Management algorithms for prostate-specific antigen progression in prostate cancer: Biochemical recurrence after definitive therapy and progression to non-metastatic castrate-resistant prostate cancer

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Abstract

Introduction: Current prostate cancer (PCa) guidelines primarily focus on localized or metastatic PCa. A multidisciplinary genitourinary oncology panel determined that additional guidance focusing on monitoring and management of biochemical recurrence (BCR) following radical therapy and non-metastatic castration-resistant prostate cancer (nmCRPC) was warranted.

Methods: The most up-to-date national and international guidelines, consensus statements, and emerging phase 3 trials were identified and used to inform development of algorithms by a multidisciplinary genitourinary oncology panel outlining optimal monitoring and treatment for patients with non-metastatic PCa.

Results: A total of eight major national and international guidelines/consensus statements published since 2015 and three phase 3 trials were identified. Working group discussions among the multidisciplinary genitourinary oncology panel led to the development of two algorithms: the first addressing management of patients with BCR following radical therapy (post-BCR), and the second addressing management of nmCRPC. The post-BCR algorithm suggests consideration of early salvage treatment in select patients and provides guidance regarding observation vs. intermittent or continuous androgen-deprivation therapy (ADT). The nmCRPC algorithm suggests continued ADT and monitoring for all patients, with consideration of treatment with apalutamide or enzalutamide for patients with high-risk disease (prostate-specific antigen [PSA] doubling time of ≤10 months).

Conclusions: Two treatment algorithms have been developed to guide the management of non-metastatic PCa and should be considered in the context of local guidelines and practice patterns.

Introduction

Prostate cancer (PCa) is the most common cancer diagnosis in Canadian men, with an estimated 21 300 new cases in 2017.[1] Following radical prostatectomy (RP) and/or radiation therapy (RT), up to 27–53% will experience a biochemical recurrence (BCR),[2,3] defined as prostate-specific antigen (PSA) >0.2 ng/ml following RP, or a PSA nadir +2 ng/ml after RT.[3-7] Many of these patients will then progress to non-metastatic castration-resistant prostate cancer (nmCRPC), defined as no visible metastases on conventional imaging and a rising PSA despite a castrate testosterone level. This is sometimes also referred to as m0CRPC.

Although national and international guidelines and consensus statements provide guidance on the management of PCa, recommendations are predominantly focused on localized or metastatic disease,[3,4,8-13] with less in-depth consideration of monitoring and management of post-BCR and nmCRPC patients.[3,4,6,7,14] Standard therapies after BCR include local salvage therapy, androgen-deprivation therapy (ADT) and observation[3,4,15] and, until recently, treatment for nmCRPC consisted of continued ADT, secondary hormonal manipulations, observation and monitoring, or clinical trials.[3,4,6,14,16] With the advent of new systemic therapies for nmCRPC,[17,18] more detailed guidance on optimal treatment for patients with BCR after radical therapy and progression to nmCRPC is warranted.

A group of Canadian multidisciplinary genitourinary specialists identified a significant gap in guidance regarding the management of BCR and subsequent nmCRPC. They, therefore, set out to develop practical algorithms for these disease states, informed by the most recent phase 3 data, national and international guidance, and Canadian multidisciplinary clinical expert opinion.

Methods

Algorithm development

The panel comprised five uro-oncologists, three radiation oncologists, two medical oncologists, and three medical advisors from Janssen, and had pan-Canadian representation. The group held iterative discussions regarding the management of patients with BCR after radical therapy and nmCRPC. Algorithms outlining monitoring and treatment sequencing were drafted and further refined through review of national and international guidelines, consensus statements, and emerging phase 3 data (see *Literature search* below).

Literature search

Guidelines and consensus statements were leveraged to identify current guidance on the management of non-metastatic PCa. PubMed, Google Scholar, and web-based searches were carried out for Canadian, North American, and European guidelines or consensus statements drafted or updated from January 2015 to March 26, 2018. Articles of interest were identified using the search strings prostate cancer AND (guideline OR consensus OR recommendations) AND (biochemical recurrence OR biochemical failure OR castrate-resistant).

