Androgen Deprivation Therapy for Prostate Cancer

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Androgen deprivation therapy (ADT; herein defined as medical or surgical castration) is the cornerstone treatment of advanced prostate cancer. In 1941, Huggins and Hodges first noted the beneficial effects of castration and injection of estrogens in patients with metastatic prostate cancer. The biological basis of the effect of ADT, the almost ubiquitous expression of the androgen receptor in prostate cancer, and growth dependence on the androgen receptor later became clear.

Today, in addition to its well-established role in treating patients with metastatic disease, ADT is sometimes used to treat patients with increasing prostate-specific antigen (PSA) levels after local treatment, even without radiographic or other evidence of metastatic disease. Androgen deprivation therapy is also used as adjunct therapy for men undergoing radiation therapy for high-risk localized disease (TABLE 1). Despite frequently dramatic and sustained responses of many patients to ADT, treatment exposes patients to a host of important adverse effects (TABLE 2). We sought to systematically review existing evidence regarding the benefits and risks of ADT in contemporary management of local and metastatic prostate cancer.

Context Prostate cancer is the most common nonskin cancer and second most common cause of cancer mortality in US men. Androgen deprivation therapy (ADT), specifically surgical or medical castration, is the first line of treatment against advanced prostate cancer and is also used as an adjuvant to local treatment of high-risk disease.

Objective To review systematically the evidence on the risks and benefits of ADT for prostate cancer as well as clinical management of its adverse effects.

Evidence Acquisition We performed MEDLINE searches of English-language literature (1966 to March 2005) using the terms androgen deprivation therapy, hormone treatment, and prostate cancer. We reviewed bibliographies of literature to extract other relevant articles. Studies were selected based on clinical pertinence, with an emphasis on controlled study design.

Evidence Synthesis Androgen deprivation therapy is effective for palliation in many patients with advanced prostate cancer and improves outcomes for high-risk patients treated with radiation therapy for localized disease. Although patients with increasing prostate-specific antigen levels after local treatment without metastatic disease frequently undergo ADT, the benefits of this strategy are not clear. Adverse effects of ADT include decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in cognition and mood.

Conclusions Androgen deprivation therapy has clear roles in the management of advanced prostate cancer and high-risk localized disease. The benefits of ADT in other settings need to be weighed carefully against substantial risks and adverse effects on quality of life.

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EVIDENCE ACQUISITION

We performed MEDLINE searches of the English-language literature (1966 to March 2005) using the terms androgen deprivation therapy, hormone treatment, and prostate cancer. Relevant bibliographies of literature were manually reviewed for additional material. In evaluating the benefits of ADT, phase 3 randomized trial data were emphasized. On review of clinical trials, clinical end points of focus, in decreasing order of importance, were survival benefit, radiographic progression-free survival, and rising PSA level. Further information was obtained in oral and abstract form at the 2005 Prostate Cancer Symposium meeting, Orlando, Fla, and the 2005 American Society of Clinical Oncology meeting, Orlando, Fla. Published guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology were also reviewed.

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ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER

**EVIDENCE SYNTHESIS**

**Medical vs Surgical Castration for Androgen Ablation**

Orchiectomy is a relatively simple procedure with minor surgical risks. Despite its low physical morbidity, orchiectomy has fallen out of favor given its psychological impact and viable medical alternatives for androgen deprivation.13

Medical castration with gonadotropin-releasing hormone agonists (GnRH-As) in prostate cancer patients was first reported in 1982.14 Leuprolide and goserelin are 2 commonly used GnRH-As and are administered in the form of 1-, 3-, 4-, and 6-month depot injections, as well as 12-month subcutaneous implants. Endogenous GnRH is physiologically released in a pulsatile manner from the hypothalamus and is directed to the anterior lobe of the pituitary (FIGURE). In response, luteinizing hormone is released from the pituitary, which in turn stimulates testosterone production in the testes. Long-term treatment with GnRH-A supplants the effect of physiologically pulsatile endogenous GnRH and is thought to down-regulate its receptors in the pituitary gland, leading to castration levels of testosterone within 3 weeks.15

