androgen suppression as an adjuvant after definitive RT associated with a reduction in disease progression and improvement in absolute survival.	Immediate androgen suppression with an LHRH analogue given during and for 3 years after external irradiation improves disease-free and overall survival
Level of evidence	**Level 1**	**Level 1**

Evidence for role of moderate hypo-fractionated radiotherapy in high risk prostate cancer		
Trials	**Incrocci et al[128]**	**Arcangeli et al[129]**
Arms	Phase III RCT 2 Arms 1. RT conventional fractionation (78 Gy/ 39 fractions) 2. Hypofractionation 64.6 Gy/ 19 fractions	Phase III RCT 2 Arms 1. RT conventional fractionation (80 Gy/ 40 fractions) 2. Hypofractionation 62 Gy/ 20 fractions ADT in both arms for 9 months
End-points	Primary end point Relapse free survival	Primary end point Freedom from failure
Results	No difference in 5 year relapse free survival Non-inferiority of the hypofractionated treatment was not demonstrated for genitourinary and gastrointestinal quality of life	No difference in 5 year biochemical, local or distal failure
Level of evidence	Level 1	Level 1
Remarks	Superiority design: Conclusion is that hypofractionated radiotherapy is not superior to conventional fractionation Trial included both intermediate and high risk groups	Results confirm the iso-effectiveness of the 2 fractionation schedules used in this study

Evidence for early salvage radiotherapy in high risk			
Trials	**Parker et al[123]**	**Kneebone et al[124]**	**Sargos et al[125]**
Arms	**Phase III RCT** 2 Arms 1. Adjuvant radiotherapy if risk factors present 2. Early salvage RT No ADT	**Phase III RCT** 2 Arms 1. Adjuvant radiotherapy if risk factors present 2. Early salvage RT No ADT	**Phase III RCT** 2 Arms 1. Adjuvant radiotherapy if risk factors present 2. Early salvage RT 2 doses ADT (Triptorelin)
End-points	Primary end point Freedom from distant failure	Primary end point Freedom from biochemical failure	Primary end point Event free survival
Results	No difference in biochemical failure Reduced urinary morbidity	No difference in biochemical failure Reduced urinary morbidity	No difference in event free survival Reduced urinary morbidity
Level of evidence	**Level 1**	**Level 1**	**Level 1**
Remarks	10 year data not available Threshold for salvage RT: PSA: 0.1 ng/mL or 3 consecutive rises	10 year data not available Threshold for salvage RT: PSA: 0.2 ng/mL Non-inferiority target not met but authors concluded that salvage RT should be considered	10 year data not available

Patients unwilling or unfit for curative intent treatment Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour[133].

Management of locally advanced prostate PCa:

There are no level 1 evidence comparing RP as part of a multi-modal treatment strategy vs. upfront EBRT with ADT. These patients with locally advanced disease can be offered an option of surgery as a part of multi-modal therapy (Adjuvant ADT+RT). An eLND should be done bilaterally as it might have survival benefit [134, 135].

Ideal: 2 - 3 years of androgen deprivation therapy (4 – 6 months neo-adjuvant, concurrent, 1.5 – 2 years adjuvant) with intensity modulated radiation therapy to a dose of 76 – 78 Gy in conventional fractionation or equivalent doses in moderate hypofractionation (Eg: 68 Gy/ 25 fractions over 5 weeks). Pelvic nodal boost should be considered.

Essential: 2 – 3 years of androgen deprivation therapy or orchidectomy (after explaining side effects to patients) with radiation therapy up to a dose of 70 Gy. It is preferable to refer such patients to centres with advanced techniques of radiation therapy.

Radiotherapy for locally advanced PCa

A combined modality approach should be used consisting of external beam radiotherapy (preferably IMRT) plus long-term ADT (2-3 years). A radiation dose of 76–78 Gy or equivalent doses E.g - 60Gy/20# in 4 weeks should be delivered. A lymph node boost may be considered.

Role of SABR in locally advanced prostate cancer:

In the absence of level 1 evidence, SABR cannot be recommended.

Role of brachytherapy boost in locally advanced prostate cancer:

In the absence of level 1 evidence, brachytherapy cannot be recommended

Particle therapy: No level 1 evidence comparing external beam photon, brachytherapy and particle therapy is available to adopt proton therapy or carbon ion therapy in routine clinical practise. Available evidence show a slightly reduced gastro-intestinal and Genito-urinary toxicity [137, 138]

Criteria for failure/recurrence after radiotherapy

Biochemical failure after external beam radiotherapy or brachytherapy is defined as a PSA rise of 2 ng/ mL or more above nadir PSA after treatment (Phoenix criteria)

Salvage RP

Salvage RP is a reasonable option for a selected group of patient with local recurrence after RT, though complication (erectile dysfunction, urinary incontinence, bladder neck contracture) rates are higher than when RP used as initial therapy [136]

6 Metastatic Castration Sensitive Prostate Cancer (mCSPC)

Recommendations:

Ideal: All patients of mCSPC should be prescribed ADT, either medical or surgical castration based on patient preference and available resources. In view of significant benefit of addition of therapy beyond ADT, it should be a routine practice to add Docetaxel/ Abiraterone/ Enzalutamide (Level 1). The therapy selection is guided by the comorbidities, and patient/physician preference. The patients should be encouraged to participate in clinical trials, if available.

Essential: All patients of mCSPC should receive ADT plus additional treatment (Docetaxel/ Abiraterone/ Enzalutamide), exception being patients with significant uncontrolled comorbidities.

Summary of evidence for mCSPC

Androgen deprivation therapy (ADT): Lowering of serum testosterone levels to castrate levels (<50 ng/ml) is an integral component of the primary approach to the systemic treatment of mCSPC. All patients undergoing ADT therapy should be monitored for diabetes, hypertension, and lipid profile at regular intervals (3-6 monthly) besides evaluation of bone health. Patients on ADT should be given calcium and vitamin D supplementation. Dual-energy x-ray absorptiometry (DEXA) scan can be considered in patients of age > 65 years, or having history of use of steroids. Patients experiencing significant vasomotor symptoms like hot flushes can be offered venlafaxine 75mg/day, or medroxyprogesterone acetate 20 mg daily [139].

