2025 Canadian Urological Association-Canadian Uro-oncology Group Guideline: Metastatic castration-naive and castration-sensitive prostate cancer (Update)

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INTRODUCTION

Metastatic prostate cancer (PCa) remains an incurable disease. In Canada, approximately 8% of men with PCa are diagnosed de novo with metastatic disease and, in 2018, roughly 1200 men were diagnosed with de novo metastatic PCa.[1] The mainstay of treatment for de novo metastatic PCa is androgen deprivation therapy (ADT), either surgical or medical castration, which is initially effective in almost all patients; however, progression is inevitable, heralded by a rise in prostate-specific antigen (PSA), increasing disease burden, and/or worsening symptoms, a disease state called metastatic castration-resistant prostate cancer (mCRPC).

Men with metastatic PCa have a poor prognosis, with an estimated median overall survival (OS) of approximately 3–4 years.[2] Compared to PCa that develops metastases after diagnosis of localized disease, de novo metastatic PCa has been shown to have a worse overall prognosis.[3,4] Over the past decade, practice-changing trials have demonstrated improved survival in men with metastatic castration-naive/castration-sensitive prostate cancer (mCNPC/mCSPC) using ADT intensification strategies that include both systemic therapy and treatment of the primary cancer.

The Canadian Urological Association (CUA), in collaboration with the Canadian Uro-oncology Group (CUOG), sought to provide management guidelines to optimize the treatment of mCNPC/mCSPC patients.

METHODOLOGY

EmBASE and Medline databases were accessed to identify all relevant articles focused on mCNPC or mCSPC published between January 2000 and January 2025 with the following key words strategy: "prostate cancer," "hormone-sensitive," "castration-naïve," "castration sensitive," "androgen deprivation," "chemotherapy," "androgen receptor-axis targeted therapy," and "metastatic." An expert panel comprised of urologists, medical oncologists, and radiation oncologists with significant experience managing mCNPC/mCSPC was used to develop the recommendations. Guidelines were developed by consensus among the panel. Levels of evidence and grades of recommendation employ the WHO-modified Oxford Center for Evidence-Based Medicine grading system.[5] Based on a modified GRADE methodology, the strength of each recommendation is represented by the words strong or weak.[5] Wherever level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.

Moving forward, the CUA will be employing GRADE methodology for all of its major guidelines. Until we shift exclusively to this model, guidelines will be updated using the methodology in which they were originally created, and in this particular document, recommendations have been assigned a level of evidence based on the WHO-modified Oxford Center for Evidence-Based Medicine and modified GRADE systems, as well as expert opinion. Because this was a minor update, it did not undergo further external review.

INDICATIONS FOR STAGING IN PROSTATE CANCER

■ RECOMMENDATION 1

For newly diagnosed PCa, staging with a computed tomography (CT) scan of the chest, abdomen, and pelvis and bone scan (technetium-99mmethylene diphosphonate [99mTc-MDP]) should be performed for men with any high-risk features: PSA >20 ng/mL, Gleason score >7, clinical stage T3 or greater *(Level of evidence 3, Strong recommendation).*

Conventional imaging to stage PCa includes bone scintigraphy using 99mTc-MDP to assess for bone metastases and abdominopelvic CT imaging to assess for lymphadenopathy and visceral metastases. In patients with high-risk disease, CT imaging of the chest may also be considered, as lung metastases are the most common site of visceral metastases.[6]

Novel diagnostic imaging to stage PCa, particularly prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET)/CT, improves the sensitivity and specificity of conventional imaging; however, these tests are not universally available in Canada and they are still considered investigational by Health Canada. Most importantly, all of the phase 3 trials in mCNPC/mCSPC used conventional imaging for staging and risk determination, and conclusions were based on these.

ASSESSMENT OF PROGNOSIS

■ RECOMMENDATION 2

Patients diagnosed with metastatic PCa should be classified as high-volume/high-risk or low-volume/low-risk based on conventional imaging and PCa biopsy for prognostication *(Level of evidence 2, Weak recommendation).*

Clinical trials of patients with mCNPC/mCSPC have used pragmatic prognostic factors to stratify prognosis. The CHAARTED trial classified PCa based on volume of disease. High-volume was defined by the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis; low-volume was defined as all other mCNPC/mCSPC.[7] The LATITUDE trial classified high-risk patients based on three different criteria: visceral metastases, ≥3 bony metastases, or Gleason score ≥8; high-risk was defined as ≥2 of these criteria, whereas low-risk was defined as having <2.[8] Interestingly, a comparative study of the classification of each of these trials showed an overall discordance of 18.2% between the CHAARTED and LATITUDE criterion; however, it appears that disease burden (defined radiologically or by PSA) and high-grade tumors portend a worse prognosis.[9]

