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Review Article

Management of metastatic castration-resistant prostate cancer: Insights from urology experts in Thailand

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ABSTRACT

Treatment options for castration-resistant prostate cancer (CRPC) are available, but clear instructions for the selection of appropriate treatment are lacking. A meeting of urology experts based in Thailand was convened with the following objectives: (1) to reach a consensus and share real-life experiences about how to identify CRPC; (2) to choose the appropriate treatment for CRPC patients; (3) to evaluate disease progression using novel inhibitors of the androgen receptor pathway; (4) to identify the frequency of monitoring disease; and (5) to promote rational use of corticosteroids in CRPC patients. This consensus document can provide guidance to other urologists in Thailand to provide appropriate treatment to metastatic CRPC patients in a timely manner.

1. Introduction

Twelve urology experts from Thailand met to share their experiences of the management of castration-resistant prostate cancer (CRPC). These urologists work in medical schools and large public hospitals in Bangkok, Chiang Mai, and Khon Kaen, and have considerable experience in the management of prostate cancer (PC) and other genitourinary diseases.

A voting system was used during the whole meeting. Voting was based on scientific evidence and not on financial/patient factors related to treatment prescription.

Standard treatment for biochemical-recurrent PC and advanced-stage PC is androgen-deprivation therapy (ADT). Once disease status shifts from hormone-sensitive prostate cancer (HSPC) to CRPC, new treatment should be offered to the patient. Various treatments for metastatic castration-resistant prostate cancer (mCRPC) are available in Thailand, including hormonal therapy and chemotherapy. In some hospitals in Thailand, the first-line treatment is secondary hormonal therapy using ketoconazole, corticosteroids, or cyproterone acetate owing to the affordability of these agents to patients. Such treatments provide only short-term decline in prostate-specific antigen (PSA) levels but no increase in overall survival (OS).

Pivotal studies of current treatments have shown an OS benefit in mCRPC patients. Also, novel inhibitors of the androgen receptor pathway (IARP), such as abiraterone acetate and enzalutamide, have shown an OS benefit and an improvement of other parameters, especially quality of life (QoL); hence, the role of IARP is

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attracting increasing interest in Thailand, and such agents are being selected more widely for mCRPC patients. Currently, the IARP approved by the Food and Drug Administration of Thailand are abiraterone acetate and enzalutamide.

2. Key topics of the urology experts' meeting

Six issues were discussed in this meeting of urology experts, as described in the following sections.

2.1. Upfront chemohormonal therapy for high-tumor volume metastatic HSPC in Thailand is promising

The urology experts agreed that chemohormonal therapy should be selected on a case-by-case basis. Only 60% of urology experts considered chemohormonal therapy in high-tumor volume metastatic HSPC because they were concerned about the side effects of chemotherapy. Patients who are fit and young, and have a survival time of >15 years can be selected to receive such chemohormonal therapy. The other (40%) urology experts thought that ADT provides benefit in terms of delaying disease progression in HSPC patients by 5–10 years. Treatment with ADT of patients with metastatic HSPC continues to have a major role in most hospitals in Thailand (Fig. 1).

The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease trial[1] and the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy trial[2] enrolled mainly Caucasian patients. Hence, a query about the docetaxel dose used in the Asian (especially Thai) population was discussed. Most urology experts (81.8%) recommended the same dose of docetaxel as that given to Caucasian patients (75 mg/m^2 every 3 weeks for 6 cycles) in both trials (Fig. 2).

Subsequent therapy was also discussed. If chemohormonal therapy failed and patients progressed to mCRPC, the next treatment option preferred by experts was novel IARP (7 of 12 experts). One urology expert thought that patients should undergo rechallenge with chemohormonal therapy (Fig. 3).

