

Management algorithms for metastatic prostate cancer



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Abstract

Introduction: Prostate cancer poses a significant lifetime risk to Canadian men. Treatment for metastatic prostatic cancer (mPCa) is an area of ongoing research with a lack of up-to-date clinical guidance. The multidisciplinary Canadian Genitourinary Research Consortium (GURC) determined that additional guidance focusing on management of mPCa was warranted.

Methods: The most up-to-date guidelines, consensus statements, and emerging phase 3 trials were identified and used to inform development of algorithms by a multidisciplinary genitourinary oncology panel outlining recommendations for the management of mPCa.

Results: A single pan-Canadian guideline and five national and international guidelines or consensus statements published since 2015 were identified, along with two new phase 3 trials and one additional randomized comparison. Iterative GURC discussions led to the development of two mPCa algorithms: the first addressing management of newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) patients and the second addressing treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). For newly diagnosed mCSPC patients with high-volume/high-risk disease, either docetaxel or abiraterone acetate and prednisone (AAP) added to androgen-deprivation therapy (ADT) is recommended. The addition of radiotherapy to ADT is suggested for those with low-volume disease and/or AAP to ADT for low-volume or low-risk disease. For first-line mCRPC, androgen receptor-axis-targeted (ARAT) therapy is recommended for most patients, while sequencing with docetaxel, radium-223, ARAT therapy, and/or cabazitaxel is recommended for later lines of therapy.

Conclusions: Two treatment algorithms were developed for the management of mPCa and can be used by multidisciplinary specialist teams to guide treatment.

Introduction

Prostate cancer (PCa) poses a significant lifetime risk to Canadian men.¹ In 2017, approximately 21% of all new cancer cases diagnosed among Canadian men were PCa (total of 21 300 cases). Every year in Canada, an average of 1187 (8.6%) patients are diagnosed with metastatic prostate cancer (mPCa).²

Treatment for mPCa is an active area of research, with new treatment data emerging in recent years. Guidelines and consensus statements address much of this evidence.³⁻⁸ However, many lack a practical perspective and do not sufficiently address clinical scenarios, such as treatment sequencing, that are not directly informed by phase 3 data.

The Canadian Genitourinary Research Consortium (GURC) is a national multidisciplinary network of clinical specialists treating advanced PCa who collaborate on research, education, and establishment of best practices. The GURC Best Practices Working Group (GURC BPW Group) identified the need to develop practical guidance on treatment options and decision-making in mPCa and worked to provide physicians with an easy-to-follow practice tool that addressed management of newly diagnosed metastatic castration-sensitive prostate cancer (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC).

Methods

Algorithm development

The GURC BPW Group included five uro-oncologists, two radiation oncologists, and two medical oncologists, and had pan-Canadian representation. The group held iterative discussions regarding the management of patients with mPCa,

followed by discussion with the GURC Steering Committee. Algorithms outlining treatment of mPCa were developed through review of national and international guidelines and consensus statements (see *Literature search* below). Final algorithms were approved by both GURC BPW Group and Steering Committee members.

Literature search

Canadian and major North American and European guidelines and consensus statements addressing management of mPCa were identified. PubMed, Google Scholar, and the internet were searched from January 1, 2015 to November 4, 2018 using the search string “prostate cancer AND (guideline OR consensus OR recommendations)” and guideline databases (Canadian Medical Association’s CPG Infobase: Clinical Practice Guidelines, National Guidelines Clearinghouse, and Guidelines International Network) were searched for guidelines or consensus statements using the keyword “prostate.” Recommendations on management options for newly diagnosed mCSPC or mCRPC were extracted from full-text and synthesized for review.

As existing guidelines were current only to June 2018 (National Comprehensive Cancer Network [NCCN] 2018 v4 data cutoff of May 2018), a supplementary search for new data was also performed. PubMed was searched from June 1, 2018 to November 5, 2018 and American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) 2018 annual meeting abstract databases were searched using the search string “prostate cancer AND metastatic AND phase 3 (OR respective aliases)” for primary reports of original phase 3 trials investigating mPCa treatment and reporting positive or practice-changing outcomes. Search results were screened at the abstract level and confirmed at full-text.

Results

Literature search findings and algorithm development

The literature search identified one pan-Canadian guideline⁶ and five guidelines or consensus statements from major North American and/or European organizations or groups^{3-5,7,8} published since 2015 (Table 1). Canadian provincial guidelines,^{9,10} Euro-Asian single-nation,¹¹⁻¹⁹ Asian consensus,²⁰ and specialty-focused guidelines²¹⁻²⁴ were excluded. Outcomes from two new phase 3 studies^{25,26} and one additional randomized comparison of the phase 3 STAMPEDE trial²⁷ were considered eligible for our review. Although not explicitly stated as such, the HORRAD study was classified as a phase 3 study based on its randomized design, size, and primary overall survival (OS) endpoint,²⁵ and both the HORRAD

Table 1. Guidelines, consensus-based guidance considered in development of the GURC algorithms

Guidelines and consensus statements	Year	Region
NCCN prostate cancer guidelines	2018	American
EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer	2018	European
Advanced Prostate Cancer Consensus Conference (APCCC)	2017	International
CUA-CUOG CRPC guidelines	2015	Canadian
ESMO clinical practice guidelines on prostate cancer	2015	European
AUA CRPC guidelines	2015	American
Phase 3 addressing treatment of metastatic prostate cancer		Year
PRINCE (intermittent vs. continuous docetaxel)		2018
STAMPEDE (addition of radiotherapy to ADT vs. ADT)		2018
HORRAD (addition of radiotherapy to ADT vs. ADT)		2018