It is well recognized that GnRH-As initially cause a surge in testosterone and can cause a “flare” reaction in patients with metastatic prostate cancer. This is due to an acute stimulation of prostate cancer growth by elevated levels of testosterone. A placebo-controlled trial has shown that androgen receptor antagonists lower the amount of bone pain with initiation of GnRH-A therapy for patients with metastatic prostate cancer.16 To prevent flare reactions, some recommend that patients with metastatic disease start with an androgen antagonist prior to initiation of treatment with a GnRH-A and continue for 2 to 4 weeks to block the effect of the testosterone surge on peripheral androgen receptors.17

Gonadotropin-releasing hormone antagonists may alternatively be used for medical castration and do not cause a testosterone surge, but they have a 3.7% incidence of anaphylaxis.18 Gonadotropin-releasing hormone antagonists are indicated for palliative treatment of men with advanced symptomatic prostate cancer, in whom GnRH-A therapy alone is not appropriate because of an initial increase in testosterone, who refuse surgical castration, and who have one or more of the following: (1) risk of neurological compromise due to metastases; (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease; or (3) severe bone pain from skeletal metastases persisting with narcotic analgesia use.18

In principle, it is important to achieve serum testosterone concentrations as

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### Table 1. Benefit of ADT for Stages of Prostate Cancer

<table>
<thead>
<tr>
<th>Prostate Cancer Stage</th>
<th>Source</th>
<th>Outcome</th>
<th>Control Arm, % (95% CI)</th>
<th>Early-ADT Arm, % (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>MRC,* 1997</td>
<td>Decrease in rate of cord compression</td>
<td>4.9</td>
<td>1.9</td>
<td>&lt;.025*</td>
</tr>
<tr>
<td>Patients with local treatment for high-risk or locally advanced disease</td>
<td>Bolla et al,* 1997, and Bolla et al,* 2002</td>
<td>Increase in 5-y survival</td>
<td>62 (52-72)</td>
<td>78 (72-84)</td>
<td>.0002</td>
</tr>
<tr>
<td>Pilepich,* 2003</td>
<td>Increase in 10-y survival</td>
<td>38</td>
<td>53</td>
<td>&lt;.004</td>
<td></td>
</tr>
<tr>
<td>D’Amico et al,* 2004†</td>
<td>Increase in 5-y survival</td>
<td>78 (68-88)</td>
<td>88 (80-95)</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Messing et al,* 1998, and Messing et al,* 2003</td>
<td>Increase in 10-y survival</td>
<td>49.0</td>
<td>72.4</td>
<td>.025</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ADT, androgen deprivation therapy; CI, confidence interval; MRC, Medical Research Council Prostate Cancer Working Party Investigators Group; NS, nonsignificant (value not reported in original study).

†This trial also included patients not at high risk.

### Table 2. Selected Adverse Effects of ADT and Evidence for Treatment

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Source</th>
<th>Treatment for Adverse Effect</th>
<th>Outcome</th>
<th>Control Arm</th>
<th>Intervention Arm</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>Loprinzi et al,* 1994</td>
<td>Megestrol acetate*</td>
<td>Reduction in hot flashes</td>
<td>20%</td>
<td>74%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Osteoporosis and increased risk of fracture</td>
<td>Smith et al,* 2001</td>
<td>Pamidronate</td>
<td>BMD change</td>
<td>Decrease of 1.8%-8.5%</td>
<td>No change</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Osteoporosis and increased risk of fracture</td>
<td>Smith et al,* 2003</td>
<td>Zoledronic acid</td>
<td>BMD change</td>
<td>Decrease of 2.2%</td>
<td>Increase of 5.6%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADT, androgen deprivation therapy; BMD, bone mineral density.

*May cause disease progression.

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low as possible for ADT to minimize stimulation of prostate cancer cells. Serum testosterone concentrations that correspond to castration levels have generally been set at less than 50 ng/dL (1.7 nmol/L), given the known variability of values in reference laboratories. However, most men achieve levels below 20 ng/dL (0.7 nmol/L) after orchiectomy, and it has been suggested that castration levels should be redefined to reflect this threshold.

