


# Management of advanced prostate cancer in a middle-income country: real-world consideration of the Advanced Prostate Cancer Consensus Conference 2017

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## Objective

To examine the results of the Malaysian Advanced Prostate Cancer Consensus Conference (MyAPCCC) 2018, held for assessing the generalizability of consensus reached at the Advanced Prostate Cancer Consensus Conference (APCCC 2017) to Malaysia, a middle-income country.

## Methods

Six key sections were chosen: (1) high-risk localized and locally advanced prostate cancer, (2) oligometastatic prostate cancer, (3) castration-naïve prostate cancer, (4) castrate resistant prostate cancer, (5) use of osteoclast-targeted therapy and (6) global access to prostate cancer drugs. There were 101 consensus questions, consisting of 91 questions from APCCC 2017 and 10 new questions from MyAPCCC 2018, selected and modified by the steering committee; of which, 23 questions were assessed in both ideal world and real-world settings. A panel of 22 experts, comprising of 11 urologists and 11 oncologists, voted on 101 predefined questions anonymously. Final voting results were compared with the APCCC 2017 outcomes.

## Results

Most voting results from the MyAPCCC 2018 were consistent with the APCCC 2017 outcomes. No consensus was achieved for controversial topics with little level I evidence, such as management of oligometastatic disease. No consensus was reached on using high-cost drugs in castration-naïve or castration-resistant metastatic prostate cancer in real-world settings. All panellists recommended using generic drugs when available.

## Conclusions

The MyAPCCC 2018 voting results reflect the management of advanced prostate cancer in a middle-income country in a real-world setting. These results may serve as a guide for local clinical practices and highlight the financial challenges in modern healthcare.

## Keywords

castration-resistant prostate cancer, castration-naïve prostate cancer, oligometastatic prostate cancer, high-risk localized prostate cancer, cost and access to treatment, low-middle income countries, #ProstateCancer, #pcsm

## Introduction

The treatment landscape for advanced prostate cancer has evolved rapidly since 2010. Recommendations from the evidence-based clinical guidelines and expert consensus reached at the Advanced Prostate Cancer Consensus Conference (APCCC) 2015 and the APCCC 2017 [1,2] are invaluable in clinical decision-making for men with advanced prostate cancer. The applicability of these recommendations in clinical practice is more complex, however, owing to variability in patient and clinical factors, including challenges faced by both patients and clinicians because of limited resources and access to certain treatments. These factors are rarely taken into account in clinical guidelines and expert consensus. The Asia Pacific APCCC 2018 reviewed the real-world application of APCCC 2017 recommendations within the Asia Pacific region [3]. It highlighted that cost and access to contemporary treatment and technologies are key factors that affect therapeutic decision-making in the region.

The Malaysian APCCC (MyAPCCC) 2018 was held to discuss topics from the APCCC 2017 that were relevant to local practices in Malaysia and to assess the applicability of recommendations from the APCCC 2017 in a real-world setting. It was also a platform to bring together the local expertise for multidisciplinary discussion on the optimal care for patients with advanced prostate cancer. Results from the MyAPCCC 2018 can serve as a reference to clinicians, particularly in low- and middle-income countries.

## Malaysian Advanced Prostate Cancer Consensus 2018

The MyAPCCC was held on 29 June 2018 in Kuala Lumpur, Malaysia. Panel members included 11 oncologists, 11 urologists and one clinical scientist, who were selected based on their experience and interest in the management of men with advanced prostate cancer (Table 1). Six of the 10 areas in the APCCC 2017 were discussed based on their local relevance (Table 2). Panel members discussed these areas and voted on the related questions with multiple options. Ninety-one questions were selected from the APCCC 2017 [1], of which some (23/91) were posed in both ideal-world and real-world settings to explore the role of medical cost, reimbursement and access in affecting clinical decision-making. In addition, 10 new questions were formed by the MyAPCCC 2018 steering committee. All panel members except one non-voting member (clinical scientist) voted on the questions publicly but anonymously using the online polling platform, Poll Everywhere (<https://www.pollerywhere.com/>). In contrast to the APCCC 2017, 'abstain' and 'unqualified to answer' were excluded as voting options. Responses to all questions were based on the idealized assumptions that all diagnostic procedures and treatments were available without considering cost, and patients were fit

with no treatment contraindication unless otherwise stated. The denominator was based on the number of panels who voted on each question. Consensus was declared if  $\geq 75\%$  of the panels voted for the same option.

## Management of Advanced Prostate Cancer in Malaysia

Prostate cancer has a low incidence rate (14.5 per 100 000 population) in less developed countries [4]; however, its high mortality rate of 6.6 per 100 000 population [4] results from patients having advanced disease at diagnosis and limited access to survival-prolonging treatments. In Malaysia, prostate cancer is the fifth most common cancer in men, with a lifetime risk of one in 117 for all men [5]. Approximately 60% of Malaysian patients with prostate cancer are diagnosed at advanced stages (stages 3 and 4) [5]; therefore, there is a high burden of advanced prostate cancer with significant impact on the healthcare system.

