Expert Group Consensus Opinion on Prostate Cancer Diagnosis and Management in India: Part 2 of 2

Amit Ghose¹, Makarand Khochikar², Ravindra Sabnis³, Naveen Magendra Parmar⁴, Indranil Purkait⁴

¹Apollo Gleneagles Hospitals Limited, Kolkata, India
²Department of Uro-Oncology, Siddhi Vinayak Ganapati Cancer Hospital, Miraj, India
³Department of Urology, Muljibhai Patel Urological Hospital, Nadiad, India
⁴Medical Affairs and Clinical Research, Ipca Laboratories Ltd., Mumbai, India

With limited/no guidelines on prostate cancer (PCa) diagnosis and management currently in India, this consensus statement has been developed to evaluate Indian literature and current clinical practices to assist healthcare professionals across India in the diagnosis and management of patients with PCa. A group of leading PCa experts from across India convened at the 2019 CAP summit in Kolkata, India, to vote on 42 consensus statements on PCa diagnosis and management. In the subsequent meeting, an expert panel discussed on the consensus results. On the basis of the voting results and the subsequent expert panel discussion, 5 of 42 statements were deleted and 37 were accepted and retained in the final draft, which is divided into 2 parts. This paper covers part 2, which describes in detail the remaining 21 of 37 statements on locally advanced PCa and metastatic PCa with varying degrees of support from the panel. The consensus statement extrapolated from Indian scientific evidences, regional clinical experiences, and international guidelines will serve as a reference guide for clinicians across India in the diagnosis and management of PCa. (Korean J Urol Oncol 2021;19:1-15)

Key Words: Prostate cancer ㆍGuideline ㆍProstate-specific antigen ㆍProstatectomy ㆍConsensus

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and the sixth leading cause of cancer death in men worldwide.¹ The data on true incidence of PCa in India is limited as this entity is not a notifiable disease, and there are very few population-based cancer registries in India.²

PCa had the fifth highest incidence rate in India in 2016 (4.8/100,000).³ Compared with western countries, the prevalence of PCa in India was previously considered to be lower; however, with increasing migration of rural population to urban areas, increasing awareness, changing life style and easy access to medical facility, more cases of PCa are being detected, suggesting that India is not very far behind western countries in the prevalence rate of PCa.¹

Hence, having a consensus on various issues related to PCa is important. This would enable early diagnosis and cure in early PCa, achieve optimum control, quality of care and provide relief in advanced PCa cases. Today, much has been achieved for curing early PCa using radical robotic prostatectomy and RT, along with huge advances in chemo-
therapy, hormone therapy, and salvage radiotherapy (SRT) for advanced disease.

MATERIALS AND METHODS

Pan-India urology experts convened at the 2019 CAP summit for a 2-day (24–25 May 2019) consultative meeting at Kolkata, India, under the aegis of Board of Education, Urological Society of India. Of the 4 major areas defined for discussion as a part of the consensus process (Fig. 1), namely PCa diagnosis, early PCa, locally advanced prostate cancer, and metastatic PCa, the former 2 have been discussed in part 1 manuscript while the latter 2 have been discussed in this paper (i.e., part 2). In each of the sections, the issues were determined according to perceived clinical importance. A total of 42 consensus statements were designed and voting of 28 experts was taken with the help of voting pads. Each major area was discussed on various international guidelines and evidences, followed by voting on consensus statements. The grade of evidence and the level of agreement were based on voting results (Table 1). When the proportion of those who voted was 80% or higher, the statement was regarded as strongly accepted. The result of the consensus and manuscript version 1 was discussed with an expert panel of 13 members (Table 2) in the consensus board meeting (CBM) on 29 November 2019, before preparing the final manuscript draft. The meeting resulted in deletion of 5 statements according to the practicability of recommendations. This manuscript is the outcome of the expert group discussion and consensus and comprises 21 statements on locally advanced PCa and metastatic PCa.

RESULTS

1. Locally Advanced PCa

1) Statement No. 1

Should radical prostatectomy (RP) be considered as a management option for men with high-risk (D'Amico) cN1 cM0 PCa?

Literature review: Kulkarni et al. analyzed PCa-specific survival (PCS), biochemical recurrence-free survival (BRFS), and metastasis-free survival (MFS) in 56 high-risk lymph node-positive PCa patients who underwent RP (Table 3). Engel et al. revealed that if RP was abandoned because of lymph node-positivity, there was a 2-fold increased risk of death, compared to men who received RP. The overall survival (OS) rate at 10 years was 64% for patients who received RP versus 28% for those who did not. Multivariate analysis demonstrated RP as a strong independent predictor of survival (hazard ratio [HR], 2.04; 95% confidence interval [CI], 1.59–2.63; p<0.0001). RP provides accurate pathological staging in men with high-risk PCa, thus allowing better stratification of patients for further therapy.

Consensus: Should radical prostatectomy be considered as a management option for men with high-risk (D'Amico)

Table 1. Grading system for consensus statement

| Voting percentage | Recommendation strength |
|-------------------|-------------------------|
| >80%              | Strong                  |
| 60%-80%           | Moderate                |
| 50%-60%           | Weak                    |
cN1 cM0 PCa? (yes: 82.1%, no:10.7%, no response: 7.1%).
The expert committee recommended RP to be a part of the multi-modality management in men with high-risk (D’Amico) cN1 cM0 PCa.

2) Statement No. 2
Should neo-adjuvant androgen deprivation therapy (ADT) be considered for men with high-risk (D’Amico) cN1 cM0 PCa prior to radical prostatectomy?

