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ASCO SPECIAL ARTICLE

Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline Endorsement provides recommendations based on the review and analysis of the relevant literature in the Cancer Care Ontario Active Surveillance for the Management of Localized Prostate Cancer Clinical Practice Guideline. Additional information, which may include methodology and data supplements, slide sets, patient versions, frequently asked questions, and other clinical tools and resources, is available at www.asco.org/endorsements/ActiveSurveillance and www.asco.org/guidelineswiki.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

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ABSTRACT

Purpose

To endorse Cancer Care Ontario's guideline on Active Surveillance for the Management of Localized Prostate Cancer. The American Society of Clinical Oncology (ASCO) has a policy and set of procedures for endorsing clinical practice guidelines developed by other professional organizations.

Methods

The Active Surveillance for the Management of Localized Prostate Cancer guideline was reviewed for developmental rigor by methodologists. The ASCO Endorsement Panel then reviewed the content and the recommendations.

Results

The ASCO Endorsement Panel determined that the recommendations from the Active Surveillance for the Management of Localized Prostate Cancer guideline, published in May 2015, are clear, thorough, and based upon the most relevant scientific evidence. ASCO endorsed the Active Surveillance for the Management of Localized Prostate Cancer guideline with added qualifying statements. The Cancer Care Ontario recommendation regarding 5-alpha reductase inhibitors was not endorsed by the ASCO panel.

Recommendations

For most patients with low-risk (Gleason score ≤ 6) localized prostate cancer, active surveillance is the recommended disease management strategy. Factors including younger age, prostate cancer volume, patient preference, and ethnicity should be taken into account when making management decisions. Select patients with low-volume, intermediate-risk (Gleason 3 + 4 = 7) prostate cancer may be offered active surveillance. Active surveillance protocols should include prostate-specific antigen testing, digital rectal examinations, and serial prostate biopsies. Ancillary radiologic and genomic tests are investigational but may have a role in patients with discordant clinical and/or pathologic findings. Patients who are reclassified to a higher-risk category (Gleason score ≥ 7) or who have significant increases in tumor volume on subsequent biopsies should be offered active therapy.

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INTRODUCTION

Prostate cancer has the highest incidence rate of any cancer (233,000 men representing 27% of all new cases) and the fourth highest mortality rate (29,480 men representing 10% of all deaths resulting from cancer) in the United States, even when considering both sexes.[1] For this reason, there is great interest in defining optimum strategies for detection, treatment, and follow-up for this patient population. Even in the absence of a formal screening program,[2] prostate cancer is detected early in many cases, is indolent or nonprogressing, and is unlikely to cause morbidity or mortality.[3] To avoid the harms associated with unnecessary treatment, active surveillance (AS) is an option for patients with prostate cancer that is less likely to cause mortality. In 2015, Cancer Care Ontario (CCO) published a Clinical Practice Guideline on Active Surveillance for the Management of Localized Prostate Cancer,[4] and the goal of this assessment was to determine whether to endorse that CCO guideline.

This American Society of Clinical Oncology (ASCO) endorsement reinforces the recommendations offered in the CCO guideline on Active Surveillance for the Management of Localized

Prostate Cancer[4] and acknowledges the effort put forth by CCO to produce an evidence-based guideline that informs practitioners who care for men with early-stage clinically localized prostate cancer (stages T1 and T2 and Gleason score ≤ 7).

The following are the five research questions on the role of AS in men with localized prostate cancer that were addressed in the original guideline as well as in this endorsement:

1. How does AS compare with immediate active treatments (e.g., RP, RT, brachytherapy, hormone therapy, cryotherapy, or high-intensity focused ultrasound) as a management strategy for patients with newly-diagnosed localized prostate cancer (T1 and T2; Gleason score ≤7)?
2. In patients with localized prostate cancer undergoing AS, which findings of the following tests predict increasing risk of reclassification to a higher-risk disease state? What are their test characteristics (i.e., positive and negative predictive values, sensitivities, specificities, and likelihood ratios)?
   - PSA kinetics (e.g., velocity or doubling time)
   - DRE
   - Imaging (e.g., magnetic resonance imaging [MRI] or ultrasound [US])
   - Prostate cancer antigen3 (PCA3)
3. In patients with localized prostate cancer undergoing AS, how does supplementation with 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) compare with no supplementation?
4. In patients with localized prostate cancer undergoing AS, how do clinical outcomes differ if treatment is managed by a: single doctor versus a multidisciplinary team of clinicians, urologist versus another oncologist (e.g., a radiation oncologist), university/teaching hospital versus a community or private clinic/hospital?
5. In patients with localized prostate cancer who are candidates for or who are undergoing AS, how does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the following factors:
   - AS protocol: order of and frequency of tests (PSA, DRE, imaging), and other test/clinical factors?
   - Care provider(s): single versus team of doctors; urologist versus other oncologist?
   - Care setting: clinic versus hospital?
   - Patient factors: clinical, psychosocial?
   - Social support: family or community?
   - Socioeconomic or geographic variables?