AUA: American Urological Association; CUA-CUOG: Canadian Urological Association-Canadian Urologic Oncology Group; CRPC: castration-resistant prostate cancer; EAU-ESTRO-ESUR-SIOG: European Association of Urology-European Society for Radiotherapy & Oncology-European Society of Urogenital Radiology-International Society of Geriatric Oncology; GURC: Genitourinary Research Consortium; NCCN: National Comprehensive Cancer Network.

and the STAMPEDE analyses of radiotherapy vs. standard of care were included in our review, as subgroup findings in low-volume patients were considered practice-changing, even though overall outcomes were negative.^{25,27}

The iterative group review and discussion of this data led to the development of two algorithms addressing the management of mPCa: the first in newly diagnosed mCSPC (Fig. 1A), and the second in mCRPC (Fig. 1B). This work builds on a prior publication in which GURC presents two treatment algorithms to guide the management of non-metastatic PCa for consideration in the context of individualized therapy, existing guidelines, and practice patterns.²⁸

Recommendations for treatment of newly diagnosed mCSPC (Fig. 1A)

For patients with mCSPC, androgen-deprivation therapy (ADT) should be initiated, with concurrent monitoring to ensure castrate levels of testosterone are achieved.^{4,8} Clinical and disease characteristics should then be considered to determine stage and prognosis.²⁹ Discussion of treatment options, including clinical trial enrolment, is best carried out in the context of a multidisciplinary consult or multidisciplinary rounds. Consultation with an oncologist or referral to a specialized tertiary center should be considered when available.

Systemic therapy

Three phase 3 studies involving five randomized comparisons have addressed the benefit of adding further systemic treatment to ADT in mCSPC (Table 2).³⁰⁻³⁶ The