Literature review: Owing to limited Indian studies, other literature was evaluated to identify the role of neo-adjuvant ADT. A cochrane review compared neo-adjuvant or adjuvant ADT combined with primary therapy (RT or RP) versus primary therapy alone in patients with localised or locally advanced PCa. Neo-adjuvant ADT before RP did not improve OS (odds ratio [OR], 1.11; p=0.69). However, a significant improvement was observed in parameters like pathological staging, organ-confined rates, and lymph node involvement. Longer duration of neo-adjuvant ADT (6 or 8 months) use prior to RP was associated with a significant reduction in positive surgical margins (OR, 0.56; 95% CI, 0.39–0.80; p=0.002). In patients receiving neo-adjuvant treatment prior RP, a decrease in postoperative positive surgical margins is observed along with reduced biochemical recurrence (BCR) although no effect has been observed on global or cancer-specific survival.

Consensus: Should neo-adjuvant ADT be considered for men with high-risk (D’Amico) cN1 cM0 PCa prior to radical prostatectomy? (yes: 39.2%, no: 53.5%, no response: 7.1%). The expert committee of CBM expressed a very weak recommendation for considering neo-adjuvant ADT in men with high-risk PCa.

3) Statement No. 3
In men with a detectable prostate-specific antigen (PSA) postprostatectomy, and pN1 cM0 disease, would you offer adjuvant docetaxel chemotherapy if fit enough?

Literature review: No Indian data exists on the use of adjuvant docetaxel chemotherapy postprostatectomy. In the Scandinavian PCa group 12 trial, 459 patients received 6 cycles of adjuvant docetaxel every 3 weeks or surveillance post-RP. No significant difference was observed in time to BCR (PSA >0.5 ng/mL) between the arms, and the restricted mean survival time was 43 months (docetaxel arm) and 46 months (surveillance arm) (p=0.06). After a median follow up of 56.8 months, biochemical progression happened in 44.8% men in the docetaxel arm versus 38.9% in the surveillance arm. Lin et al. evaluated the efficacy of adjuvant docetaxel and prednisone versus standard follow-up after RP. At a median follow-up of 62.4 months,

Table 2. Consensus board meeting members and their speciality

| Name              | Speciality     |
|-------------------|----------------|
| Dr. Amit Ghose    | Urologist      |
| Dr. Ajay Kumar    | Urologist      |
| Dr. Anant Kumar   | Urologist      |
| Dr. Aneesh Srivastava | Urologist   |
| Dr. C. Mallikarjuna | Urologist    |
| Dr. Makarand Khochikar | Urologist |
| Dr. N. P. Gupta  | Urologist      |
| Dr. Prem Kumar    | Urologist      |
| Dr. Rajeev Kumar  | Urologist      |
| Dr. Ravindra Sabnis | Urologist       |
| Dr. S. K. Raghunath | Urologist   |
| Dr. S. K. Singh   | Urologist      |
| Dr. Sudhir Rawal  | Urologist      |

Table 3. Univariate analysis assessing impact of pathological variables on PCS, BRFS, and MFS at 5, 7, and 10 years of follow-up

| Pathological stage | PCS (%) | BRFS (%) | MFS (%) |
|-------------------|---------|----------|---------|
|                   | 5 Years | 7 Years  | 10 Years| 5 Years | 7 Years | 10 Years| 5 Years | 7 Years | 10 Years|
| OC                | 94.7    | 94.7     | 88      | 91.1    | 78.8    | 74.2    | 94.9    | 90.9    | 90.9    |
| PT3a+ LN-         | 87      | 75       | 75      | 72      | 58.7    | 50.3    | 86      | 81.3    | 59.1    |
| PT3b+ LN-         | 80.9    | 72.8     | 54      | 40.7    | 28.8    | 23.8    | 72.4    | 61.3    | 39.9    |
| LN+               | 89.5    | 75.3     | 57.8    | 75      | 40.3    | 21.6    | 75      | 65.7    | 34.2    |
| p-value           | 0.05    | 0.000    | 0.001   |

PCS: prostate cancer-specific survival, BRFS: biochemical recurrence-free survival, MFS: metastasis-free survival, OC: organ confined, PT: pathological tumor, LN: lymph node.
progression-free survival (PFS) in the 2 groups was 55.5 versus 45.6 months (log-rank p=0.26). Overall, 67% of patients in the chemotherapy arm experienced at least 1 grade 3 adverse event. However, only node-negative men with postoperative PSA of 0.1 ng/mL were included in this study.

Consensus: In men with a detectable PSA postprostatectomy, and pN1 cM0 disease, would you offer adjuvant docetaxel chemotherapy if fit enough? (yes: 21.4%, no: 67.8%, no response: 10.7%). The expert committee suggested that this statement should have a strong recommendation instead of a moderate.

4) Statement No. 4
In men with an undetectable PSA following radical prostatectomy (and good urinary continence), would you recommend adjuvant radiotherapy (ART) to the prostate bed-only?

Literature review: A cochrane review evaluated the effect of ART following RP in high-risk PCa patients compared with RP alone. ART following RP did not affect OS at 5 years (risk difference [RD], 0.00; 95% CI, 0.03–0.03), but improved survival at 10 years (RD, -0.11; 95% CI, -0.20 to -0.02). ART did not improve PCA-specific mortality at 5 years (RD, -0.01; 95% CI, -0.03 to 0.00). ART did not reduce metastatic disease at 5 years (RD, -0.00; 95% CI, -0.04 to 0.03), but reduced it at 10 years (RD, -0.11; 95% CI, -0.20 to -0.01). It improved BRFS at 5 years (RD, -0.16; 95% CI, -0.21 to -0.11) and 10 years (RD, -0.29; 95% CI, -0.39 to -0.19). The ARO 96-02 study primarily compared 3 groups of PCa patients who achieved an undetectable PSA after RP. Patients who did not achieve an undetectable PSA were moved to SRT arm. Patients in the wait-and-see arm, ART arm, and SRT arm had a 10-year OS rate of 86%, 83%, and 68% respectively.

