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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Recommendations for the Initial Hormonal Management of Androgen-Sensitive Metastatic, Recurrent, or Progressive Prostate Cancer

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ABSTRACT

Purpose
To develop a clinical practice guideline for the management of men with metastatic, recurrent, or progressive carcinoma of the prostate. The focus of this document is on the use, combinations, and timing of various forms of androgen deprivation therapy (ADT) for the palliation of men with androgen-sensitive disease.

Methods
An expert panel and writing committee were formed. The questions to be addressed by the guideline were determined, and a systematic review of the literature was performed, which included a search of online databases, bibliographic review, and consultation with content experts. A priori criteria were used to select studies for analysis and study authors were contacted when necessary.

Results
There were 10 randomized controlled trials, six systematic reviews, and one Markov model available to inform the guidelines.

Conclusion
A full discussion between practitioner and patient should occur to determine which therapy is best for the patient. Bilateral orchiectomy or luteinizing hormone releasing hormone agonists are the recommended initial treatments. Nonsteroidal antiandrogen therapy may be discussed as an alternative, but steroidal antiandrogens should not be offered as monotherapy. Patients willing to accept the increased toxicity of combined androgen blockage for a small benefit in survival should be offered nonsteroidal antiandrogen in addition to castrate therapy. Until data from studies using modern medical diagnostic/biochemical tests and standardized follow-up schedules become available, no specific recommendations can be issued regarding the question of early versus deferred ADT. A discussion about the pros and cons of early versus deferred ADT should occur.

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INTRODUCTION

This guideline will address the palliation of recurrent, progressive, or metastatic prostate cancer that is sensitive to androgen deprivation and for which androgen deprivation therapy (ADT) is considered the most appropriate initial intervention. Where appropriate, this guideline includes recommendations on surveillance patients who have progressed to a point where they, and/or their oncologist, feel it is appropriate to begin ADT. A second guideline will address the management of recurrent or metastatic prostate cancer once androgen resistance has emerged.

Prostate cancer is the most common form of non–skin cancer in American men. In 1999, the incidence of prostate cancer in the Surveillance, Epidemiology, and End Results registry was 175 of 100,000[1]; an estimated 200,000 men were diagnosed with the

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disease in 2001.[2] Prostate cancer is the second leading cause of cancer death in North American men. An estimated 32,000 American men died of the disease in 2001.[2]

Prostate cancer has a long natural history, usually spanning a decade or more. Screening of asymptomatic men by the digital rectal exam or serum prostate specific antigen (PSA) allows detection of disease at an earlier stage[3] when the treatment may be more efficacious.[4,5]

Once a pathologic diagnosis of prostate cancer is made and the patient is staged, the patient may choose a treatment from available options in collaboration with his physicians. For patients with clinically localized disease (no clinical or radiologic evidence of spread to regional lymph nodes or distant sites), several management options are available, including both radical (potentially curable) and surveillance approaches. Since many men with prostate cancer die of other causes, surveillance or watchful waiting may appeal to those who can tolerate the knowledge of untreated cancer, especially those men with a limited life expectancy due to comorbidities; those with clinical data consistent with early indolent disease and those most strongly wishing to avoid the side effects of radical therapy.[6] Potentially curative options include radical prostatectomy, external beam radiation therapy, brachytherapy (radioactive implant), or combinations thereof. ADT is sometimes used in the neoadjuvant, concurrent, or adjuvant setting. The indications for the use of these therapies in locally advanced disease (including patients that are pathologically node-positive following radical prostatectomy) will be addressed in a separate American Society of Clinical Oncology (ASCO) practice guideline.

After treatment, the disease is most commonly followed by physical examination and PSA testing. A consistently rising PSA after initial curative-intent treatment is a common clinical problem that is worrisome for recurrent prostate cancer, which may represent persistent pelvic cancer or metastatic incurable cancer, or a component of each. Through a variety of evaluations, clinicians attempt to identify patients whose probability of disease confined to the pelvis is high enough to justify the toxicity of extirpative local therapies in a second attempt at cure. These evaluations may be radiologic (computed tomography scan, magnetic resonance imaging, bone scan, chest x-ray, indium-capromab pendetide scan), surgical (biopsies of the prostate or prostate bed), and/or based on trends in biochemical parameters (the duration between treatment and PSA failure—PSA doubling time). The recommended restaging investigations and the most appropriate time to apply them are beyond the scope of this guideline, as are the indications for extirpative therapies for locally progressive disease or local failure after primary definitive treatment.

Patients being managed by surveillance are sometimes offered potentially curative interventions if, while on follow-up, the disease appears likely to become symptomatic within the patient's expected lifetime.[7-9] The optimal strategy for following patients, including the frequency of clinical evaluations, the frequency and type of biochemical and radiologic evaluations, and the trigger point for offering potentially curative therapy, has not been elucidated and is beyond the scope of this guideline.

For patients with documented metastatic disease, or whose clinical parameters suggest too small a chance for cure to justify the toxicity of extirpative therapy, systemic ADT through surgical or pharmacologic castration, antiandrogen therapy, or a combination, is the standard first-line treatment. The goal of ADT is palliation. However, there are considerable practice variations in the use of ADT in these situations. The possible explanations are numerous and include: the effectiveness of ADT in suppressing the PSA; the palliative nature of ADT; its cost and toxicity; the prolonged treatment required (further extended by PSA surveillance for biochemical recurrence); the highly variable time lag between initial PSA rise and symptomatic metastatic disease; and the sometimes conflicting results of clinical trials. Because the relative efficacy of alternative approaches to ADT appears small and its toxicity is substantial, patients may weigh the balance between the favorable and adverse consequences of palliative ADT differently. Therefore, shared decision-making between patients and their physicians is necessary for optimal use of ADT.

Questions

For men with metastatic or recurrent androgen-sensitive prostate cancer, in whom ADT is considered the most appropriate initial intervention:

(1) What are the standard initial treatment options?

(2) Are antiandrogens as effective as other castration therapies?

(3) Is combined androgen blockade better than castration alone?

(4) Does early androgen deprivation therapy improve outcomes over deferred therapy?

(5) Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy?

Definition of Terms

(1) Castration: Treatment (eg, luteinizing hormone reducing hormone) or a procedure (eg, orchiectomy) that decreases serum testosterone.

(2) Antiandrogen therapy: A treatment in which the androgen receptor is competitively inhibited from being activated by testosterone; there are steroidal and nonsteroidal classes of antiandrogen therapy.

(3) ADT: A treatment or procedure in which the androgen receptor of target cells are not activated via either reduction in testosterone production or androgen receptor blockade; ADT encompasses castration, antiandrogen therapies, and combinations thereof.

(4) Combined androgen blockade (CAB): The combination of medical castration and an antiandrogen.

(5) Early deprivation therapy: Initiation of ADT at diagnosis of metastatic or recurrent/progressive prostate cancer.

(6) Deferred deprivation therapy: Withholding of ADT until the presence of clinical signs or symptoms.

