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Active Surveillance for the Management of Localized Prostate Cancer

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An assessment conducted in January 2019 deferred the review of Evidence-based Series (EBS) 17-9. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 17-9 is comprised of 3 sections. You can access the summary and full report here:

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: Development Methods, Recommendations Development, and External Review Process

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Table of Contents

Section 1: Guideline Recommendations ................................................................. 1
Section 2: Evidentiary Base .................................................................................. 12
Section 3: EBS Development Methods and External Review Process ....................... 45

List of Appendices

Appendix I: Details of the environmental scan ...................................................... 36
Appendix II: Complete search strategy .................................................................. 36
Appendix III: Details of the search for conference abstracts .................................... 37
Appendix IV: Details of the search for ongoing studies .......................................... 37
Appendix V1: Quality assessment for non-RCT study designs ............................... 38
Appendix V2: Quality assessment for diagnostic study designs ............................. 42
Appendix V3: Quality assessment for the included randomized controlled trial ......... 44
Appendix VI: Unpublished ongoing trials on active surveillance ........................... 44
Appendix VII: Members of the Working Group and Expert Panel ........................... 59
GUIDELINE OBJECTIVES

This guideline aims:

- To describe the role of active surveillance (AS) as a management strategy for patients with localized prostate cancer.
- To identify patients with prostate cancer that would most benefit from AS.
- To develop an evidence-based protocol for AS in localized prostate cancer and to identify the factors affecting the offer of, acceptance of, and adherence to AS.
- To understand the role of 5-alpha reductase inhibitors (5ARI) (e.g., finasteride and dutasteride) in patients with localized prostate cancer undergoing AS.
- To identify which physician is responsible for managing the AS protocol and if any other human resources required to offer AS (e.g., genitourinary pathologist, psychosocial specialist, etc.) would need specific training.

TARGET POPULATION

Men with clinically localized prostate cancer (stage T1 and T2, Gleason score ≤7).

INTENDED USERS

Clinicians and specialists providing care to patients with prostate cancer (i.e. urologists and radiation oncologists).

BACKGROUND

Prostate cancer is often a slowly progressive or nonprogressive indolent disease diagnosed at an early stage with localized tumours that are unlikely to cause morbidity or death (1). Standard active treatments for prostate cancer include radiotherapy (RT) or radical prostatectomy (RP). However, harms from overdiagnosis and overtreatment are a significant
concern and the risks of active treatment may outweigh the benefits in many patients, particularly those with low-grade disease. To address these concerns, AS is increasingly being considered as a management strategy to avoid or delay the potential harm caused by unnecessary radical treatment in those patients with prostate cancers that are unlikely to progress.

There are no published randomized controlled trials (RCTs) comparing AS to active interventions. Some of the evidence used in this guideline comes from trials comparing active intervention (such as RP) to watchful waiting (WW) or observation. AS differs from WW or observation in both intent and in the utilization of serial biopsy strategies. The intent of WW or observation is to avoid active intervention in patients with limited long-term survival expectancy by providing delayed noncurative therapy for patients who experience metastatic progression. Patients with Gleason ≤6 prostate cancer rarely experience metastatic progression on WW or observation and therefore the members of the Working Group and Expert Panel feel that the results from these trials give important natural history information and the results can be used to inform this guideline on AS.

The intent of AS is curative, allowing the option of active treatment for those patients on AS who are reclassified to higher risk or who show disease progression. AS involves regular follow-up testing for prostate-specific antigen (PSA), digital rectal examination (DRE), repeat prostate biopsy, and use of prostate imaging, when indicated. The goal of this strategy is to monitor cancers at low risk of future progression to select patients with occult cancers of higher grade and risk who require timely therapy, while maintaining surveillance on patients who remain classified as having low-risk cancers (1).

The majority of prostate cancers at low risk of future progression are the low-grade cancers which have the most favourable outcomes. The Gleason grading system is effective in predicting the biological behaviour and prognosis of these cancers. In combination with measurements of tumour extent, Gleason score is the most meaningful pathologic determinant of eligibility for AS protocols. Modifications to the Gleason scoring system in recent years have enabled the identification of more homogeneous, truly low-grade Gleason <6 prostate cancers (3). Pure Gleason 6 cancers defined according to these criteria showed lymph node metastases in only 0.48% of patients in a recent meta-analysis of 21960 RP specimens (4).