Consensus: In men with an undetectable PSA following radical prostatectomy (and good urinary continence), would you recommend ART to the prostate bed-only? (yes: 3.57%, no: 85.71%, no response: 10.71%)

5) Statement No. 5
In men with an undetectable PSA following radical prostatectomy (and good urinary continence), would you recommend adjuvant ADT?

Literature review: In a retrospective Indian study, prognostic risk grouping, node positivity, and high initial PSA emerged as significant factors that influenced decisions regarding ADT prescription. Rajput and Sehgal stated that adjuvant ADT benefit has been observed only for those having metastatic disease. Thus, adjuvant ADT is recommended only for the patients with evidence of metastatic disease having early time to PSA recurrence, rapid PSA doubling time, and adverse pathological features. In another study, patients with locally advanced disease who underwent RP, the median follow-up was 9.7 years. There were no statistically significant differences between the bicalutamide and placebo groups with respect to PFS (HR, 0.85; 95% CI, 0.71–1.01; p=0.065) or OS (HR, 1.03; 95% CI, 0.84–1.26; p=0.817). Overall, 98% node-negative patients did not appear to benefit from postsurgery adjuvant treatment. In a survey conducted in the United Kingdom, as a sole trigger factor, 70% of urologists considered a detectable postoperative PSA alone as an important deciding factor for adjuvant treatment.

Consensus: In men with an undetectable PSA following radical prostatectomy (and good urinary continence), would you recommend adjuvant ADT? (yes: 3.57%, no: 85.71%, no response: 10.71%)

6) Statement No. 6
In men with a detectable PSA immediately postsurgery, but no risk factors for persistent pelvic disease, would you offer ART?

Literature review: Murthy et al. studied the practice pattern of prostate RT among radiation oncologist in India. In his survey, including 126 oncologists, 86% reported using ART for high-risk pathological features after RP as their standard practice. Early SRT was practised as standard by 14% of oncologists. However, 43% of respondents observed an increasing trend of patients being offered early salvage treatment in the last 5 years. Another study evaluated patients treated with postoperative RT with a median follow-up of 32.5 months. In patients with locally advanced PCa (pT3/4), BRFS was similar in the ART and early SRT groups (HR, 0.21; 95% CI, 0.02–1.79; p=0.15). SRT administered at early PSA rise might be as effective as postoperative ART in patients with locally advanced PCa.

Consensus: In men with a detectable PSA immediately postsurgery, but no risk factors for persistent pelvic disease,
would you offer ART? (yes: 50%, no: 35.71%, no response: 14.2%). The expert committee also defined ‘immediately’ as detectable PSA levels of more than 0.2 ng/mL within 12 weeks.

7) Statement No. 7.
In men with an undetectable PSA following radical prostatectomy (and good urinary continence), who subsequently develop a PSA recurrence, would you recommend SRT to the prostate bed-only?

Literature review: Other studies were evaluated for this statement owing to lack of Indian literature on the use of SRT in patients developing PSA recurrence following RP. In a retrospective study of 2,460 patients receiving SRT, the 5-year biochemical control rate was 71%, 63%, 54%, 43%, and 37% for pre-SRT PSA levels of 0.01–0.2 ng/mL, 0.21–0.50 ng/mL, 0.51–1.0 ng/mL, 1.01–2.0 ng/mL, and >2.0 ng/mL (p<0.001) respectively. The RAVES and RADICAL trials assessed SRT in post-RP patients with PSA levels more than 0.1–0.2 ng/mL. It showed a 5-year BRFs rate of 88%. A meta-analysis on the impact of BCR after RP reported SRT to be favourable for OS and PCa-specific mortality. In particular, SRT should be initiated in patients with rapid PSA kinetics after RP and with a PSA cutoff of 0.4 ng/mL. Consensus: In men with an undetectable PSA following radical prostatectomy (and good urinary continence), who subsequently develop a PSA recurrence, would you recommend SRT to the prostate bed-only? (yes: 46.4%, no: 53.6%, no response: 0%). The expert committee recommends to providing early SRT for PSA levels below 0.4 ng/mL.

8) Statement No. 8
In men with an undetectable PSA following radical prostatectomy (and good urinary continence), who subsequently develop a PSA recurrence, what imaging would you recommend?

Literature review: In a study of post-RP patients by Natarajan et al., the detection rates for 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) at various PSA levels were 23%, 50%, and 82% for PSA <1, 1–2, and >2 ng/mL, respectively, with an overall detection rate of 56%. About 50% of the patients with nodal metastases identified in 68Ga-PSMA PET/CT in the post-RP group were negative on a CT scan by size criteria. Thus, early identification of relapse using PSMA PET may offer the option of further targeted therapy with curative intent. In another Indian study, in the post-RP cohort, the detection rate of 68Ga-PSMA PET/CT was 39.3% for PSA 0.2 to <0.5 ng/mL, 47.3% for PSA 0.5 to <1 ng/mL, 68.4% for PSA 1 to <2 ng/mL, and 93.1% for PSA ≥2 ng/mL. Only one study compared 68Ga-PSMA PET/CT with whole-body magnetic resonance imaging (MRI) in patients with BCR of PCa following RP. 68Ga-PSMA PET/CT detected 100% of the lesion in 71.4% of patients, while whole-body MRI detected 23.2% lesion in 39.3% of patients.