(7) Number needed to treat (NNT): Conceptually, the total number of individuals who would have to be treated with a defined intervention in order to have one individual achieve the desired outcome of interest (eg, living 5 years after treatment). Mathematically, NNT equals one over the absolute risk reduction.

(8) Markov model: A sophisticated decision analysis technique in which alternative management choices and their consequences are explicitly defined and assigned weights and outcome values (eg, cost, quality-adjusted life-years, survival). These probabilities and outcome values can be derived from the literature and systematically varied to explore a number of different questions. These questions may include situations where patients prefer one treatment over another or the difference in cost of one type of therapy versus another.

The tumor-node-metastasis system and the American Urological Association staging systems are provided in Appendix A.

Practice Guidelines

"Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances," according to the Canadian Task Force on the Periodic Health Examination.[10] Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.[10] Guidelines may be useful in producing better care and decreasing its cost. Specifically, utilization of clinical guidelines may provide: (1) improvements in outcomes, (2) improvements in medical practice, (3) a means for minimizing inappropriate practice variation, (4) decision support tools for practitioners, (5) points of reference for medical orientation and education, (6) criteria for self-evaluation, (7) indicators and criteria for external quality review, (8) assistance with reimbursement and coverage decisions, and (9) criteria for use in credentialing decisions.

In formulating recommendations for recurrent or metastatic androgen-sensitive prostate cancer, ASCO considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. However, it is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations, and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. Insofar that guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

METHODS

Panel Composition

The Panel was composed of experts in clinical medicine, clinical research, outcomes/health services research, and related disciplines, with a focus on expertise in prostate cancer. A patient representative was also included on the Panel. The clinical experts represented all relevant medical disciplines including medical oncology, radiation oncology, and urology. Both academic and community practitioners were included. A steering committee under the auspices of the Health Services Committee chose Panel participants for the clinical practice guideline development process. The Panel participants are listed in Appendix B.

Process Overview

In evaluating the evidence regarding the management of recurrent or metastatic prostate cancer, the literature was systematically reviewed and article selection criteria were developed a priori. The results of these data are reported in the Results section. Adopting the format developed by Cancer Care Ontario's Practice Guideline Initiative, the interpretation of these results is presented separately under the Interpretive Summary. Ongoing clinical trials are then listed, and, finally, the opinions of the Expert Panel are offered.

Literature Review and Data Collection

The Medline database (1966 through March 2003; National Library of Medicine, Bethesda, MD) was searched to identify relevant information from the published literature. A series of searches was conducted using the medical subject headings "prostatic neoplasms" and "androgen antagonists," and the text words "intermittent," "combined androgen," and "metastatic." These terms were combined with the following study design-related subject headings or text words: "meta-analysis," "systematic," "trial," and "randomized." Search results were limited to human studies and English-language articles.

In addition, the Cochrane Database of Systematic Reviews was searched using the phrase "prostate cancer," and directed searches were made of the reference lists from primary articles. Authors were contacted for clarification where needed. The Physician Data Query clinical trials database (http://www.cancer.gov/search/clinical_trials/) was searched for ongoing clinical trials in the identified subject areas.

Table 1. Details of Inclusion Criteria and Outcome Variables

Question	Inclusion Criteria	Outcomes
1. What are the standard initial treatment options?	RCTs of orchiectomy *v* placebo in men with M1 disease RCTs of estrogens *v* placebo in men with M1 disease	Overall survival Toxicity of treatment Time to treatment failure Disease progression Cost-effectiveness
2. Are antiandrogens as effective as other castration therapies?	Systematic reviews and/or meta-analyses of antiandrogens *v* castration therapy	Overall survival Time to treatment failure Toxicity of treatment
3. Is combined androgen blockade better than castration alone?	Systematic reviews of combined androgen blockade *v* castration	Overall survival Toxicity of treatment Cost-effectiveness
4. Does early androgen deprivation therapy improve outcomes over deferred therapy?	Systematic reviews or individual RCTs testing early *v* deferred androgen deprivation therapy for men with advanced prostate cancer	Overall survival Progression-free survival Complications due to progression Cost-effectiveness
5. Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy?	Systematic reviews or individual RCTs testing intermittent *v* continuous androgen deprivation therapy for men with advanced prostate cancer	Overall survival Time off therapy Time to hormone resistance Quality of life

Abbreviation: RCT, randomized controlled trial.

Inclusion Criteria

Table 1 describes the details of the inclusion criteria and outcome variables for each question addressed in this guideline.

Exclusion Criteria

For each question, the following types of evidence were not considered: (1) letters and editorials, (2) papers published in a language other than English.

In addition, for questions 4 (early *v* deferred ADT) and 5 (intermittent *v* continuous ADT), the following were excluded: (1) participants previously treated with hormonal therapy, (2) randomized clinical trials targeting men undergoing radiation as primary therapy, (3) nonrandomized prospective studies, (4) retrospective studies, and (5) randomized clinical trials targeting men with clinically localized but not pathologically advanced prostate cancer.

Consensus Development Based on Evidence

The original Panel met four times. The first meeting was intended to identify topics to be addressed by the guideline, to develop a strategy for completion of the guideline, and to do a preliminary review of the initial literature search; at the second meeting, the Panel reviewed the developed guideline and evaluated more critically the recommendations and supporting evidence. The guideline was circulated in draft form.

The draft guideline was submitted to the ASCO Health Services Committee (HSC) for review and approval in October 2002. Based on its review, the HSC recommended revisions to the draft. In particular, the HSC suggested that the Panel, with selected ad hoc members from the HSC, create two distinct guidelines from the original draft—one that addresses management of patients with androgen-dependent prostate cancer, and another that addresses the management of patients with androgen-independent prostate cancer and associated palliative and end-of-life care clinical issues. This approach was proposed to allow a more detailed and thorough review of existing evidence on the various questions of clinical importance. The ASCO Board of Directors endorsed this proposal. The two guidelines will be developed sequentially. Final text editing was performed by Dr Loblaw.

Guidelines and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the HSC and by the ASCO Board of Directors before dissemination. All members of the Expert Panel complied with ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to reveal ties to companies developing products that might potentially be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision Dates

At annual intervals, the Panel co-chairs and two Panel members designated by the co-chairs will determine the need for revisions to the guidelines based on an examination of current literature. If necessary, the entire Panel will be reconvened every 3 years to discuss potential changes; the Panel will reconvene more frequently if new information suggests that more timely modifications are warranted. When appropriate, the Panel will recommend revised guidelines to the HSC and the ASCO Board for review and approval.

