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SPECIAL ARTICLE

Pan-Asian adapted ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with prostate cancer

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The most recent version of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for the diagnosis, treatment and follow-up of prostate cancer was published in 2020. It was therefore decided, by both the ESMO and the Singapore Society of Oncology (SSO), to convene a special, virtual guidelines meeting in November 2021 to adapt the ESMO 2020 guidelines to take into account the differences associated with the treatment of prostate cancer in Asia.

These guidelines represent the consensus opinions reached by experts in the treatment of patients with prostate cancer representing the oncological societies of China (CSCO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS), Singapore (SSO) and Taiwan (TOS). The voting was based on scientific evidence and was independent of the current treatment practices and drug access restrictions in the different Asian countries. The latter were discussed when appropriate. The aim is to provide guidance for the optimisation and harmonisation of the management of patients with prostate cancer across the different regions of Asia.

Key words: ESMO, guidelines, Pan-Asian, prostate cancer, treatment

INTRODUCTION

In 2020 an estimated 19.3 million new cases of cancer were diagnosed and almost 10 million cancer-related deaths recorded, worldwide.[1] Of these, prostate cancer accounted for 7.3% (1 414 259) of new cases and 3.8% (375 304) of cancer deaths, representing 14.5% of new cases of cancer and 6.8% of cancer deaths in men worldwide. Prostate cancer is the second most frequently diagnosed cancer in men after lung cancer and the fifth most common cause of cancer death worldwide.[1] Asia historically has been considered to have a low incidence of prostate cancer, but the incidence of and mortality from prostate cancer is increasing rapidly.[2] However, the age-standardised rates for prostate cancer incidence in Western Asia, South-Eastern Asia and South-Central Asia were 28.6, 13.5 and 6.3 per 100 000 men, respectively, in 2020, compared with 73 per 100 000 for North America.[1] Both the incidence as well as the mortality-to-incidence ratio are associated with the human development index.[1] The lower incidence of prostate cancer in Asian

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men compared with Western men may also be due to less prostate-specific antigen (PSA) screening. Studies in both Japan[3] and Taiwan[4] have shown the incidence of prostate cancer to increase with PSA testing. In the case of the Japanese study,[3] PSA screening was associated with a reduction in the proportion of advanced prostate cancers detected. However, another reason for the difference in the incidence of prostate cancer may be due to the fact that the genomic features of prostate cancer differ between Asian and Western populations and also vary between different regions and countries in Asia.[2] A recent study has shown the Han Chinese, Korean and Japanese populations to have distinct genetic profiles.[5] Asian studies have also shown men with diabetes to be at a higher risk of developing prostate cancer than their non-diabetic counterparts.[6-9] Thus, differences in genetics, environment, lifestyle, diet and culture are all likely to influence the management of prostate cancer in Asia, as demonstrated by a comparison of the epidemiology, incidence, mortality and risk factors for prostate cancer in Eastern Asia, South-Eastern Asia and South-Central Asia with those for Western countries.[10]

Guidelines and recommendations for the treatment and management of patients with prostate/advanced prostate cancer in Asia have been published for the Asia Pacific region,[11] China,[12] Japan,[13,14] India,[15,16] Korea,[17] Singapore[18] and Taiwan[19] and are important for the standardisation of both diagnostic and treatment approaches, with the aim of optimising clinical outcomes for what is an increasing health care problem in Asia. The European Society for Medical Oncology (ESMO) guidelines for the diagnosis, treatment and follow-up of patients with prostate cancer were published in 2020,[20] and a decision was taken by ESMO and the Singapore Society of Oncology (SSO) that these guidelines should be adapted for patients of Asian ethnicity.

Consequently, representatives of SSO, ESMO, the Chinese Society of Clinical Oncology (CSCO), the Indian Society of Medical and Paediatric Oncology (ISMPO), the Japanese Society of Medical Oncology (JSMO), the Korean Society for Medical Oncology (KSMO), the Malaysian Oncological Society (MOS) and the Taiwan Oncology Society (TOS) convened for a virtual, 'face-to-face', working meeting on 20 November 2021, hosted by SSO, to adapt the recent ESMO Clinical Practice Guidelines for patients with prostate cancer. This manuscript summarises the Pan-Asian adapted guidelines, developed before and finalised during the meeting, accompanied by the level of evidence (LoE), grade of recommendation (GoR) and percentage consensus reached for each recommendation. The main focus was on the scientific acceptability of each recommendation, independent of the availability, reimbursement and practical challenges that may be associated with it, in certain Asian countries.

METHODOLOGY

This Pan-Asian adaptation of the current ESMO Clinical Practice Guidelines for prostate cancer,[20] together with any relevant data updates from the ESMO 2021 Annual Meeting, was prepared in accordance with the principles of ESMO standard operating procedures (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology) and was an SSO–ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and TOS.

An international panel of experts was selected from the SSO ($n = 6$), the ESMO ($n = 5$) and two experts from each of the oncological societies of China (CSCO), India (ISMPO), Japan (JSMO), Korea (KSMO), Malaysia (MOS) and Taiwan (TOS). Only two of the six expert members from the SSO (AW and MLKC) were allowed to vote on the recommendations together with the experts from each of the six other Asian oncology societies ($n = 14$). Of the 14 voting experts, 4 were urologists [YZ (CSCO), QZ (CSCO), YSP (TOS) and HK (JSMO)] and the remainder oncologists.

A modified Delphi process was used to review, accept or adapt each of the individual recommendations in the latest ESMO Clinical Practice Guidelines.[20] The 14 Asian experts were asked to vote YES or NO (one vote per society) on the 'acceptability' (agreement with the scientific content of the recommendation) and 'applicability' (availability, reimbursement and practical challenges) of each of the ESMO recommendations in a pre-meeting survey (see Supplementary Methodology, available at https://doi.org/10.1016/j.esmoop.2022.100518). For recommendations, where a consensus was not reached, the Asian experts were invited to modify the wording of the recommendation(s) at the 'face-to-face' virtual meeting using rounds of voting in order to determine the definitive acceptance or rejection of an adapted recommendation and discuss the applicability challenges. The 'Infectious Diseases Society of America-United States Public Health Service Grading System' (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100518)[21] was used to define the LoE and strength (grade) of each recommendation. Any modifications to the initial recommendations were highlighted in bold text in a summary table of the final Asian recommendations and in the main text, if and as applicable. A consensus was considered to have been achieved when $\geq$80% of experts voted that a recommendation was acceptable.

RESULTS

In the initial pre-meeting survey, the 14 Asian experts reported on the 'acceptability' and 'applicability' of the 50 recommendations for the diagnosis, treatment and follow-up of patients with prostate cancer based on the most recent ESMO Clinical Practice Guidelines[20] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100518). These recommendations were made in the 14 categories listed below and after discussion at the virtual meeting and during manuscript review were augmented by four additional recommendations one under management of local/locoregional disease, one under neoadjuvant and adjuvant hormone treatment, one under metastatic castration-resistant prostate cancer (mCRPC) and the other under precision medicine.

1. Screening and early detection (recommendations 1a-c)
2. Diagnosis and pathology (recommendations 2a-d)

3. Staging and risk assessment (recommendations 3a-c)
4. Management of local/locoregional disease (recommendations 4a-h)
5. Neoadjuvant and adjuvant hormone treatment (recommendations 5a-c)
6. Neoadjuvant docetaxel for M0 disease (recommendation 6a)
7. Post-operative RT (recommendations 7a-e)
8. Treatment of relapse after radical local treatment (recommendations 8a-d)
9. Hormone-naïve metastatic prostate cancer (recommendations 9a-d)
10. Non-metastatic castration-resistant prostate cancer (recommendation 10a)
11. Metastatic castration-resistant prostate cancer (recommendations 11a-g)
12. Precision medicine (recommendations 12a-e)
13. Palliative care (recommendations 13a-d)
14. Follow-up and long-term implications (recommendations 14a and b)

A lack of agreement (no consensus) in the pre-meeting survey was established for 'recommendations 2b and c, 6a, 12a and 13c', in terms of 'acceptability', leading to their discussion during the 'face-to-face' meeting. In addition, no consensus was established for 'recommendations 1b, 2a-d, 6a, 7d, 8a, 10a, 11a, 12a-d, 13c and 14b' in terms of 'applicability' (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100518). Of the latter, three recommendations ('recommendations 7d, 12b and 14b') were discussed due to the fact that comments relating to scientific acceptability were made under applicability. A further three recommendations ('recommendations 4f, 5b and 9a') needed to be updated and two new recommendations ('recommendations 11g and 12e') added due to the emergence of new data.

For the purposes of these guidelines, the following general definitions apply:

Early prostate cancer—localised prostate cancer without evidence of lymph node involvement or distant metastases.

