Clinical Practice Considerations for Androgen Deprivation Therapy
Expert Panel Discussion

INTRODUCTION
The indications and selection of patients for androgen deprivation therapy (ADT) for men with advanced prostate cancer are often topics of debate, specifically regarding initiation indications, selection of an ADT option (reflective of mechanism of action and mode of administration), and recognized safety and tolerability issues. Continuous and intermittent ADT regimens are both practiced, with selection by physician–patient shared decision making, especially for patients with biochemical recurrence (BCR). With the multitude of newly available therapeutics for metastatic castration-resistant prostate cancer (mCRPC), additional attention and debate has focused on therapeutic drug selection for patients newly initiated on ADT, especially as this treatment is foundational in the management of advanced prostate cancer. Setting treatment targets and monitoring the metrics of success are also important considerations. Given the advancement in both pathophysiology and precision-guided approaches for prostate cancer, we assembled a panel of expert urologists to discuss clinically important aspects of ADT that will assist busy clinician decision makers in their optimization of outcomes for their advanced prostate cancer population.

THE MEMBERS OF THE PANEL WERE:

Christopher Pieczonka, MD
Associated Medical Professionals
Syracuse, NY

Vahan Kassabian, MD
Medical Director
Georgia Urology
Atlanta, GA

Raoul S. Concepcion, MD, FACS
Director of Advanced Therapeutics
Urology Associates, Nashville
Nashville, TN

Judd W. Moul, MD, FACS
James H Semans Professor of Surgery
Duke University Medical Center
Durham, NC

Neal D. Shore, MD, FACS
Medical Director, CPI, Carolina Urologic Research Center
Atlantic Urology Clinics
Myrtle Beach, SC

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“LOWER TESTOSTERONE IS BETTER”

**QUESTION:** WHEN INITIATING ADT, WHAT ARE YOUR MAJOR OBJECTIVES?

**Dr. Shore:** When selecting an ADT strategy, I discuss with patients and their caregiver(s) that we are trying to effect regression and/or stabilization of the disease while at the same time avoiding clinical and subclinical exacerbations. A prime decision factor is to ensure that the benefits of testosterone suppression on disease stabilization/regression outweigh the recognized toxicities.

**DISCUSSION:** THE GROUP AGREED ON THE GENERAL POSITION THAT “LOWER TESTOSTERONE IS BETTER.” REDUCING TESTOSTERONE TO THE CASTRATION RANGE AS QUICKLY AS POSSIBLE AND MAINTAINING LOW LEVELS ARE THE PRIMARY OBJECTIVES, WHILE ENSURING THE BENEFITS OUTWEIGHT ANY RISKS OR TOXICITIES.

**Dr. Moul:** I group my patients into 2 general categories: those with traditional advanced or M1 (metastatic) disease, for whom multiple studies have shown that maintaining a testosterone level <20 ng/dL is associated with longer duration of response to ADT and increase in time to castration-resistant disease, and those with BCR, a more tricky group, for whom the data aren’t as clear-cut.

**Dr. Concepcion:** For patients with BCR and certain high-risk factors, I also aim to keep testosterone and consequently prostate-specific antigen (PSA) levels down, which ultimately reduces patient anxiety.

**Dr. Pieczonka:** In addition to these groups, I also consider ADT in patients undergoing radiation therapy. In such cases, my primary objective is to improve overall survival.

**QUESTION:** WHAT FACTORS HELP YOU DECIDE WHEN TO INITIATE TESTOSTERONE SUPPRESSION THERAPY IN A PATIENT WITH PROSTATE CANCER?

**Dr. Moul:** In patients who present de novo with metastatic prostate cancer, I generally start testosterone suppression therapy as soon as the diagnosis is made. In the setting of BCR, I generally base my decision on PSA doubling time (PSADT). For patients who develop BCR after surgery, radiation, or both, I usually wait until they have a PSADT of less than 9 to 12 months before initiating ADT.