GENETIC TESTING

■ RECOMMENDATION 3

All patients with mCNPC/mCSPC should undergo both germline testing and genomic profiling of tumors *(Level of evidence 2, Strong recommendation).*

As outlined in the CUA guidelines for genetic testing in PCa, men with metastatic disease should undergo both germline testing and genomic profiling of tumors.[10] Germline testing is crucial, as multiple studies have found a significantly higher prevalence of pathogenic or likely pathogenic variants (P/LP) in patients with metastatic disease compared to patients with localized disease.[11-13] In some metastatic PCa series, the frequency of germline P/LP variants was as high as 18%.[11] As stressed in the 2023 CUA guideline, genetic testing in PCa identifies P/LP variants to inform future cancer risk, and to initiate cascade testing in family members. Genomic profiling of the tumor should also be performed in patients with metastatic disease. The purposes of tumor testing include prognostication and identification of those that may benefit from targeted therapy.[10] If somatic testing is done first and shows no P/LP variants, germline testing may not be necessary.

ANDROGEN DEPRIVATION THERAPY

■ RECOMMENDATION 4

ADT should be started on men newly diagnosed with metastatic PCa *(Level of evidence 1, Strong recommendation).*

■ RECOMMENDATION 5

Continuous ADT is the standard of care (SOC) for metastatic PCa, while intermittent may be considered in select patients.

Androgen receptor (AR) signaling plays a key role in the progression of PCa, and thus de novo mCNPC remains highly driven by testosterone. Hence, the primary step in the management of mCNPC, which remains the backbone of treatment for all men with metastatic PCa until death, is ADT. ADT can be achieved by

surgical castration (orchiectomy) or pharmacologically with agents that inhibit Leydig cell production of testosterone (gonadotropin-releasing hormone [GnRH] agonists or antagonists). The optimal timing of androgen deprivation has been the subject of many trials, with two systematic reviews suggesting early treatment is associated with improved overall and cancer-specific survival and decreases the rate of skeletal events compared to deferred treatment.[14,15] More importantly, the early treatment of mCNPC with ADT is required if other systemic treatment, such as docetaxel or AR axis inhibitors, are used.

ADT is associated with increased side effects and may increase the risk of cardiovascular events, but evidence has been contradictory. Intermittent androgen suppression (IAS) that cycles ADT based on PSA values has been shown to improve quality of life; however, continuous ADT should be used in mCNPC and IAS only used as an exception in select patients with close followup.[16,17] As well, the benefit of combined treatment of mCNPC with additional systemic therapy was demonstrated in the context of continuous ADT. The treatment and prevention of adverse events caused by ADT can be found in the CUA guideline entitled, "Canadian Urological Association guideline on androgen deprivation therapy: Adverse events and management strategies."[18]

LOCAL THERAPY: TREATMENT OF THE PRIMARY CANCER IN MCNPC

RECOMMENDATION 6

Patients with low-volume metastatic disease burden should be considered for external beam radiation to the prostate *(Level of evidence 2, Strong recommendation).*

In the context of low-volume mCNPC, treatment of the primary disease in the prostate has theoretical benefits, including reducing local side effects that may occur due to local disease progression, as well as removing the cancer that could be the source of cytokines and growth factors that may induce disease progression.[19]

Two randomized trials assessed the impact of external beam radiation therapy (EBRT) in mCNPC. The HORRAD trial randomized 432 men with mCNPC and PSA >20 ng/mL to receive EBRT of the prostate with ADT or ADT alone. The initial prescribed dose was 70 Gy in 35 fractions of 2 Gy, during an overall treatment time of seven weeks. During the study period, an optional schedule considered biologically equivalent was added and consisted of a dose schedule of 57.7 Gy in 19 fractions of 3.04 Gy three times a week for six weeks. At baseline, the median PSA was 142 ng/ml and 67% of patients had >5 bone metastases. No significant difference was found in OS (hazard ratio [HR] 0.90; 95% confidence interval [CI] 0.70–1.14, p=0.4), but there was a benefit to median time to PSA progression in the radiotherapy group (15 months vs. 12 months, crude HR 0.78, 95% CI 0.63–0.97, p=0.02). Subgroup analysis showed that mCNPC with <5 metastases (HR 0.90, 95% CI 0.70–1.14, p=NS) and no bony pain (HR 0.83, 95% CI 0.69–1.14, p=NS) appeared to have the most benefit of EBRT.