**Antiandrogens and Inhibitors of Steroid Synthesis**

There are several other classes of agents that are used clinically to block the effects of androgens (Figure). Androgen receptor antagonists such as flutamide, bicalutamide, and nilutamide are often used either alone or in combination with castration to block the effects of androgens. Ketoconazole and other adrenal ablating drugs are used to inhibit cytochrome P450 enzymes, which are required for the synthesis of androgens and other steroids. Testosterone released from the testes is converted to dihydrotestosterone, a more potent activator of the androgen receptor than testosterone. Finasteride inhibits 5α-reductase, the enzyme responsible for this conversion. Finasteride has no defined role in the standard care of patients with prostate cancer but may have a role in prevention.

**Benefits of ADT**

**Advanced Prostate Cancer.** The first large randomized controlled trial to address the efficacy of orchiectomy in advanced prostate cancer was the Veterans Administration Cooperative Urological Research Group (VACURG) I study, which also included an arm with no treatment. After 9 years, all men with metastatic disease in the control arm were treated with androgen ablation. Therefore, this trial may be best described as a comparison of early vs late ADT. Survival curves for men in these arms were essentially equivalent, suggesting that there is no survival advantage to early treatment with ADT. This trial did not address any palliative end points.

The Medical Research Council conducted a randomized trial of early vs late ADT in patients with locally advanced disease or asymptomatic metastatic disease. Two hundred fifty-seven (71%) of 469 patients in the deferred-treatment arm died of prostate cancer vs 203 (62%) of 469 patients in the immediate-treatment arm ($P=.001$). Fifty-five men (11.8%) in the deferred arm and 37 (7.9%) in the immediate-treatment arm had extraskeletal metastases ($P<.05$). The number of patients with pathological fracture were 21 (4.5%) in the deferred-treatment arm vs 11 (2.3%) in the immediate-treatment arm (not statistically significant). Twenty-three patients (4.9%) in the deferred-treatment arm vs 9 (1.9%) in the immediate-treatment arm had spinal cord compression ($P<.025$). Fifty-five (11.8%) and 33 (7.0%) patients had ureteral obstruction, respectively ($P<.025$). Bone pain and other quality-of-life measures were not reported. An important

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
<th>Site of Action</th>
<th>Mechanism of Action</th>
<th>Comments/Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH Antagonists</td>
<td>Abarelix †</td>
<td>Anterior Pituitary Gland</td>
<td>Directly Inhibits GnRH Receptors</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Adrenal Ablating Drugs</td>
<td>Ketoconazole</td>
<td>Adrenal Gland</td>
<td>Decreases Androgen Synthesis From Steroid Precursors Through Inhibition of Cytochrome P450 Enzymes</td>
<td>Administration Requires Steroid Supplementation to Prevent Adrenal Insufficiency</td>
</tr>
<tr>
<td>Androgen Receptor Antagonists</td>
<td>Flutamide, Bicalutamide, Nilutamide</td>
<td>Prostate Gland</td>
<td>Inhibits Androgen Receptor Ligand-Binding Domain Through Competitive Binding</td>
<td>Gynecomastia, Increased Liver Transaminases, and Mastodynia</td>
</tr>
<tr>
<td>5α-Reductase Inhibitors</td>
<td>Finasteride</td>
<td>Prostate Gland</td>
<td>Decreases Conversion of Testosterone to DHT Through Inhibition of 5α-Reductase</td>
<td>No Defined Role in Standard Care of Prostate Cancer</td>
</tr>
</tbody>
</table>

DHT indicates dihydrotestosterone and LH, luteinizing hormone. Asterisk indicates no longer available for new patients in the United States. Illustration based on original concept by Lydia Kibiuk.
note is that this study has been criti-
cized because many of these patients
died before starting ADT.2

The efficacy of medical vs surgical
castration for advanced prostate
cancer has been addressed. Ten random-
ized trials of GnRH-A compared with
orchiectomy have been conducted and
were systematically evaluated in a pre-
viously published meta-analysis.23 All of
these trials found equivalence be-
tween GnRH-A and orchiectomy in
terms of survival, progression-related
outcomes, and time to treatment failure.