**DISCUSSION:** THE GROUP OF EXPERTS REINFORCED THE CONCEPT OF EARLY ADT RATHER THAN LATE ADT.

**Dr. Concepcion:** For patients with BCR, appropriate timing of ADT is critical (based on data from Johns Hopkins related to original Gleason score at time of radical prostatectomy, if BCR occurred <2 years from surgery with a PSADT of <12 months).

**Dr. Pieczonka:** I also consider how aggressive the PSA change has been, the patient’s overall mental well-being, and how well the patient will deal with the concern that they may not be receiving treatment.

**QUESTION:** HOW DO THE FOLLOWING FACTORS IMPACT YOUR TREATMENT DECISIONS?

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<th>Pieczonka</th>
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**Note:** Factors are listed in overall order of importance. Range is from * indicating least important to **** indicating most important.
DISCUSSION: The magnitude of testosterone reduction was the most important factor impacting experts’ treatment decisions. The group agreed with a target of continuously low testosterone below 20 ng/Dl in the setting of m1 prostate cancer, despite the historic goal for testosterone reduction to below 50 ng/Dl. This change in target level has been driven by advances in assay methodologies for determining actual testosterone levels (including levels achieved following bilateral orchiectomy) and the clinical data on the benefits of achieving these low levels.

Dr. Kassabian: Testosterone levels are a prognostic indicator for progression. The lower these levels, the more durable the response.

Dr. Shore/Dr. Moul: Avoiding miniflares and escapes is critically important.

Dr. Pieczonka: Based on my clinical experience, I see differences in the level and duration of testosterone suppression with different forms of ADT and with different routes of administration.

Dr. Moul: When it comes to sites and methods of administration, correct training of nursing staff is imperative to ensure appropriate administration of therapy.

Dr. Pieczonka: The flexibility of administration of these therapies (1-, 3-, 4-, and 6-month shots) is valuable to patients, as it provides them with options that can fit their lifestyle.

Dr. Shore: Regarding the occurrence of testosterone rise with the first administration of drug, there has been ongoing debate as to whether or not this surge will hasten the conversion of androgen-sensitive disease to castration resistance, not only on first administration but also for subsequent doses, known as the acute-on-chronic effect. Mode of administration and duration of dosing for a specific ADT drug forms part of the discussion, which also takes into account patient clinic proximity, disease biology, and patient preference.

Dr. Concepcion: Tolerability is a major factor that I consider for my patients.

Dr. Moul: I counsel patients regarding the known side effects of ADT such as hot flashes and potential weight gain as well as longer-term issues such as loss of muscle mass, risk of diabetes, and possibly cardiac disease.

QUESTION: What topics (outcomes/goals/side effects) are most relevant during the discussions with the patient and their relatives when deciding to initiate therapy?

Dr. Shore: Attempting to demystify patient misunderstandings regarding cancer in general, as well as their specific disease biology and associated comorbidities, are important considerations. I explain to patients that instituting ADT is not a cure but rather an attempt to stabilize and/or create a period of disease remission. I review in detail the potential known side effects of hot flashes, sexual dysfunction, loss of libido, abdominal weight gain, fatigue, and occasional instances of cognitive impairment. I also discuss metabolic issues that may involve cardiovascular toxicity (if there are baseline comorbidities and known prior cardiovascular events), as well as the potential for bone demineralization. Importantly, we also discuss strategies to mitigate all of these potential toxicities.

Dr. Pieczonka: Prior to instituting ADT, I explain to my patients that prostate cancer is an androgen-driven disease. It is known that if ADT is not instituted, the patient will be at risk of ultimately dying from the disease. I also discuss side effects such as metabolic syndrome, exacerbation of glucose intolerance, dyslipidemia, and the implications of bone mineral density loss secondary to lowering testosterone levels.

Dr. Pieczonka: I reinforce the topic of side effects as being very relevant, but within the context of trying to improve overall survival.

Dr. Moul: Patients value quality of life as much as quantity of life, and ultimately the efficacy/safety balance will be the primary driver in treatment decision-making.

