Guideline Resource Unit
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Advanced/Metastatic Prostate Cancer

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Cancer Care Alberta

Clinical Practice Guideline GU-010 – Version 6
www.ahs.ca/guru

Background

Prostate cancer is the most common cancer among Canadian men, and is the 3rd leading cause of cancer related death in men in Canada. In 2022, it is estimated that 24,600 men will be diagnosed with prostate cancer in Canada and 4600 men will die from their disease.[1]

Many patients with advanced prostate cancers are diagnosed after localized treatment, with disseminated disease being identified by rising PSA post-definitive treatment. However, some men present with de novo metastatic disease.

Guideline Questions

1. How should advanced/ metastatic prostate cancer be staged?
2. How should advanced/ metastatic prostate cancer be treated?
3. How should advanced/ metastatic prostate cancer patients be followed after treatment?

Search Strategy

For the 2022 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in Appendix A).

For the 2016 guideline, select literature was reviewed by a working group at the Alberta GU Tumour Team meeting. No formal systematic literature review was performed.

For the 2015 update, no formal literature review was conducted.

For the 2014 update of this guideline, the Pubmed database was searched using the search terms Locally Advanced Prostate Cancer and Metastatic Prostate Cancer from 2010 to 2014. Only phase III trials were evaluated for inclusion.

For the 2012 update of this guideline, Ovid Medline was searched using the term Prostatic neoplasms (MeSH term, subheadings drug therapy, surgery, therapy and radiotherapy), limited to clinical trials involving humans published in English, between August 2011 and August 2012. Articles were excluded if they were not phase II-IV trials, did not include survival or recurrence outcomes, was retrospective. Cochrane Database of Systematic Reviews was searched using the term “prostate cancer”, published 2011-2012.

Medline & Embase were further searched using the term prostate cancer (keyword), limited to clinical trials related to “therapy (best balance of sensitivity and specificity) involving male humans published in English between August 2011-2012.

Ovid MEDLINE and EMBASE (1965 to August 2011) and clinical practice guideline databases, including the Cochrane Library and the National Guidelines Clearinghouse, were searched in order to obtain evidence relevant to this topic.

Target Population

Adult patients (18 years of age or older) who have been diagnosed or have suspected advanced/ metastatic prostate cancer.

Recommendations

I. Bone Health

Please see the Bone Health in Patients with Prostate Cancer guideline.

II. Locally Advanced Disease (Stage T1-4, N1, M0)

Patients with nodal involvement (with or without previous local definitive therapy).

Staging
At minimum patients should have CT abdomen and pelvis, bone scan, and optional chest imaging (chest CT or chest x-ray).

Management
These patients are unique and management can vary widely; patients should be discussed at multidisciplinary rounds.

Radiotherapy is an option for low-volume pelvic lymph node only disease in addition to androgen deprivation therapy (ADT). ADT should be administered for 18-36 months.[2]

Biochemical Recurrence[3]
Please see the Local Prostate Cancer guideline.

III. Genomic testing in Metastatic Castration Sensitive Disease and Castration Resistant Disease
Genomic testing for *BRCA1*, *BRCA2*, *ATM*, and other homologous recombination repair (HRR) alterations should be strongly considered for patients with metastatic and/or castration resistant prostate cancer. Any patient who is being treated with an androgen receptor pathway inhibitor (ARPI; i.e. abiraterone, apalutamide, darolutamide, enzalutamide) should be offered testing. Genomic testing results have prognostic, therapeutic and familial screening implications. Discussion at multi-disciplinary rounds is encouraged when genomic alterations are identified. Patients with HRR alterations have a poor prognosis, develop castration resistant disease more rapidly, and can progress rapidly on androgen receptor pathway inhibitors.[4, 5] Hence, patients with HRR alterations should have close follow-up and more frequent labs and restaging.

Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

IV. Metastatic Castration Sensitive Disease (Stage T1-4, N0-1, M+) (mCSPC)

Indications include symptomatic disease or asymptomatic disease.

A biopsy should be obtained in de novo mCSPC and strongly considered in all forms of advanced prostate cancer. The biopsy should be performed as early as possible relative to the start of therapy.