The original CCO Recommendations are provided in Table 1 and online at http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=325696.

OVERVIEW OF THE ASCO GUIDELINE ENDORSEMENT PROCESS

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodologic quality using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II instrument (see Methodology Supplement for more detail).

Disclaimer

The clinical practice guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. ("ASCO") to assist providers in clinical decision making. The information therein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider because the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of this information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, expressed or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising from or related to any use of this information or for any errors or omissions.

Guideline and Conflicts of Interest

The Endorsement Panel (Appendix Table A1, online only) was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy" found at www.asco.org/rwc). All members of the Endorsement Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speakers' bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationship. In accordance with the Policy, the majority of the members of the Endorsement Panel did not disclose any relationships constituting a conflict under the Policy.

ACTIVE SURVEILLANCE GUIDELINE FOR THE MANAGEMENT OF LOCALIZED PROSTATE CANCER

Clinical Questions and Target Population

The CCO guideline[4] addressed five research questions on the role of AS in men with localized prostate cancer. The five research

Table 1. Original CCO and ASCO Endorsement Research Questions, Recommendations, and Qualifying Statements

CCO Research Question	CCO Recommendation	CCO Qualifying Statement	ASCO Endorsement Recommendation	ASCO Qualifying Statement
RESEARCH QUESTION 1 How does AS compare with immediate active treatments (eg, RP, RT, brachytherapy, hormone therapy, cryotherapy, or high-intensity focused ultrasound) as a management strategy for patients with newly diagnosed localized prostate cancer (T1 and T2 and Gleason score ≤ 7)?	For patients with low-risk (Gleason score ≤ 6) localized prostate cancer, AS is the preferred disease management strategy.	It is known that there is heterogeneity within this population and therefore factors such as younger age, high-volume Gleason 6 cancer, and patient preference must be taken into account in this recommendation. Young patients (younger than age 55 years) with high-volume Gleason 6 cancer should be closely scrutinized for the presence of higher-grade cancer, and definitive therapy may be warranted for select patients.	For ***most*** patients with low-risk (Gleason score ≤ 6) localized prostate cancer, AS is the ***recommended*** disease management strategy.	It is known that there is heterogeneity within this population and therefore factors such as younger age, high-volume Gleason 6 cancer, patient preference, ***and/or African American ethnicity*** should be taken into account in this recommendation. Young patients (younger than age 55 years) with high-volume Gleason 6 cancer should be closely scrutinized for the presence of higher-grade cancer, and definitive therapy may be warranted for select patients. ***For patients with limited life expectancy (< 5 years) and low-risk cancer, watchful waiting may be more appropriate than AS.***
RESEARCH QUESTION 2 In patients with localized prostate cancer undergoing AS, which findings of the following tests predict increasing risk of reclassification to a higher-risk disease state? What are their test characteristics (ie, positive and negative predictive values, sensitivities, specificities, and likelihood ratios)? • PSA kinetics (eg, velocity or doubling time) • DRE • Imaging (eg, MRI or ultrasound) • Prostate cancer antigen 3	Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume, intermediate-risk (Gleason 3 + 4 = 7) localized prostate cancer, AS can be considered.	Patients with Gleason score 7/10 (3 + 4) being considered for AS should include only those men with focal Gleason pattern 4 pathology, accounting for ≤ 10% total tumor. Because of known interobserver variability associated with the identification of minor Gleason pattern 4 elements, prospective intradepartmental consultation with colleagues should be considered a cornerstone of quality assurance in this area. Because volume and distribution of disease in prostate biopsies are also selection criteria for AS, pathologists should use uniform methodology when assessing and reporting the extent of cancer involvement in biopsy cores, especially when dealing with discontinuously involved cores.	Active treatment (RP or RT) is ***recommended*** for ***most*** patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume, ***intermediate-risk*** (Gleason 3 + 4 = 7) localized prostate cancer, AS ***may be offered.***	Patients with Gleason score 7 (3 + 4) being considered for AS should include only those men with ***low-volume*** Gleason ***pattern 4 pathology, and/or age older than 75 years***. Because of known interobserver variability associated with the identification of minor Gleason pattern 4 elements, prospective intradepartmental consultation with colleagues should be considered a cornerstone of quality assurance in this area. ***For patients with limited life expectancy (< 5 years), watchful waiting may be more appropriate than AS.***
RESEARCH QUESTION 3 In patients with localized prostate cancer undergoing AS, how does supplementation with 5ARIs (eg, finasteride or dutasteride) compare with no supplementation?	Daily 5ARIs may have a role in men receiving AS.	It should be noted that the RCT had short follow-up of 3 years and detected no difference between groups in survival rate outcomes. Dutasteride is the only 5ARI that has been tested in an RCT. However, it is the opinion of the CCO Expert Panel that the evidence likely demonstrates a drug class effect and that finasteride may also have a role in men receiving AS. Although the US Food and Drug Administration has issued a warning about a possible low but increased risk for high-grade prostate cancer with the use of 5ARIs based on two RCTs that did not meet inclusion criteria for this guideline, it is the opinion of the CCO Expert Panel members that the benefits of 5ARIs outweigh the risks, and they can be prescribed to a patient undergoing AS as long as the patient is adequately informed about the risks and benefits of treatment. This is consistent with the Canadian Consensus Conference statement.	**Not endorsed.**	**Not endorsed.**