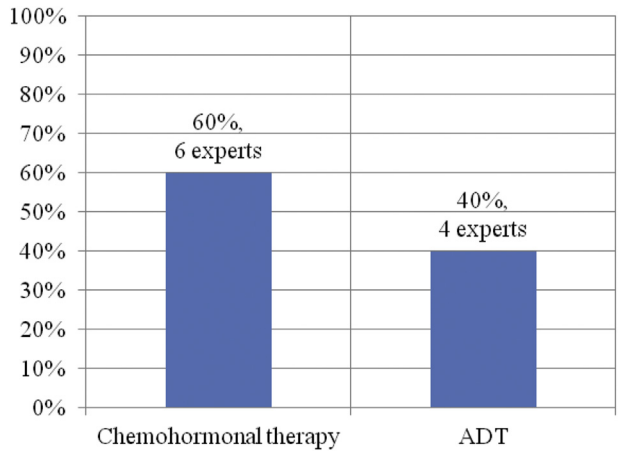

Fig. 1. Urology experts based in Thailand considered the role of chemohormonal therapy in high-tumor volume metastatic hormone-sensitive prostate cancer (HSPC). Sixty percent of urology experts voted to treat HSPC with chemohormonal therapy. The other 40% preferred to treat metastatic HSPC with androgen-deprivation therapy only. ADT, androgen-deprivation therapy.

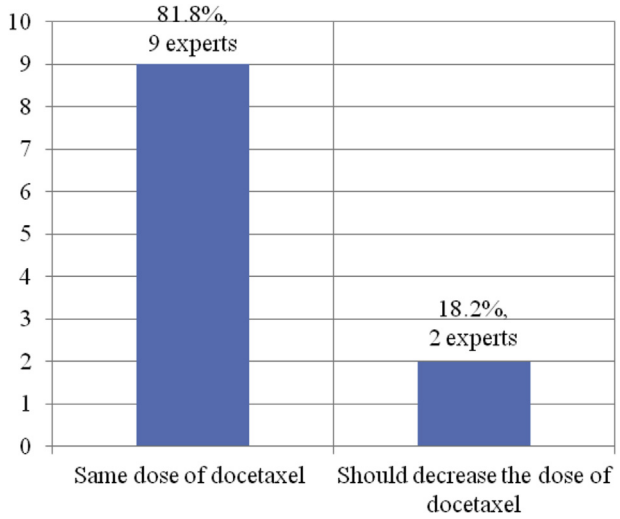

Fig. 2. Urology experts based in Thailand agreed to treat Thai patients with the same dose of docetaxel in chemohormonal therapy stated in the CHAARTED trial and STAMPEDE trials. CHAARTED, Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.

2.2. Urology experts identified CRPC patients by the following guidelines set by the European Association of Urology in 2015

The definition of CRPC status was identified as stated in the European Association of Urology (EAU) guidelines in 2015[3] (Fig. 4).

The urology experts thought that some of the parameters stated in EAU guidelines cannot be followed up in a practical manner in their real-life practice, especially the timeline of PSA measurement. Most urology experts measured PSA levels twice (and not thrice, as stated in EAU guidelines[3]). The time interval between each PSA measurement varied depending on the experts' experience. Most urology experts measured the PSA levels twice at 2- to 3-week intervals.

The measurement of serum levels of testosterone to identify castration status was discussed. Most urology experts defined medical castration as a testosterone level in serum of <50 ng/dL (1.7 nmol/L). If surgical castration was undertaken, then the testosterone level did not need to be measured to confirm CRPC.

In real-life practice, 41.7% of urology experts identified mCRPC patients as individuals with a serum level of testosterone <50 ng/dL, who show increases in PSA level, and who show radiographic progression (Fig. 5).

2.3. Patient factors prior to choosing treatment

2.3.1. Choice of chemotherapy or novel IARP

Chemotherapy is not the only treatment option for mCRPC patients. Novel IARP such as abiraterone acetate and enzalutamide have shown positive outcomes in terms of OS, radiographic progression-free survival, and other QoL benefits to mCRPC patients in COU-AA-302[4,5,6] and Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer studies.[7] Factors considered when choosing chemotherapy or novel IARP pathway inhibitors are used are discussed below.

2.3.1.1. Duration of response to ADT and symptomatic disease. All urology experts chose novel IARP in mCRPC patients if the duration of response to initial ADT ≥12 months. If patients had