Advanced prostate cancer almost al-
ways becomes androgen independent
after castration. The duration of re-
sponse after ADT in the metastatic set-
ing is typically 14 to 20 months.26,27
Secondary hormone treatment with an-
drogen receptor antagonists or keto-
conazole is often used when prostate
cancer progresses after ADT.28

In summary, in the setting of
advanced prostate cancer, ADT—
whether surgical or medical—provides
important quality-of-life benefits, in-
cluding reductions of bone pain,29 patho-
logical fracture, spinal cord compres-
sion, and ureteral obstruction. However,
it is not clear whether there is an im-
provement in long-term survival.

ADT Adjuvant to Radiation Therapy
or Prostatectomy. Several phase III ran-
domized trials have shown a benefit in
overall survival when comparing ra-
diation therapy alone to radiation
therapy plus ADT for patients with loc-
ally advanced (ie, extracapsular or
node-positive) disease. The European
Organisation for Research and Treat-
ment of Cancer conducted a phase 3
trial in 412 patients with locally ad-
vanced disease, randomizing the pa-
tients to GnRH-A plus radiation therapy
vs radiation therapy alone. In the
combination arm, ADT was started on
the first day of radiation and continued for
3 years.34 Overall survival at 5 years was
78% for combined treatment and 62%
(P<.001) for radiation therapy alone.
Among surviving patients, 74% and
40% were free of disease at 5 years in
the combined treatment and radiation-
only groups, respectively (P<.001).

In the Radiation Therapy Oncology
Group Trial 85-31, a GnRH-A was
started in the last week of radiation
therapy and continued indefinitely for
patients with evidence of extracapsular
disease or regional lymph node involve-
ment.30,31 A recent analysis of this study
found an improvement in overall sur-
vival favoring the ADT arm (estimated
10-year absolute survival of 53% vs 38%;
P<.004), and a retrospective subset
analysis of this trial suggested a signifi-
cant improvement in survival favoring
the ADT arm among patients with in-
volved regional nodes.32 D’Amico et al8
conducted a randomized controlled trial
of 3-dimensional conformal radiation
therapy (3D-CRT) with or without 6
months of GnRH-A therapy in 206 pa-
tients with prostate cancer with a Glea-
son score of at least 7, evidence of ex-
traprostatic disease, or a PSA level of
at least 10 ng/mL. The estimated 5-year sur-
vival of the combined therapy group was
88% vs 78% in the 3D-CRT-only group
(P=.04). Survival free of salvage ADT
was 82% and 57% in the combined-
therapy and 3D-CRT groups, respec-
tively (P=.002). It is also important to
note that a critique of adjuvant ADT
studies for high-risk (ie, stage
T2c, PSA
8) or lo-
dergie of 8 to 10 and biochemical re-
currence within 2 years of prostatec-
tomy were metastasis-free at 3 years.

Although many men with biochemi-
ical failure are treated with ADT, there
are no data currently available from pro-
spective trials to address a possible ben-
efit in terms of disease progression or
survival.35 Given that there is no de-
finite survival advantage to early ADT
in advanced prostate cancer, there may
be no compelling reason to treat most
men with biochemical failure. How-
ever, given the survival advantage of ad-
juvant ADT for men with locally ad-
vanced or high-grade disease and earlier
time to metastasis in men with high-
grade tumors or aggressive features,
there may be a potential benefit in treat-
ing this subset of men who have bio-
chemical failure. This matter is sub-
ject to debate, and ascertainment of the
benefit of ADT for biochemical failure
after prostatectomy or radiation therapy
awaits data from prospective studies.