Summary of Outcomes Assessed

Overall survival (OS) was the primary outcome of interest. Secondary outcomes of interest depended on the question (see Table 1 for details). There are many caveats when considering the secondary outcomes, particularly since some of the historical trials reflect a practice style, an understanding about clinical trial design/outcomes measurement, and available medical tests that are much different from today's standards. This is particularly true for response rate or time to progression. In early studies, before PSA, tumor response was measured. Stable disease may be classified as having a response (ie, without disease progression). Enrolled sub-

Table 2. Studies That Met the Inclusion Criteria for Each Question

Question	Intervention	No. of Studies
1. What are the standard initial treatment options?	Orchiectomy *v* placebo Estrogens *v* placebo LHRH *v* orchiectomy Dose dependent toxicity of estrogens	Three RCTs[*1,11,12,22] One systematic review[13] Two RCTs[1,23]
2. Are antiandrogens as effective as other castration therapies?	Antiandrogen *v* castration	One systematic review[13]
3. Is combined androgen blockade better than castration alone?	Addition of an antiandrogen to orchiectomy or LHRH agonist	Three systematic reviews[14-16] One RCT[17] One Markov model[18]
4. Does early androgen deprivation therapy improve outcomes over deferred therapy?	Early and deferred androgen deprivation therapy	One systematic review[19] Seven RCTs[11,20,21,24-26] One Markov model[18]
5. Is intermittent androgen deprivation therapy better than continuous androgen deprivation therapy?	Intermittent and continuous deprivation therapy	—

Abbreviations: RCT, randomized controlled trial; LHRH, luteinizing hormone releasing hormone.
*Only study reported twice.

jects also included those without confirmable disease progression at onset. Stable disease in these protocols may simply have been indicative of the indolent course of disease and independent of the intervention. For the above reasons, evidence based on these end points was interpreted with caution and would not be sufficient by itself to justify recommendation of the intervention.

Because ADT is palliative, requires prolonged treatment, and has substantial toxicity, quality of life was considered an important secondary outcome. Unfortunately, it was not measured in the great majority of trials available for this analysis.

The Panel considered the comparative costs of clinical strategies in formulating recommendations for the use of ADT. While the published clinical trials identified did not include formal cost-effectiveness analyses, some articles used data from these trials to develop cost-effectiveness estimates.

RESULTS

Literature Search Results

In general, there were many randomized studies available to address each question and, for some questions, there were published systematic reviews and/or meta-analyses. The studies that met the eligibility criteria for each of the five questions are listed in Table 2.

Standard Initial Treatment Options

There are two randomized controlled trials (RCTs) that compared orchiectomy to placebo and different doses of diethylstilbestrol (DES) to placebo; these results have been reported several times.[11,12] A third RCT compared DES to orchiectomy.[1] A meta-analysis of the literature addressed the effectiveness of luteinizing hormone releasing hormone (LHRH) agonists.[13]

Antiandrogens As Monotherapy

One systematic review with meta-analysis of the literature[13] was identified that addressed this question. Health-related quality of life (QOL) determinations of patients on antiandrogens, as compared to those surgically or medically castrated, were addressed in another study.[27]

Combined Androgen Blockade

Three systematic reviews (two meta-analyses of the literature[14,15] and one individual patient data meta-analysis[16]), one randomized controlled trial,[17] and one Markov model based on systematic review[18] were available to address this question.

Early Versus Deferred Androgen Deprivation Therapy

There was one systematic review,[19] three RCTs (reported together),[20,21] and one Markov model based on systematic review[18] that addressed the question.

Intermittent Androgen Blockade

There were no prospective randomized data on which to base a recommendation.

The summary of evidence and recommendations for each question are detailed in Table 3.

What Are the Standard Initial Treatment Options

Summary. Two RCTs compared orchiectomy to placebo and different doses of DES to placebo, and have been reported several times.[11,12,22] A third RCT compared DES to orchiectomy.[1] A systematic review with meta-analysis of the literature addressed the effectiveness of LHRH agonists.[13] While orchiectomy is a simple and cost-effective procedure, it is nonreversible and carries significant psychological burden to some patients. LHRH agonists are equally effective, are available in depo-injections, and are potentially reversible but costly. DES is an inexpensive oral medication that had equivalent OS compared with orchiectomy in a small RCT,[1] but carries with it significant risks of cardiovascular and thrombotic morbidities even at 1 mg/d. It should not be considered

Table 3. Summary of Evidence and Recommendations for Each Question

Question	Evidence Summary	Recommendations
1. What are the standard initial treatment options?	Two RCTs compared orchiectomy to placebo and different doses of DES to placebo, and have been reported several times.[11,12,22] A third RCT compared DES to orchiectomy.[1] A systematic review with meta-analysis of the literature addressed the effectiveness of LHRH agonists.[13] While orchiectomy is a simple and cost-effective procedure, it is nonreversible and carries significant psychological burden to some patients. LHRH agonists are equally effective, are available in depo-injections, and are potentially reversible but costly. DES is an inexpensive oral medication that had equivalent OS compared with orchiectomy in a small RCT,[1] but carries with it significant risks of cardiovascular and thrombotic morbidities, even at 1 mg/day.	Bilateral orchiectomy or medical castration with LHRH agonists are the recommended initial treatments for metastatic prostate cancer. A full discussion between practitioner and patient should occur to determine which is best for the patient. DES should not be considered as a standard first-line treatment option and is currently no longer commercially available in North America.
2. Are antiandrogens as effective as other castration therapies?	One systematic review with meta-analysis of the literature[13] was identified that addressed this question. Health related QOL determinations of patients on antiandrogens as compared to those surgically or medically castrated were addressed in another study.[27] Monotherapy with nonsteroidal antiandrogens showed equivalent survival compared to orchiectomy, but has less toxicity, particularly with respect to loss of libido and physical capacity. Steroidal antiandrogens have inferior time to progression of disease compared with LHRH agonists.	Nonsteroidal antiandrogen monotherapy may be discussed as an alternative to castration. Steroidal antiandrogens should not be offered as monotherapy.
3. Is combined androgen blockade better than castration alone?	Three systematic reviews (two with meta-analyses of the literature[14,15] and one meta-analysis of individualized patient data[16]), one large RCT,[17] and one Markov model (decision-analysis) paper[18] were available to address this question. Combined androgen blockade confers a statistically significant but questionable clinical improvement in survival over orchiectomy or LHRH monotherapy. The benefit seems to be limited to patients taking nonsteroidal antiandrogens and seems to appear only after 5 years of follow-up. Gastrointestinal, ophthalmologic, and hematologic side effects are worse on combined androgen blockade. LHRH and nonsteroidal antiandrogens have the highest estimated quality-adjusted survival but have an incremental cost of over $1 million (US) per quality-adjusted life-year over orchiectomy alone.	A discussion should occur between the patient and his practitioner. The patient needs to appreciate that there is a small potential gain in OS with the addition of a nonsteroidal antiandrogen to medical or surgical castration and that increased side effects may occur as a result.
4. Does early ADT improve outcomes over deferred therapy?	Early treatment with LHRH agonists confers a small but statistically significant survival advantage, and significant improvements in progression-free survival that are durable up to 10 years of follow-up. However, these results are based on a systematic review of trials[18] that did not select a cohort of patients who progressed post-treatment, on surveillance, or who had metastatic disease on presentation, although a subset of every sampled population did have either nodal or distant metastases. Treatment was most cost-effective when started after the onset of symptoms. Based on exploratory analyses, treatment with antiandrogen monotherapy appears unlikely to lead to a survival benefit in men with localized disease managed with non-definitive therapy (watchful waiting).	Until data from studies using modern medical diagnostic and biochemical tests and standardized follow-up schedules become available, no specific recommendations can be issued by this Panel regarding the question of early versus deferred ADT using LHRH agonists or orchiectomy. A discussion about the pros and cons of early versus deferred therapy should occur between patient and practitioner. Antiandrogen monotherapy is not recommended. Patients should be followed clinically and started on ADT once symptoms of locally progressive or metastatic disease present.
5. Is intermittent ADT better than continuous ADT?	There are no data from prospective randomized trials upon which to base a recommendation.	Two large randomized Intergroup studies are ongoing and intermittent androgen blockade should still be considered experimental.