To date, there are 108 urologists and 115 oncologists in Malaysia, serving a total population of 30 million. Urology and oncology services are provided by both public (Ministry of Health and Ministry of Education) and private hospitals. Approximately 70% of the population use public (government) services. Oncologists (medical and clinical oncologists) are responsible for prescribing and managing systemic therapy, whilst urologists prescribe and manage hormonal therapy. Radiotherapy is administered by clinical and radiation oncologists.

**Table 1** Panel members by specialty.

Name	First name	Specialty
Abdullah	Matin Mellor	Clinical oncologist
Alip	Adlinda	Clinical oncologist
Chong	Flora Li Tze	Clinical oncologist
Chua	Chong Beng	Urologist
Ismail	Fuad	Clinical oncologist
Khong	Rachael Kit-Tsan	Clinical oncologist
Lim	Chun Sen	Clinical oncologist
Lim	Jasmine	Clinical scientist (non-voting member)
Loh	Chit Sin	Urologist
Malek	Rohan	Urologist
Mohd Ghani	Khairul Asri	Urologist
Md Noor	Ibtisam	Clinical oncologist
Md Yusoff	Noor Ashani	Urologist
Nasuha	Noor Azam	Urologist
Ong	Teng Aik	Urologist
Razack	Azad	Urologist
Saad	Marniza	Clinical oncologist
Soo Hoo	Hwoei Fen	Clinical oncologist
Sundram	Murali	Urologist
Tan	Hui Meng	Urologist
Thiagarajan	Muthukkumaran	Clinical oncologist
Teh	Guan Chou	Urologist
Voon	Pei Jye	Medical oncologist

**Table 2** Sections and topics.

Sections	Topics	Questions
1	Management of high-risk and locally advanced prostate cancer	1–20
2	Oligometastatic prostate cancer	21–30
3	Management of CNPC	31–49
4	Management of CRPC	50–87
5	Use of osteoclast-targeted therapy for SRE/SSE prevention for mCRPC (not for osteoporosis/bone loss)	88–92
6	Global access to prostate cancer drugs and treatment in countries with limited resources	93–101

CNPC, castration-naïve prostate cancer; CRPC, castration-resistant prostate cancer; mCRPC, metastatic CRPC; SRE, skeletal-related event; SSE, symptomatic skeletal event.

Androgen deprivation therapy (ADT) is widely used in Malaysia, via medical or surgical techniques. Most of the latest drugs in the management of advanced prostate cancer are registered and available locally except sipuleucel-T, radium-223 and apalutamide. The cost of novel androgen receptor (AR)-targeting agents (e.g. abiraterone acetate, enzalutamide) and newer cytotoxic drugs (e.g. cabazitaxel) is approximately US\$3000 per month. Generic drugs are available for docetaxel, zoledronic acid and secondary hormonal therapy.

Although robust data are available for several life-prolonging treatments, clinical decision-making is influenced by clinical factors such as performance status, comorbidities, symptoms, disease extent and environmental factors including culture, diet and lifestyle. In general, most men with advanced prostate cancer in Malaysia prefer oral and non-cytotoxic drugs. They usually try to avoid chemotherapy and prefer to have hormonal therapy as long as possible. However, many are unable to afford the expensive novel AR-targeting agents or other life-prolonging treatments for advanced prostate cancer, unless they have adequate personal health insurance coverage or are able to pay out-of-pocket.

### Findings from the MyAPCCC 2018

Table 3 summarizes the consensus achieved at the MyAPCCC 2018 and/or the APCCC 2017, while the differences in consensus achieved between ideal-world and real-world settings at the MyAPCCC 2018 are shown in Table 4. Detailed questions and complete voting results are available in the Supporting Information.

### Management of High-Risk Localized and Locally Advanced Prostate Cancer

Consistent with the APCCC 2017, the MyAPCCC 2018 defined this patient group based on the European Association of Urology (EAU) guidelines [6], which define high-risk localized prostate cancer as PSA >20 ng/mL, Gleason score >7 (Gleason Grade Group 4/5) or cT2c disease, while patients with cT3-4 or cN+ (any PSA and Gleason score) disease are considered to have locally advanced prostate cancer. The optimal management in this group of patients remains a

challenge. At present, the main treatments with curative intent are radical prostatectomy or radiotherapy with ADT. Evidence has demonstrated a survival benefit from radiotherapy and long-term ADT in high-risk patients [7,8]; however, the use of ADT with definitive radiotherapy varied in the high-risk group, in which patients from public and regional treatment institutions were more likely to receive this treatment compared to those from private and metropolitan institutions [9]. These findings further suggest that ADT with definitive radiotherapy was underused in approximately 1/5 of high-risk patients who may benefit from it [9]. The evidence for radical prostatectomy is heterogenous and unclear [10,11]. The MyAPCCC 2018 selected key contentious questions to be addressed, focusing on radical prostatectomy and its subsequent treatments.

