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