**ABSTRACT**  Androgen deprivation therapy remains a mainstay of treatment for men with prostate cancer. New uses for hormonal therapy, including use in the adjuvant and neoadjuvant setting, are being evaluated. Prevention of the side effects of therapy has led to the development of alternative schedules and therapeutics. *(CA Cancer J Clin 2002;52:154-179.)*

**INTRODUCTION**

Hormonal or androgen deprivation therapy is utilized in multiple settings in the prostate cancer patient (Figure 1). In general, androgen deprivation induces a remission in 80 to 90 percent of men with advanced prostate cancer, and results in a median progression-free survival of 12 to 33 months.¹ At that time, an androgen-independent phenotype usually emerges, leading to a median overall survival of 23 to 37 months from the time of initiation of androgen deprivation.

In 1895, White first documented the use of androgen ablation in 111 men with prostate hypertrophy treated by castration.² David and colleagues isolated testosterone in 1935 and in 1941, Huggins and Hodges introduced androgen deprivation as therapy for advanced prostate cancer.³,⁴ In the 1950s, retrospective analyses provided data suggesting that patients treated with hormonal therapy in the form of estrogens or orchietomy enjoyed a survival and quality-of-life advantage when compared with patients followed in the pre-therapy era.⁵,⁶ Multiple strategies have been used to induce castrate serum levels of testosterone or interfere with its function (Figure 2). In order to rigorously test the previously reported data that androgen deprivation can impact the natural history of prostate cancer, the Veterans Administration Cooperative Urological Research Group (VACURG) conducted three large, randomized studies regarding the treatment of early stage and advanced prostate cancer from 1960 to 1975.⁷,²,¹⁰ These prospective studies provided data on a large cohort of men, and provided guidelines for the use of orchietomy and estrogens as treatment. In the 1980s, luteinizing hormone-releasing hormone (LHRH) agonists and antiandrogens were introduced. These compounds have been evaluated in practically every conceivable clinical setting, from the traditional role in advanced disease to use in the adjuvant and neoadjuvant settings. Combination treatment with testicular androgen suppression and an antiandrogen (called combined androgen blockade or maximal androgen blockade) soon followed. Although an impressive body of knowledge has accumulated, the variety of options and occasionally conflicting data has made the use of hormonal therapy all but straightforward.
METHODS OF PRIMARY ANDROGEN ABLATION

Orchiectomy

The first VACURG study, published in 1967, randomized 1,764 Stage III and IV patients to one of four treatment options: placebo, orchiectomy plus placebo, DES 5 mg per day, or orchiectomy plus DES 5 mg per day.8 Orchiectomy was associated with a one-year survival rate of 73 percent and a five-year survival rate of 35 percent in Stage IV patients, compared with 66 percent and 20 percent in placebo-treated patients. With longer follow-up, however, overall survival curves for all four arms were equivalent, suggesting that the type of hormonal treatment did not influence the development or course of androgen-independent disease.11 Compared with placebo, all treatments were associated with subjective improvements in pain and performance status.

Despite data regarding its efficacy, orchiectomy may be an underused form of hormonal treatment. Surgical castration is an outpatient procedure that results in an immediate reduction in circulating testosterone over a period of a few hours.12 Although data are sparse, some studies suggest that up to 50 percent of men choose orchiectomy when it is offered as an option for reasons of convenience and cost.13 The most recent data from the Prostate Cancer Outcomes Study provided an update on quality-of-life issues for patients receiving hormonal therapy.14 Men who chose LHRH agonist therapy reported greater problems with their overall sexual functioning than did orchiectomy patients, despite both groups having similar levels of function prior to treatment. LHRH agonist patients were also less likely to perceive themselves as free of cancer, due to the need for ongoing injections. Another study, however, suggested that men who underwent orchiectomy were more likely to regret this decision as compared with those treated with LHRH agonist therapy.15

Diethylstilbestrol

Diethylstilbestrol (DES), a semi-synthetic estrogen compound, was one of the first nonsurgical options for the treatment of prostate cancer. Widespread use has been limited, however, by the potential for significant cardiovascular and thromboembolic toxicity.

Initial studies from VACURG and the European Organization for Research and Treatment of Cancer (EORTC) used 3 to 5 mg of DES per day, and showed the remission rate of DES to be equivalent to orchiectomy.8 Overall mortality, however, was higher in the DES group due to an excess of cardiovascular deaths. A more recent study (EORTC 30805) demonstrated the equivalence of orchiectomy and DES at 1 mg per day.16 In this study, 13 percent of patients receiving DES had treatment discontinued due to cardiovascular complications, compared with none in the orchiectomy arm. Most of the events were venous in nature, including edema and deep venous thrombosis. DES at a dose of 3 mg per day has also shown equivalence to LHRH agonists in patients with locally advanced and metastatic disease in terms of overall survival and subjective improvement.17-21 DES proved to be superior to flutamide alone in the treatment of metastatic disease.22 Several EORTC trials (30761 and 30762) demonstrated DES 3 mg per day to be equivalent to estramustine23 and cyproterone.24 The introduction of the LHRH analogs, with no significant cardiovascular toxicity, lack of
After initial diagnosis, patients have several options regarding treatment. Androgen deprivation therapy is indicated, however, at the time of disease progression after definitive and salvage local therapy.
breast enlargement, and significant reim-
bursement for clinicians, essentially ended the 
use of DES as a first-line hormonal therapy. 
DES is no longer mass produced for human 
use in the United States.

**Cyproterone**

Cyproterone acetate (CPA) is a steroidal, 
progestational antiandrogen that blocks the 
androgen-receptor interaction and reduces 
serum testosterone through a weak anti-
gonadotropic action.\(^\text{25}\) It is commonly used in 
Canada as monotherapy or as an agent to 
prevent disease flare during initiation of LHRH 
agonist therapy. Cyproterone can also suppress hot 
flushes in response to androgen deprivation 
treatment with LHRH agonists or orchiec-
tomy.\(^\text{26}\) Although it is generally well tolerated, 
CPA is also associated with a high rate of 
cardiovascular complications, and is not 
available in the United States.

**LHRH Agonists and Antagonists**

The introduction of the LHRH agonists, the 
two most common being leuprolide and 
goserelin, revolutionized the treatment of 
advanced prostate cancer. No surgery is 
required—a potentially important physical and 
psychological benefit.

LHRH is normally released from the 
hypothalamus in pulses. This leads to the 
pulsatile release of FSH (follicle stimulating 
hormone) and LH (luteinizing hormone). LH 
attaches to receptors on the Leydig cells of the 
testes, promoting testosterone production. 
Constant exposure to LHRH after treatment 
with an LHRH agonist, however, eventually 
causes downregulation of receptors in the 
pituitary, inhibition of FSH and LH release, 
and a concomitant decrease in testosterone 
production.

Initial treatment with LHRH agonists, 
however, causes a surge of LH release, with a 
corresponding increase in testosterone levels. 
This testosterone surge can result in a transient 
increase in prostate cancer growth. Some 
patients can experience a worsening of bone 
pain, urinary obstruction, or other symptoms 
attributable to rapid cancer growth, known as the 
flare phenomenon.

LHRH agonists have different side effect 
profiles than DES and CPA, including no 
cardiovascular toxicity. Phase III studies of 
LHRH agonists versus surgical castration 
demonstrated no difference in survival between 
the two therapies.\(^\text{27}\) Depot preparations 
(injections lasting three to four months) for 
androgen ablation are now the most common 
treatments for metastatic prostate cancer. 
Multiple Phase III studies have demonstrated 
that all preparations have similar efficacy.\(^\text{28}\)

Abarelix is one of the new, modified 
gonadotropin–releasing hormone antagonists. 
Unlike the standard LHRH agonists, abarelix is 
a direct LHRH antagonist, and thus avoids the 
flare phenomenon. This compound was 
recently compared with leuprolide acetate in a 
Phase III randomized trial.\(^\text{29}\) Medical castration, 
as measured by serum testosterone levels, was 
achieved in 75 percent of the abarelix group by 
day 15, compared with 10 percent of patients in 
the leuprolide group. The percentage decrease 
in PSA was significantly greater in the abarelix 
group on day 15 after treatment. At day 29, 
post-treatment and beyond, PSA levels were 
similar between leuprolide and abarelix. As this 
study does not have mature follow-up, it is not 
possible to determine if abarelix and leuprolide 
will provide identical rates of disease control.

