Review

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Management of patients with advanced prostate cancer in the Asia Pacific region: 'real-world' consideration of results from the Advanced Prostate Cancer Consensus Conference (APCCC) 2017

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Objective

The Asia Pacific Advanced Prostate Cancer Consensus Conference (APAC APCCC 2018) brought together 20 experts from 15 APAC countries to discuss the real-world application of consensus statements from the second APCCC held in St Gallen in 2017 (APCCC 2017).

Findings

Differences in genetics, environment, lifestyle, diet and culture are all likely to influence the management of advanced prostate cancer in the APAC region when compared with the rest of the world. When considering the strong APCCC 2017 recommendation for the use of upfront docetaxel in metastatic castration-naïve prostate cancer, the panel noted possible increased toxicity in Asian men receiving docetaxel, which would affect this recommendation in the APAC region. Although androgen receptor-targeting agents appear to be well tolerated in Asian men with metastatic castration-resistant prostate cancer, access to these drugs is very limited for financial reasons across the region. The meeting highlighted that cost and access to contemporary treatments and technologies are key factors influencing therapeutic decision-making in the APAC region. Whilst lower cost/older treatments and technologies may be an option, issues of culture and patient or physician preference mean, these may not always be acceptable. Although generic products can reduce cost in some countries, costs may still be prohibitive for lower-income patients or communities. The panellists noted the opportunity for a coordinated approach across the APAC region to address issues of access and cost. Developments in technologies and treatments are presenting new opportunities for the diagnosis and treatment of advanced prostate cancer. Differences in genetics and epidemiology affect the side-effect profiles of some drugs and influence prescribing.

Conclusions

As the field continues to evolve, collaboration across the APAC region will be important to facilitate relevant research

 | doi:10.1111/bju.14489
Published by John Wiley & Sons Ltd. www.bjui.org

and collection and appraisal of data relevant to APAC populations. In the meantime, the APAC APCCC 2018 meeting highlighted the critical importance of a multidisciplinary team-based approach to treatment planning and care, delivery of best-practice care by clinicians with appropriate expertise, and the importance of patient information and support for informed patient choice.

Keywords

advanced prostate cancer, castration-naïve prostate cancer, castration-resistant prostate cancer, high-risk localised prostate cancer, oligometastatic prostate cancer, cost and access to treatment

Introduction

The 2018 Asia Pacific Advanced Prostate Cancer Consensus Conference (APAC APCCC 2018) was convened to reflect on consensus statements from the 2017 APCCC (APCCC 2017) held in St Gallen [1]. The 61 St Gallen panellists were highly regarded key opinion leaders in the field of advanced prostate cancer. Although St Gallen included global representation from 21 countries, only four panellists were from the APAC region. Voting at the APCCC 2017 was based on idealised assumptions that all diagnostic procedures and treatments were available, and participants were instructed not to consider cost, reimbursement, and access in their deliberations. Meetings in Taiwan, the Philippines and Lebanon have considered the local relevance of the APCCC outcomes. Discussions are ongoing in the APAC region about the regional appropriateness of some St Gallen recommendations, especially as much of the data informing the recommendations are based, at best, on studies involving small numbers of patients from the region. With the endorsement of the St Gallen leadership, the APAC APCCC 2018 Satellite Meeting was convened to consider the real-world application of APCCC 2017 recommendations across the APAC region.

The panel

The panel for the 1-day APAC APCCC 2018 meeting included 20 experts from 15 APAC countries (Table 1). Panellists were selected based on their expertise in advanced prostate cancer and are leaders in the region. The panel met in Melbourne, Australia, in February 2018, hosted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

Prior to the meeting, the panel considered the 10 topic areas discussed during the APCCC 2017 and agreed on the five

Table 1 The APAC APCCC 2018 panel members.

Name	First name	Specialty	Chemotherapy prescriber*		Country
			Oral agents	i.v.	
Akaza	Hideyuki	Urologist	✓	✓	Japan
Buchan	Nick	Urologist	–	–	New Zealand
Chiong	Edmund	Urologist	✓	–	Singapore
Chung	Byung Ha	Urologist	✓	✓	South Korea
Davis	Ian	Medical oncologist	✓	✓	Australia
Kanesvaran	Ravindran	Medical oncologist	✓	✓	Singapore
Khochikar	Makarand	Urologist	–	–	India
Letran	Jason	Urologist	–	–	Philippines
Lojanapiwat	Bannakij	Urologist	✓	✓	Thailand
Murphy	Declan	Urologist	✓	–	Australia
Ng	Anthony CF	Urologist	–	–	Hong Kong
Ong	Teng Aik	Urologist	✓	–	Malaysia
Pu	Yeong-Shiau	Urologist	✓	✓	Taiwan†
Saad	Marniza	Clinical oncologist	✓	✓	Malaysia
Schubach	Kathryn	Urology nurse practitioner	–	–	Australia
Türkeri	Levent	Urologist	✓	✓	Turkey
Umbas	Rainy	Urologist	✓	✓	Indonesia
Vu	Le Chuyen	Urologist	✓	–	Vietnam
Williams	Scott	Radiation oncologist	–	–	Australia
Ye	Ding-wei	Urologist	✓	✓	China