Abbreviations: RCT, randomized controlled trial; LHRH, luteinizing hormone releasing hormone; DES, diethylstilbestrol; OS, overall survival; QOL, quality of life; ADT, androgen deprivation therapy.

as a standard first-line treatment option and currently is no longer commercially available in North America.

Bilateral Orchiectomy

Biologic rationale. Testosterone (through its downstream product, dihydrotestosterone) plays a critical role in the promotion and growth of prostate cancer via androgen receptor interactions producing interference with induction of cell death by a variety of stimuli.[28,29] Most of men's testosterone is produced in the testis in response to luteinizing hormone (LH) released by the anterior pituitary gland. After bilateral orchiectomy, serum testosterone quickly falls to castrate levels (< 10 ng/mL).

Benefits. Palliation begins quickly following orchiectomy. The procedure eliminates potential problems of patient compliance with medical therapies, and the relative cost of the procedure is low.

Orchiectomy has had wide acceptance dating back to the 1940s. The Veterans Affairs Research Service Cooperative Urological Research Group (VACURG) research in the 1960s is the last available randomized, placebo-controlled data set.[11] Progression from stage III (extraprostatic extension) to stage IV (elevated prostatic acid phosphatase, demonstrated metastases) is significantly improved with orchiectomy versus placebo; 62% progression by 10 years on placebo versus 32% if randomized to orchiectomy. However, this did not translate into significant improvement in cause-specific survival (CSS) or OS. When untreated stage III and IV patients are combined, patients receiving orchiectomy + placebo (n = 469) had 1-, 5-, and 9-year CSS of 93, 71, and 56%, respectively; for those receiving placebo (n = 485), CSS for the same time points was 91%, 67%, and 55%, respectively (statistical analyses and CSS by stage not provided).[11] For the stage III patients, 5-year OS was 54% for orchiectomy + placebo and 56% for placebo alone, while for stage IV patients, 5-year OS was 32% versus 20%, respectively (not statistically significant).[22]

Harms. The procedure carries with it a small risk of surgical complications, such as wound infection, hematoma, and pain. A greater concern to many men is the emotional impact of the procedure. When given the choice of surgery or medical castration, most patients select medical approaches first.[30] In addition, due to the hypotestosteronemia, patients may suffer from vasoactive symptoms, weight gain, mood lability, gynecomastia, fatigue, lassitude, cognitive changes, and/or loss of libido. Long-term castrate levels of testosterone can also induce osteopenia and hypercholesterolemia. A recent randomized trial found that bisphosphonate treatment reduced short-term osteopenia.[31] Neither longer-term benefits nor the economic costs have been established for this costly additional therapy. Therefore, we feel it is premature to recommend it, but refer the readers to the ASCO Guideline discussing bisphosphonates in the broader oncologic context or to other well-developed clinical practice guidelines on the topic.[32]

LHRH Agonists

Biologic rationale. Treatment with these agents initially results in a 1- to 2-week rise in LH and follicle stimulating hormone with an associated rise in serum testosterone. This rise is followed by a downregulation of receptors in the pituitary gland that, in turn, results in a chemical castration.[33]

Benefits. Testosterone levels are usually within the castrate range 3 to 4 weeks after the first injection. Psychologically, these agents are easier for some men to tolerate than bilateral orchiectomy. Furthermore, while testosterone levels may not return to the same levels after prolonged use of LHRH agonists,[34,35] the symptoms of hypotestosteronemia usually resolve 6 to 9 months after the cessation of therapy.[34,35]

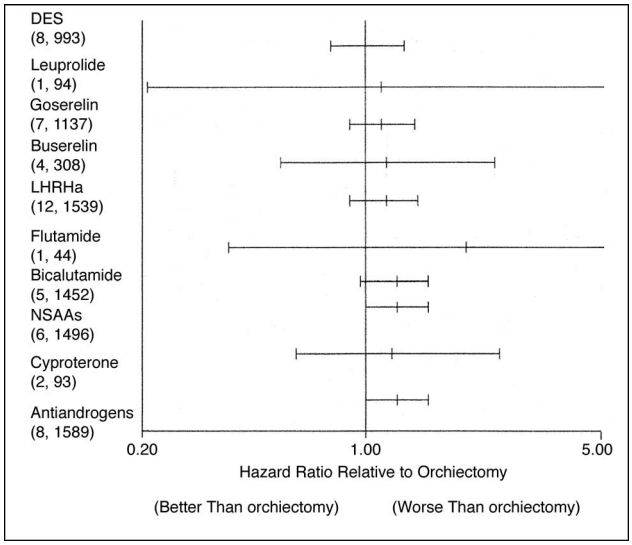

Fig 1. Source: Seidenfeld, J, Damson DJ, Hasselblad V, et al: Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Intern Med 132:566-577, 2002. Reprinted with permission from the American College of Physicians. The American College of Physicians is not responsible for the accuracy of the reprinted figure. Meta-analysis of the literature reporting survival at 2 years for different androgen deprivation therapies. Point estimates for hazard ratios (center marks) and 95% CIs (error bars) relative to orchiectomy for data on survival after 2 years of treatment are shown. Data for each monotherapy are pooled for all studies (with numbers in brackets to the left of the Forest plot listing number of studies and number of analyzable patients in these trials). DES, diethylstilbestrol; LHRH, luteinizing hormone-releasing hormone agonist; NSAA, nonsteroidal antiandrogen.