Adverse Effects of ADT

Hot Flashes. Hot flashes can signifi-
cantly affect quality of life for men un-
dergoing ADT. Up to 80% of patients
undergoing treatment with GnRH-A re-
port hot flashes and up to 27% report
this as the most troublesome adverse
effect.35 Most intervention studies for
hot flashes have evaluated treatments
in breast cancer patients taking tamoxi-
Men who were treated with GnRH-A alone had a mean decrease in lumbar, trochanter, total hip, and trabecular lumbar spine BMD of 3.3% (P < .001), 2.1% (P = .003), 1.8% (P = .005), and 8.5% (P = .02), respectively, after 48 weeks. Mean BMD did not change significantly in the GnRH-A plus pamidronate group. In a multicenter, double-blind study, 106 men with nonmetastatic prostate cancer who were starting ADT were randomized to receive placebo vs 4 mg of zoledronic acid every 3 months for 1 year. Mean lumbar spine BMD decreased in the placebo group by 2.2%, whereas BMD increased by 5.6% in the zoledronic acid group (P < .001). A randomized, placebo-controlled trial of zoledronic acid in patients with androgen-independent metastatic prostate cancer showed a significant decrease in skeletal-related events in the zoledronic acid arm (33% vs 44%; P = .02).

Men receiving or starting ADT should be evaluated for risk of osteoporosis. These risks include family history of osteoporosis, low body weight, prior fractures, excessive alcohol use, smoking, glucocorticoid use, low vitamin D levels, and other medical comorbidities. All men should start calcium and vitamin D supplementation. Baseline BMD should be determined. Routine use of bisphosphonates in patients undergoing ADT is not recommended unless there is documented osteoporosis or androgen-independent prostate cancer with skeletal metastasis. Men who smoke or have excessive alcohol consumption should be urged to abstain.

Sexual Function. Testosterone plays an important role in normal male sexual function. Decreasing serum testosterone can have a significant negative impact on quality of life for patients treated with ADT. Although erectile dysfunction is not uncommon after radical prostatectomy, men who undergo ADT have a further decline in ability for sexual intercourse and a decrease in sexual desire compared with men who are not treated with ADT.

The Prostate Cancer Outcomes Study of the SEER program examined quality-of-life outcomes for 431 men with all stages of prostate cancer who were treated with ADT and no other treatment within 1 year of initial diagnosis. The impact on sexual function of treatment with a GnRH-A or an orchietomy was noted. Men reporting no sexual interest increased from 27.6% to 63.6% after orchietomy and 31.7% to 58.0% after GnRH-A. Men who achieved no erections increased from 35.0% to 78.6% after orchietomy and 37.9% to 73.3% after GnRH-A. Men with no sexual activity increased from 47.9% to 82.8% after orchietomy and 45.0% to 80.2% after GnRH-A. Surprisingly, despite the cosmetic effects and psychological impact of orchietomy, GnRH-A and orchietomy had similar effects on sexual function. Although phosphodiesterase type 5 inhibitors are an option, there has been no study specifically evaluating these drugs in men treated with ADT. Penile implants, vacuum devices, and intracavernosal injections of prostaglandin are other available options.

Metabolic Changes. Serum testosterone levels have a negative correlation with fat mass and a positive correlation with muscle mass. Testosterone replacement has been shown to increase lean body mass in men who are deficient in testosterone because of age or chronic disease states.

Three prospective studies have compared body composition and metabolism in cohorts of men with prostate cancer before ADT and 6 to 12 months after ADT. These studies have noted increases in body mass index of 1.6% to 2.4%. Among 35 men in 1 study, fat body mass increased 10% to 20% in 7 men (20%), 20% to 50% in 8 men (22.8%), and more than 50% in 5 men (14.3%). Lean body mass was found to decrease between 2% and 5% in 8 men (22.8%) and greater than 5% in 7 men (20%). Both studies that examined total cholesterol and triglycerides found a significant increase in both of these measures. One of these studies noted increases in high-density lipoproteins, low-density lipoproteins, total cholesterol, and triglycerides of 11.3% (P < .001), 7.3% (P = .03), 9.0% (P < .001), and 26.5% (P = .01). The only study that examined changes in
fasting glucose levels noted a significant increase after ADT. A retrospective analysis of men receiving ADT suggests that such metabolic changes lead to increases in HbA1c.

A caveat for all of these studies is that they are comparisons of the same patients before and after ADT and, therefore, lack a control group. Nonetheless, these data are consistent with the physiologic changes that have been recognized in other forms of testosterone deficiency. The combination of increasing body mass, increasing cholesterol, and glucose intolerance may be related to what is recognized as the metabolic syndrome. While metastatic prostate cancer provides a compelling reason for ADT, the impact of negatively modifying cardiovascular risk factors with ADT in other clinical settings for prostate cancer patients, who have a median age of 70 years, should, we believe, be measured carefully, especially in men with biochemical recurrence in the absence of data on survival.