Consensus: In men with an undetectable PSA following radical prostatectomy (and good urinary continence), who subsequently develop a PSA recurrence, what imaging would you recommend? (MRI: 7.1%, PSMA PET: 92.9%, no response: 0%).

9) Statement No. 9
Is there a PSA value above which you would consider offering SRT?

Literature review: It is estimated that about 30% of patients undergoing RP develop an increase in PSA after radical surgery. Taguchi et al. studied pT2-3N0M0 PCa men who underwent SRT for post-RP BCR at 3 timings. During follow-up (median, 70 months), 20%, 23%, and 44% of patients failed biochemically in the ultra-early SRT (PSA values ≥0.2 ng/mL), early SRT (before PSA reached 0.5 ng/mL) and delayed SRT (after PSA reached 0.5 ng/mL) groups respectively. No survival benefit of ultra-early SRT compared with early SRT was observed, whereas delayed SRT was associated with worse prognosis. The results support use of SRT after 2 consecutive PSA values ≥0.2 ng/mL and before reaching 0.5 ng/mL. A 2014 meta-analysis evaluated 10 retrospective studies (Table 4) looking at BRFs based on early- or late-SRT. They found that the 5-year BRFs was 71.1% after early SRT (PSA <0.5 ng/mL).

Consensus: Is there a PSA value above which you would consider offering SRT? (0.2: 60.71%, 0.4: 28.57%, any rise: 7.1%, no response: 3.5%). The expert committee in the CBM was of the opinion that the statement should have a strong recommendation for the PSA value of 0.2 ng/mL.
Table 4. Oncologic outcomes\textsuperscript{27}

| Study          | No. of patients | Nodal involvement | PSA pre-RT (ng/mL), (range) | Follow-up (range) | Fraction BRFS at specific time points |
|----------------|-----------------|-------------------|----------------------------|-------------------|--------------------------------------|
| Bernard et al. | 69              | pN0               | 0.32 (0.1-0.49)            | 8 yr (0.6-15 yr)  | 5 yr: 79.8%                           |
| Liauw et al.   | 34              | pN0               | 0.27 (0.05-0.5)            | 72.4 mo (5.2-136.3 mo) | 5 yr: 71%                            |
| Terai et al.   | 21 of 37        | N0                | <0.15                      | 31.9 mo (34.3-69.8 mo) | 5 yr: 80%                            |
| Briganti et al.| 390             | pN0               | <0.5, <0.3                 | 40.6 mo           | 2 yr: 92.8%, 5 yr: 81.8%              |
| Stephenson et al. | 181       | pN0               | 0.4 (0.3-0.4)              | 33 mo (15-56 mo)  | 6 yr: 48%, 5 yr: 61%, 3 yr: 69%       |
| Ost et al.     | 48              | pN0/cN0           | 0.3 (0.1-0.5)              | 53 mo (18-132 mo) | 5 yr: 77.1%                           |
| Goenka et al.  | 143             | pN0               | <0.5                       | 60 mo (4-221 mo)  | 5 yr: 48%                            |

PSA: prostate-specific antigen, RT: radiation therapy, BRFS: biochemical recurrence-free survival.

10) Statement No. 10
Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, also be offered 6 cycles of docetaxel chemotherapy (CT) up front?

Literature review: In RTOG 0521 trial, at a median follow-up of 5.7 years, 4-year OS was 89% for the control arm versus 93% with the addition of docetaxel (p=0.034; HR, 0.69). There were 59 deaths in the ADT+RT arm and 43 in the ADT+RT+CT arm, with fewer deaths resulting from PCa in the ADT+RT+CT arm versus the ADT+RT arm (23 versus 16 deaths, respectively). The 6-year rate of distant metastasis was 14% for ADT+RT and 9.1% for ADT+RT+CT (HR, 0.60; 95% CI, 0.37-0.99; 2-sided p=0.044). The 6-year disease-free survival rate was 55% for ADT+RT and 65% for ADT+RT+CT (HR, 0.76; 95% CI, 0.58-0.99; 2-sided p=0.043). Of all patients who received CT in the RTOG 0521 trial, 65% suffered from ≥ grade 3 adverse effects (AEs) definitely or probably related to treatment.\textsuperscript{28} STAMPEDE trial also evaluated addition of docetaxel to ADT and RT (Table 5, Fig. 2).\textsuperscript{29}

Consensus: Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, also be offered 6 cycles of docetaxel chemotherapy up front? (yes: 28.6%, no: 71.4%, no response: 0%)

11) Statement No. 11
Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, also be offered 2 years of abiraterone acetate+prednisone (AAP)?