Locally advanced prostate cancer—≥T3b prostate cancer with or without lymph node involvement within the pelvis.

Metastatic prostate cancer—prostate cancer with lymph node invasion beyond the pelvis and/or bone or visceral spread.

Castration-resistant prostate cancer—prostate cancer that no longer responds to androgen deprivation therapy (ADT) despite adequate castration evidenced by serum testosterone levels <0.50 ng/ml; typically, three consecutive rises in PSA >0.2 ng/ml.

The majority of prostate cancers are adenocarcinomas, and for the purposes of this guidelines manuscript, the term prostate cancer refers to adenocarcinomas, unless otherwise specified.

1. Screening and early detection—recommendations 1a-c

In Western countries, population-based screening of middle-aged men using PSA testing has increased early diagnosis and decreased prostate cancer mortality.[22-24] Although a meta-analysis of data from five randomised controlled trials (RCTs) showed PSA testing not to decrease prostate cancer mortality,[25] the European Randomised Study of Screening for Prostate Cancer (ERSPC) reported a significant 27% reduction in prostate cancer-specific mortality in men aged between 55 and 69 years, after 13 years of follow-up.[22] As a consequence, the American (AUA) and European (EAU) Urological Associations state, respectively, that well-informed men aged 55-69 years cannot be denied PSA testing[26] and that PSA testing should be offered to well-informed men aged >50 years with a life expectancy of at least 10-15 years.[27] The Japanese Urological Association (JUA) recommends PSA-based screening.[28] However, in Asia, the level of PSA testing is low compared with Western countries. Despite this, the Pan-Asian panel of experts agreed with and accepted completely (**100% consensus**) the ESMO recommendations on Screening and early detection, 'recommendations 1a-c' below and Table 1. However, in terms of applicability, 'recommendation 1b' is not yet implemented in Taiwan (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100518).

1a. Systematic population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of overdiagnosis and overtreatment and is not recommended [I, C].

1b. Early PSA testing (baseline PSA followed by risk adapted follow-up) can be offered to well-informed men >50 years of age, in men >45 years of age and a family history of prostate cancer, and black-skinned men of African origin >45 years of age, with a life expectancy >10 years [III, B].

1c. Testing for prostate cancer in asymptomatic men should not be done in men with a life expectancy of <10 years [I, E].

2. Diagnosis and pathology—recommendations 2a-d

The risk of being diagnosed with and developing clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination.[29] Physicians are encouraged to consider these factors for risk calculations.

Until recently, transrectal (TR) ultrasound-guided prostate biopsy was the standard for detecting prostate cancer in patients with elevated PSA levels. However, several studies suggest that multi-parametric magnetic resonance imaging (mpMRI) should be carried out before biopsy,[30-32] including a systematic review and meta-analysis of mpMRI for the diagnosis of prostate cancer conducted in China,[33] which showed mpMRI to be a sensitive tool for the diagnosis and detection of prostate cancer. According to the ESMO guidelines,[20] when mpMRI is positive [i.e. Prostate Imaging—Reporting and Data System (PI-RADS) ≥3], a targeted biopsy, plus or minus systematic biopsies, should be carried out. When mpMRI is negative (i.e. PI-RADS ≤2), and clinical suspicion of prostate cancer is low, the biopsy can be omitted in well-informed patients. An algorithm for the diagnostic work-up and staging of prostate cancer, taken from the ESMO guidelines,[20] is presented in Figure 1.

Table 1. Summary of Asian recommendations

Recommendations	Acceptability consensus
Recommendation 1: Screening and early detection	
1a. Systematic population-based PSA screening of men for prostate cancer reduces prostate cancer mortality at the expense of overdiagnosis and overtreatment and is not recommended [I, C].	100%
1b. Early PSA testing (baseline PSA followed by risk adapted follow-up) can be offered to well-informed men >50 years of age, in men >45 years of age and a family history of prostate cancer and black-skinned men of African origin >45 years of age, with a life expectancy >10 years [III, B].	100%
1c. Testing for prostate cancer in asymptomatic men should not be done in men with a life expectancy of <10 years [I, E].	100%
Recommendation 2: Diagnosis and pathology	
2a. mpMRI should be performed before prostate biopsy [I, B].	100%
2b. mpMRI should be used to confirm the indication for a biopsy in men with elevated PSA, **where available [I, A].**	100%
2c. Transperineal **ultrasound-guided biopsies** are recommended**, over** transrectal biopsies **due to lower infection rates. [III, B].**	100%
2d. Each biopsy should be reported individually and evaluated using the ISUP consensus recommendations [II, B].	100%
Recommendation 3: Staging and risk assessment	
3a. Localised disease should be classified as low-, intermediate- or high-risk as a guide to prognosis and therapy [III, A].	100%
3b. Patients with intermediate-risk disease should be staged for metastases using MRI or CT of the abdomen and pelvis and bone scans [III, B].	100%
3c. Patients with high-risk disease should be staged for metastases using CT (of the chest, abdomen and pelvis) and bone scans [III, B].	100%
Recommendation 4: Management of local/locoregional disease	
4a. Watchful waiting with delayed ADT is an option for patients with localised or locally advanced disease who are not suitable for, or unwilling to have, radical treatment [I, A].	100%
4b. Active surveillance is recommended for patients with low-risk disease [II, A].	100%
4c. RP or RT (external beam or brachytherapy) are options for patients with low-risk disease **who are anxious about and/**not suitable for active surveillance [III, B].	100%
4d. RP or RT (external beam or brachytherapy) is recommended for patients with intermediate-risk disease [I, B].	100%
4e. Primary ADT alone is not recommended as standard initial treatment for non-metastatic disease [I, D].	100%
4f. External beam RT plus ADT is recommended for patients with high-risk or locally advanced prostate cancer [I, B].	100%
4g. **External beam RT plus ADT plus AAP (24 months) is recommended for patients with high-risk or locally advanced prostate cancer, as defined by the STAMPEDE trial criteria [I, B].**	100%
4h. RP plus pelvic lymphadenectomy is an option for selected patients with high-risk disease [III, B].	100%
Recommendation 5: Neoadjuvant and adjuvant hormone treatment	
5a. Patients receiving radical RT for intermediate-risk disease should be offered a short course of ADT for 4-6 months [I, A].	100%
5b. Patients receiving radical RT for high-risk disease should have a long course of ADT (18-36 months) [I, A]**.**	100%
5c. **Patients receiving radical RT for high-risk disease who fit the STAMPEDE trial criteria should have a long course of ADT (18-36 months) plus AAP (24 months) [I, A].**	100%
Recommendation 6: Neoadjuvant docetaxel for M0 disease	
6a. Neoadjuvant docetaxel chemotherapy **only impacts relapse-free survival and should be limited as a potential option for fit patients with high-risk disease, based on shared decision making [I, C].**	100%
Recommendation 7: Post-operative RT	
7a. Following RP, patients should have their serum PSA level monitored, with salvage RT recommended in the event of PSA failure [III, B].	100%
7b. Salvage RT should start early (e.g. PSA <0.5 ng/ml) [III, B].	100%
7c. Adjuvant post-operative RT after RP is not routinely recommended. Selected patients with positive surgical margins or extracapsular extension after RP may be offered adjuvant RT [I, B].	100%
7d. Concomitant ADT for 6 months or bicalutamide 150 mg daily for 2 years should be offered to men having salvage RT [I, B].	100%
7e. Patients having salvage RT to the prostate bed may be offered pelvic nodal RT [I, C].	100%
Recommendation 8: Treatment of relapse after radical treatment	
8a. For patients with a local recurrence following RP and no distant metastases, the pros and cons of local salvage therapy should be discussed, taking into account life expectancy and the long natural history of isolated local recurrences [III, C].	100%
8b. Patients with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with **next generation imaging tools such as ^{68}Ga-PSMA**-PET—CT **or whole-body MRI** [III, B].	100%
8c. Early ADT is not routinely recommended for men with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases [II, D].	100%
8d. Patients starting ADT for biochemical relapse, in the absence of metastatic disease, should be offered intermittent rather than continuous treatment [I, B].	100%
Recommendation 9: Hormone-naïve metastatic prostate cancer	
9a. **ADT plus docetaxel and AAP is recommended as first-line treatment for fit patients with mHNPC, especially in those with *de novo* multiple bone metastases (>3) or visceral metastases [I, B[a]]. In other patients with mHNPC,** ADT plus AAP [ESMO-MCBS v1.1 score 4] or apalutamide [ESMO-MCBS v1.1 score 4 or 3] or docetaxel [ESMO-MCBS v1.1 score 4] or enzalutamide [ESMO-MCBS v1.1 score 4] is recommended as first-line treatment for mHNPC [I, A].**In patients with mHNPC, ADT alone should be used only in vulnerable patients who cannot tolerate treatment intensification [III, C].**	100%
9b. ADT plus radiation to the primary is recommended for patients with low volume mHNPC [I, A].	100%
9c. ADT alone is recommended as first-line systemic treatment for mHNPC in patients who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A].	100%
9d. For patients starting on ADT, management to prevent cancer treatment-induced bone loss (CTIBL) is recommended.	100%
Recommendation 10: Non-metastatic castrate-resistant prostate cancer	
10a. Apalutamide [ESMO-MCBS v1.1 score 3], darolutamide [ESMO-MCBS v1.1 score 3] or enzalutamide [ESMO-MCBS v1.1 score 3] should be considered as options for patients with M0 CRPC and a high risk of disease progression [I, B].	100%