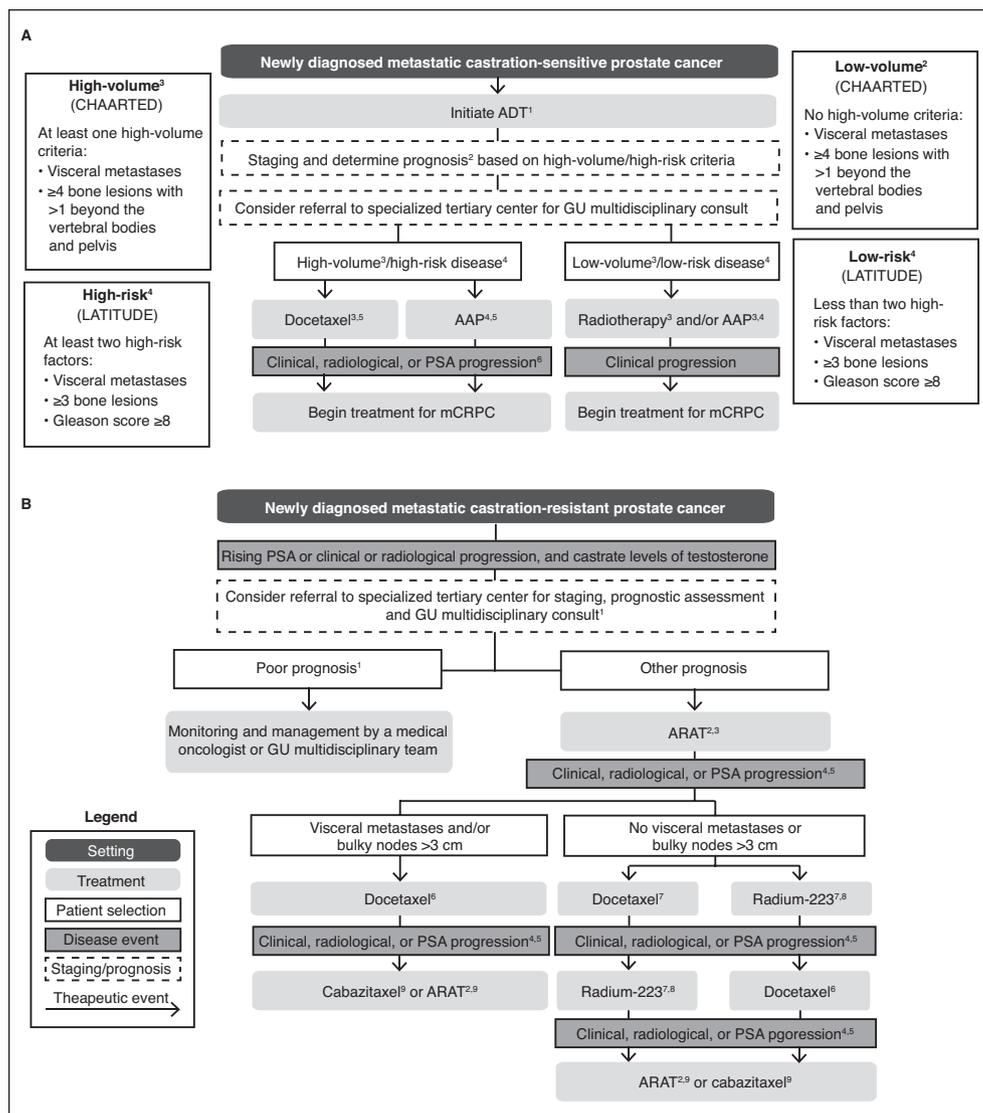


Fig. 1. Management of metastatic prostate cancer. **(A)** Management of newly diagnosed metastatic castration-sensitive prostate cancer. ¹Ensure castrate levels of testosterone. ²Consider determination of alkaline phosphatase levels as prognostic factor (Gravis et al. *Eur Urol* 2015;68:196-204). ³Patients identified according to CHAARTED criteria (see respective box; Sweeny et al. *N Engl J Med* 2015;373:737-46). ⁴Patients identified according to LATITUDE criteria (see respective box; Fizazi et al. *N Engl J Med* 2017;377:352-60). ⁵Patients who are ineligible for either docetaxel or abiraterone for medical reasons or patient preference should be offered alternate agent, if appropriate. ⁶PSA progression as defined by PCWG2 criteria. **(B)** Management of newly diagnosed metastatic castration-resistant prostate cancer. ¹Clinician should consider performance status, symptoms, comorbidities, location and extent of disease, patient preference, and previous treatment for hormone-sensitive mPCa. ²ARAT=abiraterone + prednisone, or enzalutamide. ³Use of docetaxel for first-line mCRPC may become more common, given approval of AAP for metastatic castration-sensitive prostate cancer. ⁴PSA progression as defined by PCWG2 criteria. ⁵Consider palliative care options. ⁶If docetaxel-ineligible for medical reasons or patient preference, consider referral to tertiary care center. ⁷If docetaxel or radium-223 ineligible for medical reasons or patient preference, consider use of alternate agent if appropriate. ⁸Radium-223 is indicated for patients with symptomatic bone metastases. ⁹If cabazitaxel or ARAT therapy ineligible for medical reasons or patient preference, consider use of alternate agent if appropriate. AAP: abiraterone acetate and prednisone; ADT: androgen-deprivation therapy; ARAT: androgen receptor axis targeted therapy; GU: genitourinary; LDH: lactate dehydrogenase; mCRPC: metastatic castration-resistant prostate cancer; mPC: metastatic prostate cancer; PCWG2: Prostate Cancer Working Group 2; PSA: prostate-specific antigen.

cant improvement in median OS with the addition of docetaxel (75 mg/m², q3 weeks x 6) to ADT vs. ADT alone (57.6 vs. 47.2 months; hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.59–0.89; p=0.0018). A pre-planned stratified subgroup analysis confirmed the OS benefit of docetaxel in the 65% of patients with high-volume disease, defined as those with at least one high-volume factor (i.e., visceral metastases, ≥4 bone lesions with >1 beyond the vertebral bodies and pelvis; 51.2 vs. 34.4 months; HR 0.63; 95% CI 0.50–0.79; p<0.001). No OS benefit was observed for docetaxel in the 35% of patients with low-volume disease (63.5 vs. not reached [NR] months; HR 1.04; 95% CI 0.70–1.55; p=0.86), although the analysis may have been underpowered due to small sample size. The addition of docetaxel to ADT was considered both safe and manageable, with neutropenia, febrile neutropenia, and fatigue being the most common adverse events.^{33,34}

The phase 3 LATITUDE study enrolled a total of 1199 patients with high-risk mCSPC, defined as a positive bone scan or metastatic lesions on computed tomography (CT) or magnetic resonance imaging (MRI) and at least two high-risk factors based on visceral metastases, three or more bone lesions, and Gleason score 8–10 (Table 2).³⁰ A significant improvement in median OS was seen for ADT plus abiraterone acetate and prednisone (AAP) compared to ADT plus placebo (not yet reached [NYR] vs. 34.7 months; HR 0.62; 95% CI 0.51–0.76; p<0.001).³⁰ The addition of AAP to ADT was safe and manageable, with hypertension, hypokalemia, and alanine aminotransferase (ALT) increase being the most common adverse events.³⁰

phase 3 CHAARTED study enrolled 790 newly diagnosed mCSPC patients.^{33,34} CHAARTED demonstrated a signifi-

The phase 3 multi-arm, multi-stage STAMPEDE trial enrolled patients with newly diagnosed mCSPC, node-

Table 2. Survival in phase 3 trials for newly diagnosed mCSPC

Study name and author, year	Setting	Comparison stratification	Main outcome(s)
Docetaxel			
CHAARTED Kyriakopoulos et al, 2018 ³⁴	– Newly diagnosed metastatic PCa – ECOG PS 0–2 – Prior ADT allowed if started ≤120 days before randomization	ADT + docetaxel (n=397) vs. ADT (n=393) Stratified by extent of metastases: – High-volume (defined as the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis) vs. low-volume	Median followup: 53.7 months Median OS ITT: 57.6 vs. 47.2 months (HR 0.72; 95% CI 0.59–0.89; p=0.0018) High-volume disease (n=513): 51.2 vs. 34.4 months (HR 0.63; 95% CI 0.50–0.79; p<0.001) Low-volume disease (n=277): 63.5 vs. NR months (HR 1.04; 95% CI 0.70–1.55; p=0.86)
STAMPEDE James et al, 2016 ³²	– Newly diagnosed metastatic or high-risk locally advanced PCa or relapsing with high-risk features after prior RP, RT or both – Prior ADT allowed if started ≤ 12 weeks before randomization	SOC (ADT) + docetaxel (n=592) vs. SOC (ADT; n=1184) – Stratified by metastasis status, nodal status and Gleason score (among others)	Median followup: 43 months Median OS ITT: 81 vs. 71 months (HR 0.78; 95% CI 0.66–0.93; p=0.006) M1 subgroup: 60 vs. 45 months (HR 0.76; 95% CI 0.62–0.92; p=0.005)
AAP			
LATITUDE Fizazi et al, 2017 ³⁰	– High-risk PC ^a – Chemo, RT-naive – No prior surgery for metastatic disease – ≤3 mo. ADT or orchiectomy ± AR antagonists	ADT + AAP (n= 597) vs. ADT + dual placebos (n=602) Stratified by: – Presence or absence of measurable visceral disease – ECOG PS (0 or 1 vs. 2)	Median followup: 30.4 months Median OS ITT: NYR vs. 34.7 months (HR 0.62; 95% CI 0.51–0.76; p<0.001)
STAMPEDE James et al, 2017 ³¹ Hoyle et al, 2018 ³⁶	– Newly diagnosed metastatic or high-risk locally advanced PCa or after prior RP, RT or both and relapsing with high-risk features – Prior ADT allowed if started ≤12 weeks before randomization	SOC (ADT) + AAP (n=960) vs. SOC (ADT; n=957) – Stratified by metastasis status, nodal status and Gleason score (among others)	Median followup: 40 months Median OS ITT: NYR 3-year survival ITT: 83% vs. 76% (HR 0.63; 95% CI 0.52–0.76; p<0.001) M1 subgroup: HR 0.61 (0.49–0.75) High-risk M1: 64.7% vs. 45% (HR 0.54; 95% CI 0.41–0.70; p<0.001) Low-risk M1: 82.4% vs 78% (HR 0.66; 95% CI 0.44–0.98; p=0.041) High-volume M1: HR 0.60; 95% CI 0.46–0.78; p<0.001 Low-volume M1: HR 0.64; 95% CI 0.42–0.97; p=0.034
Docetaxel vs. AAP			
STAMPEDE Sydes et al, 2018 ³⁵	– Newly diagnosed metastatic or high-risk locally advanced PCa or after prior RP, RT or both and relapsing with high-risk features – Prior ADT allowed if started ≤12 weeks before randomization	SOC (ADT) + docetaxel (n=189) vs. SOC (ADT) + AAP (n=377) – Stratified by metastasis status, nodal status and Gleason score (among others)	Median followup: 48 months Median OS: NYR 3-year survival ^b ITT: 83% vs. 78% (HR 1.16; 95% CI 0.82–1.65; p=0.404) M1 subgroup: HR 1.13; 95% CI 0.77–1.66; p=0.528