In Ontario, the selection of patients and the protocols used for AS vary across the province, and the importance of establishing a standardized protocol for AS has led to the development of these evidence-based recommendations. The term “low-risk” prostate cancer as used in this guideline is defined as the risk status for patients who have Gleason score ≤6, PSA <10, and ≤ stage T2A. The Working Group and Expert Panel have defined our target populations for AS recommendations by Gleason score ≤6 and also Gleason score 3+4.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

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

**Summary of Key Evidence for Recommendation 1**
- Eight noncomparative studies of low-risk patients undergoing AS reported prostate cancer survival rates of 100% (5-12) and another two noncomparative studies reported high prostate cancer survival rates of 97% (13) and 98% respectively (14).
- Studies comparing immediate RP with delayed RP in patients undergoing AS detected no significant differences in biochemical recurrence rate, positive surgical margins, extraprostatic extension (15-17), and risk of incurable cancer (18-19).

**Justification for Recommendation 1**
- High prostate cancer survival rates in several studies examining AS show that AS is a reasonable management strategy for patients with low-risk (Gleason score ≤6) prostate cancer.
- Clinical outcomes following immediate or delayed surgical treatment did not differ, suggesting that there is acceptably low risk associated with undergoing AS and delaying definitive therapy.
- The rate of adverse events is low in patients undergoing AS. The rate of harm due to adverse events from active treatments (RP, RT) is higher than with AS.

**Qualifying Statements for Recommendation 1**
- An RCT comparing RP with observation detected no significant difference between groups for prostate-cancer mortality rate and all-cause mortality rate after 12 years (20), and the two most commonly reported adverse events associated with AS, urinary incontinence and erectile dysfunction (19-22), are similarly reported in other studies of immediate active treatments (23, 24). Therefore AS does not present any new or different harm. However, management options including AS, RP and RT should only be undertaken after informed, shared decision-making consultation(s) with the patient.
- 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 (under age 55) 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.

**RECOMMENDATION 2**
Active treatment (RP or RT) is appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer.

**Summary of Key Evidence for Recommendation 2**
- In one noncomparative study of intermediate-risk patients undergoing AS, the prostate cancer survival rate was 100% (25).
- In one nonrandomized study comparing AS/WW versus RP versus RT, prostate cancer survival rates were similar at 95% versus 97% versus 96%, respectively (14).
- An RCT comparing RP with observation detected no significant difference between groups for prostate-cancer mortality rate and all-cause mortality rate after 12 years, including intermediate risk patients (20).

**Justification for Recommendation 2**
- Since prostate cancer survival rates in carefully selected intermediate-risk patients undergoing AS were similar to other active treatments, either AS or active treatments can be recommended in this group of patients.

**Qualifying Statements for Recommendation 2**
- 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 less than or equal to
10% total tumour. Due to 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 (26, 27). (January 2019 - A slight modification was made to Recommendation 2. See Musunuru HB, et al. J Urol. 2016 Dec;196:1651-8).

- Since 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. (26)

RECOMMENDATION 3
The AS protocol should include the following tests:
- PSA test every 3 to 6 months.
- DRE every year.
- 12- to 14-core confirmatory transrectal ultrasound (TRUS) biopsy (including anterior directed cores) within 6 to 12 months, then serial biopsy a minimum of every 3 to 5 years thereafter.

The AS protocol may include the following test:
- Multiparametric MRI (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 tumour progression in patients at risk.

Summary of Key Evidence for Recommendation 3
- All AS protocol studies included in this guideline utilized a PSA test. Six studies conducted PSA testing every 3 months (5,8,14-17), three studies conducted PSA tests every 3 months for 1 year (6,9,28), and eight studies conducted PSA tests every 3 months for 2 years (11,13,19,20,29-32). For studies following patients beyond 2 years, PSA testing was conducted every 6 months after the second year.
- Most included studies conducted a DRE as part of AS protocol. Sixteen studies conducted a DRE every 3 to 6 months (5-9,12-16,18-22,29,32,33).
- Most studies reporting their AS protocol conducted multicore (6- to 17-core) biopsies every 1 to 2 years (5,10,12,15-18,21,23,28-30,33-35). Five studies conducted multicore biopsies every 2 to 4 years (8,11,13,19,32).
- Multiparametric MRI has been shown to be a good predictor of disease reclassification (36,37). Multiparametric MRI also had a negative predictive value of 83% to 100% (38) in one study that used transperineal template mapping saturation biopsy as a reference standard, and which included patients with a PSA range of 0.9 to 29 (median 7). One study also showed mpMRI to be a predictor of high-risk disease in the AS context (37).