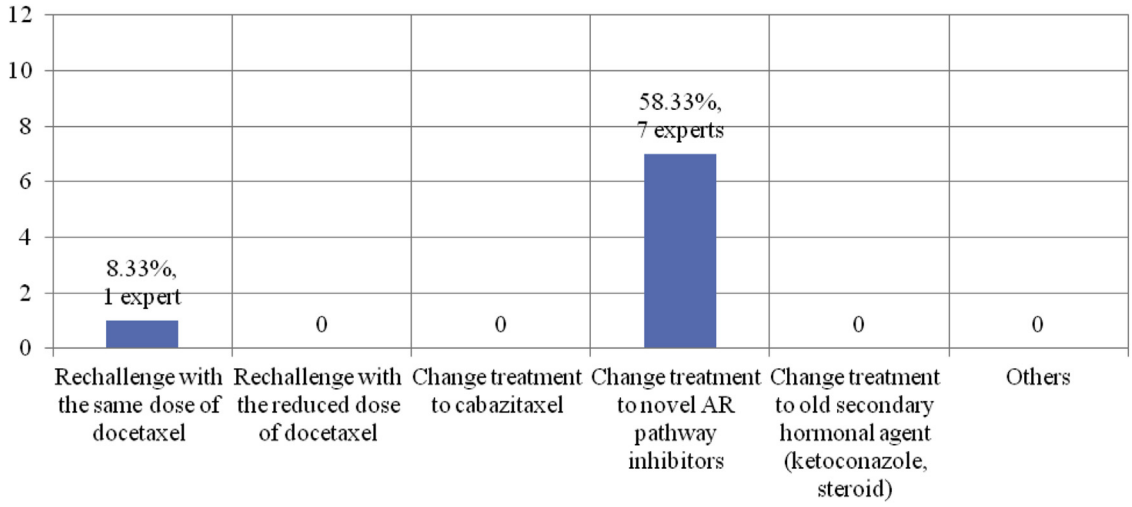

Fig. 3. A total of 58.33% experts voted for novel inhibitors of the androgen receptor pathway (IARP) as subsequent therapy for metastatic castration-resistant prostate cancer (mCRPC). AR, androgen receptor.

duration of response to initial ADT <12 months and symptomatic disease, then chemotherapy was the first-line treatment for nine out of 10 experts. If patients were asymptomatic or mildly symptomatic with duration of ADT response <12 months, then six out of 12 experts thought that IARP should be first-line treatment (Fig. 6).

2.3.1.2. Gleason score. mCRPC patients with a high Gleason Score (≥8) receive benefit from novel IARP in terms of progression-free survival and time to an increase in PSA level in a chemotherapy-naïve setting.[8] Most urology experts (63.5%) considered that novel IARP also have a role in mCRPC patients with a high Gleason Score (Fig. 7).

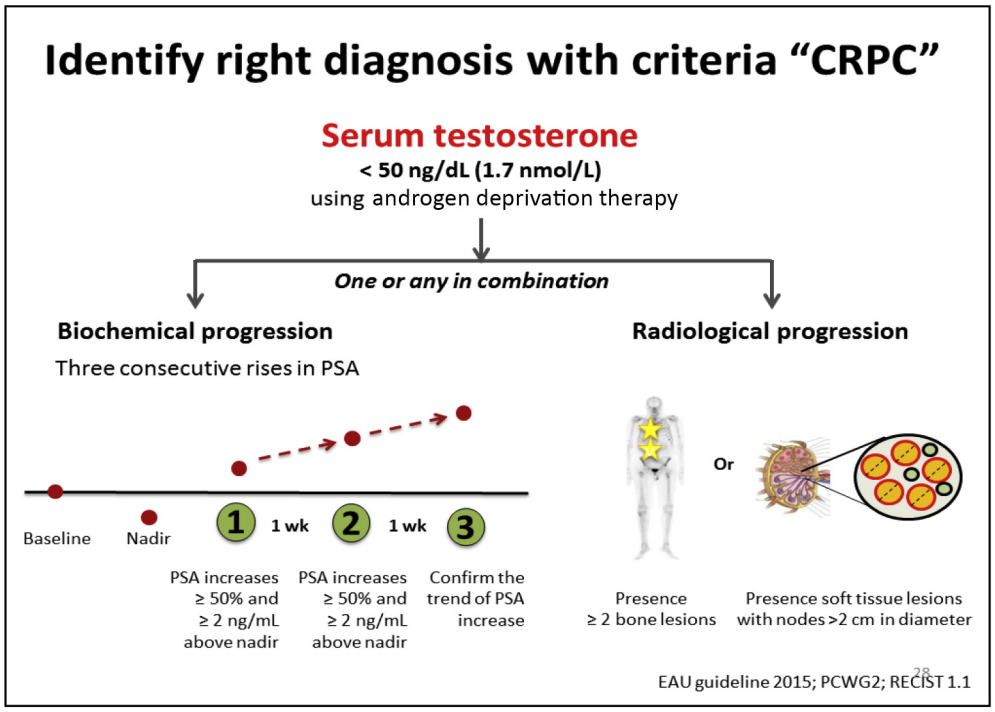

Fig. 4. Definition of mCRPC in the European Association of Urology guidelines in 2015. EAU, European Association of Urology; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostrate Cancer Working Group 2; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.
Note. "European Association of Urology guideline version, 2015," by European Association of Urology, 2015, p. 90. Retrieved from https://uroweb.org/guideline/prostate-cancer/?type=archive.