Lymph node dissection is recommended if the risk of lymph node metastasis is greater than 2–5% [6,12]. The MyAPCCC 2018 consensus was consistent with the APCCC 2017 in recommending lymph node dissection and its regions to be sampled in high-risk localized and locally advanced prostate cancer. With multiple adverse clinical features in such cases, the risk of lymph node involvement is high. Thus, performing lymph node dissection is prudent in this category. The lack of consensus regarding the number of lymph nodes to be removed is consistent with the lack of evidence in this area. The ability to harvest and detect more lymph nodes depends on the surgical technique and pathological examination of the lymph node specimens. High-volume centres can produce consistent results. In countries with low prostate cancer incidence, such as Malaysia, this could only be achieved with dedicated surgical and pathological input.

At the MyAPCCC 2018, there was a consensus (96%) for not adding adjuvant radiotherapy after radical prostatectomy in the case of Gleason score 8–10 disease. No consensus exists on other adverse pathological features, which influence the decision for adjuvant radiotherapy in patients post radical prostatectomy. The voting results for using ADT in adjuvant radiotherapy cases were mixed. Similar patterns were seen regarding recommending adjuvant radiotherapy in cases with pN1 disease. No consensus was reached at the APCCC 2017 on the use of adjuvant radiotherapy in this group of patients.

**Table 3** Areas of consensus achieved ( $\geq 75\%$  agreement) at the MyAPCCC 2018 and/or APCCC 2017.

No.	Statement	% Agreement	
		MyAPCCC 2018	APCCC 2017
<b>Management of high-risk localized and locally advanced prostate cancer</b>			
1.	Lymph node dissection in men with cN0 cM0 high-risk prostate cancer undergoing prostatectomy (Q1)	82	86
2.	Adjuvant radiation therapy in men with post-prostatectomy pN0 disease		
	(i) Not to add adjuvant radiation therapy in case of Gleason 8–10 (Gleason Grade Group 4 or 5; Q5)	86	56
3.	Minimal requirement for lymph nodes sampling in men with cN0 cM0 high-risk prostate cancer		
	(i) Obturator lymph nodes (Q15)	68	98
	(ii) External iliac lymph nodes (Q16)	73	85
	(iii) Internal iliac lymph nodes (Q17)	82	90
	(iv) Not to sample pre-sacral lymph nodes (Q18)	95	53
	(v) Not to sample common iliac lymph nodes (Q19)	95	54
	(vi) Not to sample para-aortic lymph nodes (Q20)	100	95
<b>Management of CNPC</b>			
4.	High-volume disease in CNPC as defined in CHARTED (visceral [lung or liver] and/or $\geq 4$ bone metastases with $\geq 1$ beyond pelvis and vertebral column; Q33)	82	59
5.	Docetaxel in addition to ADT in CNPC		
	(i) De novo mCNPC with high-volume disease (Q34)	100	96
	(ii) Relapsed mCNPC after prior treatment for localized prostate cancer and with high-volume disease (Q36)	91	74
	(iii) Relapsed mCNPC after prior treatment for localized prostate cancer and with high volume disease (real-world setting; Q44b)	81	n.a.
	(iv) Not to add docetaxel in <i>de novo</i> mCNPC with low-volume disease (Q35)	77	6
	(v) Not to add docetaxel in relapsed mCNPC after prior treatment for localized prostate cancer with low-volume bone metastases (Q37)	82	25
	(vi) Not to add docetaxel in CNPC (N1 M0; Q46)	95	71
	(vii) Not to add docetaxel in CNPC with biochemical relapse (N0 M0; Q47)	91	90
6.	Docetaxel in addition to ADT in CNPC with no daily dose of oral corticosteroid (Q40)	95	n.a.
7.	ADT and abiraterone as upfront therapy in mCNPC (ideal-world setting; Q41)	86	n.a.
8.	ADT alone in CNPC		
	(i) <i>De novo</i> mCNPC with low-volume disease (ideal-world setting; Q43a)	86	n.a.
	(ii) <i>De novo</i> mCNPC with low-volume disease (real-world setting; Q43b)	100	n.a.
	(iii) Relapsed mCNPC after prior treatment for localized prostate cancer and with low volume disease (ideal world setting) (Q45a)	77	n.a.
	(iv) Relapsed mCNPC after prior treatment for localized prostate cancer and with low volume disease (real-world setting; Q45b)	95	n.a.
9.	Treatment of the primary tumour in addition to systemic therapy		
	(i) Not to add treatment to primary tumour in <i>de novo</i> mCNPC with high volume disease (Q48)	86	52
<b>Management of CRPC</b>			
10.	First-line CRPC		
	(i) Abiraterone or enzalutamide for asymptomatic men without docetaxel for CNPC (ideal-world setting; Q50a)	90	86
	(ii) Docetaxel for symptomatic men without docetaxel for CNPC (real-world setting; Q51b)	91	n.a.
	(iii) Abiraterone or enzalutamide for asymptomatic men with docetaxel for CNPC (ideal-world setting; Q52a)	95	88
	(iv) Abiraterone or enzalutamide for asymptomatic men with docetaxel for CNPC and progressed $\leq 6$ months after completion of docetaxel in the CNPC setting (ideal-world setting; Q54a)	73	77
11.	Second-line CRPC		
	(i) Taxane for symptomatic mCRPC men who had progressive disease as best response to first-line abiraterone or enzalutamide (ideal-world setting; Q61a)	52	96
	(ii) Taxane for symptomatic mCRPC men who had progressive disease as best response to first-line abiraterone or enzalutamide (real-world setting; Q61b)	86	n.a.
	(iii) Abiraterone or enzalutamide in men with asymptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression after use of first-line abiraterone or enzalutamide (ideal-world setting; Q62a)	77	27
	(iv) Taxane in men with symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression after use of first-line abiraterone or enzalutamide (ideal-world setting; Q63a)	45	90
	(v) Taxane in men with symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression after use of first-line abiraterone or enzalutamide (real-world setting; Q63b)	82	n.a.
	(vi) Abiraterone or enzalutamide for asymptomatic men with mCRPC progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide; ideal-world setting; Q64a)	100	92
	(vii) Abiraterone or enzalutamide for symptomatic men with mCRPC progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide; ideal-world setting; Q65a)	67	76
12.	Three-weekly docetaxel (75 mg/mL <sup>2</sup> ) in the mCRPC setting (Q59)	86	86
13.	Criteria defining poor prognosis, aggressive variant mCRPC		
	(i) Exclusive visceral metastases (Q68)	91	70
	(ii) Low PSA levels relative to tumour burden (Q70)	95	45
	(iii) Bulky tumour masses (Q71)	91	21
	(iv) Short response to ADT ( $\leq 12$ months) for metastatic prostate cancer (Q72)	91	34
	(v) Rapid progression without correlation with PSA kinetics (Q73)	100	63
	(vi) Neuro-endocrine differentiation on a tumour biopsy and/or low or absent AR expression (Q74)	100	71