^aAt least two of the following high-risk factors: visceral metastasis, ≥3 bone lesions, Gleason score ≥8. ^bEstimated from Kaplan-Meier survival plot for ITT. AAP: abiraterone acetate plus prednisone; ADT: androgen-deprivation therapy; AR: androgen receptor; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; ITT: intention to treat population; LHRHA: luteinizing hormone releasing hormone antagonist; M1: metastatic; mCSPC: metastatic castration-sensitive prostate cancer; NR: not reported; NYR: not yet reached; OS: overall survival; PCa: prostate cancer; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS, radiographic progression-free survival; RP: radical prostatectomy; RT: radiation therapy; SOC: standard of care. WHO: World Health Organization.

positive mCSPC, or high-risk locally advanced PCa (Table 2), and has reported results from three randomized comparisons addressing the benefits of adding either docetaxel or AAP to ADT.^{31,32,35} The first comparison (n=2962) demonstrated a significant improvement in median OS for ADT

plus docetaxel vs. ADT alone (81 vs. 71 months; HR 0.78; 95% CI 0.66–0.93; p=0.006),³² and the second (n=1917) a significant improvement OS for ADT plus AAP vs. ADT alone (three-year OS 83% vs. 76%; HR 0.63; 95% CI 0.52–0.76; p<0.001).³¹ Pre-planned subgroup analyses based

Table 2 (cont'd). Survival in phase 3 trials for newly diagnosed mCSPC

Study name and author, year	Setting	Comparison stratification	Main outcome(s)
Radiotherapy			
STAMPEDE Parker, et al, 2018 ²⁷	– Newly diagnosed metastatic PCa with no prior radical treatment – Intended for long-term ADT – Prior ADT allowed if started ≤12 weeks before randomization	SOC (ADT) + RT (n=1032) vs. SOC (ADT; n=1029) – Stratified by nodal involvement, WHO performance status, metastatic burden, planned ADT, and planned docetaxel use (among others)	Median followup: 37 months Median OS ITT: 48 vs. 46 months (HR 0.92; 95% CI 0.80–1.06; p=0.266) 3-year survival Low-volume: 81% vs. 73% (HR 0.68; 95% CI 0.52–0.90; p=0.007)
HORRAD Boevé et al, 2018 ²⁵	– Newly diagnosed, primary bone metastatic PCa – PSA >20 ng/ml	ADT + RT (n=215) vs. ADT (n=216)	Median followup: 47 months Median OS 45 vs. 43 months (HR 0.90; 95% CI 0.70–1.14; p=0.4) Low-volume: HR 0.68; 95% CI 0.42–1.10

^aAt least two of the following high-risk factors: visceral metastasis, ≥3 bone lesions, Gleason score ≥8. ^bEstimated from Kaplan-Meier survival plot for ITT. AAP: abiraterone acetate plus prednisone; ADT: androgen-deprivation therapy; AR: androgen receptor; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; ITT: intention to treat population; LHRHA: luteinizing hormone releasing hormone antagonist; M1: metastatic; mCSPC: metastatic castration-sensitive prostate cancer; NR: not reported; NYR: not yet reached; OS: overall survival; PCa: prostate cancer; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS, radiographic progression-free survival; RP: radical prostatectomy; RT: radiation therapy; SOC: standard of care. WHO: World Health Organization.

on disease extent confirmed the benefit of adding either agent (docetaxel: HR 0.76; 95% CI 0.62–0.92; p=0.005 or AAP: HR 0.61; 95% CI 0.49–0.75) to ADT in metastatic patients.^{31,32} A post-hoc analysis of ADT plus AAP vs. ADT alone assessing outcomes by risk status (per LATITUDE) and disease volume (per CHAARTED) showed a three-year OS benefit in high-risk (HR 0.54; 95% CI 0.41–0.71; p<0.001) and low-risk (HR 0.66; 95% CI 0.44–0.98; p=0.041), as well as high-volume (HR 0.60; 95% CI 0.46–0.78; p<0.001) and low-volume (HR 0.64; 95% CI 0.42–0.97; p=0.034) disease.³⁶ A third more recent pre-planned but opportunistic study compared docetaxel and AAP directly in newly diagnosed, node-positive mCSPC or high-risk locally advanced PCa patients (n=556). Both agents demonstrated comparable survival overall (HR 1.16; 95% CI 0.82–1.65; p=0.404), as well as in patients with metastatic disease (HR 1.13; 95% CI 0.77–1.66; p=0.528).³⁵ Additionally, safety was comparable between treatment arms and both agents were considered safe and manageable. The most common adverse events (grades 3–5) associated with docetaxel were high rates of febrile neutropenia (17%), as well as neutropenia (13%) and endocrine disorders (9%). Endocrine (13%), cardiovascular (9%), musculoskeletal (9%), and hepatic disorders (9%) were the most common adverse events associated with AAP.³⁵

