



REVIEW ARTICLE

Optimizing the role of androgen deprivation therapy in advanced prostate cancer: Challenges beyond the guidelines

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Abstract

Background: For specific clinical indications, androgen deprivation therapy (ADT) will induce disease prostate cancer (PC) regression, relieve symptoms and prolong survival; however, ADT has a well-described range of side effects, which may have a detrimental effect on the patient's quality of life, necessitating additional interventions or changes in PC treatment. The risk-benefit analysis for initiating ADT in PC patients throughout the PC disease continuum warrants review.

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Methods: A 14-member panel comprised of urologic and medical oncologists were chosen for an expert review panel, to provide guidance on a more judicious use of ADT in advanced PC patients. Panel members were chosen based upon their academic and community experience and expertise in the management of PC patients. Four academic members of the panel served as group leaders; the remaining eight panel members were from Large Urology Group Practice Association practices with proven experience in leading their advanced PC clinics. The panel members were assigned to four separate working groups, and were tasked with addressing the role of ADT in specific PC settings.

Results: This article describes the practical recommendations of an expert panel for the use of ADT throughout the PC disease continuum, as well as an algorithm summarizing the key recommendations. The target for this publication is all providers (urologists, medical oncologists, radiation oncologists, or advanced practice providers) who evaluate and manage advanced PC patients, regardless of their practice setting.

Conclusion: The panel has provided recommendations for monitoring PC patients while on ADT, recognizing that PC patients will progress despite testosterone suppression and, therefore, early identification of conversion from castrate-sensitive to castration resistance is critical. Also, the requirement to both identify and mitigate side effects of ADT as well as the importance of quality of life maintenance are essential to the optimization of patient care, especially as more combinatorial therapeutic strategies with ADT continue to emerge.

KEYWORDS

androgen deprivation therapy, cancer, consensus, prostate

1 | INTRODUCTION

Since the seminal work by Huggins and Hodges¹ establishing that prostate cancer (PC) is an endocrine-responsive disease, PC patients—those with locally advanced, recurrent, and metastatic disease—may receive treatment with androgen deprivation therapy (ADT).^{1,2} Castration can be administered surgically (bilateral orchiectomy) or medically (administration of a gonadotropin-releasing hormone agonist or antagonist). For specific clinical indications, ADT will induce disease PC regression, relieve symptoms and prolong survival; however, ADT has a well-described range of side effects, including but not limited to, hot flashes, fatigue, depression, sarcopenia, increased visceral and abdominal fat mass, weight gain, increased cholesterol and triglycerides levels, insulin resistance, and loss of bone mineral density with an increased risk of fracture. Any of these side effects may have a detrimental effect on the patient's quality of life, necessitating additional interventions or changes in PC treatment.³ ADT is often used to manage biochemical recurrence (BCR) or rising levels of prostate-specific antigen (PSA) after failed primary therapy, despite a paucity of evidence to demonstrate a survival benefit in this clinical setting. Therefore, despite the known risk of ADT side effects, the risk-benefit analysis for initiating ADT in PC patients throughout the PC disease continuum warrants review.

Guidelines for the management of PC have been systematically reviewed and published by many associations, including the National

Comprehensive Cancer Network (NCCN), the American Urological Association (AUA), and the European Association of Urology (EAU). All have evaluated and delineated recommendations for the foundational role of ADT in the management of advanced PC. However, in clinical practice the decision to use ADT is highly variable.

To address the gaps in ADT recommendations, the Large Urology Group Practice Association (LUGPA) organized an expert panel to develop evidence-based recommendations for the use of ADT throughout the PC disease continuum, with applicability for community urologists, medical oncologists, and radiation oncologists who manage advanced PC patients. The goal of this panel was to provide guidance on a more judicious use of ADT in advanced PC patients, maximizing the benefit-to-risk ratio. The initiative was sponsored by an unrestricted grant from Tolmar Pharmaceuticals.

Importantly, the panel's recommendations were derived from a review of clinical trial data, publications, national guidelines, and expert opinion. The clinical trials, in particular, had varying entry criteria or outcomes, so many of the panel's recommendations should be prefaced by the assumption of "generally speaking," that is, patient-specific factors will also affect treatment decisions and thus may make the general recommendation suggested by the panel not applicable for a specific patient. Also, the authors recognize the importance of ongoing and future clinical trials and therefore recommend, whenever possible, encouraging patient enrollment in randomized, controlled trials, which are needed to further clarify when evidence-based data are lacking.

TABLE 1 Panel members, by state and specialty

Name	Title/institution	State	Specialty
David M. Albala	Physician—Associated Medical Professionals; Chief of Urology—Crouse Hospital	New York	Urology
Emmanuel S. Antonarakis	Professor of Oncology and Urology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Maryland	Medical oncology
Gordon A. Brown	Medical Director of Advance Therapeutics Clinical Associate; Professor of Urology, Rowan-School of Medicine; Director of Robotic Surgery Jefferson Health New Jersey	New Jersey	Urologic oncology
Raoul Concepcion	Urology Chief Clinical Officer, Integra Connect, West Palm Beach	Florida	Urology
Michael S. Cookson	Professor and Chairman, Department of Urology University of Oklahoma Stephenson Cancer Center	Oklahoma	Urologic oncology
E. D. Crawford	Clinical Professor of Urology	California	Urologic oncology
Jason Hafron	Associate Professor of Urology, Willam Beaumont School of Medicine, Oakland University, Director of Robotic Surgery Beaumont Health, Royal Oak, MI, Director of Clinical Research	Michigan	Urologic oncology
Richard Harris	CEO and President, Uropartners	Illinois	Urology
Jonathan Henderson	President, Chief Executive Officer, Regional Urology, LLC	Louisiana	Urology
Benjamin Lowentritt	Medical Director, Comprehensive Prostate Cancer Program at Chesapeake Urology Associates	Maryland	Urology
Alicia K. Morgans	Associate Professor of Medicine, Northwestern University, Robert H. Lurie Comprehensive Cancer Center	Illinois	Medical oncology
Daniel Saltzstein	Medical Director of Research at Urology San Antonio	Texas	Urology
Neal D. Shore	Carolina Urologic Research Center, Atlantic Urology Clinics, Myrtle Beach	South Carolina	Urology
Jeffrey M. Spier	Managing Partner, Rio Grande Urology, El Paso	Texas	Urology

2 | MATERIALS AND METHODS

A 14-member panel comprised of urologists, urologic oncologists, and medical oncologists were chosen based on their experience and expertise in the management of PC patients. Four members of the panel served as group leaders; they were selected from academic institutions, and the remaining eight panel members were from LUGPA practices with experience in advanced PC clinics (Table 1).

The panel members were assigned to four separate working groups, and were tasked with addressing the role of ADT in specific PC settings:

1. Primary ADT in newly diagnosed disease.
2. Neoadjuvant ADT before radical prostatectomy (RP) or radiation therapy (RT).
3. ADT as salvage therapy.
4. ADT for BCR postdefinitive therapy.
5. ADT for castrate-sensitive prostate cancer (CSPC) and castrate-resistant prostate cancer (CRPC).
6. The management of ADT adverse events (AEs) and prevention strategies.

The subdivided working groups performed a literature review and then presented the published data for their assigned topics,

which involved further discussion by the entire 14-member panel. The 1-day conference (Atlanta, GA; 23 September 2018) included presentations, debates among all participants, and voting on the key recommendations listed by each working group. The recommendations were voted upon and were tabulated as yes, no, or “indefinite,” defined if a panelist felt unable to vote clearly for or against the recommendation as it was stated. Consensus was defined as ≥ 10 of the 14 panelists ($\geq 71\%$) voting in the affirmative. All panelists have contributed to the review, analysis, and editing of the document and have also approved the final consensus document.

