2007 Update of ASCO Practice Guideline for the Initial Hormonal Management of Androgen-Sensitive Metastatic, Recurrent, or Progressive Prostate Cancer: Guideline Summary

Context

The ASCO Metastatic Prostate Cancer Expert Panel convened to update the practice guideline for hormone management of androgen-sensitive, advanced prostate cancer.¹ The guideline was originally published in 2004.² The Panel performed an updated literature review and analysis of data published since January 2003 through March 2006. The 2007 update features new evidence using a Markov probability model and delta method to inform the guideline update.

Updated 2007 Recommendations

The 2007 update addresses the most appropriate initial hormonal interventions for metastatic, progressive, or recurrent androgen-sensitive prostate cancer for men in whom androgen-deprivation therapy (ADT) is considered the best treatment approach. See Table 1 for a complete summary of the updated 2007 recommendations.

Standard Initial Treatment Options

Medical or surgical castration is the standard initial treatment approach for patients with advanced androgen-sensitive disease. Bilateral orchiectomy slows the progression of prostate cancer and carries with it the added benefits of rapid palliation, automatic patient compliance, and relative low costs. However, removal of the testes is naturally traumatic for some patients, often causing significant psychological burdens, though only minor risk of surgical complications (eg, wound infection, hematoma, and pain). Toxicities associated with bilateral orchiectomy include hypotestosteronemia, weight gain, mood lability, gynecomastia, fatigue, lassitude, cognitive changes, and loss of libido. Long-term castrate levels of testosterone also can induce osteopenia and hypercholesterolemia. The use of luteinizing hormone–releasing hormone (LHRH) agonists is a medical form of castration that many men opt for in lieu of orchiectomy. Evidence has shown that testosterone levels reach the castrate range within 3 to 4 weeks after the first LHRH agonist injection. This palliation approach is more expensive, but it is less emotionally taxing than orchiectomy. Diethylstilbestrol has been evidenced to show significant cardiovascular toxicities and is not recommended for hormonal management of men with advanced prostate cancer. This drug is no longer commercially available in North America.

Antiandrogens' Effectiveness Compared With Other Castration Therapies

Antiandrogens are classified as either steroidal (cyproterone acetate and goserelin acetate) or nonsteroidal (bicalutamide, flutamide, and nilutamide). A meta-analysis of eight clinical trials comparing antiandrogens with standard initial treatment options revealed that nonsteroidal antiandrogens (NSAA) as single agents have equivalent overall survival compared to orchiectomy. Adverse events reported with the use of NSAA include gynecomastia, breast pain, and hepatotoxicity. Health-related quality of life determinations comparing patients taking NSAA monotherapy with those opting for surgical or medical castration revealed greater sexual interest and physical capacity in the NSAA groups. There was no significant survival difference between diethylstilbestrol and cyproterone acetate, though the former showed greater cardiovascular adverse effects. Cyproterone acetate, while generally well-tolerated, is associated with liver toxicity when used long term. Quality data on overall survival and cause-specific survival for steroidal antiandrogens are, as yet, unavailable.

Combined Androgen Blockade Relative to Castration Alone

An interim analysis of a randomized controlled trial and a study employing the delta method 95% CI procedure for active controlled trials and meta-analysis inform the combined androgen blockade (CAB) recommendation. Though the interim analysis follow-up period was too short to accept the results as definitive, patients receiving LHRH agonist in combination with bicalutamide experienced significantly less disease progression than patients receiving monotherapy. Using the delta method (ie, a deductive reasoning methodology used to attribute intervention effectiveness in controlled trials), the Prostate Cancer Trialists' Collaborative Group estimated a bicalutamide CAB potential median survival advantage of 1.25 years. Though the hypothesized survival advantage reported by the group would need at least 10 years to be validated by a sufficiently powered clinical trial, it is, however, significantly cheaper than the newer systemic therapies and has minimal additional toxicity over castrate therapies alone. Though bicalutamide offers a once-daily dosing, it is still more expensive than the other NSAAs (flutamide and nilutamide), and it may not be covered by health insurance.

Table 1. Summary of Recommendations

Treatment	Recommendation
Standard initial treatment options	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 currently is no longer commercially available in North America.
Antiandrogen monotherapy	Nonsteroidal antiandrogen monotherapy may be discussed as an alternative, but steroidal antiandrogen monotherapy should not be offered.
Combined androgen blockade	Combined androgen blockade should be considered.
Early v deferred ADT	For patients with metastatic or progressive prostate cancer, there is a moderate decrease (17%) in RR for prostate cancer-specific mortality, a moderate increase (15%) in RR for nonprostate cancer-specific mortality, and no overall survival advantage for immediate institution of ADT v waiting until symptoms 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.
Intermittent androgen blockade	Currently, data are insufficient to support the use of intermittent androgen blockade outside of clinical trials.