Literature review: In a study by Sydes et al.,\textsuperscript{30} 189 of 566 patients (14%) were allocated to standard of care (SOC)+docetaxel+prednisone (DocP), and 377 (28%) to SOC+abiraterone acetate+prednisone (AAP). HR of <1 favours SOC+AAP and HR >1 favours SOC+DocP. With a median follow-up of 4 years, 149 deaths were reported. The HR for OS was 1.16 (95% CI, 0.82-1.65); for failure-free survival, HR was 0.51 (95% CI, 0.39-0.67); for PFS HR was 0.65 (95% CI, 0.48-0.88); for MFS HR was 0.77 (95% CI, 0.57-1.03); for PCS HR was 1.02 (95% CI, 0.70-1.49); and for systematic skeletal events HR was 0.83 (95% CI, 0.55-1.25). In the safety population, the proportion reporting grades 3, 4, and 5 AEs was 36%, 13%, and 1% in the SOC+DocP arm, and 40%, 7%, and 1% in the SOC+AAB arm respectively; the prevalence rate was 11% at 1 and 2 years in both arms.\textsuperscript{30}

Consensus: Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, also be offered 2 years of abiraterone+prednisolone? (yes: 28.5%, no: 67.8%, no response: 3.5%).

12) Statement No. 12
Should all patients with high-risk (D’Amico) cN0 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes?

Literature review: Andric et al.,\textsuperscript{31} analysed definitive external-beam radiotherapy (ExRT) arm, after risk adjustment according to ≥2-year ADT use. Not receiving pelvic lymphatic irradiation increased the risk of biochemical failure (p=0.048) than patients who received. Another retrospective study reported outcomes of patients with high-risk PCa who either underwent ExRT in combination with 9 months of ADT or underwent RP with pelvic lymph node sampling. The 3-year BRFS favored ExRT targeted to prostate and seminal vesicle without pelvic lymph node involvement (86.8% vs. 69.8%, p=0.001).\textsuperscript{32}
Table 5. Characteristics of the included trials

| Trial (yr)   | Stage                        | Sample size | Median age (yr) | Median PSA (ng/mL) | T stage ≥3 (%) | Gleason score ≥8 (%) | Treatments | Median follow-up (mo) | Outcomes          |
|--------------|------------------------------|-------------|----------------|-------------------|----------------|----------------------|-------------|-----------------------|--------------------|
| STAMPE DE 2016 | Metastatic, high-risk       | 690         | 65             | 65                | 81.8           | 71                   | ADT+RT+CT   | 43 months             | OS, FFS, AEs       |
| RTOG 0521 2015 | High-risk                   | 562         | 66             | 15                | 27             | 84                   | ADT+RT+CT   | 66 months             | DFS, OS, AEs       |

ADT: androgen deprivation therapy, RT: radiation therapy, CT: chemotherapy, OS: overall survival, FFS: failure-free survival, AEs: adverse events, DFS: disease-free survival.

Fig. 2. Effects of additional chemotherapy on overall survival. HR: hazard ratio, SE: standard error, CI: confidence interval.

Consensus: Should all patients with high-risk (D’Amico) cN0 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes? (yes: 75%, no: 21.4%, no response: 3.5%)

13) Statement No. 13

Should all patients with cN1 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes?

Literature review: In a study conducted by Mallick et al. in India, men with radiologically involved pelvic lymph nodes without distant metastases were treated with long-term ADT and hypo-fractionated RT to pelvic lymph nodes, prostate, and bilateral seminal vesicles. The 4-year biochemical control rate was 77.5% and the OS rate was 91%. Patients with residual enlarged nodes after 36 months of ADT and who required nodal boost had poorer biochemical control rates (4-year rate: 53.9% vs. 93.1%, p < 0.001). Incidences of late grade 2+ gastrointestinal and genitourinary toxicities were 13.1% and 18%, respectively, with no grade 4 toxicities. Bryant et al. studied the survival benefit of combined RT and ADT compared with ADT alone in node-positive PCa patients. The 5-year unadjusted cumulative mortality estimates favoured the ADT-RT group (all-cause mortality, 24% for ADT-RT vs. 42% for ADT; PCa-specific mortality, 18% vs. 27%; noncancer mortality, 6% vs. 21%).

Consensus: Should all patients with cN1 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes? (yes: 85.7%, no: 10.7%, no response: 3.5%)

14) Statement No. 14

In men with nonmetastatic PCa and a rising PSA post radical therapy (surgery or radiotherapy) is there a role for ADT monotherapy?

Literature review: Duchesne et al. analysed immediate ADT versus delayed ADT for men with PSA relapse following RP or RT. Timing of delayed ADT was ≥2 years after BCR. Immediate ADT significantly improved OS compared with delayed ADT (5-year OS was 91.2% vs. 86.4%; p = 0.047). Overall, 36% of patients had AEs in the study which required hospitalization. In another study, patients with BCR were managed by ADT, including 60% of
**Summary of Recommendations on Locally Advanced PCa**