A meta-analysis of the literature (10 RCTs, 1,908 patients) addressed the relative benefit of LHRH agonists with orchiectomy, DES, or the choice of DES or orchiectomy. No improvement in survival rate, time to progression of disease, or time to treatment failure was observed (which included drug discontinuations indicative of adverse events in the medically managed patients). Two-year hazard ratio for OS was 1.26 (95% CI, 0.91 to 1.39) compared to orchiectomy (Fig 1).[13]

Harms. LHRH agonists effectively cause hypotestosteronemia and therefore carry with them the side effects of castration (see Orchiectomy: Harms). Several formulations are available including buserelin (Canada only), goserelin acetate, and leuprolide acetate. These formulations are available in various slow-release preparations that require subcutaneous or intramuscular injections that range in frequency from once a month to once a year (via an implantable delivery device). All represent expensive forms of androgen suppression compared to orchiectomy.[18]

A disadvantage of these agents is the short-term (2- to 3-week) stimulation of testosterone before suppression of androgen production. Clinically, those individuals with advanced disease may experience a flare phenomenon, characterized by worsening signs and symptoms of disease. Thus, the agents are contraindicated as monotherapy in men with impending spinal cord compression, urinary obstruction, or pain due to the potential for exacerbating symptoms. In clinical practice, this syndrome can be prevented by administering a nonsteroidal antiandrogen such as flutamide, bicalutamide, or nilutamide for a short period of time before initiating LHRH agonist therapy[36] and continuing this for 2 weeks after. In addition, in 2003, the US Food and Drug Administration approved intramuscular injection of a chemically modified LHRH antagonist, abarelix, for this indication.[37,38]

DES

Biologic rationale. DES at a dose of 3 mg/d results in castrate levels of testosterone in 1 to 2 weeks by the inhibition of LHRH production from the hypothalamus. A small proportion of testosterone is made in the adrenal gland as part of the steroid synthesis pathway; however, the importance of castrate serum levels of testosterone is unclear. Additionally, a direct cellular cytotoxic effect via an apoptotic mechanism has been noted in hormone refractory cell lines.[39]

Benefits. DES has the advantages of ease of administration as a daily oral pill, and avoidance of the psychological negatives of a surgical procedure, and, compared to LHRH agonists, relatively low cost when available. The VACURG Study 2 examined the effect of the dose of DES. In this study, participants with stage 3 (n = 294) or 4 (n = 214) disease were randomly assigned to one of four arms: placebo, DES 0.2 mg daily, DES 1 mg daily, or DES 5 mg daily.[11] While progression from stage III to IV disease was similar between the 5-mg and 1-mg arms (15% *v* 17% at 4 years, respectively),[11] the 5-mg arm was associated with higher cardiovascular mortality (58% 5-year cardiovascular mortality *v* 32%).[12] This benefit in therapeutic ratio translated into an OS improvement for the 1-mg dose over placebo (34% *v* 20% 7-year OS; statistical difference not reported).[12] In VACURG Study 1, DES 5 mg/d was compared with orchiectomy, placebo, or orchiectomy + DES 5 mg/d in a four-arm RCT.[11] While there was no OS difference between the four arms, there was higher cardiovascular mortality for DES than with orchiedectomy or placebo, which was apparent after the first year.[12]

An European Organization for the Research and Treatment of Cancer (EORTC) study[1] has demonstrated equal outcomes of DES 1 mg daily to orchiectomy, confirming the VACURG results. Events in this trial provide a power of 80% to detect an absolute difference of 13% in the medians comparing DES with orchiectomy.

Harms. DES is associated with significant cardiovascular (CV) toxicities, including myocardial infarction, stroke, and pulmonary embolism, especially at moderate to high doses.[40] Exclusion of individuals with prior CV disease is not protective. When lower doses are prescribed or accompanied by low doses of warfarin,[41] venous thrombosis is not prevented; 13% of individuals in the EORTC study stopped DES because of complications while receiving the 1 mg daily dose.[1] This adverse event rate, however, appears lower than in historical trials that reported CV events in more than 30% of subjects.[12] The incidence of edema, cramps, and dyspnea also exceeds incidence in controls. Gynecomastia, a common adverse event, may be reduced by prophylactic irradiation of the breasts.[42] The drug is no longer commercially available in North America.

Are Antiandrogens As Effective As Other Castration Therapies?

Summary. One systematic review with meta-analysis of the literature[13] was identified that addressed this question. Health-related QOL determinations of patients on antiandrogens as compared to those surgically or medically castrated were addressed in another study.[27] Monotherapy with nonsteroidal antiandrogens showed equivalent survival compared to orchiectomy, but has less toxicity, particularly with respect to loss of libido and physical capacity. Steroidal antiandrogens have inferior time to progression of disease compared with LHRH agonists.

Nonsteroidal Antiandrogens (NSAA)

Biologic rationale. NSAA (flutamide, nilutamide, and bicalutamide) act to competitively inhibit androgen binding to receptors in target tissue. With therapy, a rise in serum testosterone is observed.

Benefits. NSAA are oral medications with reversible side effects once therapy has ceased. NSAA had equivalent OS compared to orchiectomy (hazard rate, 1.22 relative to orchiectomy; 95% CI, 0.99 to 1.50; Fig 1).[13]

Bicalutamide has a half-life of approximately 1 week, allowing for once-daily dosing. Flutamide is more rapidly metabolized; the major active form has a plasma half-life of 5 to 6 hours, requiring drug-dosing three times a day. There have been no studies that have directly compared the different antiandrogens. In the meta-analysis (eight trials, 2,717 patients),[13] wide overlapping confidence intervals are seen for the individual agents. Health-related QOL determinations were measured in patients with advanced prostate cancer on antiandrogens alone. Patients showed greater improvements in sexual interest and physical capacity (as a result of continued secretion of LH and higher testosterone values) when compared to medical or surgical castration in small RCTs.[27]

Harms. Overall, withdrawals due to adverse events occurred in 4% to 10% of patients (highest with flutamide, 9.8%).[43] During single-agent therapy, significant gynecom-

astia and breast pain were reported (in up to 39% of patients). Hepatotoxicity has been reported with all NSAAs.[44]

Steroidal Antiandrogens

Biologic rationale. Cyproterone acetate available in (Canada, Europe) is a steroidal antiandrogen with progestational properties (creating a feedback inhibition of pituitary LHRH release to suppress testosterone production) and direct effects on the androgen receptor.

Benefits. There was no significant difference in survival between DES and cyproterone acetate, though cardiovascular side effects were reported more often in patients treated with diethylstilbestrol (3 mg daily) than in those treated with cyproterone acetate.[45] As for NSAA, tumor flare while initiating LHRH agonist therapy is reduced with cyproterone.

Harms. In a phase III study of 525 patients, goserelin acetate plus cyproterone acetate was compared to cyproterone alone or goserelin alone.[46] Goserelin was shown to be more effective than cyproterone alone in delaying the time to progression of metastatic prostate cancer (median time to progression of 225 days for cyproterone *v* 346 days for goserelin; $P = .016$). OS and CSS have not been reported for this trial. Although cyproterone acetate is generally well tolerated, liver toxicity has been recognized as a complication of long-term use.[47] Edema, weight gain, and shortness of breath are rarely seen.

Is Combined Androgen Blockade Better Than Castration Alone?