3 | RESULTS

Detailed voting results are shown in Table 2. An algorithm summarizing the key recommendations from the panel is shown in Figure 1.

3.1 | The role of ADT as primary therapy for localized PC

The panel members agreed that there is not sufficient evidence to support the use of primary ADT (ie, in the absence of prostatectomy

TABLE 2 Recommendations and voting results

	Yes		No		Indeterminate	
	No./14	%	No./14	%	No./14	%
1. ADT as primary therapy for localized PC						
Is there a role for ADT alone as primary therapy for patients with newly diagnosed, localized, asymptomatic PC?	1	7	13	93	0	0
2. ADT as neoadjuvant and adjuvant therapy to RP						
Is there a role for neoadjuvant ADT with RP for <u>low- to intermediate-risk</u> patients?	0	0	13	93	1	7
Is there a role for neoadjuvant ADT with RP for <u>high-risk</u> patients?	1	7	10	71	3	22
Is there a role for adjuvant ADT following RP (N1, +/- EBR)?	14	100				
Is there a role for adjuvant ADT following RP (N0, but other high-risk features, absence of radiation)?	0	0	12	86	2	14
Is there a role for ADT with radiation therapy?	14	100				
Low-risk patients (except for reduction of volume)			14	100		
Intermediate-risk patients (4-6 months duration)	14	100				
High-risk patients (18-36 months duration)	14	100				
Timing: 1-2 months before RT	14	100				
For intermediate- and high-risk PC patients, pending RT and ADT, we recommend ADT initiation ideally 1-2 months before initiating RT	14	100				
Given the natural history of PC (ie, about 1/3 of patients will go on to progress), the majority of patients with BCR should undergo observation with BCR. For the remaining patients (high risk), ADT would generally be considered for:	14	100				
• Early recurrence (BCR <3), AND						
• High-risk features (PSADT ≤9 months OR Gleason score ≥8)						
ADT in BCR is generally not recommended in patients with:	14	100				
• Low-risk features (PSADT >15 months), AND						
• Gleason score ≤7, OR						
• Limited life expectancy, or low risk of metastases, or poor performance status						
When considering ADT in high-risk patients with BCR post-RP, post-RT, or postsalvage after RP, intermittent ADT is a reasonable alternative to continuous ADT	12	86			2	14
Proposed Intermittent Treatment Pathway (Figure 1)	13	93			1	7
There is level 1 evidence to support ADT use with salvage radiotherapy. It is reasonable to consider ADT in the setting of salvage radiotherapy as part of a shared decision-making discussion. The duration of ADT in this setting is unclear, but 6-12 months of ADT would be reasonable	12	86	1	7	1	7
3. ADT for M1 HSPC and M1 CRPC						
In men with asymptomatic oligometastatic mCSPC (without visceral metastases), metastasis-directed therapy may be a reasonable alternative to immediate ADT in select patients	7	50	4	29	3	21
In mCSPC, continuous ADT is generally strongly preferred over intermittent ADT, however in certain circumstances (eg, cardiovascular comorbidities, intolerabilities, etc), intermittent may be considered	13	93			1	7
In mCSPC, there are 3 options to achieve castration: bilateral orchiectomy, LHRH agonists, or LHRH antagonists	13	93			1	7
CAB (ie, LHRHa, LHRHantag, +1st- or 2nd-generation antiandrogen) is superior to castration alone	9	64	5	36		
In mCSPC, baseline T levels should be obtained before starting ADT	14	100				
For ADT administration, testosterone level should be T < 20 ng/dL. Confirm castrate T levels 1-4 months after surgical/medical castration, regardless of PSA levels. If PSA rises, T levels must be checked. If T levels are >20 ng/dL, clinicians should check luteinizing hormone levels to differentiate whether ADT was administered effectively	14	100				
In mCSPC, if T > 20 ng/dL despite low luteinizing hormone levels, consider switching to an alternative agent	14	100				
In the broad mCSPC population, ADT + Abi is superior to ADT alone in terms of OS	14	100				

TABLE 2 (Continued)

	Yes		No		Indeterminate	
	No./14	%	No./14	%	No./14	%
In mCSPC, the distinction between low- and high-volume disease has not been studied in this context. Thus, ADT + Abi is a reasonable standard of care irrespective of metastatic burden	12	86			2	14
In the broad mCSPC population, ADT + docetaxel is superior to ADT alone in terms of OS	14	100				
<ul style="list-style-type: none"> • In high-volume mCSPC, there is an unequivocal OS benefit to ADT + docetaxel vs ADT alone • In low-volume mCSPC, there no clear OS benefit to ADT + docetaxel vs ADT alone • Docetaxel treatment can start 6-16 wk after ADT, to avoid toxicities 						
In low-volume mCSPC, there is evidence that ADT + docetaxel does not provide an OS benefit; thus, ADT + Abi is the favored choice	13	93	1	93		
In high-volume mCSPC, there is strong evidence of benefit for ADT + docetaxel. Thus, both ADT + abiraterone or ADT + docetaxel are treatment options	14	100				
The panel cannot comment on the comparative efficacy of ADT + Abi in low- vs high-volume mCSPC, because this has not been studied	14	100				
mCRPC is defined as:	14	100				
mPC (by conventional radiology)						
Testosterone level <50 ng/dL						
Progressive disease (<i>one or more of</i>):						
<ul style="list-style-type: none"> • PSA progression (2 rises above a nadir, ≥ 4 weeks apart) • Radiographic progression (as defined by the Prostate Cancer Working Group 2: at least 2 new bone lesions on a CT or MRI scan) • Unequivocal clinical progression (bone pain progression requiring narcotics or palliative radiotherapy, pathological fracture, urinary obstruction, or spinal cord compression) 						
In mCRPC, continuation of ADT to maintain T < 20 ng/dL is strongly recommended	14	100				
Another reasonable option ("value-based model") in treating mCRPC is to stop ADT (once castrate levels are reached) and to check T levels q3 months, then restart ADT if T rises above >20 ng/dL	2	14	6	43	6	43
For patients with mCRPC on treatment, testosterone levels should be measured:	14	100				
<ul style="list-style-type: none"> • At baseline • When changing therapy • If PSA rising (to confirm castrate level: <20 ng/dL) 						
Also, PSA and CT/bone scans should be performed at regular intervals						
4. AE Management Strategies with ADT						
Should a DEXA scan and FRAX score be obtained for baseline and follow-up testing of bone fragility during treatment with ADT (pending approval by insurance provider)?	14	100				
A DEXA scan should be obtained at baseline (within 6 months of initiating ADT) and at least once every 2 years for follow-up	14					
Vitamin D levels can be monitored in men taking osteoclast inhibitors, up to annually, or more often if replenishing depleted stores with high-dose vitamin D. Daily maintenance doses for vitamin D supplementation should be 800-1000 IU daily, and calcium daily maintenance dosing should not exceed 1200 mg daily	13	93			1	7
The NCCN guidelines on determining which patients are eligible for additional pharmacologic therapy should be followed (ie calculating a patient's individual risk of fracture via FRAX calculator). For those patients who are eligible, zoledronic acid or denosumab can be used.	14	100				
Either the urologist or the PCP should monitor blood pressure (at each visit), HbA1c (annually in nondiabetic patients), and lipid profile (annually) in patients receiving ADT	13	93			1	7
Before initiating ADT, patients with CVD comorbidities should be referred to a cardiologist for comanagement	14	100				
There is no evidence to support taking metformin to improve PC-specific outcomes	12	86			2	14
The urologist should communicate with the PCP or endocrinologist when patients with diabetes initiate ADT as they may need closer monitoring of diabetes	12	86			2	14
HbA1c should be monitored up to annually by a cancer care provider or PCP in patients without a history of diabetes						
Cancer-treating physicians should encourage physical activity/exercise, healthy diet, weight control, and smoking cessation in all patients on ADT throughout the course of their treatment	14	100				

