Review

Consensus statements on the management of metastatic prostate cancer from the Hong Kong Urological Association and Hong Kong Society of Uro-Oncology

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To establish a set of consensus statements to facilitate physician management strategies for patients with metastatic prostate cancer (mPCa) in Hong Kong. A local expert consensus was organized jointly by the two main professional organizations representing prostate cancer specialists in Hong Kong. A total of 12 experts were included in the consensus panel. Six of the most crucial and relevant areas of debate regarding the management of mPCa were identified. With the use of a modified Delphi method, several panel meetings were held for the members to discuss their clinical experience and the published literature relevant to the areas of debate. At the final meeting, each drafted statement was voted on by every member based on its practicability of recommendation in the locality. After the panel voting, a total of 45 consensus statements regarding the management of mPCa were ultimately accepted and established. The consensus statements were primarily derived from the latest clinical evidence and major overseas guidelines, with the consideration of local clinical experience and practicability. These are considered applicable recommendations for Hong Kong physicians for the management of mPCa patients.

Keywords

castration-naïve prostate cancer, castration-resistant prostate cancer, consensus, metastatic prostate cancer, #PCSM, #ProstateCancer

Introduction

The management paradigm for metastatic prostate cancer (mPCa) is evolving after an increase in the number of new trials completed and novel drugs approved in recent years. For instance, there is growing evidence to support the use of chemotherapy combined with androgen deprivation therapy (ADT) in men with castration-naïve mPCa. A number of new therapies for patients with metastatic castration-resistant prostate cancer (mCRPC) have also been approved by health authorities worldwide; however, the factors affecting appropriate selection of patients for a specific treatment or sequence of therapies remain uncertain based on current clinical data. Additionally, there are fewer data on people of Chinese or Asian ethnicity than there are on white people.

To facilitate the development of management strategies for patients with mPCa in Hong Kong, a local expert consensus was organized jointly by the Hong Kong Urological Association (HKUA) and the Hong Kong Society of

Table 1 Panel members by affiliation and specialty.

Last name	First name	Affiliation	Specialty
Chan	Chi-Kwok	HKUA	Urologist
Chan	Tim-Wai	HKSUO	Clinical Oncologist
Cheung	Foon-Yiu	HKSUO	Clinical Oncologist
Ho	Lap-Yin	HKUA	Urologist
Kwong	Philip	HKSUO	Clinical Oncologist
Lee	Eric	HKSUO	Clinical Oncologist
Leung	Angus	HKSUO	Clinical Oncologist
Leung	Simon	HKUA	Urologist
Ma	Wai-Kit	HKUA	Urologist
Poon	Darren	HKSUO	Clinical Oncologist
So	Hing-Shing	HKUA	Urologist
Tam	Po-Chor	HKUA	Urologist

HKSUO, Hong Kong Society of Uro-Oncology; HKUA, Hong Kong Urological Association.

Uro-Oncology (HKSUO), which are the two main professional organizations representing prostate cancer specialists in the territory. Their aim was to establish a set of consensus statements in the locality. The statements were fundamentally derived from results of local and international clinical studies and overseas guidelines and, where the available evidence was limited or contradictory, supplemented by the insights and expertise of consensus members.

Methods

A total of 12 experts, six each from the HKUA and the HKSUO, were included in the panel (Table 1). They firstly identified the six most crucial and relevant areas of debate associated with the management of mPCa, as follows: (i) management of men with castration-naïve mPCa; (ii) management of men with mCRPC; (iii) value and use of predictive markers in mCRPC; (iv) sequencing treatment in mCRPC; (v) management of men with oligometastasis; and (vi) staging and monitoring of mCRPC treatment.

An English-language literature review of the above topics was conducted using the PubMed database with the following keywords: abiraterone; bone metastasis; cabazitaxel; castration-naïve; chemotherapy; docetaxel; enzalutamide;

guideline; hormonal treatment; hormone-naïve; hormone-sensitive; immunotherapy; metastatic castration-resistant prostate cancer; metastatic prostate cancer; modality; non-pharmaceutical treatment; oligometastasis; predictive marker; prognostic marker; radium-223; sipuleucel-T; skeletal-related event; staging; treatment sequencing; and work-up [evaluation]. Only papers published between January 2005 and August 2016 were included for review.

A modified Delphi method (Appendix S1) [1] was used to hold a series of panel meetings for the members to discuss their clinical experience and the available evidence regarding the six areas of debate, with the ultimate aim of developing consensus statements. Each statement was voted on anonymously by every panel member at the final meeting. With an abbreviated form of the method used by Ooi et al. [2] (Table 2), each statement was evaluated on its practicability of recommendation in Hong Kong. A consensus statement was accepted only if ≥80% of the panellists chose 'accept completely' (option A) or 'accept with some reservation' (option B). Full voting records for each drafted statement are provided in Appendix S2.

Results

A total of 45 consensus statements were accepted and established by panel voting.

Part 1: Management of Men with Castration-Naïve mPCa

> Statement 1: 'To confirm mPCa, imaging tools, in addition to clinical examination, should be employed.'

The responses to Part 1, Statement 1 were as follows: A: 92%; B: 8%; C: 0%; D: 0%; and E: 0%.

The panel members agreed that, based on clinical experience, apart from examining biochemical failures, such as elevated PSA levels, imaging tools including MRI, CT, bone scans, and positron emission tomography (PET)/CT are helpful for physicians to confirm mPCa in patients.

Table 2 Grading system for consensus statements [2].