**Refers to prescribing of oral agents (abiraterone and enzalutamide) and i.v. chemotherapy (docetaxel) for prostate cancer. †A review of prescribing practices among urologists in Taiwan suggests that about half of all urologists has prescribed i.v. chemotherapy but not on a regular basis.*

most contentious areas to discuss at the APAC APCCC 2018, based on their relevance for the APAC region:

- Management of castration-sensitive/naïve prostate cancer (CNPC).
- Management of castration-resistant prostate cancer (CRPC).
- Management of high-risk localised and locally advanced prostate cancer.
- Management of oligometastatic prostate cancer.
- Global access to prostate cancer drugs and treatment in countries with limited resources.

Self-nominated groups were established before the meeting to discuss the APCCC 2017 statements and review evidence relevant to the APAC region. At the meeting, nominated leads presented a summary of evidence and APAC considerations. Panellists then discussed areas of variation within and across the APAC region and agreed key themes for each of the five topics. A separate systematic review was not conducted, as our goal was to consider the existing APCCC 2017 recommendations from an APAC perspective and to use the opinions of a multidisciplinary panel of APAC prostate cancer experts to provide a regional interpretation of these recommendations. Consensus was reached by discussion amongst the 20-strong panel.

Management of advanced prostate cancer in the APAC region

Prostate cancer is the most common cancer in men globally [2]. Incidence varies according to sociodemographic index (SDI). Age-standardised incidence rates (ASIRs) and age-standardised death rates for prostate cancer are amongst the lowest globally in South Asia and East Asia, but are higher in South-East Asia, and highest in Australasia. The ASIR is increasing across all SDI quintiles globally [2].

The PREVAIL study (a multinational phase 3, randomised, double-blind, placebo-controlled efficacy and safety study of oral Mdv3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen-deprivation therapy) highlights several differences in baseline characteristics in East Asian men with prostate cancer compared with the overall study population. This includes a higher percentage of patients with a Gleason score of ≥8 and a higher percentage with bone disease (likely a result of less frequent PSA testing). However, PREVAIL also found lower median PSA levels and fewer patients with soft tissue disease and bone pain in the East Asian population [3].

Differences in genetics, environment, lifestyle, diet, and culture are all likely to influence the management of advanced prostate cancer in the APAC region. Some of these differences are highlighted in recent *post hoc* analyses of data from the PREVAIL trial in different population groups [3–5]. Whilst numbers are small, differences in the East Asian patients compared with the overall study population included more common upper respiratory tract infection, urinary frequency, falls, and decreased appetite. Fatigue and back pain were rare in East Asian patients.

Management of advanced prostate cancer may also be influenced by which disciplines are involved in treatment planning and delivery, with variation in specialties who prescribe chemotherapy in the APAC region. Table 1 provides a snapshot of chemotherapy-prescribing practices by discipline in each of the countries represented at the APAC APCCC 2018.

Another factor influencing advanced prostate cancer management is the status of registration and reimbursement for diagnostic technologies and treatments. Tables 2 and 3 provide a summary of the status of prostate cancer drugs (Table 2) and imaging technologies (Table 3) as reported for the countries represented at the APAC APCCC 2018 in early 2018.

The APAC APCCC 2018 outcomes

Management of metastatic CNPC (mCNPC)

Addition of docetaxel to androgen-deprivation therapy (ADT) in mCNPC

The APCCC 2017 reported strong consensus (96%) for the addition of docetaxel (3 weekly at 75 mg/m^2) to ADT in men with *de novo* mCNPC and high-volume disease, as defined in the chemohormonal therapy versus androgen ablation randomised trial for extensive disease in prostate cancer (CHAARTED) (visceral [lung or liver] and/or ≥4 bone metastases, at least one beyond the pelvis and vertebral column) [6]. Whilst not reaching the threshold for consensus, there was a high degree of agreement (74%) for the addition of docetaxel to ADT in men relapsing after prior treatment for localised prostate cancer, non-castrate serum testosterone, and high-volume metastatic disease (as defined in CHAARTED). There was no consensus (29%) for the addition of docetaxel to ADT in men with *de novo* mCNPC and low-volume disease (as defined in CHAARTED).

The APAC APCCC 2018 panellists reflected on the recently published 53-month follow-up data from CHAARTED showing an overall survival (OS) benefit for the addition of docetaxel (3 weekly at 75 mg/m^2) in patients with high-volume disease (hazard ratio [HR] 0.63) but no OS benefit for low-volume disease (HR 1.04) [7]. There was unanimous agreement for the addition of docetaxel to ADT in high-volume mCNPC if cost/access was not an issue. Only one panellist indicated that addition of docetaxel to ADT would

Table 2 Access in APAC countries to drugs used in the management of advanced prostate cancer.