(Continues)

TABLE 2 (Continued)

	Yes		No		Indeterminate	
	No./14	%	No./14	%	No./14	%
We recognize the importance of increasing urologists' awareness of depression risk in patients receiving ADT	14	100				
Urologists need to be aware of depression risk in patients receiving ADT	14	100				
Consider routine discussions of mental health concerns, including questions about depression and memory concerns, with evaluation performed at least annually, in men receiving ADT	14	100				
Patients over the age of 70 who have been on ADT for >2 years should be referred annually for neurocognitive assessment to evaluate for dementia	4	29	3	21	7	50
We recognize hot flashes are side effects of ADT that can negatively impact patient quality of life. Of all the agents that are currently being used to treat hot flashes in men receiving ADT, none have an FDA approved indication for this use and each is associated with side effects. Shared decision-making practices should be used to discuss the pros and cons of off-label use of medications for hot flashes for men who wish to use medical management strategies	14	100				

Abbreviations: ADT, androgen deprivation therapy; BCR, biochemical recurrence; CAB, combined androgen blockade; CT, computerized tomography; CVD, cardiovascular disease; DEXA, dexascan - bone densitometry; HSPC, hormone sensitive metastatic prostate cancer; mCRPC, metastatic castrate-resistant prostate cancer; mCSPC, metastatic castrate-sensitive prostate cancer; mPC, metastatic PC; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; OS, overall survival; PC, prostate cancer; PCP, primary care provider; PSA, prostate-specific antigen; PSADT, PSA doubling time; RP, radical prostatectomy.

or radiotherapy) in asymptomatic patients with newly diagnosed localized PC and no lymph node involvement. The multiple studies reviewed did not suggest any benefit in decreasing mortality when comparing ADT to observation/no treatment in men with clinically localized PC, thus primary ADT in localized disease is not recommended.⁴⁻⁸ Further studies with the newer androgen blocking agents are indicated. This is in accord with the NCCN guideline on PC.⁹

Is there a role for ADT alone as primary therapy for patients with newly diagnosed, localized, asymptomatic PC?

7% Yes, 93% No

3.2 | The role of ADT as neoadjuvant and adjuvant therapy to RP

The current AUA guideline states that, "Clinicians should not treat localized PC patients who have elected to undergo RP with neoadjuvant ADT or other systemic therapy outside of clinical trials (Strong Recommendation; Evidence Level: Grade A)."¹⁰ The NCCN guideline supports the use of ADT for M0 PSA persistence/recurrence after RP or external beam radiation therapy (EBRT), and neoadjuvant ADT+/-EBRT post-RP. The treatment should be individualized, based on PSA levels and rate of change, life expectancy, initial stage, grade, and PSA level at the time of definitive therapy.⁹ The panel agreed with this guideline, with the caveat that the current literature demonstrates that there may be benefit with neoadjuvant ADT with RP when restricted to high-risk patients, and studies assessing this are ongoing. A review of six studies showed that there may be a delay in time to BCR and improvement in surgical margins in high-risk patients with neoadjuvant ADT before RP, but no overall survival (OS)

benefit was observed.¹¹⁻¹⁶ There were several limitations to these studies in that they were small studies (N ranging from 55 to 297), the definition of "high risk" was not standardized, follow-up was often short, and they were underpowered to demonstrate a benefit in terms of OS. There may be an issue of patients (particularly high-risk patients) receiving "temporizing neoadjuvant therapy," that is, when the patient desires to delay definitive therapy for an important life event. While this is not ideal patient care, the panel recognizes that it is used in unique situations after shared decision making, and the effects on outcomes are unclear.

The panel did not reach consensus on the role of adjuvant ADT after prostatectomy, based on the literature. The panel reviewed four studies, which overall showed some benefit in BCR and OS, but not consistently, in part because of the variable study designs.¹⁷⁻²¹ The strongest study, in 98 men with node-positive disease, showed significantly improved OS (HR 1.84 [95% confidence interval—CI, 1.01-3.35]; $P = 0.04$), PC-specific survival (HR 4.09 [1.76-9.49]; $P = .0004$), and progression-free survival (PFS) (HR 3.42 [1.96-5.98]; $P < .0001$) after 11.9 years of follow-up.¹⁷ Given this level 1 evidence, it is rational to consider early ADT in men who are found to be node positive. Future studies are needed to define the value and duration of adjuvant ADT therapies, including novel AR-directed agents, following RP in men with high-risk features and without known lymph node metastasis.

Is there a role for neoadjuvant ADT with RP for low- to intermediate-risk patients?

93% No; 7% Indeterminate

Is there a role for neoadjuvant ADT with RP for high-risk patients?

7% Yes; 71% No; 22% Indeterminate

Is there a role for adjuvant ADT following RP (N1, +/-EBRT)?

100% Yes

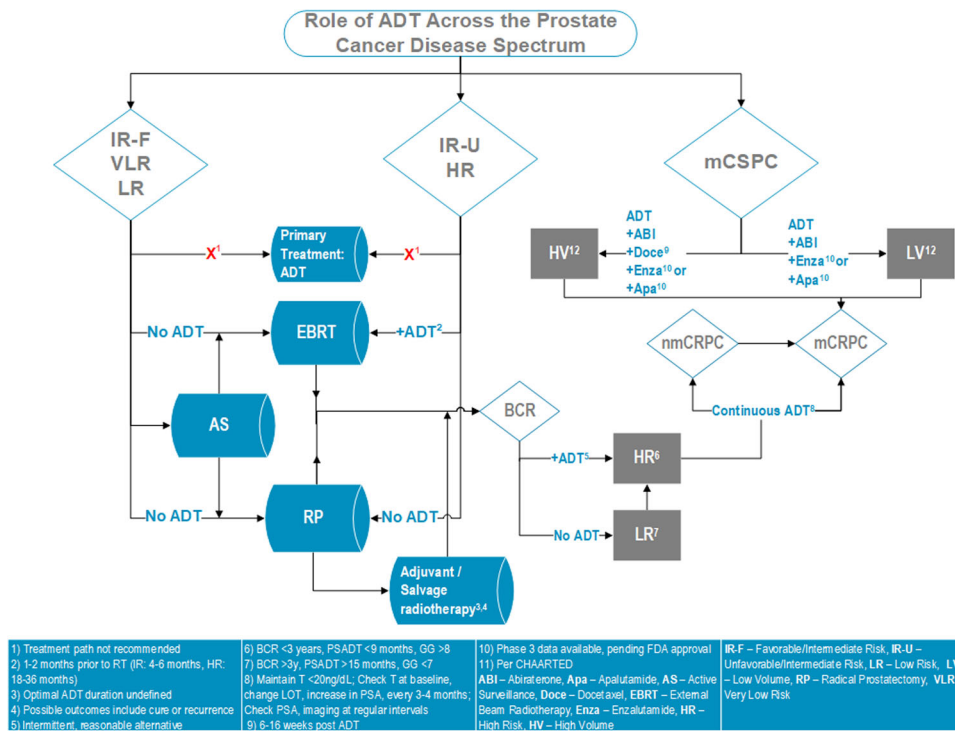


FIGURE 1 Algorithm summarizing the panel's recommendations. ADT, androgen deprivation therapy; BCR, biochemical recurrence; EBRT, mCSPC, metastatic castrate-sensitive prostate cancer; RP, radical prostatectomy