The STAMPEDE trial, also known as MRC PR08, is a multi-arm multistage (MAMS) randomized trial recruiting in the U.K. and Switzerland. It aimed to evaluate multiple therapeutic strategies in the management of high-risk locally advanced and mCNPC compared to SOC (ADT only). In the EBRT component of the study, the trial randomized 2061 men with mCNPC to either EBRT and ADT or ADT alone.[20] The median PSA was 97 ng/mL; 819 (40%) men had low metastatic burden based on CHAARTED criteria and 1664 (81%) had no pain.[7,20] EBRT was given in one of two schedules: either 36 Gy in six consecutive weekly fractions of 6 Gy, or 55 Gy in 20 daily fractions of 2.75 Gy over four weeks. Subgroup analyses were prespecified for baseline metastatic burden (low vs. high).

Similar to the HORRAD trial, EBRT improved failure-free survival (FFS) (HR 0.76, 95% CI 0.68–0.84, p<0.0001) but not OS (HR 0.92, 95% CI 0.80–1.06, p=0.266). Subgroup analysis by metastatic burden showed FFS was improved in both low and high metastatic burden (low metastatic burden: HR 0.59, 95% CI 0.49–0.72,p<0.0001 and metastatic burden, interaction p=0.002; HR 0.88, 95% CI 0.77–1.01, p=0·059). OS was improved in patients with low metastatic burden at baseline who were allocated EBRT (HR 0.68, 95% CI 0.52–0.90, p=0.007), whereas in patients with a high metastatic burden, there was no impact on OS (HR 1.07, 95% CI 0.90–1.28, p=0.420).

Although both trials showed a lack of benefit of EBRT in unselected men in mCNPC, both HORRAD and STAMPEDE reveal the benefits of local therapy in those with low-burden disease. The STOPCAP meta-analysis combining data from the trials confirms the benefits of EBRT in men with <5 bone metastases.[21] This meta-analysis showed that there was 7% improvement in three-year survival in men with <4 bone metastases.

RECOMMENDATION 7

Radical prostatectomy in mCNPC should only be performed in a clinical trial setting. *(Expert opinion, Strong recommendation).*

Currently, there is limited evidence showing the benefit of radical prostatectomy in mCNPC; however, results from HORRAD and STAMPEDE imply that there may also be certain men with mCNPC that may benefit from surgical extirpation. There are many clinical trials currently assessing this question, including TRoMBONE (testing radical prostatectomy in men with PCa and oligometastases to the bone, a randomized controlled feasibility trial),[22] SWOG1802 (standard systemic therapy with or without definitive treatment in treating participants with metastatic PCa; https://www.swog.org/clinical-trials/s1802), G-RAMPP/AUO-AP-75/13 (impact of radical prostatectomy as primary treatment in patients with PCa with limited bone metastases),[23] and IP2-ATLANTA (additional treatments to the local tumor for metastatic prostate cancer-assessment of novel treatment algorithms, protocol for a multicenter, phase 2 randomized controlled trial).[24] Until the results of these trials clarify the impact of radical prostatectomy in mCNPC and, more importantly, which patients would benefit the most, surgery of the primary is not recommended in patients with metastatic PCa.

SYSTEMIC THERAPIES: CHEMOTHERAPY, ABIRATERONE ACETATE, ENZALUTAMIDE, APALUTAMIDE, AND DAROLUTAMIDE

RECOMMENDATION 8

Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT is an option for mCNPC patients with at least two of the three: Gleason score of ≥8, presence of ≥3 lesions on bone scan, or presence of measurable visceral metastasis *(Level of evidence 1, Strong recommendation).*

RECOMMENDATION 9

Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT may be considered for patients with low-volume mCNPC *(Level of evidence 3, Weak recommendation).*

Abiraterone acetate is a prodrug of abiraterone, which is a CYP17A1 inhibitor; CYP17A1 is expressed in and is required for androgen biosynthesis. Abiraterone acetate, when combined with prednisone, was initially shown to improve survival in mCRPC both prior to and after docetaxel treatment.[25,26] Two trials, LATITUDE and STAMPEDE, assessed the impact of abiraterone in mCNPC/mCSPC.[8,27,28] In the LATITUDE trial, 1199 patients were randomly assigned to either the abiraterone acetate (1000 mg) plus prednisone (5 mg) once daily orally and ADT vs. ADT alone. Eligible patients included mCNPC with at least two of three high-risk features: Gleason score of ≥8, presence of ≥3 lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis. Updated OS data with median followup of 51.8 months showed that OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI 48.2–not reached]) than in the placebo group (median 36.5 months [95% CI 33.5–40.0]), with a HR of 0.66 (95% CI 0.56−0.78, p<0.0001). A post-hoc exploratory analysis of the impact of disease burden showed that OS was improved only in high-volume disease (n=487 in the abiraterone acetate plus prednisone and ADT and 468 in the ADT only group [HR 0.62, 95% CI 0.52−0.74. p<0·0001]); however, only few patients had low-volume disease in this study (n=110 in the abiraterone acetate plus prednisone and ADT and n=133 in the ADT only group [HR 0.72, 95% CI 0.47−1.10, p=0.1242]).