Table 3 (continued)

No.	Statement	% Agreement	
		MyAPCCC 2018	APCCC 2017
14.	Standard imaging by CT and bone scans for baseline and treatment monitoring in poor prognosis, aggressive variant mCRPC (Q76)	77	62
15.	Preferred choice between abiraterone and enzalutamide in special medical conditions:		
	(i) Abiraterone in case of stable brain metastases (Q77)	86	73
	(ii) Abiraterone in case of history of falls (Q78)	86	94
	(iii) Abiraterone in case of baseline significant fatigue (Q79)	68	88
	(iv) Abiraterone in case of baseline significant neurocognitive impairment (Q80)	86	84
	(v) Enzalutamide in case of diabetes mellitus requiring prescription drug therapy (Q82)	91	84
	(vi) Enzalutamide in case of cardiac ejection fraction below 45–50% (Q83)	91	65
	(vii) Enzalutamide in case of active liver dysfunction (Q84)	77	66
16.	Enzalutamide or apalutamide in addition to ADT in M0CRPC (ideal-world setting; Q86a)	100	n.a.
17.	Metastasis-free survival as a clinically meaningful endpoint in M0CRPC (Q87)	91	n.a.
	<b>Use of osteoclast-targeted therapy for SRE/SSE prevention for mCRPC</b>		
18.	Indefinite osteoclast-targeted treatment in mCRPC and bone metastases (ideal-world setting; Q89a)	82	28
19.	Permanent discontinuation of osteoclast-targeted treatment in men who develop osteonecrosis of the jaw while on osteoclast-targeted therapy for SRE/SSE prevention (Q92)	82	84
	<b>Global access to prostate cancer drugs and treatment in countries with limited resources</b>		
20.	Orchiectomy as ADT in the metastatic setting (Q93)	95	90
21.	In men with mCRPC who are progressing on or after docetaxel		
	(i) Platinum (carboplatin/cisplatin; Q95)	81	80
	(ii) Mitoxantrone (Q99)	91	69
	(iii) Not cyclophosphamide (Q96)	86	57
	(iv) Not paclitaxel (Q97)	50	83
	(v) Not doxorubicin (Q98)	82	88
22.	Prescription of generic drugs in the current practice (Q100)	100	n.a.