Is there a role for adjuvant ADT following RP (NO, but other high-risk features, absence of radiation)?
 86% No; 14% Indeterminate

3.3 | The role of ADT with RT

The panel reached consensus on the role of ADT with RT: the panel members agreed that ADT should not be used in low-risk patients being considered for RT, and ADT should be considered for intermediate- and high-risk patients (as defined using the D'Amico criteria).²² Specifically, the panel agreed upon the role for ADT with RT when the risk of local failure and/or distant disease is high, but not when the local control with radiation alone was expected. The strongest evidence to support adjuvant ADT with RT for intermediate-risk patients was from the RTOG 94-08 study in 1979 eligible patients, who received RT alone or 4 months of ADT (starting 2 months before radiotherapy). After a mean follow-up of 9.1 years, the OS, disease-specific mortality (DSM), PSA recurrence rates, metastasis-free survival (MFS), and rates of positive findings on repeat prostate biopsy at 2 years were significantly improved with RT plus short-term ADT. However, when the results were stratified by risk, only intermediate-risk patients saw benefit with the addition of ADT to RT, in OS and DSM.²³ A phase III clinical trial to assess whether there is an OS advantage in patients with intermediate-risk PC treated with dose-escalated RT with RT alone is ongoing (ClinicalTrials.gov identifier: NCT00936390).

The panel reached unanimous consensus on the duration and timing of ADT with RT. Studies have assessed the benefit of 3 to 36 months of ADT in patients with high-risk disease. In all studies, there was greater benefit with adjuvant ADT given for at least 3 months compared with no ADT, and the panel concluded that optimal dosing of ADT for use with RT is 4 to 6 months for intermediate-risk patients and 18 to 36 months for high-risk patients.²³⁻²⁹ The first dose of ADT should be administered 1 to 2 months before beginning RT.

*Is there a role for ADT with RT?** 100% Yes
 Low-risk patients (except for reduction of volume) 100% No
 Intermediate-risk patients (4-6 months duration) 100% Yes
 High-risk patients (18-36 months duration) 100% Yes
 Timing: 1 to 2 months before RT 100% Yes
 For intermediate- and high-risk PC patients, pending RT and ADT, we recommend ADT initiation ideally 1 to 2 months before initiating RT. 100% Yes

3.4 | The role of ADT in patients with BCR after RP and RT

Although there is a paucity of data demonstrating a survival benefit for ADT for BCR patients, ADT can be used to manage BCR or rising levels of PSA after primary therapy. BCR has been defined in the post-RP setting as two consecutive PSA values ≥ 0.2 ng/mL and rising,^{30,31} and in the post-RT setting as any PSA increase >2 ng/mL higher than the PSA nadir, regardless of nadir.³² However, as our

ability to measure PSA with ultrasensitive assays advances, these definitions may change.

The clinical course of PC in men with BCR post-RP is highly variable. Pound and colleagues showed that overall, 34% of men who developed BCR post-RP developed metastases within the 5 years of follow-up. Yet, BCR is not the only factor that determines risk of developing metastases. Several studies have shown that MFS post-BCR is strongly influenced by PSA doubling time (PSADT), pathology/Gleason score at the time of RP, interval time to BCR after RP, and age.^{33–39} On the basis of these findings, the panel *agreed unanimously* that for patients, post-RP with BCR, PSADT ≤ 9 months, and Gleason score ≥ 8 were viewed as significant metrics for consideration for initiating ADT.

Regarding optimal timing of ADT (immediate vs delayed), the literature does not suggest clear evidence to support timing of ADT in patients with BCR post-RP/XRT, who are node-positive after RP, with locally advanced, rising PSA or who are not candidates for definitive therapy, or undergoing adjuvant therapy.^{17,33,40–46} Given the unclear benefit of early ADT in patients with BCR and the known medical sequelae of chronic ADT, this therapy should be reserved for patients exhibiting high-risk features.

While the NCCN guideline states that intermittent ADT should be considered in this setting, the panel indicated no clear preference for intermittent vs continuous ADT therapy post-RP/RT.⁹ Data from one study suggest that intermittent ADT is not inferior to continuous ADT in nonmetastatic PC in terms of OS and time to progression. The number of PC-related deaths was higher in the intermittent group but the difference was not statistically significant. The number of PC-unrelated deaths was higher in the continuous treatment group. Intermittent ADT may offer some benefit in terms of quality of life (sexual desire, less fatigue), as well as less cost and more convenience.⁴⁷ The panel reached a consensus that intermittent ADT is a reasonable alternative to continuous ADT in high-risk patients with BCR post-RP/RT, or as salvage therapy post-RP, and they offer a proposed treatment pathway (Figure 2), taking into consideration PSA and testosterone levels.

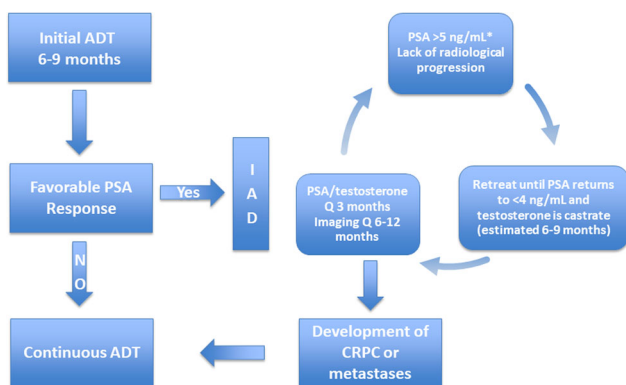


FIGURE 2 Proposed Intermittent Treatment Pathway. *The PSA threshold of 5 ng/mL is arbitrarily chosen for illustrative purposes only. In patients with other high-risk features, consider restarting treatment at a lower PSA level, but always perform imaging before reinitiation. ADT, androgen deprivation therapy; CRPC, castrate-resistant prostate cancer; PSA, prostate-specific antigen

Given the natural history of PC (ie, about 1/3 of patients will go on to progress), the majority of patients with BCR should undergo observation with BCR. For the remaining patients (high risk), ADT would generally be considered for:

- Early recurrence (BCR < 3 years), AND
- High-risk features (PSADT ≤ 9 months OR Gleason score ≥ 8)

100% Yes

ADT in BCR is generally not recommended in patients with:

- Low-risk features (PSADT > 15 months, AND
- Gleason score ≤ 7 , OR
- Limited life expectancy, or low risk of metastases, or poor performance status

100% Yes

When considering ADT in high-risk patients with BCR post-RP, post-RT, or postsalvage after RP, intermittent ADT is a reasonable alternative to continuous ADT.

86% Yes, 14% Indeterminate

Proposed Intermittent Treatment Pathway (Figure 1)

86% Yes, 14% Indeterminate

3.5 | The role of ADT in salvage therapy

The NCCN guideline states that some patients are candidates for salvage ADT after M0 PSA persistence/recurrence post-RP or EBRT.⁹ For ADT and salvage RT, the panel agreed that there is level 1 evidence to support ADT use. However, the Shipley study (RTOG 96-01), which accrued patients more than 15 years ago, may not be applicable, as RT technologies have advanced and high-dose bicalutamide is not approved within the United States. In the study, which compared RT + bicalutamide (150 mg) vs RT + placebo, the data showed that the addition of ADT resulted in significantly higher rates of OS and MFS and lower incidence of DSM compared with those with RT + placebo. However, in a subgroup analysis, men with PSA < 0.7 ng/mL at study entry did not experience a benefit of OS (HR 1.13; 95% CI, 0.77–1.65; $P = .53$).⁴⁸ Additionally, the 5-year GETUG-AFU 16 trial has reported a benefit with 6 months ADT with RT vs no ADT, and the 10-year MFS data will be reported soon. Thus, it seems reasonable to discuss a short course of ADT in the setting of sXRT, pending additional long-term data. In the GETUG-AFU 16 study, comparing RT alone with RT + ADT (goserelin), men who received salvage RT + ADT were significantly more likely to be free of biochemical progression or clinical progression at 5 years vs men who received RT alone if their pretreatment PSA was > 0.5 ng/mL, while those with lower PSA did not appear to benefit from the addition of ADT.⁴⁹

There is level 1 evidence to support ADT use with salvage radiotherapy. It is reasonable to consider ADT in the setting of salvage radiotherapy as part of a shared decision-making discussion. The duration of

ADT in this setting is unclear, but 6-12 months of ADT would be reasonable.