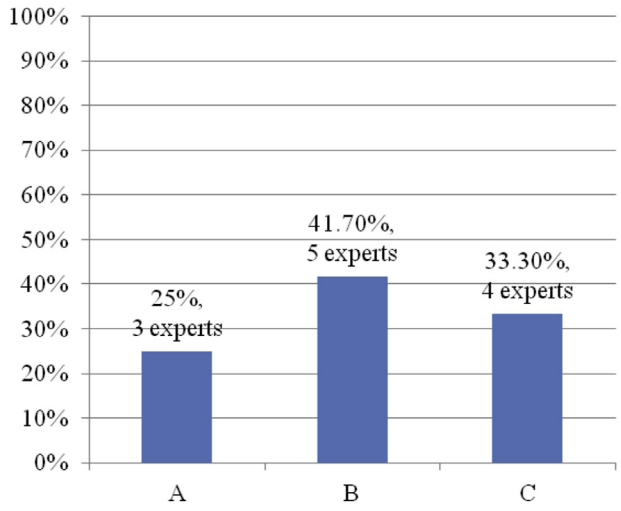

Fig. 5. Urology experts identified mCRPC patients using various criteria. (A) Serum testosterone <50 ng/dL and increase in PSA level. (B) Serum testosterone <50 ng/dL, increase in PSA level, and radiographic progression. (C) Serum testosterone <50 ng/dL, increase in PSA level, and radiographic and clinical progression. mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.

2.3.1.3. Visceral metastasis. The COU-AA-302 study did not enroll patients with mCRPC who had visceral metastasis. Nevertheless, 66.67% of urology experts agreed with the findings from the Saint Gallen Advanced Prostate Cancer Consensus Conference in 2015—that is, to extend use of abiraterone acetate in mCRPC patients who have visceral metastasis because abiraterone acetate also shows benefit in a postchemotherapy setting[9] (Fig. 8).

2.3.1.4. Androgen receptor splice variant 7. All urology experts agreed that mCRPC patients who presented with androgen receptor splice variant 7 should be treated by chemotherapy even though clinical validation of this promising predictive marker of PC is lacking (Fig. 9).

2.3.2. Choice of novel IARP or secondary hormonal therapy

Agents used for secondary hormonal therapy such as ketoconazole, corticosteroids, and cyproterone acetate continue to have a major role in mCRPC patients in some hospitals because patients can afford such treatments. If cost is not a concern, a novel IARP was considered first-line treatment for mCRPC for 77.78% of urology experts. The efficacy of abiraterone acetate in mCRPC patients treated previously with ketoconazole was also discussed: abiraterone acetate still had a role as the next treatment option. In this meeting, 88.9% of urology experts felt that abiraterone acetate provided a benefit to patients treated previously with ketoconazole (Fig. 10).

2.3.3. Choice of novel IARP (abiraterone acetate or enzalutamide)

A head-to-head comparison that can guide which treatment should be started first or what the sequence of treatment should be for mCRPC is lacking. Certain factors must be considered prior to choosing a type of treatment: comorbidities, effect of treatment on QoL, drug–drug interactions, management of side effects, and drug resistance. Treatment is selected on a case-by-case basis.