Abbreviations: LHRH, luteinizing hormone-releasing hormone; DES, diethylstilbestrol; ADT, androgen-deprivation therapy; RR, relative risk; PSA, prostate-specific antigen.

Early ADT Outcomes Compared With Deferred Therapy

To address this question, the Panel categorized patients into three distinct groups: recurrent, progressive, and pathologic node-positive. Table 2 provides definitions of the groups. Data were not available to address immediate versus deferred

ADT for the recurrent group. The Panel noted that available clinical trials should be considered for these patients.

Evidence is mixed for patients with progressive prostate cancer. Of the five randomized controlled trials comparing immediate ADT versus deferred therapy, two trials reported survival advantages with the use of immediate ADT, and two did not. A meta-analysis of four trials reported a significant overall effect for prostate cancer survival associated with progressive disease patients receiving immediate ADT. However, none of the available studies incorporated prognostic factors used in today's clinical decision making, including prostate-specific antigen doubling time, Gleason score, prostate-specific antigen response, and patient age.

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is 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 this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it 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 and setting for which better therapy is needed. Because 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.

Table 2. Androgen-Sensitive Prostate Cancer Group Definitions

Term	Definition
Recurrent	Asymptomatic patients; rising PSA (sole manifestation of disease after radical treatment); non-castrate levels of testosterone
Progressive disease*	Detectable metastases on imaging study; not exposed to radical treatment; non-castrate levels of testosterone
Pathologic node-positive	Pathologic node-positive disease found at time of radical prostatectomy (disease has been completely resected)

Abbreviation: PSA, prostate-specific antigen.

* Also includes patients diagnosed with asymptomatic metastatic prostate cancer that progressed to metastatic disease while on watchful waiting.

Table 3. Ongoing Clinical Trials

Clinical Prospective	Trial Name	Description	Status
Timing of androgen-deprivation therapy after radical radiation	Timing of Androgen Deprivation (TOAD)	Multicenter, international, randomized controlled trial	Opened in 2004
	Early v Late Androgen Ablation Trial (ELAAT)	Multicenter, Canadian, randomized controlled trial	Opened in 2006
Intermittent v continuous androgen therapy	Southwest Oncology Group (SWOG 9346)	M1 disease study, multicenter	Open and accruing patients
	National Cancer Institute Canada (PR7)	Rising PSA, post-definitive therapy patients, multicenter	Reached accrual goals first analysis in 2013

NOTE. All studies include quality of life as an outcome measure.
Abbreviation: PSA, prostate-specific antigen.

Study results conflict regarding the benefits of early versus deferred ADT for pathologic node-positive prostate cancer patients. A recent meta-analysis found a moderate improvement in prostate cancer–specific mortality, but there was no improvement in overall mortality when patients received early ADT (due to a counterbalancing increase in nonprostate cancer–specific mortality).

Intermittent ADT or Continuous ADT

The Panel identified one randomized study for the 2007 update that analyzed the efficacy of intermittent androgen blockade. Early CAB was associated with significantly lower rates of 3-year androgen-independent disease. However, these results need to be supported by longer follow-up times and larger patient cohorts. Currently, two large intergroup studies are investigating intermittent versus continuous androgen therapy. Table 3 presents a list of ongoing clinical trials.

Methodology and Discussion

Including an updated literature analysis using systemic review protocols, the Panel used an evidence-based approach incorporating consensus by experts as the model used to create the recommendations within this guideline. Though no relevant additional data were identified to change or revise the recommendations for initial treatment or the effectiveness of

antiandrogens compared with other castration therapies, updated evidence informed the recommendations for CAB, as well as the timing and method of ADT.

Additional Resources

A full-text version of the guideline update was published in the April 20, 2007, issue of the *Journal of Clinical Oncology*.¹ Additional resources, including a patient guide, summary slide set, and treatment algorithm, can be accessed at www.asco.org/guidelines/asprostate. The patient guide for androgen-sensitive patients also is available on the People Living With Cancer Web site at www.plwc.org/patientguides.

ASCO 2007 Update for the Initial Hormonal Management of Androgen-Sensitive Metastatic, Recurrent, or Progressive Prostate Cancer Practice Guideline was developed and written by D. Andrew Loblaw, Katherine S. Virgo, Robert Nam, Mark R. Somerfield, Edgar Ben-Josef, David S. Mendelson, Richard Middleton, Stewart A. Sharp, Thomas J. Smith, James Talcott, Mary-Ellen Taplin, Nicholas J. Vogelzang, James L. Wade, Charles L. Bennett, and Howard I. Scher.

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