**PC-SPES**

PC-SPES, an herbal supplement, has been 
evaluated in a prospective Phase II trial.\(^\text{30}\) The 
mechanism behind the efficacy of PC-SPES is 
not well understood. The toxicities and
biochemical effects appear to be estrogenic. Analysis of the product, however, did not yield any known estrogens. As PC-SPES is an herbal supplement, no standards exist for ensuring all pills have equal amounts of “active” extract. Additionally, PC-SPES has been shown to decrease PSA production in vitro, a finding that may play a role in evaluation of efficacy. Recently the California Department of Health Services (CDHS) found traces of warfarin in PC-SPES during laboratory analysis. Researchers at the University of California/San Francisco Medical Center then issued a statement indicating that certain lots of PC-SPES being used in a clinical trial also contained traces of DES. The CDHS has subsequently recalled all lots of existing drug.

Nonsteroidal Antiandrogens

The nonsteroidal antiandrogens bicalutamide, flutamide, and nilutamide interfere with the binding of testosterone and dihydrotestosterone to the androgen receptor (Figure 2). In a randomized, multicenter trial of 486 patients with previously untreated metastatic prostate cancer, bicalutamide 50 mg per day was compared with castration with either orchietomy or LHRH agonist therapy. Bicalutamide was almost as effective as orchietomy; treatment failure occurred in 53 percent of bicalutamide-treated patients compared with 42 percent of castrated patients. Survival was not significantly different between the two groups. Although PSA progression was not considered to be evidence of disease progression, PSA normalization occurred in 17 percent of the bicalutamide group and 47 percent in the castrated group; this represented a median decline of 88 percent and 97 percent from baseline, respectively. The authors concluded that 50 mg of bicalutamide was not as effective as castration for the treatment of patients with metastatic disease. Given this data, antiandrogens, when utilized at conventional doses, do not provide adequate androgen deprivation. Therefore, they should not be used as single agents for the treatment of advanced prostate cancer.

Combined Androgen Blockade

Monotherapy with androgen deprivation results in a decline of 90 percent of circulating testosterone (Figure 2). Ten percent of circulating testosterone is still present in castrated men due to peripheral conversion of circulating adrenal steroids to testosterone.

Few subjects have generated more controversy in the field of urologic oncology over the last ten years than the question of whether patients should be treated with monotherapy versus combined androgen blockade (CAB). CAB consists of treatment with a LHRH agonist or orchietomy plus a nonsteroidal antiandrogen.

The first trial to show a potential advantage to CAB over monotherapy was published in 1989. This randomized, double blind, placebo-controlled study evaluated leuprolide alone versus leuprolide and flutamide in 603 men with previously untreated, metastatic prostate cancer. CAB was associated with a significant improvement in median progression-free survival (16.5 months versus 13.9 months) and in median overall survival (35.6 months versus 28.3 months). Men with minimal disease and good performance status appeared to benefit the most from combined therapy, although retrospectively, only 41 men in each group qualified for this category. In addition, the use of CAB in initial therapy lessened the flare phenomenon. It was unclear if the prevention of the flare could account for the differences in survival. Testosterone levels were elevated for a few weeks at most. These results were considered to be validated by two other early trials: EORTC 30853 (originally reported in...
Hypothalamus

Estrogen → LHRH → LHRH Analogs (leuprolide, goserelin) → LHRH Antagonists (abarelix)

Anterior Pituitary

LH → Testicles

90% T 10% T Conversion

Surgical Castration

Nonsteroidal antiandrogens block binding of T and DHT to the androgen receptor. (flutamide, bicalutamide, nilutamide)

Prostate Cancer Cell

Cell Proliferation

T → 5αR → DHT

Finasteride prevents T conversion to active metabolite dihydrotestosterone.

LHRH = Luteinizing hormone-releasing hormone.
LH = Luteinizing hormone.
T = Testosterone.
DHT = Dihydrotestosterone.
5αR = 5-alpha reductase.
AR = Androgen receptor.
DNA = Deoxyribonucleic acid.
1990) and PONCAP\textsuperscript{37} (the Italian Prostatic Cancer Project, reported in 1993). These trials also demonstrated a statistically significant improvement in survival for patients treated with CAB (goserelin and flutamide) versus monotherapy (orchiectomy).

Later studies provided conflicting data. In 1998, Eisenberger and colleagues published a study of 1,387 patients (NCI-INT 0105) with previously untreated metastatic disease who were randomized to bilateral orchiectomy and placebo versus bilateral orchiectomy and flutamide.\textsuperscript{38} At the time of progression, the study was unblinded and patients receiving
placebo were allowed to cross over to flutamide. The data were reported using an intention-to-treat analysis. There were no differences between the two groups in overall survival or progression-free survival. Two factors were hypothesized to account for the discrepancy between the results of this trial and the earlier reports. The first factor was noncompliance in the 1989 study to the daily regimen of leuprolide injections, which may have resulted in incomplete testicular ablation. The superiority of flutamide may have been a simple reflection of this. Second, the flare phenomenon may have played a role in the superiority of CAB over monotherapy; as the improvements were not seen with bilateral orchiectomy. Approximately 20 other studies also failed to confirm the survival advantage detected in the earlier studies, although many were small with flawed statistical analysis and immature data.

In 2000, the Prostate Cancer Trialists’ Cooperative Group published a meta-analysis of the available trials of CAB versus monotherapy, in an attempt to summarize the available data.39 The analysis included 27 trials, which incorporated 8,275 men, representing 98 percent of men ever randomized in trials of CAB versus monotherapy (Figure 3). The five-year survival for all patients receiving CAB was 25.4 percent compared with 23.6 percent for patients receiving monotherapy. This 1 to 2% absolute difference in survival did not reach statistical significance. In subset analyses, patients treated with cyproterone seemed to fare slightly worse than those treated with flutamide or nilutamide, mostly secondary to non-prostate cancer related death. If the trials involving cyproterone were excluded, there was a significant improvement in survival with CAB including nilutamide or flutamide, but with a 95% confidence interval of 0.4 to 5.4 percent. Taken as a whole, the data suggest that there is a small survival advantage to CAB using flutamide or nilutamide, which does not exceed a 5% improvement in five-year survival, and is likely closer to a 2 to 3% improvement. With these data, the authors did not support CAB over monotherapy as the first-line hormonal treatment of choice.

At this juncture, there is no way to predict which patients, if any, would benefit from the immediate institution of CAB. No molecular markers with predictive capacity exist, unlike estrogen receptor and progesterone receptor positivity in breast cancer patients. Additionally, no trials compare CAB with monotherapy followed by the institution of CAB at the time of progression. A trial of this type may be embraced in the current environment, as treatment of prostate cancer moves toward sequential interventions, attempting to maximize the therapeutic effects of each maneuver while balancing benefits with side effects. As more data are gathered about the mechanism of change from hormone-dependence to hormone-independence, it seems unlikely that the simple manipulation of the androgen receptor could result in the complex array of gene and signal transduction activation necessary for this transformation. It is unlikely, therefore, that further trials of appropriate size and randomization will be undertaken with the primary objective of defining the survival advantage of CAB. Despite the degree of available data and analysis, there is no consensus on the use of CAB. The ultimate decision on monotherapy versus CAB remains, at this time, in the hands of the individual patient and practitioner.
prostatectomy has been investigated in several trials. The Lupron Depot Neoadjuvant Prostate Cancer Study Group conducted a multi-institutional prospective randomized trial for patients with Stage cT2b prostate cancer. One hundred thirty eight men received three months of leuprolide plus flutamide prior to radical prostatectomy and 144 underwent radical prostatectomy alone. Patients were followed with PSA measurements every six months for five years. Biochemical recurrence was defined as PSA greater than 0.4 ng/ml. Although patients who received three months of androgen deprivation had a significant decrease in the positive margin rate at the time of surgery, there was no difference in the biochemical recurrence rate at five years. PSA was less than 0.4 ng/ml in 64.8 percent of the patients in the neoadjuvant androgen ablation plus prostatectomy and 67.6 percent in the prostatectomy-only group (p = 0.663). The authors concluded that neoadjuvant androgen deprivation before radical prostatectomy was not indicated. This conclusion is supported by another study of 402 patients, 192 who underwent three months of neoadjuvant goserelin and flutamide and 210 who underwent surgery alone. These investigators similarly reported improved local control rates at the time of surgery, but no difference in the rate of biochemical recurrence at five years. The overall conclusion from these trials was that neoadjuvant therapy should not be utilized outside a clinical research setting.