ADT options:

ADT can be accomplished either by surgical orchiectomy (castration) or medical castration (using either a gonadotropin-releasing hormone [GnRH] agonist or a GnRH antagonist). Both medical castration and surgical orchiectomy are effective methods for lowering serum testosterone levels in males with advanced CSPC and confer similar survival benefit. The decision between medical and surgical treatment is based on a variety of factors, including patient preference, cost, and treatment availability.

The benefit of surgical castration being lower overall cost, avoidance of injections for continued medical castration, and potentially fewer hospital visits. The benefit of medical castration being absence of direct psychological impact of castration. Western literature suggests that only 5.4% patients undergo surgical castration, after explaining all the options [140].

However, the situation seems to be different in countries with limited resources, including India.

GnRH agonists - Synthetic gonadotropin-releasing hormone (GnRH) analogs are commonly used in the real-world practice. Leuprolide, goserelin, and triptorelin are used. The depot preparations are usually administered by intramuscular route. However, there is now data that subcutaneous administration of some formulations such as Triptorelin pamoate is equivalent and more convenient [141].

When agonists are started in patients with patients with significant disease burden, it is recommended to add Bicalutamide 50mg OD for two weeks to avoid the risk of tumor flare.

GnRH antagonists - Antagonists like Degarelix are administered subcutaneously every month and have been reported to be equally efficacious as agonists, though they cause deeper suppression of testosterone. However, the advantage of antagonist being rapid suppression of testosterone levels, which is required in patients with impending spinal cord compression, or visceral crisis. Being an antagonist, degarelix does not cause flare reactions. Also, antagonists are reported have lower risk of cardiac events, thus, preferred in patients with cardiac comorbidities. However, recent data from PRONOUNCE study failed to find any difference between degarelix and leuprolide in terms of major cardiovascular event at one-year [142].

It should be noted that a new oral LHRH antagonist, Relugolix 120 mg OD is now approved for use based on phase III HERO study. However, it is not yet available in India and has not shown superiority over Leuprolide in terms of castrate resistance free survival. Also, compliance might be uncertain as it requires once daily administration [143].

Combined Androgen Blockade (CAB): Combination of anti-androgen like Bicalutamide with surgical or medical castration is widely practised. However, no prospective randomized study has demonstrated the benefit of this approach over ADT alone. Also, CAB is expected to add to adverse effects of the ADT. Thus, CAB is not recommended in absence of data of superior efficacy over ADT alone.

ADT plus Abiraterone: Abiraterone with prednisolone 5 mg once a day is approved in combination with ADT based on survival benefit in two randomized phase 3 clinical trials of abiraterone and low-dose prednisone plus ADT that were reported in patients with newly diagnosed metastatic prostate cancer or high-risk or node-positive disease [145, 146].

Summary of evidence for ADT plus Abiraterone

STAMPEDE study recruited patients with high-risk N0, M0 disease (2 of 3 high-risk factors: stage T3/4, PSA >40, or Gleason score 8–10; n = 509), or N1, M0 disease (pelvic nodal metastases; n = 369) in addition to M1 patients, who made up the majority of patients (n = 941). OS was improved in the overall population (HR, 0.63; 95% CI, 0.5–0.76; P < .0001) and in the M1 and N1 subsets, without any heterogeneity of treatment effect by metastatic status.

The survival benefit of abiraterone was larger in patients less than 70 years of age than in older patients (HR, 0.94 vs. HR, 0.51). Severe hypertension or cardiac disorders were noted in 10% of patients and grade 3–5 liver toxicity in 7%, which illustrates the need for blood pressure, renal and hepatic function monitoring.

Abiraterone can be given at 250 mg/day and administered following a low-fat breakfast, as an alternative to the dose of 1000 mg/day after an overnight fast. Though the data for this dose is limited and derived from phase 2 studies in castrate resistant settings, the cost savings (one-fourth of full dose) may reduce financial toxicity and improve compliance, especially in resource constraint settings. This also leads to

reduction in the pill burden of patients from 4 tablets of 250 mg to 1 tablet of 250 mg, however, tablets of strength 500 mg are also now available [147].

ADT plus Enzalutamide:

ADT plus enzalutamide has improved survival in mCSPC and may be considered an option

Summary of evidence for ADT plus Enzalutamide

The open-label randomized phase 3 ENZAMET clinical trial compared enzalutamide (160 mg/day) plus ADT with a first-generation anti-androgen (Bicalutamide, nilutamide, or flutamide) plus ADT in 1125 patients with mCSPC. The primary endpoint of OS was met at the first interim analysis with median follow-up of 34 months (HR for death, 0.67; 95% CI, 0.52–0.86; P = .002). Enzalutamide also improved secondary endpoints, such as PFS using PSA levels and clinical PFS [148, 149]. Enzalutamide does not require concurrent prednisolone administration and thus, is preferred in patients where steroids need to be avoided.

ADT plus Apalutamide:

ADT plus Apalutamide has improved survival in mCSPC and may be considered an option. The drug is presently not available in India.

Summary of evidence for ADT plus Apalutamide

TITAN study found that median OS was improved with apalutamide plus ADT compared with ADT alone after a median follow-up of 44 months (NR vs. 52.2 months; HR, 0.65; 95% CI, 0.53–0.79; P < .001). Based on this data, Apalutamide is an approved option in combination with ADT in mCSPC, however it is not yet available in India [150].

ADT plus Docetaxel:

Docetaxel is also included as an upfront option for patients with mCSPC and distant metastases based on results from two phase 3 trials [151, 152].

