Androgen Deprivation Therapy: Minimizing Exposure and Mitigating Side Effects

Miren Gaztañaga, MD, and Juanita Crook, MD, FRCPC

Abstract
Despite common and occasionally serious side effects, androgen deprivation therapy (ADT) is widely used in the management of prostate cancer at all stages and presentations. ADT is frequently used in situations in which evidence of benefit is lacking, such as combined with definitive radiotherapy for favorable-risk prostate cancer, or in the primary management of elderly patients with low-risk disease. In intermediate- and high-risk disease, the role of ADT is being challenged and is decreasing in importance, as the ability to deliver very high biologically effective doses becomes more widely available, especially through the combination of external radiotherapy and brachytherapy. Appropriately selecting patients for ADT according to established indications will minimize the number exposed, whereas systematic patient education before initiating treatment can ameliorate the side effects. Minimizing the exposure to ADT and efforts to mitigate the side effects may have a beneficial effect on quality of life for many men with prostate cancer. (JNCCN 2012;10:1088–1096)

NCCN: Continuing Education

Learning Objectives
Upon completion of this activity, participants will be able to:

• Select the most appropriate patients for ADT according to established indications.
• Describe methods to mitigate side effects in order to improve quality of life for men with prostate cancer.
Since Huggins and Hodges first recognized the androgen dependence of prostate cancer in 1940, androgen deprivation therapy (ADT) has been the mainstay of treatment for metastatic prostate cancer. ADT is also commonly used in combination with external beam radiation therapy (EBRT) for high-risk or locally advanced disease for durations of 6 months to 3 years. Several large multi-institutional randomized trials have shown survival benefit when ADT is combined with conventional EBRT under these circumstances. Apart from these well-established indications, ADT is commonly used in other scenarios with far less supporting evidence. It may be prescribed as primary treatment in nonmetastatic disease, especially in elderly patients, or in conjunction with brachytherapy. As prostate cancer is the most common cancer in men in the developed world, this wide range of indications exposes ever-increasing numbers of men to the side effects of ADT.

**Adverse Effects of Androgen Deprivation**

The side effects of ADT are well documented in the literature. Initially, the most obvious symptoms of sexual dysfunction, loss of libido, and hot flashes were emphasized, but as experience grew the effects of ADT on other systems became apparent. Men on ADT run the risk of developing osteoporosis and have a 23% greater incidence of clinical fractures. They have a tendency to develop obesity, insulin resistance, and diabetes. Alterations in lipids and cardiovascular disease contribute to a 17% increase in cardiovascular-related mortality. Fatigue may be related to anemia, decreased muscle mass, and depression. Cognitive dysfunction has also been documented. The impact of these adverse effects varies from patient to patient but tends to increase with the duration of treatment, as stated in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer (to view the most recent version, visit NCCN.org).

The recently recognized metabolic syndrome, characterized by central obesity, elevated triglycerides, reduced high-density lipoproteins, elevated blood pressure, and elevated fasting glucose, is present in more than 50% of men with prostate cancer undergoing long-term ADT compared with 22% not receiving ADT. Metabolic syndrome may contribute to all-cause mortality and may also be associated with a shorter time to disease progression. In an observational study of a population-based cohort of 73,196 patients, Keating et al found that ADT was associated with a 44% increased risk of diabetes and a 16% increase in myocardial infarction and sudden cardiac death. Although Tsai et al also reported that cardiovascular deaths were 2.6 times more common in men on ADT, not all studies concur. A recently published meta-analysis of 4141 patients from 8 randomized trials found no association between ADT and increased cardiovascular death. Stratification according to preexisting cardiovascular comorbidity may be important when considering the influence of ADT on cardiovascular death.

**Minimizing Exposure to ADT**

**Low-Risk Patients**

No level 1 evidence supports ADT as primary treatment for low-risk prostate cancer, either alone or combined with EBRT. In 2011, Jones et al published the results of RTOG 9408, which randomized 1987 men with T1 to T2 disease to either 66 Gy of EBRT alone or combined with 4 months of ADT. At a median follow-up of 9.1 years, the addition of short-term ADT did not improve 10-year overall survival or decrease disease-specific mortality in low-risk disease (Table 1).