ADT, androgen deprivation therapy; AR, androgen receptor; CNPC, castration-naïve prostate cancer; CRPC, castration-resistant prostate cancer; mCNPC, metastatic CNPC; mCRPC, metastatic CRPC; n.a., not applicable (as these questions were unavailable in APCCC2017); Q, Question (see Supporting Information); SRE, skeletal-related event; SSE, symptomatic skeletal event.

The EAU guidelines recommend a PSA threshold of 0.5 ng/mL for salvage radiotherapy post-radical prostatectomy. Despite this recommendation, no consensus was reached on this threshold at either the APCCC 2017 or the MyAPCCC 2018. The highest PSA level for which salvage radiotherapy could still be considered was even less clear. The lack of high-quality evidence in this area poses a challenge for clinicians. Newer imaging methods, such as prostate-specific membrane antigen (PSMA)-positron emission tomography (PET) scans, may help to guide the decision by differentiating remnant local disease from systemic metastasis, but this is not readily accessible to many patients in Malaysia owing to limited facilities and high cost.

### Management of Oligometastatic Prostate Cancer

The definition and management strategies for oligometastatic prostate cancer remain controversial. This has generated interest in recent years because clinicians speculate that the disease can still be controlled and potentially ‘cured’ at the oligometastatic stage; however, high-level evidence on the treatment strategy and benefit is currently lacking [13].

At the APCCC 2017, only one consensus was achieved on the use of PSMA as a tracer when considering PET in men with oligometastatic castration-naïve prostate cancer (CNPC). The

MyAPCCC 2018 did not vote on this question because PSMA-PET facilities remain scarce in Malaysia. At the MyAPCCC 2018, oligometastatic prostate cancer was the only area where no consensus was reached on any question. This is unsurprising because of the lack of level 1 evidence to guide optimal management of these patients.

### Management of Castration-Naïve Prostate Cancer

Consistent with the APCCC 2017, we used the term ‘castration-naïve’ for prostate cancer either previously untreated with ADT or demonstrating ongoing ADT sensitivity.

Continuous ADT has been the standard of care for men with metastatic CNPC (mCNPC). In 2015, the CHAARTED and STAMPEDE studies showed the overall survival (OS) benefit in patients with mCNPC undergoing ADT combined with docetaxel (chemohormonal therapy) [14,15]; however, the definition of patients who would benefit from such treatment was inconsistent between the two trials.

The updated analysis of CHAARTED confirmed the OS benefit in patients with high-volume but not those of low-volume disease [16]. The large STAMPEDE trial included both patients with non-metastatic (M0) and those with

**Table 4** Comparison of areas of consensus achieved ( $\geq 75\%$  agreement) between the ideal-world and the real-world settings at the MyAPCCC 2018.

No.	Statements	% Agreement	
		Ideal-world	Real-world
<b>Management of CNPC</b>			
1.	ADT and abiraterone as upfront therapy in mCNPC (Q41)	86	27
2.	ADT alone in CNPC		
	(i) <i>De novo</i> mCNPC with low-volume disease (ideal-world setting; Q43)	86	100
	(ii) Relapsed mCNPC after prior treatment for localized prostate cancer and with low-volume disease (Q45)	77	95
3.	Docetaxel in addition to ADT in CNPC		
	(i) Relapsed mCNPC after prior treatment for localized prostate cancer and with high-volume disease (real-world setting; Q44)	36	81
<b>Management of CRPC</b>			
4.	First-line CRPC		
	(i) Abiraterone or enzalutamide for asymptomatic men without docetaxel for CNPC (Q50)	90	36
	(ii) Docetaxel for symptomatic men without docetaxel for CNPC (Q51)	50	91
	(iii) Abiraterone or enzalutamide for asymptomatic men with docetaxel for CNPC (Q52)	95	59
5.	Second-line CRPC		
	(i) Taxane for symptomatic men with mCRPC who had progressive disease as best response to first-line abiraterone or enzalutamide (Q61)	52	86
	(ii) Abiraterone or enzalutamide in men with asymptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression after use of first-line abiraterone or enzalutamide (Q62)	77	27
	(iii) Taxane in men with symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression after use of first-line abiraterone or enzalutamide (Q63)	45	82
	(iv) Abiraterone or enzalutamide for asymptomatic men with mCRPC progressing on or after docetaxel for mCRPC (without prior abiraterone or enzalutamide; Q64)	100	68
6.	Enzalutamide or apalutamide in addition to ADT in M0CRPC (Q86)	100	27
<b>Use of osteoclast-targeted therapy for SRE/SSE prevention for mCRPC</b>			
7.	Indefinite osteoclast-targeted treatment in mCRPC and bone metastases (Q89)	82	27

ADT, androgen deprivation therapy; CNPC, castration-naïve prostate cancer; CRPC, castration-resistant prostate cancer; mCNPC, metastatic CNPC; mCRPC, metastatic CRPC; Q, Question (see Supporting Information); SRE, skeletal-related event; SSE, symptomatic skeletal event.

metastatic (M1) disease, and no heterogeneity of treatment was observed [17].