2.4. Use of Prostate Cancer Working Group 2 criteria for stopping treatment

The Prostrate Cancer Working Group 2 recommended evaluation of disease progression after IARP had been given to mCRPC patients for ≥12 weeks to prevent misunderstandings about flare events.[10] Some urology experts believed that PSA flare occurred

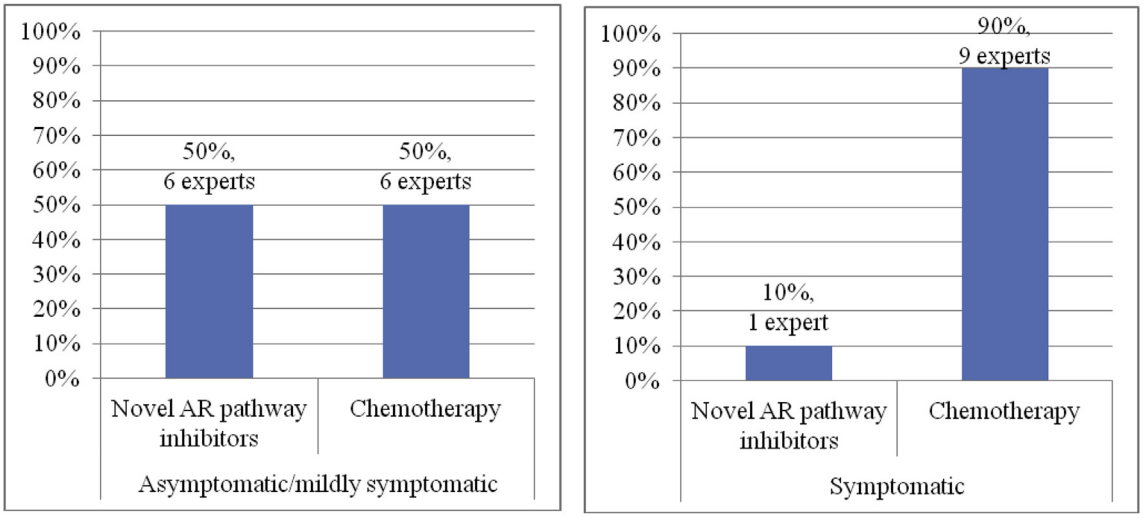

Fig. 6. If mCRPC patients had duration of response to initial ADT <12 months and were asymptomatic or mildly symptomatic, treatment can be IARP or chemotherapy. Chemotherapy would be first-line treatment for symptomatic mCRPC patients with duration of response to initial ADT <12 months. ADT, androgen-deprivation therapy; AR, androgen receptor; IARP, inhibitors of the androgen receptor pathway; mCRPC, metastatic castration-resistant prostate cancer.

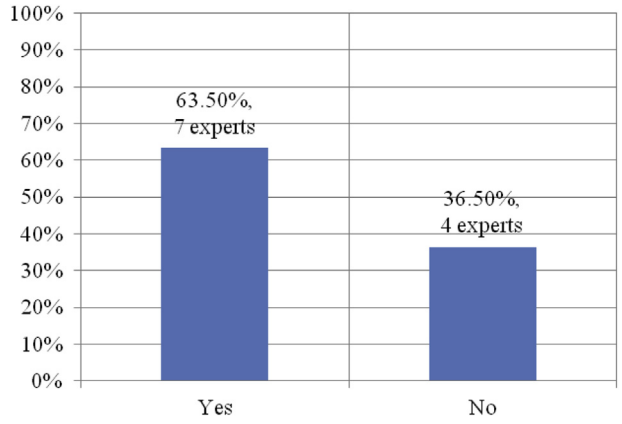

Fig. 7. Urology experts considered use of novel IARP in mCRPC patients with a high Gleason Score. IARP, inhibitors of the androgen receptor pathway; mCRPC, metastatic castration-resistant prostate cancer.

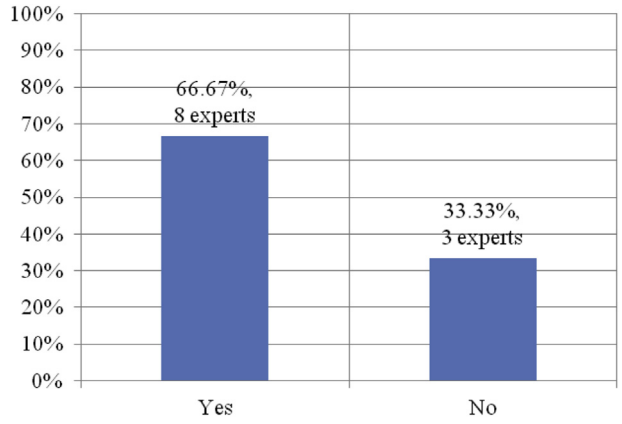

Fig. 8. Urology experts considered the role of abiraterone acetate in metastatic castration-resistant prostate cancer (mCRPC) patients with viseral metastasis.