Justification for Recommendation 3
- This recommendation is consistent with the AS protocol presented in most of the studies reviewed for this guideline. Since most studies employed PSA testing, DRE, and biopsy, these can be considered the three most important components of an AS protocol.
- Although many studies reviewed here followed a repeat biopsy frequency of 1 to 2 years in their AS protocol, the study with the most mature cohort of patients undergoing AS (13) and two other studies opted for a repeat biopsy frequency of 2 to 4 years (8,11) and found similarly high prostate-cancer survival rates of 97% to 100%.
- Current evidence shows that PSA kinetics does not reliably predict disease stability or reclassification to higher risk state.
- Although one correlational study detected that patients from multidisciplinary clinics were more likely to receive AS than patients under the care of individual practitioners (39), there is insufficient evidence to address the factors affecting the offer of, acceptance of, and adherence to AS.

Qualifying Statements for Recommendation 3
- Decisions about frequency of biopsy need to take into consideration individual patient factors including age, risk of progression, comorbidities, etc. 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 (40), which included 450 patients on 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 (41,42), 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.
- The role of magnetic resonance imaging (MRI) in AS is evolving. Prospective multicentre trials reporting utility of MRI on entrance into AS or in reclassification of disease risk are lacking. Single-centre publications looking at all men undergoing biopsy have found that mpMRI can reclassify patients when combined with systematic biopsy by identifying tumour targets missed with systematic biopsy (38). Multiparametric MRI is useful in identifying anterior and higher volume tumours, and it is good in identifying findings that predict disease reclassification (36,37). Whether this should be done 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, a 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.

**RECOMMENDATION 4**

Daily 5-alpha reductase inhibitors may have a role in men on AS.

**Summary of Key Evidence for Recommendation 4**
- An RCT found that in men with very low-risk prostate cancer undergoing AS and followed for 3 years, daily dutasteride delayed disease reclassification (hazard ratio [HR], 0.62; confidence interval [CI], 0.43 to 0.89) and improved quality of life at 18 months (28).

**Justification for Recommendation 4**
- Evidence from a high-quality RCT detected a benefit for dutasteride administered to patients undergoing AS (28).
Qualifying Statements for Recommendation 4
- It should be noted that the RCT had short follow-up of 3 years and detected no difference between groups in survival rate outcomes (28).
- Dutasteride is the only 5ARI that has been tested in an RCT. However, it is the opinion of the Expert Panel that the evidence likely demonstrates a drug class effect and that finasteride may also have a role in men on AS.
- While the U.S. Food and Drug Administration (FDA) 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 (43), it is the opinion of the 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 risk and benefits of treatment. This is consistent with the Canadian Consensus Conference statement (44).

RECOMMENDATION 5
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 tumour, consideration should be given to active therapy (e.g., RP or RT).

Summary of Key Evidence for Recommendation 5
- Based on RCTs of treatment versus observation, the patients who benefitted most from therapy had Gleason 7 and higher prostate cancer volume (20,46).

Justification for Recommendation 5
- Gleason score is a widely used disease classification measure and biopsy is the gold standard for measuring the status of disease. Thus Gleason 7 (4+3 pattern or 3+4 with Gleason pattern 4 pathology accounting for \( > 10\% \) total tumour) is the recommended indicator for disease reclassification to higher risk in prostate cancer.
- The most commonly reported active treatments received by patients on AS who were reclassified to higher risk were RP and RT (5-7,9-13,21,45).
- Although clear biopsy criteria for defining progression of high volume Gleason 6 disease have not been established, it is the consensus of the Expert Panel members that increasing volume of Gleason 6 tumour is an indicator of disease progression and of the need to consider active treatment. It is the consensus of the members of the Expert Panel that patients on AS with Gleason 7 disease on repeat biopsy can be considered for continued AS provided that Gleason pattern 4 accounts for \( \leq 10\% \) of total tumour.
- Prospective intradepartmental consultation should be encouraged as an important quality assurance activity for Gleason score interpretation (27).