The benefits of abiraterone plus prednisolone in addition to ADT were confirmed in 2017 by the LATITUDE and STAMPEDE studies. The LATITUDE study included men with *de novo* mCNPC with high-risk disease only. In that study, the median OS was significantly longer in the abiraterone group than in the placebo group [18]. This was confirmed by the STAMPEDE study showing that ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone among men with locally advanced or metastatic prostate cancer [19]. Comparative analysis of chemohormonal therapy vs ADT plus abiraterone and prednisolone from the STAMPEDE study showed comparable OS and prostate cancer-specific survival [20].

The APCCC 2017 achieved consensus on using chemohormonal therapy in *de novo* mCNPC with high-volume disease only and not to add docetaxel in non-metastatic biochemical relapse. Same outcome was achieved at the MyAPCCC 2018. In addition, the MyAPCCC 2018 also reached consensus on using chemohormonal therapy in relapsed mCNPC with high-volume disease but not in metastatic low-volume or non-metastatic disease. The role of ADT plus abiraterone and prednisolone was not discussed at the APCCC 2017 as the data were not yet available at the

time; the MyAPCCC 2018, therefore, posed several clinically relevant questions regarding this. Amongst the three treatment options (ADT alone vs chemohormonal therapy vs ADT plus abiraterone and prednisolone) in *de novo* high-volume disease, 96% voted for combination therapy rather than ADT alone in the ideal-world setting. However, in the real-world setting, 96% chose either ADT or chemohormonal therapy, while only 4% chose ADT plus abiraterone and prednisolone. This may be explained by the high cost of AR-targeting agents and lack of reimbursement within the local health system. In *de novo* low-volume disease, consensus was achieved for ADT alone in both ideal- and real-world settings.

## Management of Castration-Resistant Prostate Cancer

The treatment paradigm has expanded, with more agents showing improvement in survival since 2010. These agents include chemotherapy (docetaxel, TAX327 and SWOG studies; cabazitaxel, TROPIC study) [21–23], novel AR-targeting agents (abiraterone acetate, COU-AA-301 and 302 studies; enzalutamide, AFFIRM and PREVAIL studies) [24–27], radiopharmaceutical agent (radium-223, ALSYMPCA study) [28] and immunotherapy (sipuleucel-T, IMPACT study) [29]. Cabazitaxel and sipuleucel-T were shown to be beneficial in post-docetaxel settings [23,29]. Abiraterone,

enzalutamide and radium-223 showed survival benefits in both pre- and post-docetaxel settings [24–28]. Sipuleucel-T is unavailable outside the USA. Radium-223 is unavailable in Malaysia.

The optimal first-line agent remains unknown. In clinical practice, various factors are considered when choosing the optimal agent, including disease factors such as time-to-progression on ADT, Gleason score, presence of visceral disease, and patient factors such as comorbidities and preference. The evidence for combination therapy in the mCNPC setting (chemohormonal therapy and ADT plus abiraterone and prednisolone) will affect the choice of first-line therapy in the mCRPC setting.

In the second-line setting, data showed survival benefit post-docetaxel for cabazitaxel, abiraterone, enzalutamide and radium-223 [23,24,26,28]. For patients who received abiraterone, enzalutamide and radium-223 in first-line settings, no data exist for the optimum second-line agents. The optimal sequencing regimen is unknown as no evidence has been obtained from prospective randomized controlled studies.

No randomized data currently exist for beyond second-line setting. The optimal sequences and combinations of currently approved agents require further investigation. Some data exist on potential cross-resistance between the AR-targeting agents that limit the use of these drugs in sequence once a patient fails one. Several chemotherapeutic drugs have been used based on small studies, and platinum was the most studied agent either in single or combination regimens [30].

There are several concordances in the consensus achieved for mCRPC treatment for both the APCCC 2017 and MyAPCCC 2018. The APCCC 2017 recommends abiraterone or enzalutamide for asymptomatic men with or without docetaxel for CNPC based on high consensus achieved for both. Similar outcomes were seen at the MyAPCCC 2018 in the ideal-world but not in the real-world setting. Whilst panels voted 50% each of AR-targeting agents and docetaxel in symptomatic men without receiving docetaxel for CNPC in the ideal-world setting, 91% chose docetaxel in the real-world setting. This is an interesting finding considering that ~30% of the MyAPCCC 2018 panels work in private sectors, and implies the high cost of AR-targeting agent limits its use even in private sectors. Overall, in the real-world setting, there seemed to be fewer votes on high-cost drugs. More panels at the MyAPCCC 2018 voted for lower-cost drugs (e.g. docetaxel) in this setting including in situations where AR-targeting agents were preferred in the ideal-world setting.