Country	Abiraterone			Enzalutamide			Docetaxel			^{223}Ra			G-CSF			Bone loss therapy	
	Reg	Reimb	Gen	Reg	Reimb	Gen	Reg	Reimb	Gen	Reg	Reimb	Gen	Reg	Reimb	Gen	Zvoledronic acid	Denosumab
Australia	✓	✓	–	✓ Post-docetaxel	✓		✓	✓	✓	✓	–	–	–	–	–	Registered/reimbursed for CRPC	
China	✓	✓ CRPC	–	–	–	–	✓	✓ CRPC	–	–	–	–	✓	✓	–	Registered/reimbursed	–
Hong Kong	✓	✓ part	–	✓	✓ part	–	✓	✓ CRPC	–	✓	–	–	✓	–	–	Registered but not reimbursed	
India	✓	✓ part	x	✓	✓ part	✓	✓	✓ part	✓	–	–	–	–	–	–	✓	–
Indonesia	✓	✓ part	–	✓	–	–	✓	✓	✓	–	–	–	✓	✓ part	–	✓ part	–
Japan	–	✓	–	–	✓	–	–	✓	–	–	✓	–	–	✓	–	✓	✓
Malaysia	✓	✓ part	–	✓	✓ part	–	✓	✓ part	✓	–	–	–	✓	✓ part	✓	Registered/partially reimbursed for mCRPC	
New Zealand	✓	✓	–	✓	–	–	✓	✓	–	–	–	–	–	–	–	✓	✓
Philippines	✓	–	–	✓	–	–	✓	–	–	–	–	–	✓	–	✓	Registered but not reimbursed	
Singapore	✓	✓ part	–	✓	✓ part	–	✓	✓ part	–	✓	–	–	✓	✓ part	–	Registered/partially reimbursed for metastatic CRPC	
South Korea	✓	✓	–	✓	✓	–	✓	✓	✓	✓	–	–	✓	✓	✓	✓	Registered not reimbursed
Taiwan	✓	✓	–	✓	✓	–	✓	✓ mCRPC	✓	✓	–	–	✓	✓	–	Registered/reimbursed for bone metastases	
Thailand	✓	✓ part	–	✓	✓ part	–	✓	✓ part	–	✓	–	–	✓	✓ part	–	Registered/partially reimbursed for mCRPC	–
Turkey	✓	✓ post-chemo	–	✓	✓ post-chemo	–	✓	✓	–	✓	–	–	✓	✓	–	✓	✓
Vietnam	✓	–	–	–	–	–	✓	✓	✓	–	–	–	–	–	–	Registered/reimbursed for mCRPC	–

Reg, registered; Reimb, reimbursed; Gen, generic version available; part, partially reimbursed/reimbursed with some limitations; post-chemo, post-chemotherapy.

Table 3 Access and use in APAC countries to imaging technologies relevant to in the management of advanced prostate cancer.

Country	Bone scanner		Whole-body MRI		Choline PET-CT		PSMA-PET	
	Available	Reimbursed	Available	Reimbursed	Available	Reimbursed	Available	Reimbursed
Australia	✓	✓	✓	–	–	–	✓	–
China	✓	✓	✓	✓	✓	–	✓	–
Hong Kong	✓	–	✓	–	✓	–	✓	–
India	✓	✓	✓	✓	✓ part	–	✓	✓
Indonesia	✓	✓	✓	✓ part	–	–	–	–
Japan	✓	✓	✓	✓	✓	–	–	–
Malaysia	✓	✓ part	✓	✓ part	✓	✓ part	✓	✓ part
New Zealand	✓	✓	✓	–	–	–	✓	✓ with restrictions
Philippines	✓	–	✓	–	✓	–	✓	–
Singapore	✓	✓ part	✓	✓ part	✓	–	✓	–
South Korea	✓	✓	✓	–	✓	–	–	–
Taiwan	✓	✓	✓	–	✓	Free under trials at a few centres	✓	Free under trials at a few centres
Thailand	✓	✓ part	✓	✓ part	✓	–	–	–
Turkey	✓	✓	✓	–	–	–	✓	✓ part
Vietnam	✓	✓	✓	✓	✓	✓ part	–	–

Reg, registered; Reimb, reimbursed.

be considered in low-volume mCNPC. This contrasts with practice in the USA, UK, and other regions.

Factors identified by panellists that may influence whether docetaxel is offered in addition to ADT to men with mCNPC in the APAC region included the following:

- increased toxicity of docetaxel in Asian men, specifically a higher incidence of febrile neutropaenia.
- patient concerns about chemotherapy toxicity and a perception that chemotherapy may not be required if they are already seeing a benefit on ADT.
- differences in docetaxel registration/reimbursement for use in mCNPC (Table 2).