It has been suggested that three months of neoadjuvant androgen deprivation may not be long enough. Gleave and colleagues treated 156 men with localized prostate cancer with neoadjuvant CAB for eight months prior to radical prostatectomy. The risk of PSA recurrence with this regimen was low after five years of follow-up in relation to the presence of adverse preoperative risk factors. The lack of a control group in this study makes it impossible to say whether a longer duration of neoadjuvant androgen deprivation therapy would provide more benefit than shorter schedules or no therapy. The Gleave group has recently undertaken a randomized trial of three versus eight months of neoadjuvant therapy prior to prostatectomy. A recently published interim analysis reports a significantly higher percentage of patients with an undetectable PSA nadir in the eight-month group compared with the three-month group (75 percent versus 43 percent). Mean PSA levels decreased by 98 percent (0.12 µg/L) after three months of therapy, but continued to decline an additional 57 percent to 0.052 µg/L after eight months of therapy. Similar trends were seen in prostate volume. Radical prostatectomy has been completed in 500 men, with significantly lower rates of positive margins in the eight-month group (12 percent versus 23 percent). Recurrence rates (either biochemical or local) post-prostatectomy were not reported, as follow-up time was too short. The authors caution that these biochemical and pathological end points should not be interpreted as conclusive.

Adjuvant Therapy

Several nonrandomized, retrospective studies have suggested that adjuvant androgen deprivation therapy after radical prostatectomy may improve local control and possibly survival. In a recent review of adjuvant hormonal therapy, Zincke and colleagues systematically analyzed retrospective data from the Mayo Clinic database in addition to the existing prospective and retrospective trials from other institutions. The retrospective review of the Mayo Clinic data included 707 men who underwent prostatectomy for Stage pT3bN0M0 disease, 147 of whom received adjuvant hormonal therapy (orchiectomy or oral hormones). Adjuvant therapy was
associated with a significant improvement in biochemical progression-free survival (67 percent versus 23 percent at 10 years), systemic progression-free survival (90 percent versus 78 percent) and cause-specific survival (95 percent versus 87 percent).

The Eastern Cooperative Oncology Group (ECOG) randomized 98 men with positive lymph nodes at the time of surgery to receive immediate antiandrogen therapy (with either goserelin or orchiectomy) or to be followed until disease progression. After 7.1 median years of follow-up, 7 of 47 men who received immediate antiandrogen treatment had died, as compared with 18 of 51 men in the observation group (p = 0.02). In the adjuvant group, three men died of prostate cancer, compared with 16 men in the observation group (p < 0.01).

Interest has been increasing in the use of nonsteroidal antiandrogens as adjuvant therapy in patients with localized disease. Early results of a study of 365 patients with pT3N0 disease investigating the efficacy of flutamide (250 mg twice daily) given after radical prostatectomy demonstrated a 10% clinical recurrence rate at four years in the flutamide-treated patients compared with a rate of 31 percent for those receiving placebo (p = 0.002). The patients treated with flutamide, however, experienced a high incidence of side effects, with approximately 20 percent of the patients withdrawing from the study secondary to toxicity. The mature results of the study have not been reported. Another trial is underway to evaluate the effectiveness of adjuvant high-dose bicalutamide (150 mg) in patients undergoing definitive therapy for localized disease.

Timing of the institution of hormonal therapy for prostate cancer remains controversial, but there is a growing consensus that men with nodal disease at the time of surgery have a survival benefit from immediate androgen deprivation. This approach must be balanced by the toxicity associated with long-term adjuvant therapy.

HORMONE THERAPY IN CONJUNCTION WITH EXTERNAL BEAM RADIATION THERAPY

Several studies have addressed whether androgen deprivation therapy added to radiation therapy improves outcomes in patients with localized or locally advanced prostate cancer (Table 1).

In 1997, the EORTC reported the results of 415 patients with locally advanced prostate cancer treated with external beam radiation versus external beam radiation plus goserelin for three years. At a median follow-up of 45 months, the Kaplan-Meier estimates of overall survival at five years were 79 percent for patients who received combined treatment versus 62 percent in the group treated with external beam radiation therapy alone (p = 0.001). Eighty-five percent of surviving patients were free of disease at five years in the combined-treatment group and 48 percent in the group that received external beam treatment alone (p < 0.001). These data strongly suggested that adjuvant treatment in patients with locally advanced prostate cancer improved both local control and survival at five years.

RTOG 85-31 also sought to determine the advantage of androgen deprivation as adjunctive therapy following standard external beam radiation therapy in patients with locally advanced prostate cancer. A total of 977 patients were randomized to receive radiation only (androgen deprivation started at disease relapse) or radiation plus adjuvant goserelin. The local failure rate at eight years was 23 percent for the combination-therapy arm and 37 percent for the radiation-alone arm (p < 0.0001). The distant metastasis rate in the combination arm was 27 percent and 37 percent in the radiation-alone arm.
The disease-free survival favored the immediate androgen deprivation arm (p < 0.0001). Overall survival was not statistically different between the two groups (49 percent versus 47 percent at eight years). The length of androgen deprivation therapy necessary for the maximum benefit remains unknown. RTOG 86–10 randomized 471 patients with T2 to T4 tumors with or without pelvic lymph node involvement to receive radiation plus complete androgen blockade with goserelin and flutamide versus radiation therapy alone. Androgen deprivation therapy was administered for two months prior to radiation therapy and during radiation therapy. Analysis at eight years demonstrated that patients treated with combination therapy had an improvement in local control (30 percent versus 42 percent, p = 0.016), reduction in the incidence of distant metastases (34 percent versus 45 percent, p = 0.04), disease-free survival (21 percent versus 33 percent, p = 0.004), and disease-specific mortality (23 percent versus 31 percent, p = 0.05). However, subset analysis indicated that the beneficial effect of short-term androgen deprivation was only significant in patients with Gleason score two to six tumors (survival 70 percent versus 52 percent, p = 0.015). Patients with Gleason seven to ten tumors had no improvement in local control or survival.

RTOG protocol 92–02 treated over 1,500 patients with locally advanced prostate cancer with radiation and differing regimens of androgen deprivation therapy. All patients received two months of neoadjuvant complete

| Study                  | Eligibility                              | Intervention                                                                 | Results                                                                 |
|------------------------|------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|
| EORTC                  | T1/T2 high-grade, T3/T4 any grade, node negative disease | Definitive XRT versus XRT + goserelin beginning day 1 x 3 years. | Improvement in overall survival, disease-free survival, and local control. |
| RTOG 85-31             | Clinical Stage T3 or node positive disease | Definitive XRT or salvage XRT after having poor prognostic features at prostatectomy versus goserelin beginning the last week of XRT. | Improvement in local control, freedom from distant mets, and disease-free survival. No benefit in overall survival except in patients with high-grade cancers. |
| RTOG 86-10             | T2-T4, node negative or node positive disease | Definitive XRT versus XRT + CAB two months prior and two months during XRT. | Improvement in local control and survival in patients with Gleason 2 to 6 disease only. |
| RTOG 92-02             | Clinical Stage T2-T4                     | All patients received CAB two months prior and during radiation then CAB for an additional 24 months versus no additional CAB. | Disease-free survival improved in 24-month group. Overall survival improved in 24 month group for Gleason 8 to 10 disease. |
| Joint Center for Radiation Therapy | Clinical Stage T1-T2                | All patients received AB, two months prior, two months during, and two months after XRT, retrospective analysis. | Relative risk of biochemical failure at five years was decreased in intermediate- and high-risk patients. |
androgen blockade with goserelin and flutamide, which was continued for two months during radiation. Patients were then randomized to receive either no hormones or an additional 24 months of complete androgen blockade. The patients treated with 24 additional months of androgen deprivation demonstrated significant improvement in disease-free survival 54 percent versus 34 percent (p = 0.0001), local progression 6 percent versus 13 percent (p = 0.0001), distant metastasis 11 percent versus 17 percent (p = 0.001), and biochemical failure 21 percent versus 46 percent (p = 0.0001). At a median follow-up of 4.8 years, 54 patients died of prostate cancer in the short-term androgen deprivation group compared with 33 patients in the long-term androgen deprivation group. Disease-specific survival showed a trend in favor of the 24-month hormone group, 92 percent versus 87 percent (p = 0.07). In the subgroup of patients with Gleason eight to ten tumors, five-year survival was significantly better with long-term therapy, 80 percent versus 69 percent (p = 0.02) as was disease-specific survival, 90 percent versus 78 percent (p = 0.007).

