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Guidelines

Prostate Cancer Working Group 4 Recap

Aravind S. Ravi Kumar^{a,b,*}, Aaron R. Hansen^{b,c}

^a Integrated Theranostics Centre, Department of Radiology, Princess Alexandra Hospital, Brisbane, Australia; ^b School of Medicine, University of Queensland, Queensland, Australia; ^c Integrated Theranostics Centre, Division of Cancer Services, Princess Alexandra Hospital, Brisbane, Australia

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Abstract

The Prostate Cancer Clinical Trials Working Group (PCWG) recommendations have guided the design and interpretation of prostate cancer trials for more than two decades. Rapid advances in molecular diagnostics, imaging, and systemic therapies have substantially altered the clinical landscape, prompting the recent update to the framework. PCWG4 introduces a shift towards patient-centred terminology and end points, incorporating molecular and imaging biomarkers for trial eligibility and response assessment. The updated guidance also provides recommendations for integrating Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography into clinical trial frameworks and proposes revised definitions of radiographic progression. PCWG4 emphasises the use of patient-reported outcome measures and introduces the concept of “no longer clinically benefitting” to guide treatment continuation beyond conventional progression end points. This recap summarises key updates in PCWG4 and highlights their implications for contemporary prostate cancer clinical trial design and interpretation.

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1. Introduction

Three prior versions of Prostate Cancer Working Group (PCWG) criteria have been validated and used worldwide for decades to inform the design and interpretation of clinical trials in prostate cancer [1–3]. Rapid advances in imaging, molecular diagnostics, and systemic therapies have transformed the prostate cancer landscape, requiring updated PCWG4 guidelines to assist in the conduct of future clinical trials [4].

PCWG4 introduces new terminology, places an increased emphasis on patient experience and scientific advances in precision medicine, and recognises different disease pheno-

types and their evolution during the disease course. These major changes are summarised in this guideline recap, including the incorporation of Prostate-Specific Membrane Antigen Positron Emission Tomography/Computed Tomography (PSMA PET/CT) molecular imaging within the framework.

2. A patient-centric approach

The use of familiar but potentially pejorative terminology based on the term ‘castration’ is no longer recommended. New terminology is more patient-centred and emphasises

* Corresponding author. Integrated Theranostics Centre, Department of Radiology, Princess Alexandra Hospital, Brisbane, Australia.
E-mail address: aravind.ravikumar@health.qld.gov.au (A.S. Ravi Kumar).

treatment exposure, for example, 'Castration Sensitive Prostate Cancer' is replaced by either androgen pathway modulation naïve or sensitive prostate cancer (termed APMN and APMS, respectively). Similarly, castration-resistant prostate cancer has been revised to androgen pathway modulation resistant.

Trial protocol eligibility recommends the use of clearly defined criteria for the form of disease progression, and takes into consideration nuanced patient-related, disease-state, and disease-related biomarkers.

Biological inter- and intra-patient heterogeneity and disease evolution are now recognised. Accurate determination of disease using established prognostic markers, molecular characterisation, and imaging-based biomarkers is recommended for trial eligibility and baseline measures and upon disease progression. Serial biospecimen collection is encouraged. These recommendations reflect the increasing role of precision medicine in prostate cancer and encourage integration of genomic, imaging, and circulating biomarkers into trial eligibility and end point assessment.

Early-phase and dose-finding studies should include dose-optimisation strategies based on biomarkers, mechanism of action, and pharmacokinetics rather than a maximum tolerated dose approach based on acute clinically observed toxicities.

Increased emphasis is placed on patient-centred end points, including patient experience and symptom improvement, and on the use of relevant and tailored patient-related outcome measures. Patient-centred end points may include time to quality-of-life deterioration and freedom from subsequent therapy.

The frequency of on-treatment assessments should be tailored to disease state and mechanism of action of the intervention. Novel blood- or tissue-based biomarkers should be included in addition to imaging.