Summary of evidence for ADT plus Docetaxel

CHAARTED randomized 790 patients with metastatic, castration-naïve prostate cancer to docetaxel (75 mg/m2 IV q3 weeks x 6 doses) plus ADT or ADT alone. After a median follow-up of 53.7 months, the patients in the combination arm experienced a longer OS than those in the ADT arm (57.6 months vs. 47.2 months; HR, 0.72; 95% CI, 0.59–0.89; P = .002).755

Subgroup analysis showed that the survival benefit was more pronounced in the 65% of participants with high-volume disease (HR, 0.63; 95% CI, 0.50–0.79; P < .001). Patients with low-volume disease in CHAARTED did not derive a survival benefit from the inclusion of docetaxel (HR, 1.04; 95% CI, 0.70–1.55; P = .86).

The results of STAMPEDE trial in the M1 population essentially confirmed the survival advantage of adding docetaxel (75 mg/m2 IV q3 weeks x 6 doses) to ADT seen in the CHAARTED trial. In STAMPEDE, extent of disease was not evaluated in the 1087 patients with metastatic disease, but the median OS for all patients with M1 disease was 5.4 years in the ADT-plus-docetaxel arm versus 3.6 years in the ADT-only arm (a difference of 1.8 years between groups compared with a 1.1-year difference in CHAARTED). The results of the STAMPEDE trial seem to confirm the results of the CHAARTED trial.

7 Castration-Resistant Prostate Cancer (CRPC)

Definition of CRPC

Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL

or

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours) [153].

Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

First-line treatment of metastatic CRPC

Ideal: The patients diagnosed with mCRPC should be offered testing for HRR and MSI testing, if available and feasible. If patient was on medical castration, it should be continued to maintain castrate levels of testosterone. If patient has not received anything other than ADT previously, the patients can be offered Docetaxel/ Abiraterone, or Enzalutamide based on patient / physician preference, and the comorbidities (Level 1). Since there is clear data that Abiraterone does not have activity in patients treated previously with Enzalutamide but Enzalutamide retains some of the activity post use of Abiraterone, it is usually recommended to use Abiraterone first, however, this is subject to physician preference and the comorbidities of the patient. If patient has received Abiraterone/ Enzalutamide previously, docetaxel should be offered, if patient is fit enough to receive the same. Sequential use of Abiraterone and Enzalutamide should be avoided in view of significant cross-resistance.

Essential: In absence of availability of testing of MMR and HRR, the patient can be offered treatment with Docetaxel/ Abiraterone/ Enzalutamide as outlined in ideal recommendations.

Summary of evidence for abiraterone in CRPC

The phase III COU-AA-302 trial evaluated Abiraterone in 1,088 chemo-naive, asymptomatic or mildly symptomatic mCRPC patients. At a median follow up of 22 months, there was an absolute improvement of median radiographic PFS by 8 months ($p < 0.001$). At a longer follow up of 49.2 months, OS improved by 4 months (34.7 vs. 30.3 months, $p = 0.0033$). Adverse events related to mineralocorticoid excess and

liver function were more frequent with Abiraterone, but were mostly grade 1–2. Sub-set analysis of this trial found the drug to be equally effective in people > 75 years [154, 155].

Enzalutamide

Summary of evidence for enzalutamide in CRPC

A randomized phase III trial (PREVAIL) included a similar patient population to COU-AAA-302 trial and compared enzalutamide and placebo. The trial also included patients with visceral metastases, though their numbers were small. PREVAIL showed a significant improvement in both rPFS and OS The median OS improved by approximately 2 months (32.4 vs 30.2 months). Fatigue and hypertension were the most common clinically relevant adverse events. Enzalutamide was equally effective and well tolerated in men > 75 years as well as in those with or without visceral metastases [156 – 161].

Docetaxel

Summary of evidence for docetaxel in CRPC

A statistically significant improvement in median survival of 2.0–2.9 months has been shown with docetaxel based chemotherapy compared to mitoxantrone plus prednisone in trials. The standard first-line chemotherapy presently should be docetaxel 75 mg/m2, 3-weekly doses combined with prednisone 5 mg twice a day (BID), up to 10 cycles. Prednisone can be omitted in absence of major symptoms or if contraindicated. Only consideration by age should not be a contraindication to docetaxel. In men with mCRPC who are unable to tolerate the standard dose and schedule, docetaxel 50 mg/m2 every two weeks appears well tolerated with less grade 3–4 adverse events [162 – 165].

Sipuleucel-T

Summary of evidence for Sipuleucel-T in CRPC

In 2010 a phase III trial of sipuleucel-T showed a survival benefit in 512 asymptomatic or minimally symptomatic mCRPC patients [166]. It is not available in most of the countries now and thus, not in clinical use.

Ipatasertib

Summary of evidence for Ipatesertib in CRPC

The AKT inhibitor ipatasertib in combination with abiraterone plus prednisone was studied in asymptomatic or mildly symptomatic patients with PTEN loss by IHC and previously untreated for mCRPC. The randomized phase III trial (IPAtential) showed an increase in rPFS by 2 months in the PTEN loss (IHC) population (18.5 vs. 16.5 months; p = 0.0335). The OS results are still pending. Side effects of the AKT inhibitor ipatasertib include rash and diarrhea. This combination is still investigational [167].

Cabazitaxel

Summary of evidence for Cabazitaxel in CRPC

Cabazitaxel is a newer taxane with activity in docetaxel-resistant cancers. It was studied in a large prospective, randomized, phase III trial (TROPIC) comparing cabazitaxel plus prednisone vs. mitoxantrone plus prednisone in 755 patients with mCRPC, who had progressed after or during docetaxel-based chemotherapy.

