Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer

Alan I. So, MD[1]; Kim N. Chi, MD[2]; Brita Danielson, MD[3]; Neil E. Fleshner, MD[4]; Anil Kapoor, MD[5]; Tamim Niazi, MD[6]; Frederic Pouliot, MD[7]; Ricardo A. Rendon, MD[8]; Bobby Shayegan, MD[5]; Srikala Sridhar, MD[9]; Eric Vigneault, MD[10]; Fred Saad, MD[11]

[1]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; [2]Department of Medicine, University of British Columbia, Vancouver, BC, Canada; [3]Department of Oncology, Division of Radiation Oncology, University of Alberta, Edmonton, AB, Canada; [4]Division of Urology, University of Toronto, Toronto, ON, Canada; [5]Division of Urology, McMaster University, Hamilton, ON, Canada; [6]Department of Oncology, Division of Radiation Oncology, McGill University, Montreal QC, Canada; [7]Division of Urology, Department of Surgery, Université Laval, Quebec City, QC, Canada; [8]Department of Urology, Dalhousie University, Halifax, NS, Canada; [9]Division of Hematology and Medical Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada; [10]Department of Radiation Oncology, CHUQ, Université Laval, Quebec City, QC, Canada; [11]Department of Surgery, Université de Montréal, Montreal, QC, Canada

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Introduction

Metastatic prostate cancer remains an incurable disease. In Canada, approximately 8% of men with prostate cancer are diagnosed de novo with metastatic disease and, in 2018, roughly 1200 men were diagnosed with de novo metastatic prostate cancer (PC).[1] The mainstay of treatment for de novo metastatic PC is androgen-deprivation therapy (ADT), which is initially effective in almost all patients. Progression is inevitable, however, 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 de novo metastatic PC have a poor prognosis, with an estimated median overall survival (OS) of approximately 3–4 years.[2] This has only improved slightly, even with the advent of improved management of mCRPC.[2,3] Compared to PC that develops metastases after diagnosis, de novo metastatic PC has been shown to have a worse prognosis.[4,5] Recent practice-changing trials have shed light on new directions to improve survival in men with metastatic castration-naive/castration-sensitive PC (mCNPC/mCSPC), and include both systemic therapies and treatment of the primary cancer.

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

Methods

EmBASE and Medline databases were accessed to identify all relevant articles focused on mCNPC or mCSPC between January 2000 and August 2019 with the following key-word 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.[6] Based on a modified GRADE methodology, the strength of each recommendation is represented by the words "Strong" or "Weak."[6] Wherever Level 1 evidence is lacking, the guideline attempts to provide expert opinion to aid in the management of patients.

Indications for staging in PC

For newly diagnosed PC, staging with computed tomography (CT) scan of the abdomen and pelvis and bone scan (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 PC includes bone scintigraphy using technetium-99mmethylene diphosphonate (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.[7]

Novel diagnostic imaging to stage PC, including choline-based positron emission tomography (PET)/CT, fluciclovine PET/CT, and prostate-specific membrane antigen (PSMA)-targeted PET/CT, appear to improve the sensitivity and specificity of conventional imaging; however, these tests are not universally available Canada, their clinical utility is not clear, 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 conclusion were based on these. Novel imaging remains investigational.

Assessment of prognosis

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

Using data from two large mCNPC/mCSPC trials, SWOG8894 and GETUG15, possible prognostic features suggestive of worse prognosis have been identified and include: appendicular disease (defined as bone lesions in the chest, skull, and/or extremities), worse performance status, PSA >65, Gleason score ≥8, high alkaline phosphatase (ALP), high pain intensity, anemia, and elevated lactate dehydrogenase (LDH).[4,5] Data from SWOG8894 suggests that appendicular disease is the strongest predictor prognosis, whereas GETUG15 suggested, based on univariate analysis, that ALP is the strongest predictor of prognosis.[4,5]

Recent clinical trials of mCNPC/mCSPC patients have used different pragmatic prognostic factors to stratify prognosis. The CHAARTED trial classified PC 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, and "low-volume" was defined as all other mCNPC/mCSPC.[8] 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 having two or more of these criteria, whereas low-risk was defined having less than two.[9] 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.[10]

ADT

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

Continuous ADT is the standard of care for metastatic PC, while intermittent may be considered in select patients.