The Joint Center for Radiation Therapy conducted a retrospective analysis of 1,586 patients with localized prostate cancer treated with definitive radiation therapy versus those patients treated with radiation therapy plus six months of androgen deprivation. Complete androgen blockade was given two months prior, two months during, and two months after radiation therapy. Low-risk patients had a PSA of 10 µg/L or less, a Gleason score of six or less, and a T1c or T2a tumor. Patients classified as intermediate-risk had a T2b tumor or a PSA of 10.1 to 20 µg/L or a Gleason score of seven. High-risk patients had a T2c tumor, PSA of more than 20 µg/L or Gleason score of eight or higher. The group estimated the biochemical relapse rate of patients at five years, i.e., the proportion of patients that had a rising PSA. Overall survival data were not described. The relative risks of PSA failure in intermediate-risk and high-risk patients treated with radiation therapy plus androgen deprivation compared with radiation therapy alone were 0.2 (95 percent CI, 0.1 to 0.3) and 0.4 (95 percent CI, 0.2 to 0.8), respectively. These data suggested a significant benefit in five-year PSA outcomes for men with clinically localized prostate cancer in intermediate- and high-risk groups treated with radiation therapy plus androgen deprivation.

All of the above studies can be criticized because they compared radiation therapy with radiation therapy plus androgen deprivation for some period of time. None of these studies have an androgen deprivation therapy arm alone, and hormonal therapy without radiation may have produced results similar to those seen with combination therapy. This question is being addressed by RTOG-0011, a Phase III study of adjuvant therapy for high-risk prostate cancer patients. Patients are randomized to receive radiation therapy alone, androgen deprivation for two years, or a combination of radiation therapy and androgen deprivation for two years. The general consensus at this time is that patients with high-grade localized tumors and patients with locally-advanced tumors benefit from two to three years of adjuvant androgen deprivation.

HORMONE THERAPY IN CONJUNCTION WITH BRACHYTHERAPY

Brachytherapy has been used in men with low-to-intermediate grade tumors (Gleason ≤ six). Neoadjuvant hormone therapy has been given to men who have large prostates,
generally greater than 40 grams, to shrink the prostate prior to seed implantation. Merrick and colleagues evaluated the five-year biochemical disease-free outcome for men with clinical T1b–T3aNxM0 prostate cancer who underwent transperineal ultrasound-guided permanent prostate brachytherapy using either $^{103}$Pd or $^{125}$I.56 A total of 77 patients received neoadjuvant androgen deprivation in conjunction with either $^{103}$Pd or $^{125}$I monotherapy and 86 patients received neoadjuvant therapy in conjunction with moderate-dose external beam radiation therapy and a prostate brachytherapy boost. At a median follow-up of 31 months, patients with low-, intermediate-, and high-risk disease demonstrated five-year biochemical disease-free rates of 97.1 percent, 97.5 percent, and 84.4 percent, respectively. Stone and colleagues biopsied a series of 296 patients, 115 of whom received complete androgen blockade for three months prior to implant and for three months after implant.57 Biopsies were positive in 4 of 115 (3.5 percent) who had received androgen deprivation versus 26 of 181 (14 percent) in those who had not ($p = 0.002$). When patients were separated into low risk (PSA $\leq 10$ ng/ml, Stage $< or = T (2a)$, and Gleason score $< or = 6$) and high risk (all others), it was observed that low-risk patients did not benefit from the addition of hormonal therapy while the high-risk patients not treated with androgen deprivation had a significantly higher rate of positive biopsies (3.4 percent versus 21.1 percent; $p = 0.003$).

Potters and colleagues assessed the role of neoadjuvant androgen deprivation and transperineal interstitial permanent prostate brachytherapy using a matched-pair analysis of 612 consecutive patients with clinically confined prostate cancer.58 Patients were treated with either $^{103}$Pd or $^{125}$I as monotherapy or combined with external radiation. One hundred sixty-three patients with prostate glands greater than 60 grams underwent neoadjuvant androgen deprivation to reduce the prostate volume. The median duration of hormonal therapy was 3.4 months (range one to eight months). Two hundred sixty-three patients were matched, with a median follow-up duration of 46 months (range 24 to 46 months). The five-year PSA relapse free rate for patients treated with combination therapy was 87.1 percent compared with 86.9 percent for those treated with brachytherapy alone. Subgroup analysis by Gleason score groupings, pretreatment PSA, and stage of disease failed to identify any factors for which androgen ablation was beneficial.

Until prospective, randomized studies are done, the role of androgen deprivation therapy in conjunction with brachytherapy, specifically in relation to improvement in outcome, remains unclear.59

### ANDROGEN DEPRIVATION FOR ADVANCED DISEASE: WHEN TO INTERVENE

Another controversial area in the treatment of men with metastatic prostate cancer is the timing of androgen ablation.60 In the past, this was an easy decision. Prostate cancer, left untreated, almost universally metastasizes to bone. Most men presented with bone pain from these skeletal lesions, prompting therapy. The discovery of PSA radically altered the treatment landscape.

PSA is produced by normal prostate epithelial cells and prostate cancer cells. After prostatectomy, the PSA should be undetectable. After external beam radiation therapy or brachytherapy, the PSA declines and reaches a plateau and should remain stable. A detectable and rising PSA after surgery or radiation therapy indicates recurrent cancer.
The decision regarding when to initiate therapy remains difficult, although data from several sources may provide direction to physicians and patients. The concept of watchful waiting, i.e., waiting to treat until the development of symptoms, was first piloted in the 1970s after the results of VACURG trials suggested that delaying therapy until the onset of symptoms did not increase prostate cancer-specific mortality in patients with locally advanced or metastatic disease. In this study, however, only 41 percent of men died from prostate cancer. As aggressive treatment of other medical conditions has improved life expectancy, it was postulated that this data might no longer be applicable. In a reanalysis of the VACURG studies, early medical castration with DES was found to improve actuarial survival rates for patients with locally advanced and metastatic disease when compared with placebo. Early treatment appeared to be most beneficial for younger patients.

Four more recent studies have attempted to evaluate watchful waiting in the modern era. From 1985 until 1993, the Medical Research Council Trial randomized 938 men with locally advanced or asymptomatic metastatic prostate cancer to either immediate (at the time of diagnosis) or deferred (upon development of symptoms) treatment with monotherapy. In this study, 67 percent of patients died secondary to prostate cancer, a significant increase from the findings of the VACURG trial. Although this study has been criticized due to the lack of uniform staging in the patients, it demonstrated an increase in disease-specific and overall survival in patients treated with immediate androgen deprivation. Patients treated with deferred therapy suffered significantly more comorbid events associated with their disease. Additionally, men with metastatic disease at presentation developed an indication for treatment at a median of nine months of observation, and few remained untreated at the time of death. A recent abstract regarding longer-term data from the MRC Trial, however, reported that although immediate therapy continued to improve disease-specific survival, overall survival differences were becoming considerably smaller. Interestingly, more patients in the immediate arm died of nonprostate cancer, and no excess mortality from cardiovascular disease was observed. It is unclear whether the hormonal therapy conferred adverse events leading to morbidity and mortality. It may be possible that hormonal treatment controlled the prostate cancer, allowing other comorbid conditions to run their natural course.

As described above, EORTC randomized 415 men with locally advanced prostate cancer at presentation to radiation alone versus radiation with concurrent goserelin therapy. The Kaplan-Meier estimate of overall survival at five years was 79 percent for the combined treatment group, compared with 62 percent for the group receiving radiation alone (p = 0.001). Disease-free survival at five years was 85 percent in the combined-treatment arm, compared with 48 percent in the radiation-alone arm (p < 0.001). Local control was also significantly improved in the combined-treatment group, with only three percent of patients experiencing a local failure compared with 23 percent with radiation alone (p < 0.001). Similarly, RTOG 85-31, 86-10, and 92-02 investigated the benefit of the addition of androgen deprivation to radiation therapy. A recent subset analysis of data from RTOG 85-31 and 86-10 was recently reported. In this analysis, only patients with T2-3N0M0 disease who were treated with definitive XRT were included. The purpose of the study was to determine if long-term hormonal therapy is more advantageous than short-term hormonal therapy (four months of
Biochemical disease-free survival (bNED, defined as a post-treatment PSA of < 1.5 ng/ml more than one year from randomization), rates of distant metastasis failure, and cause-specific failure were significantly improved in the long-term hormone treatment group as compared with the short-term hormone treatment group or the radiation alone group. There was no difference in these outcomes between short-term hormonal therapy and radiation alone. However, no significant difference was found in overall survival among the three groups. In the group receiving long-term androgen deprivation, the benefit seen for bNED, rate of distant metastasis failure, and cause-specific failure was limited to patients with Gleason scores of seven or greater.

