Androgen Deprivation for Prostate Cancer: When and How, the Good and the Bad
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OVERVIEW

Androgen deprivation therapy (ADT) is the mainstay systemic treatment of prostate cancer because of the androgen dependence of the disease. Although ADT has long been used to manage prostate cancer, its use continues to evolve as data from clinical trials mature and long-term effects are recognized. For patients with localized disease and high-risk features, short and long courses of ADT as neoadjuvant/adjuvant therapy have been shown to improve survival when used with radiation therapy, but this has not been demonstrated with radical prostatectomy. The role of ADT with salvage radiotherapy after radical prostatectomy continues to be defined. Lifelong ADT in patients with node-positive disease after surgery or with radiation is also associated with increased survival. Increasingly though, the adverse effects of ADT that go beyond those on libido and hot flashes are being acknowledged. The metabolic effects on lipids, glycemic control, and bone loss from ADT can lead to an increased risk of cardiovascular events and osteoporosis, which needs to be considered when deciding to initiate and treat patients with ADT. Large, randomized trials comparing intermittent to continuous ADT have now been reported. Although the hope for improved cancer outcomes with intermittent therapy has not come to realization, an interrupted approach to therapy may help mitigate some of the negative effects of ADT in selected patients by allowing for off-treatment intervals.

It has been over 70 years since the initial description of prostate cancer androgen dependence by Huggins and Hodges leading to androgen deprivation becoming a mainstay treatment for the disease. Despite this long history, the use of androgen deprivation therapy (ADT) in the management of prostate cancer continues to evolve and be defined across multiple parameters: disease status, long-term adverse effects, optimal timing of initiation, duration of therapy, and schedule of treatment. The purpose of this review is to update the reader on the current status and latest developments on the use of ADT for patients with localized and recurrent prostate cancer.

ADT AS NEOADJUVANT/ADJUVANT THERAPY FOR HIGH-RISK DISEASE

Short-Course ADT and Radiation Therapy for Intermediate- and High-Risk Localized Disease

A short course (4 to 6 months) of neoadjuvant and concurrent ADT has been shown to improve overall survival when added to conventional-dose radiation in men with mainly intermediate- and high-risk clinically localized disease. In the Dana-Farber 95–096 randomized trial, 206 men with cT1b–T2b and a PSA level greater than 10, a Gleason score of 7 or higher, or MRI evidence of extracapsular extension were treated with 70 Gy of external radiation with or without 6 months of combined androgen blockade. Overall survival was 74% versus 61% at 8 years favoring ADT (p = 0.01).1 Similarly, the RTOG 94–08 trial found that 4 months of combined androgen blockade added to 66 Gy of radiation for men with cT1b–T2b and a PSA level of less than 20 improved 10-year overall survival (62% vs. 57%, p = 0.03). An unplanned postrandomization analysis suggested that the benefit was limited to men with intermediate-risk disease, and that among high-risk men, 4 months of ADT was not associated with an improvement in overall survival (p = 0.47).2 This may reflect a lack of power in the high-risk group (who represented only 11% of the study), or alternatively it is possible that at least 6 months of ADT is needed to improve survival for high-risk disease and 4 months was truly not adequate. The latter notion is somewhat supported by the TROG 96.01 trial that found that for men with cT2b–T4 disease treated with 66 Gy of radiation, 6 months of ADT improved overall survival compared with 0 months (hazard ratio (HR) 0.63, p = 0.0008), but 3 months of ADT did not (HR 0.84, p = 0.18).3 Currently, the TROG 03.04 RADAR trial is testing whether 18 months of ADT could further improve prostate-cancer–specific survival compared with 6 months of ADT when added to radiation for men with mostly cT2 and a Gleason score of 7 or higher and...
a PSA level of 10 or higher, and survival results are expected in 2014.4