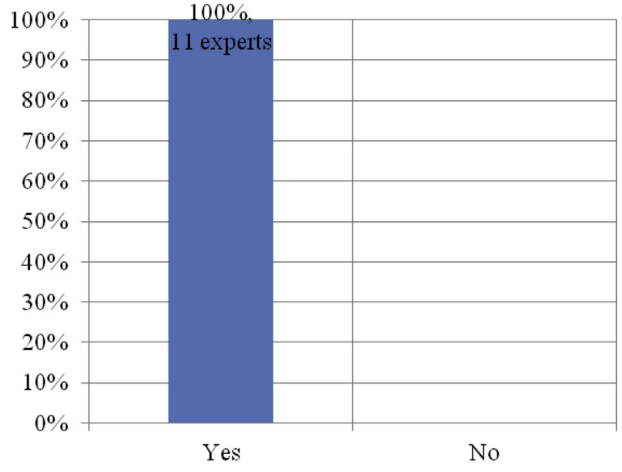

Fig. 9. All urology experts agreed that chemotherapy should be given to mCRPC patients who presented with AR splice variant 7. AR, androgen receptor; mCRPC, metastatic castration-resistant prostate cancer.

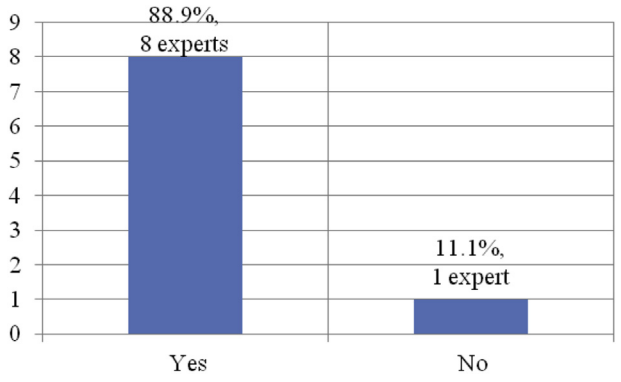

Fig. 10. Most urology experts agreed to select a novel IARP for mCRPC patients if it was available in their center. IARP, inhibitors of the androgen receptor pathway; mCRPC, metastatic castration-resistant prostate cancer.

occasionally in real-life practice, and agreed that increases in PSA levels is not a sole criterion to stop treatment.[11] In a chemotherapy-naïve setting, 90% of urology experts considered stopping novel IARP if mCRPC patients met two of the three criteria for disease progression stated by the Prostrate Cancer Working Group 2 (Figs. 11 and 12).

In real-life practice, 70% of urology experts identified increases in PSA levels and radiographic progression to be the two of three criteria to stop treatment; 20% used increases in PSA levels and symptoms; 10% used increases in PSA levels, radiographic progression, and symptoms.

2.5. Disease monitoring during IARP administration

Monitoring disease in each patient was dependent on the urologist's experience and symptoms of each patient.

2.5.1. PSA testing

A total of 54.55% of urology experts measured serum levels of PSA every 3–4 months on average. The remainder measured serum levels of PSA more frequently (e.g., every 3–4 weeks) because each novel IARP is expensive. These levels must be monitored closely for the reimbursement system used in Thailand (Fig. 13).

2.5.2. Bone scintigraphy

A total of 54.55% urology experts repeat bone scintigraphy only in symptomatic patients. Some experts (36.36%) undertake bone scintigraphy routinely every 6 months (Fig. 14).

2.6. Rational use of corticosteroids

If abiraterone acetate causes mineralocorticoid excess (hypertension, hypokalemia, fluid retention), corticosteroids (especially prednisone or prednisolone, 5 mg, twice daily) are used to reduce these side effects. Urology experts (87.5%) accepted that corticosteroids provide benefit to mCRPC patients in terms of PSA response. The side effect of corticosteroids they were most concerned about was hyperglycemia. They discussed how to manage this side effect, with the consensus being it could be reduction of dose (e.g., changing prednisone from 10 mg/d to 5 mg/d). Close monitoring of patients was considered important.