In local clinical practice, concerns exist that Asian patients may be unable to tolerate chemotherapy as well as their Western counterparts; therefore, dosing schedules are of interest. The TAX 327 study showed a survival benefit with

the 3-weekly regimen, while the 1-weekly regimen showed no benefit over the mitoxantrone control arm. The docetaxel 2-weekly regimen showed a comparable benefit to the 3-weekly regimen with a better toxicity profile [31]. Despite this, consensus was achieved for use of a 3-weekly docetaxel (75 mg/m<sup>2</sup>) regimen. This is probably related to logistics, especially in the public sector.

Both abiraterone and enzalutamide have specific side effect profiles related to their mechanisms of action. No head-to-head trials have compared the efficacy and side effects of these drugs. Panels were asked to vote between the two drugs in various clinical situations that may put patients at higher risk for certain adverse effects. High concordance was seen with the APCCC 2017 consensus in the choice of AR-targeting agents based on patients' comorbidities.

People with poor prognosis, aggressive-variant mCRPC are a clinical subset of patients with highly aggressive disease. They can be recognized by their histological features of small-cell or neuroendocrine carcinoma, but many show clinical features suggesting aggressive behaviour. Identifying this patient group is important as they are less likely to benefit from endocrine therapy, but may benefit from platinum-based chemotherapy [32]. The MyAPCCC 2018 achieved consensus in several criteria defining this disease entity.

Men with non-metastatic prostate cancer and rapidly rising PSA level despite being on ADT are considered as having non-metastatic CRPC (nmCRPC). They are at high risk of progression to metastatic disease. This disease has a largely unmet need because of the lack of treatment with a survival benefit. A significant milestone in advanced prostate cancer treatment was achieved when positive results from two randomized studies using novel AR-targeted therapy in nmCRPC were presented at the American Society of Clinical Oncology – Genitourinary Cancers Symposium in February 2018. Both the PROSPER and SPARTAN studies [33,34] showed improvements in their primary endpoint and metastasis-free survival using enzalutamide and apalutamide, respectively. These data were unavailable at the time of the APCCC 2017 meeting. All panels at the MyAPCCC 2018 voted for use of these drugs in nmCRPC in the ideal-world setting only, reflecting the burden of cost in the real-world setting.

### Use of Osteoclast-Targeted Therapy for Skeletal-Related Events or Symptomatic Skeletal Event Prevention for Metastatic Castration-Resistant Prostate Cancer

Zoledronic acid and denosumab have been shown to delay and reduce the occurrence of skeletal-related events (SREs) in mCRPC without impacting survival [35,36]. Denosumab was shown to be better than zoledronic acid [36]. Systemic therapies for mCRPC (e.g. abiraterone, enzalutamide and

radium-223) have also shown benefits in delaying SREs/symptomatic skeletal events (SSEs) [24,26,28]. Some data showed that adding osteoclast-targeted therapy to systemic therapies (e.g. docetaxel and radium-223) further reduces SSEs compared with systemic therapies alone [37,38].

The overall treatment duration and optimum frequency of administration remain controversial. Limited evidence suggests a less frequent administration schedule (e.g. 12-weekly) is comparable to the standard 4-weekly schedule [39,40]. As osteoclast-targeted therapy is used over a prolonged duration, the risk of osteonecrosis of the jaw must be monitored as the incidence may increase over time.

Currently, these agents are approved for mCRPC only, but not in mCNPC or nmCNPC. The only question that achieved consensus at the APCCC 2017 was on the discontinuation of osteoclast-targeted therapy in men who develop osteonecrosis of the jaw while on treatment for SRE or SSE prevention. Same consensus was achieved at the MyAPCCC 2018.

The voting results at the MyAPCCC 2018 showed that most clinicians treating men with mCRPC believe osteoclast-targeted therapy still plays a role in preventing SREs in the current era of novel systemic therapy; however, the optimal frequency and duration remain unknown. More panels would use short-interval therapy for longer durations in ideal-world than in real-world settings. Again, this reflects issues with cost and affordability.

## Global Access to Prostate Cancer Drugs and Treatment in Countries with Limited Resources

The APCCC 2017 recommends orchidectomy as ADT for metastatic disease in a country with limited resources available for healthcare. The MyAPCCC 2018 panels voted in the same manner.