Continued

Table 1. Continued

Recommendations	Acceptability consensus
Recommendation 11: Metastatic CRPC	
11a. Abiraterone (AAP) or enzalutamide [ESMO-MCBS v1.1 score 4] are recommended for asymptomatic/mildly symptomatic patients with chemotherapy-naïve mCRPC [I, A].	100%
11b. Docetaxel [ESMO-MCBS v1.1 score 4] is recommended for patients with mCRPC [I, A].	100%
11c. In patients with mCRPC in the post-docetaxel setting, abiraterone (AAP) [ESMO-MCBS v1.1 score 4], enzalutamide [ESMO-MCBS v1.1 score 4] and cabazitaxel [ESMO-MCBS v1.1 score 2] are recommended options [I, A].	100%
11d. In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended (see section on palliative care) [I, B].	100%
11e. Radium-223 [ESMO-MCBS v1.1 score 4] is recommended for patients with bone-predominant, symptomatic mCRPC without visceral metastases, **if available** [I, B].	100%
11f. Radium-223 is not recommended in combination with AAP [I, E].	100%
11g. **In patients with mCRPC who have received a novel androgen receptor pathway inhibitor (abiraterone, apalutamide, darolutamide or enzalutamide) and docetaxel, treatment with cabazitaxel or Lu-PSMA [ESMO-MCBS v1.1 score 4, approved by FDA on 22 March 2022] should be used if available and if the patient is fit to receive these treatments [I, A].**	100%
Recommendation 12: Precision medicine	
12a. Tissue-based molecular assays may be used in conjunction with all clinico-pathological factors for treatment decision making in localised prostate cancer [IV, C].	100%
12b. Germline testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer [III, B].	100%
12c. Consider tumour testing for homologous recombination genes and mismatch repair defects (or microsatellite instability) in patients with mCRPC [II, B].	100%
12d. Patients with pathogenic mutations in cancer-risk genes identified through tumour testing should be referred for germline testing and genetic counselling [IV, A].	100%
12e. **Olaparib [ESMO-MCBS v1.1 score 3] can be considered after novel hormonal agents for patients with mCRPC with alterations in *BRCA1* or *BRCA2* [I, B].**	100%
Recommendation 13: Palliative care	
13a. A single fraction of external beam RT is recommended for palliation of painful, uncomplicated bone metastasis [I, A].	100%
13b. In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended [I, B].	100%
13c. MRI of the spine to detect subclinical**/asymptomatic** cord compression **may be considered** in patients with CRPC with vertebral metastases [III, **C**].	100%
13d. Urgent MRI of the spine to detect cord compression is very strongly recommended in patients with CRPC with vertebral metastases and neurological symptoms [III, A].	100%
Recommendation 14: Follow-up and long-term implications	
14a. Lifestyle measures to maintain bone health are recommended for patients on ADT: weight bearing exercise, stopping smoking, $\leq$2 units alcohol daily, adequate calcium intake and vitamin D status (reach and maintain reference vitamin D levels) [IV, B].	100%
14b. Patients starting long-term ADT should: (i) EITHER be offered a bone health agent (oral bisphosphonate, or zoledronic acid every 12 months or denosumab every 6 months) [I, B] (ii) OR be monitored with DEXA scanning and then treated according to the guidelines for CTIBL [IV, B].	100%

AAP, abiraterone acetate and prednisone/prednisolone; ADT, androgen deprivation therapy; *BRCA*, breast cancer susceptibility gene: CRPC, castration-resistant prostate cancer; CT, computed tomography; CTIBL, cancer treatment-induced bone loss; DDR, DNA damage and repair; DEXA, dual-energy X-ray absorptiometry; ESMO, European Society for Medical Oncology; ESMO-MCBS, ESMO-magnitude of clinical benefit scale; HNPC, hormone-naïve prostate cancer; ISUP, International Society of Urological Pathology; mCRPC, metastatic CRPC; mHNPC, metastatic HNPC; MRI, magnetic resonance imaging; mpMRI, multi-parametric magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SREs, skeletal-related events.
[a]Not currently regulatory approved.

In addition, a Korean study has shown biparametric magnetic resonance imaging (bpMRI) to have similar efficacy to mpMRI in the detection of prostate cancer and clinically significant prostate cancer.[34] More recently, comparison of bpMRI with mpMRI in combination with PSA density (PSAD) in the detection of clinically significant prostate cancer showed bpMRI combined with PSAD to achieve a better detection rate than mpMRI in Asian patients.[35] Diffusion-weighted imaging as part of mpMRI techniques has recently been investigated in a Japanese study for the detection of clinically significant prostate cancer in patients with elevated PSA levels,[36] and further refinement to the use of these techniques in Asia is likely to be forthcoming.

Thus, the Pan-Asian experts agreed with and 'accepted' completely (**100% consensus**) the ESMO 'recommendation 2a' below without change, although in terms of 'applicability' MRI may not be available/reimbursed in some Asian countries (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100518).

2a. mpMRI should be performed before prostate biopsy [I, B].

However, there was considerable discussion around ESMO 'recommendations 2b and c' with a lack of consensus in terms of acceptability and applicability in the pre-meeting survey (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100518).

Prostate cancer risk calculation tools provide quantitative guidance for decision making regarding whether or not to carry out a biopsy. It was emphasised during discussions

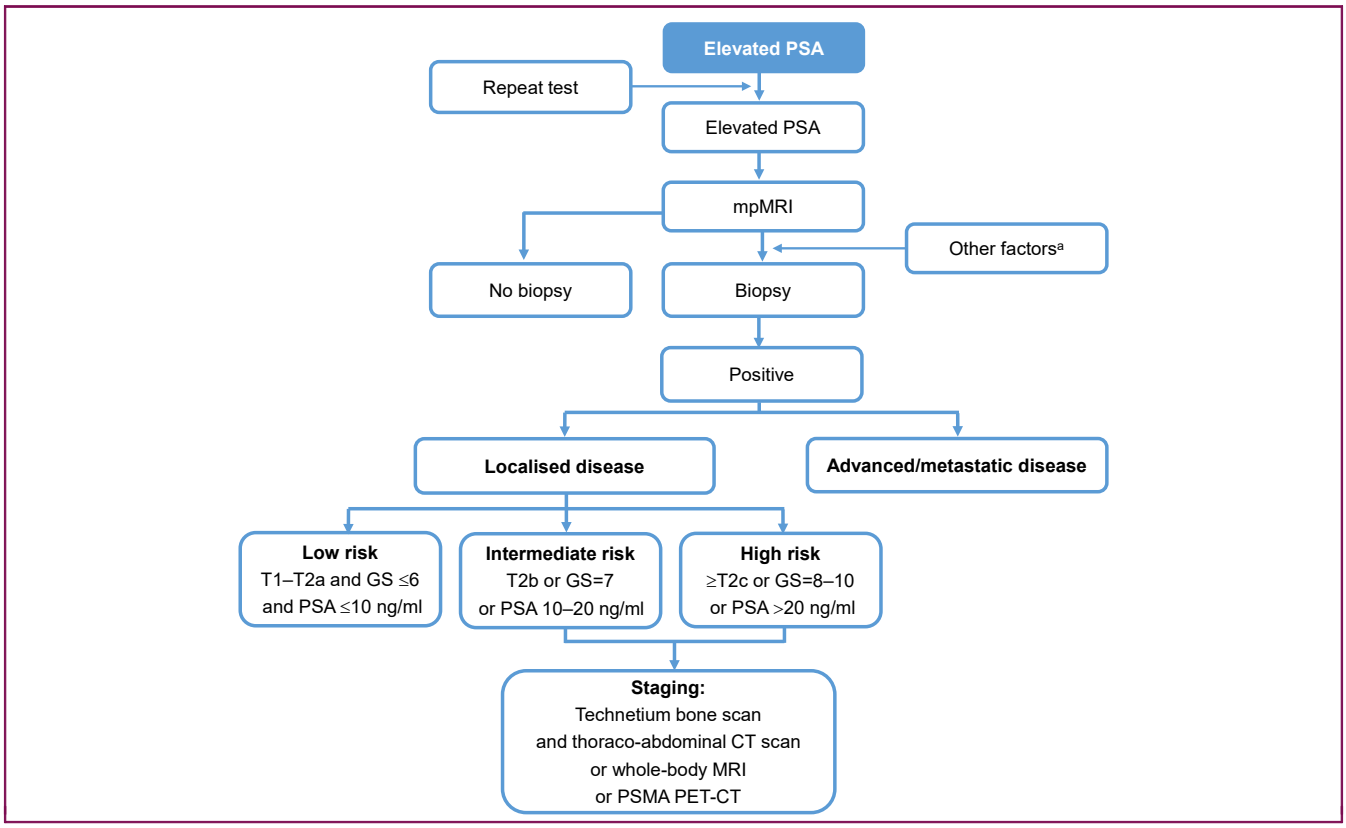

Figure 1. Diagnostic work-up and staging for prostate cancer.
CT, computed tomography; DRE, digital rectal examination; GS, Gleason score; mpMRI, multi-parametric magnetic resonance imaging; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.
[a]In addition to PSA level and MRI results, the decision to biopsy or not should be made in light of DRE findings, ethnicity, age, comorbidities, free/total PSA, history of previous biopsy and patient values.