In the abiraterone component of the STAMPEDE trial, the efficacy of abiraterone acetate and prednisolone was assessed in men with mCNPC.[27] In this study, 1917 mCNPC patients were enrolled with: newly diagnosed and metastatic, node-positive, or high-risk locally advanced (with at least two of following: cT3 or cT4, a Gleason score of 8–10, or PSA level ≥40 ng/mL) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (PSA >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse). Men were randomized to receive abiraterone acetate (1000 mg daily) plus prednisolone (5 mg) plus ADT or ADT alone; 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, non-metastatic disease; 95% had newly diagnosed disease. In a subgroup analysis, the OS benefit was seen in PCa patients with metastatic disease (HR 0.61, 95% CI 0.49–0.75) but not those with non-metastatic high-risk patients (HR 0.75, 95% CI 0.48–1.18).27 The impact of volume tumor burden was not reported.

An unplanned post-hoc analysis of 759 evaluable patients with bone metastases in the above STAMPEDE

trial was reclassified using the CHAARTED high- or low-volume criterion or LATITUDE's high- or low-risk" criterion.[29] Men with mCNPC had OS benefit with the addition of abiraterone acetate and prednisone to ADT irrespective of risk stratification for risk or volume. Using CHAARTED criteria, low-volume HR was 0.66 (95% CI 0.44–0.98) and high-volume HR was 0.54 (95% CI 0.41–0.70); using the LATITUDE criteria, low-risk HR was 0.64 (95% CI 0.42–0.97) and high-risk HR was 0.60 (95% CI 0.46–0.78). Although these results are intriguing, the retrospective nature of the reclassification of risk and tumor volume is a significant limitation and thus the results can only be considered hypothesis-generating.

■ RECOMMENDATION 10

Enzalutamide (160 mg/day) is a treatment option for mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Strong recommendation).*

■ RECOMMENDATION 11

Enzalutamide may be considered in mCSPC patients previously treated with docetaxel chemotherapy (sequential use) *(Level of evidence 1, Weak recommendation).*

Enzalutamide binds to the AR and inhibits the AR nuclear translocation and interaction with DNA. Suppression of the AR with enzalutamide was initially shown to improve survival in docetaxel-naive or treated mCRPC.[30,31] Two studies assessed the role of enzalutamide in mCNPC: ARCHES and ENZAMET.[32,33] The ARCHES trial randomized 1150 mCNPC/mCSPC patients to either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiologic progression-free survival (rPFS), defined as the time from randomization to the first objective evidence of radiographic disease progression or death. The combination of enzalutamide plus ADT improved rPFS compared to placebo-ADT (HR 0.39, 95% CI 0.30-0.50, p=0.001; median not reached vs. 19.0 months). A final analysis showed improved OS in the enzalutamide treatment arm (HR 0.66, 95% CI 0.53-0.81, p<0.0001).[34] Prior docetaxel of up to six cycles was allowed, and 18% (205) men received at least one dose of docetaxel prior to randomization; subgroup analysis showed that rPFS benefit was seen in both chemotherapy-treated and chemotherapy-naive patients. Benefit with enzalutamide in rPFS and OS was seen regardless of disease burden and timing of metastases (de novo vs. metachronous).

ENZAMET was an open-label clinical trial that randomized 1125 men with mCNPC/mCSPC to receive ADT and enzalutamide daily (160 mg) or a non-steroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide) with a primary endpoint of OS. Initial interim analysis with followup at 34 months showed an OS benefit in the enzalutamide plus ADT arm compared to NSAA (HR 0.67, 95% CI 0.52–0.86, p=0.002). A later pre-planned analysis performed at 470 deaths showed continued benefit at 68-month followup (HR 0.70, 95% CI 0.58–0.84, p<0·0001), with five-year overall survival of 57% in the control arm and 67% in the enzalutamide arm.[35]

■ RECOMMENDATION 12

Apalutamide (240 mg) is a treatment option for men with mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Strong recommendation).*

Apalutamide inhibits the AR by preventing its nuclear translocation and DNA binding. The first large randomized clinical trial assessing apalutamide in mCNPC/mCSPC was the TITAN trial, which randomized 1052 men with mCNPC/mCSPC (any) to receive apalutamide (240 mg once daily) plus ADT or ADT alone. In addition, 10.7% received previous docetaxel therapy and 37.3% had low-volume disease. With a median of 40.0 months of followup, rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (HR 0.48, 95% CI, 0.39–0.60, p<0.001). The benefit with apalutamide in rPFS was seen regardless of prior chemotherapy use or disease burden. Final analysis of OS showed apalutamide improved OS, reducing the risk of death by 35% (median OS for apalutamide not reached vs. 52.2 months in the placebo group; HR 0.65; 95% CI 0.53–0.79; p<0.0001).[36,37] The benefit with apalutamide in rPFS and OS was seen regardless of disease burden and timing of metastases (de novo vs. metachronous).