86% Yes; 7% No; 7% Indeterminate

3.6 | The role ADT in metastatic castrate-sensitive prostate cancer

While the NCCN guideline identifies ADT as the gold standard treatment for metastatic PC (mPC), the panel did not reach consensus on whether immediate ADT is always necessary in asymptomatic patients with oligometastatic hormone sensitive metastatic prostate cancer without visceral metastases who wish to consider delaying ADT in favor of metastasis-directed therapy (MDT).⁹ The panelists were not able to reach consensus on whether MDT is a reasonable alternative to immediate ADT in select low-risk patients. Data from a phase II study evaluating MDT for oligorecurrent PC showed a trend toward improved ADT-free survival at 3 years' follow-up (median ADT-free survival) was 13 months (80% CI, 12-17 months) for the surveillance group and 21 months (80% CI, 14-29 months) for the MDT group (HR, 0.60 [80% CI, 0.40-0.90]; $P = .11$). Other similar studies to answer this question are ongoing.⁵⁰ While these studies alone are not sufficient to warrant a recommendation, MDT is being studied in phase II trials.⁵¹

The panel reached consensus regarding its preference to maintain patients with metastatic castrate-sensitive prostate cancer (mCSPC) on continuous ADT rather than intermittent ADT, but acknowledged that for certain patients (eg, those with cardiovascular comorbidities), intermittent ADT may be considered to reduce complications. Results from a randomized SWOG study comparing continuous vs intermittent ADT in men with newly diagnosed mCSPC were statistically inconclusive: the CI for survival exceeded the upper boundary for noninferiority with intermittent therapy (HR > 1.20, as per the study design) suggesting that intermittent ADT was inferior to continuous ADT in terms of survival, but the study investigators noted that too few events occurred to rule out significant inferiority of intermittent therapy. Of note, the study included only patients with PSA ≤ 4.0 ng/mL after 7 months of ADT, which constituted only 60% of those enrolled in the study and suggests that there was not confidence that patients with a higher PSA should receive intermittent therapy.⁵² Noninferiority of intermittent therapy with respect to OS, cancer-specific survival, and PFS was confirmed in a subsequent meta-analysis including 15 trials.⁵³ The NCCN guideline discusses the data that indicate no preference for intermittent or continuous ADT in this setting.⁹

The panel reached a consensus on the three options to achieve castration (bilateral orchiectomy, LHRH agonists, and LHRG antagonists), as recommended by the American Society of Clinical Oncology.^{54,55} The panel did not reach consensus on whether combined androgen blockade (CAB) is superior to castration alone, but CAB was considered a reasonable alternative to castration alone, in agreement with the NCCN guideline.^{9,56}

TABLE 3 Monitoring serum testosterone levels in mCSPC

Testosterone levels should be checked:

1. At baseline, before initiating ADT
2. 1-4 mo after initiation of ADT, regardless of PSA levels
3. GOAL: <20 ng/dL
4. If PSA rises
 - If T > 20 ng/dL, check luteinizing hormone (to differentiate between incorrect administration [nonsuppressed LH level] vs ineffective castration [suppressed LH level but nonsuppressed T level])
 - Consider switching to an alternative agent or offering bilateral orchiectomy

Abbreviations: ADT, androgen deprivation therapy; mCSPC, metastatic castrate-sensitive prostate cancer; PSA, prostate-specific antigen.

Unanimous consensus was reached on the role of monitoring serum testosterone (T) (Table 3). Obtaining a baseline T level before initiating ADT is essential. Subsequently, in the patient with mCSPC and CRPC, the optimal T level should be <20 ng/dL, based on several studies reviewed.^{57,58} Of note, the NCCN guideline defines castration as testosterone <50 ng/dL.⁹ The panel felt that T levels should be checked 1 to 4 months after initiation of ADT, regardless of PSA levels. Once ADT is initiated and a PSA rise occurs, T levels should be obtained to distinguish noncastrate vs castrate-resistant progression. If T levels are >20 ng/dL, clinicians should check luteinizing hormone levels to determine whether ADT was administered effectively. If T levels are >20 ng/dL despite low luteinizing hormone, consider switching to an alternative agent.

There was unanimous consensus on the superiority of ADT + abiraterone acetate (AA) compared with ADT alone in terms of OS in mCSPC, based on two large clinical trials (LATITUDE and STAMPEDE), consistent with the NCCN recommendation in this setting.^{59,60} The panel's recommendation was made irrespective of metastatic burden (86% consensus). Recent data from the ARCHES, ENZAMET, and TITAN studies suggest clinical benefit with enzalutamide and apalutamide in this setting as well.⁶¹⁻⁶³ US FDA approval for these agents in mHSPC is pending.

Likewise, there was unanimous consensus on the superiority of ADT + docetaxel compared with ADT alone in terms of OS for men with mCSPC. In subgroup analyses, there is an unequivocal OS benefit with ADT + docetaxel vs ADT alone in high-volume disease, defined as ≥ 4 bone metastases, at least one of which is outside the axial skeleton, and/or visceral (ie, lung or liver) metastases, but not in low-volume disease.⁶⁴⁻⁶⁶ The panel recommended that docetaxel should be initiated 6 to 16 weeks after the first ADT dose, to enhance pharmacologic metabolism and tolerability of docetaxel.⁶⁷

When considering which up-front combination for high-volume mCSPC is superior (ADT + AA or ADT + docetaxel), a prespecified (but not prepowered) analysis of patients from the STAMPEDE trial when recruitment to the two research arms overlapped, showed that ADT + AA was significantly better in failure-free survival (which included PSA progression) and PFS, with trends to improved MFS, and symptomatic skeletal events (not significant), but there was no significant difference between AA and docetaxel in survival

TABLE 4 Systemic therapy for mCSPC based on volume

	Preferred agent	
	ADT + abiraterone acetate	ADT + docetaxel
Low-volume mCSPC	×	...
High-volume mCSPC	×	×

Note: High volume = 4 or more bone metastases (at least one outside of axial skeleton) or visceral (lung, liver) metastases.

Low volume = if criteria for high volume are not met.

Abbreviations: ADT, androgen deprivation therapy; mCSPC, metastatic castrate-sensitive prostate cancer.

(no significant difference between arms).⁶⁸ Cost considerations, access to therapy, duration of therapy, and comorbidities may influence the choice of therapy.⁶⁹

When considering optimal systemic therapy for low-volume and high-volume disease in mCSPC, the panel reached a consensus that in low-volume mCSPC, there is strong evidence that ADT + docetaxel does not provide an OS benefit beyond ADT alone; thus, ADT + AA is favored in the low-volume setting. However, there was unanimous consensus that in high-volume mCSPC, there is strong evidence of OS benefit for ADT + docetaxel.^{70,71} Thus, both ADT + AA or ADT + docetaxel are equally preferred treatment options in the high-volume setting (Table 4). These recommendations are in line with the NCCN guideline.⁹

In men with asymptomatic oligometastatic mCSPC (without visceral metastases), metastasis-directed therapy may be a reasonable alternative to immediate ADT in select patients.