Long-Course ADT Plus Radiation Therapy for High-Risk Localized/Locally Advanced Disease
Two randomized trials have demonstrated the benefits of longer-duration ADT for mainly locally advanced disease. The randomized RTOG 92–02 trial treated men with cT2c-T4 and a PSA level lower than 150 to 65 to 70 Gy of radiation with either 4 months or 28 months of ADT, and found that long-course ADT improved prostate-cancer–specific survival from 84% to 89% at 10 years (p = 0.0042), but not overall survival (p = 0.36).5 However, a hypothesis-generating postrandomization analysis found that overall survival was improved among the men with a Gleason score of 8 to 10 (45% vs. 32%, p = 0.0061). Similarly, the European Organisation for Research and Treatment of Cancer ran a noninferiority trial of radiation plus either 6 months or 36 months of ADT in men with mainly cT2c-T4 disease and found that short-course ADT had inferior survival. At 5 years, long-course ADT reduced overall mortality by 3.8%, from 19.0% to 15.2%.6 Although both of these trials establish long-course ADT as the standard of care for men with locally advanced disease, it should be noted that neither trial specifically addresses whether long-course is needed for men with high-risk clinically localized disease (e.g., cT1c with a Gleason score of 8), and it is possible that a shorter course of ADT may be adequate for select men with these tumor characteristics.

Lifelong ADT for Node-Positive Disease
Two randomized trials demonstrated an improvement in overall survival from lifelong ADT for men with node-positive disease. The RTOG 85–31 randomized trial included 977 men with T3 or N1 disease administered radiation with or without lifelong ADT and found that lifelong ADT improved 10-year overall survival (49% vs. 39%, p = 0.002).7 A post-randomization subgroup analysis limited to the 173 pathologically node-positive suggested on multivariable analysis that node-positive men treated with radiation alone had a higher all-cause mortality (relative risks (RR) 1.62, p = 0.03).8 For surgically treated men, the ECOG/EST 3886 randomized trial by Messing et al. treated 98 men with pathologically node-positive disease after prostatectomy to lifelong ADT versus observation, and found that lifelong ADT improved overall survival (HR for mortality 1.84, p = 0.04).9

Salvage ADT Plus Radiation Therapy for Rising PSA after Prostatectomy
The RTOG 96–01 randomized trial evaluated whether 2 years of antiandrogen therapy using bicalutamide 150 mg could improve outcomes when added to salvage radiotherapy for men with pT3 or pT2 margin-positive disease and a rising PSA after prostatectomy. Initial results in abstract form with a median follow-up of 7.1 years found that antiandrogen therapy reduced metastases at 7 years from 12.6% to 7.4% (p < 0.04), and overall survival was 91% versus 86%, but no statistical test was performed on this difference as the study had not yet reached the prespecified number of events.10 Because bicalutamide 150 mg is generally not used in the United States or Canada, some clinicians extrapolate from the results of the RTOG study and substitute a gonadotropin-releasing hormone (GnRH) agonist for the bicalutamide. Whether a shorter course of hormone therapy could achieve the same result is one of the questions being asked in the United Kingdom/Medical Research Council/NCIC RADICALS randomized trial that includes men receiving either adjuvant or salvage radiation to either no hormones, 6 months of hormones, or 2 years of hormones.11 The hormone therapy in that study can either be bicalutamide 150 mg or combined androgen blockade. Also, the RTOG 05–34 trial is randomly assigning over 1,700 men with a rising PSA after prostatectomy to prostate bed radiation, prostate bed radiation with 4 to 6 months of ADT, or pelvis and prostate bed radiation and 4 to 6 months of ADT. The trial will also help clarify whether short-course ADT would be a viable alternative to 2 years of bicalutamide.