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Table 1. Original CCO and ASCO Endorsement Research Questions, Recommendations, and Qualifying Statements (continued)

CCO Research Question	CCO Recommendation	CCO Qualifying Statement	ASCO Endorsement Recommendation	ASCO Qualifying Statement
RESEARCH QUESTION 4 In patients with localized prostate cancer undergoing AS, how do clinical outcomes differ if treatment is managed by • A single physician versus a multidisciplinary team of clinicians? • A urologist versus another oncologist (eg, a radiation oncologist)? • A university or teaching hospital versus a community or private clinic or hospital?	The AS protocol should include the following tests: PSA test every 3 to 6 months, DRE every year, 12- to 14-core confirmatory TRUS biopsy (including anterior-directed cores) within 6 to 12 months and then serial biopsy a minimum of every 3 to 5 years thereafter. The AS protocol may include mpMRI. This is indicated when a patient's clinical findings are discordant with the pathologic findings, and it is useful in identifying occult cancers or changes indicative of tumor progression in patients at risk.	Decisions about frequency of biopsy need to take into consideration individual patient factors including age, risk of progression, comorbidities, and so on. The repeat biopsy frequency recommendation of a minimum of once every 3 to 5 years is based on the series reported by Klotz et al[5], which included 450 patients undergoing AS with a median follow-up of 6.8 years (range, 1 to 13 years). Overall survival rate was 78.6%. The 10-year prostate cancer actuarial survival rate was 97.2%. Compared with shorter repeat biopsy intervals, this recommended frequency potentially reduces the risk of complications that are associated with TRUS biopsy, including urosepsis, without negatively affecting outcomes. A shorter interval between biopsies may be reasonable in selected patients and should be at the discretion of the ordering physician in consultation with the patient. Serial biopsy should not continue past the age of 80 years. • The role of MRI in AS is evolving. Prospective multicenter trials reporting the utility of MRI on entrance into AS or in reclassification of disease risk are lacking. Single-center publications looking at all men undergoing biopsy have found that mpMRI can reclassify patients when combined with systematic biopsy by identifying tumor targets missed with systematic biopsy. • mpMRI is useful in identifying anterior and higher-volume tumors, and it is good for identifying findings that predict disease reclassification. Whether this should be performed on all patients or only on those in whom there is discordance between clinical findings such as PSA and DRE is an open question. However, being cognizant of both the high cost of mpMRI and its promise, it is recommended that when a patient's clinical findings are discordant with the pathologic findings, an mpMRI is indicated. When indicated, it may be considered at entry or during follow-up. • Discordant findings between a patient's clinical course and pathologic findings can include rapidly rising PSA, PSA density over 0.2, higher PSA than expected for prostate size, DRE abnormality, and very low PSA free:total ratio. Presence of these findings requires further investigation with mpMRI or earlier repeat biopsy.	The AS protocol should include the following tests: • A PSA test every 3 to 6 months • DRE ***at least*** every year • ***At least*** a 12-core confirmatory TRUS ***guided*** biopsy (including anterior-directed cores) within 6 to 12 months, and then serial biopsy every **2** to 5 years thereafter ***or more frequently if clinically warranted. Men with limited life expectancy may transition to watchful waiting and avoid further biopsies.***	The AS protocol may include ***ancillary tests that are still under investigation. These could include*** mpMRI ***and/or genomic testing***. ***mpMRI and genomic testing may be*** indicated when a patient's clinical findings are discordant with the pathologic findings and ***could be*** useful in identifying occult cancers or changes indicative of tumor progression in patients at risk. ***These tests may also be helpful when the decision regarding AS versus active treatment is uncertain (eg, in cases of low-volume Gleason 3 + 4). mpMRI should not be used as a replacement for rebiopsy.***

