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NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Prostate Cancer

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NCCN National Comprehensive Cancer Network®

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Clinically Localized (N0,M0) Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- ADT should not be used as monotherapy in clinically localized prostate cancer unless there is a contraindication to definitive local therapy such as life expectancy ≤5 years and comorbidities. Under those circumstances, ADT may be used [see ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy ≤5 Years (PROS-G, 5 of 5)].
- Giving ADT before, during, and/or after radiation (neoadjuvant, concurrent, and/or adjuvant ADT) prolongs survival in selected patients treated with radiation. For short-term ADT with prostate-only RT, concurrent/adjuvant ADT is preferred over neoadjuvant ADT. Options are:
  - Luteinizing hormone-releasing hormone (LHRH) agonist alone
    - ◊ Goserelin, leuprolide, or triptorelin
  - LHRH agonist (as above) plus first-generation antiandrogen
    - ◊ Nilutamide, flutamide, or bicalutamide
  - LHRH antagonist
    - ◊ Degarelix or relugolix
  - LHRH agonist or antagonist with abiraterone (very high risk only)
- For additional details on the use of RT with ADT by risk group, see PROS-I.
- Studies of short-term (4–6 mo) and long-term (2–3 y) neoadjuvant, concurrent, and/or adjuvant ADT all have used combined androgen blockade. Whether the addition of an antiandrogen is necessary requires further study.
- The largest randomized trial to date using the antiandrogen bicalutamide alone at high dose (150 mg) showed a delay in recurrence of disease but no improvement in survival; however, longer follow-up is needed.
- Abiraterone can be added to EBRT and 2 years of ADT in patients with very-high-risk prostate cancer. In the STAMPEDE trial, the hazard ratios for OS with the addition of abiraterone to EBRT and ADT in patients with node-negative disease was 0.69 (95% CI, 0.49–0.96). Severe hypertension or cardiac disorders were noted in 10% of patients in the abiraterone arm and grade 3–5 liver toxicity was noted in 7%.
  - Abiraterone should be given with concurrent steroid:
    - ◊ Prednisone 5 mg PO once daily for the standard formulation
    - ◊ Methylprednisolone 4 mg PO twice daily for the fine-particle formulation (category 2B)

ADT for Regional (N1,M0) Disease

- Patients with N1,M0 prostate cancer and a life expectancy >5 years or who are symptomatic can be treated with:
  - EBRT and neoadjuvant, concurrent, and/or adjuvant ADT as for patients with N0,M0 disease (see above) without abiraterone
  - EBRT and neoadjuvant, concurrent, and/or adjuvant LHRH agonist or antagonist with abiraterone
  - ADT alone or with abiraterone (see below)
- Abiraterone should be given with concurrent steroid:
  - Prednisone 5 mg PO once daily for the standard formulation
  - Methylprednisolone 4 mg PO twice daily for the fine-particle formulation (category 2B)
  - Abiraterone with ADT should be considered for a total of 2 years for those patients with N1 disease who are treated with radiation to the prostate and pelvic nodes.
- Options for ADT are:
  - Orchiectomy
  - LHRH agonist alone
    - ◊ Goserelin, leuprolide, or triptorelin
  - LHRH agonist (as above) plus first-generation antiandrogen
    - ◊ Nilutamide, flutamide, or bicalutamide
  - LHRH antagonist
    - ◊ Degarelix or relugolix
  - Orchiectomy plus abiraterone
  - LHRH agonist (as above) plus abiraterone
  - LHRH antagonist plus abiraterone
- The use of ADT plus abiraterone in patients with N1 M0 prostate cancer is based on the STAMPEDE trial, which demonstrated improved OS of the combination compared with ADT alone.
- Patients with regional disease and life expectancy ≤5 years who chose ADT can receive LHRH agonist, LHRH antagonist, or orchiectomy.

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for pN1 Disease

- In one randomized trial, immediate and continuous use of ADT in patients with positive nodes following RP resulted in significantly improved OS compared to patients who received delayed ADT. Therefore, such patients should be considered for immediate LHRH agonist, LHRH antagonist, or orchiectomy. EBRT may be added (category 2B), in which case the ADT options are as for neoadjuvant, concurrent, and/or adjuvant ADT for clinically localized disease (see above). Many of the side effects of continuous ADT are cumulative over time on ADT.