Androgen receptor signaling plays a key role in the progression of PC 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 PC 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 GnRH antagonists). The optimal timing of androgen deprivation has been the subject of many trials, with two large, recent 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.[11,12] More importantly, the early treatment of mCNPC with ADT is required if other systemic treatments, such as docetaxel or androgen receptor-axis inhibitors, are used.

ADT is associated with increased side effects and may increase the risk of cardiovascular events. 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.[13,14] As well, combined treatment of mCNPC with any systemic therapy requires continuous ADT.

Local therapy: Treatment of the primary cancer in mCNPC

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

Treatment of the primary PC has theoretical benefits, including reducing local side effects that may occur due to disease progression during mCRPC, as well as removing the cancer that could be source of cytokines and growth factors that may induce disease progression.

Two recent, 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 was added that was considered biologically equivalent and consisted of a dose schedule of 57.76 Gy in 19 fractions of 3.04 Gy three times a week for six weeks. The median PSA was 142 ng/ml and 67% of patients had more than five 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 vs. 12 m, 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 impact of EBRT.

The STAMPEDE trial, also known as MRC PR08, is a multi-arm, multi-stage (MAMS), randomized trial recruiting in the U.K. and Switzerland. It aims to evaluate multiple therapeutic strategies in the management of high-risk, locally advanced and mCNPC compared to standard of care (androgen deprivation only). In the EBRT component of the study, the trial randomized 2061 men with mCNPC to either EBRT and ADT or ADT alone.[15] The median PSA was 97 ng/mL; 819 (40%) men had low metastatic burden based on CHAARTED criteria and 1664 (81%) had no pain.[8,15] EBRT was given as 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<0·0001and metastatic burden, interaction p=0.002; high metastatic burden 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 negative impact of EBRT in unselected men in mCNPC, both HORRAD and STAMPEDE reveal the benefits of local therapy in those with low-burden disease. A recent STOPCAP meta-analysis combining data from the trials confirm the benefits of EBRT in men with fewer than five bone metastases.[16] This meta-analysis showed that there was 7% improvement in three-year survival in men with fewer than four bone metastases.

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, the 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 PC and oligometastases to the bone: a randomized, controlled, feasibility trial),[17] SWOG1802 (Standard systemic therapy with or without definitive treatment in treating participants with metastatic PC; https://www.swog.org/clinical-trials/s1802), and G-RAMPP/AUO –AP-75/13 (Impact of radical prostatectomy as primary treatment in patients with PC with limited bone metastases).[18] 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 PC.

Systemic therapies: Chemotherapy, abiraterone acetate, enzalutamide, and apalutamide

Docetaxel (75 mg/m² every three weeks for six cycles) plus ADT is an option for men with mCNPC/mCSPC with good performance status and high-volume metastatic disease, defined as: presence of visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis *(Level 1, Strong recommendation)*.

Docetaxel plus ADT may also be an option in patients with mCNPC/mCSPC with good performance status with low-volume disease *(Level 2, Weak recommendation)*.

"High risk" mCNPC/mCSPC patients (defined as at least two of: Gleason score of 8–10, visceral metastases, and three or more bone metastases) with good performance status can also be considered for docetaxel chemotherapy *(Level 1, Strong recommendation*).

Docetaxel, a taxane derivative that binds to tubulin that inhibits mitosis and tumor proliferation, was the initial chemotherapeutic agent that improved survival in men with mCRPC.[19] Three different, large, randomized trials assessed the impact of introducing docetaxel in mCNPC/mCSPC: CHAARTED, STAMPEDE, and GETUG-AFU 15.[8,20,21] The CHAARTED trial randomized 790 with mCNPC/mCSPC patients to ADT plus docetaxel (75 mg/m² every three weeks for six cycles) or ADT alone.[8] Within this trial, 35% (277 patients) had low-volume metastases and 65% (513 patients) had high-volume metastases (high-volume of metastases was defined by the presence of visceral metastases or four or more 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 vs. 44.0 months; HR 0.61; 95% CI 0.47–0.80; p<0.001). Subgroup analysis showed that OS benefits of combination were maintained in the high-volume mCNPC/mCSPC (n=513; HR 0.63; 95% CI 0.50–0.79; p<0.001), whereas survival benefits were lost in low-volume disease (n=277; HR 1.04; 95% CI 0.70–1.55; p=0.86).[22]