As existing guidelines were current to March 2018 (National Comprehensive Cancer Network [NCCN] 2018 v2; data cutoff February 2018),[4] a supplementary search for new data was performed. PubMed and the American Society of Clinical Oncology Genitourinary (ASCO GU) sites were searched for reports of original phase 3 trials on management of BCR after local radical therapy and non-metastatic PCa published or presented from January 2018 to April 5, 2018, using the following keywords: prostate cancer AND biochemical recurrence OR castrate-resistant (OR respective aliases). Search results were screened at the abstract level and studies of interest were confirmed at full-text.

Results

Literature search findings and algorithm development

Two pan-Canadian guidelines or consensus statements[14,15] and six guidelines or consensus statements from major North-American and/or European organizations or groups[3,4,6,7,12,16] published since 2015 were identified (Table 1), along with one new monitoring study for BCR after radical therapy,[19] and two studies on new treatments for nmCRPC (Table 1).[17,18] Canadian provincial guidelines,[8-10] European single-nation[11,20-22] and specialty PCa guidelines[23] were excluded. The iterative group discussion process and review of national and international guidance led to the development of two algorithms: the first addressing monitoring and management of patients post-BCR (Fig. 1), and the second addressing management of nmCRPC (Fig. 2).

Table 1. Guidelines, consensus-based guidance, and original research considered in development of the algorithms

Guidelines and consensus statements	Year	Region
Testosterone suppression Canadian consensus statement	2018	Canadian
NCCN prostate cancer guidelines	2018	American
EAU-ESTRO-ESUR-SIOG guidelines on prostate cancer	2018	European
Advanced Prostate Cancer Consensus Conference (APCCC)	2017	International
ASCO CRPC provisional clinical opinion	2017	American
CUA-CUOG CRPC guidelines	2015	Canadian
ESMO clinical practice guidelines on prostate cancer	2015	European
AUA CRPC guidelines	2015	American
Original research on treatment for nmCRPC		**Year**
FALCON (Role of ^{18}F-fluciclovine PET/CT)	2018	
SPARTAN (apalutamide)	2018	
PROSPER (enzalutamide)	2018	

ASCO: American Society of Clinical Oncology; AUA: American Urological Association; CUA-CUOG: Canadian Urological Association-Canadian Urologic Oncology Group; CRPC: castration-resistant prostate cancer; EAU-ESTRO-ESUR-SIOG: European Association of Urology-European Society for Radiotherapy & Oncology- European Society of Urogenital Radiology-International Society of Geriatric Oncology; FALCON: Fluciclovine (18F) PET/CT in biochemicAL reCurrence Of Prostate caNcer; NCCN: National Comprehensive Cancer Network; PET/CT: positron emission tomography/computed tomography; PROSPER: Safety and Efficacy Study of Enzalutamide in Patients With Non-metastatic Castration-Resistant Prostate Cancer; SPARTAN: A Study of Apalutamide (ARN-509) in Men With Non-Metastatic Castration-Resistant Prostate Cancer.

Monitoring and treatment after BCR but before progression to nmCRPC

Definitions of BCR and local salvage treatment options depend on the type of therapy received for localized disease. Following RT, BCR is defined as PSA level of 2 ng/ml or more above the PSA nadir achieved following therapy (PSA nadir +2 ng/ml) (Fig. 1).[3-5] The definition of BCR in patients after RP is PSA >0.2 ng/ml (Fig. 1).[3,4,6,7]

Post-RT salvage therapy

European Association of Urology (EAU) guidelines recommend local salvage therapy after RT via surgery (i.e., salvage RP), while NCCN recommendations include surgery, brachytherapy, or cryotherapy in patients with limited initial disease (T1–T2), a PSA <10 ng/ml, localized disease (NX–N0), and a reasonable life expectancy (>10 years).[3,4] To ensure the earliest possible referral, the panel suggests a PSA threshold <5 ng/ml and biopsy-proven local recurrence.[3,4]

Post-RP salvage therapy

It is beneficial to initiate salvage therapy early, when pre-treatment PSA is low.[3,4,12] EAU, NCCN, and the European