Patients received a maximum of ten cycles of cabazitaxel (25 mg/m2) or mitoxantrone (12 mg/m2) plus prednisone (10 mg/day). Overall survival improved by 3.4 months (median: 15.1 vs. 12.7 months, $p < 0.0001$). There was also an improvement in PFS by 1.4 months (median: 2.8 vs. 1.4 months, $p < 0.0001$). Treatment-associated WHO grade 3–4 adverse events developed significantly more often in the cabazitaxel arm, particularly hematological (68.2% vs. 47.3%, $p < 0.0002$) but also non-hematological (57.4 vs. 39.8%, $p < 0.0002$) toxicity. In two post-marketing randomized phase III trials, cabazitaxel was shown not to be superior to docetaxel in the first-line setting; In the second-line setting in terms of OS, 20 mg/m2 cabazitaxel was not inferior to 25 mg/m2, but less toxic. Therefore, the lower dose should be preferred. Cabazitaxel should preferably be given with prophylactic granulocyte colony-stimulating factor (G-CSF) and should preferably be administered in settings with expertise in handling neutropenia and sepsis [168 – 172]. In selected patients who do not seem to be fit to receive docetaxel in mCRPC setting, can be considered for Cabazitaxel upfront. This recommendation is based on a randomized trial showing less fatigue and better quality of life in patients receiving Cabazitaxel before Docetaxel.

Treatment after docetaxel

Summary of evidence for Abiraterone acetate after prior docetaxel

In the COU – AA – 301 trial, a total of 1,195 patients with mCRPC were randomized 2:1 to abiraterone acetate plus prednisone or placebo plus prednisone. All patients who progressed (as per Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria) after docetaxel therapy (with a maximum of two previous chemotherapeutic regimens) were included. After a median follow-up of 20.2 months, the median survival in the abiraterone group improved by 4.6 months (15.8 vs 11.2 months; HR: 0.74, $p < 0.0001$). The benefit was observed in all subgroups. The incidence of the most common grade 3–4 adverse events did not differ significantly between arms, but mineralocorticoid-related side effects were more frequent in the abiraterone group, mainly grade 1–2 (fluid retention, edema and hypokalemia) [173, 174].

Summary of evidence for Enzalutamide after docetaxel

AFFIRM trial randomized 1,199 patients with mCRPC in a 2:1 fashion to enzalutamide or placebo. All patients had progressed after docetaxel treatment (as per PCWG2 criteria). After a median follow-up of 14.4 months, the median survival in the enzalutamide group improved by almost 5 months (18.4 vs 13.6 months; HR: 0.63, $p < 0.001$). The benefit was observed irrespective of age, baseline pain intensity, and type of progression. The final analysis with longer follow-up also showed improved OS results in the Enzalutamide group despite crossover and extensive post-progression therapies. Patients with visceral metastases also benefitted from Enzalutamide. Side effect profile was similar in both arms, with a lower incidence of grade 3–4 adverse events in the enzalutamide arm. There was a 0.6% incidence of seizures in the enzalutamide group compared to none in the placebo arm [175].

Radium-223

The only bone-specific drug that is associated with a survival benefit is the alpha emitter radium-223. In a large phase III trial (ALSYMPCA) 921 patients with symptomatic mCRPC, who failed or were unfit for docetaxel, were randomized to six injections of 50 kBq/kg radium-223 or placebo, plus standard of care. The primary endpoint was OS. Radium-223 significantly improved median OS by 3.6 months

(HR: 0.70, p < 0.001) and was also associated with prolonged time to first skeletal event, improvement in pain scores and improvement in QoL. The associated toxicity was mild and, apart from slightly more hematologic toxicity and diarrhea with radium-223, it did not differ significantly from that in the placebo arm. Radium-223 was effective and safe whether or not patients were docetaxel pre-treated. Due to safety concerns, use of radium-223 was recently restricted to after docetaxel and at least one AR targeted agent. However, it is seldom used in real clinical practice as it works only in patients with skeletal only metastasis [176 – 179].

Treatment after docetaxel and one line of hormonal treatment for mCRPC

Summary of evidence for second line treatment for mCRPC

For men progressing quickly on AR targeted therapy (< 12 months), cabazitaxel is the treatment supported by the best data. The CARD trial, an open label randomized phase III trial, evaluated cabazitaxel after docetaxel and one line of androgen receptor targeting agent (ARTA) (either abiraterone plus prednisolone or enzalutamide). It included patients progressing in less than 12 months on previous abiraterone or enzalutamide for mCRPC. The median overall survival improved by 2.6 months (13.6 vs 11.0 months; HR: 0.64; 95% CI, 0.46 to 0.89; P=0.008). The median progression-free survival increased by almost 2 months (4.4 vs 2.7 months; p <0.001). The rPFS with cabazitaxel remained superior regardless of the ARTA sequence and if docetaxel was given before, or after, the first ARTA [180].

The choice of further treatment after docetaxel and one line of hormonal treatment for mCRPC is open for patients who have a > 12 months' response to first-line abiraterone or enzalutamide for mCRPC. Either radium-223 or second-line chemotherapy (cabazitaxel) are reasonable options [181 – 185]. In general, subsequent treatments in unselected patients are expected to have less benefit than with earlier use and there is evidence of cross-resistance between enzalutamide and abiraterone. Poly (ADP-ribose) polymerase inhibitors have shown high rates of response in men with somatic homologous recombination repair (HRR) deficiency in initial studies. Men previously treated with both docetaxel and at least one ARTA and whose tumours demonstrated homozygous deletions or deleterious mutations in DNA repair genes showed an 88% response rate to olaparib and in another confirmatory trial a confirmed composite response of 54.3% (95% CI: 39.0–69.1) in the 400 mg cohort and in 18 of 46 (39.1%; 25.1–54.6) evaluable patients in the 300 mg cohort [186 – 190].