The GETUG-AFU15 trial randomized 385 mCNPC/mCSPC patients to receive ADT plus docetaxel or ADT alone.[21] 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 in the two studies. Although 65% of patients in CHAARTED had high-volume metastases, less than 25% of the patients had low-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 vs. 35.1 months; HR 0.78; 95% CI 0.56–1.09).[23] A recent 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.[24]

The third trial to assess the impact of docetaxel in mCNPC/mCSPC was the docetaxel component of the STAMPEDE trial.[20] Unlike the CHAARTED and GETUG-AFU15 trials, patients with high-risk, non-metastatic PC were included. Eligible patients included: newly diagnosed metastatic, node-positive, or 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). Although patients were not classified having high- or low-volume metastases, only patients with metastatic disease had evidence of benefit with ADT and docetaxel (HR 0.76; 95% CI 0.62–0.92; p=0.005).

A recent post-hoc, non-prespecified analysis of STAMPEDE was published.[25] Metastatic burden was assessable in only 76% of patients for the analysis (830 of 1086 patients) and 362 (44%) had low and 468 (56%) high metastatic burden. Although OS was neither statistically significant in low-burden nor in high-burden disease (HR 0.76; 95% CI 0.54–1.07; p=0.107 vs. HR 0.81; 95% CI 0.64–1.02; p=0.064), the authors found no evidence of heterogeneity of docetaxel effect between metastatic burden subgroups (interaction p=0.827). The authors concluded that upfront docetaxel is considered for mCNPC/mCSPC patients regardless of metastatic burden. This retrospective analysis contradicts the results of CHAARTED, but the authors point out that this may be due to the larger number of de novo mCNPC/mCSPC (n=362) in the low-burden group compared to the low-burden group in the CHAARTED trial (n<160).

A recent meta-analysis of CHAARTED, GETUG-AFU15, and STAMPEDE confirms the benefit of 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%.

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 three or more lesions on bone scan, or presence of measurable visceral metastasis *(Level of evidence 1, Strong recommendation).*

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.[26,27] Two trials, LATITUDE and STAMPEDE, assessed the impact of abiraterone in mCNPC/mCSPC.[9,28,29] In the LATITUDE trial, 1199 patients were randomly assigned to either the abiraterone acetate (1000 mg) plus prednisone (5 mg) once daily orally or matching placebo plus ADT. Eligible patients included mCNPC with at least two of three high-risk features (Gleason score of ≥8, presence of three or more 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.[28] 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 PC 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).[28] The impact of volume tumor burden was not reported.

In a recent, unplanned, post-hoc analysis of 759 evaluable patients with bone metastases in the above STAMPEDE trial, patients were reclassified using CHAARTED "high- or low-volume" criterion or LATITUDE "high- or low-risk" criterion.[30] 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.

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

Enzalutamide should not be used in combination (concurrent use) with docetaxel to treat mCNPC/mCSPC *(Level of evidence 2, Strong recommendation).*

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

Enzalutamide binds to the androgen receptor (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.[31,32] Two recent studies assessed the role of enzalutamide in mCNPC: ARCHES and ENZAMET.[33,34]

The ARCHES trial randomized 1150 mCNPC/mCSPC patients to either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiological 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). Due to the immaturity of the study and the median duration of OS, median OS was not reached in either arm and no survival differences were observed between the two arms. 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. As well, although 35% (405 patients) of men were low-volume based on CHAARTED criteria, benefit in rPFS with enzalutamide-treated patients was seen regardless of volume of disease.

ENZAMET was an open-label clinical trial that randomized 1125men 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. There was an OS benefit in the enzalutamide plus ADT arm compared to NSAA (HR 0.67; 95% CI 0.52–0.86; p=0.002). Kaplan-Meier estimates of OS at three years were 80% in the enzalutamide group and 72% in the NSAA arm. Unlike ARCHES, concurrent use of docetaxel was allowed and the decision to treat with chemotherapy was at the discretion of the investigator. 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). In a subgroup analysis, the benefits of enzalutamide on OS appeared only in the group without planned early docetaxel use (concurrent docetaxel: HR 0.9; 95% CI 0.62–1.31; no concurrent docetaxel: HR 0.8; 95% CI 0.59–1.07). Although the authors state that the study is underpowered and data is too immature to specifically answer whether combination docetaxel and enzalutamide is beneficial in mCNPC/mCSPC, these results demonstrate that this combination should not be used until further evidence is shown for its benefits.