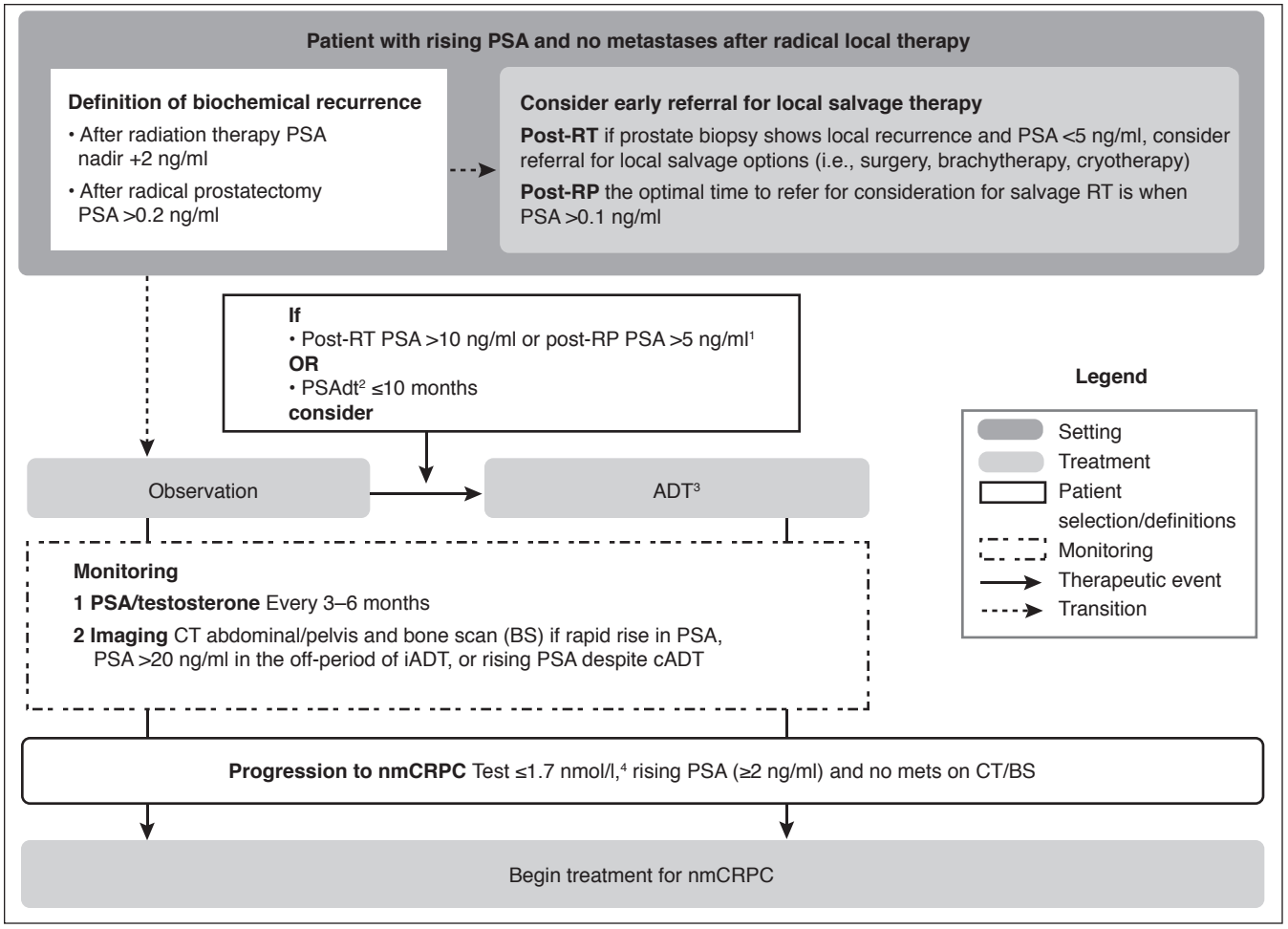

Fig. 1. Management algorithm for prostate cancer patients with a biochemical recurrence after radical local therapy. This algorithm does not address other aspects of care such as bone health and cardiovascular health. [1]Clinicians should consider a lower PSA threshold when there is no prostate in situ. [2]PSA doubling time can be easily calculated using an online calculator: https://www.mskcc.org/nomograms/prostate/psa_doubling_time. [3]If iADT and PSA nadir ≥1 ng/ml or off-treatment interval <10 months, consider switching to cADT; clinicians should also consider switching from iADT to cADT if patients do not achieve a PSA nadir of at least 1 ng/ml after six months of iADT.[50] [4]Lower testosterone levels (testosterone ≤0.7 nmol/L) have been associated with improved outcomes; secondary hormonal manipulations (switch ADT or add AA) may be considered if testosterone is >0.7 nmol/L.[15] AA: antiandrogen; (c/i)ADT: (continuous/intermittent) androgen-deprivation therapy; BS: bone scan; CRPC: castration-resistant prostate cancer; CT: computed tomography; dt: doubling time; mets: metastases; nm: non-metastatic; PSA: prostate-specific antigen; pts: patients; RP: radical prostatectomy; RT: radiation therapy; test: testosterone.