Staging

1. Physical Exam.
2. PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.
3. Bone scan within the last 3 months.
4. CT scan, (abdomen and pelvis, +/- chest) within the last 3 months.
5. Genomic testing for *BRCA1*, *BRCA2*, *ATM*, and other homologous recombination repair (HRR) alterations should be strongly considered for patients with metastatic and/or castration resistant prostate cancer. Any patient who is being treated with an androgen receptor pathway inhibitor (i.e. abiraterone, apalutamide, darolutamide, enzalutamide) should be offered testing. Genomic testing results have prognostic, therapeutic and familial screening implications. Discussion at multi-disciplinary rounds is encouraged when genomic alterations are identified. Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

Management

Androgen deprivation therapy (ADT) to achieve a castration level serum testosterone (<1.7 nmol/L) is the backbone of therapy. Medical and surgical castration are equivalent in terms of efficacy and both are viable options. Lower rates of fracture, peripheral arterial disease, and cardiac-related complications have been reported in surgical castration patients when compared to medical castration patients in a large retrospective cohort study.[7]

Castration level serum testosterone (<1.7 nmol/L) can cause several undesirable side effects. For this reason, intermittent ADT has theoretical advantages. However, in patients with metastatic prostate cancer, continuous ADT is recommended unless survival is considered secondary to quality of life. The phase III intergroup trial reported that intermittent ADT cannot be considered non-inferior compared to continuous ADT in terms of overall survival.[8, 9]

Medical castration:

Treatment with an GnRH agonist: (e.g. leuprolide, goserelin, buserelin)

- Leuprolide is the primary GnRH agonist funded for use in Alberta, available in 3, 4, and 6-month formulations (e.g. 22.5mg, 30mg, and 45mg).
- When a GnRH agonist is first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily) should be given concurrently with (or started prior to) the first injection and continued for a

minimum of 14 days (and up to 1 month) in order to block the potential initial testosterone flare.

- Ongoing total androgen blockade (e.g. treatment with GnRH agonist plus a nonsteroidal antiandrogen) is not recommended for patients in this setting.
- Patients who are intolerant to leuprolide or unable to achieve castration testosterone should have a trial of the GnRH agonist goserelin.

Treatment with an GnRH antagonist

- The GnRH antagonist degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster[7] than GnRH agonists ~~GnRH Agonists~~. Treatment with a GnRH antagonist (degarelix) avoids the risk of testosterone 'flare" that occurs with GnRH agonists.[10, 11] A non steroidal antiandrogen is not required to be given concurrently with the first dose of GnRH antagonist. There may be a lower cardiovascular risk with degarelix, so it can be considered in patients with a history of previous stroke, myocardial infarction, angina, TIA, abdominal aortic disease, previous coronary revascularization, or peripheral arterial disease.
    - Degarelix is no longer funded in Alberta, so patients without coverage from their private insurance would have to pay out of pocket for this medication. There is a Patient Support Program that can assist in coordinating the monthly injections.

Single agent antiandrogens: Monotherapy with non-steroidal antiandrogen is inferior to medical castration with LHRH or GnRH agents. However, it may be considered for rare circumstances. To date there is insufficient data to recommend bicalutamide at 150 mg/day (not Health Canada approved). The preferred non-steroidal antiandrogen is bicalutamide (50 mg orally once a day). Other options are flutamide (250 mg orally three times daily), or nilutamide (300 mg orally once a day for one month, then decrease to 150 mg daily), both of which typically have more side effects than bicalutamide.

Patients ~~undergoing~~ receiving androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.[12]

Systemic therapy: All patients presenting with metastatic castration sensitive prostate cancer who are starting ADT should be considered for intensification of systemic therapy beyond ADT. An ARPI (i.e., apalutamide, enzalutamide, abiraterone acetate) is typically used in this setting, with consideration of docetaxel in certain circumstances in combination with specific ARPI's (see below).

1. Abiraterone Acetate:
    - Patients should be considered per the LATITUDE trial criteria to qualify for this treatment. The LATITUDE inclusion criteria are[13]:
    - Adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology.

- Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI.
- At least 2 of the following high-risk prognostic factors: Gleason score ≥8; presence of 3 or more lesions on bone scan; presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI.