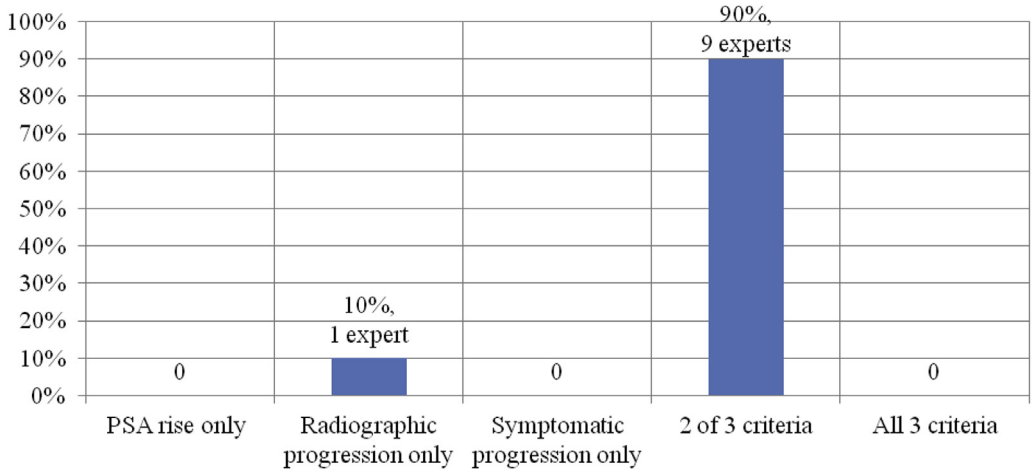

Fig. 11. Urology experts considered stopping IARP treatment if mCRPC patients met two of the three criteria of disease progression described by the PCWG2. IARP, inhibitors of the androgen receptor pathway; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostrate Cancer Working Group 2; PSA, prostate-specific antigen.