Qualifying Statements for Recommendation 5
- An RCT comparing RP to WW found that RP reduced the risk of distant metastases and reduced prostate cancer mortality rates (46).
- In six studies, 17% to 31% of patients undergoing AS were reclassified to a higher risk group over time (8-15,45).
- In 11 studies, 14% to 42% of patients undergoing AS received active treatment because of disease reclassification to higher risk, anxiety, patient choice, or another reason (5-13,19,45).
- Since evidence to predict disease reclassification in prostate cancer was conflicting for PSA level and lacking for DRE and prostate cancer antigen3 (PCA3) level, these were not included in the recommendation. This recommendation is based on a consensus of opinion of the Expert Panel members.

FURTHER QUALIFYING STATEMENTS
Currently, there is insufficient evidence to make recommendations with regard to the personnel who should be responsible for the management of AS protocols. However, patients should have access to a multidisciplinary consultative approach when a change to active treatment is considered.

FUTURE RESEARCH
Although a National Cancer Institute trial has previously shown that RCTs comparing AS with immediate active treatments for prostate cancer are difficult to conduct because of insufficient patient accrual (ClinicalTrials.gov registration number: NCT00499174), RCTs would still provide the best evidence on which to base clinical recommendations. Should RCTs become available in the future, these Guideline Recommendations may change. Every few years, the PEBC conducts a review and assessment of its guidelines to update the evidence and any new relevant studies identified will be taken into consideration to evaluate whether these Guideline Recommendations are still valid.
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REFERENCES


INTRODUCTION
Prostate cancer is the most common cancer affecting men in Canada and in 2012, the Canadian Cancer Society estimated that 41% of cases (N=10900) would be diagnosed in Ontario alone (1). Prostate cancer is typically a slowly progressive indolent disease with most cases diagnosed at an early stage with low-risk localized tumours that are unlikely to cause death (2).

The current practice for treating localized prostate cancer in Ontario for low- or intermediate-risk patients is external beam radiation therapy (RT) or radical prostatectomy (RP), with brachytherapy as another alternative for low-risk patients, and active surveillance (AS) as an option for low-risk or favourable-prognosis intermediate-risk patients. With many available options, the choice of treatment is often at the physician’s discretion. However due to the slow-growing nature of the disease, harms from overdiagnosis and overtreatment are a concern and risks may outweigh benefits of active treatment. Some of the adverse events linked to surgical and radiation treatments are urinary incontinence, erectile dysfunction, and impotence (3). To alleviate concerns about these potential harms and risks, observational management strategies such as watchful waiting (WW) and AS are options; both allow patients to avoid unnecessary radical treatment, thereby minimizing adverse events.

WW predates AS and although the terms (along with other synonyms such as conservative management, expectant management, and deferred treatment) are sometimes used interchangeably in the medical literature, they are actually different, as explained in Table 1. Historically, WW was more common before the era of prostate specific antigen (PSA) testing, where patients were followed-up only when symptoms arose (4-6). AS, which evolved from WW, employs regular follow-up testing for PSA, digital rectal examination (DRE), prostate imaging, and repeat biopsy, to detect disease progression before symptoms appear so that if treatment becomes necessary, patients can be referred to appropriate care in a timely fashion (2).

<table>
<thead>
<tr>
<th>Table 1. Differences between watchful waiting and active surveillance</th>
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<td><strong>Purpose and intent</strong></td>
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<tr>
<td>- Palliative disease management strategy that initiates</td>
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interventions to relieve symptoms of disease progression when disease progresses

| Eligibility criteria | 1. Any-stage nonmetastatic prostate cancer, allows for PSA >10 ng/mL and includes men with more chronic illness  
2. Suitable for older men or those who cannot receive curative treatment due to comorbidity  
3. Stage T1c to T2a low risk clinically localized prostate cancer, PSA <10 ng/mL, Gleason score ≤6  
4. Suitable for men with indolent disease |  
| Follow-up protocol | 1. Passive follow-up strategy; follow-up only when symptoms arise  
2. Regular, multifactorial follow-up with PSA, DRE, prostate imaging, and repeat biopsy |  
| Indicators for treatment | 1. Development of symptoms such as urinary obstruction, pain or bony fractures  
2. Disease progression measured by increased Gleason score ≥7, faster PSA doubling time (<3 years), or increased extent of disease on biopsy |  