50% Yes, 29% No, 21% Indeterminate

In mCSPC, continuous ADT is generally strongly preferred over intermittent ADT, however in certain circumstances (eg, cardiovascular comorbidities, intolerabilities, etc), intermittent may be considered.

93% Yes, 7% Indeterminate

In mCSPC, there are 3 options to achieve castration: bilateral orchiectomy, LHRH agonists, or LHRH antagonists.

93% Yes, 7% Indeterminate

CAB (ie, LHRHa, LHRHantag, +1st- or 2nd-generation antiandrogen) is superior to castration alone.

64% Yes, 36% No

In mCSPC, baseline T levels should be obtained before starting ADT.

100% Yes

For ADT administration, testosterone level should be T < 20 ng/dL. Confirm castrate T levels 1-4 months after surgical/medical castration, regardless of PSA levels. If PSA rises, T levels must be checked. If T levels are >20 ng/dL, clinicians should check luteinizing hormone levels to differentiate whether ADT was administered effectively.

100% Yes

In mCSPC, if T > 20 ng/dL despite low luteinizing hormone levels, consider switching to an alternative agent.

100% Yes

In the broad mCSPC population, ADT + Abi is superior to ADT alone in terms of OS.

100% Yes

In mCSPC, the distinction between low- and high-volume disease has not been studied in this context. Thus, ADT + Abi is a reasonable standard of care irrespective of metastatic burden.

86% Yes, 14% Indeterminate

In the broad mCSPC population, ADT + docetaxel is superior to ADT alone in terms of OS.

- *In high-volume mCSPC, there is an unequivocal OS benefit to ADT + docetaxel vs ADT alone.*
- *In low-volume mCSPC, there is no clear OS benefit to ADT + docetaxel vs ADT alone.*
- *Docetaxel treatment can start 6 to 16 weeks after ADT, to avoid toxicities*

100% Yes

In low-volume mCSPC, there is evidence that ADT + docetaxel does not provide an OS benefit; thus, ADT + Abi is the favored choice.

93% Yes, 7% No

In high-volume mCSPC, there is strong evidence of benefit for ADT + docetaxel. Thus, both ADT + abiraterone or ADT + docetaxel are treatment options.

100% Yes

The panel cannot comment on the comparative efficacy of ADT + Abi in low- vs high-volume mCSPC, because this has not been studied.

100% Yes

3.7 | The role of ADT in metastatic castrate-resistant prostate cancer

Metastatic castrate-resistant prostate cancer (mCRPC) has been defined as men with PC on ADT with T level <50 ng/dL, a rising PSA (defined as two consecutive rises, ≥4 weeks apart), and radiographic evidence of metastatic disease on imaging studies.⁷² However, based on current literature, the panel agreed unanimously that the goal of ADT should be to achieve a T level <20 ng/dL, which differs from the NCCN guideline treatment goal of maintain T levels <50 ng/dL.⁹ There was no consensus on a value-based model of ADT continuation, that is, whether ADT could be stopped once castrate levels are reached and then to check T levels every 3 months (restarting ADT if T rises ≥20 ng/dL). The American Society of Clinical Oncology and NCCN recommend that ADT should be continued indefinitely in the setting of mPC despite the development of castration resistance.^{9,73} But a survey of PC physicians from five European countries (France, Germany, Italy, Spain, and the United Kingdom) found that up to one third of physicians used chemotherapy as a monotherapy and stopped administering ADT after the development of castration resistance.⁷⁴ The panel did not endorse discontinuing ADT after emergence of castration-resistant disease.

In the context of mCRPC, the panel agreed unanimously that T should be checked at the time of diagnosis of castration resistance, when changing therapy, and if PSA is rising (to confirm castrate levels of T, ie, <20 ng/dL). PSA measures and CT/bone scans should also be

TABLE 5 Monitoring serum testosterone levels in mCRPC

Testosterone levels should be checked:

1. At baseline
2. When changing therapy
3. If PSA is rising (to confirm castrate levels of T, ie, <20 ng/dL)
4. If ADT has been discontinued

Abbreviations: ADT, androgen deprivation therapy; mCRPC, metastatic castrate-resistant prostate cancer; PSA, prostate-specific antigen.

obtained at regular intervals (Table 5). These recommendations are in accordance with the Prostate Cancer Clinical Trials Working Group recommendations.^{72,75}

mCRPC is defined as:

mPC (by conventional radiology)

Testosterone level < 50 ng/dL

Progressive disease (one or more of):

- *PSA progression (2 rises above a nadir, ≥4 weeks apart)*
- *Radiographic progression (as defined by the PC Working Group 2: at least 2 new bone lesions on a CT or MRI scan)*
- *Unequivocal clinical progression (bone pain progression requiring narcotics or palliative radiotherapy, pathological fracture, urinary obstruction, or spinal cord compression)*

100% Yes

In mCRPC, continuation of ADT to maintain T < 20 ng/dL is strongly recommended.

100% Yes

Another reasonable option ("value-based model") in treating mCRPC is to stop ADT (once castrate levels are reached) and to check T levels q3 months, then restart ADT if T rises above >20 ng/dL.

14% Yes, 43% No, 43% Indeterminate

For patients with mCRPC on treatment, testosterone levels should be measured:

- *At baseline*
- *When changing therapy*
- *If PSA rising (to confirm castrate level: <20 ng/dL)*

Also, PSA and CT/bone scans should be performed at regular intervals.

100% Yes

3.8 | AE management strategies with ADT and combination therapies

With ADT being the most commonly prescribed agent by clinicians for the management of advanced PC, understanding all of the potential effects of therapy is critical to optimizing patient health outcomes. While there are numerous medical and quality-of-life adverse events attributable to the use of ADT, the panel focused on the

following: bone fragility and associated skeletal events, cardiovascular disease (CVD), diabetes, neurocognitive effects, and hot flashes. A consistent theme of our discussions was that achieving optimal outcomes requires a multidisciplinary approach of cancer care providers, potentially involving primary care providers (PCPs), and other appropriate specialists to coordinate the care of PC patients on ADT to prevent and minimize complications of ADT therapy. The panel noted that the primary cancer provider (urologist, radiation oncologist, or medical oncologist) needs to be fully engaged in identifying these risks and engaging with the overall medical team.

3.9 | Bone health

The risk of osteoporosis in aging men on ADT increases due to both advancing age as well as the suppression of T and estrogen, which are both bone protective for fracture risk. ADT has been shown to accelerate bone loss and hypogonadism is a leading cause of osteoporosis in men within the United States.⁷⁶⁻⁷⁹ Prolonged exposure to ADT also increases fracture risk in a dose-dependent manner.⁸⁰ The panel reached unanimous consensus on several aspects of risk management of skeletal events with ADT: obtaining a dexascan - bone densitometry (DEXA) scan and calculating a FRAX score at baseline (within 6 months of initiating ADT) and at least once every 2 years for follow-up; assessing vitamin D levels in men who are taking osteoclast inhibitors, by either the PCP or cancer care provider. All men on ADT should receive appropriate maintenance supplementation of vitamin D and calcium (not to exceed 800-1000 IU vitamin D daily after restoring vitamin D stores to normal levels and 1200 mg calcium daily), all in accordance with the NCCN guidelines on bone health for men on ADT (Table 6).⁹ Likewise, the panel supported the NCCN guidelines on determining which patients are eligible for additional pharmacologic therapies (denosumab or zoledronic acid) to increase bone mineral density in men with osteoporosis, men with osteopenia, and men with an elevated risk of fracture based on personal risk factors as estimated by calculating a patient's FRAX score (eg, FRAX Fracture Risk Assessment Tool, available at: <https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9>).