In elderly patients with localized disease, ADT has been used as primary therapy as an alternative to surgery, radiation, or watchful waiting. A population-based cohort of 19,271 men aged 66 years or older with localized prostate cancer (median age, 77 years), 41% received ADT as monotherapy, whereas the rest were managed conservatively with no surgery, radiation, or ADT in the first 180 days after diagnosis. During the median follow-up of 81 months, 1560 prostate cancer deaths and 11,045 deaths from all causes occurred. Primary ADT was associated with lower 10-year prostate cancer–specific survival (80.1% vs. 82.6%; hazard ratio [HR], 1.17; 95% CI, 1.03–1.33) and similar 10-year overall survival (30.2% vs. 30.3%; HR, 1.00; 95% CI, 0.96–1.05) compared with conservative management. Although ADT improved disease-specific survival in men with poorly differentiated cancer, it had no impact on overall survival even in this subset. Primary ADT
in elderly men with localized prostate cancer is not associated with improved survival when compared with watchful waiting.17

ADT is often used to reduce prostate volume before prostate brachytherapy. Although a short course of ADT is usually sufficient (3–6 months), hot flushes and impotence affect quality of life and persist after therapy ceases. Beyer et al19 reported a deleterious effect on overall survival for the 20% of 2378 patients who received ADT for downsizing before prostate brachytherapy. At follow-up ranging to 12.6 years (median, 4.1 years), overall survival decreased with increasing age, increasing Gleason score, and ADT use. Other approaches, such as oral antiandrogens and/or 5-α reductase inhibitors, are associated with less sexual toxicity, but prostate volume reduction may be less.

**Intermediate-Risk Patients**

The role of ADT in the intermediate-risk group is controversial, and is based largely on extrapolation of data from studies in which intermediate- and high-risk patients are combined and treated with conventional EBRT. No prospective randomized data focus exclusively on the use of ADT in an intermediate-risk setting. Likewise, no prospective, randomized data define the role of ADT in the setting of dose-escalated radiotherapy.

In RTOG 9408, analysis of the intermediate-risk group showed that the addition of short-term ADT to EBRT increased 10-year overall survival from 54% to 61% (P = .03) and reduced disease-specific mortality from 10% to 3% (P < .01). Another study by D’Amico et al20 randomized 206 men with intermediate-to high-risk disease to EBRT (70 Gy) with or without 6 months of ADT and found benefits in overall survival (88% vs. 78%; P = .04), cause-specific survival, and biochemical control, but did not stratify by risk categories. However, both of these trials used conventional EBRT doses of 66.6 to 70 Gy. Results should not be extrapolated to patients treated using optimal-dose escalation with EBRT doses greater than 80 Gy or combined with brachytherapy. Whether the same benefits will be seen with optimal dose escalation is unknown; in the absence of pre-existing subclinical micrometastatic disease, a high enough radiation dose to the prostate may obviate the need for ADT.

Ample evidence shows the benefits of dose-escalated radiotherapy in terms of biochemical disease-free survival, local eradication of tumor, and improved freedom from distant metastases through prevention of a second wave of metastatic seeding from uncontrolled recurrent local tumor. Posttreatment prostate biopsies are more frequently negative.

| Table 1  Summary of Evidence for ADT According to Risk Categories |
|---------------------------------|---------------------------------|---------------------------------|
| **Risk Category**               | **Indication**                  | **Comments**                    |
| Low                             | Not recommended as a primary    |                                 |
|                                 | treatment17                     |                                 |
|                                 | Volume downsizing before        |                                 |
|                                 | brachytherapy                   |                                 |
| Intermediate                    | Combined with radiotherapy (4–6 mo) to increase overall survival16,20 | • Some controversy on benefits/harms19 • Consider alternative approaches |
| High                            | Combined with radiotherapy (2–3 y) to increase overall survival24,29–31 | • Patients were treated with conventional doses of radiotherapy • Lack of randomized data with dose escalation • Series of patients treated with dose-escalated radiotherapy show no biochemical impact of addition of ADT16 |
| Recurrent                       | Primary treatment               |                                 |
| Metastatic                      | Primary treatment               |                                 |

Abbreviations: ADT, androgen deprivation therapy; ELAAT, Early Versus Late Androgen Ablation Trial; PSA, prostate-specific antigen; TOAD, Timing of Androgen Deprivation.
with escalated doses of radiation, and this not only correlates with freedom from biochemical failure (bNED) but also is the strongest predictor of freedom from distant metastases and cancer death.21 Eradicating the primary tumor is essential to prevent ultimate death from subsequent metastatic disease. Multiple randomized trials of dose escalation with mature follow-up have also shown reduction in biochemical and clinical failure rates comparing 70 with 78 Gy,22 70.2 with 79.2 Gy,23 and 68 with 78 Gy.24