ADT for M0 PSA Persistence/Recurrence After RP or RT (ADT for M0 Castration-Sensitive Disease)

- The timing of ADT 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.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.
- Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT 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 ADT earlier.
- Some patients are candidates for secondary therapy after PSA persistence/recurrence. See PROS-10 and PROS-11.
- Patients with prolonged PSADTs (>12 months) and who are older are candidates for observation.
- Patients who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm. An unplanned subset analysis showed that patients with Grade Group 4 or 5 prostate cancer in the continuous arm had a median OS that was 14 months longer (8 years) than those in the intermittent arm (6.8 years).
- ADT options are:
  - ▸ M0 RP PSA persistence/recurrence:
    - ◊ EBRT +/- neoadjuvant, concurrent, and/or adjuvant ADT [see ADT for Clinically Localized (N0,M0) Disease, see PROS-G 1 of 5]
    - ◊ EBRT + LHRH agonist or antagonist with abiraterone (studies positive for pelvic nodal recurrence only)
  - ▸ M0 RT recurrence:
    - ◊ Orchiectomy
    - ◊ LHRH agonist alone
      - – Goserelin, leuprolide, or triptorelin
    - ◊ LHRH agonist (as above) plus first-generation antiandrogen
      - – Nilutamide, flutamide, or bicalutamide
    - ◊ LHRH antagonist
      - – Degarelix or relugolix
    - ◊ Orchiectomy, LHRH agonist (as above), or LHRH antagonist plus abiraterone (studies positive for pelvic nodal recurrence only)
  - ▸ Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease, see PROS-G 1 of 5].

ADT for M0 Castration-Sensitive Disease After Maximal Pelvic Therapy

- Monitoring until diagnosis of metastatic disease is preferred for patients with non-metastatic castration-sensitive disease who are not candidates for pelvic therapy.
- 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.
  - ▸ Options for ADT are the same as listed above for M0 RT recurrence.
- Enzalutamide with or without leuprolide is an option for patients who have the following high-risk criteria: M0 by conventional imaging; PSADT ≤9 months; PSA ≥2 ng/mL above nadir after RT or ≥1 ng/mL after RP with or without postoperative RT; and not considered a candidate for pelvic-directed therapy. In the EMBARK trial, metastasis-free survival (MFS) was improved in participants treated with enzalutamide plus leuprolide or with enzalutamide monotherapy compared with leuprolide alone. The most common adverse events associated with combination therapy and enzalutamide monotherapy were hot flashes and fatigue. Enzalutamide monotherapy was also significantly associated with gynecomastia (45% compared with 8% to 9% in the combination and leuprolide alone groups), nipple pain (15% compared with 1%–3%), and breast tenderness (14% compared with 1%).

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Metastatic Castration-Sensitive Disease

- ADT with treatment intensification is strongly recommended for most patients with metastatic prostate cancer. The use of ADT monotherapy in metastatic castration-sensitive disease is discouraged unless there are clear contraindications to combination therapy. If ADT monotherapy is given, intermittent ADT can be considered to reduce toxicity.
- Treatment options for patients with M1 castration-sensitive disease are:
  - ADT alone (orchiectomy, LHRH agonist, LHRH agonist plus first-generation antiandrogen, or LHRH antagonist)
    - ◊ LHRH agonists: Goserelin, leuprolide, or triptorelin
    - ◊ First-generation antiandrogens: Nilutamide, flutamide, or bicalutamide
    - ◊ A first-generation antiandrogen must be given with LHRH agonist for ≥7 days to prevent testosterone flare if metastases are present in weight-bearing bone
  - Orchiectomy plus abiraterone, enzalutamide, or apalutamide
  - Orchiectomy plus docetaxel and abiraterone or darolutamide
  - LHRH agonist (as above) plus abiraterone, enzalutamide, or apalutamide
  - LHRH agonist (as above) plus docetaxel and abiraterone or darolutamide
  - LHRH antagonist plus abiraterone, enzalutamide, or apalutamide
  - LHRH antagonist plus docetaxel and abiraterone or darolutamide
- Abiraterone should be given with concurrent steroid [see ADT for Regional (N1,M0) Disease, see PROS-G 1 of 5].
- When EBRT to primary tumor is given with ADT in low metastatic burden M1, the options for ADT are:
  - Orchiectomy alone or with abiraterone or docetaxel
  - LHRH agonist alone or with abiraterone or docetaxel
  - LHRH antagonist alone or with abiraterone or docetaxel
- Two randomized phase 3 clinical trials of abiraterone with prednisone plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. Adverse events were higher with abiraterone and prednisone but were generally mild in nature and were largely related to mineralocorticoid excess (ie, hypertension, hypokalemia, edema), hormonal effects (ie, fatigue, hot flushes), and liver toxicity.
- Cardiac events, severe hypertension, and liver toxicity were increased with abiraterone.
- A double-blind randomized phase 3 clinical trial of apalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. Adverse events that were more common with apalutamide than with placebo included rash, hypothyroidism, and ischemic heart disease.
- An open-label randomized phase 3 clinical trial of enzalutamide plus ADT in patients with castration-sensitive metastatic prostate cancer demonstrated improved OS over ADT alone. In a separate double-blind randomized phase 3 clinical trial, enzalutamide reduced the risk of metastatic progression or death compared with placebo and showed an OS benefit. Adverse events associated with enzalutamide included fatigue, seizures, and hypertension.
- A phase 3 trial compared continuous ADT to intermittent ADT, but the study could not demonstrate non-inferiority for survival. However, quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months of ADT compared to the continuous ADT arm.
- In addition, three meta-analyses of randomized controlled trials did not show a difference in survival between intermittent and continuous ADT.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.