From 1988 to 1993, the Eastern Cooperative Oncology Group (ECOG) evaluated the impact of immediate hormonal therapy on 98 men who underwent radical prostatectomy and pelvic lymphadenectomy who were found to have nodal metastases. Patients were randomized to androgen deprivation with goserelin or bilateral orchiectomy (treatment arm) or to routine follow-up (control arm). After a median follow-up of 7.1 years, the group who received immediate hormonal therapy had a statistically significant improvement in overall survival (p = 0.02), progression-free survival (p < 0.001), and prostate cancer-specific survival (p = 0.001). After ten years, the actuarial survival of patients treated with immediate therapy was approximately 80 percent, compared with only 55 percent in patients treated with deferred androgen deprivation (p = 0.02). Although such data cannot be extrapolated to patients with clinically localized prostate cancer who do not receive local therapy, the conclusions of this study provide additional evidence in support of early androgen deprivation for patients with high-risk prostate cancer.

Although no clear-cut guidelines have been established, there is a growing tendency to treat patients with recurrent prostate cancer with androgen deprivation at some point when the PSA is rising, prior to symptom development. This is especially true in patients with aggressive disease (Gleason ≥ eight). This has led to a renewed interest in the side effects of therapy and potential methods to circumvent them.

Side Effects of Androgen Deprivation Therapy

Initially, hormonal therapy was considered to be well tolerated. Loss of libido was often the only adverse side effect mentioned to the patient. Several other toxicities have now been noted (Figure 4). These include fatigue, weight gain, depression, osteopenia, anemia, muscle atrophy, gynecomastia, hot flashes, loss of cognitive function, and decrease in high-density lipoprotein. Severe symptoms may warrant consideration of a change in therapy. For example, fewer patients experience distressing hot flashes on estrogens compared with LHRH agonist therapy or orchiectomy. Replacement of an LHRH agonist with an estrogen, or the addition of an estrogen to post-orchiectomy patients, may lessen the frequency or severity of this often debilitating problem. Other agents, such as venlafaxine, have also been shown to reduce the severity of hot flashes. The antiandrogens and cyproterone are associated with a rare but potentially fatal hepatotoxicity, and should be used with caution in patients with pre-existing liver disease. Patients on therapy should have liver enzyme measurements monitored. Gynecomastia can often be lessened with a very short course of radiation therapy to the breasts, but only if initiated prior to treatment. For patients who desire preservation of potency, high-dose antiandrogen therapy or a combination of finasteride and antiandrogen may be warranted as first-line treatment.
FIGURE 4

Side Effects of Androgen Deprivation

All numbers are estimates based on data from a variety of sources. Ranges vary considerably.
Osteopenia/Osteoporosis

Once initiated, most men remain on hormonal therapy for years, if not the rest of their lives. Long-term treatment with androgen deprivation can lead to debilitating osteoporosis.\textsuperscript{72,73} Even in a study of intermittent androgen blockade, evaluation of bone mineral density in the lumbar spine and hip revealed osteopenia in 46 percent and osteoporosis in 20 percent of patients.\textsuperscript{74} A similar study found that 50 percent of men on androgen blockade for at least 12 months had asymptomatic vertebral fractures.\textsuperscript{75} The precise incidence of clinically relevant fractures remains undefined.

Prevention of osteopenia/osteoporosis in these patients may be useful in prevention of fractures and other skeletal events, as has been documented in breast cancer.\textsuperscript{76} A recent study of 47 men with hormone-sensitive prostate cancer compared bone mineral density in men receiving leuprolide alone with the combination of pamidronate and leuprolide.\textsuperscript{77} Pamidronate showed significant protection of bone mineral density in the lumbar spine, greater trochanter, and total hip. Although the study was only of a 48-week duration, it underscored the startling amount of bone loss in patients on leuprolide alone for this period: 3.3 percent in the lumbar spine, 2.1 percent in the trochanter, and 1.8 percent in the total hip.

The US Food and Drug Administration has recently approved zoledronic acid, the newest intravenous bisphosphonate, for the treatment of skeletal events in men with documented metastatic disease (both androgen-dependent and androgen-independent). Zoledronic acid has been evaluated in a randomized, placebo-controlled trial of 422 patients with androgen-independent prostate cancer.\textsuperscript{78} Significantly fewer patients in the zoledronic acid group experienced skeletal-related events and pathologic fractures. The time elapse to first skeletal event, vertebral fracture, and pathologic fracture was significantly longer in the treatment group. Pain control at three months and nine months was also significantly improved.

An even more important effect of bisphosphonates may be their anti-metastatic potential.\textsuperscript{72} In-vitro data suggest that bisphosphonates can inhibit adhesion of tumor cells to the bony matrix,\textsuperscript{79} prevent tumor cell invasion into the bony matrix, and inhibit matrix metalloproteinases, known mediators of uncontrolled cell growth.\textsuperscript{80} Further studies are underway to determine if administration of bisphosphonates can actually slow or prevent the development of bone metastases in prostate cancer.

Alternatives to Classic Androgen Deprivation

Because of the side effects associated with androgen deprivation, several strategies are being tested to lessen the toxicity of therapy while still depriving the prostate cancer cells of testosterone.

Intermittent Androgen Blockade (IAB)

In 1986, Klotz and colleagues published a study of 20 patients with advanced prostate cancer treated with intermittent endocrine therapy.\textsuperscript{81} Nineteen patients received DES, and the other received flutamide. Treatment was continued until a clinical response was demonstrated, with a median initial-treatment duration of ten months (range 2 to 70). Therapy was then interrupted, and re-started after evidence of disease progression. The median time to relapse was eight months after treatment interruption (range 1 to 24). After relapse, all patients responded to reintroduction of therapy.
Therapy with intermittent androgen blockade. After institution of androgen deprivation, the patient continues on therapy until a PSA response is achieved. Serum testosterone levels decline accordingly. Once response is achieved, therapy is discontinued. PSA and serum testosterone rise, at which time therapy is re-instituted. The cycles continue until PSA fails to decline, or there is other evidence of disease progression. This usually coincides with the development of androgen independent disease.
Sato and colleagues demonstrated in vitro that cycling of reversible androgen suppression appeared to allow recovery of apoptotic potential in androgen-sensitive prostate cancer cells, with subsequent slower progression to an androgen-independent state. In clinical studies, the possibility that IAB could decrease the side effects of continuous androgen blockade was supported in multiple Phase II trials. Men reported better quality of life during their off periods. One study demonstrated that while off treatment, 42 percent of men noted an improvement in energy; hot flashes disappeared in 60 percent and decreased in 33 percent; libido increased in 75 percent; and erections improved in 62 percent. Retrospective comparison of survival in men who underwent IAB was similar to those treated with continuous therapy. Of note, approximately 20 to 25 percent of men who undergo androgen ablation for 6 to 12 months do not recover their gonadal function and do not experience a rise in serum testosterone and amelioration of symptoms when androgen blockade is stopped.

The concept of IAB is demonstrated in Figure 5. Patients are placed on androgen blockade for a period of six to nine months and after nadir of PSA is established, treatment with LHRH analog is withheld. Over the course of the next several months, testosterone rises. Subsequent with the testosterone rise and improvement in quality of life, however, the androgen-dependent cancer cells begin to proliferate. At some point, generally when the PSA rises to between four and ten, androgen deprivation is re-instituted. This cycling continues until the patient develops androgen independent cancer.

The Southwest Oncology Group (SWOG), the National Cancer Institute of Canada (NCIC), the South European Uro-Oncological Group (SEUG), and the German Cancer Society are studying the effects of IAB on progression-free survival, overall survival, and quality of life via large, multicenter, randomized, Phase III clinical trials. Until the results of these ongoing Phase III studies are available, this approach has to be regarded as experimental. One form of intermittent androgen blockade currently being used in a small number of centers is triple androgen blockade (TrAB). Patients are treated with complete androgen blockade for approximately 12 months and then placed on finasteride monotherapy during their “off time.” Early results suggest that this may increase the time between cycles of the triple drug therapy. At this time, however, this type of treatment must also be considered experimental and Phase III studies of traditional IAB versus TrAB are not yet underway.