Brachytherapy as a form of dose escalation achieves biologically effective doses much higher than can be achieved with EBRT. Deutsch et al25 reported on a retrospective comparison of biochemical outcomes using an ultra-high dose of conventionally fractionated intensity-modulated radiotherapy (IMRT; 86.4 Gy; n = 470) versus a lower dose of IMRT (50.4 Gy) combined with high-dose-rate brachytherapy (21 Gy/3 fractions; n = 160). The 5-year actuarial prostate-specific antigen (PSA) relapse-free survival was improved for patients treated with the high-dose-rate boost versus IMRT alone, with the most significant benefit being seen for intermediate-risk patients (98% vs. 84%; P < .001).

No prospective randomized trials specifically address the issue of ADT in combination with brachytherapy for intermediate-risk disease, but retrospective data suggest at best an equivocal effect.19,26 In 2010, Stock et al26 analyzed 432 patients treated with optimal dose escalation using combination of EBRT and brachytherapy, 350 of whom received ADT. With a median follow-up of 56 months, ADT did not impact on the 8-year biochemical failure-free rate.

The role of ADT combined with high-dose radiotherapy remains to be defined. Retrospective data suggest a lesser role and do not show a survival benefit. A subset analysis of 883 patients from the RTOG 9406 phase I/II clinical trial of dose escalation evaluated the effect on biochemical and disease-free survival rates from the addition of ADT to dose-escalated radiotherapy (mean dose, 78.5 Gy). After stratifying by risk groups, no difference in bNED or disease-free survival was observed, although in high-risk patients the difference approached significance.27 In 1260 patients with intermediate- to high-risk prostate cancer, Martinez et al28 reported that the addition of a short course of ADT to EBRT and a brachytherapy boost did not improve overall survival, disease-free survival, biochemical control, or local control. In fact, the addition of ADT in this retrospective study correlated with higher rates of metastases and cancer-related deaths. The phase III RTOG 0815 trial is currently addressing the role of ADT with dose escalation through randomizing intermediate-risk patients to dose escalation with or without 6 months of ADT.

High-Risk Patients

The benefit of ADT combined with conventional EBRT in high-risk disease has been established in several randomized trials2–4,29–31 showing improved biochemical, local, and distant control and disease-free and overall survival (Table 2). The EORTC published the 10-year results of a randomized study of 415 patients that assessed the benefit of the addition of 3 years of ADT to conventional EBRT and showed an increase in overall survival (39.8% vs. 58.1%; P = .0004).3 Similarly, Denham et al31 randomized 818 patients to either radiotherapy alone or combined with 3 or 6 months of ADT. The best outcome was achieved with 6 months of ADT. The 10-year follow-up of RTOG 92-02 established that long-term ADT (2 or 3 years) is superior to short-term (4 months).2 RTOG 85-31 showed improved survival for adjuvant ADT after EBRT rather than ADT reserved for relapse.29

However, all of these studies used conventional EBRT doses of 65 to 70 Gy; the potential benefit of ADT combined with an optimal radiation dose has not been defined. Whether an intermediate duration such as 9 to 12 months would provide equivalent benefit remains to be proven, although Stock et al342 reported consistently excellent results in high-risk patients treated with “trimodality” therapy using 9 months of ADT and achieving optimal dose escalation with a combination of EBRT and a brachytherapy boost.

Recurrent Disease

Patients with a rising PSA after definitive treatment are often asymptomatic and have no clinical evidence of disease. Although early intervention increases both cost and side effects, delaying the start of ADT may increase the risk of serious morbidity, such as spinal cord compression.33 Patients with adverse factors such as high Gleason score, younger age,35 and short PSA doubling time34,35 should be considered for earlier ADT rather than deferred. Patients without any of the above factors and who have
shown a previous response to ADT may not require immediate intervention. Selection for deferred ADT may be clarified by 2 recently closed randomized clinical trials: TOAD (Timing of Androgen Deprivation), sponsored by the Trans Tasman Radiation Oncology Group, and ELAAT (Early versus Late Androgen Ablation Trial) by the Ontario Clinical Oncology Group. Both trials closed prematurely but are in the follow-up period and will combine their data on more than 350 patients.