Secondary Hormone Therapy for M0 or M1 CRPC

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone (<50 ng/dL) should be maintained by continuing LHRH agonist or antagonist while additional therapies are applied.
- Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by conventional imaging, M0 CRPC vs. M1 CRPC, and whether or not the patient is symptomatic.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

- Administration of secondary hormonal therapy can include novel hormone therapy (ie, certain second-generation antiandrogens, androgen metabolism inhibitors) and certain novel hormone therapy/targeted therapy combinations (see PROS-14 and PROS-16). Other secondary hormone therapy options for M0 and M1 CRPC are:
  - ◊ First-generation antiandrogen (nilutamide, flutamide, or bicalutamide)
  - ◊ Corticosteroids (hydrocortisone, prednisone, or dexamethasone)
  - ◊ Antiandrogen withdrawal
  - ◊ Ketoconazole plus hydrocortisone
  - ◊ Abiraterone or enzalutamide following progression on other novel hormone therapies
  - ◊ Abiraterone plus dexamethasone following progression on either formulation of abiraterone
- Abiraterone should be given with concurrent steroid, either prednisone 5 mg PO twice daily for the standard formulation or methylprednisolone 4 mg PO twice daily for the fine-particle formulation.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed apalutamide (240 mg/day) improved the primary endpoint of MFS over placebo (40.5 months vs. 16.2 months). After a median follow-up of 52 months, final OS analysis showed an improved median OS with apalutamide versus placebo (73.9 months vs. 59.9 months). Adverse events included rash (24% vs. 5.5%), fracture (11% vs. 6.5%), and hypothyroidism (8% vs. 2%). Bone support should be used in patients receiving apalutamide.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed enzalutamide (160 mg/day) improved the primary endpoint of MFS over placebo (36.6 months vs. 14.7 months). Median OS was longer in the enzalutamide group than in the placebo group (67.0 months vs. 56.3 months). Adverse events included falls and nonpathologic fractures (17% vs. 8%), hypertension (12% vs. 5%), major adverse cardiovascular events (5% vs. 3%), and mental impairment disorders (5% vs. 2%). Bone support should be used in patients receiving enzalutamide.
- A phase 3 study of patients with M0 CRPC and a PSADT ≤10 months showed darolutamide (600 mg twice daily) improved the primary endpoint of MFS over placebo (40.4 months vs. 18.4 months). OS at 3 years was 83% (95% CI, 80–86) in the darolutamide group compared with 77% (95% CI, 72–81) in the placebo group. Adverse events that occurred more frequently in the treatment arm included fatigue (12.1% vs. 8.7%), pain in an extremity (5.8% vs. 3.2%), and rash (2.9% vs. 0.9%). The incidence of fractures was similar between darolutamide and placebo (4.2% vs. 3.6%).
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone and low-dose prednisone (5 mg BID) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. An improvement in OS was demonstrated. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.
- A phase 3 study of docetaxel-sensitive patients with M1 CRPC showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and OS. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of patients on enzalutamide).
- In the post-docetaxel M1 CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized controlled trials. Therefore, each agent has a category 1 recommendation.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/day enzalutamide improved progression-free survival (PFS) compared to 50 mg/day bicalutamide in patients with treatment-naïve M1 CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side effect profiles of the agents and the increased cost of enzalutamide.
- Although the optimal sequence of therapies remains undefined, some data are emerging that can help with treatment selection in some cases. See Discussion.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Patients on Observation Who Require Treatment and Those with Life Expectancy ≤5 Years

- **Treatment for patients whose cancer progressed on observation of localized disease is LHRH agonist or antagonist or orchiectomy.**

Optimal ADT

- **Medical castration (ie, LHRH agonist or antagonist) and surgical castration (ie, bilateral orchiectomy) are equally effective.**
- **Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.**
- **Antiandrogen therapy should precede or be coadministered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.**
- **Antiandrogen monotherapy appears to be less effective than medical or surgical castration and is not recommended.**
- **No clinical data support the use of finasteride or dutasteride with combined androgen blockade.**
- **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.**
- **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.**

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 for diabetes and cardiovascular disease. The intensity and spectrum of these side effects vary greatly, and many are reversible or can be avoided or mitigated. For example, physical activity can counter many of these symptoms and should be recommended (NCCN Guidelines for Survivorship). Use of statins also should be considered. Patients and their medical providers should be advised about these risks prior to treatment.**

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