2. Apalutamide (All risks/volumes)[14]

3. Enzalutamide (All risks/volumes). [15, 16]

4. Docetaxel plus abiraterone acetate with prednisone 5 mg twice a day (triplet therapy) may be considered for patients, who are chemotherapy candidates with de novo high volume metastatic disease (defined as the presence of visceral metastases or ≥4 bony lesions with 1 beyond the vertebral bodies and pelvis), as per the PEACE-1 trial.[17]
    - If administering docetaxel, an ARPI (i.e. abiraterone acetate, darolutamide though this option is not funded) should be strongly considered, per the PEACE-1 and the ARASENS trials.[18] Combination docetaxel plus abiraterone acetate demonstrated an improved overall survival benefit in contrast to docetaxel plus placebo in patients with de novo mCSPC. Although not funded, docetaxel plus darolutamide demonstrated an improved overall survival benefit in contrast to docetaxel plus placebo in patients with de novo mCSPC.
    - Patients receiving chemotherapy for this indication should be offered 6 cycles of docetaxel chemotherapy at a starting dose of 75 mg/m^2 every 3 weeks (given with or without prednisone). Androgen deprivation therapy and ARPI, as above, is continued throughout and after docetaxel completion.

There is insufficient evidence to recommend one single agent ARPI strategy or triplet therapy of docetaxel plus ARPI over another. Clinical decision making should be based on patient factors and access.

Radiation therapy: Referral to Radiation Oncology for consideration of radiation therapy to the prostate for patients with de novo low volume metastatic disease (see Management of Oligometastatic Disease below), ~~as~~ per STAMPEDE.[19]

Follow-up Frequency

If on either docetaxel chemotherapy or ARPI (eg: abiraterone acetate, enzalutamide, apalutamide), patients should be evaluated as per standard protocol.

If on ADT alone, patients should be monitored q3–6 months following the initiation of therapy to evaluate and then as clinically indicated.

At a minimum, patients should be restaged annually with a CT and bone scan.

Patients should be treated until development of castration resistant disease, which is defined as either clinical, biochemical, or radiographic disease progression in the presence of castration level (<1.7nmol/L) testosterone levels.

Patients with clinical and/or radiographic progression on ARPI (i.e. abiraterone acetate, apalutamide, darolutamide, enzalutamide) should be referred for consideration of chemotherapy with medical oncology.

Patients with HRR alterations and mCSPC should have close follow-up and more frequent labs (repeated at a minimum frequency of every 3 months) and restaging with CT and bone scan (repeated at a minimum frequency of every 6 months), since patients with HRR alterations have a poor prognosis, develop castration resistant disease more rapidly, and can progress rapidly on ARPI. Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

III. Non-Metastatic Castration Resistant Disease (Stage M0, M+) (nmCRPC)

Castration resistant disease is defined as either clinical, biochemical, or radiographic disease progression in the presence of castration level (<1.7nmol/L) testosterone levels.

Staging

1. Physical Exam.
2. PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.
3. Bone scan within the last 3 months.
4. CT scan, (abdomen and pelvis, +/- chest) within the last 3 months.
5. Genomic testing for *BRCA1*, *BRCA2*, *ATM*, and other homologous recombination repair (HRR) alterations should be strongly considered for patients with metastatic and/or castration resistant prostate cancer. Any patient who is being treated with an androgen receptor pathway inhibitor (i.e. apalutamide, darolutamide, enzalutamide) should be offered testing. Genomic testing results have prognostic, therapeutic and familial screening implications. Discussion at multi-disciplinary rounds is encouraged when genomic alterations are identified. Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

Management of M0 CRPC Disease

Monitoring:

- Baseline ECG recommended. PSA, testosterone, and TSH should be monitored q3-6monthly.

- Systemic therapy may be considered in patients with high-risk disease, where a PSA doubling time is ≤ 10 months and no measurable disease on conventional imaging (bone scan and CT chest, abdomen, and pelvis). A PSA doubling time calculator is recommended for calculation (e.g. MSKCC).