Neoadjuvant ADT before Prostatectomy
At least eight randomized trials have evaluated the role of a 3-month course of neoadjuvant ADT before prostatectomy. A recent meta-analysis of these trials found that neoadjuvant ADT was associated with a significant reduction in positive margins (RR 0.49, p < 0.00001), increase in organ-confined disease (RR 1.63, p < 0.0001), and reduction in lymph node positivity (RR 0.66, p = 0.02), but this did not translate into a benefit in disease-free survival (RR 1.04, p = 0.48), disease-specific survival (RR 1.00, p = 0.77), or overall survival (RR 1.00, p = 0.95).12 Interest in neoadjuvant ADT before prostatectomy has been renewed with the presentation at the
of 150 mg/dL (1.64 nmol/L) or higher, low high-density lipoproteins less than 40 mg/dL (1.0 mmol/L), increased waist circumference of 40 inches (102 cm) or larger, or increased blood pressure of 130/85 mmHg or higher. Medical treatment for hypertension or lipid-lowering drugs constitutes the presence of that criterion.

Table 2 shows that ADT is also associated with many of the features that define metabolic syndrome and hypogonadism. However, possibly because of the rapid onset of castration associated with ADT, the findings in men treated with ADT differ in some respects from those of the classic metabolic syndrome associated with hypogonadism. Although fasting glucose levels remain normal after 3 months of ADT, insulin levels and glycated hemoglobin are increased at that time point, and after one year of ADT, fasting glucose levels are also increased. The effect on lipids, however, can be mixed, with serum triglycerides increasing but serum high-density lipoproteins (HDL) remain stable or increasing. The enlargement of waist circumference seen in ADT-treated men is caused by an increase in both visceral and subcutaneous fat, although men with classic metabolic syndrome have greater girth primarily caused by an increase in visceral fat. And finally, for unknown reasons, an increase in blood pressure has not been observed when compared with normal controls, although an increase in vascular stiffness was reported in men on ADT.

Although there is significant evidence that ADT affects risk factors for cardiovascular disease (decreased insulin sensitivity, hypertriglyceridemia, and obesity) and hypogonadism is associated with increased cardiac death, several retrospective analyses of large databases or randomized trials have been published with conflicting results with respect to cardiac outcomes. A scientific advisory published in 2010 noted that ADT adversely affects several risk factors for cardiovascular disease and that it is therefore “plausible that ADT could increase cardiovascular risk.”

More recently, a meta-analysis of eight prospective randomized trials that included cardiovascular death as an end point analyzed over 4,000 men with nonmetastatic hormone-sensitive disease. In this report, cardiovascular death was not significantly different in patients treated with ADT (11.0%) compared with the control (11.2%), and further, neither duration of ADT (<6 months or ≥3 years) nor median age (<70 years vs. ≥70 years) was associated with

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**TABLE 1. Potential Complications from ADT from the Patient Perspective**

<table>
<thead>
<tr>
<th>What Physicians Commonly Tell You</th>
<th>What You Feel</th>
<th>What You See</th>
<th>What You Don't See</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of libido</td>
<td>Fatigue or loss of energy, initiative</td>
<td>Weight gain</td>
<td>Loss of bone mineral density</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Aches and pains</td>
<td>Loss of muscle mass and strength</td>
<td>Changes in lipids</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Low spirits, depression</td>
<td>Increased subcutaneous tissue, especially hips and thighs</td>
<td>Glucose intolerance, diabetes</td>
</tr>
<tr>
<td></td>
<td>Emotional liability</td>
<td>Gynecomastia</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Cognitive changes</td>
<td>Decrease in testicular size and penile length</td>
<td>Increased cardiovascular risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of body hair</td>
<td></td>
</tr>
</tbody>
</table>

excess cardiovascular deaths at median follow-up times of 7.6 to 13.2 years. Importantly, men with unfavorable risk disease had improved prostate-cancer–specific (RR 0.69, p < 0.001) and overall survival (RR 0.86, p < 0.001). A subsequent analysis by the same group retrospectively evaluated over 14,500 patients with a history of congestive heart failure or myocardial infarction before treatment with brachytherapy for localized prostate cancer.19 After a median of only 4 months of ADT and median follow-up of 4.3 years, all-cause mortality was greater in those who received ADT compared with those treated only with radiation (5-year estimates of all-cause mortality of 22.71% for ADT compared with 11.62% for no ADT, (log-rank < 0.0001). As discussed previously, although the addition of ADT to radiation should benefit those with high-risk prostate cancer in terms of overall survival, this study suggests that a subgroup of men with known congestive heart failure or myocardial infarction could be harmed by the addition of ADT.