Radiotherapy

A fourth comparison from the STAMPEDE trial assessed the benefit of radiotherapy for newly diagnosed mPCa patients. The trial randomized patients (n=2061) to receive either ADT plus radiotherapy or ADT alone.²⁷ Although a failure-free survival benefit in favor of radiotherapy plus ADT vs. ADT was observed in patients overall (HR 0.76; 95% CI 0.68–0.84; p<0.0001), it did not translate into an improvement in the primary endpoint of OS (median OS 48 vs.

46 months; HR 0.92; 95% CI 0.80–1.06; p=0.266). A pre-specified exploratory subgroup analysis by volume of disease per CHAARTED did, however, show improved OS with the addition of radiotherapy to ADT for patients with low metastatic burden (three-year OS 81% vs. 73%, n=819; HR 0.68; 95% CI 0.52–0.90; p=0.007). No benefit was found for patients with high metastatic burden. Radiotherapy was well-tolerated in the intent-to-treat population.²⁷ These findings are supported by outcomes from the recently published HORRAD randomized trial, which assigned patients with primary bone mPCa (n=432) to receive ADT plus radiotherapy or ADT alone. The study showed a non-significant improvement in the primary endpoint of OS with the addition of radiotherapy to ADT (median 45 vs. 43 months; HR 0.90; 95% CI 0.70–1.14; p=0.4), with a trend similar to that of STAMPEDE showing improved (albeit non-significant) survival among patients with low-volume disease (<5 metastases; HR 0.68; 95% CI 0.42–1.10).²⁵

Level 1 evidence supports the addition of docetaxel or AAP to ADT for high-volume/risk mCSPC.^{30,31,33,34,36} The addition of docetaxel to ADT has been used in high-volume, fit patients in Canada^{37–39} since the release of CHAARTED data in 2015,³³ and the addition of AAP to ADT recently received Health Canada approval (February 2018) for use in high-risk mCSPC.⁴⁰ NCCN and European Association of Urology (EAU) guidelines recommend both docetaxel and AAP as options for high-volume or high-risk groups^{4,8} and, given the high degree of concordance between the definitions of high-volume and high-risk disease, as indicated in the CHAARTED and LATITUDE studies (86%),⁴¹ **GURC recommends the addition of either agent to ADT for newly diagnosed mCSPC patients with high-volume/risk disease** (Fig. 1A).

Recommendations for low-volume/risk disease vary across guidelines.^{3,4,8} Based on results of STAMPEDE demonstrating

improved OS for the addition of radiotherapy or AAP to ADT in newly diagnosed mCSPC with a low-volume disease^{27,36} and AAP to ADT in low-risk disease,³⁶ **GURC suggests the addition of radiotherapy to ADT as a treatment option in mCSPC with low-volume disease and/or AAP to ADT in low-volume or low-risk disease** (Fig. 1A). **However, AAP is not yet approved for use in the treatment of low-volume disease in Canada.** Upon clinical, radiological, or prostate-specific antigen (PSA) progression, as defined by Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria,⁴² treatment for mCRPC should be considered.^{4,8}

Recommendations for treatment of newly diagnosed mCRPC (Fig. 1B)

CRPC is diagnosed when a patient has rising PSA or clinical or radiological progression, despite castrate levels of testosterone.^{4-6,8,43} At this stage, management is best explored in the context of a genitourinary multidisciplinary consult. **GURC recommends consultation with either a uro-oncologist and/or medical oncologist for staging and prognostic assessment.**

Prognostic stratification

The Advanced Prostate Cancer Consensus Conference (APCCC) guidelines stratify patients with mCRPC based on features indicative of clinical outcome. Poor prognosis features include small cell histology on a tumor biopsy and/or low or absent androgen receptor expression, exclusive visceral metastases, rapid clinical progression without correlation with PSA kinetics, low PSA levels relative to tumor burden, predominantly lytic bone metastases, short response to ADT (≤ 12 months), and bulky tumor masses.³ GURC suggests consideration of a similar set of poor prognostic factors, including elevated lactate dehydrogenase (LDH), widespread and/or visceral metastasis, poor performance status (Eastern Cooperative Oncology Group performance score [ECOG PS] ≥ 2), low hemoglobin, short response (< 12 months) to initial ADT, clinical symptoms, elevated alkaline phosphatase, and small cell pathology.⁴⁴⁻⁴⁷

First-line treatment of mCRPC

First-line mCRPC therapy largely depends on patient prognosis. For patients with a poor prognosis, disease progression can be rapid. Therefore, **GURC recommends referral to a medical oncologist or multidisciplinary genitourinary team for monitoring and management.** In this setting, treatment should include consideration of docetaxel, enrolment in a clinical trial, or other therapeutic strategies. Current guidelines recommend that treatment selection be made with consideration of performance status, symptoms, comorbidities, location and extent of disease, patient preference, and previous treatment for hormone-sensitive mPCa.^{4,8} First-line treatments for non-poor prognosis patients include androgen receptor-axis-targeted (ARAT) treatment, chemotherapy,

radio-isotope therapy, and immunotherapy (Table 3). Two phase 3 trials have demonstrated improved median OS for sipuleucel-T vs. placebo in asymptomatic or minimally symptomatic mCRPC (25.8 vs. 21.7 months; HR 0.78; 95% CI 0.61–0.98; $p=0.03$ ⁴⁸ and 25.9 vs. 21.4 months; HR 1.70; 95% CI 1.13–2.56; $p=0.01$,⁴⁹ respectively). **Sipuleucel-T is not approved or available in Canada and, therefore, will not be discussed further in this article.**