Systemic therapy:

1. Apalutamide:
    - In the SPARTAN phase III clinical trial[20], apalutamide compared to placebo, in men with PSA doubling times ≤10 months, demonstrated an improvement in metastasis-free survival from 16.2 m to 40.5 m (p< 0.001). After a median 52 m follow-up, median OS was 73.9 m in the apalutamide group versus 59.9 m in the placebo group (HR: 0.78; 95%CI: 0.64-0.96; p=0.016).[21]
    - Apalutamide can be considered in patients meeting the doubling time criteria with no bone metastases but with lymph node less than 2 cm in the short axis.

2. Enzalutamide:
    - In the PROSPER phase III clinical trial[22], enzalutamide compared to placebo in men with PSA doubling times ≤10 months, demonstrated an improvement in metastasis-free survival from 14.7 m to 36.6 m (p<0.001). After a median 48 m follow-up, median OS was 67.0 m in the enzalutamide group vs 56.3 m in the placebo group (HR: 0.73; 95%CI: 0.61-0.89; p=0.001).[23]

3. Darolutamide:[14]
    - ARAMIS criteria: ≥18 years of age, baseline PSA ≥2 ng/mL, nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less. After a median 29.0 m follow-up, OS at 3 years was 83% in the darolutamide group versus 77% in the placebo group (HR: 0.69; 95%CI: 0.53-0.88; p=0.003.[24]

Follow-up Frequency

If on an ARPI (eg: abiraterone acetate, enzalutamide, apalutamide), patients should be evaluated as per standard protocol.

If on ADT alone, patients should be monitored q3–6 months following the initiation of therapy to evaluate and then as clinically indicated.

At a minimum, patients should be restaged annually with a CT and bone scan.

Patients should be treated until development of clinical and/or radiographic progression. Patients with clinical and/or radiographic progression on ARPI (i.e. abiraterone acetate, apalutamide, darolutamide, enzalutamide) should be referred for consideration of chemotherapy with medical oncology.

Patients with HRR alterations and nmCRPC should have close follow-up and more frequent labs (repeated at a minimum frequency of every 3 months) and restaging with CT and bone scan (repeated at a minimum frequency of every 6 months), since patients with HRR alterations have a poor prognosis and can progress rapidly on ARPI. Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

Management of M+ Castration Resistant Prostate Cancer (mCRPC)

Staging

1. Physical Exam.
2. PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.
3. Bone scan within the last 3 months.
4. CT scan, (abdomen and pelvis, +/- chest) within the last 3 months.
5. Genomic testing for *BRCA1*, *BRCA2*, *ATM*, and other homologous recombination repair (HRR) alterations should be strongly considered for patients with metastatic and/or castration resistant prostate cancer. Any patient who has been treated with an androgen receptor pathway inhibitor (i.e. abiraterone, apalutamide, darolutamide, enzalutamide) should be offered testing. Genomic testing results have prognostic, therapeutic and familial screening implications. Discussion at multi-disciplinary rounds is encouraged when genomic alterations are identified. Referral to hereditary cancer care services should be arranged by the ordering physician for patients identified to harbour HRR alterations.[6]

Systemic therapy: Clinical trials should be given first consideration where appropriate.

Following an ARPI (e.g. ARPI in the mCSPC or nmCRPC setting), subsequent ARPI is discouraged, and taxane-based chemotherapy should be strongly considered. Hence, patients with clinical and/or radiographic progression on ARPI (i.e. abiraterone acetate, apalutamide, darolutamide, enzalutamide) should be referred for consideration of chemotherapy with medical oncology.

In patients who are ARPI naïve, mCRPC should be considered for novel anti-androgen therapy (abiraterone acetate plus prednisone or enzalutamide) or clinical trial options ***prior*** to initiation of previously used agents (such as NSAA's).

Poly ADP ribose Polymerase (PARP) inhibitor treatment (e.g. olaparib) should be considered for patients identified to have a *BRCA1*, *BRCA2* or *ATM* alteration, who have previously received treatment with an ARPI at any point of advanced prostate cancer management. Platinum-based

chemotherapy may be considered if a *BRCA1*, *BRCA2*, *ATM*, or other HRR gene alteration is identified. *ATM* alterations may require strong consideration of chemotherapy prior to PARP inhibitor therapy. Hence, medical oncology should be involved in the care of these patients prior to initiation of PARP inhibitor. Other HRR gene alterations do not qualify for olaparib therapy.