Society for Medical Oncology (ESMO) guidelines recommend initiation of salvage RT when PSA becomes detectable (<0.5 ng/ml),[3,4,12] up to a PSA limit of 2 ng/ml (25% agreement, Advanced Prostate Cancer Consensus Conference [APCCC]).[7] Similarly, to ensure the earliest possible referral, the panel suggests consideration of salvage therapy when PSA becomes detectable >0.1 ng/ml (Fig. 1).[3]

Imaging prior to salvage therapy

When a patient experiences a BCR after radical local therapy and salvage therapy is being considered, standard imaging, including computed tomography (CT) of the abdomen and pelvis and a bone scan (BS) are recommended to rule out metastatic disease. Use of magnetic resonance imaging (MRI) may also be indicated if local recurrence after prostatectomy is suspected and salvage therapy is being considered. Novel imaging modalities currently being evaluated, such as ^{18}F-fluciclovine positron emission tomography/computed tomography (PET/CT) and prostate-specific membrane antigen-positron emission tomography (PSMA-PET), may be helpful in staging patients to guide consideration of salvage therapy.[19,24,25]

Other treatment and monitoring options for BCR

Observation and ADT are appropriate management options for patients with BCR who do not undergo salvage therapy, or who experience a BCR despite salvage therapy (Fig. 1). In order to appropriately tailor treatment, the panel suggests regular monitoring consisting of PSA and testosterone every 3–6 months,[3,4,15] and imaging via CT and BS when PSA rises