■ RECOMMENDATION 13

Darolutamide (600 mg twice a day) is a treatment option for men with mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Moderate recommendation).*

Darolutamide is an AR pathway inhibitor that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. The use of darolutamide and ADT in metastatic PCa was studied in the ARANOTE study.[38] This double-blind, placebo-controlled, phase 3 trial randomized, in a 2:1 ratio, 669

metastatic PCa patients to receive darolutamide (600 mg twice a day) and ADT or placebo and ADT. The primary endpoint was rPFS, with secondary efficacy endpoints being OS, time to PSA progression, time to CRPC, and time to initiation of subsequent systemic anticancer therapy. Darolutamide plus ADT significantly improved rPFS, reducing the risk of radiologic progression or death by 46% vs. placebo plus ADT (HR 0.54, 95% CI 0.41–0.71, p<0.0001), with consistent benefits across subgroups, including high- and low-volume disease. At a median followup of 24 months, OS results trended to benefit with darolutamide vs. placebo (HR 0.81, 95% CI 0.59–1.12); clinical benefits were seen across all other secondary enendpoints, including delayed time to mCRPC (HR, 0.40, 95% CI 0.32–0.51). Although the duration and size of the study did not allow for proper OS assessment compared to other more mature studies assessing AR pathway inhibitors (ARPis) in CSPC, a recent network meta-analysis suggested oncologic equipoise to the already known doublet therapies for PFS.[39]

TRIPLET THERAPY

■ RECOMMENDATION 14

In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, triplet regimen (docetaxel plus ARPi and ADT) should be the treatment option, and not docetaxel and ADT alone *(Level of evidence 1, Strong recommendation).*

■ RECOMMENDATION 15

Abiraterone acetate plus prednisone in combination with ADT and docetaxel is a treatment option for men with mCNPC/mCSPC in hig-volume of disease *(Level of evidence 1, Strong recommendation).*

■ RECOMMENDATION 16

Abiraterone acetate plus prednisone in combination with docetaxel may be considered for men with mCNPC/mCSPC with low-volume *(Level of evidence 3, Weak recommendation).*

Although there is evidence of the benefit of docetaxel with ADT, there is evidence of improved outcomes with the addition of an ARPi to the doublet combination, called triplet therapy. Docetaxel, a taxane derivative that binds to tubulin and inhibits mitosis and tumor proliferation, was the initial chemotherapeutic agent that improved survival in men mCRPC.[40] Three different large, randomized trials assessed the impact of introducing docetaxel in mCNPC/mCSPC: CHAARTED, STAMPEDE, and GETUG-AFU 15.[7,41,42]

The CHAARTED trial randomized 790 with mCNPC/mCSPC patients to ADT plus docetaxel (75 mg/m^2 every three weeks for six cycles) or ADT alone.7 Within this trial, 35% (277pts) had low-volume metastases and 65% (513 patients) had high-volume metastases (high volume of metastases was defined by the presence of visceral metastases ≥4 bone lesions with at least one beyond the vertebral bodies and pelvis). Overall, the median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 months vs. 44.0 months; HR 0.61, 95% CI 0.47–0.80, p<0.001).

The GETUG-AFU15 trial randomized 385 mCNPC/mCSPC patients to receive ADT plus docetaxel or ADT alone.[42] Although the dosage of docetaxel was the same as in CHAARTED, patients were allowed to receive up to nine cycles compared to the six cycles in CHAARTED. There was no survival difference between the groups (58.9 months in the combined group vs. 54.2 months in the ADT alone group; HR 1.01, 95% CI 0.75–1.36). The differences in the outcomes of the two studies is likely due to the differences in the burden of disease. Although 65% of patients in CHAARTED had high-volume metastases, only 48% in the docetaxel arm of GETUG-AFU15 had high-volume disease. An unplanned post-hoc analysis of the high-volume cohort of GETUG-AFU 15 showed a non-significant trend toward improved OS in this cohort (39.8 months vs. 35.1 months; HR, 0.78, 95% CI 0.56–1.09).[43] A pooled analysis of both studies confirm the benefit of combined docetaxel and ADT in high-volume disease and lack of benefit on low-volume metastatic burden.[44]

The third trial to assess the impact of docetaxel in mCNPC/mCSPC was the docetaxel component of the STAMPEDE trial.[41] Unlike the CHAARTED and GETUG-AFU15 trials, patients with high-risk non-metastatic PCa were included. Eligible patients included: newly diagnosed metastatic, node-positive, high-risk locally advanced (with high-risk features defined as at least two of: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL), or previously treated with radical surgery and/or radiotherapy with high-risk features. Of the 2962 patients randomized, 1817 (61%) men had bony metastases and 592 patients received only ADT and six cycles of docetaxel (75 mg/m^2 every three weeks for six cycles). The combination of ADT and docetaxel had a survival advantage compared to ADT alone (HR 0.78, 95% CI 0.66–0.93, p=0.006).