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Table 1. Original CCO and ASCO Endorsement Research Questions, Recommendations, and Qualifying Statements (continued)

CCO Research Question	CCO Recommendation	CCO Qualifying Statement	ASCO Endorsement Recommendation	ASCO Qualifying Statement
RESEARCH QUESTION 5 In patients with localized prostate cancer who are candidates for or who are undergoing AS, how does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the following factors: • AS protocol: order of and frequency of tests (PSA, DRE, imaging), and other test or clinical factors? • Care providers: single physician versus team of clinicians or urologist versus other oncologist? • Care setting: clinic versus hospital? • Patient factors: clinical or psychosocial? • Social support: family or community? • Socioeconomic or geographic variables?	For patients undergoing AS who are reclassified to a higher-risk category, defined by repeat biopsy showing Gleason score ≥ 7 and/or significant increases in the volume of Gleason 6 tumor, consideration should be given to active therapy (eg, RP or RT).	Because evidence to predict disease reclassification in prostate cancer was conflicting for PSA level and lacking for DRE and prostate cancer antigen 3 level, these were not included in the recommendation. This recommendation is based on a consensus of opinion of the CCO Expert Panel members.	For patients undergoing AS who are reclassified to a higher-risk category, defined by repeat biopsy showing Gleason score ≥ 7 and/or significant increases in the volume of Gleason 6 tumor, consideration should be given to active therapy (eg, RP or RT).	

Note. ASCO qualifying statements to the original CCO recommendations and qualifying statements appear in ***bold italics***. Abbreviations: 5ARI, 5-alpha reductase inhibitor; AS, active surveillance; CCO, Cancer Care Ontario; DRE, digital rectal examination; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate-specific antigen; RCT, randomized controlled trial; RP, radical prostatectomy; RT, radiotherapy; TRUS, transrectal ultrasound.

questions asked (1) How does AS compare with immediate active treatments (eg, RP, RT, brachytherapy, hormone therapy, cryotherapy, or high-intensity focused US) as a management strategy? (2) Which of the following tests predict increasing risk of reclassification to a higher-risk disease state: PSA kinetics, DRE, imaging, or PCA3? (3) How does supplementation with 5ARIs (eg, finasteride or dutasteride) compare with no supplementation? (4) How do clinical outcomes differ if treatment is managed by a single physician versus a multidisciplinary team of clinicians, a urologist versus another oncologist, or a university or teaching hospital versus a community or private clinic or hospital? and (5) How does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the AS protocol (eg, the order of and frequency of tests [PSA, DRE, imaging] and other test or clinical factors), care providers (single physician *v* a multidisciplinary team of clinicians; urologist *v* other oncologist), care setting (eg, clinic *v* hospital), patient factors (eg, clinical, psychosocial), social support (eg, family or community), and socioeconomic or geographic variables? The complete set of clinical questions and corresponding recommendations in the original CCO guideline are provided in Table 1. The target population for the CCO guideline is men with early-stage clinically localized prostate cancer (stages T1 and T2 and Gleason score $\leq$ 7).