during the virtual, 'face-to-face' meeting that the most popular prostate cancer risk calculator was that developed by the team at the Memorial Sloan Kettering Cancer Center (MSKCC).[37] However, the prostate cancer risk is significantly higher in Western patients with more patients at risk of high-grade prostate cancer (Gleason score ≥7). There is no reliable nomogram available for Asian patients. Thus, the wording of the original ESMO 'recommendation 2b' was revised, with the removal of 'A prostate cancer risk calculator and/or' from the front to the sentence and the addition of the new text highlighted in bold below and in Table 1, to read as follows:

2b. mpMRI should be used to confirm the indication for a biopsy in men with elevated PSA, **where available**[30-32] **[I, A; consensus = 100%].**

Transperineal prostate (TP) biopsy is emerging as one of the options for prostate cancer diagnosis, and when compared with TR prostate biopsy it offers a non-inferior cancer detection rate,[38] with a lower infection rate. A systematic comparison of TR and TP prostate biopsies in terms of efficacy and complications in the detection of prostate cancer in Asian studies showed no significant difference in prostate cancer detection rate and complications between the TR and TP approaches,[39,40] with the TP approach shown, in a meta-analysis conducted in China, to have a lower risk of fever and rectal bleeding.[41]

Thus, in the case of 'recommendation 2c' below, the original text was revised for the sake of clarification (with the changes highlighted in bold text below and Table 1) to read as follows:

2c. Transperineal **ultrasound (US)-guided biopsies** are recommended, **over** transrectal biopsies **due to lower infection rates [III, B; consensus = 100%].**

All 14 Pan-Asian experts accepted completely (**100% consensus**) 'recommendation 2d' below without change.

2d. Each biopsy should be reported individually and evaluated using the International Society of Urological Pathology (ISUP) consensus recommendations[42] [II, B].

3. Staging and risk assessment—recommendations 3a-c

Patients should be assessed with regard to their general health and comorbidities, and those who are not suitable for treatment with curative intent, by virtue of poor general health, do not normally require staging investigations. MRI provides tumour staging information.[43] The Gleason score is recommended for pathological grading of prostate adenocarcinomas and comprises a system of primary and secondary scores.[44] The degree of differentiation is defined/determined by the sum of the two scores. Thus, patients with localised disease can be classified as outlined in Figures 1 and 2 as:

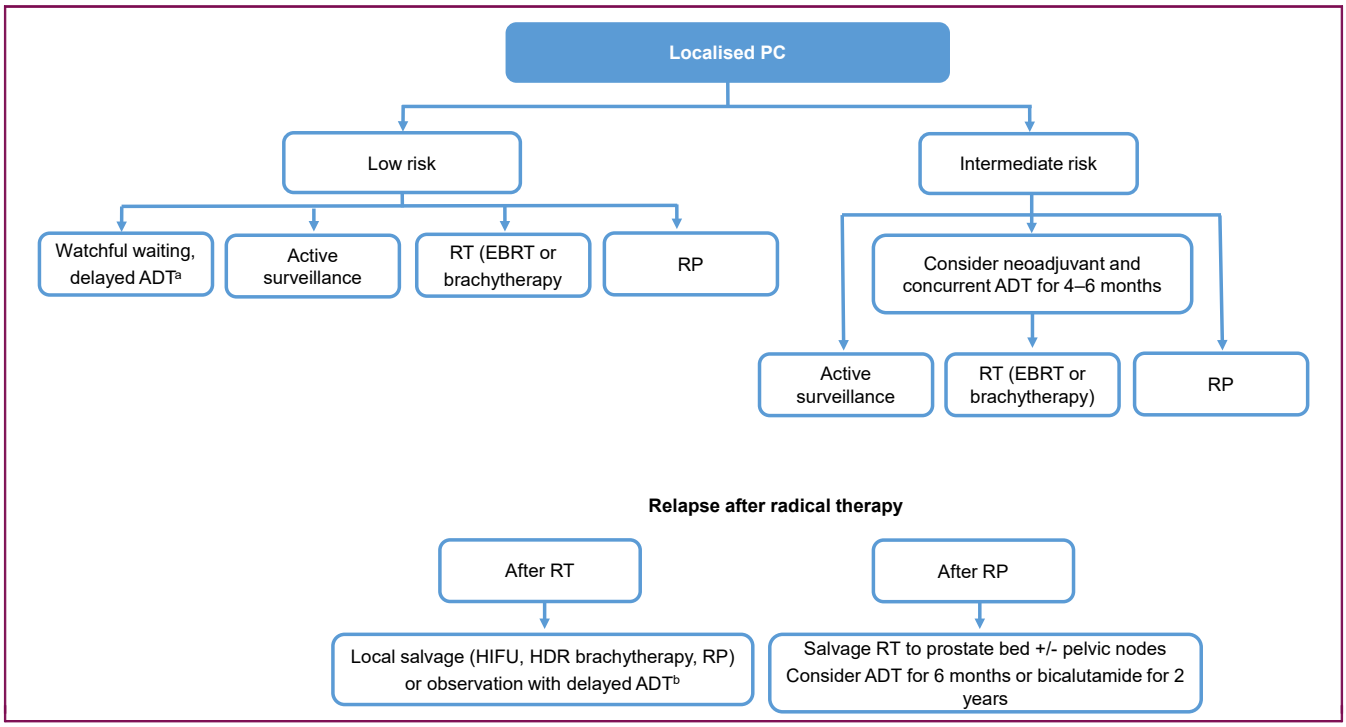

Figure 2. Localised prostate cancer treatment algorithm.
ADT, androgen deprivation therapy, EBRT, external beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.
[a]Also suitable for localised/locally advanced disease if patient not suitable for (or unwilling to have) radical treatment.
[b]For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

- Low risk: a Gleason score of ≤6, a PSA level of ≤10 ng/ml and an early tumour stage T1-T2a
- Intermediate risk: a Gleason score of 7 or a PSA of between 10 and 20 ng/ml or a tumour stage of T2b or T2c
- High risk: a Gleason score of ≥8 or a PSA level of >20 ng/ml or a more advanced tumour (≥T3a)[45]

All 14 Pan-Asian experts agreed completely (**100% consensus**) with the original 'recommendations 3a-c' below without change, in terms of both acceptability and applicability.

3a. Localised disease should be classified as low-, intermediate- or high-risk as a guide to prognosis and therapy [III, A].

3b. Patients with intermediate-risk disease should be staged for metastases using MRI or CT (computed tomography) of the abdomen and pelvis and bone scans [III, B].

3c. Patients with high-risk disease should be staged for metastases using CT (of the chest, abdomen and pelvis) and bone scans [III, B].

Patients with intermediate- or high-risk disease may undergo imaging for nodal or metastatic disease, with whole-body MRI, positron emission tomography—CT (PET—CT)[46] or the emerging prostate-specific membrane antigen (PSMA)-PET—CT.[47-49] ^{68}Gallium PSMA-PET—CT has been shown to have value as a diagnostic and clinical decision-making tool in Asian patients with rapid biochemical recurrence.[50,51]

4. Management of local/locoregional disease—recommendations 4a-h

According to the ESMO guidelines,[20] there is no consensus regarding the optimum management and treatment of patients with localised disease (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100518). Where possible, patients should be treated within a multidisciplinary team environment which should include both urologists and radiation oncologists as well as medical oncologists. Prostate cancer can be slow growing and may never cause patients any problems during their lifetime. Thus, 'watchful waiting' is an option for those patients with other health problems who may be unsuitable for or unwilling to undergo treatment with curative intent such as surgery[52,53] or radiotherapy (RT). It generally applies to patients with shorter life expectancies (<10 years). Active surveillance, on the other hand, involves careful patient monitoring such as PSA testing, repeat biopsies and MRI, to avoid patients having unnecessary treatment, and is for patients with slow-growing tumours who would benefit from curative treatment if required.[12,18,20] Curative options for these low-risk patients include external beam RT (EBRT), low-dose rate brachytherapy and radical prostatectomy (RP)[20] (Figure 2 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100518).