A meta-analysis of CHAARTED, GETUG-AFU15, and STAMPEDE confirms the benefit of the addition of docetaxel to ADT in mCNPC/mCSPC (HR 0.77, 95% CI 0.68–0.87, p<0.0001). The authors of the meta-analysis show that this translates to an absolute improvement in four-year survival of 9%.

RECOMMENDATION 17

Although docetaxel and ADT combination is an effective treatment, the addition of an ARPi improves outcomes, and triplet therapy should be used when docetaxel therapy is considered for the treatment of mCNPC/mCSPC *(Level 1, Strong recommendation).*

Data from the PEACE-1 trial showed the benefits of the combination of ADT plus prednisone plus docetaxel and abiraterone acetate compared to docetaxel and ADT.[45] In a 2×2 factorial design, patients with de novo mCSPC (n=1173) were randomly assigned to receive SOC (n=296), SOC plus abiraterone and prednisone (n=29), SOC plus radiotherapy (n=293), or SOC plus abiraterone plus radiotherapy (n=291). Standard of care treatments included ADT with or without docetaxel, and overall 60% of participants received a median of six cycles of docetaxel.

Compared with SOC (ADT plus docetaxel) without abiraterone, the addition of abiraterone improved the median OS, reduced the relative risk of death from any cause by 25% (adjusted HR for OS 0.75, 95.1% CI 0.59–0.95, p=0.017). Using CHAARTED study criteria, high-volume patients treated with abiraterone and prednisone with SOC (including docetaxel) compared to SOC alone reduced the relative risk of radiographic progression or death (adjusted HR 0.47, 99.9% CI 0.30–0.72, p<0.0001); OS was improved from 3.47 years with SOC without abiraterone to 5.14 years when abiraterone was added, corresponding to a 28% reduction in relative risk of death (adjusted HR 0.72, 95.1% CI 0.55–0.95, p=0.019). In low-volume patients, the addition of abiraterone to SOC reduced the relative risk of radiographic progression or death (adjusted HR 0.58, 99.9% CI 0.29–1.15, p=0.0061); OS benefits were not found due to lack of maturity of the data (median OS not reached in either group). Importantly, although the addition of abiraterone to SOC increased the risk of hypertension (22% vs. 13%), the combination did not significantly increase grade 3 adverse events or other severe adverse events, such as neutropenia or fatigue.

RECOMMENDATION 18

Darolutamide in combination with ADT and docetaxel is a treatment option for men with mCNPC/mCSPC regardless of volume of disease *(Level of evidence 1, Strong recommendation).*

The ARASENS trial randomized 1306 mCSPC patients to receive docetaxel and androgen deprivation with (651 patients) or without (655 patients) darolutamide.[46] A significant improvement in OS was observed in those receiving darolutamide; the risk of death was 32.5% lower in the darolutamide group than in the placebo group (HR 0.68, 95% CI 0.57-0.80, p<0.001) and OS at four years was 62.7% (95% CI 58.7-66.7) in the darolutamide group and 50.4% (95% CI 46.3-54.6) in the placebo group. Although efficacy based on volume of disease was not defined, the benefits of the addition of darolutamide with docetaxel were seen regardless of metastatic stage at initial diagnosis (M1: HR 0.71, CI 0.59-0.85; M0: HR 0.61, CI 0.35-1.05). The addition of darolutamide to docetaxel did not increase adverse events such as neutropenia or fatigue; the addition darolutamide slightly increased the rate of rash (16.6% vs. 13.5%) and hypertension (13.7% vs. 9.2%).

The ARASENS and PEACE-1 trials both show the benefits of adding an ARPi to docetaxel in CSPC. The studies show the benefits of triplet therapy (ADT, ARPi, and docetaxel) compared to ADT and docetaxel, but did not directly compare efficacy of triplet therapy to the combination therapy of ADT and ARPi.[45,46] As such, these guidelines do not identify an "optimal" treatment option and various triplet or doublet treatments are recommended.

In subgroup analyses, both studies show that there are limited patient characteristics that may influence the use of triplet vs. doublet therapy, as benefits in OS and rPFS were seen in a majority of prespecified patient factors. One patient characteristic, tumor volume based on CHARRTED study criteria,[7] was shown to be important in the PEACE-1 trial; in low-volume patients, the addition of abiraterone to SOC reduced the relative risk of radiographic progression or death (adjusted HR 0.58, 99.9% CI 0.29–1.15, p=0.0061) but OS benefits seen in high-volume patients were not found, likely due to lack of maturity of the data (median OS not reached in either group). The influence of tumor volume was not reported in the ARASENS trials, but survival benefit was regardless of stage of diagnosis.46 In summary, although the volume of disease appears to differentiate survival advantage in the PEACE-1 trial, recommenda-

tions of triplet therapy, regardless of volume of disease, have been made.