Platinum agents, paclitaxel, doxorubicin and cyclophosphamide are examples of essential medicines according to the WHO that have shown anti-tumour activity without OS benefit in patients with mCRPC. The APCCC 2017 does not recommend use of any of these agents except platinum agents. Conversely, the MyAPCCC 2018 accepted mitoxantrone as a reasonable cytotoxic agent, which showed pain palliation benefits with no OS advantage in patients with mCRPC [21]. In addition to these cytotoxic agents, older androgen-signalling pathway-targeted drugs, including bicalutamide, ketoconazole and corticosteroids are still widely used in Malaysia, although there is a lack of evidence on survival benefit. Since these drugs are substantially cheaper, they are still considered acceptable options for men with advanced prostate cancer in low- and middle-income countries.

## Discussion

The MyAPCCC 2018 was held to review areas from the APCCC 2017 that are relevant to local practice and to explore the applicability of recommendations from the APCCC 2017 in a real-world setting. The MyAPCCC 2018 panels consisted of urologists and oncologists who treat general urological and oncological conditions, with interest in prostate cancer. This is strikingly different from the panels of the APCCC 2017 who were world-renowned experts specializing in urological malignancies, mainly prostate cancer. The MyAPCCC 2018 panels closely resembled clinicians who are managing advanced prostate cancer in many parts of the world especially in Asia.

The overall findings of six areas reviewed at the MyAPCCC 2018 are deemed comparable to those of the APCCC 2017 in the ideal-world setting. Despite the clear evidence of clinical benefit, cost remains a major determinant of whether clinicians consider these options and discuss them with their patients. In low- and middle-income countries, patients have limited access to high-cost drugs, which are not covered under the publicly funded health system such as Malaysia. Only 18% of Malaysian patients, particularly those in the high-income groups, have personal insurance coverage [41]. Most men with mCRPC cannot afford abiraterone (~US\$ 2800/month) or enzalutamide (~US\$ 3400/month), which cost more than twice the country's median monthly household income (~US\$ 1300) [42].

Recent findings from the ACTION (Association of Southeast Asian Nations [ASEAN] Costs in Oncology) study showed the degree of financial catastrophe (out-of-pocket health costs  $\geq 30\%$  of annual household income) and economic hardship (inability to make necessary household payments) experienced by patients with cancer from low- and middle-income countries of the ASEAN [41]. For example, the 1-year risks for financial catastrophe and economic hardship after a cancer diagnosis in Malaysia were 48% and 45%, respectively. These adverse financial catastrophes were mainly attributed to medical costs for inpatient/outpatient care and purchasing drugs, medical supplies and equipment [41]. To overcome this economic hardship, 28% of affected families took personal loans, and 60% used savings that were previously set aside for other uses [41].

Whilst evidence-based clinical practice guidelines and expert consensus recommendations are pivotal for clinicians and patients, it may place enormous strain on a country's healthcare system and patients' financial health. While the efficacy of an individual treatment may be confirmed in well-conducted clinical trials, its role in real-world clinical practice is influenced by many factors which are rarely evaluated in these studies. The APCCC 2017 stated that the achievement of new advanced prostate cancer treatments in improving



patients' survival is suboptimal if such treatments are unavailable to most patients globally [1]. This is indeed a difficult call for the oncology community, ranging from policy makers, the pharmaceutical industry, clinicians and patients. Recently, the National Comprehensive Cancer Network has published guidelines on prostate cancer management based on resource stratification [43] and within the Asian context [44]. These resource-stratified guidelines may be a medium of providing recommendations for management based on levels of healthcare resources [45], and adherence to these guidelines could be further enhanced through a focused, clinician-centred education programme at regional level [46]. Collaboration between various countries, especially in the Asian region, may help to overcome some common challenges in the long run.

In conclusion, advanced prostate cancer is an important health issue, especially in countries with a high percentage of patients who present with advanced metastatic disease. A review of consensus statements from the APCCC 2017 in the local setting is extremely valuable to create awareness of the current evidence and challenges amongst clinicians in managing patients with advanced prostate cancer. It also provides real-world guidance for both clinicians and patients' decision-making under the financial constraints with regard to healthcare access. The consensus meeting outcomes highlighted key areas to be addressed to better serve our patients, especially in health economics and resource allocation.

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## Conflict of Interest

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**Abbreviations:** MyAPCCC, Malaysian Advanced Prostate Cancer Consensus Conference; APCCC, Advanced Prostate Cancer Consensus Conference; ADT, androgen deprivation therapy; EAU, European Association of Urology; PSMA, prostate-specific membrane antigen; PET, positron-emission tomography; AR, androgen receptor; CNPC, castration-naïve prostate cancer; OS, overall survival; mCRPC, metastatic castration-naïve prostate cancer; nmCRPC, non-metastatic castration-naïve prostate cancer; SRE, skeletal-related event; SSE, symptomatic skeletal event; ASEAN, Association of Southeast Asian Nations.

## Supporting Information

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

**Data S1.** Summary of the list of drafted questions in MyAPCCC.

**Data S2.** Detailed voting results.