Quality of evidence	Classification of recommendation	Practicability of recommendation*
I: Evidence obtained from at least one randomized controlled trial	A: There is good evidence to support the statement	A: Accept completely
II-1: Evidence obtained from well-designed control trials without randomization	B: There is fair evidence to support the statement	B: Accept with some reservation
II-2: Evidence obtained from well-designed cohort or case–control study	C: There is poor evidence to support the statement but recommendation made on other grounds	C: Accept with major reservation
II-3: Evidence obtained from comparison between time or places with or without intervention	D: There is fair evidence to refute the statement	D: Reject with reservation
III: Opinion of respected authorities, based on clinical experience and expert committee	E: There is good evidence to refute the statement	E: Reject completely

*The panel voted on each consensus statement based on the practicability. The quality of evidence and classification of recommendation are for reference only.

Statement 2: 'The definition of high-volume disease in castration-naïve mPCa remains uncertain, but the general principle of ≥4 sites of bone metastases (with at least one bone metastasis beyond the pelvis and axial skeleton), or any visceral metastases, is being accepted.'

The responses to Part 1, Statement 2 were as follows: A: 58%; B: 42%; C: 0%; D: 0%; and E: 0%.

Distinct natural histories and disease courses were observed for subsets of patients with mPCa, stratified by the disease extent. Patients with high-volume disease (visceral metastasis and multiple bone metastases, e.g. ≥4) had poorer outcomes, whereas other studies illustrated that those with ≤5 bone metastases performed better than those with >5 at the time of relapse after radiotherapy (RT) for localized disease [3–5]. In the CHAARTED study, a randomized phase III trial [6], high-volume disease in castration-naïve mPCa was defined as having visceral metastases and/or ≥4 bone metastases, with at least one metastasis beyond the pelvis vertebral column. Subsequently, the National Comprehensive Cancer Network guidelines in the USA followed the same principle to distinguish high-volume disease from low-volume disease [7]. Considering the local context, the panel accepted the general principle for identifying disease volume.

Statement 3: 'Regarding a basic work-up investigation, whole-body MRI or dual-tracer PET/CT scan is preferred if resources or facilities are available. Otherwise, CT scan (from thoraces to pelvis) plus bone scan is an acceptable option. Ultrasound alone is not recommended.'

The responses to Part 1, Statement 3 were as follows: A: 33%; B: 67%; C: 0%; D: 0%; and E: 0%.

The major role of imaging is to detect any metastases at lymph nodes or bone by evaluating anatomical and functional characteristics, so that the type of prostate cancer can be characterized, facilitating the selection of the optimal treatment. After reviewing major references on the sensitivity and specificity of the available imaging tools [8–10], the panel agreed that whole-body MRI or dual-tracer PET/CT scan (either prostate-specific membrane antigen or choline can be adopted based on local availability) are the preferable evaluation methods; however, it should be noted that, as discussed in the Advanced Prostate Cancer Consensus Conference (APCCC), 2017, despite a proven accuracy for detecting metastases, the performance of these novel imaging methods in improving treatment efficacy and patient outcome has not been evaluated [11]. Further research is still required to investigate their optimal utility.

Given that costs and availability may be a concern for some local healthcare institutions, CT imaging spanning the thoraces to pelvis, together with a bone scan, is also an acceptable practice, based on current evidence [8,12–15] and

the clinical experience of the panel members. Ultrasonography alone, however, is not recommended under any circumstances.

Statement 4: 'ADT is the standard of care. Supplemental calcium/vitamin D3 is recommended following ADT, in view of the risk of osteoporosis associated with ADT.'

The responses to Part 1, Statement 4 were as follows: A: 67%; B: 25%; C: 8%; D: 0%; and E: 0%.

The standard treatment for mPCa is ADT, using LHRH agonists/antagonists or bilateral orchiectomy [16–19]. These two ADT measures are expected to be equally effective [20–22]. Moreover, intermittent ADT could not be proven to be non-inferior to continuous ADT for survival [23–25].

A retrospective cohort study conducted in Hong Kong showed that the use of ADT was associated with an increased risk of osteoporotic fracture in Chinese patients with mPCa (4.8% in the ADT group vs 1.0% in the non-ADT group), especially those with diabetes (hazard ratio [HR] 4.39, 95% CI 1.08–17.83) and poor performance status (HR 3.14, 95% CI 1.24–8.00) [26]. The fracture risk associated with the use of ADT was also revealed in overseas studies [19]. In this regard, the panel agreed that supplemental calcium and vitamin D3 is recommended as prophylaxis to prevent osteoporosis in patients treated with ADT. Other options to increase bone density, including zoledronic acid and denosumab, were also discussed by the panel members, but it was stressed that patients should be alerted to the risk of osteonecrosis of the jaw associated with these medications [27].

Statement 5: 'Chemotherapy (six cycles of docetaxel) should be considered in addition to ADT for all M1 patients who are fit enough for chemotherapy. The following factors should be taken into account: (a) volume of castration-naïve mPCa (i.e. high vs low); and (b) performance status.'

The responses to Part 1, Statement 5(a) were as follows: A: 42%; B: 42%; C: 8%; D: 8%; and E: 0%, and responses to Statement 5(b) were as follows: A: 33%; B: 50%; C: 17%; D: 0%; and E: 0%.