1. First line options:
    a. Abiraterone acetate 1000 mg oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.[25, 26]
    b. Docetaxel 75mg/m^2 IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.
    c. Enzalutamide 160mg oral daily can be used prior to docetaxel (PREVAIL).[27]

2. Second line options:
    a. Post progression on docetaxel chemotherapy:
        i. Cabazitaxel IV every 3 weeks in combination with prednisone 10 mg oral daily.20 mg or 25 mg can be considered, as the PROSELICA trial.[28] demonstrated that 20 mg dose was non-inferior to the 25 mg dose and was associated with decreased toxicity. Per the CARD trial, cabazitaxel is shown to improve overall survival, in contrast to another ARPI.[29]
        ii. Abiraterone acetate[30] or enzalutamide.[31]
        iii. Radium 223 is not funded or available in Alberta. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).[32, 33] Ra 223 is administered upon referral to nuclear medicine and given at a dose of 50 kBq (1.35 microcurie) per kg body weight at 4 week intervals for a total of 6 injections.
    b. Post progression on abiraterone, apalutamide, darolutamide or enzalutamide:
        i. Docetaxel chemotherapy.
        ii. Olaparib - for patients with *BRCA1*, *BRCA2* or *ATM* alterations. [34] *ATM* alterations may require strong consideration of chemotherapy prior to PARP inhibitor therapy. Hence, medical oncology should be involved in the care of these patients prior to initiation of PARP inhibitor. Other HRR gene alterations do not qualify for olaparib therapy.
        iii. Platinum-based chemotherapy options should be considered for patients with DNA damage repair mutations (*BRCA1*, *BRCA2*, *ATM*, or other HRR alteration), and discussion at multidisciplinary tumour board rounds is encouraged.[6]

3. Subsequent lines:
    a. Sequencing with another agent listed above not previously used. Optimal sequencing of these agents is unknown.
    b. If a patient has already received docetaxel and one ARPI, the CARD trial would suggest

that cabazitaxel would be the preferred subsequent agent provided the patient is medically fit for therapy.[29]

c. Docetaxel re-challenge every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.

Bone targeted therapy: Treatment with bisphosphonates bone targeted agents should be considered for some patients with metastatic castration resistant prostate cancer. See the Bone Health in Patients with Prostate Cancer guideline

Palliative radiotherapy: For a complete list of recommendations, see the Alberta Palliative Radiotherapy guidelines located at www.ahs.ca/guru under the Palliative & Supportive Care heading.

Management of Oligometastatic Disease

Radiotherapy to the prostate:

- The STAMPEDE trial[19] failed to demonstrate improvement in overall survival after radiotherapy in newly diagnosed metastatic prostate cancer. However, pre-specified subgroup analysis of patients with low metastatic burden (by CHAARTED clinical trial criteria) demonstrated an improvement in overall survival with radiotherapy to the prostate compared to standard of care (81% vs. 73% OS at 3 years; HR:0.68, 95%CI: 0.52-0.90). Patients with de novo low volume mCSPC (e.g. 3 or less bone metastases) should be referred to Radiation Oncology for a discussion regarding radiotherapy to the prostate.
- SBRT to oligometastatic disease is an investigational option and may be considered for some patients. Discussion at multidisciplinary tumour board rounds is recommended.
- PSMA PET/CT is an investigational imaging modality and is not currently standard of care. ~~Patient~~ Patients undergoing PSMA PET imaging should understand that there is not currently level 1 evidence to guide management. PSMA PET results should be reviewed at multidisciplinary tumour board rounds to discuss management options.

Follow-up:

- Patients on docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide, cabazitaxel, or olaparib should be monitored as per standard protocols. [Olaparib Product Monograph]
- Patients with clinical and/or radiographic progression on ARPI (i.e. abiraterone acetate, apalutamide, darolutamide, enzalutamide) should be referred for consideration of chemotherapy with medical oncology.
- Once therapy with one of these agents has been discontinued, patients should be assessed for further therapy.
- Repeat staging investigations are recommended at the time of progression on any therapy. During the course of chemotherapy and PARP inhibitor, restaging should be considered approximately every 3 months, or as clinically indicated.