■ RECOMMENDATION 19

Enzalutamide in combination with ADT and docetaxel is a treatment option for men with mCNPC/mCSPC in those with synchronous (de novo) metastases *(Level of evidence 2, Weak recommendation).*

As previously described, ENZAMET was an open-label study that randomized 1125 men with mCNPC/mCSPC to receive ADT and enzalutamide daily (160 mg) or a NSAA (bicalutamide, nilutamide, or flutamide) with a primary endpoint of OS. High-volume disease was present in 602 (54%) of 1125 participants and 683 (61%) had synchronous metastatic disease.[35] Concurrent use of docetaxel was allowed and decision to treat with chemotherapy was at the discretion of the investigator. At initial analysis, use of chemotherapy was well-balanced between the two arms (45% of those receiving enzalutamide and 44% of those receiving a NSAA planned for early docetaxel use).[32]

In the updated analysis at 470 deaths and a median followup of 68 months, the use of chemotherapy continued to be balanced between the control arm and enzalutamide arm (240 vs. 243).[35] Although docetaxel use was not randomized, subgroup analysis showed that the benefit of the addition of enzalutamide to docetaxel was seen only in those with synchronous metastases (HR 0.73, 95% CI 0.55–0.99) and not in those with metachronous metastases (HR 1.1, 95% CI 0.55–0.99); however, the authors stress that the numbers in each group may be too small to make a conclusion on this, with only 141 patients in the docetaxel group with metachronous metastases. Interestingly, the benefit of the addition of enzalutamide to docetaxel in the synchronous subgroup was seen in both high- and low-volume patients (low-volume disease: HR 0.57, 95% CI 0.29–1.12; high-volume disease: HR 0.79, 95% CI 0.57–1.10), but numbers in these groups were small.

PREVENTION OF OSTEOPOROSIS

■ RECOMMENDATION 20

All men with mCNPC/mCSPC treated with ADT should be assessed for fracture risk. All men treated with ADT require vitamin D supplementation (800–1200 IU daily) and calcium supplementation (800–1000 mg daily). Those at high risk of fractures should be treated (zoledronic acid 5 mg once a year, alendronate 70 mg weekly, denosumab 60 mg every six months).

Due to the evolution of combined therapy with ADT to treat mCNPC, the survival of men with de novo PCa is increasing, and the length of time bone is exposed to the effects of ADT is increasing. As such, these men are at risk of significant bone loss, as well as osteoporosis and fragility fractures. Bone loss occurs quickly while on ADT and within one year men can lose up to 10% of their bone mineral density (BMD).[47-49] Men with mCNPC initiating ADT should have baseline BMD with dual-energy X-ray absorptiometry (DXA), as well as the use of fracture risk calculators such as FRAX.[50] DXA should be performed at least every two years and more often in untreated patients at high risk or if there is a history of osteoporosis/osteopenia.

Men with mCNPC/mCSPC treated with ADT should be encouraged to take vitamin D (1000 IU daily) and a total calcium intake of 800–1000 mg daily. Specific lifestyle changes include smoking cessation, reduction in alcohol and caffeine intake, and increased weight-bearing exercises. If DXA scanning shows any evidence of osteopenia (T-score of <-1 and >-2.5) or osteoporosis (T-score <-2.5), men should be started a bone-targeted therapy to improve BMD and reduce the risk of fragility fractures (zoledronic acid 5 mg once a year, alendronate 70 mg weekly, denosumab 60 mg every six months).[48,49,51] Bone-targeted therapy at these doses are much lower than those to prevent skeletal-related events in mCRPC and, therefore, are associated with significantly reduced side effects; incidence of clinically significant hypocalcemia and osteonecrosis of the jaw is rare using denosumab or zoledronic acid with these lower doses.[52,53]

TREATMENT OF OLIGO-METASTATIC DISEASE

There is evolving evidence of the role of radiation in asymptomatic distant metastases, especially in low-burden oligometastatic disease.

Currently, there is limited data to provide general recommendations; however, optimal management consideration in a multidisciplinary setting should be undertaken on a case-by-case basis, with consideration for ongoing clinical trials.