Based on the CHAARTED trial [6] and another randomized phase III study, the STAMPEDE trial [28], combination therapy of ADT plus docetaxel could significantly improve overall survival (OS) in castration-naïve mPCa patients compared with ADT alone. The median OS in patients treated with combination therapy was 13.6 months longer [6] and 10 months longer [28] in these two studies. In the CHAARTED trial, the sub-group analysis showed that the benefit of combination therapy was more substantial in the patients with high-volume disease than in the overall study population, with a median OS 17.0 months longer in the

combination group than in the ADT-alone group [6]. A Hong Kong retrospective study showed that, compared with their western counterparts, Chinese castration-naïve patients with mPCa treated with the combination therapy could gain similar benefits at an early stage, with promising biochemical responses [29]. It found that the median time to castration resistance among the patients was 19.5 months, which is similar to the finding in the CHAARTED study (i.e. 20.2 months), even though a greater proportion of patients with high-volume disease was included in the former trial (96.9% in the Hong Kong study vs 66.2% in the CHAARTED trial) [6,29]. The risk of chemotherapy-related haematological toxicities, however, may be higher among Chinese patients, so careful patient selection and consideration of granulocyte colony-stimulating factor is necessary before starting the combination therapy [29].

Regarding the selection of patients who are suitable for ADT plus chemotherapy, there was a consensus among the panel that the volume of disease and patient performance status should be considered, in view of their clinical experience and current evidence [6,30]. As per the CHAARTED trial [6] and another randomized phase III trial [30], the efficacy of combination therapy was more favourable in patients with high-volume disease than in those with low-volume disease. In the APCCC, 2017, there was a consensus for adding docetaxel to ADT in the majority of patients who are suitable for chemotherapy and have *de novo* castration-naïve mPCa with high-volume disease as defined by CHAARTED [11]. As such, the volume of disease is consistently agreed by both the overseas panel and the local consensus as an important factor influencing the decision on the use of chemohormonal therapy.

In addition, patient performance status, rather than age, should be considered to evaluate eligibility for chemotherapy before combination therapy is adopted. As per clinical experience in Hong Kong, ADT plus docetaxel has been given to patients aged up to 80 years; therefore, age may not necessarily be a critical factor in deciding whether to initiate the chemohormonal treatment. Instead, other factors, such as patient performance status, should be considered. Although not covered by the panel, some factors, including severe hepatic impairment, neuropathy grade ≥2, and platelets $<50 \times 10^9$/L and/or neutrophils $<1.0 \times 10^9$/L, would render a patient 'unfit' for chemotherapy, as per the consensus from the APCCC, 2017 [11]. These factors are worth considering in the local context.

Statement 6: 'Chemotherapy with docetaxel should NOT be given to patients with M0 disease.'

The responses to Part 1, Statement 6 were as follows: A: 75%; B: 25%; C: 0%; D: 0%; and E: 0%.

For patients with non-metastatic (M0) disease, chemotherapy in addition to ADT, was not recommended by the panel because of the absence of clinical data on the survival benefits brought about.

Statement 7: 'Anti-androgen monotherapy or oestrogen is NOT recommended as first-line treatment'.

Responses to Part 1, Statement 7 were as follows: A: 58%; B: 33%; C: 8%; D: 0%; and E: 0%.

After reviewing several major references [7,31–33], the panel recommended against the use of anti-androgen monotherapy or oestrogen as first-line treatment of castration-naïve mPCa because, compared with ADT, inferior efficacy was observed from clinical settings.

Part 2: Management of Men with mCRPC

Statement 1: 'In general, castration resistance is determined when there is (a) first-line ADT failure, (b) castrate serum testosterone <50 ng/dL or 1.7 nmol/L, and (c) three consecutive rises in PSA 1 week apart, resulting in two 50% increases over the nadir, and a PSA >2 ng/mL OR (d) either two or more new bone lesions on bone scan or a soft tissue lesion using Response Evaluation Criteria in Solid Tumours (RECIST).'

Responses to Part 2, Statement 1, were as follows: A: 25%; B: 75%; C: 0%; D: 0%; and E: 0%.

Regarding the definition of castration resistance, several practical guidelines from Europe and the USA [7,31,34,35] and the criteria from the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) [36] were reviewed and discussed by the panel. It was noted that the PCWG3 recommendations are primarily focused on a clinical trial setting. Given that the aim of the consensus panel was to facilitate real-life clinical practice, the overseas practical guidelines [7,31,34,35], rather than PCWG3 criteria, were referred to for formulating the consensus statement. As a result, the panellists generally accepted that the statement can be applied to identify patients with mCRPC in the local context so as to decide on an appropriate treatment accordingly.

Statement 2: 'First-line treatment options include, in alphabetical order, abiraterone, docetaxel, enzalutamide, and radium-223. Choice of treatment should be based on the following factors: (a) presence of symptomatic disease and (b) response to primary ADT (i.e. ≤12 months vs >12 months).'

The responses to Part 2, Statement 2(a) were: A: 67%; B: 25%; C: 8%; D: 0%; and E: 0% and responses to Statement 2 (b) were: A: 0%; B: 92%; C: 8%; D: 0%; and E: 0%.

As per the significantly improved OS and radiological progression-free survival (PFS) shown in two pivotal randomized trials, namely the COU-AA-302 [37] and

PREVAIL studies [38], androgen receptor (AR) pathway inhibitors, including abiraterone and enzalutamide, were accepted by the panel as a first-line treatment option for patients with mCRPC. In the COU-AA-302 trial, which included patients with mCRPC who are asymptomatic or mildly symptomatic without visceral metastasis, patients treated with abiraterone had significantly longer median OS (34.7 months vs 30.3 months) and radiographic PFS (16.5 months vs 8.3 months) compared with the placebo group [37]. As for the PREVAIL study, which recruited asymptomatic or mildly symptomatic patients with/without visceral metastasis, the median OS (35.3 months vs 31.3 months) and radiographic PFS (20.0 months vs 5.4 months) were significantly improved in patients treated with enzalutamide compared with those who received placebo [38].