- Regardless of therapy, patients with HRR alterations and mCRPC should have close follow-up and more frequent labs (repeated at a minimum frequency of every 2 months) and restaging with CT and bone scan (repeated at a minimum frequency of every 6 months), since patients with HRR alterations have a poor prognosis and can progress rapidly on ARPI.

Future Therapies

The following therapies are Health Canada approved, but they are not funded, as they are currently under review CADTH. Special access programs and co-pay programs may be available.

177Lu-PSMA may be considered in PSMA PET/CT positive mCRPC patients, who have previously received ARPI and docetaxel. 177Lu-PSMA IV 7.4 GBq given up to 6 cycles demonstrated an improved overall survival, in contrast to best supportive care, per the VISION trial.[35]

Combination PARP inhibitor plus ARPI may be considered in patients with mCRPC with *BRCA1* or *BRCA2* alterations who are deemed chemotherapy unfit by medical oncology in the first line of mCRPC treatment. Combination PARP inhibitor plus ARPI requires an assessment by medical oncology for chemotherapy fitness. The following are the Health Canada approved, potentially accessible options:

- Niraparib plus abiraterone demonstrated improved radiographic progression free survival and overall survival, in contrast to placebo plus abiraterone in patients with *BRCA1* or *BRCA2* alterations, per the MAGNITUDE trial.[36]
- Olaparib plus abiraterone demonstrated improved radiographic progression free survival, in contrast to placebo plus abiraterone, particularly in patients with HRR alterations, per the PROPEL trial[37]
- NOTE: Talazoparib plus enzalutamide is **not** Health Canada approved at the time of this publication, but demonstrates an improvement radiographic progression free survival and overall survival, in contrast to placebo plus enzalutamide in patients with HRR alterations, per the TALAPRO2 trial.[38]

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Appendix A: Clinical Trial Summaries