Summary. Three systematic reviews (two with meta-analyses of the literature[14,15] and one meta-analysis of individualized patient data[16]), one large RCT,[17] and one Markov model (decision-analysis) paper[18] were available to address this question. CAB confers a statistically significant but questionable clinical improvement in survival over orchiectomy or LHRH monotherapy. The benefit seems to be limited to patients taking nonsteroidal antiandrogens and seems to appear only after 5 years of follow-up. Gastrointestinal and ophthalmologic side effects are worse on combined androgen blockade. LHRH and nonsteroidal antiandrogens have the highest estimated quality-adjusted survival but have an incremental cost of over $1 million (US) per quality-adjusted life-year over orchiectomy alone.

Biologic rationale. Medical or surgical castration significantly reduces testosterone but does not eliminate production from the adrenal glands. Adding an antiandrogen to castration provides more complete androgen deprivation.

Benefits. All three of the meta-analyses indicated that CAB[14-16] may modestly prolong life. The largest systematic review (meta-analysis of individualized patient data from 27 RCTs; 8,275 men, 88% with stage D2 disease) reported by the Prostate Cancer Trialists' Collaborative Group (PCTCG), found a reduction in mortality of borderline statistical and clinical significance for all trials (72.4% crude mortality rate with androgen deprivation alone *v* 70.4% with combined blockage; relative risk, 0.97; 95% CI, 0.94 to 1.00).[16] A sensitivity analysis of nonsteroidal antiandrogens, (excluding seven trials of 1,784 men treated with the steroidal antiandrogen cyproterone acetate) indicated a small reduction in mortality from combined androgen blockade (75.3% with androgen deprivation alone *v* 72.4% combined with nonsteroidal antiandrogens; absolute risk reduction, 2.9%; $P < .005$).

The trial by Eisenberger et al[17] of orchiectomy ± flutamide was not included in the PCTCG, but was included in the Schmitt analysis.[15] The study was designed to have 90% power to detect a hazard rate of 0.8 for the CAB group, with a type I error (α) of 0.05 and a one-sided test to detect CAB superiority. Seven hundred men were randomly assigned to flutamide + orchiectomy while 687 were randomly assigned to orchiectomy alone, representing an overaccrual of 139 patients. There was no difference in OS between the two groups ($P = .14$).

The Schmitt et al[15] meta-analysis of the literature (20 RCTs, 6,320 men) was limited to studies where men were randomly assigned to castration ± an antiandrogen. They reported an improved OS at 2 years (odds ratio [OR], 1.16; 95% CI, 1.00 to 1.33; n = 5,286 men from 14 trials) and 5 years (OR, 1.29; 95% CI, 1.11 to 1.50; n = 3,550 men from seven trials), but not at 1 year (OR 1.03; 95% CI, 0.85 to 1.25; n = 4,970 men from 13 trials).

The most recent review (21 RCTs; 6,871 men) by Samson et al,[14] compared androgen deprivation alone (orchiectomy or LHRH agonist) versus combined blockade combined with steroidal or nonsteroidal antiandrogens. Overall, the review found a larger survival improvement than the previous meta-analyses favoring combined androgen blockade, which first appeared at 5 years for men receiving (HR = 0.871; 95% CI, 0.805 to 0.942). Five years follow-up data were only provided in ten of the 21 studies.

Harms. The review by Samson et al[14] did not report on adverse events. An overlapping earlier systematic review of 6,320 men in 20 RCTs by Schmitt et al[15] found that combined androgen blockade using nonsteroidal antiandrogens increased the risk of diarrhea (10% *v* 2%), gastrointestinal pain (7% *v* 2%), and nonspecific ophthalmologic events (29% *v* 5%). The trial by Eisenberger et al[17] found the CAB patients had more frequent trial dropout due to drug toxicity (33% *v* 10%; $P = .003$), grade 2 or worse diarrhea (6.3% *v* 2.7%; $P = .002$), and grade 2 or worse anemia (8.5% *v* 5.4%; $P = .024$).

The additional costs of antiandrogens over orchiectomy or LHRH agonists are modeled in the paper by Bayoumi et al.[18] LHRH agonists with NSAA were associated with the highest quality-adjusted survival, followed by orchiectomy alone. NSAA plus orchiectomy and LHRH agonists alone had higher costs, lower survival, and lower

quality-adjusted survival than orchiectomy. The cost-effectiveness of CAB with NSAA plus LHRH compared with orchiectomy was US $1,110,000 per quality-adjusted life-year. These observations were robust to sensitivity analyses in which meta-analysis-derived effectiveness estimates were varied through the 95% CIs.

Comments. The group felt that an individual patient data meta-analysis (PCTCG study[16]) should be given greater consideration over a meta-analysis of the literature (Schmitt et al[15]) due to known differences between these two types of meta-analyses.[48] The individual patient data meta-analysis did not include a large, well-powered RCT, which concluded that CAB did not prolong OS compared with orchiectomy alone. However, the Eisenberger trial[17] was included in the methodologically less rigorous Schmitt et al meta-analysis of the literature, and in this meta-analysis the results also favored the use of CAB. Overall, the group felt that given this evidence, a small survival advantage was likely with CAB over castration alone, although the benefit must be balanced against great toxicity and extraordinarily poor cost-effectiveness.

Does Early Androgen Deprivation Therapy Improve Outcomes Over Deferred Therapy?

Summary. There was one systematic review with meta-analysis of the literature[19] and one Markov model (decision analysis) based on a systematic review[18] that addressed the question. Early treatment using LHRH agonists confers a small but statistically significant survival advantage, and significant improvements in progression-free survival that were durable up to 10 years of follow-up. However, these results are based on a systematic review of trials[18] that did not select a cohort of patients who progressed post-treatment, on surveillance, or who had metastatic disease on presentation, although a subset of every sampled population did have either nodal or distant metastases. Treatment was most cost-effective when started after the onset of symptoms. Antiandrogen monotherapy in patients who have not yet undergone definitive primary therapy is unlikely to provide a survival benefit compared to delayed systemic treatment.

Biologic rationale. The biologic activity of each type of therapy is described above in the relevant section. Early initiation of therapy delays progression of disease to a more advanced state,[12] and it is theorized that a smaller burden of disease will be controlled longer with ADT, such that complications such as painful bony metastases, spinal cord compression, and hypercalcemia can be reduced.