PARP inhibitors for mCRPC

So far, two PARP inhibitors, olaparib and rucaparib, are licensed by the FDA (EMA only approved olaparib) and several other PARP inhibitors are under investigation (e.g., talazoparib, niraparib). A randomized phase III trial (PROfound) compared the PARP inhibitor olaparib to an alternative ARTA in mCRPC with alterations in > 1 of any qualifying gene with a role in HRR and progression on an ARTA. Most patients were heavily pre-treated with 1–2 chemotherapies and up to 2 ARTAs. In patients with BRCA 1 / 2 or ATM mutation, median rPFS improved by almost 4 months (7.4 vs. 3.6 months; HR: 0.34; 95%CI: 0.25 to 0.47; P<0.001) [191]. Of note, patients in the physician's choice of enzalutamide/abiraterone-arm who progressed, 66% (n = 86/131) crossed over to olaparib. In patients harboring other mutations, there was no improvement in rPFS or OS. The most common adverse events were anaemia (46.1% vs. 15.4%), nausea (41.4% vs. 19.2%), decreased appetite (30.1% vs. 17.7%) and fatigue (26.2% vs. 20.8%) for olaparib vs. enzalutamide/abiraterone. Among patients receiving olaparib 16.4% discontinued treatment secondary

to an adverse event, compared to 8.5% of patients receiving enzalutamide/abiraterone. Interestingly, 4.3% of patients receiving olaparib had a pulmonary embolism, compared to 0.8% among those receiving enzalutamide/abiraterone, none of which were fatal. There were no reports of myelodysplastic syndrome or acute myeloid leukemia. This is the first trial to show a benefit for genetic testing and precision medicine in mCRPC. The olaparib approval by the FDA is for patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone. The EMA approved olaparib for patients with BRCA1 and BRCA2 alterations. The recommended olaparib dose is 600 mg daily (300 mg taken orally twice daily), with or without food. Rucaparib has also been approved for patients with deleterious BRCA mutations (germline and/or somatic) who have progressed after ARTA and a taxane-based chemotherapy based on the results of the single-arm TRITON2 trial (NCT02952534) trial and not based on OS data. [191, 192].

Sequencing treatment

Ideal: Based on results of CARD trial, patients should be offered cabazitaxel in preference to other agents after progression on docetaxel and one line of hormonal treatment in addition to ADT. In suitable patients Lu177-PSMA therapy can be offered before cabazitaxel. Those having HRR mutation, can be offered Olaparib in preference to other agents.

Essential: Patients who have received Docetaxel and Abiraterone or Enzalutamide, should be given Cabazitaxel 20 mg/m2 protocol.

ARTA –> ARTA (chemotherapy-naive patients)

The use of sequential ARTAs in mCRPC showed limited benefit as shown in multiple retrospective series and one prospective trial. In particular in patients who had a short response to the first ARTA for mCRPC (< 12 months), this sequence should be avoided because of known cross resistance and the availability of chemotherapy and PARP inhibitors (if a relevant mutation is present). In highly selected patients treated for more than 24 weeks with abiraterone plus prednisolone, the sequence with enzalutamide showed some activity with a median rPFS of 8.1 months (95% CI: 6.1–8.3) and an unconfirmed PSA response rate of 27%. An ARTA-ARTA sequence should never be the preferred option but might be considered in patients not fit for chemotherapy and not suitable for PARP inhibitors if the PS still allows for active treatment and the potential side effects seem manageable. First prospective cross-over data on an ARTA-ARTA sequence and a systematic review and meta-analysis suggest improvements in endpoints PFS and PSA PFS, but not OS Abiraterone followed by enzalutamide is the preferred choice [193 – 203].

ARTA –> PARP inhibitor/olaparib

This sequence in patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated mCRPC is supported by data from the randomised phase III PROfound trial. A subgoup of patients in this trial was pre-treated with one or two ARTAs and no chemotherapy. The ARTA – docetaxel - PARP inhibitor vs. ARTA – PARP inhibitor - docetaxel sequences are still under investigation.

Docetaxel for mHSPC –> docetaxel re-challenge

There is limited evidence for second- or third-line use of docetaxel after treatment with docetaxel for mCSPC. Docetaxel seems to be less active than ARTA at progression to mCRPC following docetaxel for mCSPC.

ARTA –> docetaxel or docetaxel –> ARTA followed by PARP inhibitor

Both olaparib and rucaparib are active in biomarker-selected mCRPC patients after ARTA and docetaxel in either sequence.

ARTA before or after docetaxel

There is level 1 evidence for both sequences.

ARTA –> docetaxel –> cabazitaxel or docetaxel –> ARTA –> cabazitaxel

Both third-line treatment sequences are supported by level 1 evidence. Of note, there is high level evidence favouring cabazitaxel vs. a second ARTA after docetaxel and one ARTA. CARD is the first prospective randomized phase III trial addressing this question.

Immunotherapy for mCRPC

The immune checkpoint inhibitor pembrolizumab was approved by the FDA for all MMR–deficient cancers or in those with instable microsatellite status (MSI-high). Though, this is very rare in PCa but if present still applicable. In all other PCa patients pembrolizumab monotherapy is still experimental. It shows limited anti-tumour activity with an acceptable safety profile, again in a small subset of patients. A phase II trial enrolled 258 patients treated with pembrolizumab. The objective response rate was around 4%, but those responses were durable. Combination immunotherapy is under investigation [210 – 212].