**Sequential Androgen Blockade (SAB)**

Combining a nonsteroidal antiandrogen (flutamide, bicalutamide, nilutamide) with finasteride blocks the conversion of testosterone to its active metabolite dihydrotestosterone, and also prevents testosterone and dihydrotestosterone from binding to the androgen receptor (Figure 1). This approach, termed sequential androgen blockade (SAB), results in androgen deprivation at the cellular level but leaves circulating testosterone levels intact. In Phase II trials, this therapy has resulted in a decrease in serum PSA in the majority of men while maintaining sexual potency. This form of treatment has not been tested against traditional androgen deprivation in the Phase III setting, and its impact on survival remains unknown. While initially used mainly in men with advanced disease who wished to maintain potency, it is now being used in the nonprotocol setting to
**FIGURE 6**

Comparison of Lifetime Cost and Effectiveness of Different Androgen Deprivation Strategies

**Legend:**
- **Orchiectomy**
- **NSAA plus Orchiectomy**
- **LHRH Agonist**
- **NSAA plus LHRH Agonist**
- **NSAA**
- **DES**

**Notes:**
- **NSAA** = Nonsteroidal antiandrogen.
- **LHRH** = Luteinizing hormone-releasing hormone.
- Adapted from the *Journal of the National Cancer Institute.*

---

**CA Cancer J Clin 2002;52:154-179**
treat men with biochemical failure after primary therapy (PSA-only disease). This type of treatment remains unproven and its impact is uncertain. At least one study, however, has demonstrated that approximately 80 percent of men treated with SAB respond to androgen deprivation therapy when their PSA starts to rise. This suggests that SAB may become a first-line treatment of choice in the future for men with advanced prostate cancer.

**Peripheral Androgen Blockade (PAB)**

The traditional dose of bicalutamide to achieve its effect as a nonsteroidal antiandrogen is 50 mg per day. Studies have reported that a dose of 150 mg per day is as effective as castration or CAB in patients with advanced prostate cancer. This high dose approach has sometimes been referred to as peripheral androgen blockade (PAB). PAB has been compared with classic androgen deprivation in two open-label, randomized trials. Data were collected from 805 patients with demonstrable metastatic (M1) prostate cancer and 480 patients with biochemically advanced (M0) disease. Analysis at a median follow-up period of 6.3 years in M0 patients demonstrated no statistically significant difference in overall survival or time to progression between bicalutamide 150 mg monotherapy and medical or surgical castration. There was an overall survival advantage of six weeks in favor of castration in patients with M1 disease. PAB with high-dose bicalutamide was generally well tolerated as compared with androgen deprivation treatment. There was a high rate (approximately 50 percent) of gynecomastia. These data suggest that PAB may become a viable alternative for patients requiring androgen blockade.

**Cost**

On a societal level, cost becomes an issue when evaluating options for androgen deprivation therapy. On average, a patient with metastatic but hormone-sensitive disease will respond to hormonal treatment for 18 to 24 months. Patients with rising PSA only may respond to therapy for an even longer period. Many patients remain on androgen deprivation therapy even after their disease becomes androgen independent. Even in older studies with long inpatient hospitalization post-orchiectomy, the cost of the surgical procedure was less than an average course of LHRH agonist therapy. Expected patient survival plays a critical role in decision-making. Patients with very advanced disease and a limited life expectancy may achieve both improved palliation and cost-effectiveness with one or two injections of an LHRH agonist.

Cost also enters into decision-making when considering monotherapy versus CAB. A recent study evaluated the cost-effectiveness of different types of androgen ablation (DES, orchiectomy, medical monotherapy, and CAB), incorporating a quality-of-life analysis. Orchiectomy, LHRH agonists, antiandrogens, and CAB had similar effects on quality of life and survival estimates. The annual cost estimates included: DES: $36, LHRH agonist depot injection: $4,995, and antiandrogens: $2,842. Orchiectomy had a one-time cost of $3,360. CAB was associated with the smallest degree of benefit for the most relative cost. In this study, the lifetime cost of an antiandrogen plus orchiectomy was $20,700, while the cost of an antiandrogen plus LHRH agonist was $40,300. Figure 6 illustrates the relative lifetime costs of each therapy in comparison to effectiveness.

A review by the Blue Cross and Blue Shield Association determined that in order for CAB
to be cost-effective, the combination of LHRH agonist plus antiandrogen must increase survival by 20 percent compared with orchiectomy alone.\(^98,99\) In order for orchiectomy plus antiandrogen to be cost-effective, the combination must increase survival by ten percent compared with orchiectomy alone. The data from the Prostate Cancer Trialists Collaborative Group and other systematic reviews\(^99,100\) do not support this degree of impact from the use of CAB, suggesting that CAB, as currently described, is not a cost-effective intervention in comparison to orchiectomy. Extrapolating this concept, as orchiectomy and LHRH agonists have equivalent efficacy, CAB does not appear to be a cost-effective strategy compared with LHRH agonist monotherapy.

TOO MANY CHOICES?

Many choices are available for hormonal therapy. One choice is timing. Patients could be considered for therapy at various points: immediately after local therapy, at the first detectable PSA rise after local therapy, at a certain PSA value (e.g., four), at the time of development of a positive bone scan, at the time of development of symptoms, or when the PSA starts to double at a certain rate, (e.g., in less than six months).

Overall, the literature suggests that patients with advanced local tumors with adverse prognostic markers or positive nodes benefit from adjuvant therapy after definitive local therapy. Clearly, patients with symptomatic metastatic disease need to be treated. Data from multiple studies support a growing trend to treat patients earlier in their disease course, but currently, there is no single correct answer regarding timing of hormonal therapy for patients with PSA progression or asymptomatic metastatic disease.

If the decision is made to begin hormonal therapy, choosing the appropriate therapy requires an assessment of the patient’s needs within the context of existing data. If side effects are an issue, consideration should be given to a trial of intermittent, peripheral, or sequential androgen blockade. LHRH agonists, CAB, or orchiectomy would all still be considered the standard of care. Cost and patient preference may assist in this choice. DES is available in the United States, but only from a few pharmacies. Because of cardiovascular toxicity, DES may be best reserved as a secondary hormonal option. Some patients may opt for alternative strategies, such as nutritional therapy or herbal supplements.

In the final analysis, however, we must keep our eyes on the prize: the proper use of hormonal therapy to decrease the morbidity and mortality associated with prostate cancer. As discussed in the section on “when to intervene,” evidence exists to support a mortality benefit to early androgen deprivation therapy. A recent study by Demers and colleagues suggests that the sharp decline in prostate cancer mortality in a cohort of 56,000 men paralleled the increased use of adjuvant or early hormonal therapy, along with improvements in diagnostic techniques and local therapy.\(^101\) Use in the adjuvant setting and the appropriate timing of therapy, based on quality of life, quantity of life, and cost all require more stringent definition. For those who remain strictly bound to Phase III evidence, the “standards” described above may dictate the course of all clinical decision-making. The practitioners or patients who desire a more individualized approach may explore other options.
REFERENCES

1. Denis L, Murphy GP. Overview of phase III trials on combined androgen treatment in patients with metastatic prostate cancer. Cancer 1993;72:3888-3895.

2. White JW. The results of double castration in hypertrophy of the prostate. Ann Surg 1895;22:1-80.

3. Burrows H. Biological Actions of Sex Hormones. Cambridge, Cambridge University Press, 1949:176.

4. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, estrogen and androgen injection on serum phosphates in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-297.

5. Nesbit RM, Plumb RT. Prostatic carcinoma, follow-up on 795 patients treated prior to endocrine era and comparison of survival rates between these and patients treated by endocrine therapy. Surg 1946;20:263-272.

6. Nesbit RM, Baum WC. Endocrine control of prostatic carcinoma, clinical and statistical survey of 1,818 cases. JAMA 1950;143:1317-1320.

7. The Veterans Administration Cooperative Urological Research Group. Carcinoma of the prostate: Treatment comparisons. J Urol 1967;98:516-522.

8. The Veterans Administration Cooperative Urological Research Group. Treatment and survival of patients with cancer of the prostate. Surg Gynecol Obstet 1967;124:1011-1017.