For patients with intermediate disease, RT (EBRT/brachytherapy) or RP is recommended if active surveillance is not an option[20] (Figure 2 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100518). For high-risk localised disease, RT plus ADT has been shown to

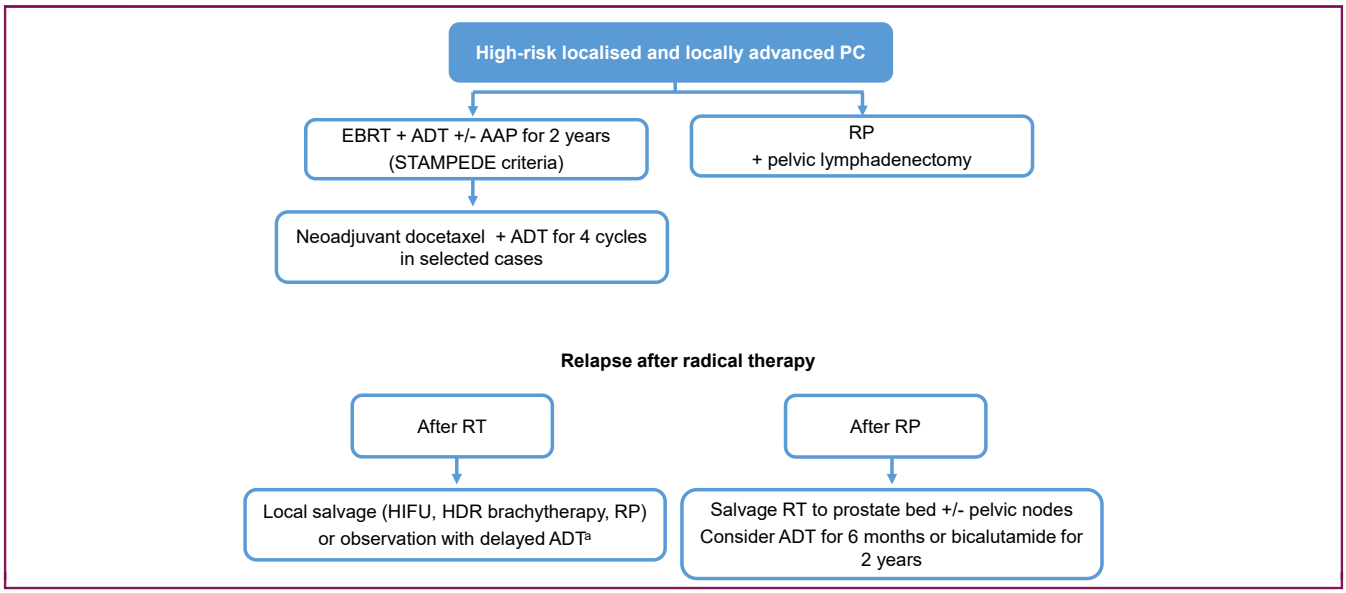

Figure 3. High-risk localised and locally advanced prostate cancer treatment algorithm.
AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen deprivation therapy; EBRT, external beam radiotherapy; HDR, high-dose rate; HIFU, high-intensity focused ultrasound; PC, prostate cancer; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.
[a]For men with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months.

improve survival over RT alone[54-56] (Figure 3). More recently, combination therapy with abiraterone acetate plus prednisone/prednisolone (AAP) has been shown to be associated with significantly higher rates of metastasis-free survival compared with ADT alone in patients with high-risk localised disease meeting the STAMPEDE trial criteria.[57] RP plus pelvic lymphadenectomy is also an option for high-risk disease[12,20] (Figure 3 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100518).

For patients relapsing after RT, local salvage using high-intensity focused ultrasound (HIFU), high-dose rate brachytherapy or RP may be required. Observation with delayed ADT may be appropriate for those patients with biochemical relapse and symptomatic local disease, proven metastases or a PSA doubling time of <3 months (Figures 2 and 3, and also Section 8 below.). For those patients who have undergone RP, RT to the prostate bed plus or minus pelvic nodes may be required or observation with delayed ADT (Figure 3). These patients, however, often require post-operative RT plus or minus ADT.

All the Asian experts agreed completely with 'recommendations 4a and b' below, in terms of acceptability (**100% consensus**) and applicability, without change.

4a. Watchful waiting with delayed ADT is an option for patients with localised or locally advanced disease who are not suitable for, or unwilling to have, radical treatment[58] [I, A].

4b. Active surveillance is recommended for patients with low-risk disease [II, A].

The Asian experts did, however, have reservations (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100518) about how to define the patients who were not suitable for active surveillance. The wording of recommendation 4c was thus revised as per the bold text below.

4c. RP or RT (external beam or brachytherapy) are options for patients with low-risk disease **who are anxious about and/**not suitable for active surveillance [III, B; **consensus = 100%**].

All the Asian experts accepted completely (**100% consensus**) 'recommendations 4d-f and 4h' below, in the pre-meeting survey without change. However, 'recommendation 4f' was updated at the virtual 'face-to-face' meeting and a new recommendation 4g added (as denoted by the bold text below and in Table 1) due to new data presented during the presidential session of the ESMO 2021 Annual Meeting, from the phase III STAMPEDE trial[57] which showed the addition of 2 years of abiraterone acetate and prednisone (AAP) to improve both metastases-free survival [hazard ratio (HR) 0.54; 95% confidence interval (CI) 0.43-0.68; $P = 3.2 \times 10^{-7}$] and overall survival (HR 0.63; 95% CI 0.48-0.82; $P = 0.0005$) in patients with high-risk M0 (N1 or ≥2 risk factors among T3-4, PSA >40 ng/ml, Gleason score 8-10).

4d. RP or RT (external beam or brachytherapy) is recommended for patients with intermediate-risk disease[59-62] [I, B].

4e. Primary ADT alone is not recommended as standard initial treatment for non-metastatic disease[63,64] [I, D]

4f. External beam RT plus ADT is recommended for patients with high-risk or locally advanced prostate cancer [I, B; **consensus = 100%**].

4g. **External beam RT plus ADT plus AAP (24 months) is recommended for patients with high-risk or locally advanced prostate cancer as defined by the STAMPEDE trial criteria[57] [I, B; consensus = 100%].**

4h. RP plus pelvic lymphadenectomy is an option for selected men with high-risk disease[65,66] [III, B].

5. Neoadjuvant and adjuvant hormone treatment—recommendations 5a-c

The benefit of neoadjuvant and concurrent ADT together with RT has been established in RCTs[67,68] for men with high-risk localised and locally advanced prostate cancer.[20] Furthermore, RCTs in patients with unfavourable intermediate-risk prostate cancer risk [primary Gleason score 4, ≥50% positive biopsy scores or ≥2 intermediate-risk factors (cT2b-c, Gleason score 7, PSA 10-20 ng/ml)], and therefore an anticipated poorer outcome, showed long-course (18-36 months) adjuvant ADT after RT to improve overall survival in those patients.[69-71]

All the Asian experts agreed completely with 'recommendations 5a and b' below in terms of both acceptability (**100% consensus**) and applicability in the pre-meeting survey. However, as for 'recommendation 4f' above, new data from the phase III STAMPEDE trial[57] showing the addition of 2 years of AAP to improve both metastases-free survival ($P = 3.2 \times 10^{-7}$) and overall survival ($P = 0.0005$) in patients with very-high-risk M0 disease also necessitated an update to 'recommendation 5b', and a new recommendation 5c added (as denoted by the bold text below and in Table 1).

5a. Patients receiving radical RT for intermediate-risk disease should be offered a short course of ADT for 4-6 months[67,68] [I, A].

5b. Patients receiving radical RT for high-risk disease should have a long course of ADT (18-36 months)[71] [I, A; **consensus = 100%**].