QUESTION: What factors help you decide which therapy to choose?

Dr. Kassabian: In my practice, we follow a protocol with 1 product as our preferred luteinizing hormone-releasing hormone (LHRH) agonist. However, we also use an LHRH antagonist for patients in whom we want to avoid the flare phenomenon. We can then convert them to an agonist when PSA stability has occurred, which is usually after 3 or 4 months.

Dr. Moul: For patients with advanced disease who are starting hormone therapy for the first time, we initiate treatment with an antagonist because it is quick-acting and lowers testosterone levels within the first 72 hours. However, we communicate to our patients that this drug is only available in a
1-month formulation such that they will need to return to the clinic every month for subsequent injections. As such, some patients choose convenience and elect to switch to a longer-acting LHRH agonist (3–6 months dosing).

**Dr. Pieczonka:** While standard practice might be to perform surgical castration on these patients, very few of them actually opt for surgery. In my practice, we use a 6-month, subcutaneous formulation of leuprolide acetate, based on the clinical evidence of the levels of testosterone suppression achieved and because of the convenience to the patient.

**Dr. Shore:** In order to decide which therapy to choose, I review the patient’s clinical disease state, whether they have metastatic disease or BCR, and also consider other factors: their age (life expectancy), baseline fatigue, and cognitive levels. I assume that all of the therapies will result in significant, if not complete, sexual dysfunction, and I also address issues of convenience and accessibility for the patient.

### Testing and Monitoring

**Question:** What baseline testing do you do and why? What action do you take if target test levels are not achieved? Do you have treatment targets and how do you assess them?

**Dr. Moul:** I ensure that patients have a baseline PSA, testosterone, liver function test, and imaging or metastatic workup prior to initiating testosterone suppression therapy. They then return every month to check PSA and testosterone for the first few visits. Unless testosterone decreases to 20 ng/dL or less, I consider switching to a different agent. PSA is important for me, and my main goal is trying to achieve the best or lowest PSA nadir at 7 months into treatment, which is an important prognostic factor. Patients who achieve a PSA level less than 0.2 ng/dL 7 months into hormone therapy for advanced prostate cancer have a better prognosis than patients who nadir between 0.2 ng/dL and 4.0 ng/dL. The worst group would be patients who have a nadir PSA greater than 4.0 ng/dL at 7 months. These arguably already have castration-resistant disease and could therefore be eligible for some of the novel therapies for mCRPC. I emphasize, though, that this standard was developed in the pre-docetaxel era. Interestingly, there used to be controversy and some hesitation for starting hormone therapy in new M1 disease, but now and moving forward, if you have a new M1 patient, it’s routine to start ADT and treat with 6 cycles of docetaxel right away. There’s no longer much discussion about early versus late hormonal therapy with M1 disease.

**Discussion:** The group agreed that it is essential to check both baseline PSA and testosterone levels as part of practicing good medical care.

**Dr. Shore:** I recommend that we, as urologic oncologists, also measure at baseline: complete blood count, a comprehensive metabolic panel, and lactate dehydrogenase.

**Dr. Kassabian:** Depending on the clinical situation, I prefer a 3-month visit schedule, which allows me to evaluate PSA, bone health, weight gain/loss, and hot flashes at each appointment. I may repeat the bone scan or computed tomography scan. Using a PSA target, I like to see PSA decrease, and I personally don’t measure testosterone again unless the patient begins to fail ADT therapy (development of a clinical change or PSA increase).

**Dr. Pieczonka:** Baseline and subsequent testosterone testing are important and also allow for a clearer demonstration of testosterone suppression, which may help facilitate reimbursement claims. In order to properly manage patients, it is important to monitor testosterone during therapy to ensure that it is effectively being suppressed to the treatment target.

**Question:** Are there specific adverse events you monitor for, and how do you manage them?

**Dr. Pieczonka:** It is important to prepare your patients for potential concerns about decreased libido and erection issues that are almost always present with these medicines. I tell my patients that they are probably going to experience hot flashes, and this helps them be prepared to manage them (I might occasionally use megestrol acetate 20 mg bid). I will inform my patients’ primary care physician (PCP) that hormonal manipulation is being started, so the PCP can make sure any increased cardiovascular risks associated with ADT are not ignored.