Monitoring of treatment

Baseline examinations should include a medical history, clinical examination as well as baseline blood tests (PSA, total testosterone level, full blood count, renal function, baseline liver function tests, alkaline phosphatase), PSMA PET/CT or combination of bone scan + CT of chest, abdomen and pelvis. The use of choline or PSMA PET/CT scans for progressing CRPC is unclear and is not as beneficial as for patients with BCR or hormone-naive disease. The PSA response or the progression on ARTA may not corroborate well with the results due to flares or PSMA upregulation. Prostate-specific antigen alone is not reliable enough for monitoring disease activity in advanced CRPC since visceral metastases may develop in men without rising PSA. Instead, either PSMA PET/CT or a combination of bone scan + CT scans, PSA measurements and clinical benefit to the patient may be recommended in response assessment of CRPC (PCWG 2). A majority of experts at the 2015 Advanced Prostate Cancer Consensus Conference (APCCC) suggested regular review and repeating blood profile every two to three months with bone scintigraphy and CT scans at least every six months, even in the absence of a clinical indication. This reflects that the agents with a proven OS benefit all have potential toxicity and considerable cost and patients with no objective benefit should have their treatment modified. The APCCC participants stressed that at least two of the three criteria (PSA progression, radiographic progression and clinical deterioration) should be fulfilled to stop treatment and not for PSA progression alone. Instead, for trial purposes, the updated PCWG3 put more weight on the importance of documenting progression in existing lesions

and introduced the concept of no longer 'clinically benefiting' to distinguish between first evidence of progression and the clinical need to terminate or change treatment. These recommendations also seem valid for clinical practice outside trials [213 – 217].

When to change treatment

The timing of mCRPC treatment change remains a matter of debate in mCRPC although it is clearly advisable to start or change treatment immediately in men with symptomatic progressing metastatic disease. Preferably, any treatment should change only due to development of de novo symptoms or worsening of existing symptoms. Although, the number of effective treatments is increasing, head-to-head comparisons are still rare, as are prospective data assessing the sequencing of available agents. Therefore, it is not clear how to select the most appropriate 'second-line' treatment, in particular in patients without HRR alterations or other biomarkers.

However, is the CARD trial clearly established cabazitaxel as the better third-line treatment in patients pretreated with docetaxel and one ARTA compared to the use of a second ARTA. Generally, men with good PS of 0–1 are likely to tolerate treatments well and those with a PS of > 2 are less likely to derive benefit or tolerate treatment. However, it is important that treatment decisions are individualized, when symptoms related to disease progression are impacting on PS. In such cases, a trial of active life-prolonging agents to establish if a given treatment will improve the PS may be appropriate [218 – 220].

Oral Metronomic Chemotherapy (OMCT)

therapeutic option not only in those mCRPC patients unfit for standard treatments but also in those heavily pre-treated patients. The advantage being very low cost, oral treatment and low adverse effects, with close to 50% patients having PSA response, defined as >50% reduction in PSA. It is recommended to consider enrolling patients planned for OMCT in a multicenter study across India [246, 247]. There are small retrospective studies from Italy and India, which suggest that oral metronomic cyclophosphamide plus low dose of oral dexamethasone or prednisone may be a good and safe

8 Palliative Care in Prostate Cancer

Castration-resistant PCa is usually a debilitating disease often affecting the elderly male. A multidisciplinary approach is required with input from urologists, medical oncologists, radiation oncologists, nurses, psychologists and social workers. Critical issues of palliation must be addressed when considering additional systemic treatment, including management of pain, constipation, anorexia, nausea, fatigue and depression. Pain due to bone metastases is the major complaint in patients with mPCa. Multiple options are available for its management.

Common complications due to bone metastases

Most patients with CRPC have painful bone metastases. External beam radiotherapy is highly effective, even as a single fraction. A single infusion of a third generation bisphosphonate could be considered when RT is not available. Common complications due to bone metastases include vertebral collapse or deformity, pathological fractures and spinal cord compression. Cementation can be an effective treatment for painful spinal fracture whatever its origin, clearly improving both pain and QoL. It is important to offer standard palliative surgery, which can be effective for managing osteoblastic metastases. Impending spinal cord compression is an emergency. It must be recognized early and patients should be educated to recognize the warning signs. Once suspected, high-dose corticosteroids must be given and MRI performed as soon as possible. A systematic neurosurgery or orthopaedic surgeon consultation should be planned to discuss a possible decompression, followed by EBRT. Otherwise, EBRT with, or without, systemic therapy, is the treatment of choice [221 -228].

Preventing skeletal-related events

Bisphosphonates

Zoledronic acid has been evaluated in mCRPC to reduce skeletal-related events (SRE). This study was conducted when no active anti-cancer treatments, but for docetaxel, were available. Six hundred and forty-three patients who had CRPC with bone metastases were randomized to receive Zoledronic acid, 4 or 8 mg every three weeks for 15 consecutive months, or placebo. The 8 mg dose was poorly tolerated and reduced to 4 mg but did not show a significant benefit. However, at 15 and 24 months of follow-up, patients treated with 4 mg Zoledronic acid had fewer SREs compared to the placebo group (44 vs. 33%, $p = 0.021$) and in particular fewer pathological fractures (13.1 vs. 22.1%, $p = 0.015$). Furthermore, the time to first SRE was longer in the zoledronic acid group. No survival benefit has been seen in any prospective trial with bisphosphonates [229].

RANK ligand inhibitors

Denosumab is a fully human monoclonal antibody directed against RANKL (receptor activator of nuclear factor kappa-B ligand), a key mediator of osteoclast formation, function, and survival. In M0 CRPC, denosumab has been associated with increased bone-metastasis-free survival compared to placebo (median benefit: 4.2 months, HR: 0.85, p = 0.028). This benefit did not translate into a survival difference (43.9 compared to 44.8 months, respectively) and neither the FDA or the EMA have approved denosumab for this indication.