Cognitive and Mood Changes. There is conflicting literature on the issue of cognitive function changes in men undergoing ADT. A study that randomized 82 men to GnRH-A vs close clinical monitoring suggests that there may be worsening on some tests of attention and memory. However, a second study does not suggest any cognitive impairment in men being treated with ADT but, rather, noted an improvement in object recall. A more recent prospective study associates declines in verbal fluency, visual memory, and visuospatial recognition with declines in estradiol. However, a second study did not suggest any cognitive impairment in men being treated with ADT but, rather, noted an improvement in object recall. A more recent prospective study associates declines in verbal fluency, visual memory, and visuospatial recognition with declines in estradiol.

A quality-of-life study of 144 men given a choice of immediate or deferred ADT found significantly worse scores for fatigue and psychological distress for the men receiving ADT. Men with prostate cancer surveyed at Massachusetts General Hospital were found to have 8 times the national rate of depression. However, this was not associated with ADT.

Other Changes. Normocytic, normochromic anemia is seen in many patients receiving ADT. Strom et al prospectively evaluated patients receiving combined androgen blockade. They found a hemoglobin decrease of at least 10% in 90% of their patients and a hemoglobin decrease of at least 25% in 13% of patients. Anemia may be a contributing factor to fatigue that is associated with ADT.

Gynecomastia occurs in 1% to 16% of men treated with ADT. Treatment options include breast irradiation, surgery, and tamoxifen. Surgical therapies are also an option. Other adverse effects of ADT include dry eyes, body hair loss, and vertigo.

CONTROVERSIES

Combined Androgen Blockade

Despite medical or surgical castration, continued release occurs of a lower level of androgens, mainly from the adrenal glands. A long-standing debate exists on the use of combined androgen blockade, which is treatment with castration along with an androgen receptor antagonist. An earlier study comparing daily injections of a GnRH-A vs GnRH-A plus an androgen antagonist found survival benefit for combined androgen blockade. However, a second large, randomized study found no survival benefit for combined androgen blockade when surgical castration was used.

A meta-analysis of 27 randomized trials found a slight but significant 5-year survival benefit for combined androgen blockade. The number of patients needed to treat with combined androgen blockade to prevent 1 death is estimated at 20 to 100. It is estimated that the increased costs amount to $1 million per quality-adjusted life-year.

Intermittent Androgen Blockade

Some have argued that intermittent ADT will delay progression to androgen independence compared with sustained ADT and that a testosterone increase when ADT is not in use decreases adverse effects. Although phase 3 trials are under way, there currently are no data from prospective randomized trials, and the American Society of Clinical Oncology considers intermittent androgen blockade to be experimental.

Antiandrogen Monotherapy

Nonsteroidal antiandrogen monotherapy has a less severe adverse-effects profile than that of ADT, making it a potential alternative. In a meta-analysis comparing bicalutamide and castration, overall survival with bicalutamide monotherapy was statistically not worse than that with castration.

The American Society of Clinical Oncology states that monotherapy with a nonsteroidal antiandrogen may be discussed as an alternative to ADT, but steroidal antiandrogens (currently not approved in the United States) should not be offered as monotherapy.

CONCLUSIONS

Androgen deprivation therapy is the most widely used systemic treatment for prostate cancer. In the metastatic setting, ADT has clear quality-of-life benefits but has not been shown to have survival benefit. Patients receiving local treatment with radiation therapy for high-risk disease have proven survival benefit. However, the role and benefit of ADT in biochemical failure after local therapy is unclear.

Adverse effects of ADT often mimic testosterone deficiency due to other causes. When anticipated prior to or early in ADT, some adverse effects, such as bone loss, can be prevented. Adverse effects, such as hot flashes and sexual effects, can significantly affect quality of life. Metabolic changes also occur, some of which are risk factors for cardiovascular disease. Clearly, further study is required to help physicians carefully weigh the benefits against the morbidity associated with ADT and to optimize the management of adverse effects.

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