Abbreviations: DRE = digital rectal exam; PSA = prostate specific antigen  
References: (2, 7, 8)

In Ontario, the practice of AS varies across the province and the importance of establishing a standardized protocol for AS has led to the development of this three-part clinical practice guideline. For this guideline, AS will be defined as a management strategy for prostate cancer with a curative intent that includes a multifactorial patient follow-up after diagnosis, usually comprised of PSA testing, DRE, prostate imaging, and biopsy. It is only when the results of these follow-up tests indicate a reclassification of disease to a higher-risk state that the course of treatment changes.

In order to make clinical practice recommendations, a working group comprised of two urologists, two pathologists, one radiation oncologist, and one methodologist within the Active Surveillance Guideline Development Group developed this evidentiary base upon which the recommendations are based. Based on the guideline objectives in Section 1, the Working Group derived the research questions outlined below.

**RESEARCH 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 antigen (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?

METHODS

This evidentiary base was developed using a planned two-stage method, summarized here and described in detail below.

1. Search and evaluation of existing practice guidelines and systematic reviews:
   - Practice guidelines: If one or more existing practice guidelines that address the guideline objectives are identified, then clinical recommendations from those guidelines could be considered for adaptation into our guideline.
   - Systematic reviews: If one or more systematic reviews of reasonable quality that address the research questions are identified, they could form the core of the evidentiary base.

2. Systematic review of the primary literature: This review would focus on the areas not covered by existing reviews if identified and accepted.

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Search for Existing Practice Guidelines and Systematic Reviews

The search for existing practice guidelines and systematic reviews on AS that could be incorporated into this guideline began with an environmental scan of 12 databases from
various guideline organizations and cancer agencies, as detailed in Appendix I. Identified practice guidelines considered for their clinical recommendations were assessed for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool (9). Identified systematic reviews considered for the evidence base were assessed for quality using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool (10). Identified guidelines or reviews with important deficiencies in quality were not incorporated in our guideline and were not further described or discussed, but were reported in the reference list.

Systematic Review of Primary Literature

If a suitable guideline or review was found from the environmental scan, a systematic review of the primary literature would have been conducted to update the evidence from the identified guideline or review. Since no existing guidelines or reviews were found suitable for incorporating into our guideline, the evidence base was established by carrying out a systematic review of the primary literature. Databases of published studies, conference abstracts, and ongoing studies were searched and reference lists of relevant articles were scanned.

Literature Search Strategy

No existing guidelines or reviews from the environmental scan were suitable for incorporating into our guideline; therefore our evidence was gathered by searching the primary literature using the following strategy.

Using the OVID interface, one large broad-based literature search was conducted on the MEDLINE and EMBASE databases to gather the entire pool of relevant full-text studies published from 1996 to September 2013 that might address all research questions. Evidence was allocated to question based on different study selection criteria. The search strategy used was similar to that used by a recent review (8) and is detailed in Appendix II. The main search keywords were “active surveillance,” “watchful waiting,” “conservative management,” “expectant management,” “deferred treatment,” and “prostate cancer.” The following six conference proceedings from years 2010 to 2012 were searched for relevant abstracts: American Society of Clinical Oncology (ASCO) Annual Meeting, ASCO's Genitourinary Cancers Symposium, American Urological Association (AUA), European Association of Urology (EAU), Canadian Urological Association (CUA), and American Society for Radiation Oncology (ASTRO). Ongoing studies were identified by searching three online databases: clinicaltrials.gov, cancer.gov, and eortc.org. Search terms and details for conference abstracts and ongoing studies can be found in Appendices III and IV, respectively.