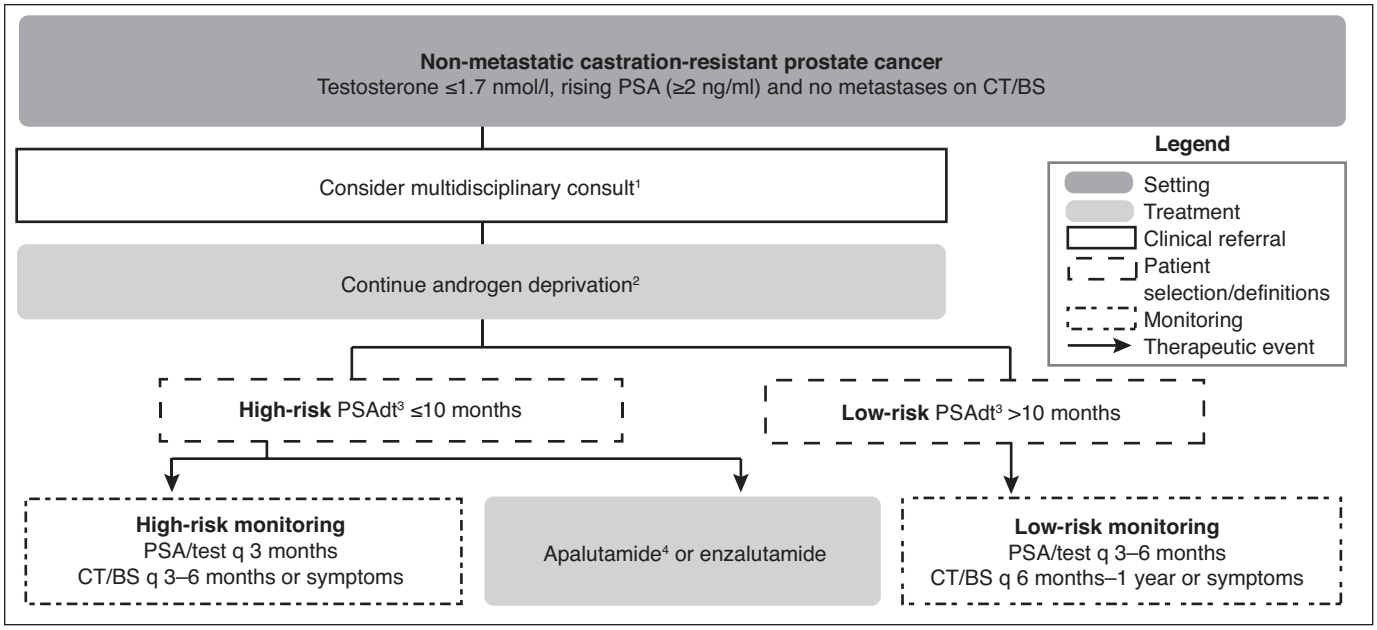

Fig. 2. Management algorithm for nmCRPC. This algorithm does not address other aspects of care such as bone health and cardiovascular health. [1]An individualized approach to treatment selection should take into consideration the pros and cons of therapy, as well as patient characteristics and preference. [2]There is emergent evidence for the benefit of local therapy in select nmCRPC patients. [3]PSA doubling time can be easily calculated using an online calculator: https://www.mskcc.org/nomograms/prostate/psa_doubling_time. [4]Health Canada has approved apalutamide and enzalutamide; both treatments have shown a statistically significant improvement in the primary endpoint of metastasis-free survival in phase 3 trials; overall survival data is not yet mature. AA: anti-androgen; (c/i)ADT: (continuous/intermittent) androgen-deprivation therapy; BS: bone scan; CRPC: castration-resistant prostate cancer; CT: computed tomography; dt: doubling time; mets: metastases; nm: non-metastatic; PSA: prostate-specific antigen; pts: patients; RP: radical prostatectomy; RT: radiation therapy; test: testosterone.

rapidly[3,4,7] or if PSA is >20 ng/ml in the off-treatment period of intermittent ADT (iADT). CT and BS should also be considered if PSA is rising (>2 ng/ml) despite castrate levels of testosterone, or if a patient is symptomatic.

Both NCCN and EAU guidelines recommend observation in men with prolonged (>12 months) PSA doubling time (PSAdt).[3,4] The panel suggests observation with lower PSA levels (<10 ng/ml after RT; <5 ng/ml after RP) and longer PSAdt (>10 months) (Fig. 1). Guidance related to administration of ADT, either intermittent or continuous, is limited in guidelines and consensus statements. The panel suggests use of iADT[3,4,7] when PSA thresholds are reached (RT >10 ng/ml or RP >5 ng/ml, or with PSAdt ≤10 months) (Fig. 1). Although most patients respond to initial iADT,[26,27] switching to continuous ADT (cADT) is suggested if the PSA nadir is ≥1 ng/ml after six months of iADT or if the iADT off-treatment interval is <10 months (Fig. 1). Achieving lower testosterone levels (≤0.7 nmol/l) has been associated with improved outcomes; therefore, secondary hormonal manipulations may also be considered to maintain optimal castrate levels, especially if PSA does not reach a nadir of <1 ng/ml.[15]

Progression to nmCRPC

Progression to CRPC is defined as a rising PSA despite a testosterone level of ≤1.7 nmol/l.[3,4,14] Management of CRPC varies depending on the presence or absence of metastases; suggested treatment for patients with nmCRPC, confirmed via CT/BS, is summarized in Fig. 2.[3,4,6,7,14,15] Treatment for patients with metastatic CRPC will be discussed in a subsequent publication.