The efficacy and safety of denosumab (n = 950) compared with zoledronic acid (n = 951) in patients with mCRPC was assessed in a phase III trial. Denosumab was superior to zoledronic acid in delaying or preventing SREs as shown by time to first on-study SRE (pathological fracture, radiation or surgery to bone, or spinal cord compression) of 20.7 vs. 17.1 months, respectively (HR: 0.82, p = 0.008). However, these findings were not associated with any survival benefit and in a recent post-hoc re-evaluation of endpoints, Denosumab showed identical results when comparing SREs and symptomatic skeletal events. The potential toxicity (e.g., osteonecrosis of the jaw, hypocalcaemia) of these drugs must always be kept in mind (5–8.2% in M0 CRPC and mCRPC, respectively). Patients should have a dental examination before starting therapy as the risk of jaw necrosis is increased by several risk factors including a history of trauma, dental surgery or dental infection. Also, the risk for osteonecrosis of the jaw increased numerically with the duration of use in a pivotal trial (one year vs. two years with denosumab), but this was not statistically significant when compared to zoledronic acid. According to the EMA, hypocalcaemia is a concern in patients treated with denosumab and zoledronic acid. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Hypocalcaemia should be identified and prevented during treatment with bone protective agents (risk of severe hypocalcaemia is 8% and 5% for denosumab and zoledronic acid, respectively). Serum calcium should be measured in patients starting therapy and monitored during treatment, especially during the first weeks and in patients with risk factors for hypocalcaemia or on other medication affecting serum calcium. Daily calcium (> 500 mg) and vitamin D (> 400 IU equivalent) are recommended in all patients, unless in case of hypercalcemia [230 – 237].

Prostate-specific membrane antigen (PSMA) therapy

Background

During the 90s several radiopharmaceuticals including phosphorous-32, strontium-89, yttrium-90, samarium-153, and rhenium-186 were developed for the treatment of bone pain secondary to metastasis from PCa. They were effective at palliation; relieving pain and improving QoL, especially in the setting of diffuse bone metastasis. However, they never gained widespread adoption. The first radioisotope to demonstrate a survival benefit was radium-223.

PSMA-based therapy

The increasing use of PSMA PET as a diagnostic tracer and the realization that this allowed identification of a greater number of metastatic deposits led to attempts to treat cancer by replacing the imaging isotope with a therapeutic isotope which accumulates where the tumour is demonstrated (theranostics).

Therefore, after identification of the target usually with diagnostic 68Gallium-labelled PSMA, therapeutic radiopharmaceuticals labelled with beta (lutetium-177 or ytrium-90) or alpha (actinium-225) emitting isotopes could be used to treat metastatic PCa.

The PSMA therapeutic radiopharmaceutical supported with the most robust data is 177Lu-PSMA-617. The first patient was treated in 2014 and early clinical studies evaluating the safety and efficacy of Lu-PSMA therapy have demonstrated promising results, despite the fact that a significant proportion of men had already progressed on multiple therapies. Nonetheless, most of the literature is based on single-centre experience and RCTs are lacking [206 – 209]. Recently, data from uncontrolled prospective phase II trials have been published reporting high response rates with low toxic effects. Positive signals are coming from a randomised phase II trial comparing Lu-PSMA with cabazitaxel in ARTA and docetaxel pre-treated patients. The primary endpoint of PSA reduction > 50% was achieved in highly selected patients (PSMA- and FDG PET/ CT criteria) was superior with Lu-PSMA. Recently following the VISION (NCT03511664) trial, which showed 177Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care recently the U.S. FDA approved 177Lu-PSMA-617 for the treatment of patients with PSMA positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy.

9 Aggressive Variant Prostate Cancer (AVPC)

There is increasing recognition of AVPC in patients with mCRPC. The criteria to stamp a mCRPC as AVPC includes 7 clinicopathologic features:

1. Histological evidence of small-cell prostate carcinoma,
2. Exclusive visceral metastases,
3. Predominant lytic bone metastases,
4. Bulky lymphadenopathy or primary tumor at diagnosis
5. Gleason score of ≥8,
6. Low prostate-specific antigen (PSA) and high-volume bone metastases,
7. Elevated lactate dehydrogenase (LDH) or carcinoembryonic antigen (CEA), and
8. Short interval response at androgen deprivation therapy (ADT).

Patients were considered to have aggressive phenotype if they had at least 1 of the above criteria. No recommendations for ideal treatment can be made as of now and needs future research.

10 Management of Oligometastatic Disease

Oligo metastatic disease has not been defined uniformly through out literature. But more commonly it is defined as less than 5 metastatic sites or lesions.

Types of oligo-metastatic disease

1. Synchronous (At the time of diagnosis of primary disease)
2. Meta-chronous (develops subsequently during treatment or follow up)

Metastatic disease in prostate cancer can be broadly divided into

Low volume & high volume disease (CHHARTED TRIAL)

Low Risk & high risk (LATTITUDE TRIAL)

	High	Low
CHAARTED (volume)	> 4 Bone metastasis including > 1 outside vertebral column or pelvis OR Visceral metastasis	Not high
LATITUDE (risk)	> 2 high-risk features of: • > 3 Bone metastasis • Visceral metastasis • > ISUP grade 4	Not high

Management of synchronous oligo-metastatic disease

Treatment of prostate with radiotherapy along with the ADT with or without other standard systemic therapy improves overall survival in low volume disease and therefore recommended (Level 1). Radiation dose fractionation recommended are 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6-weekly fractions of 6 Gy.

Summary of evidence for prostate radiotherapy in oligo-metastatic disease

The first trial giving an insight into local radiotherapy in metastatic setting was HORRAD trial which compared ADT vs ADT with Radiotherapy to prostate in metastatic castrate sensitive prostate cancer and showed an improved median time to PSA progression in the radiotherapy arm (HR: 0.78 [0.63–0.97]) but no improvement in overall survival [238]. The STAMPEDE trial evaluated 2,061 men with mHSPC who were randomized to ADT alone vs. ADT plus radiotherapy to the prostate confirmed the lack of OS benefit in unselected group of patients but when the outcome was evaluated according to the disease

subgroup proposed by the CHHARTED Trial of low volume and high volume high volume disease, there was no OS benefit in unselected group in spite of an failure free survival benefit (HR 0 76, 95% CI 0 68–0 84; p<0 0001) but both OS (HR 0 68 95% CI 0 52–0 90 ; P <0.007) and FFS (HR 0 59, 95% CI 0 49–0 72; p<0 0001) improved in low volume subgroup with prostate RT [239]. In a meta-analysis looking into ADT with or without prostate RT in mHSPC an absolute improvement of 7% in 3-yr survival in men who had four or fewer bone metastases was shown [240]. Role Radical prostatectomy in mHSPC setting has been explored only in small retrospective and prospective studies but it still remains investigational [241 – 243].