The issue of increased toxicity of docetaxel in Asian men was notable during discussions about mCNPC and metastatic CRPC (mCRPC). Studies in CRPC have shown an incidence of Grade 3 or 4 neutropenia in Asian men almost double that of Caucasian cohorts (57.7% vs 32%) [8,9]. A requirement for dose reduction has been demonstrated in some studies due to toxicity [8,10,11]. The question of whether to use granulocyte colony-stimulating factor (G-CSF) in men receiving docetaxel also generated significant discussion at the APAC APCCC 2018. The USA and European guidelines state that G-CSF prophylaxis should be considered in men with risk factors [12–14]. No consensus was reached at the APCCC 2017 for the use of white blood cell growth factors from start of therapy (6% voted for use in a majority of patients and 50% for use in a minority of patients). Most of the APAC APCCC 2018 panellists indicated that G-CSF is used routinely in men receiving docetaxel for the management of mCNPC in the APAC region. However, in some areas, including Australia, G-CSF is not used at all in the palliative setting.

The toxicity in Asian men of docetaxel at a dose of 75 mg/m^2 has been reported in men with CRPC [15]. Panellists reported that toxicity concerns also result in dose reductions in the management of mCNPC, with four panellists indicating that docetaxel is routinely started at a dose of 60 mg/m^2. A similar finding was reported from the Taiwan consensus meeting held after the APCCC 2017: only 50% of participating doctors indicated that they use a starting dose of docetaxel of 75 mg/m^2 [Personal correspondence. Dr Yeong-Shiau Pu, Department of Urology, National Taiwan University Hospital, Taipei, Taiwan]. In addition to toxicity concerns, the cost of treatment (including the cost of G-CSF) was also identified as a factor influencing the starting dose.

Addition of abiraterone to ADT in mCNPC

Panellists at the APCCC 2017 did not vote on the addition of abiraterone to ADT in mCNPC as data from the randomised, double-blind, comparative study of abiraterone acetate plus low-dose prednisone plus ADT vs ADT alone in newly diagnosed subjects with high-risk, metastatic hormone-naive prostate cancer (LATITUDE) [16] and systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) [17] trials were not yet available. European Association of Urology (EAU) guidelines were updated in late 2017 [18] to reflect these updated data.

No differences in side-effect profile for abiraterone have been reported in Asian men compared with the global population [19]. At the APAC APCCC 2018, 83% of panellists indicated that they would consider addition of abiraterone to ADT in patients with mCNPC if cost/access was not an issue. However, in reality, prescribing is influenced by the registration and reimbursement status of abiraterone across the region (Table 2).

Imaging to determine therapeutic strategies

The APCCC 2017 focused on the use of increasingly sensitive imaging techniques, such as ^{68}Ga- prostate-specific membrane antigen (PSMA)-positron emission tomography (PET), as a diagnostic modality, means of response assessment, and guide to decisions about therapy [20].

The availability of new or more conventional imaging technologies varies across the APAC region and may have implications for the implementation of clinical trial outcomes (Table 3). For example, limited availability of bone scanners and radioisotopes can be an obstacle to the detection of high-volume disease according to CHAARTED criteria. There was significant interest amongst panellists in the potential to use other imaging techniques, such as MRI, as a means of determining stage of disease [21,22].

Other issues related to management of mCNPC

Other issues discussed in relation to mCNPC included the following:

- agreement that local treatment of the primary in mCNPC should best be undertaken in the context of a clinical trial.
- an interest in identifying biomarkers specific to the Asian population that may improve understanding of mechanisms of resistance to ADT and help to inform the therapeutic strategy for men with mCNPC (noting that, in the absence of biomarkers, phenotypic and clinical characteristics can provide some indication of risk level).
- when to start ADT in men with rising PSA (on an LHRH agonist) and non-castrate testosterone levels.

Management of mCRPC

The APCCC 2017 reflected on the remarkable progress in prostate cancer drug development over the past 10 years and since the first APCCC meeting in 2015. Questions focused on

Table 4 Areas of consensus from the APCCC 2017 regarding the management of mCRPC.

Statement	% agreement
First-line CRPC	
Abiraterone or enzalutamide for	
Asymptomatic men without docetaxel for CNPC	86
Asymptomatic men with docetaxel for CNPC	90
Asymptomatic men with docetaxel for CNPC and progressed within ≤6 months after completion of docetaxel in the CNPC setting	77
Not to combine ^{223}Ra and docetaxel	88
Second-line CRPC	
Taxane in men with	
Symptomatic mCRPC with progressive disease as best response to first-line abiraterone or enzalutamide	96
Symptomatic mCRPC and secondary (acquired) resistance after first use of first-line abiraterone or enzalutamide	90
Abiraterone or enzalutamide in men with	
Asymptomatic mCRPC progressing on or after docetaxel for mCPRC (without prior abiraterone or enzalutamide)	92
Symptomatic mCRPC progressing on or after docetaxel for mCPRC (without prior abiraterone or enzalutamide)	76
Third-line CRPC	
No randomised prospective data	
Use of platinum-based chemotherapy in a range of situations if all approved treatments are exhausted and no clinical trial available	96

sequencing and treatment combinations in the management of mCRPC for which evidence is limited and clinical trials underway.