9. Bailar J, Byar DP. Estrogen treatment for cancer of the prostate. Early results with 3 doses of diethylstilbestrol and placebo. Cancer 1970;26:257-261.

10. Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group’s studies of cancer of the prostate. Cancer 1973;32:1126-1130.

11. Blackard CE, Byar DP, Jordan WP Jr. Orchiectomy for advanced prostatic carcinoma: A re-evaluation. Urology 1973;1:553-560.

12. Maatman TJ, Gupta MK, Montie JE. Effectiveness of castration versus intravenous estrogen therapy in producing rapid endocrine control of metastatic cancer of the prostate. J Urol 1985;133:620-621.

13. Chadwick DJ, Gillatt DA, Gingell, JC. Medical or surgical orchiectomy: The patients’ choice. BMJ. 1991;302:372.

14. Potosky AL, Knopf K, Clegg LX, et al. Quality-of-life outcomes after primary androgen deprivation therapy: Results from the Prostate Cancer Outcomes Study. J Clin Oncol 2001;19:3750-3757.

15. Clark JA, Wray NB, Ashton CM. Living with treatment decisions: Regrets and quality of life among men treated for metastatic prostate cancer. J Clin Oncol 2001;19:72-80.

16. Robinson MR, Smith PH, Richards B, et al. The final analysis of the EORTC Genito-Urinary Tract Cancer Co-Operative Group phase III clinical trial (protocol 30805) comparing orchiectomy, orchiectomy plus cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. Eur Urol 1995;28:273-283.

17. Entage LA, Trehovathan C, Kelly K, et al. A phase III open randomized study of Zoladex 3.6 mg depot versus DES 3 mg per day in untreated advanced prostate cancer: A West Midlands Urological Research Group Study. Prog Clin Biol Res 1989;303:47-52.

18. Peeling, WB. Phase III studies to compare goserelin (Zoladex) with orchiectomy and with diethylstilbestrol in treatment of prostatic carcinoma. Urology 1989;33:45-52.

19. Citrin DL, Resnick MI, Guinan P, et al. A comparison of Zoladex and DES in the treatment of advanced prostate cancer: Results of a randomized, multicenter trial. Prostate 1991;18:139-146.

20. Waymont B, Lynch TH, Dunn JA, et al. Phase III randomized study of zoladex versus stilboestrol in the treatment of advanced prostate cancer. Br J Urol 1992;69:614-620.

21. Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984;311:1281-1286.

22. Chang A, Yeap B, Davis T, et al. Double-blind, randomized study of primary hormonal treatment of stage D2 prostate carcinoma: Flutamide versus diethylstilbestrol. J Clin Oncol 1996;14:2250-2257.

23. Smith PH, Suciu S, Robinson MRG, et al. A comparison of the effect of diethylstilbestrol with low dose estramustine phosphate in the treatment of advanced prostatic cancer: Final analysis of a phase III trial of the European Organization for Research on Treatment of Cancer. J Urol 1986;136:619-623.

24. Pavone-Macaluso M, de Voogt HJ, Viggiano G, et al. Comparison of diethylstilbestrol, cyproterone acetate, and medroxyprogesterone acetate in the treatment of advanced prostatic cancer: Final analysis of a randomized phase III trial of the European Organization for Research on Treatment of Cancer. J Urol 1986;136:624-631.

25. de Voogt HJ. The position of cyproterone acetate (CPA), a steroidal anti-androgen, in the treatment of prostate cancer. Prostate Suppl 1992;4:91-95.

26. Goldenberg SL, Bruchovsky N. Use of cyproterone acetate in prostate cancer. Urol Clin North Am 1991;18:111-122.

27. Denis L. European Organization for Research and Treatment of Cancer (EORTC) prostate cancer trials, 1976-1996. Urology 1998;51:50-57.

28. Tunn UW, Bargelloni U, Cosciani S, et al. Comparison of LH-RH analogue 1-month depot and 3-month depot by their hormone levels and pharmacokinetic profile in patients with advanced prostate cancer. Urol Int 1998;60:9-16.

29. McLeod D, Zinner N, Tomera K, et al. A phase 3, multicenter, open-label, randomized study of abarelix versus leuprolide acetate in men with prostate cancer. Urology 2001;58:756-761.

30. Small EJ, Frohlich MW, Bok R, et al. Prospective trial of the herbal supplement PC-SPES in patients with progressive prostate cancer. J Clin Oncol 2000;18:3595-3603.

31. California Department of Health Services. MedWatch Product Recall Press Release. Available at: www.fda.gov/medwatch/SAFETY/2002/safety02.htm#spes. Accessed February 8, 2002.

32. Herndon, R. Two herbal supplements recalled amid rising regulatory concerns; health: One is a popular treatment for prostate cancer that has shown promise in testing. The Los Angeles Times. Feb 9, 2002:A1.
33. California Department of Health Services, Office of Public Affairs. State health director warns consumers about prescription drugs in herbal products. Available at: www.applications.dhs.ca.gov/pressreleases/02-03.html. Accessed February 7, 2002.

34. Chodak G, Sharifi R, Kasimis B, et al. Single-agent therapy with bicalutamide: A comparison with medical or surgical castration in the treatment of advanced prostate carcinoma. Urology 1995;46:849-855.

35. Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989;321:419-424.

36. Denis L, Robinson M, Maher C, et al. Orchiectomy versus Zoladex plus Eulexin in patients with metastatic prostate cancer (EORTC 30853). J Steroid Biochem Mol Biol 1990;37:951-959.

37. Boccardo F, Pace M, Robagotti A, et al. Goserelin acetate with and without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer. Eur J Cancer 1993;29:1088-1093.

38. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036-1042.

39. Prostate Cancer Trialsists’ Collaborative Group. Maximum androgen blockade in advanced prostate cancer: An overview of the randomised trials. Lancet 2000;355:1491-1498.

40. Saloway MS, Pareek K, Sharifi R, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bN0M0 prostate cancer: 5-year results. Lupon Depot Neoadjuvant Prostate Cancer Study Group. J Urol 2002;167:112-116.

41. Schulman CC, Debruyne FM, Forster G, et al. 4-Year follow-up results of a European prospective randomized study on neoadjuvant hormonal therapy prior to radical prostatectomy in T2–T3N0M0 prostate cancer. European Study Group on Neoadjuvant Treatment of Prostate Cancer. Eur Urol 2000;38:706-713.

42. Gleave ME, La Bianca SE, Goldenberg SL, et al. Long-term neoadjuvant hormone therapy prior to radical prostatectomy: Evaluation of risk for biochemical recurrence at 5-year follow-up. Urology 2000;56:289-294.

43. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: Biochemical and pathological effects. J Urol 2001;166:500-507.

44. Zincke H, Lau W, Bergstrahl E, et al. Role of early adjuvant hormonal therapy after radical prostatectomy for prostate cancer. J Urol 2001;166:2208-2215.

45. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med 1999;341:1781-1788.

46. Kolvenbag GJ, Iversen P, Newling DW. Antiandrogen monotherapy: A new form of treatment for patients with prostate cancer. Urology 2001;58:16-23.

47. Wirth M, Frohmuller H, Marz E, et al. Randomized multicenter trial on adjuvant flutamide therapy in locally advanced prostate cancer after radical surgery: Interim analysis of treatment effect and prognostic factors [abstract]. Br J Urol 1997;80:263.

48. See WA, McLeod D, Iversen P, et al. The bicalutamide Early Prostate Cancer Program: Demography. Urol Oncol 2001;6:43-47.

49. Ditonno P, Battaglia M, Selvaggi FP. Adjuvant hormone therapy after radical prostatectomy: Indications and results. Tumori 1997;83:567-575.

50. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.

51. Lawton CA, Winter K, Murray K, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognostic carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;49:937-946.

52. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001;50:1243-1252.

53. Hanks GE, Lu J, Machtay M, et al. RTOG Protocol 92-02: A phase III trial of the use of long term androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate. Proc Am Soc Clin Oncol 2000;19:1284.

54. D’Amico AV, Schultz D, Loffredo M, et al. Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer. JAMA 2000;284:1280-1283.

55. Horwitz EM, Winter K, Hanks GE, et al. Subset analysis of RTOG 85–31 and 86–10 indicates an advantage for long-term versus short-term adjuvant hormones for patients with locally advanced nonmetastatic prostate cancer treated with radiation therapy. Int J Radiat Oncol Biol Phys 2001;49:947-956.