| S/N | Statement                                                                 | Strength of recommendation |
|-----|---------------------------------------------------------------------------|----------------------------|
| 1   | Should radical prostatectomy be considered as a management option for men  | Strong                     |
|     | with high-risk (D’Amico) cN1 cM0 PCa?                                    |                            |
|     | Yes: 82.1%, no: 10.7%, no response: 7.1%                                 |                            |
|     | Radical prostatectomy should be considered as a management option for men |                            |
|     | with high-risk (D’Amico) cN1 cM0 PCa.                                    |                            |
| 2   | Should Neo-adjuvant ADT be considered for men with high-risk (D’Amico)    | Weak                      |
|     | cN1 cM0 PCa prior to radical prostatectomy?                               |                            |
|     | Yes: 39.2%, no: 53.5%, no response: 7.1%                                 |                            |
|     | Neo-adjuvant ADT should not be considered for men with high-risk (D’Amico) |                            |
|     | cN1 cM0 PCa prior to radical prostatectomy.                               |                            |
| 3   | In men with a detectable PSA post-prostatectomy, and pN1 cM0 disease,    | Moderate                  |
|     | would you offer adjuvant docetaxel chemotherapy if fit enough?           |                            |
|     | Yes: 21.4%, no: 67.8%, no response: 0%                                   |                            |
|     | In men with a detectable PSA post-prostatectomy, and pN1 cM0 disease,    |                            |
|     | we should not offer adjuvant docetaxel chemotherapy.                     |                            |
| 4   | In men with an undetectable PSA following radical prostatectomy (and good | Strong                    |
|     | urinary continence), would you recommend ART to the prostate bed-only?   |                            |
|     | Yes: 7.1%, no: 89.2%, no response: 3.5%                                  |                            |
|     | In men with an undetectable PSA following radical prostatectomy (and good|                            |
|     | urinary continence), we should not recommend ART to the prostate bed-only.|                            |
| 5   | In men with an undetectable PSA following radical prostatectomy (and good | Strong                    |
|     | urinary continence), would you recommend adjuvant ADT?                   |                            |
|     | Yes: 3.5%, no: 85.7%, no response: 10.7%                                 |                            |
|     | In men with an undetectable PSA following radical prostatectomy (and good|                            |
|     | urinary continence), we should not recommend adjuvant ADT.               |                            |
| 6   | In men with a detectable PSA immediately postsurgery, but no risk factors| Weak                      |
|     | for persistent pelvic disease, would you offer ART?                      |                            |
|     | Yes: 50%, no: 35.7%, no response: 14.2%                                  |                            |
|     | In men with a detectable PSA immediately postsurgery, but no risk factors|                            |
|     | for persistent pelvic disease, we should offer ART.                     |                            |
| 7   | In men with an undetectable PSA following radical prostatectomy (and good | Weak                      |
|     | urinary continence), who subsequently develop a PSA recurrence, would you |                            |
|     | recommend SRT to the prostate bed-only?                                  |                            |
|     | Yes: 46.4%, no: 53.6%, no response: 0%                                   |                            |
|     | In men with an undetectable PSA following radical prostatectomy (and good|                            |
|     | urinary continence), who subsequently develop a PSA recurrence, we should|                            |
|     | not recommend SRT to the prostate bed-only.                              |                            |
| 8   | In men with an undetectable PSA following radical prostatectomy (and good | Strong                    |
|     | urinary continence), who subsequently develop a PSA recurrence, what imaging would you recommend? |      |
|     | MRI: 7.1%, PSMA PET: 92.9%, no response: 0%                              |                            |
|     | PSMA PET should be performed in a man with high-risk (D’Amico) cN0 cM0 PCa |                            |
|     | prior to receiving radical Hormone-Radiotherapy                          |                            |
| 9   | Is there a PSA value above which you would consider offering SRT?        | Moderate                  |
|     | 0.2: 60.71%, 0.4: 28.57%, any rise: 7.1, no response: 3.5%              |                            |
|     | PSA value above 0.2 should be considered for offering SRT.              |                            |
| 10  | Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT,  | Moderate                  |
|     | also be offered 6 cycles of docetaxel chemotherapy upfront?              |                            |
|     | Yes: 28.6%, no: 71.4%, no response: 0%                                   |                            |
|     | Patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, should |                            |
|     | not be offered 6 cycles of docetaxel chemotherapy upfront.              |                            |
Summary of Recommendations on Locally Advanced PCa

| S/N | Statement                                                                 | Strength of recommendation |
|-----|---------------------------------------------------------------------------|-----------------------------|
| 11  | Should patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, also be offered 2 years of abiraterone+prednisolone? | Moderate                    |
|     | Yes: 28.5%, no: 67.8%, no response: 3.5%                                  |                             |
|     | Patients with high-risk PCa (STAMPEDE criteria) receiving ADT+RT, should not be offered 2 years of abiraterone+prednisolone. |                             |
| 12  | Should all patients with high-risk (D’Amico) cN0 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes? | Moderate                    |
|     | Yes: 75%, no: 21.4%, no response: 3.5%                                     |                             |
|     | All Patients with high-risk (D’Amico) cN0 cM0 PCa should receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes. |                             |
| 13  | Should all patients with cN1 cM0 PCa receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes? | Strong                      |
|     | Yes: 85.7%, no: 10.7%, no response: 3.5%                                   |                             |
|     | All patients with cN1 cM0 PCa should receive ADT+RT to the prostate, seminal vesicles, and pelvic lymph nodes. |                             |
| 14  | In men with nonmetastatic PCa and a rising PSA post radical therapy (surgery or radiotherapy) is there a role for ADT monotherapy? | Strong                      |
|     | Yes: 82.1%, no: 17.9%, no response: 0%                                       |                             |
|     | In men with nonmetastatic PCa and a rising PSA post radical therapy (surgery or radiotherapy), there is a role for ADT monotherapy |                             |

Consensus: In men with nonmetastatic PCa and a rising PSA post radical therapy (surgery or radiotherapy), there is a role for ADT monotherapy (yes: 82.1%, no: 17.9%, no response: 0%).

2. Metastatic PCa

1) Statement No. 1

What is the optimum first-line androgen deprivation strategy for men with hormone-sensitive metastatic PCa in the Indian context?

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).

2) Statement No. 2

What additional systemic therapy should be considered for men with hormone-sensitive metastatic PCa?

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).