MULTIDISCIPLINARY CONSULTATION

■ RECOMMENDATION 21

Men with mCNPC/mCSPC should be assessed in a multidisciplinary manner whenever possible *(Level of evidence 3, strong recommendation).*

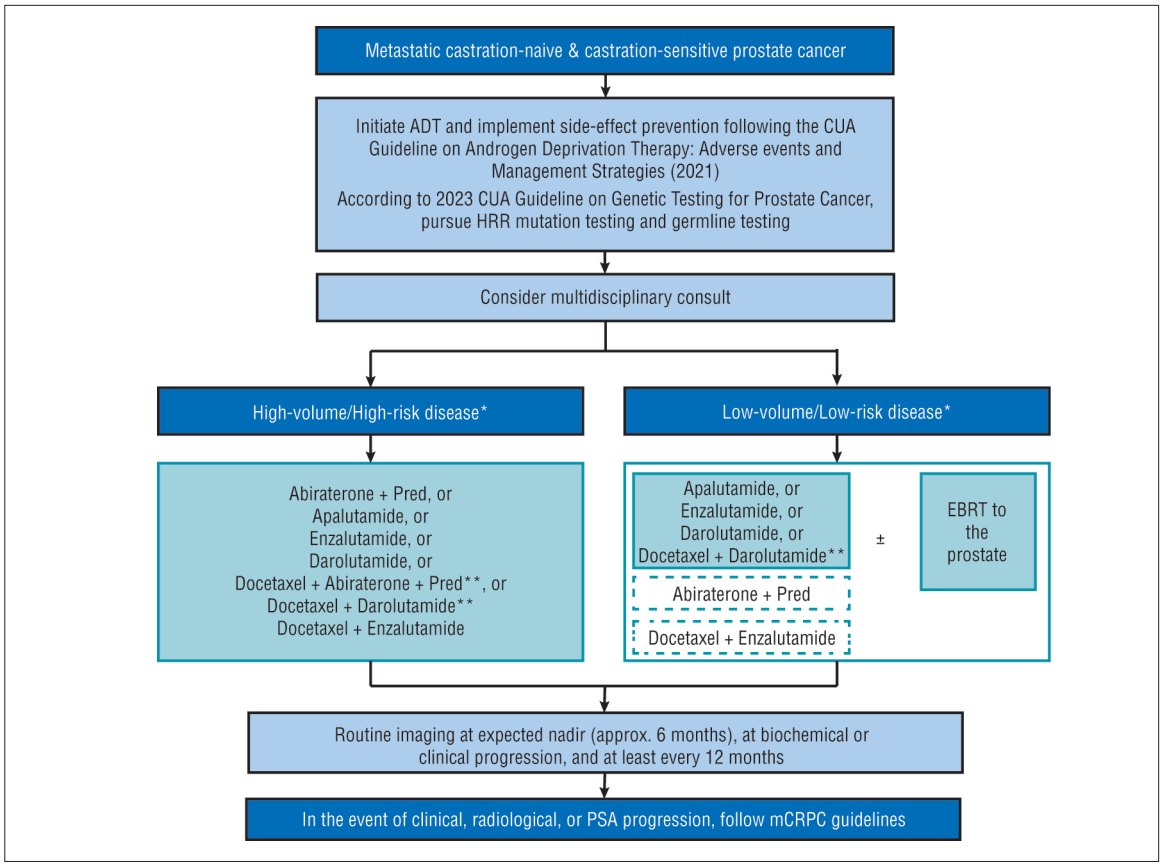

Figure 1. Algorithm for the treatment of metastatic castration-sensitive prostate cancer. *High-volume is defined by the presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis; low-volume is defined as all other metastatic castration-naive and castration-sensitive prostate cancer. **In patients who can safely tolerate docetaxel and in whom docetaxel is felt to be appropriate, triplet regimen should be considered as a treatment option. Dark teal shading=Level 1 evidence, Strong. Light teal shading=Level 2 evidence, Strong. No shading with dashed border=Level 3 evidence, Weak.

Timing of initiation and choosing the optimal systemic therapy from a multitude of options requires careful consideration of a multitude of different clinical factors, such as eligibility of chemotherapy, side effect profile of medications, disease burden, symptoms, and presence of visceral metastases. Since treatment may require a multifaceted approach, including upfront docetaxel-based regimens, early assessment of eligibility for chemotherapy is essential. As well, combined opinions from urology, medical oncology, and radiation oncology may be required to provide optimal care for mCNPC/mCSPC patients. Additionally, as mCNPC /mCSPC continues to be an incurable disease, strong consideration should be given to the inclusion of patients in clinical trials.

Figure 1 provides an algorithm for the treatment of mCNPC/CSPC.

CONCLUSIONS

There has been a significant growth of life-extending therapies for patients that has changed the landscape of treatment for mCNPC/mCSPC. All men with mCNPC/mCSPC, regardless of disease volume and whether metastases were de novo or metachronous, should be offered systemic therapy in addition to ADT. For those with low-risk/low-volume disease, prostate radiation therapy should be strongly considered in addition to systemic therapy.

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