56. Merrick GS, Butler WM, Galbreath RW, et al. Five-year biochemical outcome following permanent interstitial brachytherapy for clinical T1–T3 prostate cancer. Int J Radiat Oncol Biol Phys 2001;51:41-48.

57. Stone NN, Stock RG, Unger P. Effects of neoadjuvant hormonal therapy on prostate biopsy results after (125)I and (103)Pd seed implantation. Mol Urol 2000;4:163-168.

58. Potters L, Torre T, Ashley R, et al. Examining the role of neoadjuvant androgen deprivation in patients undergoing prostate brachytherapy. J Clin Oncol 2000;18:1187-1192.

59. Grimm PD, Blasko JC, Sylvester JE, et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. Int J Radiat Oncol Biol Phys 2001;51:31-40.

60. Grossfeld GD, Small EJ, Lubecka DP, et al. Androgen deprivation therapy for patients with clinically localized (stages T1 to T3) prostate cancer: and for patients with biochemical recurrence after radical prostatectomy. Urology 2001;58:56-64.
61. Byar DP, Corle DK. Hormone therapy for prostate cancer: Results of the Veterans Administration Cooperative Urological Research Group studies. NCI Monogr 1988;7:165-170.

62. Cox RL, Crawford ED. Estrogens in the treatment of prostate cancer. J Urol 1995;154:199-198.

63. Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: Initial results of the Medical Research Council trial. Br J Urol 1997;79:235-246.

64. Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred hormone therapy for prostate cancer: How safe is androgen deprivation? BJU Int 2000;86:220.

65. Stone P, Hardy J, Huddart R, et al. Fatigue in patients with prostate cancer receiving hormone therapy. Eur J Cancer 2000;36:1134-1141.

66. Tayeck JA, Heber D, Byerley LO, et al. Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. Metabolism 1990;39:1314-1319.

67. Diamond T, Campbell J, Bryant C, et al. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: Longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998;83:1561-1566.

68. Hedlund PO. Side effects of endocrine treatment and their mechanisms: Castration, antiandrogens, and estrogens. Prostate Suppl 2000:10:32-37.

69. Atala A, Amin M, Harty JJ. Diethylstilbestrol in treatment of post orchectomy vasomotor symptoms and its relationship with serum follicle-stimulating hormone, luteinizing hormone, and testosterone. Urology 1992;39:108-110.

70. Spetz AC, Hamm M, Lindberg B, et al. Prospective evaluation of hot flashes during treatment with parenteral estrogen or complete androgen ablation for metastatic carcinoma of the prostate. J Urol 2001;166:517-520.

71. Quella SK, Loprinzi CL, Sloan J, et al. Pilot evaluation of venlafaxine for the treatment of hot flashes in men undergoing androgen ablation therapy for prostate cancer. J Urol 1999;162:98-102.

72. Hellerstedt B, Pienta KJ. Androgen independent prostate cancer: The evolving role of chemotherapy. In: The Handbook of Prostate Cancer. In press.

73. Stege R. Potential side-effects of endocrine treatment of long duration in prostate cancer. Prostate 2000;10:38-42.

74. Malone S, Donker R, Perry G, et al. Long term side effects of intermittent androgen suppression therapy in prostate cancer: Results of a phase II study. Proc Am Soc Clin Oncol 2001;20:2390.

75. Modl S, Wood L, Siminoski K, et al. A comparison of the prevalence of osteoporosis and vertebral fractures in men with prostate cancer on various androgen deprivation therapies: Preliminary report. Proc Am Soc Clin Oncol 2001;20:2420.

76. Theriault RL, Lipton A, Horrobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: A randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. J Clin Oncol 1999;17:846-854.

77. Smith MB, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948-955.

78. Saad F, Murray R, Venner P, et al. Zoledronic acid is effective in treatment of bone metastases from prostate cancer: Results of a large, phase III, double-blind, randomized trial. Presented at: American Association for Cancer Research Special Conference New Discoveries in Prostate Cancer Biology and Treatment; December 5-9, 2001; Naples, FL.

79. Boissier S, Magnetto S, Frappart L, et al. Bisphosphonates inhibit prostate and breast carcinoma cell adhesion to unmineralized and mineralized bone extracellular matrices. Cancer Res 1997;57:3890-3894.

80. Boissier S, Ferreras M, Peyruchaud O, et al. Bisphosphonates inhibit breast and prostate carcinoma cell invasion, an early event in the formation of bone metastases. Cancer Res 2000;60:2949-2954.

81. Klotz LH, Herr HW, Morse MJ, et al. Intermittent endocrine therapy for advanced prostate cancer. Cancer 1986;58:2546-2550.

82. Sato N, Gleave ME, Bruchovsky N, et al. Intermittent androgen suppression delays progression to androgen-independent regulation of prostate-specific antigen gene in the LNCaP prostate tumour model. J Steroid Biochem Mol Biol 1996;58:139-146.

83. Wolf JM, Tunn UW. Intermittent androgen blockade in prostate cancer: Rationale and clinical experience. Eur Urol 2000;38:365-371.

84. Bruchovsky N, Klotz LH, Sadar M, et al. Intermittent androgen suppression for prostate cancer: Canadian Prospective Trial and related observations. Mol Urol 2000;4:191-199.

85. Grossfeld GD, Small EJ, Carroll PR. Intermittent androgen deprivation for clinically localized prostate cancer: Initial experience. Urology 1998;51:137-144.

86. Bales GT, Sinner MD, Kim JH, et al. Impact of intermittent androgen deprivation on quality of life. J Urol 1996;155:1069.

87. Lebowitz RIL, Tucker SJ. Treatment of localized prostate cancer with intermittent triple androgen blockade: Preliminary results in 110 consecutive patients. Oncologist 2001;6:177-182.

88. Fleschner NE, Trachtenberg J. Combination finasteride and flutamide in advanced carcinoma of the prostate: Effective therapy with minimal side effects. J Urol 1995;154:1642-1645.

89. Ornstein DK, Rao GS, Johnson B, et al. Combined finasteride and flutamide therapy in men with advanced prostate cancer. Urology 1996;48:901-5.

90. Kirby R, Robertson C, Turkes A, et al. Finasteride in association with either flutamide or goserelin as combination hormonal therapy in patients with stage M1 carcinoma of the prostate gland. International Prostate Health Council
91. Brufsky A, Fontaine-Rothe P, Berlane K, et al. Finasteride and flutamide as potency-sparing androgen ablative therapy for advanced adenocarcinoma of the prostate. Urology 1997;49:913-920.

92. Ornstein DK, Smith DS, Andriole GL. Biochemical response to testicular androgen ablation among patients with prostate cancer for whom flutamide and/or finasteride therapy failed. Urology 1998;52:1094-1097.

93. Kolvenbag GJCM, Iversen P, Newling DWW. Antiandrogen monotherapy: A new form of treatment for patients with prostate cancer. Urology 2001;58:16-22.

94. Hellerstedt B, Pienta KJ. Prostate cancer and the geriatric patient. In: Principles of Geriatric Medicine and Gerontology, 5th edition. In press.

95. Varenhorst E, Carlson P, Pedersen K. Clinical and economic considerations in the treatment of prostate cancer. Pharmacoeconomics 1994;6:127-141.

96. McClinton S, Moffat LE, Ludbrook A. The cost of bilateral orchidectomy as a treatment for prostatic carcinoma. Br J Urol 1989;63:309-312.

97. Bayoumi AM, Brown AD, Garber AM. Cost-effectiveness of androgen suppression therapies in advanced prostate cancer. J Natl Cancer Inst 2000;92:1731-1739.

98. Agency for Health Care Policy and Research, Rockville, MD. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostatic cancer. Summary, Evidence Report/Technology Assessment: Number 4. Available at: www.ahrq.gov/clinic/pros-summ.htm. Accessed January 1999.

99. Collette L, Studer UE, Schroder FH, et al. Why phase III trials of maximal androgen blockade versus castration in M1 prostate cancer rarely show statistically significant differences. Prostate 2001;48:29-39.

100. Laufer M, Denmeade SR, Sinibaldi VJ, et al. Complete androgen blockade for prostate cancer: What went wrong? J Urol 2000;164:3-9.

101. Demers RY, Tiwari A, Wei J, et al. Trends in the utilization of androgen-deprivation therapy for patients with prostate carcinoma suggest an effect on mortality. Cancer 2001;92:2309-2317.