Should a DEXA scan and FRAX score be obtained for baseline and follow-up testing of bone fragility during treatment with ADT (pending approval by insurance provider)?

100% Yes

TABLE 6 Management of bone health during ADT

1. Obtain a DEXA scan and FRAX score at baseline (within 6 mo of initiating ADT) and at least once every 2 y for follow-up
2. Monitor vitamin D levels, by either the PCP or cancer care provider, with appropriate supplementation (not to exceed 800-1000 IU vitamin D, 1200 mg calcium)

Abbreviations: ADT, androgen deprivation therapy; DEXA, dexascan - bone densitometry; PCP, primary care provider.

A DEXA scan should be obtained at baseline (within 6 months of initiating ADT) and at least once every 2 years for follow-up.

100% Yes

Vitamin D levels can be monitored in men taking osteoclast inhibitors, up to annually, or more often if replenishing depleted stores with high-dose vitamin D. Daily maintenance doses for vitamin D supplementation should be 800-1000 IU daily, and calcium daily maintenance dosing should not exceed 1200 mg daily.

93% Yes; 7% Indeterminate

The NCCN guidelines on determining which patients are eligible for additional pharmacologic therapy should be followed (ie, calculating a patient's individual risk of fracture via FRAX calculator). For those patients who are eligible, zoledronic acid or denosumab can be used.

100% Yes

3.10 | Cardiovascular risks

Several studies have documented the increased risk of CVD in men on ADT.⁸¹⁻⁸⁴ This increased risk appears to be more pronounced in older men (>75 years of age), for whom prolonged ADT increases the risk of both CVD and diabetes, especially in those with cardiovascular comorbidities.^{85,86} The NCCN guidelines stress the assessment of traditional risk factors for CVD using the ABCDE approach (Awareness and Aspirin, Blood pressure, Cholesterol and Cigarette smoking, Diet and Diabetes, and Exercise) as well as the importance of a multidisciplinary team approach to address these risks, potentially including the PCP, a geriatrician, and a cardio-oncologist or cardiologist, when both practical and accessible.^{9,87} The panel *agreed unanimously* that either the cancer care provider or the PCP should monitor blood pressure (at each visit), HbA1c (annually to screen for DM, and quarterly by the clinician managing diabetes), and lipid profile (annually) in patients receiving ADT. Obtaining a baseline EKG can be considered in patients initiating ADT, particularly for men with a history of CVD. In addition, before initiating ADT in men with significant CVD comorbidities, referral to a cardiologist for comanagement is recommended.

Either the urologist or the PCP should monitor blood pressure (at each visit), HbA1c (annually in nondiabetic patients), and lipid profile (annually) in patients receiving ADT.

93% Yes; 7% Indeterminate

Before initiating ADT, patients with CVD comorbidities should be referred to a cardiologist for comanagement.

100% Yes

3.11 | Diabetes and glucose intolerance

Akin to cardiovascular risks, several studies have shown an increased risk of diabetes with ADT.^{85,88,89} The NCCN guidelines again stress traditional assessment of risk factors for diabetes (HbA1c and/or fasting blood glucose), using a team approach among the PCP, geriatrician, and endocrinologist.^{9,87} The panel strongly encourages

multidisciplinary and integrative care with PCPs and other medical specialists, when possible, to optimize the well-recognized adverse event profile of ADT. The panel had unanimous consensus that either the cancer care provider or the PCP should monitor diabetes risk factors in diabetic patients receiving ADT, both at baseline and annually. Cancer-treating physicians should encourage activity/exercise, healthy diet, weight control, and smoking cessation in all patients on ADT throughout the course of their treatment. While some data suggest that metformin may be associated with improved survival in patients on ADT, the data were not strong enough to garner unanimous consensus on recommending metformin for patients on ADT.⁹⁰

There is no evidence to support taking metformin to improve PC-specific outcomes.

86% Yes, 14% Indeterminate

The urologist should communicate with the PCP or endocrinologist when patients with diabetes initiate ADT as they may need closer monitoring of diabetes.

86% Yes; 14% Indeterminate

HbA1c should be monitored up to annually by a cancer care provider or PCP in patients without a history of diabetes.

86% Yes; 7% No; 7% Indeterminate

Cancer-treating physicians should encourage physical activity/exercise, healthy diet, weight control, and smoking cessation in all patients on ADT throughout the course of their treatment.

100% Yes

3.12 | Neurocognitive dysfunction

There is increasing evidence regarding the effects of ADT on psychological and cognitive functioning. Some studies suggest that ADT may be associated with depression and/or cognitive dysfunction. However, specific guidelines for evaluation are lacking. Depression is common in patients with cancer, and men who are taking ADT may have a higher risk of depression.⁹¹ The data suggesting that exposure to ADT is associated with an increased risk of cognitive decline are inconsistent.⁹²⁻⁹⁵ While effective treatments for depression are available, there are no standardized interventions to reverse cognitive decline for this patient population. Studies are being developed to address this unmet need in men treated with ADT. Management of depression and any potential cognitive dysfunction represent a significant unmet need in men with PC. The panel *agreed unanimously* on the importance of increasing urologists' awareness of depression risk in patients receiving ADT, in accordance with the USPSTF recommendations on screening for depression in anyone with a chronic illness.⁹⁶ The NCCN guideline notes the potential link between ADT and depression and ADT and cognitive function, with side effects of continuous ADT increasing with duration of treatment. As such, the guideline recommends that patients be advised of these risks before initiating treatment.⁹ The panel recommends consideration of routine discussions of mental health concerns, including questions about depression and memory concerns, with evaluation performed at least

annually. There was not consensus regarding specific screening tools or treatment for depression or cognitive impairment, although involving primary care and other specialists, psychiatrists, psychologists, and neurologists for further management was supported.

We recognize the importance of increasing urologists' awareness of depression risk in patients receiving ADT.

100% Yes

Urologists need to be aware of depression risk in patients receiving ADT.

100% Yes

Consider routine discussions of mental health concerns, including questions about depression and memory concerns, with evaluation performed at least annually, in men receiving ADT.

100% Yes

Patients over the age of 70 who have been on ADT for >2 years should be referred annually for neurocognitive assessment to evaluate for dementia.

29% Yes; 21% No; 50% Indeterminate

3.13 | Vasomotor symptoms

Recent studies suggest that up to 80% of men on ADT have vasomotor symptoms, principally involving hot flashes, and 27% cited this side effect as the most bothersome.⁹⁷ Hot flashes can be associated with sleep disturbance and are a major contributor to the discontinuation of ADT. Currently, there are no approved drugs to treat men with hot flashes and there have been very few placebo-controlled trials. The panel recognizes that hot flashes are a significant side effect of ADT. Of all the agents that are currently being used to treat hot flashes in men receiving ADT, none have an FDA approved indication for this use and each is associated with side effects (Table 7). Clinicians should have an informed discussion of off-label options for pharmacologic management of hot flashes in men who wish to use medical therapies to reduce their symptoms. The NCCN guideline notes that vasomotor symptoms are a known side effect of ADT, with side effects of continuous ADT increasing with

duration of treatment. As such, the guideline recommends that patients be advised of these risks before initiating treatment.⁹

We recognize that hot flashes are side effects of ADT and can negatively impact patient quality of life. Of all the agents that are currently being used to treat hot flashes in men receiving ADT, none have an FDA approved indication for this use and each is associated with side effects. Shared decision making practices should be used to discuss the pros and cons of off-label use of medications for hot flashes for men who wish to use medical management strategies.