Monitoring and treatment of nmCRPC

With progression to nmCRPC, discussion of treatment options, including clinical trial eligibility, should be conducted within the context of a multidisciplinary consultation.[3,4,6,12,14] Testosterone should be monitored to ensure castrate levels.[3,4,15] Guidelines and consensus recommendations for monitoring PSA and testosterone while on ADT vary from every 3–6 months for those with low-risk disease and slow PSAdt and/or good prior response to ADT, to more intensive schedules for those with a rapidly rising PSA.[3,4,16] The panel suggests distinct monitoring schedules based on disease risk (Fig. 2).[4,7,16-18] For high-risk disease, characterized by a PSAdt of ≤10 months or a PSA level >8 ng/ml,[28-30] PSA and testosterone should be assayed every three months,[3,4,7,15,16] with CT and BS every 3–6 months or when symptomatic (Fig. 2).[3,4,7,12,14] For low-risk disease, defined as PSAdt of >10 months, PSA and testosterone should be assayed every 3–6 months[3,4,7,15,16] with CT and BS every six months to one year, or when symptomatic (Fig. 2).[3,4,7,12,14]

Due to a historical lack of treatment options for nmCRPC, most guidelines published prior to 2018 recommend con-

tinued ADT and monitoring with observation for both high-risk and low-risk disease.[3,4,12,14] Based on recent data from phase 3 trials and the latest NCCN guidelines,[4] the panel recommends consideration of the emerging therapies for high-risk disease (i.e., apalutamide and enzalutamide).[17,18] The recent placebo-controlled SPARTAN[18] and PROSPER[17] trials demonstrated that addition of each drug to ADT significantly improved the primary endpoint of metastasis-free survival in patients with PSAdt of ≤10 months. Apalutamide prolonged the metastasis-free interval by 24.3 months compared to placebo (40.5 vs. 16.2 months, hazard ratio [HR] 0.28; 95% confidence interval [CI] 0.23–0.35; p<0.001),[18] while enzalutamide extended the interval by 21.9 months (36.6 vs. 14.7 months; HR 0.29; 95% CI 0.24–0.35; p<0.001).[17] Although not statistically significant, a trend toward improved overall survival compared to placebo was apparent for both apalutamide (median followup of 20.3 months; not reached [NR] vs. 39.0 months; HR 0.70; 95% CI 0.47–1.04; p=0.07) and enzalutamide (median followup of 18.5 months and 15.1 months for enzalutamide and placebo, respectively; NR vs. NR; HR 0.80; 95% CI 0.58–1.09; p=0.15).[17,18]

Addition of either apalutamide or enzalutamide to ADT led to an increase in adverse events compared to placebo.[17,18] The rate of treatment discontinuation due to toxicity for apalutamide was 10.6% compared to 7.0% for placebo. There were higher rates of grade 3/4 rash (5.2% vs. 0.3%) and fracture (2.7% vs. 0.8%) for apalutamide vs. placebo.[18] Rates of adverse events leading to treatment discontinuation were 9% for enzalutamide compared with 6% for placebo. There were higher rates of grade 3/4 hypertension (5% vs. 2%) and major adverse cardiovascular events (4% vs. 2%) with enzalutamide vs. placebo.[17] Both drugs were well-tolerated overall,[17,18,31] and the safety profile of enzalutamide was consistent with prior trials in the metastatic CRPC setting.[32-35]

Discussion

Strengths and limitations

The treatment algorithms for patients post-BCR (Fig. 1) and for nmCRPC (Fig. 2) represent practical and easy-to-follow tools to guide the management of non-metastatic PCa. Although streamlined and helpful in guiding decision-making, especially among community clinicians, the algorithms have limitations. Inspired by current guidance, the algorithms reflect clinical opinion and consideration of recent evidence, but do not represent all available treatment options or the sum of all available evidence. Therefore, they should not be considered definitive or replacements for evidence-based clinical guidelines or consensus statements, but rather used to foster multidisciplinary discussions of treatment options, including clinical trial enrolment, in light of individual disease characteristics and history, as well as patient preferences.