Once ADT has been initiated, an intermittent approach should be considered. Intermittent androgen deprivation (IAD) is defined as cycles of ADT followed by periods of testosterone recovery. It was first described in the pre-PSA era in 1986 by Klotz et al, with cycles defined by symptomatic progression. Laboratory data using androgen-dependent cell lines, such as the Shionogi mouse mammary tumor and the LNCaP cell line, have shown the ability of androgen-dependent cells to undergo repeated cycles of apoptosis secondary to cyclical hormonal withdrawal. Results of clinical phase II studies have shown feasibility and improvement in quality of life with reduced side effects.

### Metastatic Disease

For the past 7 decades, ADT has been widely used for systemic management of metastatic prostate cancer. Although the standard approach is continuous ADT until castration resistance is manifested, the role of intermittent ADT is also being

### Table 2 Summary of Level 1 Evidence for Androgen Deprivation Therapy in High-Risk Patients

<table>
<thead>
<tr>
<th>Author (Group and Study)</th>
<th>n</th>
<th>Follow-Up</th>
<th>Radiotherapy</th>
<th>Randomization</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolla et al(EORTC 22863)</td>
<td>415</td>
<td>9.1 y</td>
<td>70 Gy</td>
<td>No ADT vs. ADT 3 y</td>
<td>Improvement in 10-y DFS (22.7 vs. 47.7%) and OS (39.8% vs. 58.1%; P = .0004)</td>
</tr>
<tr>
<td>Denham et al(TROG 9601)</td>
<td>818</td>
<td>5.9 y</td>
<td>66 Gy</td>
<td>No ADT vs. ADT 3 mo vs. ADT 6 mo</td>
<td>Equal OS, improved cancer-specific survival with 6 mo (HR, 0.56; 0.32–0.98; P = .04)</td>
</tr>
<tr>
<td>Pilepich et al(RTOG 8531)</td>
<td>977</td>
<td>7.6 y</td>
<td>65–70 Gy</td>
<td>Adjuvant ADT (until relapse) vs. ADT at relapse</td>
<td>Improvement in 10-y OS (39% vs. 49%; P = .002), especially if Gleason score 7–10</td>
</tr>
<tr>
<td>D’Amico et al(RTOG 8610)</td>
<td>206</td>
<td>4.5 y</td>
<td>70 Gy</td>
<td>No ADT vs. ADT 6 mo</td>
<td>Improvement in 5-y OS (78% vs. 88%; P = .04)</td>
</tr>
<tr>
<td>Roach et al(RTOG 8610)</td>
<td>456</td>
<td>12.5 y</td>
<td>65–70 Gy</td>
<td>No ADT vs. ADT 4 mo</td>
<td>10-y OS (34% vs. 43%; P = .12)</td>
</tr>
<tr>
<td>Bolla et al(EORTC 22961)</td>
<td>970</td>
<td>6.4 y</td>
<td>70 Gy</td>
<td>ADT 6 mo vs. ADT 36 mo</td>
<td>Improvement in 5-y OS (overall mortality reduced from 19% to 15.2%; noninferiority P = .65)</td>
</tr>
<tr>
<td>Horwitz et al(RTOG 9202)</td>
<td>1554</td>
<td>11.3 y</td>
<td>65–70 Gy</td>
<td>ADT 4 mo vs. ADT 28 mo</td>
<td>Gleason score 8–10: improvement in 10-y OS (32% vs. 45%; P = .0061)</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen deprivation therapy; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 10 Number 9 | September 2012
Nutritional Counseling
As weight gain and endocrine dysfunction are common while on ADT, nutritional counseling and diet management are recommended.

Exercise Program
Exercise is important in both weight control and the prevention of bone loss. Resistance exercise develops and maintains skeletal muscle strength and bulk, providing significant functional benefits and improvement in overall health and well-being. In a randomized controlled trial, regular sessions of both resistance and aerobic exercise mitigated fatigue compared with usual care. A recently published study randomized men on ADT to a 6-month program of metformin, a low-glycemic-index diet, and exercise. Significant reductions were seen in abdominal girth, weight, body mass index, and systolic blood pressure in the intervention arm compared with controls. Biochemical markers of insulin resistance did not differ significantly.

The potential benefits of metformin and lifestyle changes in ADT-treated men are being further investigated; effects on overall survival remain to be determined.

Cognitive Status and Mental Health
A decrease in attention and memory was reported in the ADT arm of a randomized trial and cognitive changes have been described during intermittent ADT. Although not all studies are in agreement and larger sample sizes and longer follow-up are required, patients should nonetheless be advised concerning potential effects on cognitive function. A mental health history should be obtained before initiating ADT, and monitoring for the onset of depressive symptoms is suggested.