100% Yes

4 | DISCUSSION

For more than half a century, castration has been the standard of care in the management of advanced PC patients. A major breakthrough for ADT came in the 1980s with the development of LHRH agonists, which were initially approved for patients with metastatic disease. These agents resulted in an increased use of ADT in PC beyond those with documented metastasis. Practicing urologists have used ADT therapies across the entire spectrum of PC, from newly diagnosed localized disease to mCRPC, but its implementation in specific patient populations has evolved. For example, a review of Medicare data from 1991 to 2005 found that 44.8% of men with PC were exposed to ADT within the first year of treatment. Of those, 51.8% were ages 75% to 79% and 60.1% were age ≥ 80 years old, which raises concern for heightened use of ADT in settings with greater potential geriatric comorbidities.²

With both retrospective and prospective trials, the urologic oncology community has become aware and more knowledgeable regarding the myriad potential adverse events and side effects associated with T suppression. Thus, there exists a clinical need for more judicious use and management of ADT across the PC spectrum. To develop an effective therapeutic management plan, we have reviewed the literature and delineated a list of pathway recommendations of the optimal uses of ADT as well as the side effect profiles associated with ADT. In this way, we can best identify,

TABLE 7 Common medications used to address hot flashes in men with prostate cancer

Medication	Common doses used for hot flashes	Common adverse effects
Megace (megestrol acetate)	20 mg PO qd	Weight gain, CV risk (DVT/PE), cost
Effexor XR (venlafaxine)	75 mg PO qd	Feelings of being activated/jittery if not titrated properly Suicidal ideation Withdrawal issues
Paxil (paroxetine HCl)	...	Weight gain, loss of libido, suicidal ideation, withdrawal issues
Clonidine
Gabapentin	...	Drowsiness, dyspepsia
Depo-Provera (medroxyprogesterone) 150	150 mg IM	Increased risk of thrombotic issues

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolus.

manage, and counsel patients who would most benefit from ADT and choose the most effective, risk-mitigating guidance for ADT management.

Since 2004, and especially within the last 10 years, given the numerous approvals of therapies for advanced PC, multiple treatment guidelines have been developed to aid in the delivery of these agents which, for the most part, were approved within monotherapy phase 3 trials in conjunction with ADT use. Although ADT has been the mainstay of advanced PC therapy, to our knowledge, no consensus statement has been developed to assist practitioners for the optimal use and management of ADT across the PC disease continuum.

5 | LIMITATIONS

There were several limitations to this consensus panel and its recommendations. This panel was chosen subjectively, based on clinician experience, research interests, and publication history. We also recognize that the panel did not include a radiation oncologist, which might have added an important perspective to some of the discussions. The studies reviewed for these recommendations was not selected by a formal literature review, but by the knowledge and expertise of the panel subcommittee members. In the medical literature, there is a lack of level 1 evidence to make conclusive statements about ADT use in all settings. In those instances, the panel members based their recommendations on their expertise and clinical experience. Finally, this field is rapidly evolving based on new clinical trial data and developing technologies; hence, these recommendations will likely need to be updated every 2 to 3 years.

6 | CONCLUSIONS

The goal of this panel's effort is not to replace existing guidelines that have been published and painstakingly developed by several national and international organizations with input from highly respected experts. Rather, we have attempted to provide a practical and user-friendly reference for all clinicians who participate in the management of PC, specifically as it involves the utilization of ADT across the various stages of the disease. Of note, the NCCN guideline is broad and includes recommendations for several different treatments in M0 and M1 disease, as the guideline seeks to synthesize all of the published literature. Our goal in this report is to assist physicians in making treatment decisions from among these choices. As we would prefer to have recommendations solely based on level I evidence, we acknowledge that the luxury of having data-driven information does not always exist, and thus, level III/expert opinion can be solicited and enumerated via a consensus panel of PC experts, thereby providing an educational algorithm to optimize patient care where variability in treatment patterns may exist.

The panel has provided recommendations for monitoring PC patients while on ADT, recognizing that due to the heterogeneity of

PC, patients with PC patients will progress despite testosterone suppression and, therefore, early identification of conversion from castrate-sensitive to castration resistance is critical. Also, the requirement to both identify and mitigate side effects as a result of ADT as well as the importance of quality of life maintenance are essential to the quality of patient care, especially important as more combinatorial ADT therapies emerge throughout the spectrum of disease management. Often, existing guidelines focus upon monitoring workflows for all patients, regardless of their disease stage, and thus we have attempted to improve the granularity of recommendations for all disease states when ADT might be initiated. We have explored, discussed, and debated the current literature and have enumerated our recommendations for our colleagues' consideration and are hopeful that this will serve as a template for the optimization of patient care.

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CONFLICT OF INTERESTS

Neal D. Shore, MD, FACS, Research/consulting: Amgen, Astellas, AstraZeneca, Bayer, BMS, Dendreon, Ferring, Janssen, Merck, Myovant, Nymox, Pfizer, Sanofi-Genzyme, and Tolmar; Emmanuel S. Antonarakis, MD, Paid consultant/advisor: Janssen, Pfizer, Sanofi, Dendreon, Bayer, Bristol Myers Squibb, Amgen, Merck, AstraZeneca, Clovis Research grants to his institution: Janssen, Johnson&Johnson, Sanofi, Bristol Myers Squibb, Pfizer, AstraZeneca, Celgene, Merck, Bayer, Clovis Inventor of a biomarker technology that has been licensed to Qiagen; Michael S. Cookson, MD, Advisory board: MDxHealth, Janssen Scientific Affairs, LLC; Bayer Healthcare Pharmaceuticals Inc; Ferring Pharmaceuticals Inc; Consulting agreement: Astellas Pharma US Inc; E. D. Crawford, MD, Consultant advisor: Tolmar, Bayer, MDx, Genomic Health, Janssen, Dendreon, Ferring, Spouse employee: Dendreon Meeting participant or lecturer: Bayer Scientific study or trial: NIH, University of Colorado Cancer Center; Alicia K. Morgans, MD, Honoraria for consulting: Astellas, Sanofi, Bayer, AstraZeneca, Janssen, Genentech Research funding: Bayer; David M. Albala, MD, Speaker: Blue Earth Diagnostics, Genomic Health Advisory board: Cellanix; Jason Hafron, MD, Scientific study/trial: Janssen Biotech Inc, Pfizer Inc/Astellas Pharma Inc Meeting participant/lecturer: Blue Earth Diagnostics, Janssen Biotech Inc, Pfizer Inc/Astellas Pharma Inc Consultant/Advisor: Dendreon Pharmaceuticals LLC, Janssen Biotech Inc, Pfizer Inc/Astellas Pharma Inc; Richard G. Harris, MD, Advisor/speaker: Jansen, Astellas, Bayer, Advisor Dendreon, and Clovis; Daniel Saltzstein, MD, Speaker/advisor: Janssen and Astellas Pharmaceuticals; Jonathan Henderson, MD, Consultant: Myriad Genetics, Clovis Pharmaceuticals

Speaker: Janssen; Benjamin Lowentritt, MD, Speaker and/or consultant: Bayer, Dendreon, Janssen, Astellas, Pfizer, Genomic Health and Myriad; Raoul Concepcion, MD, FACS, Consultant: CUSP, Integra Connect, Clovis, Cellay, Merck, Invitae, Astellas, Janssen, Sun Pharma, Dendreon Speaker's Bureau: Astellas, Pfizer, Amgen, Sun Pharma, Dendreon. The remaining authors declare that there are no conflict of interests.

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