Considerations for emerging therapies

Historically, there has been a clinical need for effective therapeutic options for patients with nmCRPC. Recent data from the SPARTAN and PROSPER trials of apalutamide and enzalutamide, respectively, demonstrated that treatment prolonged metastasis-free survival in this setting without detriment to overall quality of life.[17,18] However, careful consideration should be given to use of these agents, as they involve increased side effects and high costs, as well as a prolonged treatment duration. It also remains unclear whether the metastasis-free survival benefits will translate into improved overall survival.

PSAdt calculation

The importance of accurate PSAdt calculation was highlighted in the SPARTAN and PROSPER trials,[17,18] which required a PSAdt <10 months for eligibility. PSAdt calculation was performed using an online computation tool.[36] For both trials, the median PSAdt was <6 months,[17,18] and the majority of screening failures in the SPARTAN trial were due to the presence of metastatic disease,[18] suggesting that early and accurate PSAdt assessments are important in treatment selection. Assessments should begin when PSA starts to rise and should include at least three PSA values, with at least one value >2 ng/ml.

Role of novel imaging modalities

The limitations in sensitivity and specificity of conventional imaging, including CT and BS, in detection of PCa metastases are well-recognized.[37,38] Incorporation of more sensitive PCa-specific radiotracers, including ^{18}F-fluciclovine, ^{11}C-choline, and ^{68}Ga-PSMA, can improve early detection of recurrence, even at low PSA levels.[24,25,39-41] Randomized trials are currently evaluating the role of PET scans in this patient population.[42-45] Evidence now indicates a role for novel imaging in the management of local disease.[19] The FALCON study, a prospective phase 3 trial of 85 patients post-BCR, demonstrated that ^{18}F-fluciclovine PET/CT has substantial impact on clinical decisions, as 61.2% had a change in management strategy post-scan,[19] while another prospective study of 188 patients post-BCR demonstrated that ^{68}Ga-PSMA PET/CT detected tumor relapse in 165 patients (87.8%), with a high level of sensitivity (98.8%), specificity (100%), and accuracy (98.8%).[24] Although conventional imaging via CT and BS remains standard practice in detecting metastatic disease, use

of novel imaging modalities may be considered as they gain approval for use in Canada. In the nmCRPC setting, the phase 3 SPARTAN and the PROSPER trials established a benefit for apalutamide and enzalutamide, respectively, based on conventional imaging.[17,18] It remains unclear how management recommendations will change, as newer imaging modalities detect metastatic disease in patients previously thought to have nmCRPC.

Patient-centered care, access to treatment, and clinical trials

Additional considerations in optimizing care for non-metastatic PCa include ensuring equitable access to treatment, providing patient-centered and multidisciplinary care, and considering clinical trial participation at each treatment juncture. Management of PCa is complex and involves multiple clinical specialties, many treatment options, and may involve travel to multiple centers. This may be daunting for some patients, placing them at higher risk for experiencing disparities in care.[46] Care plans should, therefore, include psychological and emotional support, facilitated access to treatment, and patient-centered decision-making whenever possible.[46,47] Clinical trials play a critical role in improving PCa care and may represent important treatment options for patients, especially when access to emerging therapies is limited. Discussion of clinical trial options and dedicated efforts to remove demographic, socioeconomic, and attitudinal factors that may hinder enrolment[48,49] is an important part of optimal PCa management.

Summary

The PCa treatment landscape is continually evolving and presents an ongoing challenge for clinicians to consider and incorporate the latest systemic therapies and monitoring techniques. Management algorithms are practical and easy-to-use tools that can help streamline practice and inform multidisciplinary management, leading to improved standards of care for non-metastatic PCa.

Competing interests: Dr. Danielson has received advisory board honoraria and speaker fees from Amgen, Astellas, Bayer, and Janssen. 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. 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. Morgan has been an advisory board member for and received honoraria from Astellas, Bayer, and Janssen; and has participated in clinical trials supported by Janssen. Dr. Malone has been an advisory board member for and received honoraria from Astellas, Janssen, and Sanofi. Ms. Park-Wyllie and Mr. Zardan are employees of Janssen. Dr. Shayegan has been an advisory board member for Astellas, Bayer, and Janssen; and has received a research grant from Janssen.

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