5c. **Patients receiving radical RT for high-risk disease who fit the STAMPEDE trial criteria should have a long course of ADT (18-36 months)[71] plus AAP (24 months)[57] [I, A; consensus = 100%].**

6. Neoadjuvant and adjuvant docetaxel for M0 disease—recommendation 6a

There was a major discussion amongst the Asian experts at the virtual, 'face-to-face' meeting concerning both the acceptability and applicability of recommendation 6a (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100518). Neoadjuvant docetaxel is not routinely used in Asia. Six RCTs have investigated docetaxel-based therapy in high-risk M0 disease.[72-78] The first three of these[72-75] and a meta-analysis of them[79] showed docetaxel to confer an improvement in relapse-free survival (RFS) in patients with high-risk localised disease (HR 0.70; 95% CI 0.61-0.81; $P < 0.0001$). However, the overall survival data were immature, and the preliminary data from the remaining three trials failed to demonstrate a statistically significant benefit for docetaxel on RFS.[76-78] As a consequence of the lack of overall survival data, the wording of 'recommendation 6a' below:

6a. Neoadjuvant docetaxel chemotherapy may be offered prior to RT for young, fit men with very high-risk localised prostate cancer [I, C], was revised (with the revisions emphasized in bold text) to read

6a. Neoadjuvant docetaxel chemotherapy **only impacts RFS and should be limited as a potential option for fit patients with high-risk disease, based on shared decision making[80] [I, C; consensus = 100%].**

7. Post-operative RT—recommendations 7a-e

RT can be administered post-operatively as either adjuvant or salvage therapy,[20] but it is unclear which is more appropriate for patients with localised or locally advanced prostate cancer following RP. Adjuvant RT (ART) had been shown to improve biochemical control but not overall survival.[81] A prospectively planned, systematic review and meta-analysis of event-free survival (EFS) data for 2153 patients from three trials comparing immediate ART ($n = 1075$) with early salvage RT (SRT, $n = 1078$) (the ARTISTIC collaboration)[82] showed no evidence that ART improved EFS over SRT (HR 0.95; 95% CI 0.75-1.21; $P = 0.70$). ART was associated with bladder and bowel morbidity but not with any proven benefit in terms of biochemical progression-free survival (PFS). Thus, observation followed by SRT in the case of PSA failure is the current standard in Europe and Asia after RP, with better outcomes achieved when a patient's PSA is <0.5 ng/ml.[83,84] ART may be offered to selected patients with positive resection margins or extracapsular extension.[85]

Comparison of SRT with SRT plus either 6 months of ADT or 24 months of bicalutamide showed 24 months of bicalutamide to reduce the rate of prostate cancer death (HR 0.77; 95% CI 0.59-0.99; $P = 0.04$) and improve overall survival (HR 0.49; 95% CI 0.32-0.73; $P < 0.001$).[86] The randomised phase III GETUG-AFU 16 trial showed ADT to improve metastasis-free survival (HR 0.73; 95% CI 0.54-0.98; $P = 0.034$), but not overall survival.[87] In a United States study, comparison of pelvic node RT plus 6 months of ADT with prostate bed-only RT or prostate bed RT plus 6 months of ADT showed the addition of pelvic RT to improve freedom from failure and freedom from metastases compared with prostate bed-only RT (HR 0.52; 95% CI 0.30-0.92; $P = 0.014$).[88]

Thus, all the Asian experts accepted completely (**100% consensus**) 'recommendations 7a-e' below.

7a. Following RP, patients should have their serum PSA level monitored, with SRT recommended in the event of PSA failure [III, B].

7b. Salvage RT should start early (e.g. PSA <0.5 ng/ml) [III, B].

7c. Adjuvant post-operative RT after RP is not routinely recommended. Selected patients with positive surgical margins or extracapsular extension after RP may be offered adjuvant RT [I, B].

7d. Concomitant ADT for 6 months or bicalutamide 150 mg daily for 2 years should be offered to men having salvage RT [I, B].

7e. Patients having SRT to the prostate bed may be offered pelvic nodal RT [I, C].

There were some concerns over the 'applicability' of 'recommendation 7d' (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100518) in that in

some Asian countries, ADT is not routinely offered following salvage RT, as patients are referred for early salvage RT when their PSA levels are <1.0 ng/ml, and the benefit of ADT in these patients is less certain.

8. Treatment of relapse after radical local treatment—recommendations 8a-d

For patients with biochemically recurrent prostate cancer, PSMA-PET imaging is replacing conventional imaging, based on its superior sensitivity and specificity, in terms of diagnosis.[89]

There are three treatment approaches for patients who relapse after radical local treatment and these are (i) local salvage therapy, (ii) metastasis-directed therapy and (iii) systemic therapy.[20]

Since the natural history of PSA recurrence following treatment is long, life expectancy needs to be taken into account when considering local treatment options.[20] In the case of patients with local recurrence, in the absence of metastases, the local treatment options in Europe include salvage RP, HIFU, cryoablation and brachytherapy, and typically only provide temporary control.

Early detection of recurrence theoretically provides the opportunity to selectively ablate metastases with the possibility of prolonging survival. Recently, a European trial has shown metastasis-directed therapy to improve biochemical progression and the time to palliative ADT,[90] while another trial conducted in Canada, the Netherlands, Scotland and Australia, in different solid tumour types (of which 16% were prostate cancer) showed the addition of stereotactic body RT to standard of care to improve overall survival.[91]

Systemic ADT is not routinely recommended for patients with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases. Early administration of ADT has been shown to confer no survival benefit[92] and is associated with an adverse effect on quality of life.[93] Intermittent ADT when compared with continuous ADT had a more favourable toxicity profile with no difference in overall survival (HR 1.02; 95% CI 0.86-1.21).[94]

Thus, all the Asian experts accepted completely (**100% consensus**) 'recommendations 8a-d' below, with a revision to the text of 'recommendation 8b' for clarification.

8a. For patients with a local recurrence following RP and no distant metastases, the pros and cons of local salvage therapy should be discussed, taking into account life expectancy and the long natural history of isolated local recurrences [III, C].

8b. Patients with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with **next generation imaging tools such as ^{68}Ga-PSMA-PET—CT[50,95] or whole-body MRI** [III, B].

8c. Early ADT is not routinely recommended for men with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases [II, D].

8d. Patients starting ADT for biochemical relapse, in the absence of metastatic disease, should be offered intermittent rather than continuous treatment [I, B].

9. Metastatic hormone-naïve prostate cancer—recommendations 9a-d

The addition of abiraterone, apalutamide, enzalutamide or docetaxel to ADT has been shown to improve overall survival in patients with metastatic hormone-naïve prostate cancer (mHNPC) in a range of phase III trials. However, it should be noted that most of the relevant trials included patients with *de novo* metastatic disease. Thus, caution is required when extrapolating to patients who have relapsed after previous local treatment. The Western trials CHAARTED[96] and STAMPEDE[74] demonstrated the benefit of the addition of docetaxel (75 mg/m^2 every 21 days for 6 cycles) to ADT. This benefit was seen particularly in M1 patients, in combination with ADT, and also in combination with zoledronic acid, in the STAMPEDE trial,[74] and in patients with high-volume disease in the CHAARTED trial.[96] The GETUG-AFU 15 trial showed docetaxel (75 mg/m^2 every 21 days for 9 cycles) added to ADT to improve PSA PFS and radiographic PFS but not overall survival. However, a meta-analysis of the data from these three trials confirmed the benefit of the addition of docetaxel to ADT regardless of disease volume (HR 0.77; 95% CI 0.68-0.87).[77,79]

The benefit of the addition of AAP to ADT was demonstrated in the randomised phase III LATITUDE trial,[97] a subgroup analysis of the LATITUDE trial in Japanese patients[98] and in the STAMPEDE[99] trial. However, recent data from the phase III PEACE-1 trial showed the addition of AAP to ADT plus docetaxel to improve both radiographic PFS (HR 0.50; 99.9% CI 0.34-0.71; $P < 0.0001$) and overall survival (HR 0.75; 95% CI 0.59-0.95; $P = 0.017$). In patients with high-volume disease (at least four bone metastases including at least one in the peripheral skeleton, or visceral metastasis), the survival medians were 5.14 and 3.47 years, respectively, for those patients receiving abiraterone versus those receiving docetaxel ADT (HR 0.72; 95% CI 0.55-0.95; $P = 0.019$).[100]

The randomised phase III TITAN trial showed the addition of apalutamide to ADT to improve overall survival in patients with mHNPC.[101] The benefit of adding enzalutamide to ADT for the treatment of patients with mHNPC has been shown in the phase III ARCHES[102] and ENZAMET[103] trials. The randomised HORRAD[104] and STAMPEDE[105] trials have compared ADT alone (docetaxel was allowed in addition to ADT in both arms of the STAMPEDE trial) or in combination with RT to the prostate in patients with mHNPC. RT improved time to PSA progression in the HORRAD trial,[104] and time to treatment failure in the STAMPEDE trial.[105]

The Asian experts agreed and accepted completely 'recommendations 9a-d' in the pre-meeting survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100518). However, based on the new data presented at ESMO 2021 outlined above, the wording of the original recommendation 9a below:

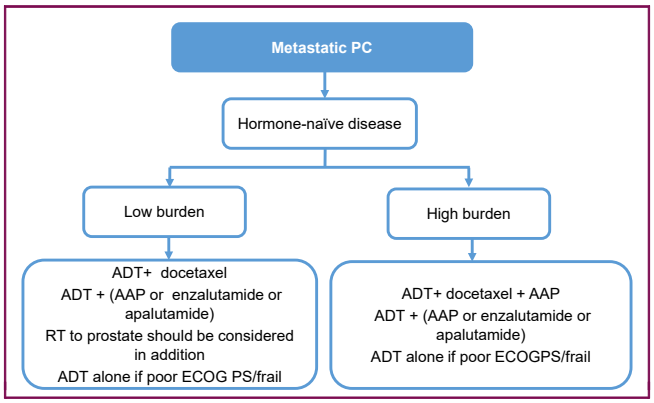

Figure 4. Metastatic prostate cancer treatment algorithm.
AAP, abiraterone acetate plus prednisolone/prednisone; ADT, androgen deprivation therapy, ECOG PS, Eastern Cooperative Oncology Group performance status; PC, prostate cancer; RT, radiotherapy.