Study Selection Criteria

For full-text publications, the eligible study types for our evidence base were: practice guidelines, systematic reviews, randomized controlled trials (RCTs), and other comparative studies. As explained in a previous section, “Search for Existing Practice Guidelines and Systematic Reviews,” practice guidelines and systematic reviews were considered for the possibility that their clinical recommendations or evidence base could be incorporated into our guideline. Included studies from all systematic reviews were individually assessed to see if they would meet our inclusion criteria. For conference abstracts, only RCTs reporting complete analyses were eligible for inclusion. More details and any exceptions to these inclusion criteria are described in the next subsection, “Inclusion Criteria.”
Inclusion Criteria

Each of the five research questions in this guideline had different study inclusion criteria as described below.

For Q1, the primary research question on the effectiveness of AS, cohort and other noncomparative studies with a population size of n≥30 were also considered for inclusion given that the members of the Guideline Development Group knew from a recent systematic review that no published comparative studies about AS were available (2, 8). The target population was men with newly diagnosed early-stage localized prostate cancer (stage T1 and T2 and Gleason score ≤7). Studies had to evaluate AS and report clinically meaningful outcomes including but not limited to prostate-cancer specific survival rate (PCS) or mortality rate, overall survival rate (OS) or all-cause mortality, morbidity, disease progression or reclassification, quality of life, adverse events, receipt of active treatment and outcomes of that treatment in patients who received it.

For Q2, the research question on the factors that predict reclassification of disease to a higher-risk state, the inclusion criteria was diagnostic studies that evaluated PSA, DRE, MRI or US imaging, and PCA3 marker against the gold standard of biopsy. The target population was men with localized prostate cancer (stage T1 and T2 and Gleason score ≤7) undergoing AS. Studies had to report diagnostic outcomes including sensitivities, specificities, positive (PPV) and negative predictive values (NPV) or likelihood ratios (LRs).

For Q3, the research question on 5ARIs and AS, only RCTs were included. The target population was men with localized prostate cancer (stage T1 and T2 and Gleason score ≤7) undergoing AS. RCTs had to compare AS plus 5ARI (e.g., finasteride or dutasteride) with AS alone and report the same clinically meaningful outcomes as those listed in the inclusion criteria of Q1.

For Q4, the research question on the type of clinician or clinical setting for management of AS, studies had to compare the management of men with localized prostate cancer (stage T1 and T2 and Gleason score ≤7) undergoing AS by one clinical setting or care provider (e.g., doctor, specialist, clinician, or other human resource) with a different type of clinical setting or care provider and report the same clinically meaningful outcomes as those listed in the inclusion criteria of Q1.

For Q5, the research question on the factors that affect the offer, receipt, or choice of treatment, and adherence to or compliance with AS, there were two subsets of inclusion criteria. (i) Studies had to compare one patient, clinical, environmental, or other factor with a different factor and evaluate their association with the treatment chosen or received in men with localized prostate cancer (stage T1 and T2 and Gleason score ≤7) who were candidates for undergoing AS. (ii) Studies had to compare one factor with a different factor and evaluate their association with continuing AS, stopping AS, or changing to another treatment, in men with localized prostate cancer already undergoing AS.

Exclusion Criteria

The following exclusion criteria were applied to the entire literature search:

- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Studies on cost-effectiveness, utility, and economics.
- Studies about diet and lifestyle factors and high-risk prostate cancer.
- Studies published in a language other than English, due to the lack of funding and resources for translation.
Study Selection Protocol
A review of the titles and abstracts that resulted from the search was done independently by one reviewer (RT). For those items that warranted full-text review, RT reviewed each item. A subset of articles that did not provide clear descriptions on their observational management strategy was also reviewed by the clinical lead author (CM) to ensure that the articles were about AS.

Data Extraction and Assessment of Study Quality and Potential for Bias
Data from the included studies were independently extracted by RT. If more than one publication addressed the same study, only the most updated or recent version of the data was reported in the results. All extracted data and information were audited by an independent auditor (EK).

Quality assessment of included studies was based on important quality features such as study design, sample size, patient characteristics, length of follow-up, follow-up rate, support, and funding. For diagnostic study designs, additional quality features evaluated were gold standard, blinding, details of test administration, and outcomes. For RCTs, trial details and type of analysis, randomization method, statistical power, and blinding were also reported.

Synthesizing the Evidence
Since it was anticipated that few of the included studies would be trials or comparative studies, no data pooling or meta-analysis was planned. However, meta-analysis would have been considered if the found data was suitable, particularly for Q3 on 5ARIs and AS where a known RCT exists on the topic. Outcomes reported in each study are presented individually in the results section below.