Bone Density
The National Osteoporosis Foundation guidelines recommend supplemental calcium (1200 mg daily) and vitamin D (800–1000 IU daily) for all men older than 50 years, and additional treatment for those at higher risk. Bisphosphonates increase bone mineral density and reduce the risk of fracture. Currently, treatment with either zoledronic acid (4 mg intravenously annually) or alendronate (70 mg orally weekly) is recommended when the absolute fracture risk is significant. Denosumab, a human monoclonal antibody against RANK (receptor activator of nuclear factor κB) ligand, has been studied. The SWOG 9346 randomized trial of continuous versus intermittent ADT for metastatic prostate cancer closed in 2008. Of 3040 accrued patients, only 1535 were eligible for randomization, having achieved a nadir PSA of less than 4 ng/mL at 7 months. Results were presented at ASCO 2012. At a median follow-up of 9.2 years, median overall survival for continuous treatment was 5.8 versus 5.1 years for intermittent (HR for intermittent vs. continuous: 1.09; 95% CI, 0.95–1.24), with rates of grade 3 and 4 adverse events at 30.3% for intermittent and 32.6% for continuous therapy. Intermittent therapy could not be declared as noninferior to continuous.

Mitigating the Side Effects of ADT
The most important strategy to reduce the burden of ADT toxicity is to limit its use to situations where it is clearly indicated. When use of ADT is supported by level 1 evidence, then several strategies can potentially reduce the adverse consequences.

Optimization Before Treatment
The constellation of symptoms associated with ADT should be explained to patients before initiating treatment. Unfortunately, lifestyle recommendations, such as smoking cessation, adopting a healthy diet, and undertaking regular exercise, are offered infrequently. Strategies for symptom management help patients cope and reduce distress, although ongoing support may be required to maintain these changes. The NCCN Guidelines for Prostate Cancer include strategies on risk reduction, such as those outlined in the following sections (to view the most recent version of these guidelines, visit NCCN.org).

Monitoring of serum lipid profiles is recommended both before and during treatment; statin drugs are indicated for dyslipidemia. Blood pressure should be monitored before and after ADT initiation, and HbA1c and fasting blood glucose levels should also be monitored in patients with diabetes or obesity. The role of the oral biguanide metformin is currently being studied, although preliminary data suggest that metformin together with lifestyle changes may abrogate ADT-induced metabolic syndrome. The antineoplastic effect of metformin is also being investigated.
shown in a phase III randomized trial to increase bone mineral density and reduce new vertebral fractures among men receiving ADT for nonmetastatic prostate cancer.\textsuperscript{54} When compared with zoledronic acid, denosumab was superior in preventing skeletal-related events. The choice of agent may depend on underlying comorbidities, whether the patient has already received zoledronic acid, and cost considerations.\textsuperscript{6}

**Conclusions**

The hormonal dependence of prostate cancer provides the option of ADT as a comparatively nontoxic systemic treatment. However, the side effects of castration are not trivial and ADT should be used rationally and only when indicated. Limiting exposure to ADT and systematic efforts to reduce side effects will benefit the quality of life of many men.

**References**


Focused Review

Gaztañaga and Crook

Instructions for Completion
To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the post-test with a 70% minimum passing score and complete the evaluation at http://education.nccn.org/node/2399; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. Software requirements: Internet

Post-Test Questions
1. Use of ADT in intermediate-risk prostate cancer
   a. Improves survival when combined with EBRT
   b. Improves survival when combined with BT
   c. Is of uncertain benefit when optimal radiation doses are used
   d. Prevents late metastatic failures
   e. Is not currently being studied in a large randomized clinical trial
2. Use of ADT in high-risk prostate cancer
   a. Does not improve overall survival when a 6-month course of ADT is combined with 70 Gy EBRT
   b. Should be long term for improved overall survival when combined with conventional EBRT
   c. Is proven to be of benefit in overall survival when combined with dose-escalated EBRT ± brachytherapy
   d. Shows equal benefit for high Gleason score cancers as for high-risk patients with a Gleason score ≤ 7
   e. The side effects of ADT
      a. Are largely insignificant
      b. Are not important in men who are not sexually active
      c. Can be improved with exercise, nutritional counseling, optimization of lipids and blood pressure
      d. Do not include cognitive impairment
      e. Do not result in increased cardiovascular death in any subgroup of patients