Summary of the Active Surveillance for the Management of Localized Prostate Cancer Guideline Development Methodology

The CCO guideline[4] was developed by a working group that included experts in urology, pathology, radiation oncology, and research methodology. A systematic review of the literature, covering the years 1996 through 2013 was performed by using the Ovid MEDLINE and EMBASE databases. In addition, conference proceedings for the following were also searched for the years 2010 through 2012: ASCO Annual Meeting, ASCO Genitourinary Cancers Symposium, American Urological Association, European Association of Urology, Canadian Urological Association, and American Society for Radiation Oncology. Details of the search strategies and the study inclusion criteria and outcomes of interest are available at http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=325696.

The literature search identified 62 studies eligible for inclusion in the guideline. The CCO working group reviewed data from practice guidelines, systematic reviews, randomized controlled trials, and other comparative studies that reported on AS in males with newly diagnosed early-stage localized prostate cancer (stages T1 and T2 and Gleason score $\leq$ 7) that included 30 or more patients. The panel provided evidence-based recommendations for all clinical questions informed by expert consensus.

RESULTS OF THE ASCO METHODOLOGY REVIEW

The methodology review of the CCO guideline[4] was completed independently by two ASCO guideline staff members using the Rigour of Development subscale from the Appraisal of Guidelines for Research and Evaluation II instrument. Detailed results of the scoring for this guideline are available upon request to guidelines@asco.org. Overall, the Active Surveillance for the Management of Localized Prostate Cancer guideline scored 6.5 of 7, with a Rigour of Development score of 98%. The preliminary ASCO content reviewers of the Active Surveillance for the Management of Localized Prostate Cancer guideline, as well as the ASCO Endorsement Panel, found the recommendations well supported in the original guideline. Each section, including the guideline recommendations, the evidentiary base, the development methods, and external review process, was clear and well referenced in the systematic review.

This is the most recent information as of the publication date. For updates and the most recent information and to submit new evidence, please visit www.asco.org/endorsements/ActiveSurveillance and the ASCO Guidelines Wiki (www.asco.org/guidelineswiki).

METHODS AND RESULTS OF ASCO UPDATED LITERATURE REVIEW

ASCO guidelines staff updated the Active Surveillance for the Management of Localized Prostate Cancer literature search. The original CCO literature search strategy was rerun using MEDLINE on March 19, 2015 (for 2012 through February 2015). The search strategy can be found in the Data Supplement 1. The updated search yielded 634 records. After reviewing the title and abstract for each of these hits, 35 were ordered for full text review. Of these, none were retained for discussion.

RESULTS OF ASCO CONTENT REVIEW

The ASCO Endorsement Panel reviewed the Active Surveillance for the Management of Localized Prostate Cancer guideline and concurred that the recommendations are clear, thorough, and based on the most relevant scientific evidence in this content area and present options that will be acceptable to many patients. Overall, the ASCO Endorsement Panel agrees with the recommendations as stated in the guideline, with the minor qualifications discussed here.

DISCUSSION

The ASCO Endorsement Panel wants to highlight and qualify some of the statements from the Active Surveillance for the Management of Localized Prostate Cancer[4] guideline.

The distinction between AS and watchful waiting is important for clinical decision making. AS, which carries a curative intent and involves regular monitoring with PSA, DRE, and biopsy (see Recommendation 3), is appropriate for patients who have sufficient life expectancy[6] to benefit from active treatment if disease progression is detected. Note that calculation of life expectancy is based on a variety of individual factors and circumstances. A number of life expectancy calculators (eg, http://www.socialsecurity.gov/OACT/population/longevity.html) are available in the public domain; however, ASCO does not endorse any one calculator over another. For patients with a life expectancy of less than 5 years, watchful waiting (cessation of routine monitoring with treatment initiated only if symptoms develop) is appropriate and further reduces the issue of overtreatment in prostate cancer, including

THE BOTTOM LINE

Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

The American Society of Clinical Oncology (ASCO) endorses the Cancer Care Ontario (CCO) guideline on Active Surveillance for the Management of Localized Prostate Cancer, with qualifying statements (in ***bold italics***).