**Dr. Moul:** In addition to hot flashes, I also monitor for weight gain, loss of muscle mass, development of diabetes, loss of bone mineral density, and cardiac toxicity. In my practice, we employ advanced practice providers (both nurse practitioners and physician’s assistants) who take an active role in cancer survivorship issues. They make sure my patients are receiving appropriate assessments during long-term ADT.

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Avoiding miniflares and escapes is critically important.

— Dr. Shore/Dr. Moul
CONTINUITY OF ADT

**QUESTION:** DO YOU CONTINUE TESTOSTERONE SUPPRESSION THERAPY THROUGHOUT THE PATIENTS’ LIFE? DOES IT DIFFER BETWEEN M1 PATIENTS AND THOSE WITH BCR?

**Dr. Moul:** Most patients with M1 prostate cancer will be on ADT for the remainder of their lives, both during the period with hormone-sensitive disease and when they are being treated for mCRPC. On the other hand, patients with BCR may reach a point when they become elderly and have stable disease, allowing them to potentially discontinue ADT. Furthermore, patients with earlier-stage disease and locally advanced prostate cancer receiving short-term testosterone reduction therapy in conjunction with radiation usually only get a discrete period of ADT (4, 6, or sometimes 18 months). It is anticipated that these patients could then discontinue ADT and decide later whether to restart.

**Dr. Kassabian:** Typically, yes, I do continue ADT therapy. However, if the patient has an undetectable PSA after 9 or 10 years (particularly in the BCR setting), I will consider discontinuing ADT therapy at that point and monitor the patient on a 6-monthly basis rather than every 3 months.

**QUESTION:** DO YOU EVER CONSIDER USING INTERMITTENT THERAPY? IF YES, WHEN AND IN WHICH PATIENTS? IF NO, WHY?

**Dr. Shore:** I do consider intermittent therapy selectively on a case-by-case basis. I consider an intermittent protocol if the patient is poorly tolerating ADT, due to issues with worsening fatigue, sexual dysfunction, etc. There are some cited advantages for intermittent ADT regarding quality of life, cost, and perhaps fewer cardiovascular events, which should be balanced against the disadvantages of cancer progression.

**DISCUSSION:** THE GROUP AGREED THAT INTERMITTENT THERAPY MAY BE APPROPRIATE IN SOME PATIENT POPULATIONS (E.G., ELDERLY PATIENTS WITH NONMETASTATIC DISEASE), BUT THEY FELT THAT THERE SHOULD BE NO CONSIDERATION OF INTERMITTENT THERAPY IN THE METASTATIC SETTING UNLESS THE PATIENT ABSOLUTELY REQUESTS IT, MAYBE DUE TO SIDE EFFECTS.

**Dr. Concepcion:** For those with nonmetastatic disease, I will generally start intermittent therapy for at least 12 to 18 months and ensure that their PSAs have not risen, then discuss with the patient about taking a drug holiday. The data are fairly clear that in the nonmetastatic space, intermittent therapy is noninferior to continuous therapy. I believe patients appreciate the fact that they are able to come off ADT.

**Dr. Kassabian/Dr. Moul:** We are believers in intermittent ADT in selected BCR patients who have no evidence of metastatic disease and who want to avoid side effects.

**Dr. Pieczonka:** I think intermittent therapy is very tempting to use in a patient who has BCR with nonmetastatic disease, but several factors prevent me from considering it, including studies that only show statistical noninferiority to continuous therapy. Furthermore, intermittent therapy makes it almost impossible to identify whether patients may be eligible for clinical studies or novel cancer therapies such as sipuleucel-T, abiraterone, enzalutamide, or radium-223. When I have a patient with BCR, I think long and hard before I put them on hormonal manipulation, as I believe that they will need to stay on it forever.