9a. ADT plus abiraterone/prednisone or apalutamide or docetaxel or enzalutamide is recommended as first-line treatment for mHNPC [I, A] was revised to read as follows with the changes denoted by the bold text:

9a. **ADT plus docetaxel and AAP is recommended as first-line treatment for fit patients with mHNPC, especially in those with *de novo* multiple bone metastases (>3) or visceral metastases[100] [I, B; consensus = 100%]. In other patients with mHNPC,** ADT plus AAP [ESMO-MCBS v1.1 score: 4] or apalutamide [ESMO-MCBS v1.1 score: 4] or docetaxel [ESMO-MCBS v1.1 score: 4] or enzalutamide [ESMO-MCBS v1.1 score: 4 or 3] is recommended as first-line treatment for mHNPC **[I, A; consensus = 100%].**

In patients with mHNPC, ADT alone should be used only in vulnerable patients who cannot tolerate treatment intensification [III, C; consensus = 100%].

All 14 Asian experts agreed and accepted completely (**100% consensus**) 'recommendations 9b-d' below.

9b. ADT plus radiation to the primary is recommended for patients with low volume mHNPC [I, A].

9c. ADT alone is recommended as first-line systemic treatment for mHNPC in patients who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel [III, A].

9d. For patients starting on ADT, management to prevent cancer treatment-induced bone loss (CTIBL) is recommended (link to the CTIBL guideline).

The treatment recommendations for mHNPC are presented in Figure 4.

10. Non-metastatic castration-resistant prostate cancer—recommendation 10a

According to the EAU-ESTRO-SIOG guidelines, patients are classified as castration-resistant if their disease progresses during ADT with serum testosterone at castrate levels.[106]

The phase III SPARTAN trial has shown apalutamide to significantly increase median metastasis-free survival (40.5 versus 16.2 months, HR 0.28; 95% CI 0.23-0.35) and time to symptomatic progression (HR 0.45; 95% CI 0.32-0.63) when compared with placebo.[107] Similarly in the PROSPER trial in patients with high-risk CRPC, enzalutamide has been shown to be superior to placebo in terms of median metastasis-free survival (36.6 versus 14.7 months, HR 0.29; 95% CI 0.24-0.35), and the key secondary end points of median time to PSA progression (37.2 versus 3.9 months; HR 0.07; 95% CI 0.05-0.08) and time to subsequent antineoplastic therapy (39.6 versus 17.7 months; HR 0.21; 95% CI 0.17-0.26).[108] Median overall survival was 67.0 (95% CI 64.0-not reached) months in the enzalutamide group and 56.3 (95% CI 54.4-63.0) months in the placebo group (HR 0.73; 95% CI 0.6-0.89; $P = 0.001$).[109] The phase III ARAMIS trial has shown darolutamide to significantly increase median metastasis-free survival (40.4 versus 18.4 months, HR 0.41; 95% CI 0.34-0.50).[110] Darolutamide also significantly improved overall survival (HR 0.69; 95% CI 0.53-0.88; $P = 0.003$) and significantly delayed time to deterioration of prostate cancer-specific quality of life and disease-related symptoms versus placebo.[111,112]

All 14 Asian experts accepted completely (**100% consensus**) 'recommendation 10a' below, without change.

10a. Apalutamide [ESMO-MCBS v1.1 score 3], darolutamide [ESMO-MCBS v1.1 score 3] or enzalutamide [ESMO-MCBS v1.1 score 3] should be considered as options for patients with M0 CRPC and a high risk of disease progression [I, B].

11. Metastatic castration-resistant prostate cancer—recommendations 11a-g

A range of therapeutic options is now available for the treatment of patients with metastatic disease (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100518).

Bicalutamide and low-dose corticosteroids have both shown a benefit in patients with mCRPC in terms of PSA and symptomatic responses.[113,114] Abiraterone plus prednisone has been shown to significantly improve overall survival (HR 0.79; 95% CI 0.66-0.96) in patients with chemotherapy-naïve asymptomatic/mildly symptomatic mCRPC in the COU-AA-302 trial.[115] In the PREVAIL trial,[116] enzalutamide was shown to be superior to placebo in terms of overall survival (HR 0.71; 95% CI 0.60-0.84).

The phase III TAX-327[117] and SWOG-9916[118] trials showed docetaxel (75 ng/m^2 every 21 days) combined with prednisone, and docetaxel (60 mg/m^2 every 21 days) combined with estramustine and prednisone to improve overall survival, compared with mitoxantrone plus prednisone, with HRs of 0.76 (95% CI 0.62-0.94)[117] and 0.80 (95% CI 0.67-0.97),[118] respectively, while the ALSYMPCA trial showed radium 223 (Ra-223) to significantly increase overall survival (HR 0.70; 95% CI 0.55-0.83) and time to first symptomatic skeletal event (HR 0.66; 95% CI 0.0.53-0.83) in patients with symptomatic, bone-predominant mCRPC.[119] In Japan, a study of Ra-223, in a real-life setting, showed Ra-223 to be well tolerated in all groups. However, the incidences of serious or $\geq$ grade 3 treatment-emergent adverse events (TEAEs)/drug-related TEAEs and $\geq$ grade 3 haematological TEAEs were numerically higher in the prior-chemotherapy group than in the no prior-chemotherapy group. The safety

and effectiveness of Ra-223 in patients without concomitant use of ADT were encouraging, and similar to those in the overall population.[120] However, due to the fact that Ra-223 has been associated with an increased incidence of fractures in combination with AAP in the ERA trial,[121] its use in Europe has been restricted to patients who have received at least two lines of systemic therapy for CRPC (abiraterone/enzalutamide and docetaxel) or who are ineligible to receive these therapies.[122] Administration of Ra-223 in combination with AAP is not permitted.[20]

For patients who had previously received docetaxel chemotherapy, cabazitaxel improved overall survival (HR 0.70; 95% CI 0.59-0.83) when compared with mitoxantrone in the TROPIC trial,[123] AAP improved overall survival (HR 0.74; 95% CI 0.64-0.86) compared with placebo plus prednisone in the COU-301 trial[124] and enzalutamide improved overall survival (HR 0.63; 95% CI 0.53-0.75) compared with placebo in the AFFIRM trial.[125]

However, the optimal sequencing of these agents is still being investigated with evidence to suggest that there may be cross-resistance between the androgen receptor inhibitors abiraterone and enzalutamide. More recently, cabazitaxel has been shown to improve both median radiographic PFS (HR 0.54; 95% CI 0.40-0.73; $P < 0.001$; 8.0 versus 3.7 months) and median overall survival (HR 0.64; 95% CI 0.46-0.89; $P = 0.008$; 13.6 versus 11.0 months) compared with AAP or enzalutamide in patients with mCRPC pre-treated with docetaxel and one of the 'novel' androgen receptor pathway inhibitors, and who progressed within 12 months.[126] Also, an international, open-label, phase III trial has been conducted to evaluate ^{177}Lutetium (Lu)-PSMA-617 (Lu-PSMA) plus standard of care versus standard of care alone in patients who had PSMA-positive mCRPC previously treated with at least one androgen receptor pathway inhibitor and one or two taxane regimens. Standard of care excluded chemotherapy, immunotherapy, Ra-223 and investigational drugs. The addition of Lu-PSMA to standard of care improved both median radiographic PFS (HR 0.40; 99.2% CI 0.29-0.57; $P < 0.001$; 8.7 versus 3.4 months) and median overall survival (HR 0.62; 95% CI 0.52-0.74; $P < 0.001$; 15.3 versus 11.3 months) compared with standard of care alone in pre-treated patients with mCRPC.[127]

All 14 Asian experts accepted completely (**100% consensus**) the 'recommendations 11a-f' below in the pre-meeting survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100518) with one minor change.