Guideline Questions

1. How does AS compare with immediate active treatments (e.g., RP, RT, brachytherapy, hormone therapy, cryotherapy, or high-intensity focused ultrasound) as a management strategy for patients with newly-diagnosed localized prostate cancer (T1 and T2; Gleason score ≤7)?
2. In patients with localized prostate cancer undergoing AS, which findings of the following tests predict increasing risk of reclassification to a higher-risk disease state? What are their test characteristics (i.e., positive and negative predictive values, sensitivities, specificities, and likelihood ratios)?
   - PSA kinetics (e.g., velocity or doubling time)
   - DRE
   - Imaging (e.g., magnetic resonance imaging [MRI] or ultrasound [US])
   - Prostate cancer antigen3 (PCA3)
3. In patients with localized prostate cancer undergoing AS, how does supplementation with 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) compare with no supplementation?
4. In patients with localized prostate cancer undergoing AS, how do clinical outcomes differ if treatment is managed by a: single doctor versus a multidisciplinary team of clinicians, urologist versus another oncologist (e.g., a radiation oncologist), university/teaching hospital versus a community or private clinic/hospital?
5. In patients with localized prostate cancer who are candidates for or who are undergoing AS, how does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the following factors:
   - AS protocol: order of and frequency of tests (PSA, DRE, imaging), and other test/clinical factors?
   - Care provider(s): single versus team of doctors; urologist versus other oncologist?
   - Care setting: clinic versus hospital?
   - Patient factors: clinical, psychosocial?
   - Social support: family or community?
   - Socioeconomic or geographic variables?

Target Population

Men with ***early*** clinically localized prostate cancer (stages T1 and T2 and Gleason score ≤ 7)

Target Audience

Clinicians and specialists providing care to patients with prostate cancer (ie, urologists, radiation oncologists, primary care physicians)

Methods

The ASCO Endorsement Panel was convened to consider endorsing the CCO guideline on Active Surveillance for the Management of Localized Prostate Cancer that was based on a systematic review of the medical literature. The ASCO Endorsement Panel considered the methodology used in the CCO guideline by considering the results from the Appraisal of Guidelines for Research and Evaluation II review instrument. The ASCO Endorsement Panel carefully reviewed the CCO guideline content to determine appropriateness for ASCO endorsement.

ASCO Key Recommendations for Active Surveillance for the Management of Localized Prostate Cancer

ASCO qualifying statements are presented in ***bold italics***. See Table 1 for the original CCO research questions and recommendations.

1. For ***most*** patients with low-risk (Gleason score ≤ 6) localized prostate cancer, AS is the ***recommended*** disease management strategy.

ASCO qualifying statement: It is known that there is heterogeneity within this population and therefore factors such as younger age, high-volume Gleason 6 cancer, patient preference, ***and/or African American ethnicity*** should be taken into account in this recommendation. Young patients (younger than age 55 years) with high-volume Gleason 6 cancer should be closely scrutinized

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THE BOTTOM LINE (CONTINUED)

for the presence of higher-grade cancer, and definitive therapy may be warranted for select patients. ***For patients with limited life expectancy (< 5 years) and low-risk cancer, watchful waiting may be more appropriate than active surveillance.***

2. Active treatment (RP or RT) is ***recommended*** for ***most*** patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume**,** ***intermediate-risk*** (Gleason 3 + 4 = 7) localized prostate cancer, AS ***may be offered.***

ASCO qualifying statement: Patients with Gleason score 7 (3 + 4) being considered for AS should include only those men with ***low-volume*** Gleason ***pattern 4 pathology and/or age older than 75 years.*** Because of known interobserver variability associated with the identification of minor Gleason pattern 4 elements, prospective intradepartmental consultation with colleagues should be considered a cornerstone of quality assurance in this area. ***For patients with limited life expectancy (< 5 years), watchful waiting may be more appropriate than AS.***

3. The AS protocol should include the following tests:

   - A PSA test every 3 to 6 months
   - DRE ***at least*** every year
   - ***At least*** **a** 12-core confirmatory transrectal ultrasound ***guided*** biopsy (including anterior directed cores) within 6 to 12 months, and then serial biopsy every ***2*** to 5 years thereafter ***or more frequently if clinically warranted***. ***Men with limited life expectancy may transition to watchful waiting and avoid further biopsies.***