RESULTS
Search for Existing Practice Guidelines and Systematic Reviews
Of 126 guidelines and 20 systematic reviews retrieved from the environmental scan, two documents on AS were identified. However, they were not incorporated into our guideline and therefore, no quality assessments were done. One was an ongoing unpublished guideline, titled “Active surveillance for prostate cancer,” by the CUA. The other was a 2011 systematic review by the Agency for Healthcare Research and Quality (AHRQ), “An evidence review of active surveillance in men with localized prostate cancer” (8) that did not address all the objectives in our guideline. Although the AHRQ’s research question on the effectiveness of AS was similar to our primary research question, the authors did not identify any studies comparing AS with immediate active treatments and then elected to evaluate comparative studies on WW and other observational strategies instead (8).

The members of our Working Group wanted the recommendations in this guideline to be based on actual AS studies and given the lack of comparative studies, they felt that it would be more meaningful to use an evidence base of noncomparative studies on AS than comparative studies on other observational strategies. Studies on WW are referenced in the introduction of our guideline because they are useful for understanding the natural history of prostate cancer and the origin of AS.

Primary Literature Systematic Review
The primary literature search yielded a total of 1982 articles from MEDLINE plus EMBASE after duplicates were removed, and 1068 conference abstracts to screen as summarized in Figure 1.
57 full text reports and 2 abstracts were retrieved from the primary literature search. Of these 59 references, 41 were relevant to Q1, seven were relevant to Q2, three were relevant to Q3, and eight were relevant to Q5. No studies were found that addressed Q4. The 4 systematic review articles found were used to identify individual studies that might meet our inclusion criteria.

Study Design and Quality

Details on the study design and quality assessment can be found in tables in Appendices V1 to V3. Most were prospective cohort studies (33%), followed by retrospective database or registry reviews (18%), case series or case control studies (18%), retrospective cohort studies (15%), and prospective database review (13%). One report compared two cohorts from different studies (11) and one RCT was found relevant to Q3 on the use of 5ARIs with AS (12).

Not all quality features were reported by all studies. Most studies had sample sizes of >100 patients and half of the studies had >80% follow-up or >80% patients included in the analysis. Only five studies reported median follow-up durations of >5 years (13-17). None of the diagnostic studies reported details about blinding. It should be noted that the noncomparative studies may be subject to potential biases including selection bias, performance bias, detection bias or reporting bias (18).

AS Protocol

Several studies reported details about their AS protocol as summarized in Table 1. Most AS protocols included PSA testing, DRE, and biopsy. Some studies also included transrectal ultrasound (TRUS) (15, 19-22) and clinical exam (17, 22, 23). For most studies, the frequency of PSA testing ranged from every 2 to 6 months, more frequently in the first two years and less frequently thereafter. DREs were conducted every three to six months. One study conducted PSA tests and DRE every two to four years (20, 21). Multicore (6 to 17-core) biopsies, with or without TRUS, were typically conducted every six months to one year and a few studies conducted repeat biopsies every two to 3 years after the first repeat biopsy (24-29).

One study compared biopsy using TRUS with transperineal prostate mapping (TPM) and found that TPM detected more cases of prostate cancer than TRUS biopsy did (85% versus 33%), and that TRUS biopsy missed 76% to 80% of clinically important cancer and missed multifocal prostate cancer in the anterior apex (30). Using TPM as the reference standard, TRUS biopsy had a sensitivity of 9% to 24%, specificity of 88% to 100%, PPV of 50% to 100% and NPV of 23% to 60% for detecting different classifications of clinically important disease (30).
# Table 1. AS protocols in different studies