Sequencing of treatment for mCRPC

Table 4 summarises the areas of consensus at the APCCC 2017 related to sequencing of treatment for mCRPC.

The APAC APCCC 2018 panellists reflected on the large number of trials that have shown an OS advantage for survival-prolonging agents in mCRPC when used before and after chemotherapy [9,23–29]. Benefits are particularly apparent in the pre-chemotherapy setting, where stratification informs the choice of treatment.

Studies in Asian populations (China, Malaysia, Thailand) suggest no difference in safety data for abiraterone [19] or enzalutamide [3] compared with data from global studies. The APAC APCCC 2018 panellists agreed with the APCCC 2017 conclusions that clinical factors, such as performance status, symptoms, comorbidities, disease site, and extent of disease, are important in influencing choice and sequence of treatment.

Specific issues relevant to the APAC region noted by panellists included the following:

- a preference in the APAC region for enzalutamide over abiraterone for patients with diabetes mellitus (especially when poorly controlled) because of the potential for symptom exacerbation and complications through concomitant steroid use.
- use of lower starting doses for docetaxel due to concerns about toxicity [11].

A recurring theme at the APAC APCCC 2018 was the impact of cost and access on prescribing habits (Table 2). As with docetaxel, dose adjustment of abiraterone occurs in some countries as a way of reducing treatment costs [30]. A small prospective phase 2 study has shown low-dose abiraterone with a low-fat meal may have benefits comparable to the standard dosing schedule in the fasting state [31]. Data were presented showing the cost of generic abiraterone in India, which is 5% of the cost of branded abiraterone in the USA. If generic abiraterone was to become more widely available in the region, this would likely lead to significant changes in patterns of care for mCRPC.

It was also noted that older treatments targeting androgen synthesis or activity, such as ketoconazole and bicalutamide, are still widely used in some countries instead of newer androgen-receptor pathway-targeted therapies. Surgical castration was also discussed as a lower cost option; noting that cultural and other patient factors play a role in influencing its use.

Combined treatment

The APCCC 2017 noted that no combined treatment strategies using survival-prolonging agents have shown an OS benefit compared with monotherapy. Results from ongoing combined therapy trials (NCT02194842M, NCT02043678, NCT01949337) are awaited.

Although trials using radium-223 (^{223}Ra) dichloride were acknowledged at the APAC APCCC 2018, this treatment is not yet reimbursed in any of the countries represented at the meeting. The panellists agreed that clinical trial outcomes for ^{223}Ra combinations in mCRPC will be required before progress will be seen in ^{223}Ra use in the region.

Other issues related to the management of mCRPC

Other issues discussed in relation to mCRPC included the following:

- whether the clinical benefits of starting treatment for mCRPC earlier (e.g. whilst patients are asymptomatic or have a lower Gleason score or PSA level) [32] are sufficient to justify the additional cost.
- a comparison of approaches used across the region to manage skeletal-related events in men with mCRPC receiving ADT.

Variation was noted in the use of bisphosphonates/RANK ligand inhibitor for the management of bone density loss. The panellists noted inconsistency in clinical uptake of information about benefits of exercise programmes offering advice on resistance training or access to an exercise physiologist, to mitigate loss of bone density associated with ADT.

High-risk localised and locally advanced prostate cancer

The APCCC 2017 highlighted discipline-specific variation in the definition of 'high risk' as it relates to prostate cancer. The EAU, European Society for Radiation Therapy and Oncology, and International Society of Geriatric Oncology (EAU-ESTRO-SIOG) definition was used at the APCCC 2017 meeting (localised disease: PSA level >20 ng/mL, or Gleason score >7 or cT2c; locally advanced disease: any PSA level, any Gleason score, cT3–4 or cN+) [33]. In the APAC region, the National Comprehensive Cancer Network (NCCN) definition of high risk is more commonly used (T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9–10/Gleason grade group 5 and PSA level >20 ng/mL) [12].

Treatment preferences for high risk and locally advanced prostate cancer

The APCCC 2017 did not discuss the choice of primary treatment for high risk and locally advanced prostate cancer.

The panellists at the APAC APCCC 2018 discussed primary treatment for high risk and locally advanced disease. It was noted that the use of radical prostatectomy (RP) with or without radiation therapy (RT) and ADT depends on a range of factors, including patient age and fitness, comorbidities, and the likelihood of local complications based on symptoms and performance status. Access to appropriate expertise and contemporary RT technology was recognised as important with treatment choice influenced by which discipline the patient sees first.