Consensus: What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? (surgical castration: 67.8%, luteinizing hormone-releasing hormone [LHRH] analogues: 14.2%, LHRH antagonist: 7.1%, antiandrogen: 0%, no response: 10.7%).
ADT alone (Table 6).\(^{41}\) LATITUDE trial randomized patients to receive ADT+abiraterone (1,000 mg daily)+prednisone (5 mg daily) or ADT+dual placebos. In the treatment arm, the risk of death reduced by 38% compared to the control arm (HR, 0.62; 95% CI, 0.51–0.76; \(p<0.0001\)), while risk reduction in terms of progression was 53% compared to placebo (HR, 0.47; 95% CI, 0.39–0.55; \(p<0.0001\)). The median OS was significantly longer in the treatment arm than in the control arm (not reached vs. 34.7 months) and median length of radiographic PFS was 33.0 months in the treatment arm versus 14.8 months in the control arm. Docetaxel was the most common post-progression treatment in both the groups.\(^{42}\)

Consensus: What additional systemic therapy should be considered for men with hormone-sensitive metastatic PCa? (6 cycles docetaxel +/- prednisolone: 32.1%, abiraterone+prednisolone: 35.7%, none: 28.5%, no response: 3.5%). The expert committee recommends systemic therapy of abiraterone or docetaxel with moderate recommendation.

3) Statement No. 3
Is prostate radiotherapy indicated in low-volume hormone-sensitive PCa?

Literature review: In a meta-analysis, authors identified 2 completed (HORRAD and STAMPEDE) eligible trials. Pooled results of these trials showed no overall improvement in survival (HR, 0.92; 95% CI, 0.81–1.04; \(p=0.195\)) or PFS (HR, 0.94; 95% CI, 0.84–1.05; \(p=0.238\)) with prostate RT. There was an overall improvement in biochemical progression (HR, 0.74; 95% CI, 0.67–0.82; \(p=0.94\times10\) raise to -8) and failure-free survival (HR, 0.76; 95% CI, 0.69–0.84; \(p=0.64\times10\) raise to -7), equivalent to 10% benefit at 3 years. There was a 7% improvement in 3-year survival in men with fewer than 5 bone metastases. The effect of prostate RT varied with metastatic burden. This study concluded that prostate RT should be considered for men with metastatic hormone-sensitive PCa with a low metastatic burden.\(^{43}\)

Consensus: Is prostate radiotherapy indicated in low-volume castration-sensitive PCa? (yes: 35.7%, no: 60.71%, no response: 3.5%)

4) Statement No. 4
What is the optimal first-line management option for men with Castration-resistant metastatic PCa in the Indian context?

Literature review: In a study by Shridhar et al.,\(^{44}\) metastatic PCa patients with progressive disease following ADT

### Table 6. Outcome analysis\(^{41}\)

| Outcome measure | ADT+ docetaxel | ADT+ abiraterone | ADT alone | Total |
|------------------|----------------|------------------|-----------|-------|
| Sample size      | 28             | 18               | 30        | 76    |
| Median follow-up (mo) | 19             | 8                | 21        | 18    |
| PSA decline >90% | 24 (86%)       | 17 (94%)         | 22 (73%)  | 63 (83%) |
| Serological complete response, i.e., PSA<0.2 ng/mL | 10 (36%) | 9 (50%) | 5 (17%) | 24 (32%) |
| Progresses to CRPC | 11 (39%) | 2 (11%) | 18 (60%) | 31 (41%) |

ADT: androgen deprivation therapy, PSA: prostate-specific antigen, CRPC: castrate-resistant prostate cancer.

### Table 7. Definition of oligometastatic disease used in representative studies of oligometastatic prostate cancer\(^{48}\)

| Study            | Type | Sample size (n) | Location of metastases | Cutoff for oligometastases (n) |
|------------------|------|----------------|------------------------|--------------------------------|
| Jereczek-Fossa et al.\(^{59}\) | P; SA | 69 | LN | \(\leq 1\) |
| Berkovic et al.\(^{60}\) | P; SA | 24 | Bone or LN | \(\leq 3\) |
| Singh et al.\(^{61}\) | R; NA | 369 | Any | \(\leq 5\) |
| Decaestecker et al.\(^{62}\) | P; SA | 50 | Bone or LN | \(\leq 3\) |
| Ost et al.\(^{63}\) | P; SA | 119 | Any | \(\leq 3\) |
| Ost et al.\(^{64}\) | P; RA | 62 | Any | \(\leq 3\) |
| Schick et al.\(^{65}\) | P; SA | 50 | NR | \(\leq 4\) |

NR: not reported, P: prospective, R: retrospective, RA: randomized, SA: single arm, LN: lymph node.
were given docetaxel-based chemotherapy (78.82%) and the remaining 21.18% patients did not receive further treatment. The OS was 32.61±6.09 months in patients receiving docetaxel-based chemotherapy as compared to 12.83±2.40 months in patients with no treatment. In another retrospective Indian study, the OS rate in patients treated with abiraterone was 3–6 months for 45% patients. Thirty-two percent patients had more than 6 months of survival rate without progression, and 23% had progression after starting the drug. In an Enzalutamide trial (PREVAIL), after 12 months of follow-up, radiographic PFS data for enzalutamide versus placebo was evaluated (median not reached vs. 3.9 months; 81% risk reduction; p < 0.001). In an earlier interim analysis, median OS had been estimated as 32.4 months for enzalutamide versus 30.2 months for placebo. Consensus: What is the optimal first-line management option for men with Castration-resistant metastatic PCa in the Indian context? (abiraterone+pred: 53.5%, enzalutamide: 0%, abiraterone+pred OR enzalutamide: 14.2%, docetaxel: 28.5%, no response: 3.5%).

5) Statement No. 5
What is the definition of oligometastatic PCa?