Table 1. Systemic Therapy Trials for the Treatment of Metastatic Castration Sensitive Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
ADT (Intermittent versus continuous)[8]	INT 0162 (NCT00002651)	Newly diagnosed mCSPC	(n=765) continuous ADT Vs. (n=770) intermittent ADT	N/A	N/A	5.8 years (Continuous) vs. 5.1 years (intermittent)	HR for intermittent 1.10 (90%CI 0.99-1.20)
Abiraterone[13]	LATITUDE (NCT01715285)	Newly diagnosed mCSPC	(N=1199) ADT + placebo Vs. ADT + Abiraterone	ADT+ placebo: 14.8m ADT+ Abiraterone: 33.0 months	HR: 0.47, 95%CI: 0.39-0.55, p<0.001	ADT+ placebo: 34.7 months ADT+ Abiraterone: not reached	HR:0.62, 95%CI 0.51-0.76, P<0.001
Abiraterone[39]	STAMPEDE (NCT00268476)	mCSPC (52%), N1/Nx M0 (20%), N0M0 (28%)	(N=1917) ADT + placebo Vs. ADT + Abiraterone	(3-year) ADT+placebo: 45% ADT+Abiraterone: 75%	HR: 0.29, 95%CI: 0.25-0.34, p<0.001	(3-year) ADT+ placebo: 76% ADT+ Abiraterone: 83%	HR: 0.63, 95%CI: 0.52-0.76, p<0.001, HR for M0: 0.75 HR for M1: 0.61
Docetaxel/ Zoledronic acid[40]	STAMPEDE (NCT00268476)	high-risk, locally advanced, metastatic or recurrent PC, starting long-term hormone therapy	(2:1:1:1 randomization, N=2962) (2)Standard of care (SOC) Vs. (1)SOC + zoledronic acid (ZA) Vs. (1)SOC + docetaxel (Doc) Vs. (1)SOC+ ZA + Doc	SOC: 20m SOC+ZA: 22m SOC+Doc: 37m SOC+ZA+Doc: 36m	SOC+ZA: HR: 0.92, p=0.198 SOC+Doc: HR: 0.61, p<0.001 SOC+ZA+ Doc: HR:0.62, p<0.001	SOC: 71m (5y: 55%) SOC+ZA: not reached (5y:57%) SOC+Doc: 81m (5y: 63%) SOC+ZA+Doc: 76m (5y: 60%)	SOC+ZA: HR: 0.94, p=0.450 SOC+Doc: HR:0.78, p=0.006 SOC+ZA+ Doc: HR:0.82, p=0.022
Docetaxel[41]	CHAARTED (NCT00309985)	mCSPC with bone metastases	(N=790) ADT + placebo Vs. ADT + Docetaxel (Doc)	(Median time to CRPC) ADT+ Placebo: 11.7m ADT+ Doc: 20.2m	HR: 0.61, 95%CI: 0.51-0.72, P<0.001	ADT+ Placebo: 44.0m ADT+ Doc: 57.6m	HR: 0.61, 95%CI: 0.47-0.80, P<0.001
Docetaxel[42]	GETUG-AFU 15 (NCT00104715)	mCSPC	(N=385) ADT + placebo Vs. ADT + Docetaxel (Doc)	(bRFS) ADT+ Placebo: 12.9m ADT+ Doc: 22.9m	HR: 0.72, 95%CI: 0.57-0.91, p=0.005	ADT+ Placebo: 54.2m ADT+ Doc: 58.9m	HR: 1.01, 95%CI: 0.75-1.36, p=0.955
Enzalutamide[15]	ARCHES (NCT02677896)	mCSPC	(N=1150) Enzalutamide + ADT vs. Placebo + ADT	(radiographic) rPFS (events) Enzalutamide+ ADT =15..9% Placebo+ ADT =34.9%	HR: 0.39, 95%CI: 0.30-0.50, p>0.001	Deaths Enzalutamide+ ADT (n=39) Placebo+ ADT (n=45)	HR:0.81, 94%CI: 0.53-1.25, p=0.3361
Enzalutamide[16]	ENZAMET (NCT02446405)	mCSPC	(N=1125) Testosterone suppression plus either Enzalutamide vs. nonsteroidal antiandrogen therapy (Standard care)	PSA Events: Enzalutamide: 174 SOC: 333	HR: 0.39 p<0.001	Deaths: Enzalutamide: 102 SOC: 143	HR: 0.67, 95%CI: 0.52-086, p=0.0002
Apalutamide[43]	TITAN (NCT02489318)	mCSPC	(N=525) Apalutamide+ ADT vs Placebo+ ADT	rPFS at 24 mo Apalutamide: 68.2% Placebo: 47.5%	HR: 0.48, 95%CI: 0.39-0.60, p<0.001	OS at 24 mo Apalutamide: 82.4% Placebo: 73.5%	HR: 0.67, 95%CI: 0.51-0.89, p=0.005

