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.

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