By contrast, a retrospective study conducted in Hong Kong found that abiraterone may have inferior efficacy as first-line treatment in patients with mCRPC who have symptomatic disease or short duration of response to prior ADT (i.e. <10 months) [39]. The median OS in the cohort of patients treated with abiraterone (18.1 months) was substantially shorter than that found in the COU-AA-302 study (34.7 months) [38,39]. The inferior survival outcome in the Hong Kong study might have been caused by the inclusion of patients with higher tumour burden, visceral metastases, or symptomatic disease, as proposed by the researchers [39].

In an extended survival analysis of the TAX 327 study [40], in which patients with symptomatic mCRPC or evident disease progression were included, docetaxel could bring about significantly longer median OS (19.2 months) in patients when compared with mitoxantrone (16.3 months). The OS advantage of docetaxel was also consistent across varied patient subgroups. Given the similar benefits among subgroups and the possible deterioration of quality of life caused by disease progression, it is considered appropriate to offer docetaxel to patients with mCRPC with symptoms.

Radium-223, an α-emitter, was also accepted as a first-line therapy for patients with mCRPC. The ALSYMPCA randomized trial found that, in patients with symptomatic mCRPC and no visceral metastases who failed or were unfit for chemotherapy, radium-223 significantly improved the median OS by 3.6 months compared with the placebo [41].

Apart from the presence of symptomatic disease, the panel agreed that, based on their clinical experience, the response to primary ADT is also a factor to be considered in deciding on a first-line treatment for patients with mCRPC.

It was noted that sipuleucel-T was not included in the consensus statement because of its unavailability in the locality, despite its proven efficacy in some clinical trials [42,43].

Statement 3: 'In patients with mCRPC and progression following docetaxel chemotherapy, further life-prolonging treatment options should be offered, including, in alphabetical order, abiraterone, cabazitaxel, enzalutamide, and radium-223.'

The responses to Part 2, Statement 3 were as follows: 75%; B: 25%; C: 0%; D: 0%; and E: 0%.

The panel agreed that abiraterone or enzalutamide can be offered to patients with mCRPC with progressive disease after docetaxel therapy, based on their experience and the results of the COU-AA-301 trial [44] and the AFFIRM study [45]. Both of the randomized trials recruited patients with mCRPC who had received first-line docetaxel [44,45]. The COU-AA-301 trial found that patients treated with abiraterone had significantly longer median OS compared with the placebo group (15.8 months vs 11.2 months) [44]. In the AFFIRM study, the median OS in patients treated with enzalutamide was significantly improved compared with the placebo arm (18.4 months vs 13.6 months) [45].

In addition, the clinical efficacy of abiraterone in terms of OS and PFS among post-chemotherapy patients with mCRPC in Hong Kong was found to be comparable to that observed in the COU-AA-301 trial (median OS 15.5 months vs 15.8 months; median PFS 6.4 months vs 5.6 months) [39]. Another Hong Kong retrospective study showed that abiraterone and cabazitaxel were significantly associated with increased OS in post-docetaxel patients with mCRPC [46].

In view of the local experience and the findings of the TROPIC randomized trial [47], cabazitaxel was accepted by the panel to be used in post-chemotherapy patients with mCRPC and disease progression for enhancing OS and PFS. In the TROPIC study, patients who received cabazitaxel as post-docetaxel treatment had significantly longer OS compared with those treated with mitoxantrone (median OS 15.1 months vs 12.7 months) [47].

As shown in the ALSYMPCA study [41], radium-223 was effective and safe in patients with symptomatic mCRPC and no visceral metastases regardless of pre-treatment with docetaxel. With the panellists' experience, it was agreed that radium-223 can be offered to prolong the OS of patients with mCRPC after chemotherapy.

Statement 4: 'Radium-223 is the only bone-targeted agent that is associated with a survival benefit.'

The responses to Part 2, Statement 4 were as follows: A: 75%; B: 25%; C: 0%; D: 0%; and E: 0%.

Along with radium-223, bone-targeted agents also include zoledronic acid, a bisphosphonate, and denosumab, a fully human monoclonal antibody that targets the receptor activator of nuclear factor κB (RANK) ligand, both of which

are indicated for bone metastases but have no significant proven survival benefits [48,49]. Based on current evidence [41,48,49], the panel accepted that radium-223 is the only bone-targeted agent that may lead to survival benefits.

Despite no definite survival advantages, zoledronic acid and denosumab can reduce the risk of skeletal-related events in patients with mCRPC [48,49]. As shown in a cohort study conducted in Hong Kong, skeletal-related events could worsen the prognosis of patients with mCRPC in terms of OS and cancer-specific survival [50]. In this regard, among patients with mCRPC with bone metastases, zoledronic acid or denosumab can be considered for prevention of skeletal-related events.

> Statement 5: External beam radiotherapy (RT) is highly effective to treat painful bone metastases.

The responses to Part 2, Statement 5 were as follows: A: 83%; B: 17%; C: 0%; D: 0%; and E: 0%.

The effectiveness of palliative external RT, with an overall pain response rate of 60%, has been shown in various studies and it is regarded as one of the most cost-effective palliative treatments for mPCa with symptomatic bone metastases [51,52]. Based on the panellists' experience, most patients with mCRPC have painful bone metastases, which can be treated effectively with external beam RT.

Part 3: Value and Use of Predictive Markers in mCRPC

> Statement 1: 'Factors considered potentially predictive on first-line treatment options include: (a) response to primary ADT (i.e. ≤12 months vs >12 months) and (b) presence of AR-splice variants, if such investigation is available.'