Intriguing new data was recently presented suggesting that the risk for cardiovascular events and death from any cause during the first year of treatment is 50% lower in men with pre-existing cardiovascular disease who were treated with the LHRH antagonist degarelix compared to those treated with a LHRH agonist.20 Although both therapies lower testosterone to castrate levels, LHRH agonists might interact with GnRH receptors located on cardiomyocytes, lymphocytes, and macrophages. Prospective trials with the primary endpoint of cardiovascular events are clearly needed.

**ADT Effects on Bone**

Hypogonadism is also associated with loss of bone mineral density (BMD) and increased risk for fractures and, in addition to alcoholism and glucocorticoid therapy, is one of the most common causes of osteoporosis in men. Hip fractures in men account for one-third of all hip fractures worldwide. Compared with women, men who suffer hip fractures are more likely to die within the year and are less likely to return to independent living.21 Hence, osteoporosis and/or fractures can cause significant morbidity and mortality in men.

ADT causes a rapid loss of BMD in the first 6 to 12 months of treatment and continues thereafter at a slower rate. In addition to direct effects on BMD as a risk factor for fracture, the effects of ADT on lean body mass and strength also contribute to the risk for falling and fracture. In a retrospective, population-based study of over 50,000 men with prostate cancer, the incidence of fracture at 5 years from diagnosis was higher in the ADT-treated men compared with those who were not treated (19.4% compared with 12.6%).21 The mortality rate for those who sustained a fracture was double that of those who did not have a fracture.23

Recommendations for baseline assessments are listed in Table 3. These are common sense approaches based on what is known about the side effects of ADT and also incorporate recommendations from specialty groups. Educating the patient about the potential side effects of ADT at the outset empowers patients to be active participants in their own care and to better understand the importance of engaging in healthy behaviors, including exercise. It is well recognized that exercise plays a significant role in overall good health and has been shown to improve survival in patients with breast and colorectal cancer. In addition, exercise can abrogate many of the side effects of ADT. At the present time, however, the optimal exercise regimen for men treated with ADT is not clear. Resistance exercises are important in several phase III trials but the advantage of adding aerobic exercise is unclear.24 Further research is indicated to better define the appropriate combination of resistance, aerobic, and balance training.

If baseline studies indicate a history of hip or vertebral fracture, osteoporosis by T-score, or osteopenia by T-score plus the World Health Organization’s Fracture Risk Assessment Tool (FRAX) estimates the 10-year probability of hip fracture is 3% or higher or major osteoporosis-related fracture is 20% or higher, initiation of bone-directed therapy to prevent or treat osteoporosis and fracture should be considered. FRAX is an online assessment tool that incorporates age, body mass index, and other clinical risk factors to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporosis-related fracture. Because the sensitivity of the dual-energy X-ray absorptiometry (DXA) scan with respect to predicting fractures is low (many patients who suffer fractures have BMD values above the osteoporotic threshold of T-score of −2.5 SD), results of the FRAX can help stratify patients who may not have frank

### TABLE 2. Features of Hypogonadism versus ADT

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hypogonadism</th>
<th>ADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition by T level</td>
<td>T &lt;325 ng/dL (11.3 nmol/L)</td>
<td>T &lt;50 ng/dL (1.7 nmol/L) or &lt;20 ng/dL (0.7 nmol/L)</td>
</tr>
<tr>
<td>Time to reach low T levels</td>
<td>Years</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Yes</td>
<td>Metabolic abnormalities</td>
</tr>
<tr>
<td>Insulin resistance/diabetes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lipid abnormalities</td>
<td>Yes</td>
<td>Triglycerides increased</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cardiovascular death increased</td>
<td>Yes38</td>
<td>No38</td>
</tr>
<tr>
<td>Increased all cause mortality</td>
<td>Yes38</td>
<td>Yes in selected high risk: previous hx CHF, MI19</td>
</tr>
</tbody>
</table>

Abbreviations: T, testosterone; Hx, history; CHF, congestive heart failure; MI, myocardial infarction.
osteoporosis but who are at risk for fracture and might benefit from drug therapy. When using FRAX, it is not necessary to have the DXA results but the answer to “secondary osteoporosis” should be answered “yes” in men who are on or about to start ADT.