Two phase 3 trials have assessed ARAT therapy in asymptomatic or mildly symptomatic CRPC with no prior docetaxel. PREVAIL showed a significant improvement in median OS for enzalutamide ($n=872$) vs. placebo ($n=845$; 32.4 vs. 30.2 months; HR 0.71; 95% CI 0.60–0.84; $p<0.001$)⁵⁰ while the COU-AA-302 demonstrated significantly improved median OS for AAP ($n=546$) vs. placebo plus prednisone ($n=542$; 34.7 vs. 30.3 months; HR 0.81; 95% CI 0.70–0.93; $p=0.0033$ with pre-specified efficacy boundary, $\alpha=0.0035$).⁵¹

Two phase 3 trials showed improved survival for docetaxel among chemotherapy-naïve, mCRPC patients. SWOG 99-16 demonstrated improved median OS for docetaxel plus estramustine ($n=338$) vs. mitoxantrone plus prednisone ($n=336$; 17.5 vs. 15.6 months; HR 0.80; 95% CI 0.67–0.97; $p=0.02$)⁵² and TAX 327 demonstrated improved OS with docetaxel (every three weeks) plus prednisone ($n=335$) vs. mitoxantrone plus prednisone ($n=337$; 18.9 vs. 16.5 months; HR 0.76; 95% CI 0.62–0.94; $p=0.009$)⁵³ — a benefit that remained consistent with extended followup.⁵⁴ The phase 3 PRINCE trial demonstrated the non-inferiority of an intermittent schedule of docetaxel based on the primary endpoint of one-year survival (two-sided 95% CI -12–18; $p=0.022$).²⁶

The phase 3 ALSYMPCA trial demonstrated improved median OS for radium-223 ($n=614$) vs. placebo ($n=307$) in patients with symptomatic bone metastases and free of visceral metastases (14.9 vs. 11.3 months; HR 0.70; 95% CI 0.58–0.83; $p<0.001$),⁵⁵ as well as in patients with no prior docetaxel ($n=349$; 16.1 vs. 11.5 months, HR 0.69, 95% CI 0.52–0.92, $p=0.01$).⁵⁶

There is level 1 evidence to support use of ARAT therapy, docetaxel, or radium-223 for symptomatic mCRPC and ARAT or docetaxel for asymptomatic mCRPC,^{26,50-56} as well as associated recommendations from the NCCN and EAU guidelines.^{4,8} **GURC recommends ARAT therapy for first-line mCRPC, keeping in mind that treatment strategy may vary depending on prior therapy received for mCSPC.** A recent survey showed that 94% of responding clinicians treating PCa in Canada ($n=49$) selected ARAT therapy as first-line mCRPC therapy.⁵⁷ AAP is now approved for use in mCSPC and as such, the use of AAP in earlier settings may lead to an increase in the use of docetaxel for first-line mCRPC. Upon clinical, radiological, or PSA progression, as defined by PCWG2 criteria reflective of common clinical practice, consideration of further therapy is recommended.

Table 3. Survival outcomes in phase 3 trials for first-line treatment of mCRPC*

Study name and author, year	Setting	Comparison	Main outcome
Sipuleucel-T Kantoff et al, 2010 ⁴⁸	Some with previous docetaxel; ECOG PS 0–1; asymptomatic or mildly symptomatic	Sipuleucel-T (n=341) vs. placebo (n=171)	Followup: 34.1 months OS: 25.8 vs. 21.7 months (HR 0.78; 95% CI 0.61–0.98; p=0.03)
Small et al, 2006 ⁴⁹	No corticosteroids; ECOG PS 0–1; no bone or cancer pain; no visceral metastases	Sipuleucel-T (n=82) vs. placebo (n=45)	Followup: 36 months OS: 25.9 vs. 21.4 months (log-rank HR 1.70; 95% CI 1.13–2.56; p=0.01)
Docetaxel SWOG 99-16 Petrylak et al, 2004 ⁵²	Chemo-naive; SWOG PS 0–3; asymptomatic or symptomatic	docetaxel/EMP every 3 weeks + EMP 3 times/day (n= 338) vs. mitoxantrone every 3 weeks + prednisone BID (n=336)	Followup: 32 months OS: 17.52 vs. 15.6 months (HR 0.80; 95% CI 0.67–0.97; p=0.02)
TAX 327 Tannock et al, 2004 ⁵³	Chemo-naive; 13% with Karnofsky PS >70%; asymptomatic or symptomatic	Docetaxel every 3 weeks + prednisone BID (n=335) vs. mitoxantrone every 3 weeks + prednisone BID (n=337)	Followup: 20.8 months OS: 18.9 vs. 16.5 months for weekly (HR 0.76; 95% CI 0.62–0.94; p=0.009)
PRINCE Cash et al, 2018 ²⁶	Chemo-naive with primarily bone metastatic disease; Karnofsky PS ≥60%	Intermittent weekly or 3-weekly docetaxel (35 mg/m ² or 75 mg/m ² , respectively) vs. continuous weekly or 3-weekly docetaxel (35 mg/m ² or 75 mg/m ² , respectively)	Followup: 26.8 months vs. 33.8 months (p=0.396) 1-year OS: 78% vs. 75% (non-inferiority criteria met; two-sided 95% CI -12–18; p=0.022)
Abiraterone COU-AA-302 Ryan et al, 2015 ⁵¹	No previous docetaxel; ECOG PS 0–1; PSA or radiographic progression; asymptomatic or mildly symptomatic; no visceral metastases	Abiraterone + prednisone (n=546) vs. placebo + prednisone (n=542)	Followup: 49.2 months OS: 34.7 vs. 30.3 months (HR 0.81; 95% CI 0.70–0.93; p=0.0033)
Enzalutamide PREVAIL Beer et al, 2014 ⁵⁰	No previous docetaxel; ECOG PS 0–1; PSA or radiographic progression; asymptomatic or mildly symptomatic; 10% had visceral metastases	Enzalutamide (n=872; rPFS n=832) vs. placebo (n=845; rPFS n=801)	Followup: 22 months OS: 32.4 vs. 30.2 months (HR 0.71; 95% CI 0.60–0.84; p<0.001)
Radium-223 ALSYMPCA Parker et al, 2013 ⁵⁵ Hoskin et al, 2014 ⁵⁶	Previous or no previous docetaxel; ECOG PS 0-2; two or more symptomatic bone metastases; no visceral metastases	Radium-223 (n=614; docetaxel-naive n=236) vs. placebo (n=307; docetaxel-naive n=113)	OS (ITT): 14.9 vs. 11.3 months (HR 0.70; 95% CI 0.58–0.83; p<0.001) OS (docetaxel-naive): 16.1 vs. 11.5 months (HR 0.69; 95% CI 0.52–0.92; p=0.01)