The AS protocol may include ***ancillary tests that are still under investigation. These could include*** multiparametric MRI (mpMRI) ***and/or genomic testing. mpMRI and genomic testing may be*** indicated when a patient's clinical findings are discordant with the pathologic findings and ***could be*** useful in identifying occult cancers or changes indicative of tumor progression in patients at risk. ***These tests may also be helpful when the decision regarding AS versus active treatment is uncertain (eg, in cases of low-volume Gleason 3 + 4). mpMRI should not be used as a replacement for rebiopsy.***

4. For patients undergoing AS who are reclassified to a higher-risk category, defined by repeat biopsy showing Gleason score ≥ 7 and/or significant increases in the volume of Gleason 6 tumor, consideration should be given to active therapy (eg, RP or RT).

Additional Resources

More information, which may include Data and Methodology Supplements, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/ActiveSurveillance and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. A link to the Active Surveillance for the Management of Localized Prostate Cancer guideline can be found at http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=325696.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

biopsies which carry a small but nonzero risk of infection and hospitalization.[7]

AS is the recommended disease management strategy for low-risk prostate cancer. Older patients may start on AS, potentially transition to watchful waiting if there is no disease progression, and be able to avoid treatment altogether. However, the ASCO Endorsement Panel recognizes that there is disease heterogeneity, and select patients with low-risk prostate cancer may appropriately choose immediate treatment instead of AS, including patients who are younger, have high-volume Gleason 6 cancer,[8] and have African American ethnicity,[9] because these patients have a higher likelihood for disease progression during their lifetime. A potential drawback to AS is the use of more intensive treatments when cancer progresses. That is, RT for intermediate- or high-risk prostate cancer often involves concurrent androgen deprivation therapy or external beam RT with or without brachytherapy boost; patients who undergo RP with intermediate- or high-risk cancer may be more likely to need adjuvant RT. However, this needs to be balanced against the benefits of AS, including delaying treatment and associated short-term and long-term adverse effects, and decisions need to take patient preference into account.

Use of ancillary tests beyond DRE, PSA, and biopsy to improve patient selection or as part of monitoring in an AS regimen remains investigational. Although there is a potential for genomic tests[10-12] that use biopsy tissue to predict patients who are more rather than less likely to have disease progression and cancer-specific mortality and for multiparametric magnetic resonance imaging (mpMRI)[13] to guide biopsies to find more clinically aggressive disease,[14] prospective validation of these tests is needed to assess their impact on patient outcomes such as survival. Selective use of these ancillary tests in patients with discordant clinical and/or pathologic findings may be appropriate.

There is no clear role for 5ARIs in a routine AS regimen. 5ARIs such as finasteride and dutasteride block the conversion of testosterone to dihydrotestosterone.[15] A randomized trial compared dutasteride with placebo in 302 patients undergoing AS for low-

risk prostate cancer.[16] After 3 years of follow-up, there was no significant difference between the two groups with respect to pathologic disease progression (defined as increase in either disease volume and/or Gleason score; 29% dutasteride versus 33% placebo; $P = .079$).[17] There was also no difference in progression to Gleason 7 or higher disease. It should also be noted that 5ARIs significantly alter PSA kinetics, and clinical decisions regarding rebiopsy in patients taking these medications need to take this into account. Although the CCO guideline included a recommendation stating that daily 5ARIs may have a role in men receiving AS, the ASCO Endorsement Panel chose not to include this recommendation, because the evidence does not support the routine use of 5ARIs in this setting.

The ASCO Endorsement Panel was in agreement with the CCO guideline that there is currently insufficient evidence to make recommendations with regard to the personnel who should be responsible for the management of AS protocols. However, in the opinion of the ASCO Endorsement Panel, a multidisciplinary team approach should be taken when a change to active treatment is considered.

ENDORSEMENT RECOMMENDATION

ASCO endorses all but one recommendation from CCO's Active Surveillance for the Management of Localized Prostate Cancer[4] guideline published in the *Canadian Urological Association Journal*, with qualifying statements.

ADDITIONAL RESOURCES

More information, which may include a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/endorsements/ActiveSurveillance and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

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Appendix

Table A1. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement Panel Members

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