Options for bone-directed therapy include bisphosphonates (pamidronate, zoledronic acid, alendronate, risedronate), denosumab, a RANKL inhibitor, and selective estrogen-receptor modulators or SERMs (raloxifene, toremifene) result in increased BMD and decreased markers of bone turnover in men treated with ADT. Fracture risk was reduced only in the denosumab and toremifene trials.25

The frequency of follow-up studies varies. Weight and blood pressure should be recorded at each visit. The fasting glucose should be followed as outlined in Fig. 1. The DXA scan should be repeated at one year from baseline and indicated thereafter. The fasting lipid panel should also be followed annually. Other studies suggested can be followed as clinically indicated.

In addition to strategies that address individual side effects, use of intermittent androgen deprivation is another approach to minimizing the effects of ADT. A detailed discussion of recent data comparing intermittent ADT to continuous ADT follows below.

**INTERMITTENT OR CONTINUOUS HORMONE THERAPY?**

The preclinical rationale for intermittent hormone therapy arose 20 years ago from the work of Bruchovsky et al. in androgen-dependent cancer models demonstrating a delay in the time to development of androgen-independent growth when tumors were re-exposed to androgens.26,27 The underlying hypothesis was that cancer stem cells would remain sensitive if re-exposed to androgens rather than undergoing adaptive changes to a treatment-resistant phenotype in an androgen-deprived environment.28,29 Several phase II trials and case series have reported on the clinical feasibility of this approach in patients of various stages of their disease with demonstration of sometimes prolonged off-treatment intervals during which a recovery of testosterone and a decrease in side effects related to androgen deprivation were documented.30,31

Thus, the promise of intermittent therapy held several potential benefits: improved cancer outcomes by...
delaying development of castration resistance, and a decrease in cost of drug administration and treatment morbidity by allowing for extended periods off therapy. Several randomized studies comparing intermittent versus continuous androgen deprivation have now been reported. The largest and most recently reported trials were those led by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG)\(^2\) and the Southwest Oncology Group (SWOG).\(^3\)

The NCIC CTG PR7 study enrolled 1,386 patients with rising PSA after primary or salvage radiotherapy and no metastases, and randomly assigned them to continuous hormone therapy or intermittent therapy based on an 8 month treatment cycle with luteinizing hormone-releasing analogs and a minimum of 4 weeks of nonsteroidal antiandrogen therapy. The primary endpoint was overall survival and designed to test for equivalence, with an interim analysis for noninferiority if there was 99.5% certainty that the absolute difference in overall survival was less than 8% (HR < 1.25, 95% CI < 1.00, < 1.25). At the interim analysis, the HR for death for intermittent therapy versus continuous therapy was 1.02 (95% CI 0.86, 1.21) with a p value for noninferiority of 0.009, and the study was stopped at the recommendation of the Data and Safety Monitoring Board. After a median follow-up of 6.9 years, the median overall survival was 8.8 years for intermittent therapy and 9.1 years for continuous therapy. Notable was that the majority of deaths (59%) were unrelated to prostate cancer. Disease-specific survival was in favor of continuous therapy but this was nonsignificant (HR 1.18, 95% CI 0.90, 1.55, p = 0.24) and balanced by a greater number of deaths unrelated to prostate cancer in the continuous-therapy group. There was no differential treatment effect for Gleason score. Quality-of-life assessments were performed at fixed time points and thus did not necessarily reflect on-and off-treatment phases for patients on the intermittent therapy arm. Nevertheless, differences were observed in favor of intermittent therapy for hot flashes, sexual activity, urinary symptoms, and a trend for improved fatigue. Consistent with phase II studies, patients on the intermittent arm received considerably less therapy, receiving a median of 15.4 months of therapy with a cumulative off-treatment time of 37.6 months, and the continuous treatment arm received a median of 43.9 months of treatment on study.