*Only studies reporting survival outcomes as primary endpoints have been included. BID: twice a day; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; EMP: estramustine; FU: followup; HR, hazard ratio; mCRPC: metastatic castration-resistant prostate cancer; OS: overall survival; PFS: progression-free survival; PS: performance status; PSA: prostate-specific antigen; rPFS: radiographic progression-free survival.

Later lines of mCRPC therapy

Selection of second-line treatment is dependent on many factors, including prior treatment exposure, as well as clinical and disease characteristics. EAU guidelines recommend consideration of performance status, symptoms, patient preference, comorbidities, and extent of disease.⁴ Treatment options for later lines include ARAT therapy, chemotherapy, or radium-223 in patients receiving prior docetaxel (Table 4).

Two phase 3 trials support use of ARAT therapy for mCRPC following docetaxel. COU-AA-301 showed a sig-

nificant improvement in median OS for AAP (n=797) vs. placebo plus prednisone (n= 398; 15.8 vs. 11.2 months; HR 0.74; 95% CI 0.64–0.86; p<0.0001),⁵⁸ while AFFIRM showed a similar significant improvement in median OS for enzalutamide (n=800) vs. placebo (n=399; 18.4 vs. 13.6 months; HR 0.63; 95% CI 0.53–0.75; p<0.001).⁵⁹

Chemotherapy and radium-223 are also second-line treatment options. The phase 3 TROPIC trial showed a significant improvement in median OS for cabazitaxel plus prednisone and (n=378) vs. mitoxantrone plus prednisone

Table 4. Survival outcomes of phase 3 trials for second-line treatment of mCRPC*

Study name and author, year	Setting	Comparison	Main outcome
Abiraterone			
COU-AA-301 Fizazi et al, 2012 ⁵⁸	Previous docetaxel; ECOG PS 0–2; PSA or radiographic progression	Abiraterone + prednisone (n=797) vs. placebo + prednisone (n=398)	Followup: 20.2 months OS: 15.8 vs. 11.2 months (HR 0.74; 95% CI 0.64–0.86; p<0.0001)
COU-AA-301 de Bono et al, 2011 ⁶⁶	Previous docetaxel; ECOG PS 0–2; PSA or radiographic progression	Abiraterone + prednisone (n=797) vs. placebo + prednisone (n=398)	Followup: 12.8 months OS: 14.8 vs. 10.9 months (HR 0.65; 95% CI 0.54–0.77; p<0.001)
Radium-223			
ALSYMPCA Hoskin et al, 2014 ⁵⁶	Previous or no previous docetaxel; ECOG PS 0-2; two or more symptomatic bone metastases; no visceral metastases	Radium-223 (prior docetaxel n=352) vs. placebo (prior docetaxel n=174)	OS (prior docetaxel): 14.4 vs. 11.3 months (HR 0.70; 95% CI 0.56–0.88; p=0.002)
Cabazitaxel			
TROPIC de Bono et al, 2010 ⁶⁰ Bahl et al, 2013 ⁶⁷	Previous docetaxel; ECOG PS 0–2	Cabazitaxel + prednisone (n=378) vs. mitoxantrone + prednisone (n=377)	Followup: 12.8 months OS: 15.1 vs. 12.7 months (HR 0.70; 95% CI 0.59–0.83; p<0.0001)
			Followup: 25.5 months OS: 318/378 vs. 346/377 events (odds ratio 2.11; 95% CI 1.33–3.33) OS≥2 years 27% vs. 16%
Enzalutamide			
AFFIRM Scher et al, 2012 ⁵⁹	Previous docetaxel; ECOG PS 0–2	Enzalutamide (n=800) vs. placebo (n=399)	Followup: 14.4 months OS: 18.4 vs. 13.6 months (HR 0.63; 95% CI 0.53–0.75; p<0.001)

*Only studies reporting survival outcomes as primary endpoints have been included. CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; rPFS: radiologic progression-free survival.