Literature review: The biological definition of oligometastatic PCa is open to interpretation, no formal cutoff for “oligo” has been defined in the literature. Clinical trials have generally used either 3 or 5 metastatic sites on conventional imaging as the cutoff to define oligometastatic disease (Table 7).

Consensus: What is the definition of oligometastatic PCa? (4 or less skeletal: 89.2%, lymph nodal only: 0%, visceral only: 3.5%, no response: 7.1%)

6) Statement No. 6
What is the optimum management for men with oligometastatic PCa?

Literature review: The randomized CHAARTED trial first showed an OS benefit with the addition of docetaxel to ADT (median OS 57.6 months with docetaxel vs. 44.0 months with ADT alone, p < 0.001). A predefined subgroup analysis of long-term data concluded docetaxel to have an OS advantage in patients with high-volume (presence of visceral metastases and/or > 4 bony metastases with at least 1 bony metastasis outside the spine or pelvis) but not in patients with low-volume disease. The survival benefit of abiraterone in hormone-sensitive metastatic PCa was observed in 2 trials, STAMPEDE and LATITUDE. Grade 3 toxicity was experienced by 33% of patients in the ADT arm, and 47% of patients in the ADT+abiraterone arm in the STAMPEDE trial; with even higher rates of grade 3 toxicity were observed in the LATITUDE trial (48% in the ADT arm and 63% in the ADT+abiraterone arm).

Consensus: What is the optimum management for men with oligometastatic PCa? (ADT only: 35.7%, ADT+abiraterone: 39.2%, ADT+chemo: 17.8%, ADT+enzalutamide: 0%, no response: 7.1%). The expert committee suggested that with evolution, surgery or local RT may be considered along with ADT.

7) Statement No. 7
What imaging should men with a rising PSA and no evidence of metastatic disease on conventional imaging undergo?

Literature review: An Indian study included men, who underwent previous RP or RT. In the post-RP cohort, the detection rate of 68Ga-PSMA PET/CT was 39.3% for PSA 0.2 to <0.5 ng/mL, 47.3% for PSA 0.5 to <1 ng/mL, 68.4% for PSA 1 to <2 ng/mL and 93.1% for PSA ≥2 ng/mL. In this group, local recurrence was identified in 28.73% and lymph nodal metastases in 65.1% of men. In the post-RT group, the detection rate was 88.8% for PSA 2 to <4 ng/mL and 100 % for PSA ≥4 ng/mL. Local recurrence after RT was present in 79.5% of the group and 63.6% had lymph nodal metastases. In the study of Natarajan et al., PSMA PET/CT revealed nodal metastases in 54% patients while CT scan showed pathological nodes only in 28% patients. In a study by Sawick et al., 68Ga-PSMA PET/CT detected 56 of 56 lesions (100%) in 20 patients (71.4%), while whole-body MRI detected 13 lesions (23.2%) in 11 patients (39.3%). 68Ga-PSMA PET/CT out-performed whole-body MRI in the detection of BCR in PCa patients after RP in this study.

Consensus: What imaging should men with a rising PSA and no evidence of metastatic disease on conventional imaging undergo? (PSMA PET/CT: 75%, whole-body MRI: 21.4%, no response: 3.5%). The expert committee was of the opinion that the statement should have strong recommendation.
### Summary of Recommendations on Metastatic PCa

| S/N | Statement                                                                 | Strength of recommendation |
|-----|---------------------------------------------------------------------------|-----------------------------|
| 1   | What is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context? Castration: 67.8% LHRH analogues: 14.2% LHRH antagonist: 7.1% antiandrogen: 0% no response: 10.7% Castration is the optimum first-line androgen deprivation strategy for men with castration-sensitive metastatic PCa in the Indian context. | Moderate                     |
| 2   | What additional systemic therapy should be considered for men with Castration-sensitive metastatic PCa? 6 cycles docetaxel +/- prednisolone: 32.1%, abiraterone+prednisolone: 35.7%, none: 28.5%, no response: 3.5% | Weak                         |
| 3   | Is prostate radiotherapy indicated in low-volume castration-sensitive PCa? Yes: 35.7%, no: 60.7%, no response: 3.5% Prostate radiotherapy is not indicated in low-volume castration-sensitive PCa. | Moderate                     |
| 4   | What is the optimal first-line management option for men with Castration-resistant metastatic PCa in the Indian context? Abiraterone+pred: 53.5%, enzalutamide: 0%, abiraterone+pred OR enzalutamide: 14.2%, docetaxel: 28.5%, no response: 3.5% Abiraterone+pred is the optimal first-line management option for men with Castration-resistant metastatic PCa in the Indian context. | Weak                         |
| 5   | What is the definition of oligometastatic PCa? 4 or less skeletal: 89.2%, lymph nodal only: 0%, visceral only: 3.5%, no response: 7.1% 4 or less skeletal involvement should be the definition of oligometastatic PCa. | Strong                       |
| 6   | What is the optimum management for men with oligometastatic PCa? ADT only: 35.7%, ADT+abiraterone: 39.2%, ADT+chemo: 17.8%, ADT+enzalutamide: 0%, no response: 7.1% ADT+abiraterone is the optimum management for men with oligometastatic PCa. | Weak                         |
| 7   | What imaging should men with a rising PSA and no evidence of metastatic disease on conventional imaging undergo? PSMA PET/CT: 75%, whole-body MRI: 21.4%, no response: 3.5% Men with a rising PSA and no evidence of metastatic disease on conventional imaging should undergo PSMA PET/CT scan. | Moderate                     |

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