Results of the SWOG 9346 study were reported at the 2012 ASCO Annual Meeting. Patients with hormone-sensitive metastatic prostate cancer were treated with 7 months of goserelin and bicalutamide with those achieving a PSA level of 4 ng/mL or less randomized to continuous or intermittent therapy. Patients with a PSA level higher than 4 at this time point have been previously shown to have a poor prognosis.\(^34\) The study was designed as a noninferiority trial, with the intermittent therapy arm considered not inferior if the 95% CI for the HR excluded 1.2. 3,040 patients were accrued and 1,535 assigned treatment. Patients on intermittent therapy were on an off-treatment interval approximately 50% of the time. Median overall survival from time of randomization was 5.1 years for those on intermittent therapy and 5.8 years for patients on continuous therapy (HR = 1.09, 95% CI 0.95, 1.24). Because the upper boundary of the 95% CI exceeded 1.2, the authors concluded that intermittent therapy was not proven to be noninferior. This interpretation is controversial however, as the 95% CI lower boundary crossed unity (and thus a benefit of intermittent therapy cannot be ruled out), making the results inconclusive for noninferiority.\(^35\) No interaction with therapy was significant except for a suggestion with disease extent: patients with extensive disease had a median overall survival of 5.0 years with intermittent therapy versus 4.4 years on continuous therapy (HR = 0.96, 95% CI 0.80, 1.16, p = 0.64) while those with minimal disease resulted with a HR of 1.23 (95% CI 1.02, 1.49, p = 0.035). This somewhat counter-intuitive finding may reflect a false-positive result or be related to the way disease extent was defined, which might not have truly reflected high-burden disease. Preliminary quality-of-life data from questionnaires taken at baseline and 3-months postrandomization demonstrated differences for the two arms with patients on continuous therapy reporting statistically significantly more impotence (p < 0.01) and less libido (p < 0.01) than those on intermittent therapy, and emotional functioning was also better for the intermittent therapy arm (p < 0.01).\(^36\)

So what can we take away from these studies to inform our practice? First, it can be assumed that the medication costs would be substantially less for an intermittent approach particularly in patients without evidence of metastases, although a formal cost analysis has not been reported and the increased monitoring required would likely blunt this benefit. Second, preliminary quality-of-life data supports the anecdotal and single-arm study evidence of decreased side effects, better sexual function, and improved well-being associated with the off-treatment periods of intermittent therapy. Lastly, despite the promise of improved cancer outcomes, there is no benefit on survival with intermittent therapy. But neither does there appear to be substantial harm. In patients without clinical metastases, the NCIC CTG PR7 study demonstrates intermittent therapy as noninferior, but carries with it the caveat that these patients could have had a delayed approach and spared treatment altogether.\(^37\) The SWOG 9346 study in patients with metastases is inconclusive for noninferiority, but there is a trend to worse outcomes with intermittent therapy. Additionally, any quality-of-life benefits of intermittent therapy in this population are mitigated by the relatively fewer number of treatment cycles and shorter time off therapy. The optimal schedule of intermittent therapy (e.g., duration of therapy before interruption, when to reinitiate treatment) and criteria for patients to proceed with treatment interruption (e.g., disease extent, PSA value) is unknown. Thus, in patients starting hormone therapy for recurrent prostate cancer, continuous therapy remains a standard treatment. However, patients that are motivated to have an off-treatment interval time and the quality-of-life benefits associated with that, particularly in those without metastases and with a good response to induction therapy, should be given the opportunity for an intermittent therapy approach provided careful follow-up and reinstitution of treatment is carried out in a defined manner.
Disclosures of Potential Conflicts of Interest

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References