A key agreement from the APAC APCCC 2018 was the importance of a multidisciplinary team (MDT) approach to developing treatment recommendations for advanced prostate cancer. Whilst geography and access to specialist cancer centres can be a significant barrier to MDTworking, the benefits of virtual participation in MDT discussions were noted. For example, in China, a virtual network of 100 centres provides the option of a second opinion to inform treatment planning [34].

Pelvic lymph node dissection (PLND) for high risk and locally advanced prostate cancer

At the APCCC 2017, there was consensus for the use of PLND in most men with cN0cM0 high-risk prostate cancer undergoing RP (84%), and for removal of >10 lymph nodes (76%). European [33] and NCCN guidelines [12] recommend RP with an extended PLND (ePLND) for men with high risk and locally advanced prostate cancer.

The APAC APCCC 2018 panellists discussed a range of questions about PLND, including what constitutes an 'adequate' LND, the importance of appropriate pathology review of removed nodes, and the appropriateness of ePLND in the absence of OS benefit and given the potential for poorer intraoperative and perioperative outcomes [35].

The panellists noted differing preferences regarding standard or ePLND. Concerns were noted about possible complications following ePLND and their potential to limit opportunities for further treatment such as RT. The panellists concluded that PLND is helpful for staging but should be undertaken by health professionals with appropriate expertise who undertake a sufficient volume of the procedures to minimise the risk of complications. The importance of appropriate pathology expertise and processes was also noted.

Use of adjuvant vs salvage RT after RP

No consensus was reached at the APCCC 2017 on the use of adjuvant RT for the treatment of high-risk localised prostate cancer (pN0 or pN1). It was noted that no trial has compared 'pure' adjuvant RT at undetectable PSA levels with salvage RT at 'appropriately' low PSA levels. There was also no consensus on the most appropriate radiation field, with responses split between the prostatic bed and the prostatic bed plus whole pelvis.

Whilst EAU and AUA guidelines recommend the use of RP plus RT and ADT for high-risk prostate cancer [33,36], RT use is reported to be in decline [37]. The APAC APCCC 2018 panellists reflected on data showing the benefits of RT in men with node-positive prostate cancer [38], noting that RT has been mandatory in STAMPEDE for men with N1M0 disease since 2011.

A range of factors were identified that would influence the decision to use adjuvant or salvage RT after RP, including likelihood of cure as well as the potential to exacerbate complications of surgery. Regardless, the importance of the patient seeing a radiation oncologist to discuss the option of adjuvant RT was noted.

In relation to the optimal radiation field, radiation oncology panellists reflected on the lack of definitive evidence to guide field selection but noted that the evidence base is evolving as improved imaging technologies, such as ^{68}Ga-PSMA-PET, become available [39].

As with the APCCC 2017, no clear agreement was reached on whether ADT should be added to adjuvant RT in high-risk pN0 disease, noting the absence of high-level evidence to inform practice in this area.

Management of 'oligometastatic' prostate cancer

The APCCC 2017 highlighted the lack of an agreed definition of oligometastatic disease and different treatment preferences for synchronous or metachronous oligometastatic disease. The considerable variation in practice reflected the choice of imaging technique used to define oligometastatic disease.

The APAC APCCC 2018 panellists also reflected on the variation in definitions [40,41] and the lack of a definitive threshold for what constitutes oligometastatic prostate cancer. Some APAC APCCC 2018 panellists expressed different views to the APCCC 2017 findings about the management of oligometastatic disease. Variation was noted in the approach to treatment of newly diagnosed patients with an untreated primary, including whether to add docetaxel to local treatment plus ADT, and the choice of local treatment. Some differences in preference for treatment of oligometastatic recurrent CNPC after local treatment were also noted.

The role of prostate-directed and metastasis-directed therapy was also discussed. Retrospective trial data exist and prospective data are emerging.

Factors identified as influencing the approach to management of oligometastatic disease in the APAC region included the following:

- limited availability in many APAC countries of imaging technologies, such as ^{68}Ga-PSMA-PET, required to detect oligometastatic disease (Table 3).
- the challenge of recommending metastasis-directed treatments that carry additional cost (such as surgery or stereotactic body RT) in the context of metastatic disease in the absence of evidence of a survival benefit.
- whether treatment is being undertaken with long-term control/curative intent.

It was noted that this is an area in which registry data and collaboration in the APAC region are likely to be helpful.

Global access to prostate cancer drugs and treatment in countries with limited resources

Voting at the APCCC 2017 occurred on the basis of no restrictions in access and no issues with cost.