In order to properly manage patients, it is important to monitor testosterone during therapy to ensure that it is effectively being suppressed to the treatment target. — Dr. Pieczonka

**QUESTION:** IF THE PATIENT PROGRESSES AND DEVELOPS mCRPC, WHAT TRIGGERS DO YOU USE WHEN CONSIDERING ADDITIONAL THERAPIES AND WHAT RECOMMENDATIONS DO YOU MAKE REGARDING CONTINUING ADT?

**Dr. Moul:** At this point, I would repeat a metastatic disease workup, and a patient showing clinical progression on scans would certainly qualify for some of the novel agents for mCRPC. I would continue ADT and simply add in the appropriate new therapy. I also may suggest orchiectomy to some patients at this time. These patients will likely be on ADT for the rest of their lives, and although only about 10% of patients opt for surgery, those who do seem to be satisfied.

**Dr. Pieczonka:** The gold standard is to perform surgical castration, but I believe few patients want this in the modern era and it takes more effort than using simple injection therapy. For patients who develop metastatic disease, I prescribe sipuleucel-T as early as possible. There are other therapies including novel hormonal agents and/or radium-223, but I believe that sipuleucel-T should be used first while continuing with ADT, as Dr. Moul described.
Dr. Shore: It is important to individualize patient care and consider the patient’s life expectancy when deciding on a management plan.

Dr. Kassabian/Dr. Concepcion: We are also advocates for earlier imaging, based on the RADAR guidelines. Once metastatic disease is documented, however, treatment should be driven by the guidelines, either American Urological Association or National Comprehensive Cancer Network.

**QUESTION: DO YOU EVER STOP TESTOSTERONE SUPPRESSION THERAPY? IN WHAT PATIENT TYPES?**

Dr. Kassabian: Yes. Sometimes, the patient will ask me to discontinue therapy due to toxicity. However, if they have metastatic disease, I strongly encourage them to continue treatment. I will discontinue treatment if there is an undetectable PSA for close to a decade.

Dr. Shore: Yes, I discontinue ADT when patients have been on it for very prolonged periods of time and have chronically suppressed testosterone levels, suggesting exhaustion of the endocrine pathway. I may also stop therapy as a cost reduction strategy or to reduce adverse events.

Dr. Moul: I discontinue testosterone suppression in patients who are receiving short-term therapy associated with radiation. Patients with BCR typically receive an initial cycle of 6 to 9 months of ADT and would only resume if there was a certain level of PSA recurrence. Most patients who have metastatic advanced prostate cancer should be on continuous ADT for the rest of their lives.

Dr. Pieczonka: No, I typically do not discontinue ADT.

**CONCLUSIONS AND FUTURE DIRECTIONS**

Instituting ADT will benefit patients when chosen judiciously by ensuring that the benefits outweigh the risks. There has been widely accepted discussion regarding initiation of ADT for patients with M1 disease. For patients with high-volume, androgen-sensitive disease, ADT is now being administered in combination with chemotherapy.

While still controversial, the use of intermittent ADT in patients with BCR is generally accepted for patients with a perceived less-aggressive biologic phenotype. The benefits of continuous therapy versus intermittent therapy for patients with newly diagnosed metastatic disease have been described, but for patients with BCR alone, the debate continues, recognizing the importance of physician–patient shared decision-making.

Employing appropriate judgment on a case-by-case basis ensures that the benefits of testosterone suppression outweigh the risks, attempting to foster clinical and economic efficiency as well as optimal patient outcomes. Setting treatment targets, such as a level of less than 20 ng/dL for testosterone and monitoring of treatment success, are also important.

In general, testosterone suppression remains the mainstay of therapy for advanced prostate cancer. As clinical trials continue to investigate newer agents in mCRPC, patients, effective strategies for testosterone suppression may vary and often require individualization for maximizing patient care. Ultimately, there is a consensus that, for most patients initiating an ADT regimen, they will invariably remain on therapy and be impacted by its benefits and risks during their continuum of care.

**SUGGESTED READING**


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