Metastasis directed therapy in meta-chronous M1 disease setting.

Currently there is no level 1 evidence to suggest an improvement in OS with metastatectomy or SABR to all metastases. Despite the results of small prospective trials, the approach still should be considered experimental.

Summary of evidence for metastases directed therapy in oligo-metastatic disease

In patients relapsing after complete local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment.Two phase 2 trials have examined this scenario. STOMP trial examined ADT free survival with metastasis directed treatment in patients with oligo metastatic disease who had already completed their planned treatment for the primary disease. In the 62 patients who were included both SABR or metastatectomy were allowed as a part of protocol. At a median follow-up time of 3 years (interquartile range, 2.3-3.75 years), the median ADT-free survival was 13 months (80% CI, 12 to 17 months) for the surveillance group and 21 months (80% CI, 14 to 29 months) for metastases directed therapy [244]. In ORIOLE trial mHSPC patients who had completed their planned treatment for the primary disease were enrolled. Progression at 6 months was the primary outcome. Progression after 6 months was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [245].

11 Follow-up in Prostate Cancer

Follow up in non-metastatic prostate cancer	
Active surveillance	Serum PSA every 6 months DRE every 12 months No clarity on mpMRI and repeat biopsy
After definitive treatment (RT+/- ADT, Surgery etc)	Serum PSA every 3 months in the first year, 6 monthly after that for 5 years Phoenix criteria to be used for biochemical failure after radiotherapy The threshold for biochemical failure after surgery should be kept low i.e. PSA ≥ 0 1 ng/mL or three consecutive rises by 50% or more Imaging only if symptoms/ signs suggest recurrence **Monitoring of treatment toxicity (If ADT > 1 year)** Liver function monitoring 6 monthly Hemoglobin monitoring 6 monthly Blood pressure monitoring HbA1c and lipid profile monitoring 6 monthly DEXA scan yearly for bone density
Follow up in metastatic prostate cancer (mHSPC and CRPC)	Serum PSA every 3 months; Routine imaging not required unless suspicion of progression. PSMA PET/CT or Bone scintigraphy and CT scans at least every six months may be considered Serum testosterone monitoring (< 50 ng/mL) to detect CRPC **Monitoring of treatment toxicity** Liver function monitoring 6 monthly Blood pressure monitoring Hemoglobin monitoring 6 monthly HbA1c and lipid profile monitoring 6 monthly DEXA scan yearly for bone density Psychological support

12 Research Questions

- Frequency and utility of serial multiparametric-MRI in active surveillance
- In PSMA only detected metastases (i.e. Bone scan being Normal): Treat as localised disease or metastatic disease
- Role of SABR in high risk prostate cancer
- Sequencing of ADT in intermediate risk prostate cancer
- Post radical prostatectomy, N1 ds: ADT only or ADT + Radiotherapy
- PEACE 1 Study has shown that Abiraterone + Docetaxel combination in mCSPC gives survival benefit. The tolerability of this combination has not yet been tested in Indian patients.
- PSMA therapy has shown clinically meaningful benefit in mCRPC patients post docetaxel and next generation ADT. However, there is a strong rationale for using PSMA therapy in earlier lines of therapy, where it can provide significant benefit as opposed to limited benefit post multiple lines of therapy.
- Enzalutamide does not require coadministration of steroids, thus, Enzalutamide plus Docetaxel combination might be better suited for selected sub-group of mCSPC patients. This requires phase II and phase III studies in Indian patients.
- There has been some data of oral metronomic therapy (OMCT) with cyclophosphamide plus dexamethasone in Indian patients, with response rates of 40-50%. However, this has not yet been tested in randomised settings. It will be useful to do a RCT comparing OMCT versus physician choice treatment beyond three lines of therapy in metastatic prostate cancer.
- Practically there is no Indian data on the use of PARP inhibitors in Indian patients. There should be an Indian registry of BRCA mutant prostate cancer patients, and the outcomes of these patients with PARP inhibitors, and/or Platin based treatment should be recorded.

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14 Executive Summary

- Population based screening not recommended in Indian population in any age group
- Routine screening with serum PSA cannot be recommended for persons carrying BRCA2 mutation
- PSMA PET CT has higher accuracy (92% of PSMA v/s 65% of conventional imaging) in detecting metastases and leads to change in management in higher number of patients (27% with PSMA v/s 5% with conventional imaging)
- Active surveillance should be considered for all patients of low risk prostate cancer
- If a patient is decided to be changed to an active treatment strategy due to any reason he may either, choose between Radical prostatectomy (RP) and radical radiotherapy in low risk cancer.
- Intermediate risk patients may be treated either with radical prostatectomy and lymph node dissection or 6 months of ADT and radiotherapy (2 months neoadjuvant, concurrent and adjuvant)
- High risk patients to be considered for 2 – 3 years of ADT with radiotherapy (4 – 6 months of neo-adjuvant ADT)
- All patients of mCSPC should be prescribed ADT, either medical or surgical castration based on patient preference and available resources. In view of significant benefit of addition of therapy beyond ADT, it should be a routine practice to add Docetaxel/ Abiraterone/ Enzalutamide.
- The patients diagnosed with mCRPC should be offered testing for HRR and MSI testing, if available and feasible.
- If CRPC patient on medical castration, it should be continued to maintain castrate levels of testosterone. If patient has not received anything other than ADT previously, the patients can be offered Docetaxel/ Abiraterone, or Enzalutamide based on patient / physician preference, and the comorbidities.
- Prostate radiotherapy should be added to systemic therapy in oligo-metastatic prostate cancer