At the APAC APCCC 2018, access and cost were strong themes for each of the topics discussed and were often cited as having the greatest influence on prescribing decisions. The high cost of newer drugs such as abiraterone and enzalutamide was noted, with an estimated cost of $2.8 billion (American dollars) expenditure in the USA alone if abiraterone plus prednisone is used in CNPC [42]. Availability of generic treatments and country-level price negotiations result in a variable picture across the APAC region, meaning a region-wide statement on access cannot be made. However, there was strong agreement with the APCCC 2017 that 'it is a suboptimal clinical achievement to show that new treatments can improve the duration and quality of survival of men with advanced prostate cancer but to have such treatments unavailable to a large segment of the global population of men with advanced prostate cancer' [1].

Lower-cost options in countries with limited resources

The APCCC 2017 panellists voted on appropriate alternative options for treatment of advanced prostate cancer in countries with limited resources. There was consensus for the use in the setting of limited healthcare resources of:

- orchidectomy as ADT in the metastatic setting (90%) (noting sociocultural and psychological barriers that may need to be considered).
- use of platinum-based chemotherapy in men with mCRPC progressing on or after docetaxel (77%).

The APAC APCCC 2018 panellists noted that addressing the issue of limited resources is not as simple as choosing a lower-cost option. For example, the choice of orchidectomy over a LHRH agonist or antagonist requires consideration of patient preference and follow-up requirements, as well as cost. Many panellists indicated that patients in the APAC region would be more likely to choose medical ADT over surgery and emphasised the need to provide men with clear information about options that includes potential benefits, side-effects, and cost.

Dose reduction as a means of reducing cost and the likely requirement for supportive therapies was noted [30,31]. Resource-stratified guidelines were identified as a means of providing recommendations for treatment based on differing levels of healthcare resources [43,44].

What can be done to address resource limitations?

The APAC APCCC 2018 panellists recognised the requirement for universal health coverage as highly relevant in the APAC region. Opportunities for consideration include the WHO Sustainable Development Goals (*Goal 3: Ensure*

healthy lives and promote well-being for all at all ages) [45], as well as the Union for International Cancer Control (UICC) City Cancer Challenge [46]. The panellists noted that collaboration between academia, government, industry (pharmaceutical), non-government organisations, and other sectors will be key to the achievement of universal health coverage for cancer.

Given the inequalities in the standard and availability of cancer treatments in the APAC region, a 'one-size fits all' approach to guidelines and recommendations will not work. Resource-stratified recommendations and frameworks are therefore urgently needed to reflect the diversity of health systems in APAC countries at different stages of development. There was strong support from the panellists for a review and update of the *Management of prostate cancer in Asia: resource stratified guidelines from the Asian Oncology Summit 2013* [43].

The likely value of further development of local registries such as the Prostate Cancer Outcomes Registry – Australia and New Zealand [47] and contributions to the Asian Prostate Cancer Study Group (A-CaP) registry [48] in identifying differences in access and variation in practice was also noted.

Discussion

The APAC APCCC 2018 was convened to review how statements of consensus and non-consensus from the APCCC 2017 apply in everyday practice in the APAC region. The aim was to provide real-world insight into the application of the statements, focusing on the five issues most relevant to the APAC region. The meeting generated significant interest, with all invitees attending and contributing to discussions. This included one panellist participating via videoconference because of last minute travel issues.

The APAC APCCC 2018 differed in format to the APCCC 2017. The panel included more urologists, reflecting how treatment for men with prostate cancer is frequently managed in the APAC region. Whilst there is likely to be some variation in views based on which disciplines are consulted, it is worth noting, that in several APAC countries, urologists have responsibility for prescribing and managing systemic therapy including i.v. chemotherapy. RT is usually administered by radiation oncologists, although in some countries (e.g. Malaysia), both chemotherapy and RT are administered by clinical oncologists.

No formal voting mechanism was used at the APAC APCCC 2018. Discussion focused instead on practical considerations relating to the areas of consensus and non-consensus from the APCCC 2017. The views of the APAC APCCC 2018 panellists highlighted several caveats related to implementation of the APCCC 2017 statements, as well as some differences in opinion. As was the case with the APCCC 2017, differences in opinion do not reflect a failure of the process but highlight areas of controversy and evolving evidence where further research may be beneficial.

Real-world Implications of the APCCC 2017 statements in the APAC region

There was clear value in the process of discussion and in consideration of the real-world application of the APCCC 2017 consensus statements. A number of consistent themes emerged from the APAC APCCC 2018 discussions (Box 1).

Access, cost of treatments, and toxicity concerns influence prescribing decisions in the management of advanced prostate cancer and have a significant influence on the sequencing and timing of treatment. Specific examples include the following:

- a lack of established safety data for docetaxel in Asian men and concerns about febrile neutropaenia influencing prescribing, particularly in men with poorer performance status.
- increased use of G-CSF in men receiving docetaxel, with the associated cost having a significant impact in terms of health economics and prescribing even in the presence of generic docetaxel.
- whilst abiraterone may be more acceptable for Asian men than docetaxel due to lower toxicity, the cost is prohibitive in some countries and concerns exist about the toxicity of concomitant steroids.