Benefits. According to a systematic review[19] (four RCTs, n = 2,167 patients),[11,24,26] the benefits of early versus deferred ADT for men with advanced prostate cancer were significant reductions in both disease progression (definitions varying by study) and complications due to progression. Progression-free survival was significantly higher for early ADT at year 1 (OR = 3.99; 95% CI, 2.55 to 6.24; NNT = 9), year 2 (OR = 4.79; 95% CI, 2.36 to 9.71; NNT = 5), year 5 (OR = 3.15; 95% CI, 2.11 to 4.68; NNT = 4), and year 10 (OR = 3.48; 95% CI, 2.44 to 4.95; NNT = 3). A small but statistically significant improvement in OS at 10 years was also detected (OR = 1.5; 95% CI, 1.04 to 2.16; NNT = 20). From a cost-effectiveness perspective, androgen suppression therapies were most effective if initiated after patients became symptomatic from prostate metastases.[18]

There are two additional studies that were not included in the Cochrane review that may help inform the question of early versus deferred ADT. Conducted as part of the Casodex Early Prostate Cancer Program, a multicenter, randomized, double-blind, placebo-controlled trial enrolled 3,603 men in Europe, South Africa, Australia, and Mexico with localized or locally advanced (T1b-T4, any N, M0) prostate cancer.[20] The study included patients who underwent curative treatment, as well as those who chose watchful waiting. A significant reduction in the risk of progression was identified for immediate bicalutamide (150 mg) compared with placebo ($P < .0001$) after a median follow-up of 2.6 years (HR = 0.57; 95% CI, 0.48 to 0.69). The benefit was consistent across stage and whether bicalutamide was given as adjuvant therapy or after watchful waiting. The time to PSA doubling was also significantly increased ($P < .001$) for immediate bicalutamide versus placebo (HR = 0.37; 95% CI, 0.32 to 0.43). After a planned second analysis with a median follow-up of 5.4 years, progression-free survival continued to favor bicalutamide (HR = 0.73; $P < .0001$). With the longer follow-up there continued to be no survival benefit or detriment for this intervention. However, in exploratory subgroup analysis, a trend towards a survival deficit was seen in patients in the watchful waiting subgroup who took high-dose bicalutamide.[21] The manufacturer has issued a recommendation in Canada to discontinue the drug in those with localized disease on watchful waiting.[21]

In an EORTC-conducted trial (EORTC 30891, February 1990 through January 1999) published only in abstract form,[49] 1,002 patients without local treatment with curative intent for asymptomatic T0-4 N0-2 M0 prostate cancer were randomized to immediate hormonal treatment with orchiectomy, or to buserelin versus deferred treatment at symptomatic disease progression. After a median follow-up of 3.2 years, preliminary results show a median OS of 6.3 years (95% CI, 5.7 to 7.0 years). An inverse Kaplan-Meier survival analysis method was used in which death was counted as a censored observation and alive was counted as an event, allowing a longer median survival than the median follow-up. As per correspondence with the study statistician, unpublished current data show that 50% of patients have now died and median OS remains the same. Survival results by treatment arm are not yet available.

Harms. Early therapy is associated with higher costs and greater frequency of treatment-related adverse effects.[18] Deferred treatment risks the loss of hormone sensitivity in the tumor as well as serious complications, such as spinal cord compression.

Comments. The populations included in the Wilt et al[19] review had advanced prostate cancer, defined as regional or disseminated metastasis (D1 or D2; N+/M0 or M1) or minimally advanced disease (C; T3-4/N0 or Nx/M0). It is also notable that studies that used androgen deprivation solely as adjuvant therapy to radiation treatment were excluded. Disease progression was identified by radiographic or symptomatic evidence of metastatic disease.

Strictly speaking, these trials did not select a cohort of patients who progressed post-treatment, on surveillance, or who had metastatic disease on presentation, although patients in at least part of every sampled population did have either nodal or distant metastases. The Messing et al[25] (Eastern Cooperative Oncology Group) trial included patients who were disease-free after radical prostatectomy and pelvic lymphadenopathy, but were still considered to have residual cancer because of the nodal metastases. The Medical Research Council Prostate Cancer trial[26] consisted of patients with asymptomatic metastatic prostatic cancer, as well as patients with locally advanced (T2-4) prostate cancer that was too advanced for curative treatment. The VACURG studies[24] included stage III (prostate cancer extended beyond the prostatic capsule but without evidence of distant metastases or elevated prostatic acid phosphatase levels) and stage IV (distant metastases or elevated prostatic acid phosphatase or both) patients.

A limitation of the review is that all of the trials were conducted before the routine use of PSA testing. The review is further limited by variability in the interventions as well as in the stages of the cancers of the patients enrolled across trials. A specific limitation of the Medical Research Council trial is that roughly half the men who died in the deferred treatment arm never received ADT,[26] perhaps due to the pragmatic trial design in which patients were followed, based on the preference of the individual practitioner.[50] Though the study protocol was in keeping with standard practice in the United Kingdom at the time, this finding highlights the need for initiation of ADT before the development of major complications.

For these reasons, we feel that it is reasonable to generalize the data from this meta-analysis of the literature to the target population of this guideline, with some caution. Further studies addressing this question in patients with recurrent or metastatic disease, managed with modern medical diagnostic and biochemical tests and identical follow-up schedules in both the early- and deferred-therapy groups, would help inform this question further.

Is Intermittent ADT Better Than Continuous ADT?

Summary. There were no data from prospective randomized trials on which to base a recommendation. Two large randomized Intergroup studies are ongoing and intermittent androgen blockade should still be considered experimental.

Biologic rationale. The premise for testing intermittent deprivation therapy is two-fold. First, prolonged ADT may have the negative effect of facilitating progression from androgen dependence to androgen independence. Second, both acute and chronic side effects are associated with achieving castrate levels of testosterone. Preliminary results have shown that increases in testosterone during off-therapy periods have been associated with decreases in side effects.[51,52]

Benefits. The benefits of intermittent versus continuous ADT are unclear, as neither systematic reviews nor completed randomized clinical trials have been identified.

Harms. Similarly, there are insufficient data to assess harms.

Comments. Smaller nonrandomized studies have shown that patients spent 35% to 55% of each cycle off therapy when treated intermittently.[53,54] After the first cycle, greater than 90% responded to reinstitution of ADT. Limitations of these nonrandomized studies include lack of standardized rules for starting and stopping therapy, and absence of data regarding recovery of testosterone levels, hemoglobin levels, bone density, sexual function, and quality of life.

Two clinical trials are currently underway.[55] A phase III randomized clinical trial, which began in 1995, is comparing intermittent versus continuous combined ADT composed of bicalutamide and goserelin in patients with metastatic stage IV prostate cancer responsive to such therapy. The study will analyze the effects of treatment on survival time, PSA levels, impotence, libido, vitality/fatigue, emotional well-being, general symptoms, global perception of QOL, and social functioning. Participating groups include the National Cancer Institute, National Cancer Institute of Canada Clinical Trial Group, EORTC Genito-Urinary Tract Cancer Group, Southwest Oncology Group, Cancer and Leukemia Group B, and Eastern Cooperative Oncology Group. A second phase III randomized clinical trial, which began in 1999, is comparing intermittent versus continuous androgen suppression in patients with PSA progression in the clinical absence of distant metastases after prior radiotherapy for prostate cancer (whether post-radical prostatectomy or as primary management). The study will analyze the effects of treatment on survival time, time to development of hormone resistance, QOL, duration of treatment and nontreatment intervals, and time to testosterone recovery. The lead participating groups include the National Cancer Institute and the Southwest Oncology Group.

Ongoing Clinical Trials

There are a number of ongoing large single institution and Intergroup studies examining research questions identified in this guideline that will be evaluated in future updates. There are two trials examining the additive role of chemotherapy in recurrent or advanced/metastatic prostate cancer. The Radiation Therapy Oncology Group (RTOG P-0014) has a trial of patients demonstrating biochemical failure (M0) following radical therapy who were randomly assigned to androgen deprivation and chemotherapy versus androgen deprivation alone. The M.D. Anderson Cancer Center (Houston, TX) has an in-house phase III RCT of chemotherapy and androgen ablation versus androgen ablation alone for unresectable and stage IV prostate cancer.

There are two large Intergroup studies of intermittent versus continuous androgen therapy for patients with M1 disease (participating groups include the National Cancer Institute [INT-0162], National Cancer Institute of Canada Clinical Trial Group [NCIC's PR8 & JPR8], EORTC Genito-Urinary Tract Cancer Group [EORTC 30985], Southwest Oncology Group [SWOG 9346], Cancer and Leukemia Group B [CLB-9594], and Eastern Cooperative Oncology Group [E-59346]); and a rising PSA following definitive therapy for patients with M0 disease (participating groups include the National Cancer Institute of Canada Clinical Trial Group [NCIC's PR7 & JPR7], Southwest Oncology Group [SWOG JPR7], and the Clinical Trials Service Unit of the National Cancer Institute).

Interpretive Summary

Bilateral orchiectomy or medical castration with LHRH agonists are the recommended initial palliative treatments for metastatic prostate cancer. While orchiectomy is a simple and cost-effective procedure, it is nonreversible and carries significant psychological burden to some patients. LHRH agonists are equally effective, are available in depo-injections, and potentially reversible but very expensive, particularly when used early in the disease or in men with indolent disease.[18,56]

DES is an inexpensive oral medication that had equivalent OS compared with orchiectomy in a small RCT,[1] but carries with it significant risks of cardiovascular and thrombotic morbidities even at 1 mg/d. DES should not be considered as a standard first-line treatment option and currently is no longer commercially available in North America.

Nonsteroidal antiandrogens show equivalent survival when used as monotherapy, but, since the side-effect profile may be more attractive than castration, men and their practitioners may opt for this management strategy after a full discussion. Steroidal antiandrogens are not recommended as monotherapy.

The estimated absolute reduction in overall mortality with CAB at 5 years ranges from 1% to 5%. The NNT to prevent one death is 20 to 100 patients treated for 5 years. LHRH and nonsteroidal antiandrogens have the highest estimated quality-adjusted survival but have an incremental cost of over $1 million (US) per quality-adjusted life-year over orchiectomy alone. Patients willing to accept this trade should be offered a nonsteroidal antiandrogen.

Until data from studies using modern diagnostic and biochemical tests and standardized follow-up schedules become available, no specific recommendations can be issued by the Panel regarding the question of early versus deferred ADT in asymptomatic patients. Strictly speaking, the Cochrane systematic review of trials discussed here[19] did not select a cohort of patients who progressed post-treatment, on surveillance, or who had metastatic disease on presentation, though a subset of every sampled population did have either nodal or distant metastases. However, patients should be followed clinically and be started on ADT once symptoms of local progression and/or metastases present. The optimal frequency and nature of the follow-up has not been fully elucidated, but should consider known prognostic factors for progression to metastatic disease (time of biochemical failure, PSA doubling time, Gleason score, and PSA nadir after primary therapy).[56,57]

No clinical trials or systematic reviews on the topic of intermittent versus deferred ADT were identified. Thus, no specific recommendations can be made. Two large randomized Intergroup studies are ongoing and intermittent androgen blockade should still be considered experimental.

Opinions of the ASCO Metastatic Prostate Guideline Expert Panel

The central issue in the management of patients with progressive, recurrent, or metastatic androgen-sensitive prostate cancer is striking an appropriate balance between effective palliation and acceptable toxicity. Numerous randomized trials and meta-analyses have, at best, demonstrated small improvements in overall or cause-specific survival.

Shared decision-making is central to obtaining informed consent; in particular, a detailed discussion of the pros and cons surrounding ADT for androgen-sensitive progressive, recurrent, or metastatic prostate cancer is important since many of the trade-offs involve small, if any, differences in OS. Given the different values that different men may place on the symptoms associated with the various combinations of ADT, it is imperative to individualize these decisions. For example, a man who is impotent after his surgery may have no trouble with the prospect of losing his libido and opt for early initiation of treatment for his asymptomatic recurrent disease, whereas a man who is

potent but has osteopenia may wish to delay ADT to later in his disease process.

An effective palliative treatment should improve or maintain QOL to a greater extent than is seen with no treatment. This can be achieved through improving symptoms or preventing complications of advanced disease. Patient-reported QOL has been repeatedly shown to be better than provider-assessed QOL, and today there is a multitude of patient-assessed questionnaires that assess health-related QOL. In order to properly measure patient-reported QOL, a questionnaire should be reliable, valid, and feasible to administer in the research setting with high response rates. There are both generic and prostate-specific instruments available that meet these criteria.

Many of the trials described above were performed at a time when QOL measurement was not well established nor recognized as being important by the medical community or the investigators who designed the clinical trials. It is therefore impossible to conclude that overall QOL is improved on ADT, as there are no formal data to substantiate this claim. While practitioners and patients are keenly aware of the benefits of ADT, they are also aware of the toxicity of the treatment, and we need the QOL data in order to define the nature and magnitude of the trade-offs in the QOL domains.

The group strongly recommends that appropriate QOL measures be included in all subsequent research questions that address these groups of patients. Many clinicians believe that ADT is a very effective treatment (where the balance between efficacy and toxicity favors the treatment) when patients have symptomatic metastatic disease. In our minds, there are three priority areas of research that will help to define more precise cost/benefit estimates. At the time of writing this document, the Panel feels that the most pressing research need is to define the optimal time to initiate ADT. The second is to test whether other more effective systemic treatment options confer additive benefit or are better than ADT. The third area, which will be of most importance to health care planners, is to quantify the magnitude of the trade-offs between orchiectomy and LHRH agonists. DES has an uncertain role in the primary management of progressive, metastatic, or recurrent prostate cancer, but may be useful as a secondary therapy, to verify androgen independence or to defer chemotherapy administration.

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APPENDIX A. Prostate Cancer Staging Systems

1992 TNM Staging System[58]	American Urological Association Staging System[59]
Tx–tumor cannot be assessed	
T1–clinically inapparent tumor, not palpable or visible by imaging	A–incidental finding
T2–palpable tumor confined to gland	B–palpable tumor confined to gland
T3–tumor extends through prostatic capsule	C–extension beyond prostate capsule without evidence of metastases
T4–tumor is fixed or involves adjacent structures other than seminal vesicle	
N1-3–regional lymph node(s) positive	D1–involvement of lymph nodes below aortic bifurcation
M1–distant metastases	D2–lymph node involvement above bifurcation or distant metastases involving other sites

APPENDIX B. ASCO Metastatic Prostate Cancer Expert Panel

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