The responses to Part 3, Statement 1(a) were: A: 25%; B: 58%; C: 17%; D: 0%; and E: 0%, and responses to Statement 1(b) were: A: 42%; B: 42%; C: 17%; D: 0%; and E: 0%.

Duration of response to primary ADT was identified as a predictor of OS and of sensitivity to AR axis-targeted drugs in patients with mCRPC [53,54]. A relatively short time to castration resistance (i.e. <12 to 16 months) in previous ADT was found to be a factor lowering the efficacy of subsequent endocrine therapies in patients with mCRPC [55,56]. The panel agreed that the response to primary ADT is a potentially predictive marker by which to select an appropriate first-line treatment option for patients with mCRPC. A shorter time to castration resistance is considered to favour the use of chemotherapy.

The most common AR variant in human tissues is AR variant 7 (AR-V7) [57], which was found to be associated with resistance to enzalutamide and abiraterone in patients with mCRPC [57]. Chemotherapy was shown to be more

efficacious than AR pathway inhibitors among AR-V7-positive patients, whereas comparable efficacy was observed between chemotherapy and AR pathway inhibitors in AR-V7-negative patients [57,58]. Based on the available evidence, the panel considered the presence of AR-splice variants as a potentially predictive factor for the choice of first-line treatment of mCRPC; however, it is worth noting that, in the APCCC, 2017, there was a consensus not to use AR-V7 testing for deciding on a treatment option, partly because of the low detection levels of AR-V7 before first- and second-line treatment and the high chance that abiraterone or enzalutamide would be prescribed in this situation [11]. At present, an assessment of AR-V7 is not used in routine clinical practice among Hong Kong physicians. To further verify the use of AR-V7 in a real-life clinical setting, more research is warranted to investigate its impact on long-term patient outcomes and the practicability of the tests.

In addition to the above two factors, it is noteworthy that the presence of symptomatic disease, as mentioned in Part 2, Statement 2, is also an important marker when a first-line treatment option is chosen for patients with mCRPC.

> Statement 2: 'Factors considered prognostic but which might not affect choice of first-line treatment options include: (a) Gleason score (i.e. <8 vs ≥8), (b) presence of visceral metastases, (c) performance status and (d) presence of comorbidities.'

The responses to Part 3, Statement 2(a) were: A: 25%; B: 75%; C: 0%; D: 0%; and E: 0%; responses to Statement 2(b) were: A: 58%; B: 33%; C: 8%; D: 0%; and E: 0%; responses to Statement 2(c) were: A: 17%; B: 67%; C: 8%; D: 8%; and E: 0%; and responses to Statement 2(d) were: A: 33%; B: 50%; C: 17%; D: 0%; and E: 0%.

In an observational study [59], patients with mCRPC with a higher Gleason score had a lower chance of being responsive to abiraterone. By contrast, the survival benefit gained with docetaxel in the TAX 327 trial was most pronounced in patients with a higher Gleason score (i.e. ≥7) [60]. It is noteworthy, however, that the TAX 327, COU-AA-302, and PREVAIL studies all included patients with high-grade tumours [37,38,40], suggesting that docetaxel, abiraterone and enzalutamide are possible treatment options for patients with mCRPC with a high Gleason score. The panel agreed that a Gleason score is a prognostic factor, but might not affect the choice of treatment option on its own.

Based on the TAX 327 [38] and PREVAIL studies [40], both of which included patients with visceral metastases, it was suggested that docetaxel may be preferable for symptomatic patients with mCRPC with visceral metastases, while asymptomatic or mildly symptomatic patients with visceral metastases can be treated with enzalutamide or docetaxel. Because patients with visceral metastases were not

included in the COU-AA-302 trial [37], extrapolation of the trial results may be required when the use of abiraterone is considered in this group of patients. Presence of visceral metastases was accepted as a prognostic factor, but additional considerations should be made when deciding on a treatment option.

A poorer performance status was found to be associated with lower treatment responses and reduced OS among patients with mCRPC [53,61]. The toxicity profile of a treatment option is of particular concern in patients with a poor performance status; however, as clinical trials generally have excluded patients with a poorer performance status (Eastern Cooperative Oncology Group [ECOG] score of 3 or 4) [53], treatment options cannot merely be based on a performance status. Instead, they should be individualized, depending on other characteristics of a patient.

Based on the panellists' experience, certain comorbidities, which include active infection, liver failure and uncontrolled diabetes, may not favour the use of docetaxel and abiraterone in patients with mCRPC [62], while enzalutamide may be less preferred if patients have a history of seizure and are taking multiple medications with a concern over potential drug interactions. Although comorbidities provide prognostic information, a treatment option is not necessarily influenced by them, as agreed by the panel, and other factors should be taken into account.

> Statement 3: 'Factors considered neither predictive nor prognostic include: (a) neutrophil-lymphocyte ratio, (b) age and (c) presence of bone metastases.'

The responses to Part 3, Statement 3(a) were: A: 67%; B: 25%; C: 8%; D: 0%; and E: 0%; responses to Statement 3(b) were: A: 17%; B: 75%; C: 8%; D: 0%; and E: 0%; and responses to Statement 3(c) were: A: 17%; B: 67%; C: 8%; D: 8%; and E: 0%.

After reviewing a number of references [61,63–67], the panel concluded that neutrophil-lymphocyte ratio, age, and presence of bone metastases are not meaningful factors in the physician's selection of an appropriate first-line treatment option for patients with mCRPC.

Part 4: Sequencing Treatment in mCRPC

> Statement 1: 'After first-line docetaxel/AR pathway inhibitor fails, the following factors should be considered when deciding on a second-line treatment: (a) patient's fitness/performance status (i.e. ECOG 0-1 vs ECOG 2); (b) age (i.e. <75 years vs ≥75 years); (c) time to disease progression after initial chemotherapy/AR pathway inhibitor (during or ≤3 months vs >3 months); (d) clinical symptoms, such as bone pain and complications arising from the metastatic lesions; and (e) presence of visceral metastases.'

Responses to Part 4, Statement 1(a) were: A: 67%; B: 33%; C: 0%; D: 0%; and E: 0%; responses to Statement 1(b) were: A: 8%; B: 83%; C: 8%; D: 0%; and E: 0%; responses to Statement 1(c) were: A: 25%; B: 58%; C: 17%; D: 0%; and E: 0%; responses to Statement 1(d) were: A: 42%; B: 42%; C: 8%; D: 8%; and E: 0%; and responses to Statement 1(e) were: A: 25%; B: 67%; C: 0%; D: 8%; and E: 0%.

According to a review of clinical studies [68], among patients with mCRPC with an ECOG score of 2 who progressed after docetaxel, the risk of death was significantly reduced with the use of abiraterone or enzalutamide, but not cabazitaxel. It was discussed by the panel that different geriatric assessment evaluations and nutritional status should be considered to identify a patient's fitness and performance status, in order to select a tailored treatment regimen.

Based on some reports [69–71], advanced age (≥75 years) may be associated with an increased risk of adverse events related to some treatment options; however, as shown in previous consensus statements, age is not necessarily a decisive factor when deciding on an appropriate therapy. Other patient characteristics should be taken into account in a holistic manner.

A retrospective study found that patients with mCRPC who had early disease progression on docetaxel would have limited responses to abiraterone, while docetaxel would cause minimal anti-tumour activity in patients who discontinued abiraterone because of progression [72]. The time to disease progression after initial treatment with either chemotherapy or AR pathway inhibitors is considered to be a factor predicting the choice of second-line treatment of mCRPC.

The presence of clinical symptoms was identified by some studies as an important factor affecting the choice of treatment of mCRPC [73]. This is consistent with the panel's consensus in the above statement and Statement 2 of Part 2 previously. In addition, patients with the presence of visceral metastases were found to be less sensitive to hormone therapy [68].

> Statement 2: 'If first-line docetaxel fails, second-line treatment options include AR pathway inhibitors, cabazitaxel, or radium-223. Cabazitaxel should be considered in patients who are less likely to respond to AR pathway inhibitors, such as those with a high Gleason score (i.e. 8–10).'

Responses to Part 4, Statement 2 were: A: 17%; B: 75%; C: 8%; D: 0%; and E: 0%.

Current evidence has shown that AR pathway inhibitors, including abiraterone and enzalutamide, cabazitaxel, and radium-223 can be used to treat patients with mCRPC after first-line docetaxel failed [41,74,75]; however, based on *post hoc* analyses of a randomized controlled trial, patients with

tumours of a high Gleason score (8–10) were found to be possibly more responsive to cabazitaxel than to AR pathway inhibitors, which may be more suitable for those with a lower Gleason score (<8), especially with a durable response to initial hormone therapy [74].

> Statement 3: 'Radium-223 is indicated for the treatment of mCRPC patients with symptomatic bone metastases and no known visceral metastatic disease, with or without prior chemotherapy.'

Responses to Part 4, Statement 3 were: A: 58%; B: 42%; C: 0%; D: 0%; and E: 0%.

Based on the results of the pivotal study [41], radium-223 can bring about significant survival benefits to patients with mCRPC with symptomatic bone metastases and no visceral metastases. It was also effective and safe whether or not patients were pre-treated with docetaxel.

> Statement 4: 'There is no evidence to show a major cross-resistance between radium-223 and other systemic agents. However, the sequencing between radium-223 and other systemic agents remains undetermined.'

Responses to Part 4, Statement 4 were: A: 50%; B: 50%; C: 0%; D: 0%; and E: 0%.

No study has investigated the cross-resistance between AR pathway inhibitors, docetaxel and radium-223, but in view of the non-overlapping mechanisms of action and toxicity profiles, radium-223 potentially could be used irrespective of other systemic agents [75].

Part 5: Management of Men with Oligometastasis

> Statement 1: 'The definition of oligometastasis in prostate cancer remains undetermined but the general principle of ≤5 metastases is being accepted.'

Responses to Part 5, Statement 1 were: A: 42%; B: 50%; C: 8%; D: 0%; and E: 0%.

Based on the current literature [76,77], oligometastasis in prostate cancer is often defined as having 3 to ≤5 sites of isolated metastatic spread. After discussion, the panel agreed that the general principle of ≤5 metastases can be adopted to identify oligometastasis in actual clinical practice. Patients with oligometastasis are perceived to have a relatively indolent course, which may be treated effectively with metastasis-directed local ablative therapy.

> Statement 2: 'Oligometastasis can be either synchronous (de novo with uncontrolled primary prostate tumour) or metachronous (oligo-recurrence with controlled primary prostate tumour).'

Responses to Part 5, Statement 2 were: A: 67%; B: 25%; C: 8%; D: 0%; and E: 0%.

Clinical cases in the literature showed that oligometastasis with durable disease control was less aggressive compared with extensive metastases [78]. Some cases were recurrent with a controlled or controllable primary prostate lesion, while some were de novo with uncontrolled primary prostate tumour [79,80].

> Statement 3: 'The presence of oligometastasis may occur with prior ADT (castration-resistant oligoprogression) or without prior ADT (castration-naïve oligometastasis).'