Variation in the availability of imaging technologies may limit the ability of clinicians in some APAC countries to prescribe according to precise definitions. Within the APAC region, the question of whether more sensitive imaging results in changes

Box 1 Management of advanced prostate cancer in the APAC region: real-world challenges in implementing the St Gallen APCCC recommendations.

1 **Differences in toxicity**: safety data for docetaxel are not fully established in Asian men and concerns about the toxicity profile and risk of neutropaenia may influence prescribing.
2 **Disparities in access to imaging technology**: variable access to imaging technology may limit prescribing according to precise definitions.
3 **Disparities in access and cost of treatment**: availability and cost of treatments are the most significant factor influencing prescribing decisions in the region; lower-cost alternatives are not always culturally acceptable, and informed choice is important.
4 **Variability in MDT approaches**: the importance of multidisciplinary input to treatment recommendations is understood but MDTs are a challenge in some APAC countries; virtual MDT participation should be encouraged.
5 **Variability in demographics**: genetics and epidemiology in Asian men with prostate cancer may result in different treatment responses; collaborative registry studies and trials in APAC populations are likely to be valuable.

to treatment and ultimately improved outcomes is of particular interest. In the meantime, alternative imaging technologies such as whole-body MRI may need to be considered.

As is the case in all countries, a multidisciplinary approach and provision of best-practice care by clinicians with appropriate expertise are the cornerstones of treatment for high-risk localised prostate cancer. While MDTs can be a challenge to set up in some APAC regions, the view of the APAC APCCC 2018 panellists is that options to support MDT consultation, including virtual participation, should be encouraged. While it was noted that cultural factors may affect individual patient preferences to participate in shared decision-making, the importance of informed patient choice was also a strong theme.

To address issues of cost, a collaborative approach to driving universal health coverage in the APAC region is likely to reap benefits and create greater parity across the region. However, access and cost are not the only considerations, with the discussions also pointing to the need to consider long-term therapeutic benefit before widely adopting new technologies and treatments in countries with limited resources.

In the era of evidence-based medicine, the importance and value of prospective clinical research to address areas of limited or conflicting evidence are significant. The APAC APCCC 2018 highlights the opportunity for studies in APAC populations where genetics/epidemiology may result in different responses. The value of registries as a mechanism to collect real-world data was noted, with strong support for collaborative input into the A-CaP registry.

The APAC APCCC 2018 was the first region-wide meeting to discuss the management of advanced prostate cancer. The panellists noted a commitment to ongoing discussion and collaboration across the region to ensure that as evidence of benefit emerges for new treatments and technologies in improving outcomes in advanced prostate cancer, the benefits can be realised for all men.

Acknowledgements

The authors gratefully acknowledge the support from Silke Gillessen and Aurelius Omlin for the concept of the APAC APCCC 2018 meeting. Our sincere thanks go to the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group for hosting and coordinating the meeting, with particular thanks to Margaret McJannett and Michelle Bowers for their input. We also thank Alison Evans for her assistance in manuscript preparation. Ian D. Davis is supported by a National Health and Medical Research Council (NHMRC) Practitioner Fellowship (APP1102604). We also acknowledge sponsorship from Astellas (platinum sponsor), AstraZeneca, Ipsen, Janssen and Tolmar. Sponsors did not contribute to the APAC APCCC 2018 discussions and were not involved in the development or review of this manuscript.

Conflict of Interest Statement

Dr Ong reports grants and honoraria from Johnson & Johnson, and honoraria from Astellas, Sanofi and Novartis outside the submitted work Associate Professor Williams reports being a member of industry advisory boards for Astellas, Bayer and Janssen outside the submitted work, with all remuneration for this work being retained by his employer. Dr Nicholas Ruchan is on the Board of ANZUP Cancer Trials Group, Associate Professor Chiong reports support for manuscript preparation from the ANZUP Cancer Trials Group during the conduct of the submitted work, and honoraria from Astellas, Johnson & Johnson, Amgen, Bayer, Astra Zenica, Sanofi, Menarini and Transmedic International outside the submitted work.

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Abbreviations: (e)PLND, (extended) pelvic lymph node dissection; (m)CNPC, (metastatic) castration-naïve prostate cancer; (m)CRPC, (metastatic) castration-resistant prostate cancer; A-CaP, Asian Prostate Cancer Study Group; ADT, androgen-deprivation therapy; ANZUP, Australian and New Zealand Urogenital and Prostate (Cancer Trials Group); APAC, Asia Pacific; APCCC, Advanced Prostate Cancer Consensus Conference; ASIR, age-standardised incidence rate; CHAARTED, chemohormonal therapy versus androgen ablation randomised trial for extensive disease in prostate cancer; EAU, European Association of Urology; G-CSF, granulocyte colony-stimulating factor; MDT, multidisciplinary team; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiation therapy; SDI, sociodemographic index; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy.