

Initial Hormonal Management of Androgen-Sensitive Metastatic, Recurrent, or Progressive Prostate Cancer: 2007 Update of an American Society of Clinical Oncology Practice Guideline

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A B S T R A C T

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Submitted December 11, 2006; accepted February 13, 2007; published online ahead of print at www.jco.org on April 2, 2007.

Approved by the Board on November 2, 2006.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2512-1596/\$20.00

DOI: 10.1200/JCO.2006.10.1949

Purpose

To update the 2004 American Society of Clinical Oncology (ASCO) guideline on initial hormonal management of androgen-sensitive, metastatic, recurrent, or progressive prostate cancer (PCa).

Methods

The writing committee based its recommendations on an updated systematic literature review. Recommendations were approved by the Expert Panel, the ASCO Health Services Committee, and the ASCO Board of Directors.

Results

Seven randomized controlled trials (four new), one systematic review, one meta-analysis (new), one Markov model, and one delta-method 95% CI procedure for active controlled trials (new) informed the guideline update.

Recommendations

Bilateral orchiectomy or luteinizing hormone–releasing hormone agonists are recommended initial androgen-deprivation treatments (ADTs). Nonsteroidal antiandrogen monotherapy merits discussion as an alternative; steroidal antiandrogen monotherapy should not be offered. Combined androgen blockade should be considered. In metastatic or progressive PCa, immediate versus symptom-onset institution of ADT results in a moderate decrease (17%) in relative risk (RR) for PCa-specific mortality, a moderate increase (15%) in RR for non-PCa-specific mortality, and no overall survival advantage. Therefore, the Panel cannot make a strong recommendation for early ADT initiation. Prostate-specific antigen (PSA) kinetics and other metrics allow identification of populations at high risk for PCa-specific and overall mortality. Further studies must be completed to assess whether patients with adverse prognostic factors gain a survival advantage from immediate ADT. For patients electing to wait until symptoms for ADT, regular monitoring visits are indicated. For patients with recurrence, clinical trials should be considered if available. Currently, data are insufficient to support use of intermittent androgen blockade outside clinical trials.

J Clin Oncol 25:1596-1605. © 2007 by American Society of Clinical Oncology

INTRODUCTION

The American Society of Clinical Oncology (ASCO) published clinical practice guidelines on the initial hormonal management of androgen-sensitive, metastatic, recurrent, or progressive prostate cancer in 2004.¹

The guideline addressed the following questions: “For men with metastatic or recurrent androgen sensitive prostate cancer, in whom ADT [androgen-deprivation therapy] 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?”¹

ASCO updates a guideline when data or publications might change a prior recommendation or when the Panel feels clarifications are required for the oncology community.

The last guideline’s literature search included reports published up to March 2003. Because a number of publications have been reported in the literature since then, a decision was made to update the guideline.

UPDATE METHODOLOGY

Literature Review and Data Collection

For the 2007 update, the MEDLINE database (January 2003–March 2006; 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 (PDQ) clinical trials database (http://www.cancer.gov/search/clinical_trials/) was searched for ongoing clinical trials in the identified subject areas.

Inclusion and Exclusion Criteria

Table 1 describes the details of the inclusion criteria and outcome variables for each question addressed in this guideline. For each guideline question, letters, editorials, and articles published in a language other than English were not considered. 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
5. Trials or trial arms that used diethylstilbestrol

Consensus Development Based on Evidence

An evidence-based approach incorporating consensus by experts was the model used to create the recommendations. To this end, a subset of the original writing committee met via teleconference in February and March 2006 to consider the evidence for each of the 2004 recommendations. The guideline update was circulated in draft form to the full Expert Panel for review and approval. Suggestions from the Expert Panel were incorporated into the document, yielding a final set of recommendations.

The draft guideline was then submitted to the ASCO Health Services Committee (HSC) for review and was endorsed in July 2006. The ASCO Board reviewed and approved the document in November 2006. Final text editing was performed by D.A.L. and H.S.

RESULTS

Summary of Literature Review

Since the first guideline literature review, several randomized studies have been published for the first time or have published updated results. Not all guideline questions had new data available. Studies that met the eligibility criteria for each of the five questions are listed in Table 2.

Standard initial treatment options. No studies that met the selection criteria were published since the last guideline.

Antiandrogens as monotherapy. No studies that met the selection criteria were published since the last guideline.

Table 1. Details of Literature Search Inclusion Criteria and Outcome Variables

Question	Inclusion Criteria	Outcome
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 delta-method 95% CI procedure for active controlled trials*	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.
*New since original guideline.

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

Question	Intervention	Study
1. What are the standard initial treatment options?	Orchiectomy v placebo, estrogens v placebo, LHRH v orchiectomy, dose-dependent toxicity of estrogens	No new studies
2. Are antiandrogens as effective as other castration therapies?	Antiandrogen v castration	No new studies
3. Is combined androgen blockade better than castration alone?	Addition of an antiandrogen to orchiectomy or LHRH agonist	1 RCT ² ; 1 delta-method ³
4. Does early androgen-deprivation therapy improve outcomes over deferred therapy?	Early and deferred androgen-deprivation therapy	1 systematic review ¹⁹ ; 7 RCTs ^{4-8,27,29} ; 1 Markov model ²³
5. Is intermittent androgen-deprivation therapy better than continuous androgen-deprivation therapy?	Intermittent and continuous deprivation therapy	1 RCT ¹⁰

Abbreviations: LHRH, luteinizing hormone-releasing hormone agonist; RCT, randomized controlled trial; delta-method, delta-method 95% CI procedure for active controlled trials.

Combined androgen blockade. One randomized controlled trial (RCT)² and a delta-method 95% CI procedure for active controlled trials³ were available to update this question.

Early versus deferred ADT. There were new three RCTs,⁴⁻⁶ two updated RCTs,^{7,8} and one new systematic review and meta-analysis of the literature (MAL; submitted for publication) available to update this question.

Intermittent androgen blockade. One RCT¹⁰ was available to address this question.

GUIDELINE RECOMMENDATIONS

1. What Are the Standard Initial Treatment Options?

2007 recommendation. Bilateral orchiectomy or medical castration with luteinizing hormone-releasing hormone (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. Diethylstilbestrol should not be considered as a standard first-line treatment option and currently is no longer commercially available in North America.

Literature update. There is no change from the original guideline recommendation. No relevant additional data were identified on initial treatments for metastatic prostate cancer in a review of the literature published since 2003.

2. Are Antiandrogens As Effective As Other Castration Therapies?

2007 recommendation. Nonsteroidal antiandrogen (NSAA) monotherapy may be discussed as an alternative, but steroidal antiandrogen (AA) monotherapy should not be offered.

Literature update. There is no change from the original guideline recommendation. No relevant additional data were identified on the question of whether AAs are as effective as other castration therapies were identified from in a review of the literature published since 2003.

3. Is Combined Androgen Blockade Better Than Castration Alone?

2007 recommendation. Combined androgen blockade (CAB) should be considered.

Literature update and discussion. An interim analysis of an RCT² and a study that combined data from an individual patient data meta-

analysis and a randomized active control study,³ were published since the last guideline. Overall survival is greater with the addition of an NSAA to medical or surgical castration, but increased adverse effects may occur as a result.

The two new studies that inform this question involve the NSAA bicalutamide, which is a commonly used AA today because of its once-a-day dosing and lower GI and ophthalmologic adverse effects, as compared with the other NSAAs, flutamide and nilutamide. Although generic products are now available in Canada, bicalutamide is still more expensive than flutamide or nilutamide and may not be covered by private health insurance or Medicare health plans.

The interim analysis of the RCT included 205 patients with previously untreated locally advanced or metastatic prostate cancer.² Patients received an LHRH agonist and were randomly assigned to bicalutamide 80 mg (the dose licensed in Japan) orally once daily or placebo. This interim analysis was reported with a minimum of 6 months of follow-up (median, 15 months). The primary outcomes for the study were 12-week prostate-specific antigen (PSA) normalization (< 4.0 ng/mL), 12-week tumor response rate, and withdrawals caused by adverse drug reactions (ADRs). There were too few deaths (four in the CAB arm, six in the control arm) to analyze survival outcomes, although the study continues.

Nine patients (8.8%) in the CAB group and 11 (10.9%) in the control arm withdrew because of ADRs, an estimated difference of -2.1% (95% CI, -10.7% to 6.4%). A full list of the ADRs is shown in Table 3. A secondary outcome in the study was time to disease progression. It was reported that 17 patients (16.7%) in the CAB group and 30 (29.7%) in the monotherapy group experienced disease progression ($P = .016$). The risk of progression during follow-up was reduced by 54% in the CAB group relative to the control group (hazard ratio [HR], 0.46; 95% CI, 0.25 to 0.84; $P = .011$). However, the follow-up is too short to accept these results as definitive.

The second study applied an unusual methodology,^{11,12} referred to as the delta-method 95% CI procedure for active controlled trials (delta-method for short). Its validity is accepted by the US Food and Drug Administration and has been used to approve capecitabine in colorectal cancer.¹¹ The principle of the method is logical. If it can be demonstrated that treatment "B" is better than placebo ("C") and if treatment "A" is better than/the same as "B," then "A" should be better than "C."

Table 3. AEs and ADRs in the Akaza Randomized Study² of LHRH ± Bicalutamide

Event/Reaction	%			
	MAB (n = 102)		LHRH Agonist Monotherapy (n = 101)	
	AEs	ADRs	AEs	ADRs
Any*	88.2	59.8	83.2	58.4
Any serious*	14.7	2.9	14.9	6.9
Any grade 3/4	13.7	5.9	17.8	9.9
Hot flushes NOS	19.6	18.6	31.7	31.7
Nasopharyngitis*	18.6	1.0	12.9	1.0
Any abnormal hepatic function test	NA	13.7	NA	17.8
Back pain	10.8	1.0	5.9	2.0
Anemia NOS	8.8	7.8	5.0	4.0
Increased blood alkaline phosphatase NOS	8.8	8.8	5.0	4.0
Increased alanine aminotransferase	7.8	2.9	10.9	7.9
Increase blood lactate dehydrogenase	7.8	3.9	6.9	3.0
Pruitis NOS*	7.8	0.0	2.0	0.0
Increased aspartate aminotransferase	6.9	2.9	8.9	6.9
Arthralgia	6.9	0.0	3.0	0.0
Eczema	6.9	3.9	2.0	1.0
Increased γ -glutamyltransferase	5.9	3.9	5.0	3.0
Constipation*	2.9	0.0	7.9	1.0
Abnormal hepatic function NOS	2.0	1.0	6.9	5.9

Abbreviations: AE, adverse event; ADR, adverse drug reaction; MAB, maximum androgen blockade (goserelin/leuprorelin + bicalutamide 80 mg); LHRH, luteinizing hormone-releasing hormone (LHRH agonist monotherapy: goserelin or leuprorelin); NOS, not otherwise specified.
*Adverse events with a frequency greater than 5% between the arms.

The Prostate Cancer Trialists' Collaborative Group (PCTCG) published an individual patient data meta-analysis of combined androgen blockade, showing that NSAAs conferred a small but statistically significant reduction in all-cause death over castrate therapy alone (72.4% *v* 75.3%; HR, 0.92; *P* < .005).¹³ For flutamide, the HR was 0.92 (95% CI, 0.86 to 0.98; this represents "B" better than "C"). Schellhammer et al¹⁴ performed an 813-patient double-blind, placebo-controlled trial of bicalutamide versus flutamide in addition to an LHRH agonist. They reported a decrease in all-cause mortality for patients randomly assigned to bicalutamide, which did not reach statistical significance (HR, 0.87; 95% CI, 0.72 to 1.05; *P* = .15); this represents "A" equal to "B." Combining these results (bicalutamide *v* flutamide AND flutamide *v* castration), Klotz et al³ calculated an HR of 0.80 (95% CI, 0.66 to 0.98) for bicalutamide CAB versus castrate therapy alone.

The study authors recognized some assumptions that are critical to the validity of this analysis, as follows: "This would require there to be no important prognostic factors that were represented differently between the study populations (such as the extent of metastatic disease) on which the size of the effect of bicalutamide relative to flutamide would differ, and that patients in the trials included in the PCTCG meta-analysis were managed similarly to those in the comparative trial of bicalutamide and flutamide."³ Almost all of the patients in the PCTCG meta-analysis (88%), and all of the Schellhammer patients had D2 disease, despite the latter trial's being performed in the PSA era. Other prognostic factors were not reported from the meta-analysis.

This effect size is significant. Docetaxel is now the standard of care across North America for patients with metastatic androgen-independent disease because of a survival advantage observed in

two large randomized studies, and many other systemic therapies are currently being tested.^{15,16} The hazard ratios reported by Tannock et al¹⁵ (HR, 0.76) and Petrylak et al¹⁶ (HR, 0.80) are similar to that reported in the Klotz analysis. Even with complete follow-up, the Akaza study² (n = 205) lacks sufficient power to detect a hazard rate of 0.80 (the Petrylak and Tannock trials had 674 and 1,006 patients, respectively).

The survival advantage seen in the Petrylak and Tannock trials were 1.9 and 2.4 months, respectively, compared with patients on the control arm (mitoxantrone and prednisone). In Pound et al's series of surgical patients,¹⁷ median survival from the onset of metastatic disease was 5 years. An estimated HR of 0.80 predicts that bicalutamide CAB could translate into a median survival of 6.25 years (calculated by D.A.L.), a potential median survival advantage of 1.25 years.

This potential survival advantage is hypothetical and should be confirmed by a sufficiently powered clinical trial. The Akaza et al² trial was not designed to detect a meaningful difference in overall or cause-specific survival and, therefore, is underpowered to detect a hazard ratio of 0.80. If such a trial is undertaken, the first results will not be available for at least 10 years.

If one has concerns about the delta-method or the assumptions that are built into the analysis, bicalutamide would have an equivalent survival advantage compared with the other NSAAs (2.9% from the PCTCG analysis).¹³ Given that the bicalutamide CAB has minimal, if any, additional toxicity over castrate therapies alone,² and is significantly cheaper than the newer systemic therapies, until the results of a trial designed to address the potential survival benefit is available, patients should be made aware of the findings described herein, and bicalutamide CAB should be considered.

4. Does Early ADT Improve Outcomes Over Deferred Therapy?

2007 recommendation. For patients with metastatic or progressive prostate cancer, there is a moderate decrease (17%) in relative risk (RR) for prostate cancer–specific mortality, a moderate increase (15%) in RR for non–prostate cancer–specific mortality, and no overall survival advantage for immediate institution of ADT versus waiting until symptom onset for patients. Therefore, the Panel cannot make a strong recommendation for the early use of ADT. PSA kinetics and other metrics allow the identification of populations at high risk for prostate cancer–specific and overall mortality. Further studies must be completed to assess whether patients with adverse prognostic factors gain a survival advantage from immediate ADT. If a patient decides to wait until symptoms for ADT, he should have regular visits for monitoring. For patients with recurrent disease, clinical trials should be considered if available.

2007 literature update and discussion.

Population stratification. The target population addressed by this guideline represents a diverse group of patients. For patients who are symptomatic from prostate cancer, the standard of care is to initiate ADT, so called “deferred therapy.” The critical issue is to determine whether there is benefit and how large it is for starting ADT while patients are asymptomatic, given the known toxicities of this treatment.

Asymptomatic patients are most easily divided into three different groups on the basis of the clinical trial selection criteria of the trials. It is recognized that, within each group, there will be patients who range from having very aggressive disease who are at high risk of prostate cancer death, even with an aggressive management approach, to those with very indolent disease who may die as a result of other causes without any treatment.

More recently, a new clinical states model based on disease extent and hormonal status, useful to understand an individual’s prognosis, select treatment, and to predict outcomes, has been developed.¹⁸ Although none of the trials was performed before this model was introduced, future trials may select patients in reference to this model and are therefore referenced according to this model.

The first group includes asymptomatic patients with a rising PSA as the sole manifestation of the disease after radical treatment (radiotherapy and/or surgery) with noncastrate levels of testosterone, termed the “recurrent” group here (or the “rising PSA” group in the clinical states model).¹⁸ The second group is patients with noncastrate levels of testosterone and detectable metastases on an imaging study who have not been exposed to radiation or surgery to the prostate (“progressive disease” here; “clinical metastases, noncastrate” group in the clinical states model).¹⁸ Patients who progress to metastatic disease while on watchful waiting, and those who are diagnosed with asymptomatic metastatic prostate cancer, were considered to be in the same group because the only difference between them was the lead time introduced by their biopsy. The third group is patients with pathologic node-positive disease. It is important to note that patients with pathologic node-positive disease found at the time of radical prostatectomy are also considered in the “clinical metastases, noncastrate” group,¹⁸ even though the disease has been completely resected.

It was felt to be important to address each group separately because there are no RCTs that address the first group, five RCTs that address the second group, and two RCTs that address the third.

Recurrent prostate cancer. No studies that met the selection criteria were published since the last guideline. Clinical trials should be considered (see Ongoing Clinical Trials, herein), if available.

Progressive disease on watchful waiting. Recommendations of the original guideline were primarily derived from results of a Cochrane review by Wilt et al¹⁹ that informed the question of early versus deferred ADT for progressive prostate disease on watchful waiting. Two RCTs^{6,8} were published since the Wilt review, and one RCT included in the Wilt review has been updated.⁷

Previously published in abstract,²⁰ European Organisation for Research and Treatment of Cancer (EORTC) 30891 randomly assigned 1,002 patients who had not undergone curative-intent treatment for asymptomatic T0-4 N0-2 M0 prostate cancer to either immediate hormonal treatment with orchiectomy or to buserelin versus deferred treatment at symptomatic disease progression. Results are now available for 985 patients.⁸ Among the 493 patients receiving deferred treatment, 25.6% died without ever requiring hormonal therapy. It should be noted that, despite the plan to defer ADT until after the onset of symptomatic disease, 65 (26.5%) of the 245 patients started treatment because of an asymptomatic rising PSA, and 10% (25 of 245) started because of new objective evidence of metastases (which were asymptomatic). After a median follow-up of 7.8 years, the absolute increase in mortality rate was 6.9% at 5 years and 11.1% at 10 years for deferred compared with immediate treatment, although this was not statistically significant. There was also no significant difference in the 10-year prostate cancer–specific mortality rate (26% v 24.8%, respectively), the overall symptom-free survival rate, or the cardiovascular event rate. The rates of time to first subjective (symptomatic) and objective (documented metastases) progression after entry onto the study were significantly higher ($P < .0001$) for patients undergoing deferred therapy, but subsequent rates of subjective and objective progression (ie, when the cancers became androgen independent) were not different between the arms.

Including primarily M1 patients, Swiss Group for Clinical Cancer Research trial (SAKK) 08/88 was closed to accrual prematurely in February 1992 due to competition for M0 patients with EORTC 30891.⁶ After 4 years of accrual, only 197 of the required 360 T0-4, N0-2, M0-1 patients had been successfully randomly assigned to either immediate or deferred subcapsular orchiectomy on symptomatic progression. Follow-up time was extended to ensure sufficient statistical power to detect a difference of 65% in survival between treatment groups. As with EORTC 30891, a large percentage (42%) of the 92 patients in the deferred treatment group never required treatment. There was no difference in either overall survival or time to symptoms after orchiectomy (ie, when androgen independent at second symptom onset). However, overall median time to onset of first symptoms (ie, when androgen sensitive, before ADT was started) was significantly improved (+2.8 years; $P < .01$) for patients undergoing immediate treatment. There was a trend ($P = .09$) toward longer cancer-specific survival for patients undergoing immediate versus deferred treatment. In multivariate analyses, both immediate treatment and absence of metastases at study entry independently ($P < .001$) predicted time to progression. Predictors of significantly shorter ($P < .05$) overall survival were presence of metastatic disease, node-positive disease, baseline hemoglobin of 14 g/dL or lower, PSA of 5 ng/mL or higher, and concomitant cardiovascular disease.

The Early Prostate Cancer Program (EPCP) comprised three randomized, double-blind, placebo-controlled trials designed for

combined analysis. Of the 8,113 enrollees, 2,284 patients on watchful waiting were randomly assigned to bicalutamide 150 mg daily by mouth or placebo. Patients who progressed (not defined) while receiving placebo were unblinded, and therapy at that point was left to the discretion of the physician.⁴ After a median follow-up of 7.4 years, 458 (41.1%) of 1,114 patients randomly assigned to the immediate-bicalutamide arm died (all-cause mortality) versus 462 (39.5%) of 1170 in the deferred arm (odds ratio [OR], 1.02; 95% CI, 0.88 to 1.16, estimated from forest plot).⁴ The prostate cancer-specific mortality rates (personal communication with D.A.L., April 2006) were 13.6% (151 of 1,114) for patients treated immediately versus 16.2% (189 of 1,170) for those undergoing deferred treatment (OR, 0.81). Objective progression-free survival was improved with the early use of bicalutamide (OR, 0.77; 95% CI, 0.68 to 0.87, estimated from forest plot). Gynecomastia (68.8% v 7.6%) and breast pain (73.6% v 7.6%) were more frequently reported in the early bicalutamide arm (pooled results from all three studies).⁴

Also available is an update of the Medical Research Council (MRC) trial PR03,⁷ the 1997 version of which was included in the previously reported meta-analysis.¹⁹ As of June 2003, the study data have now reached maturity, with 92.5% of deaths having occurred. Patients receiving immediate treatment still maintain a significant disease-specific survival advantage ($P < .01$) compared with those in the deferred treatment arm. It should be noted that the indications for treatment “were left at the discretion of the participant.”²¹ A trend existed toward longer overall survival ($P = .09$) for patients treated immediately. Time to non-prostate cancer death did not differ significantly. Kirk⁷ suggests that studies powered to identify significant differences in disease-specific survival will be underpowered to detect clinically meaningful differences in overall survival. The intervention’s effect lessens as competing mortality increases with age.

Table 4 summarizes the trials including the triggers for intervention in the deferred arms. Most often, trials specified the trigger for deferred ADT as the onset of symptoms from metastatic disease, which falls into the “clinical metastases, noncastrate” group of the clinical states model.¹⁸ None of the trials had a trigger based either on an absolute value of PSA or on PSA doubling time (PSAdt). It remains unknown whether initiating treatment on the basis of a rise to a

predetermined PSA level or documenting a specific PSAdt, before detecting of metastatic disease by imaging (ie, at the transition to an asymptomatic clinical metastases noncastrate state) would provide equivalent outcomes to those triggers used in the clinical trials.

A planned subgroup analysis from a recently conducted MAL by Loblaw et al (submitted for publication; four RCTs; $n = 3,065$)^{6-8, 22} compared early ($n = 1,526$) versus deferred ($n = 1,539$) ADT for men with progressive prostate cancer on watchful waiting, and detected a significant overall effect ($P = .0001$) for prostate cancer survival. The RR of prostate cancer death was 0.84 (95% CI, 0.77 to 0.92) for early versus deferred therapy (Fig 1). The MRC study has been criticized because 29 (6%) of the 469 patients of patients in the deferred arm died as a result of prostate cancer without being treated with ADT.²¹ The prostate-cancer mortality advantage remained unchanged in sensitivity analyses when the MRC results⁷ were eliminated from the analysis ($P = .03$; RR, 0.84; 95% CI, 0.72 to 0.98). There was no overall survival benefit (RR, 0.98; 95% CI, 0.95 to 1.01; $P = .18$) for early or deferred treatment for the subset overall or in the sensitivity analysis (Fig 2). Figures 1 and 2 and Table 5 summarize the results for both outcomes, including the sensitivity analyses.

The Loblaw meta-analysis did not include the EPCP trial in the untreated prostate cancer subgroup. A meta-analysis of all studies was performed. Although a 17% reduction in prostate cancer-specific mortality was evident (RR, 0.83; 95% CI, 0.74 to 0.94; $P = .003$), no gain in overall survival was observed (RR, 0.83; 95% CI 0.74 to 0.94; $P = .18$; submitted for publication). Because the Messing ECOG trial was a visual but borderline statistical outlier (overall mortality tests of heterogeneity: $P = .36$, $I^2 = 10\%$; prostate cancer-specific mortality: $P = .09$, $I^2 = 47\%$), when it was excluded in a sensitivity analysis there were no visual or statistical outliers seen (overall mortality tests of heterogeneity: $P = .44$, $I^2 = 0\%$; prostate cancer-specific mortality: $P = .61$, $I^2 = 0\%$). Moreover, the benefit in prostate cancer-specific survival and no effect on overall mortality were maintained (Table 1). The authors concluded that “this supports the hypothesis that the effectiveness of early ADT is similar across the three subsets, . . . [with] either orchiectomy, luteinizing hormone releasing hormone or bicalutamide monotherapy 150 mg per day with metastatic, progressive

Table 4. Summary of the Trials That Examined the Question of the Timing of ADT

Trial	Reference	Year	No. of Patients	Population	Form of ADT	Planned Trigger(s) for Deferred Arm
VACURG 1	Byar ²²	1973	954*	LA 55%, M1 45%	Orch	At progression, (not defined)
MRC PR03	Kirk ⁷	2004	938	LA 72%, M1 28%	Orch, LH	Participant’s discretion
SAKK 08/88	Studer ⁶	2004	188	LA 68%, cN+ 20%, M1 23%	Orch	Symptom onset
EORTC 30891	Studer ⁸	2006	985	L 44%, LA 47%, cN+ 7%	Orch, LH	Symptom onset
ECOG	Messing ²⁷	1999	98	pN+ 100%, rP 100%	Orch, LH	Objective (non-PSA) progression
EORTC 30846	Schroder ⁵	2004	234	pN+ 100%, rP 0%	Orch, LH	Painful bony mets, new cN+, or primary tumor progression
EPCP	McLeod ⁴	2005	2284	L 71%, LA 29%	Bicalutamide†	At progression, (not defined)

NOTE. Percentages may not add up to 100% because categories are not mutually exclusive or status within category was not known for some patients. Abbreviations: VACURG, Veterans’ Administration Cooperative Urological Research Group; ADT, androgen-deprivation therapy; L, localized disease; LA, locally advanced disease; M1, metastatic disease; cN+, radiographically node positive disease; pN+, pathologic node-positive disease at surgery; PSA, prostate-specific antigen; rP, radical prostatectomy; Orch, orchidectomy; MRC, Medical Research Council; SAKK, Swiss Group for Clinical Cancer Research; LH, luteinizing hormone-releasing hormone; EORTC, European Organisation for the Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; mets, metastases; EPCP, Early Prostate Cancer Program.

*1,903 patients were entered into the trial but 949 received diethylstilbesterol.

†Patients were initially assigned to bicalutamide 150 mg/d or placebo; therapy on progression was left to the discretion of the physician.

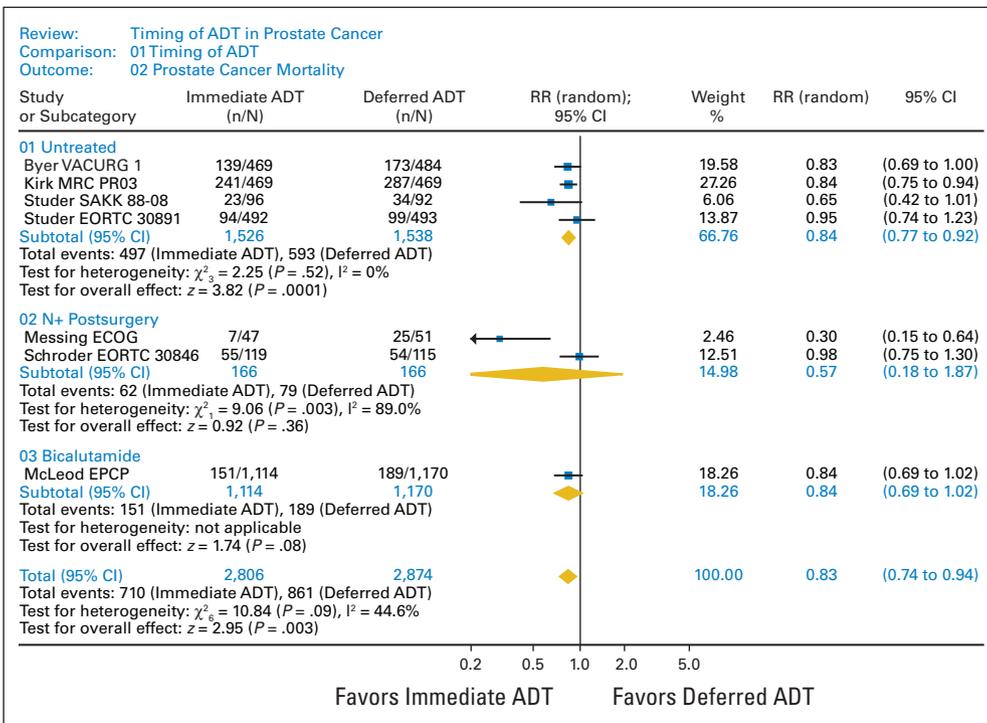


Fig 1. Forest plot of immediate versus deferred androgen-deprivation therapy (ADT) for prostate-specific death for patients with progressive or metastatic prostate cancer (submitted for publication). RR, relative risk; VACURG, Veterans' Administration Cooperative Urological Research Group; MRC, Medical Research Council; SAKK, Swiss Group for Clinical Cancer Research; EORTC, European Organisation for the Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; EPCP, Early Prostate Cancer Program.

disease on watchful waiting or for patients with pathologic node-positive disease at the time of radical prostatectomy.”

Early therapy is associated with higher costs and greater frequency of treatment-related adverse effects.²³ Deferred treatment risks the development of hormone independence in the tumor as well as serious complications such as spinal cord compression. The effects

of these complications occurring during the treatment deferral period might not be completely reversible.

It should be noted that none of these trials incorporated prognostic factors that have emerged in recent years, but which are starting to be used in today's clinical decision making. These include PSA_t,^{17,24,25} Gleason score,¹⁷ PSA response to ADT,²⁶ and age.²⁴

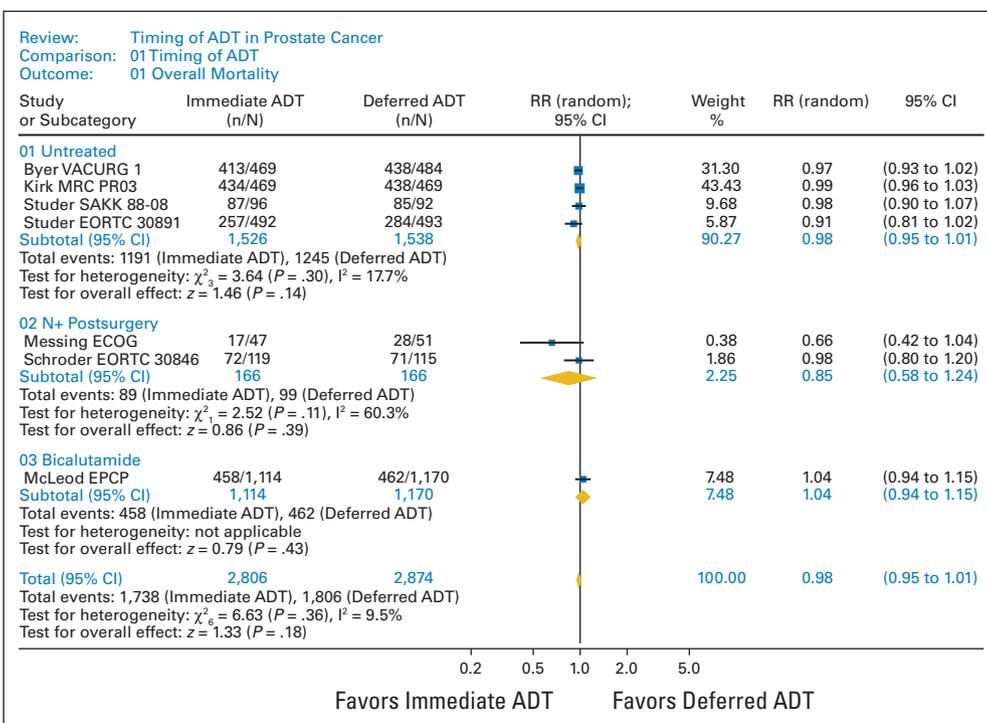


Fig 2. Forest plot of immediate versus deferred androgen-deprivation therapy (ADT) for all-cause death for patients with progressive or metastatic prostate cancer (submitted for publication). RR, relative risk; VACURG, Veterans' Administration Cooperative Urological Research Group; MRC, Medical Research Council; SAKK, Swiss Group for Clinical Cancer Research; EORTC, European Organisation for the Research and Treatment of Cancer; ECOG, Eastern Cooperative Oncology Group; EPCP, Early Prostate Cancer Program.

Table 5. Summary of the Meta-Analysis of the Literature Regarding the Timing of Androgen-Deprivation Therapy

All Studies	Overall Mortality		Prostate-Cancer Mortality	
	RR	95% CI	RR	95% CI
Overall	0.98*	0.95 to 1.01	0.83†	0.74 to 0.94
Untreated	0.98*	0.95 to 1.01	0.84†	0.77 to 0.92
N+ postsurgery	0.85*	0.58 to 1.24	0.57*	0.18 to 1.87
Bicalutamide	1.04*	0.94 to 1.15	0.84	0.69 to 1.02
Sensitivity analyses				
Exclude Messing ECOG				
Overall	0.98*	0.96 to 1.01	0.85†	0.79 to 0.92
Untreated	0.98*	0.95 to 1.01	0.84†	0.77 to 0.92
N+ postsurgery	0.98*	0.80 to 1.20	0.98*	0.75 to 1.30
Bicalutamide	1.04*	0.94 to 1.15	0.84	0.69 to 1.02
Exclude Kirk MRC				
Overall	0.97*	0.93 to 1.02	0.82†	0.69 to 0.97
Untreated	0.97*	0.93 to 1.01	0.84†	0.72 to 0.98
N+ postsurgery	0.85*	0.58 to 1.24	0.57*	0.18 to 1.87
Bicalutamide	1.04*	0.94 to 1.15	0.84	0.69 to 1.02

Abbreviations: RR, relative risk; ECOG, Eastern Cooperative Oncology Group; MRC, Medical Research Council.
 * $P < .10$.
 † $P > .05$.
 ‡Indicates a change after sensitivity analysis.

PSAdt is the most robust prognosticator because shorter PSAdt predicts for shorter overall survival,²⁴ cause-specific survival,^{25,26} and time to metastatic disease.¹⁷ Further studies must be completed to assess whether patients with adverse prognostic factors gain a survival advantage from immediate ADT. Investigators will likely be more interested in investigating the role of active cytotoxic chemotherapies and new biologic agents in individuals at higher risk for metastatic disease and prostate cancer death.

Pathologic node-positive prostate cancer. There are conflicting results about the benefit of early ADT in patients with pathologic node-positive disease. A trial originally published in 1999 with a median follow-up of 7.1 years²⁷ was recently updated with a median follow-up of 11.9 years.²⁸ Seventeen of 47 men who received immediate ADT died compared with 28 of 51 men who received ADT at disease progression (HR, 1.84; $P = .04$). Prostate cancer-specific mortality was seven (15%) of 47 and 25 (49%) of 51, respectively (HR, 4.09; $P = .0004$).

Schroder et al⁵ recently reported a study that included 234 patients with pathologic node-positive disease randomly assigned to immediate versus deferred ADT (EORTC 30846). The main difference between this and the Messing trial is that the prostatectomy was not completed. After a median follow-up of 8.7 years, there was no difference in overall survival (HR 1.23; 95% CI, 0.88 to 1.71). Fifty-five of the 119 (46.2%) patients allocated to the immediate arm and 54 (47.0%) of 115 allocated to the deferred arm died as a result of prostate cancer (not statistically significant, P value not reported).

In the MAL (submitted for publication), the Messing et al and Schroder et al trials are included in an a priori subset (Figs 1 and 2). However, overall, the Messing et al trial is a visual outlier and, within the node-positive subset, has a significant test for heterogeneity for overall death ($P = .11$; $I^2 = 60.3\%$) and prostate-specific mortality (P

$= .003$; $I^2 = 89\%$). This means that the Messing trial was visually and statistically significantly different from the Schroder et al trial. The meta-analysis authors therefore felt that it would not be appropriate to combine the two trials within the subgroup.

Although Schroder et al hypothesized that the difference between the two trials was the completion of radical prostatectomy, this would need to be confirmed in a randomized study. However, because of PSA screening, the population of patients available to answer this question (at least in North America) would be small, limiting the feasibility of completing an adequately powered trial in a timely manner.

Even combined, these two trials are underpowered to detect meaningful differences in prostate-cancer or all-cause mortality. In the Loblaw meta-analysis, with Messing et al removed, the effect of immediate ADT in the Schroder et al study appears to be similar to effect immediate ADT has in the other studies for both overall and prostate cancer-specific mortality ($I^2 = 0\%$ for both outcomes with Messing et al removed). It would therefore seem reasonable to generalize the results of the meta-analysis to the pathologic node-positive population; that is, that there is a moderate improvement in prostate cancer mortality seen with the immediate use of ADT, but no improvement in overall mortality.

5. What Is the Role of Intermittent Androgen Blockade?

2007 recommendation. Currently, data are insufficient to support the use of intermittent androgen blockade outside of clinical trials.

2007 literature update and discussion. The randomized study by De Leval et al¹⁰ compared the efficacy of intermittent CAB (IAD) to total continuous CAB (CAD) for patients with hormone-naïve advanced or relapsing prostate cancer. A total of 68 patients were randomly assigned to receive combined androgen blockade according to a continuous ($n = 33$) or intermittent ($n = 35$) regimen. The primary outcome was time to androgen independence of the tumor, which was defined as increasing serum PSA levels despite androgen blockade. Overall survival or quality-of-life outcomes were not reported. Four patients (12.1%) receiving CAD and two patients (5.7%) receiving IAD have died as a result of prostate cancer. Median follow-up was 29 months. The median cycle length and percentage of time off therapy for the IAD group were 9.0 months and 59.5, respectively. The estimated 3-year androgen-independent disease rate was significantly lower in the IAD group ($7.0\% \pm 4.8\%$) than in the CAD group ($38.9\% \pm 11.2\%$; log-rank $P = .0052$). The authors concluded that further studies with longer follow-up times and larger patient cohorts are needed to determine the comparative impact of CAD and IAD on survival. With such short follow-up and small numbers, it is unlikely that this difference between the arms in IAD rate will persist with further follow-up. Furthermore, if these results were not caused by chance, similar results would have been detected and announced by the data safety and monitoring boards of the two large ongoing studies discussed in the next section.

ONGOING CLINICAL TRIALS

Multiple ongoing Intergroup and single cooperative group studies are examining research questions gaps identified in this Guideline; these will be evaluated in future updates.

Two large studies are addressing the timing of ADT after radical radiation. The Timing of Androgen Deprivation is a multicenter, international randomized controlled trial coordinated by the Trans-Tasmanian Radiation Oncology Group that opened in 2004. ELAAT (Early v Late Androgen Ablation Trial) is a multicenter, Canadian randomized controlled trial coordinated by the Canadian Urologic Oncology Group (CUOG) and the Ontario Clinical Oncology Group (OCOG) opened in March 2007.

Two large Intergroup studies of intermittent versus continuous androgen therapy have yet to be reported. The Southwest Oncology Group (SWOG 9346) study for M1 disease is still open and accruing patients (SWOG is the lead group and participating groups include the National Cancer Institute [INT-0162], National Cancer Institute of Canada Clinical Trial Group [NCI Canada's PR8 and JPR8], EORTC Genito-Urinary Tract Cancer Group [EORTC 30985], Cancer and Leukemia Group B [CLB-9594], and Eastern Cooperative Oncology Group [E-59346]). For patients with a rising PSA post-definitive therapy without distant metastases, NCI Canada's PR7 has reached its accrual goals, and the first analysis is planned for 2013. Participating groups included SWOG (JPR7), and the Clinical Trials Service Unit of the National Cancer Institute.

All of the above ongoing studies include quality of life as an outcome measure.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being

evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** D. Andrew Loblaw, Astra Zeneca; Nicholas J. Vogelzang, Sanofi Aventis; Charles L. Bennett, Sanofi, Millenium **Stock:** N/A **Honoraria:** D. Andrew Loblaw, Astra Zeneca; James Talcott, Dendreon; Maryellen Taplin, Astra Zeneca; Nicholas J. Vogelzang, Astra Zeneca **Research Funds:** D. Andrew Loblaw, Astra Zeneca; Nicholas J. Vogelzang, Astra Zeneca; Charles L. Bennett, Amgen, Sanofi **Testimony:** N/A **Other:** D. Andrew Loblaw, Astra Zeneca, Sanofi-Aventis

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Acknowledgment

We thank Melissa Brouwers, the late Chris Desch, MD, and other members of the ASCO Health Service Committee for thoughtful comments on an earlier draft of the Update.

Appendix

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ERRATA

The July 20, 2007, article by Gish et al, entitled “Phase III Randomized Controlled Trial Comparing the Survival of Patients With Unresectable Hepatocellular Carcinoma Treated With Nolatrexed or Doxorubicin” (J Clin Oncol 25:3069-3075, 2007) contained an error. Jennifer Knox (Princess Margaret Hospital, Toronto, Canada) was inadvertently omitted from the author list.

The Author Contribution section and the Authors’ Disclosures of Potential Conflicts of Interest section are correct as published. The corrected author list is reprinted below in its entirety.

Robert G. Gish, Camillo Porta, Lucian Lazar, Paul Ruff, Ronald Feld, Adina Croitoru, Lynn Feun, Krzysztof Jeziorski, John Leighton, **Jennifer Knox**, José Gallo, and Gerard T. Kennealey

The online version has been corrected in departure from the print.

DOI: 10.1200/JCO.2007.14.0137



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In the Guidelines Recommendations section, the heading for subsection 4 referred to SDT, whereas it should have been ADT, as follows:

“Does Early **ADT** Improve Outcomes Over Deferred Therapy?”

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