Responses to Part 5, Statement 3 were: A: 67%; B: 33%; C: 0%; D: 0%; and E: 0%.

Based on the literature [80] and the panellists' clinical experience, oligometastasis may occur in both patients treated with ADT and those without prior ADT.

> Statement 4: 'Metastasis-directed therapy (MDT) provides excellent local control at the sites of oligometastasis. MDT may have the potential to spare or to delay the toxicity associated with the use of systemic therapies in the setting of oligometastasis. Both RT, particularly stereotactic body RT, and surgery have been investigated for this approach.'

Responses to Part 5, Statement 4 were: A: 42%; B: 58%; C: 0%; D: 0%; and E: 0%.

In a Belgian case series [81], among the patients with limited prostate cancer metastases at bone or lymph node who were treated with repeat stereotactic body RT (SBRT), palliative ADT was deferred with a median period of 38 months, with no grade 3 toxicity observed. Moreover, a retrospective study found that the patients with ≤3 prostate cancer metastases who were treated with SBRT had a median distant PFS of 21 months, with no grade 3 or above toxicity reported [82]. A median period of 28 months was observed from first SBRT to the initiation of palliative ADT [82]. Despite the benefits observed in the studies, the effect of MDT on OS in patients with oligometastasis has not been validated by any prospective randomized controlled trials [83]. As such, MDT is still highly controversial and should only be used after thorough consideration of a patient's clinical needs.

> Statement 5: 'At this juncture, the practice of MDT in patients with oligometastasis remains investigational. Optimal patient selection for MDT remains challenging.'

The responses to Part 5, Statement 5 were: A: 25%; B: 75%; C: 0%; D: 0%; and E: 0%.

There is a lack of randomized controlled trials regarding the use of MDT in patients with oligometastatic prostate cancer. Various clinical trials, such as the UK-based CORE study [84] and the multi-national SABR-COMET study [85], are currently ongoing, with the aim of investigating the survival benefits brought about by SBRT in patients with oligometastatic prostate cancer. Their results may provide

further information on the appropriate patient selection for MDT.

Statement 6: 'Local treatment to the primary prostate tumour in the presence of oligometastasis remains investigational'.

The responses to Part 5, Statement 6 were: A: 33%; B: 58%; C: 8%; D: 0%; and E: 0%.

Although RT or surgery at the primary prostate tumour in the context of oligometastasis remains uncertain, it was discussed that the abscopal effect of RT (i.e. the signals induced by RT can convert the irradiated tumour into an immunogenic antigen and the host's immune response to the tumour can contribute both to the local response to RT and to a systemic rejection of metastasis) is a potential theoretical advantage, although not well proven. In addition, survival benefits were observed in patients treated with prostate RT in a Korean retrospective study [86]. In a Hong Kong retrospective cohort study [87], intensity-modulated RT was shown to be well tolerated by Chinese patients with clinically localized prostate cancer, with <5% of patients experiencing grade ≥3 late complications, and this favourable RT tolerance provides the feasibility of exploring safe local prostate treatment in the presence of oligometastasis. There is ongoing research on local treatment to the primary prostate tumour in the presence of oligometastasis, which includes the STAMPEDE trial Arm H [88] and the STOMP study [89].

Statement 7: 'In patients with locally advanced prostate cancer with limited regional nodal oligometastases, ADT together with surgery or RT, or surgery followed by RT, seems better in terms of disease control than ADT alone.'

The responses to Part 5, Statement 7 were: A: 42%; B: 58%; C: 0%; D: 0%; and E: 0%.

Based on the results of several studies [90–96], radical prostatectomy together with ADT, compared with ADT alone, could lead to additional survival benefits in patients with locally advanced prostate cancer with limited oligometastases. Furthermore, prostate RT plus ADT was also found to be associated with a longer OS when compared with ADT alone (5-year OS 49% vs 33%) [96]. A local therapy, either surgery or RT, in addition to ADT is considered to be associated with better survival outcomes when compared with ADT alone.

Statement 8: 'A multi-modal approach is needed, with surgery, RT and systemic therapy, alone or in combination, for the improvement of patient outcomes in patients with oligometastases.'

The responses to Part 5, Statement 8 were: A: 67%; B: 33%; C: 0%; D: 0%; E: 0%.

In view of the complexities of oligometastatic prostate cancer, different approaches, including MDT, radical prostatectomy, prostate RT and systemic therapy, alone or in combination, should be considered for suitable patients after a careful assessment of benefits and risks; however, it was noted that a multi-modal approach remains controversial and more evidence is required to further prove its efficacy and safety profiles; therefore, its use in men with oligometastatic prostate cancer should not be encouraged outside of clinical trials, unless a favourable benefit–risk balance is justified.

Part 6: Staging and Monitoring of mCRPC Treatment

Statement 1: 'Before starting a new line of treatment, re-staging in mCRPC should be undertaken as a baseline to monitor any subsequent response to the treatment that may potentially cause side effects, e.g. chemotherapy.'

The responses to Part 6, Statement 1 were: A: 33%; B: 58%; C: 8%; D: 0%; and E: 0%.

It was discussed that, before a new line of treatment is to be initiated in mCRPC patients, scanning to establish a new baseline is warranted [97] in order to assess patients' subsequent responses to the new treatment.

Statement 2: 'For re-staging in mCRPC, bone scan and CT scan are recommended, while MRI and PET scan are optional depending on available resources and facilities. However, eligibility criteria for imaging, the type of imaging modality, and the frequency of scanning for metastatic disease remain undetermined based on current available evidence.'

The responses to Part 6, Statement 2 were: A: 42%; B: 50%; C: 8%; D: 0%; and E: 0%.

