The 2019 CUA- CUOG Guidelines for the Management of Castration-Resistant Prostate Cancer (CRPC)

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Disclosures

- Details available on the CUA website cua.org or at cuaj.ca

Methods

- MEDLINE search of the English language and conference proceedings were used to produce the present document.
- Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.
- Levels of evidence and grades of recommendation employing the International Consultation on Urologic Disease (ICUD)/WHO modified Oxford Centre for Evidence-Based Medicine grading system.
- Based on a modified GRADE methodology, the strength of each recommendation is represented by the words STRONG or WEAK.

Therapeutic options

- Given the rapid pace of clinical trials and publications it was felt to be beyond the scope of a guideline to include any agent was not health Canada approved

- As new agents are approved the guidelines will be updated rapidly

Definition

- **Castration-resistant prostate cancer (CRPC) is defined by disease progression despite castrate levels of testosterone and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.**

Management of CRPC

Androgen deprivation therapy and first-generation androgen receptor antagonists

- **Because the androgen receptor remains active in most patients who have developed castration-resistant disease, it is recommended that ADT be continued for the remainder of a patient's life *(Level 3, Weak Recommendation)*.**
- **In patients who develop CRPC, the addition or change of first-generation androgen receptor antagonists may be considered *(Level 3, Weak Recommendation)*.**

Guideline statements regarding nmCRPC

- **ADT should be maintained in the nmCRPC state.**
- **First-generation androgen receptor antagonists (i.e., bicalutamide, flutamide, etc.) should be discontinued if patients are receiving these agents *(Level 3, Weak Recommendation)*.**

Non-metastatic CRPC (nmCRPC)

- **For men with high-risk nmCRPC, defined as a PSA doubling time (PSADT) of less than 10 months, with an estimated life expectancy of greater than five years should be offered apalutamide or enzalutamide *(Level 1, Strong Recommendation)*.**

Non-metastatic CRPC (nmCRPC)

- **In men with high-risk nmCRPC who are felt to be unsuitable or refuse approved therapies, observation or use of first-generation androgen receptor antagonists may be attempted *(Level 3, Weak Recommendation).***

- **Patients who are untreated for nmCRPC should be followed with regular imaging every 6–12 months depending on PSADT *(Level 3, Weak Recommendation).***

Detection of metastases and imaging in untreated patients

- For patients who progress on ADT without evidence of distant metastases, it is suggested to screen for metastases

- Imaging techniques most commonly used include nuclear bone scans and abdominal/pelvic CT and chest X-ray.

- The role of positron-emission tomography (PET) such as PSMA-PET are still unclear and the benefits unknown.

Frequency of imaging

- Patients with a rapid PSADT (<10 months) or elevated PSA levels (>20)
  - Imaging in these patients should be performed every 3–6 months.

- Patients with a slower PSADT (>10 months) should be screened every 6–12 months *(Expert opinion)*.

Treatment of metastatic CRPC (mCPRC)

- **Since mCRPC is generally associated with a high risk of morbidity and cancer-related mortality, patients with mCRPC detected on conventional imaging should be considered for systemic therapy with demonstrated survival benefits.**
- **Patients with mCRPC should optimally receive multidisciplinary care to maximize survival and quality of life.**
- **Because any treatment for advanced disease remains non-curative, patients with advanced prostate cancer should be encouraged to participate in clinical trials.**

Chemo-Naïve or First Line therapy for mCRPC

- **Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily is recommended for first-line therapy for asymptomatic or minimally symptomatic metastatic CRPC *(Level 1, Strong Recommendation).***

- **Enzalutamide 160 mg per day is recommended as first-line therapy for asymptomatic or minimally symptomatic mCRPC *(Level 1, Strong Recommendation)*.**

First line or Chemo-naive mCRPC:

- **Docetaxel 75 mg/m^2 every three weeks plus 5 mg oral prednisone twice daily can be offered *(Level 1, Strong Recommendation)*.**
  - The timing of therapy in men without symptoms should be discussed with the patient and therapy should be individualized based on the patient's clinical status and preference.

- This is the first line therapy for recommended mCRPC if the patient progressed on an ARAT for nmCRPC or mHSPC

mCRPC with moderate or severe symptoms

- **Docetaxel 75 mg/m^2 every three weeks plus 5 mg oral prednisone twice daily is recommended *(Level 1, Strong Recommendation).***
- ***If unable to receive docetaxel:* Radium-223 every four weeks for six cycles *(Level 1, Strong Recommendation)***
- **Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily or enzalutamide 160mg/day may be considered as first-line therapy in patients who cannot receive or refuse docetaxel *(Expert opinion).***

Metastatic CRPC who progress after docetaxel-based chemotherapy

- **Cabazitaxel (25 mg/m^2) plus prednisone (5 mg/day) *(Level 1, Strong Recommendation)***
- **Radium-223 every four weeks for six cycles *(Level 1, Strong Recommendation)***

- **If not received prior to docetaxel:**
- **Abiraterone acetate (1000 mg per day) plus prednisone (5 mg twice daily) *(Level 1, G Strong Recommendation)***
- **Enzalutamide (160 mg/day) *(Level 1, Strong Recommendation)***

Metastatic CRPC who progress after docetaxel-based chemotherapy

- ***Options with unknown survival benefit***
- Docetaxel plus prednisone re-exposure in patients who have had a previous favorable response to docetaxel may be reasonable *(Expert opinion*).
- Mitoxantrone plus prednisone may be offered for palliative pain relief *(Grade C).*

Patients with CRPC and bone metastases

- **Denosumab (120 mg subcutaneous) or zoledronic acid (4 mg intravenous) every four weeks, is recommended to prevent disease-related skeletal complications *(Level 1, Strong Recommendation).***
- **The optimal duration of zoledronic acid and denosumab in men with CRPC and bone metastases is undefined.**
  - **The risk of ONJ appears to be related to time on bone-targeted therapy, therefore, caution should be taken in using these agents beyond two years.**
- **Denosumab and zoledronic acid are not approved and not indicated for SRE prevention in the treatment of metastatic castration-sensitive prostate cancer or for bone metastases prevention.**

Summary of guidelines

CRPC without metastases	mCRPC first-line (if not received in the past)	mCRPC second-line (if not received in the past)	mCRPC third-line (if not received in the past)
High-risk (PSADT <10 m) Apalutamide Enzalutamide	Abiraterone	Docetaxel	Cabazitaxel
Not high-risk (PSADT >10 m) Observation	Enzalutamide	Radium-223 (symptomatic and no visceral metastases)	Radium-223
	Docetaxel (select cases)	Abiraterone or Enzalutamide (if neither received previously)	Clinical trial
	Clinical trial	Cabazitaxel (only post-docetaxel)	
		Clinical trial	

In the presence of bone metastases:
Denosumab or zoledronic acid are recommended to reduce the risk of skeletal complications
Palliative radiation therapy should be considered in patients with pain

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