Treatment may be continued beyond radiographic progression if a patient is deriving ongoing clinical benefit. The no longer clinically benefitting criteria allow treatment beyond other definitions of progression until the no longer clinically benefitting clinical deterioration end point is met. As additional local treatment of progressive lesions is often undertaken, objective progression end points should still be documented, and care should be exercised to ensure overall symptomatic or quality-of-life deterioration does not occur during this period.

3. Imaging response assessment

PCWG4 recommends including baseline PSMA PET/CT, where feasible, in addition to conventional imaging (CT or magnetic resonance imaging and bone scan), and independently recording their results. PSMA PET/CT is considered investigational for assessing treatment response and progression and non-investigational for assessing disease extent at staging or relapse. PCWG4 recognises that PSMA uptake may be heterogeneous and be dynamically modulated by some therapies. Standardised reporting criteria are beyond the remit of PCWG4, and readers are referred elsewhere, for example, the SPARC consensus [5].

PSMA PET/CT quantitative parameters remain investigational, as many are currently without vendor-neutral, broadly applicable standards. Complete response may be documented by PSMA PET, and predefined criteria for progression are proposed. There are no PSMA PET categories for stable disease or partial response.

PSMA PET complete response may be accompanied by progressive disease on other imaging if there is dedifferentiated histology. As PSMA expression may be acutely modulated by some androgen receptor (AR)-targeted therapies, a minimum duration of 8 wk is recommended before re-imaging after commencing a new therapy; earlier imaging results are considered non-actionable.

PCWG4 proposes some different definitions of progression, which require validation in future clinical trials. PSMA PET/CT progression is defined early without the need for a future confirmation scan if a single new non-pulmonary visceral metastasis is demonstrated, or if there are more than five new lesions in bone, lymph nodes, or lung ('rule of 5'). This is designed to mitigate the risks of continuing futile therapy in patients with rapidly progressive disease and thus compromising patient outcomes.

There is a similar new criterion for bone scan progression, whereby a confirmation scan is not required if more than five new bone lesions are demonstrated.

If there are five or fewer lesions in bone, lymph nodes, or lung, the PCWG3 '2+2' rule is applied to both bone scans and PSMA PET/CT scans in the updated PCWG4 guidance. For patients with five or fewer new lesions, at least two new lesions should be confirmed on a subsequent scan. It is also recognised within PCWG4 that metastasis-directed therapy may be used to augment treatment if a limited number of new lesions are detected on PSMA PET/CT. If this situation occurs, it is recommended that the event is recorded, but the progression timeline should remain unchanged if protocol-defined by conventional imaging criteria.

Response assessment definitions with conventional imaging are unchanged for patients with measurable disease, and it is recommended that these are recorded independent of changes in bone scan.

4. Circulating biomarker response assessment

These values often fluctuate and require at least two consecutive confirmatory measurements. Changes in these biomarkers should not be used as an approval end point or to change therapy.

The definition of prostate-specific antigen (PSA) progression has also been changed in the setting of androgen pathway modulation to any increase in PSA level ≥ 0.2 mg/ml from baseline/nadir, confirmed at least 21 d apart. It is explicitly recognised with next-generation AR-targeted agents that radiographic or clinical progression may occur in the absence of PSA progression.

5. Conclusion

PCWG4 provides an updated conceptual framework for prostate cancer clinical trials that integrates contemporary

advances in molecular diagnostics, imaging and patient-centred end points. There are numerous patient-centric recommendations on trial conduct and end point assessment. Logical frameworks are presented for both early discontinuation of ineffective therapy and continuation of therapy post-progression if there is ongoing clinical benefit. New imaging and other biomarkers require validation in prospective clinical trials to further refine this framework. These recommendations aim to improve the consistency and interpretability of future clinical trials while accommodating the rapidly evolving diagnostic and therapeutic landscape.

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