11a. Abiraterone (AAP) or enzalutamide [ESMO-MCBS v1.1 score 4] are recommended for asymptomatic/mildly symptomatic patients with chemotherapy-naïve mCRPC [I, A].

11b. Docetaxel [ESMO-MCBS v1.1 score 4] is recommended for patients with mCRPC [I, A].

11c. In patients with mCRPC in the post-docetaxel setting, abiraterone (AAP) [ESMO-MCBS v1.1 score 4], enzalutamide [ESMO-MCBS v1.1 score 4] and cabazitaxel [ESMO-MCBS v1.1 score 2] are recommended options [I, A].

11d. In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended (see section on palliative care) [I, B].

11e. Radium-223 [ESMO-MCBS v1.1 score 4] is recommended for patients with bone-predominant, symptomatic mCRPC without visceral metastases, **if available** [I, B].

11f. Radium-223 is not recommended in combination with AAP [I, E].

However, based on the publication of the new data on the potential sequencing of agents in the treatment of patients with mCRPC outlined above,[126,127] the new recommendation, 'recommendation 11g' below, was discussed and voted on at the virtual meeting and added below and in Table 1.

11g. **In patients with mCRPC who have received a novel androgen receptor pathway inhibitor (abiraterone, apalutamide, darolutamide or enzalutamide) and docetaxel, treatment with cabazitaxel[126] or Lu-PSMA[127] [ESMO-MCBS v1.1 score 4, approved by the Food and Drug Administration on 22 March 2022] should be used if available and if the patient is fit to receive these treatments [I, A; consensus = 100%].**

12. Precision medicine—recommendations 12a-e

Tissue-based molecular assays may be used in conjunction with all clinico-pathological factors for treatment decision making in patients with localised prostate cancer. Potentially actionable somatic or germline events have been identified in ~90% of patients with mCRPC.[128] The *BRCA2* gene is commonly altered and prostate tumours associated with a germline *BRCA2* mutation have a high Gleason score, nodal and distant metastases at the time of diagnosis and poor survival.[129] Approximately 20% of metastatic prostate cancers have mutations and alterations involved in DNA damage and repair (DDR) genes[128] with ~30% metastatic prostate cancer patients carrying a germline DDR mutation found not to have a previous family history Thus, in Europe, the recommendation is that germline testing for *BRCA2* and other DDR gene changes should be offered to all patients with a family history and should be considered for all patients with metastatic prostate cancer.[20]

There was a lack of consensus amongst the Asian experts with regard to 'recommendation 12a' in the pre-meeting survey (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100518). Molecular testing is not used in all countries in Asia as an aid to treatment decision making for patients with localised disease and not covered by insurance. However, independently of their local situation, the Asian experts decided to accept 'recommendation 12a' without change.

12a. Tissue-based molecular assays may be used in conjunction with all clinico-pathological factors for treatment decision making in localised prostate cancer [IV, C; **consensus = 100%**].

All 14 Asian experts accepted completely (**100% consensus**) 'recommendations 12b-d' without change.

12b. Germline testing for *BRCA2* and other DDR genes associated with cancer predisposition syndromes is recommended in patients with a family history of cancer and should be considered in all patients with metastatic prostate cancer [III, B].

12c. Consider tumour testing for homologous recombination genes and mismatch repair defects (or microsatellite instability [MSI]) in patients with mCRPC [II, B].

12d. Patients with pathogenic mutations in cancer-risk genes identified through tumour testing should be referred for germline testing and genetic counselling [IV, A].

Also, based on new PFS and overall survival data from the PROFOUND trial,[130] for olaparib versus a second androgen receptor pathway inhibitor, a new recommendation 'recommendation 12e' was added below and in Table 1.

12e. **Olaparib [ESMO-MCBS v1.1 score 3] can be considered after novel hormonal agents for patients with mCRPC with alterations in *BRCA1* or *BRCA2* [I, B; consensus = 100%].**

13. Palliative care—recommendations 13a-d

Single-fraction RT is recommended for treatment of bone pain.[131,132] For the prevention or delay of skeletal-related events (SREs), the bisphosphonate zoledronic acid[133] or denosumab can be used. Comparison of the two agents showed denosumab to be superior to zoledronic acid in terms of time to first SRE (HR 0.82; 95% CI 0.71-0.95; $P = 0.0002$). There was no difference in overall survival.[134] Radioactive samarium can be considered for painful and extensive bone metastases.[135]

The Asian experts accepted 'recommendations 13a and b' below without change (**100% consensus**).

13a. A single fraction of external beam RT is recommended for palliation of painful, uncomplicated bone metastasis [I, A].

13b. In patients with bone metastases from CRPC at risk for clinically significant SREs, a bisphosphonate or denosumab are recommended [I, B].

However, there was considerable discussion around 'recommendation 13c' with regard to the limited access to MRI especially for asymptomatic patients. Also, the Asian experts considered that there was little point in conducting MRI, if they were not going to use RT in the treatment of asymptomatic patients. Thus, the original 'recommendation 13c' below was revised to cover a more individual approach to the palliative treatment of patients, depending on the individual patient situation, with experts maybe electing to start with a bone-targeting agent or change the existing anticancer treatment depending on the general condition of the patient. Thus, the wording of the initial recommendation was revised to make the use of MRI optional as indicated by the bold text below and Table 1, and the GoR revised from B to C.

13c. MRI of the spine to detect subclinical/**asymptomatic** cord compression **may be considered** in patients with CRPC with vertebral metastases [III, C; **consensus = 100%**].

'Recommendation 13d' below was accepted completely (**100% consensus**) by the Asian experts without any revision.

13d. Urgent MRI of the spine to detect cord compression is very strongly recommended in patients with CRPC with vertebral metastases and neurological symptoms [III, A].

14. Follow-up and long-term implications—recommendations 13a and b

The increase in survival times for patients with prostate cancer means that patients spend longer receiving ADT. ADT may cause hot flushes, lethargy, mood swings and significantly osteoporosis. The latter, together with the adverse effects on bone health of abiraterone, enzalutamide, steroids and Ra-223, means that bone health in patients with prostate cancer has become a more important issue. Thus, lifestyle measures to improve bone health are recommended and patients starting long-term ADT should either be offered an oral bisphosphonate or be offered a bone density dual-energy X-ray absorptiometry (DEXA) scan and be treated according to the ESMO guidelines for CTIBL.[136] A management manual exists for CTIBL in Japan.[137]

There was some discussion about access to and costs of bone-targeting agents and the interpretation of DEXA scans in relation to 'recommendation 14b', but all 14 Asian experts accepted 'recommendations14a and b' without change (i.e. **100% consensus**).

14a. Lifestyle measures to maintain bone health are recommended for patients on ADT: weight bearing exercise, stopping smoking, $\leq$2 units alcohol daily, adequate calcium intake and vitamin D status (reach and maintain reference vitamin D levels) [IV, B].

14b. Patients starting long-term ADT should:

(i) EITHER be offered a bone health agent (oral bisphosphonate, or zoledronic acid every 12 months or denosumab every 6 months) [I, B]

(ii) OR be monitored with DEXA scanning and then treated according to the guidelines for CTIBL[136] [IV, B].

Drug and treatment availability

The drug and treatment availability for each of the seven Asian countries is summarised in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100518, and the ESMO-MCBSs for the different systemic therapy options and new therapy combinations for the treatment of prostate cancer are presented in Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2022.100518. Resource limitations are the most important barrier to offering optimal diagnosis and treatment to patients with prostate cancer across the different Asian countries.

Recently, pembrolizumab monotherapy has shown promising antitumour activity, with an acceptable safety profile, in a small cohort of patients with bone-predominant mCRPC (mostly with MSI disease) previously treated with docetaxel and targeted endocrine therapy,[138] and has been included in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100518.

CONCLUSIONS

The results of the voting by the Asian experts both before and after the 'face-to-face' meeting showed >80% concordance (Supplementary Tables S2 and S3, available at https://doi.org/10.1016/j.esmoop.2022.100518) with the ESMO recommendations for the treatment of patients with prostate cancer.[20] Following the virtual 'face-to-face' discussions, the revisions were made to the wording of 'recommendations 2b and c, 4f, 6a and 9a' and two new recommendations added, recommendations 11g and 12e (Table 1), and resulted in a **100% consensus** in terms of acceptability being achieved for all the recommendations listed in Table 1.

Thus, the recommendations listed in Table 1 can be considered to constitute the consensus clinical practice guidelines for the treatment of patients with prostate cancer in Asia. As mentioned previously, the acceptance of each recommendation by each of the Asian experts was based on the available scientific evidence and was independent of the approval and reimbursement status of certain procedures and drugs in their individual countries. A summary of the availability of the recommended treatment modalities and recommended drugs, as of November 2021, is presented for each participating Asian country in Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2022.100518, and will obviously impact some of the disease and patient management strategies that can be adopted by certain countries.

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