After reviewing the recommendations from some expert consensus groups in Europe and the USA [36,97,98], the panel agreed that bone scintigraphy, together with CT scan (possibly from thoraces to pelvis), are to be recommended as the imaging tools for re-staging in patients with mCRPC. MRI and PET scan are considered optional and can be carried out based on physicians' judgement and resources of individual healthcare institutions. Nevertheless, because of a lack of devoted trials, there is still uncertainty regarding the eligibility criteria for imaging and the time to initiate imaging.

Statement 3: 'For treatment monitoring in mCRPC, regular blood tests (at least 3-monthly), including PSA, alkaline phosphatase and lactate dehydrogenase, are highly recommended. If resources are available, regular follow-up imaging with bone scan or CT scan can be performed after treatment completion.'

The responses to Part 6, Statement 3 were: A: 33%; B: 50%; C: 17%; D: 0%; and E: 0%.

Considering the overseas expert recommendations in the local context [36,97,98], the panel agreed that regular measurements of PSA, alkaline phosphatase and lactate dehydrogenase should be taken at least quarterly for monitoring the treatment in mCRPC patients. Bone scan and CT scan are optional and can be performed at the discretion of physicians.

> Statement 4: 'If two of three criteria (PSA progression, radiographic progression and clinical deterioration) are fulfilled, termination of current treatment can be considered.'

The responses to Part 6, Statement 4 were: A: 50%; B: 50%; C: 0%; D: 0%; and E: 0%.

In view of the consensus established in the St Gallen Advanced Prostate Cancer Consensus Conference in 2015 [98], the panel agreed that, if two or above of three criteria, i.e. PSA progression, radiographic progression and clinical deterioration, are fulfilled in a patient, the current treatment can be terminated.

> Statement 5: 'The treatment can be continued if it is still able to slow down disease progression (e.g. patient symptoms under control, pain controlled as measured by Brief Pain Inventory, satisfactory quality of life remaining) and only causes minimal side effects.'

The responses to Part 6, Statement 5 were: A: 33%; B: 50%; C: 17%; D: 0%; and E: 0%.

The panel agreed that treatment can be continued in patients if disease progression can be slowed down, including controlling symptoms and pain, and maintaining satisfactory quality of life.

> Statement 6: 'Temporary PSA rise could be observed during the initial phase of systemic treatment, and sufficient time for monitoring (3 months) should be considered in order to determine whether it is a PSA flare (initially rising PSA under therapy, dropping thereafter to values below baseline) or genuine progression.'

The responses to Part 6, Statement 6 were: A: 42%; B: 58%; C: 0%; D: 0%; and E: 0%.

A PSA flare can be defined as an initial rise in serum PSA levels under therapy, followed by a drop to values below baseline [99]. This has been observed in ~5% to 30% of patients receiving hormonal therapies with LHRH analogues and in ~8% to 20% of patients treated with chemotherapy for mCRPC [100]. It also occurred in some patients who received abiraterone after docetaxel, as per a cohort study [100]. It was noted that the PSA flare phenomenon does not necessarily cause clinically relevant issues regarding OS or PFS [99,100]. Moreover, it does not indicate therapeutic failure. These observations are corroborated by a local retrospective study on patients with mCRPC who received abiraterone, which showed that more than half of patients with initial PSA flare had ultimate PSA response to abiraterone, and there was no substantial difference in clinical outcomes in patients with or without PSA flare [39]. The panel agreed, therefore, that, as long as patients are not clinically deteriorating, a temporary PSA increase during an initial phase of systemic treatment should only be monitored for a sufficient period (i.e. 3 months) so as to avoid early withdrawal from treatment in the absence of genuine disease progression.

Discussion

The local consensus panel attempted to formulate a set of statements through a series of discussions and voting based on the current scientific evidence and the panellists' clinical experience. In the face of the evolving management paradigm for patients with mPCa, these consensus statements aimed to facilitate appropriate treatment choices among Hong Kong physicians. It is noteworthy that several areas in the management of mPCa remain uncertain, especially with regard to the optimal sequencing of therapies and the eligibility criteria for imaging with a view to achieving ideal patient outcomes. Prospective studies are urgently needed to address these issues. More importantly, clinical data on the response of Asian or Chinese patients with mPCa to different therapies should be further explored in future randomized trials. These data would be even more relevant to assist Hong Kong physicians in making suitable treatment decisions.

In conclusion, the consensus statements established were primarily derived from the recent clinical evidence and major overseas guidelines, with the consideration of local clinical practice. They are considered practical recommendations for local physicians in the management of patients with mPCa. In view of the results anticipated from upcoming clinical studies, these statements as well as physicians' practice are subject to regular review and necessary updating.

Acknowledgements

Conflict of Interest

None declared.

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Abbreviations: mPCa, metastatic prostate cancer; ADT, androgen deprivation therapy; mCRPC, castration-resistant prostate cancer; HKUA, Hong Kong Urological Association; HKSUO, Hong Kong Society of Uro-Oncology; PET, positron-emission tomography; RT, radiotherapy; APCCC, Advanced Prostate Cancer Consensus Conference; HR, hazard ratio; OS, overall survival; PCWG3, Prostate Cancer Clinical Trials Working Group 3; PFS, progression-free survival; AR, androgen receptor; AR-V7, AR variant 7; ECOG, Eastern Cooperative Oncology Group; MDT, metastasis-directed therapy; SBRT, stereotactic body radiotherapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix SI. The modified Delphi method aimed at reaching consensus.

Appendix S2. Full voting records for each drafted statement.

Appendix S3. Summary conflict of interest statements from all panel members.