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. As well, 10.7% received previous docetaxel therapy and 37.3% had low-volume disease. With a median of 22.7 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). Benefit with apalutamide in rPFS was seen regardless of prior chemotherapy use or disease burden. OS at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; HR 0.67; 95% CI 0.51–0.89; p=0.005).[35] Benefit with apalutamide in OS was seen regardless of disease burden.

Prevention of osteoporosis

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 total intake 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 PC is increasing and the length of time bone is exposed to the effects of ADT is also increasing. As such, these men are at risk of significant bone loss, osteoporosis, and fragility fractures. Bone loss occurs quickly while on ADT; within one year, men can lose up to 10% of their bone mineral density (BMD).[36-38] Men with mCNPC initiating ADT should have baseline BMD with dual-energy x-ray absorptiometry (DXA), as well as use of fracture risk calculators such as FRAX.[39] 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 total calcium intake of at 800–1000 mg daily, and to make specific lifestyle changes, including smoking cessation, reduction in alcohol and caffeine intake, and increase in weight-bearing exercises. If DXA scanning shows any evidence of osteopenia (T-score of <-1 and > -2.5) or osteoporosis (T-score of less than -2.5), men should be started on 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).[37,38,40] Bone-targeted therapy at these doses are much lower than those to prevent skeletal-related events (SREs) 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 at these lower doses.[41,42]

Treatment of oligo-metastatic disease

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

Currently, there is limited data to provide general recommendations; however, consideration in a multidisciplinary setting would provide the best setting to determine optimal management consideration on a case-by-case basis.

Multidisciplinary consultation

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

Timing of initiation and choosing the optimal systemic therapy from a multitude of options requires careful consideration of several 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, 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 inclusion of patients in clinical trials.

Conclusions

The last five years has seen a significant growth of life-extending therapies for patients that has changed the landscape of treatment for mCNPC/mCSPC. These range from treatment of the primary cancer with EBRT to chemotherapy. All men with mCNPC should be considered for treatments that are combined with ADT; those with high-risk/high-volume disease should be given systemic therapy and those with low-risk/low-volume should be strongly considered for prostate radiation therapy and/or systemic therapy.

Competing interests: Dr. So has been an advisory board member for Abbvie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Chi has received honoraria from Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, AstraZeneca, Bayer, Eli Lilly, Essa, Janssen, Merck, Novartis, Pfizer, Roche, and Sanofi. Dr. Danielson has received advisory board honoraria and speaker fees from Amgen, Astellas, Bayer, and Janssen. Dr. Fleshner has been a consultant or advisory board member for Abbvie, Amgen, Astellas, Bayer, Ferring, Hybridyne Health, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bavarian Nordic, Bayer, Ferring, Janssen, Medivalion, Nucleix, Progenics Pharmaceutical, Sanofi, and Spectracure AB. Dr. Kapoor has been an advisory board member for BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche; a speakers' bureau member for Eisai, Ipsen, Novartis, and Roche; and has received grants/honoraria from BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche. Dr. Niazi has received research grants and honoraria from Abbvie, Amgen, Astellas, Astra Zeneca, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Ferring, Janssen, and Sanofi. Dr. Pouliot has been an advisory board member for Amgen, Astellas, Bayer, and Janssen; has received payment from Abbott, Amgen, Astellas, Astra Zeneca, Bayer, Ferring, Janssen, and Sanofi; has received grants from Astra Zeneca and Sanofi; and has participated in clinical trials supported by Astellas, Bayer, Ferring, and Janssen. Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from Abbvie, Amgen, Astellas, Astra Zeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Shayegan has been an advisory board member for Astellas, Bayer, and Janssen; and has received a research grant from Janssen. Dr. Sridhar has been an advisory board member for Astellas, AstraZeneca, Bayer, Janssen, Merck, and Roche; and has participated in several pharma-supported clinical trials. Dr. Vigneault has been an advisory board member for Abbvie, Bayer, Ferring, and Sanofi. Dr. Saad has been an advisory board member for and has received payment/honoraria from Abbvie, Amgen, Astellas, Bayer, Janssen, and Sanofi; and has participated in clinical trials supported by Amgen, Astellas, Bayer, Janssen, and Sanofi.

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Correspondence: Dr. Alan So, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; alan.so@ubc.ca