Prostate Cancer Clinical Practice Guidelines Update

Selected updates relevant to ADT:
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
Clinical Practice Guidelines for Prostate Cancer

Selected updates adapted from v2.2025 (Apr 16, 2025) to v2.2026 (Sept 15, 2025)

Sumitomo Pharma | Pfizer Oncology

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DEFINED AS:

- Clinically localized (N0, M0) disease
- Regional (N1, M0) disease
- Positive lymph notes (pN1 disease) and/or adverse features post-RP
- First M0 RP PSA persistence/recurrence

RT with one of the following ADT options*:
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH agonist (as above) + first generation anti-androgen
Nilutamide, flutamide, or bicalutamide
LHRH antagonist
Degarelix or **relugolix**
LHRH agonist or antagonist + abiraterone *(2 years; only for very-high-risk localized disease or positive lymph nodes)*

NOTES from National Comprehensive Cancer Network® (NCCN®):

- ADT is not recommended with RT for most patients with favorable intermediate-risk prostate cancer. If it is given, the duration should be short term (4-6 mo)
- **For unfavorable intermediate risk PC** treated with RT, short-term ADT (4-6 mo) is recommended. Concurrent/adjuvant ADT is preferred over neoadjuvant ADT in this setting.
- **For high- and very high-risk PC** treated with EBRT alone, long-term ADT (18-36 mo) is recommended
- **For high-risk PC** treated with combination EBRT + brachytherapy, a shortened duration of ADT (12 mo) can be considered

*All recommendations are NCCN Category 2A unless otherwise indicated.

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NOTES from NCCN regarding first M0 PSA persistence/recurrence:

- The timing of secondary treatment for patients whose only evidence of cancer after definitive treatment is an increasing PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient
- Earlier treatment may be better than delayed treatment, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early treatment is not clear, treatment should be individualized until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider treatment earlier
- For patients with secondary RT in the setting of first RP recurrence, if ADT is given, it should be for a duration of 6-24 months
- Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation
- Patients who choose ADT monotherapy in the secondary treatment setting should consider intermittent ADT

RT with one of the following ADT options*:
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH agonist (as above) + first generation anti-androgen
Nilutamide, flutamide, or bicalutamide
LHRH antagonist
Degarelix or **relugolix**
LHRH agonist or antagonist + abiraterone *(2 years; only for very-high-risk localized disease or positive lymph nodes)*

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Principles of Androgen Deprivation Therapy

DEFINED AS:

Regional (N1, M0) disease

First M0 RT recurrence

ADT options*:
Orchiectomy
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH agonist (as above) + first generation anti-androgen
Nilutamide, flutamide, or bicalutamide
LHRH antagonist
Degarelix or **relugolix**
LHRH agonist, antagonist, or orchiectomy + abiraterone *(only for positive lymph nodes)*

NOTES from NCCN regarding M0 PSA persistence/recurrence:

- The timing of secondary treatment for patients whose only evidence of cancer after definitive treatment is an increasing PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient
- Earlier treatment may be better than delayed treatment, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early treatment is not clear, treatment should be individualized until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider treatment earlier
- Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation
- Patients who choose ADT monotherapy in the secondary treatment setting should consider intermittent ADT

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Principles of Androgen Deprivation Therapy

NOTES from NCCN:

- Monitoring until diagnosis of metastatic disease is preferred for patients with M0 CSPC in the low-risk BCR2 setting
- PSADT and Grade Group should be considered when deciding whether to begin ADT for patients with M0 disease
- ADT monotherapy is an option for these patients, and intermittent ADT can be considered to reduce toxicity

ADT options*:
Orchiectomy
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH agonist (as above) + first generation anti-androgen
Nilutamide, flutamide, or bicalutamide
LHRH antagonist
Degarelix or **relugolix**
Useful in certain circumstances
Enzalutamide ± leuprolide *(for high-risk BCR2)*
Apalutamide with LHRH agonist or antagonist *(for high-risk BCR2)*

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ADT with treatment intensification (systemic therapy)*:
Orchiectomy + abiraterone, apalutamide, darolutamide, or enzalutamide
LHRH agonist or antagonist + abiraterone, apalutamide, darolutamide, or enzalutamide
Orchiectomy + docetaxel and abiraterone, apalutamide, darolutamide, or enzalutamide
LHRH agonist or antagonist + docetaxel and abiraterone, apalutamide, darolutamide, or enzalutamide

ADT with treatment intensification (EBRT to primary tumor)
EBRT with orchiectomy ± abiraterone, apalutamide, docetaxel, or enzalutamide
EBRT with LHRH agonist or antagonist ± abiraterone, apalutamide, docetaxel, or enzalutamide

ADT alone for select patients*:
Orchiectomy
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH agonist (as above) + first generation anti-androgen
Nilutamide, flutamide, or bicalutamide
LHRH antagonist
Degarelix or **relugolix**

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Secondary hormone therapy for M0 or M1 CRPC*:
Castrate levels of testosterone (<50 ng/dL) should be maintained while additional therapies are applied
Orchiectomy, LHRH agonist or antagonist with specific therapies noted for M0 and M1 CRPC
Orchiectomy, LHRH agonist or antagonist with other secondary hormone options
Abiraterone or enzalutamide after progression on ARPIs (M1 only)
Abiraterone + 0.5 mg/d dexamethasone after progression on abiraterone (M1 only)
Anti-androgen withdrawal
Corticosteroids (hydrocortisone, prednisone, or dexamethasone)
First-generation anti-androgen (nilutamide, flutamide, or bicalutamide)
Ketoconazonle + hydrocortisone

NOTES from NCCN:

- Although optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection

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Principles of Androgen Deprivation Therapy

ADT monotherapy options*:
Orchiectomy
LHRH agonist monotherapy
Goserelin, leuprolide, or triptorelin
LHRH antagonist
Degarelix or **relugolix**

NOTES from NCCN:

- ADT monotherapy is appropriate for patients with life expectancy ≤5 years whose cancer progressed on observation of localized disease, who are symptomatic, or who have N1M0 disease
- ADT monotherapy is also used for asymptomatic patients with regional disease and life expectancy ≤5 years whether or not RT is given

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Principles of Androgen Deprivation Therapy

Optimal ADT

- Medical castration (ie, LHRH agonist or antagonist) and surgical castration (ie, bilateral orchiectomy) are equally effective.
- Patients who do not achieve adequate suppression of serum testosterone (<50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. Consider monitoring testosterone levels 12 weeks after first dose of LHRH therapy, then upon increase in PSA. The optimal level of serum testosterone to affect "castration" has yet to be determined.

Monitor/Surveillance

- ADT has a variety of adverse effects, including hot flashes, loss of libido, erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, anemia, breast enlargement and tenderness/soreness, depression and mood swings, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk of diabetes and cardiovascular disease. The intensity and spectrum of these side effects vary greatly, and many are reversible or can be avoided or mitigated. Patients and their medical providers should be advised about these risk prior to treatment.

Optimal ADT bullet removed (no longer in the latest guidelines):

Data are limited on long-term adherence to oral relugolix and the potential effects on optimal ADT. Ongoing monitoring for sustained suppression of testosterone (<50 ng/dL) can be considered, and relugolix may not be a preferred agent if adherence to the prescribed regimen is uncertain

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