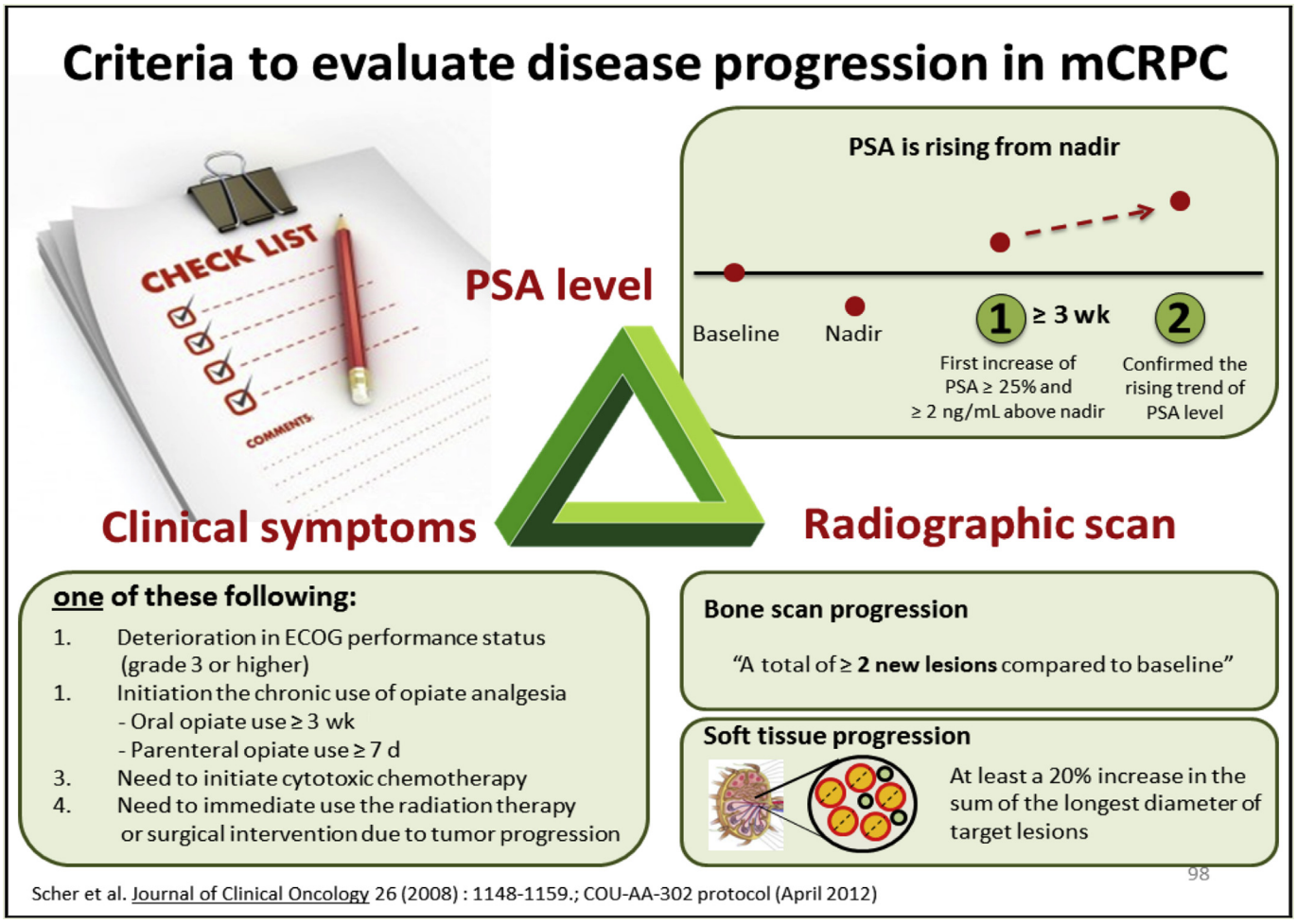

Fig. 12. Criteria set by the PCWG2 to evaluate disease progression in mCRPC patients. ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; PCWG2, Prostrate Cancer Working Group 2; PSA, prostate-specific antigen.
Note. From "End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice," by H.I. Scher, M.J. Morris, E. Basch, G. Heller, 2011, *J Clin Oncol*, 29, p. 3695–704. With permission.

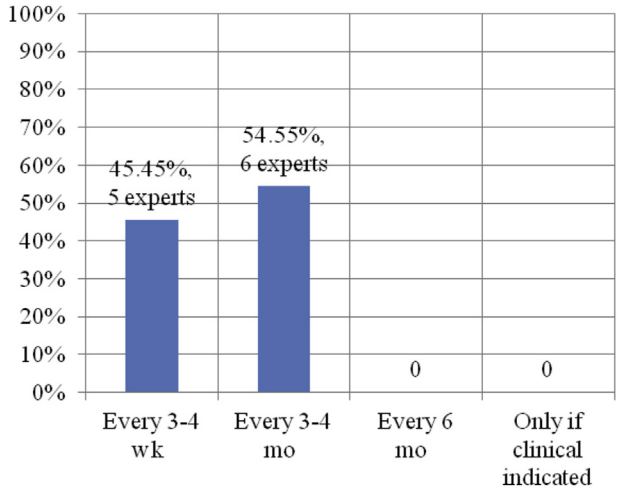

Fig. 13. PSA testing: some urology experts measured serum levels of PSA on average every 3–4 months whereas others did do every 3–4 weeks. PSA, prostate-specific antigen.

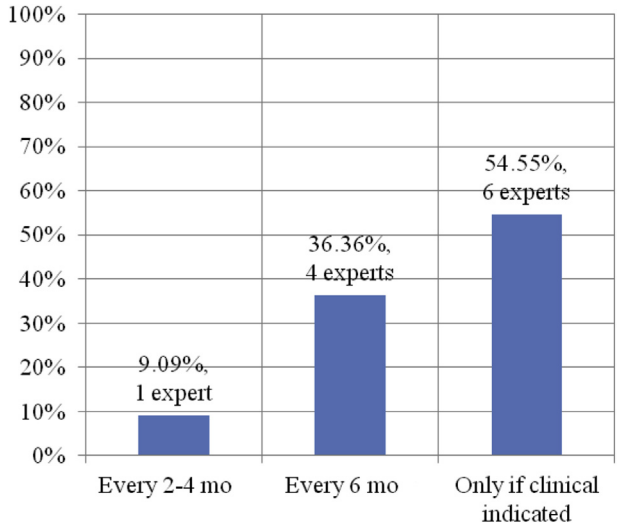

Fig. 14. Most urology experts repeated bone scintigraphy in symptomatic patients.

3. Conclusion

This is the first consensus document for urologist experts based in Thailand with respect to real-life mCRPC management. Clinical practice must be tailored depending on symptoms. This consensus document can provide guidance to other urologists in Thailand to provide appropriate treatment to mCRPC patients in a timely manner.

Conflicts of interest

The authors declared no conflict of interest.

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