Table 2. Systemic Therapy Trials for the Treatment of Metastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Abiraterone[30, 44]	COU-AA-301 (NCT00638690)	Post Docetaxel	5 mg of prednisone twice daily with 1000mg (4x 250mg) of abiraterone acetate (797 patients) or placebo (4x 250mg) daily	Abiraterone group: 5.6mo Placebo: 3.6 mo	p <0.001	Abiraterone group: 14.8mo Placebo: 10.9mo Median follow-up: 12.8mo	p<0.001, HR: 0.65, 95%CI: 0.54-0.77
Abiraterone[25, 26]	COU-AA-302 (NCT00887198)	Pre Docetaxel	Abiraterone acetate 1000mg (4 x 250mg) plus prednisone (5mg twice daily) (544 patients) vs placebo plus prednisone (544 patients)	Radiographic PFS Abiraterone group: 16.5mo vs placebo: 8.2mo median follow-up 22.2mo	p<0.0001, HR: 0.52, 95%CI: 0.45-0.61	Abiraterone: 35.3mo Placebo: 30.1 mo	p=0.0037 HR: 0.80; 95%CI: 0.69-0.93
Enzalutamide[27]	PREVAIL (NCT01212991)	Pre Docetaxel	872 in the enzalutamide group, 845 in the placebo group	Radiographic PFS at 12 months was 65% in the enzalutamide group compared to 14% in the placebo group	p<0.001, HR: 0.19, 95%CI: 0.15-0.23	OS was 72% (626 patients) in the enzalutamide group vs 63% (532 patients) in the placebo group	p<0.001, HR: 0.71, 95%CI: 0.60-0.84
Enzalutamide[31, 45]	AFFIRM (NCT00974311)	Post Docetaxel	Enzalutamide 160mg once daily (four capsules) (800 patients) vs placebo (399 patients).	Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo	p<0.001, HR: 0.40	Enzalutamide group: 18.4mo Placebo: 13.6mo	p=0.0151, HR: 0.79, 95%CI: 0.66-0.95
Docetaxel[46-48]	TAX 327	Metastatic CRPC	Docetaxel 75 mg/m^2 q3 weekly + prednisone 5 mg bid vs. Mitoxantrone 12 mg/m^2 + prednisone 5 mg bid (3rd arm of weekly docetaxel demonstrated no benefit)	N/A	N/A	Docetaxel 18.9 vs Mitoxantrone 16.5 months	p=0.009, HR: 0.76, 95%CI: 0.62-0.94)
Cabazitaxe[49, 50]	TROPIC (NCT00417079)	Post Docetaxel	10mg oral prednisone daily and 12mg/m^2 mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m^2 cabazitaxel intravenously over 1h (378 patients) every 3 weeks	cabazitaxel group:2.8mo mitoxantrone group:1.4mo	p<0.0001, HR:0.74 95%CI: 0.64-0.86	Cabazitaxel group: 15.1mo Mitoxantrone group: 12.7mo	p<0.001, HR: 0.63, 95%CI: 0.53-0.75
Sipuleucel-T (Not Health Canada Approved)[51]	IMPACT (NCT000065442)	Asymptomatic or minimally symptomatic CRPC	Sipuleucel-T (341 patients) vs placebo (171 patients).	Similar	p=0.40, HR: 0.92, 95%CI: 0.75-1.12	Sipulencel-T group: 25.8mo Placebo: 21.7mo	p=0.03, HR 0.78, 95%CI: 0.61-0.98
Radium-233 (Xofigo)[32, 33]	ALSYMPCA (NCT00699751)	Post docetaxel or non-docetaxel candidates	Radium-233- six injections (1 every 4 weeks), 50kBq/kg of body weight, intravenously vs matching placebo	Time to First Symptomatic Skeletal Event (median): Radium-223: 15.6mo Placebo: 9.8mo	p<0.001, HR: 0.66, 95%CI: 0.52-0.83	Radium-233: 14.9mo Placebo: 11.3mo	p=0.03, HR: 0.78, 95%CI: 0.61-0.98
Cabazitaxel vs. Abiraterone or Enzalutamide[29]	CARD (NCT02485691)	mCRPC, previously treated with docetaxel, with progression within 12 mo while on abiraterone or enzalutamide	(N=255) Cabazitaxel vs. Abiraterone or Enzalutamide (whichever wasn't used initially)	median PFS: Cabazitaxel: 4.4 mo Abi/Enz: 2.7 mo	HR: 0.52, 95%CI: 0.40-0.68, p<0.001	median OS Cabazitaxel: 13.6 mo Abi/Enz: 11.0 mo	HR: 0.64, 95%CI: 0.46-0.89, p=0.008

Table 3. Systemic Therapy Trials for the Treatment of Nonmetastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Darolutamide[14]	ARAMIS (NCT02200614)	M0 CRPC with a PSA doubling time of 10 months or less	(N=1509) (2:1) Darolutamide+ ADT vs. Placebo+ ADT	Metastasis-free survival Darolutamide: 40.4 mo Placebo: 18.4 mo	HR: 0.41, 95%CI: 0.34-0.50, p<0.001	Deaths: Darolutamide: n=78 Placebo: n=58	HR: 0.71, 95%CI: 0.5-0.99, p=0.045

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial GU Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial GU Tumour Team who were not involved in the guideline's development, including urologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2019.

Maintenance

A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

ADT Androgen deprivation therapy, ALT Alanine transamine, AST Aspartate transaminase, BUN Blood urea nitrogen, CBC Complete blood count, CT Computed tomography, EBRT External beam radiotherapy, GnRH Gonadotropin-releasing hormone agonist, LHRH Luteinizing hormone-releasing hormone, PSA Prostate-specific antigen

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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