(n=377; 15.1 vs. 12.7 months; HR 0.70; 95% CI 0.59–0.83; p<0.0001) for patients progressing on first-line docetaxel.⁶⁰ More recently, the phase 3 ALSYMPCA trial demonstrated a significant improvement in median OS for radium-223 (n=352) vs. placebo (n=174) in a subgroup receiving prior docetaxel (n=526; 14.4 vs. 11.3 months; HR 0.70; 95% CI 0.56–0.88; p=0.002).⁵⁶

There is level 1 evidence for use of ARAT, cabazitaxel, and radium-223 as second-line therapy following docetaxel,^{56,58-60} and support for use of docetaxel in this setting is derived primarily from first-line phase 3 trials,⁵²⁻⁵⁴ as well as prospective and retrospective cohort studies demonstrating >25% PSA response to docetaxel re-challenge following a good response to initial therapy.⁶¹⁻⁶⁵ However, there is little evidence to guide optimal sequencing following first-line treatment of mCRPC with intensive therapy,^{4-6,8,43} and national and international treatment recommendations for later lines of therapy vary.^{5,6,8,43} **GURC recommendations take into account available evidence, patterns of practice, and access to therapy in providing sequencing options following first-line ARAT therapy (Fig. 1B); an individualized**

approach to treatment sequencing is encouraged, along with special consideration of disease burden, symptomatology, prior therapy, drug eligibility, and patient preference. At each mCRPC treatment juncture, management strategies should include consideration of palliative and supportive care measures, as well as clinical trial eligibility.

For patients with visceral metastases and/or bulky nodes >3 cm following first-line ARAT therapy, GURC recommends docetaxel followed by cabazitaxel or ARAT. Referral to a tertiary care center should be considered for docetaxel-ineligible patients. In cases of ARAT or cabazitaxel ineligibility, the alternate agent should be considered. For patients with no visceral metastases or bulky nodes >3 cm following first-line ARAT therapy, consideration of patient symptoms is important in guiding therapy. For second- and third-line treatment of symptomatic patients, GURC recommends consideration of docetaxel or radium-223 followed by the alternate agent upon progression. For asymptomatic patients, GURC recommends docetaxel while referral to a tertiary care center is warranted for patients ineligible for docetaxel. For patients progressing on either radium-223 or docetaxel,

GURC recommends ARAT or cabazitaxel. In cases of drug ineligibility or lack of access for any line of therapy, the alternate agent should be considered.

Discussion

Strengths and limitations

The treatment algorithms are presented as practical tools to guide the management of mPCa. The therapeutic options suggested for consideration by clinicians are inspired by evidence and reflect the clinical expertise of a multidisciplinary team of Canadian clinical experts specializing in PCa. Although not comprehensive in representation of all available evidence or potential treatments, the algorithms are designed to inspire multidisciplinary discussion that considers individual disease characteristics, patient history, and preferences.

Summary

The GURC recommendations reflect results of multidisciplinary clinical discussion, with the goal of providing clear and practical guidance on the management of mPCa. The treatment algorithms indicate the addition of ARAT or docetaxel to ADT for newly diagnosed high-volume/high-risk mCSPC, the addition of radiotherapy to ADT for low-volume mCSPC, and/or AAP to ADT for low-volume or low-risk mCSPC. ARAT therapy is recommended for first-line treatment of mCRPC, and sequencing of later lines of therapy should be carried out in an individualized manner, accounting for clinical and disease characteristics, and may include docetaxel, radium-223, cabazitaxel, or ARAT therapy.

Summary: GURC...

...recommends the addition of either docetaxel or AAP to ADT for newly diagnosed mCSPC patients with high-volume/risk disease.

...suggests the addition of radiotherapy or AAP to ADT for newly diagnosed mCSPC patients with low-volume disease and/or AAP to ADT for low-volume or low-risk disease.

...recommends ARAT therapy first-line for the majority of mCRPC patients, although patients with poor prognosis should be referred to a medical oncologist or multidisciplinary genitourinary team for monitoring and management.

...recommends an individualized approach to treatment sequencing for later lines of mCRPC therapy, which may include docetaxel, radium-223, ARAT, and cabazitaxel.

Competing interests: Dr. Malone has served on advisory boards and/or received honoraria from Abbvie, Astellas, Bayer, Janssen, Sanofi, and Tersera; and has participated in clinical trials sponsored by Bayer and Janssen. Dr. Shayegan has received grants or honoraria from Abbvie, Astellas, Janssen, and Sanofi; and has participated in clinical trials sponsored by Astellas and Janssen. Dr. Basappa has served on advisory boards and received honoraria and/or grants from Astellas, AstraZeneca, Bayer,

BMS, Eisai, Ipsen, Janssen, Merck, Pfizer, and Roche. Dr. Chi has served on advisory boards and received honoraria and/or grant funding from Astellas, Bayer, Janssen, Roche, and Sanofi. Dr. Conter has received grants and/or honoraria from Astellas, BMS, Eli Lilly, Janssen, and Novartis; and has participated in clinical trials sponsored by AstraZeneca, Merck, Pfizer, Roche, and Takeda. Dr. Hamilton has served on advisory boards and/or received honoraria from Abbvie, Amgen, Astellas, Bayer, Janssen, and Tersera; and has participated in clinical trials sponsored by Bayer and Janssen. Dr. Hotte has received institutional research funding or consulting honoraria from Astellas, Bayer, and Janssen. Dr. Saad has served as a consultant for, and received funding from, Amgen, Astellas, AstraZeneca, Bayer, BMS, Janssen, and Sanofi. Dr. So has received honoraria and served on advisory boards for Abbvie, Amgen, Astellas, Bayer, Ferring, Janssen, and Sanofi; and has participated in clinical trials sponsored by Astellas and Janssen. Ms. Park-Wyllie and Mr. Hew are employed by Janssen Canada. Ms. McLeod owns Kaleidoscope Strategic, who received funding for preparing this review by Janssen Canada. Dr. Gotto has received honoraria and served on advisory boards for Amgen, Astellas, AstraZeneca, Bayer, Janssen, Merck, Roche, and Sanofi; and has participated in clinical trials sponsored by Amgen, Astellas, AstraZeneca, Bayer, Janssen, and Myovant.

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