<table>
<thead>
<tr>
<th>Reference(s)</th>
<th>Sample size</th>
<th>PSA test</th>
<th>DRE</th>
<th>Biopsy</th>
<th>Other details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleshner N. et al. 2012 (12)</td>
<td>302</td>
<td>Every 3mo for 1y, then every 6mo</td>
<td>At screening, 18mo and 3y</td>
<td>12-core TRUS biopsy at 18mo and 3y, or upon abnormal PSA/DRE</td>
<td>No other details</td>
</tr>
<tr>
<td>Choo R. et al. 2002 (41) (13, 31-41)</td>
<td>450</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>8- to 14-core biopsy at 6 to 12mo, then every 3 to 4y</td>
<td>Definitive intervention offered if PSAdt &lt;3y, Gleason &gt;4+3, or clinical progression</td>
</tr>
<tr>
<td>Kravchick S et al. 2011 (14)</td>
<td>48</td>
<td>Every 3mo</td>
<td>Every 3mo</td>
<td>TRUS biopsy every 18mo or upon abnormal PSA/DRE</td>
<td>No other details</td>
</tr>
<tr>
<td>Roemeling S. et al. 2006 (15)</td>
<td>64 (WW), 136 (RP), 91 (RT)</td>
<td>Every 3mo for 1y, then every 6mo</td>
<td>Every 3mo for 1y, then every 6mo</td>
<td>Sextant biopsy upon abnormal PSA/TRUS/DRE</td>
<td>TRUS was also done but no details provided</td>
</tr>
<tr>
<td>Stattin P. et al. 2010 (16)</td>
<td>8304</td>
<td>Every 3mo</td>
<td>Every 3mo</td>
<td>NR</td>
<td>No other details</td>
</tr>
<tr>
<td>Seiler D. et al. 2012 (17)</td>
<td>61 had RP (from 283 AS patients)</td>
<td>Every 6mo</td>
<td>NR</td>
<td>TRUS biopsy every 1y</td>
<td>Physical exam every 6mo</td>
</tr>
<tr>
<td>Dall'Era M. et al. 2010 (19)</td>
<td>33 had delayed RP (from 233 AS patients), 278 had immediate RP</td>
<td>Every 3mo</td>
<td>Every 3mo</td>
<td>12-core biopsy every 12 to 24mo</td>
<td>TRUS every 6 to 12mo</td>
</tr>
<tr>
<td>van den Bergh R. et al. 2009 (20, 21)</td>
<td>Every 2 to 4y</td>
<td>Every 2 to 4y</td>
<td>Sextant to 10- to 12-core biopsy upon abnormal PSA/TRUS/DRE</td>
<td>TRUS every 2 to 4y</td>
<td></td>
</tr>
<tr>
<td>Grimaldi J. et al. 2002 (22)</td>
<td>8 had RP (from 38 offered radical treatment out of 200 AS patients)</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>TRUS biopsy at 12 to 18mo</td>
<td>Clinical exam every 3mo for 2y, then every 6mo</td>
</tr>
<tr>
<td>Ischia J. et al. 2012 (23)</td>
<td>154</td>
<td>Every 3mo</td>
<td>Every 6mo</td>
<td>6- to 17-core biopsy at 12 to 18mo, then every 3y</td>
<td>Clinical exam every 6mo</td>
</tr>
<tr>
<td>Ercole B. et al. 2008 (24)</td>
<td>40</td>
<td>Every 3 to 6mo</td>
<td>Every 6 to 12mo</td>
<td>Repeat TRUS biopsy every 2y or upon abnormal PSA/DRE</td>
<td>No other details</td>
</tr>
<tr>
<td>Bul M. et al. 2012 (25, 26)</td>
<td>2494</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>Every 6mo for 2y, then every 1y</td>
<td>8- to 12- core, volume dependent biopsy at 1, 4, 7y or every 1y if PSAdt =3 to 10y</td>
<td>Radical treatment offered upon reclassification to higher risk</td>
</tr>
<tr>
<td>Finelli A. et al. 2011 (27)</td>
<td>288</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>Every 6mo</td>
<td>6-16 core biopsy at 1y, then every 2-3y or upon abnormal PSA/DRE</td>
<td>No other details</td>
</tr>
<tr>
<td>Radomski L. et al. 2012 (28)</td>
<td>443</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>Every 6mo</td>
<td>6- to 16-core biopsy at 1y, then every 2 to 3y or upon abnormal PSA/DRE</td>
<td>No other details</td>
</tr>
<tr>
<td>Ng M. et al. 2008</td>
<td>NR</td>
<td>Every 1 to 3mo for 1y, NR</td>
<td>Octant TRUS biopsies at 18 to 24mo</td>
<td>No other details</td>
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<tr>
<td>Study</td>
<td>Follow-up</td>
<td>Biopsy Schedule</td>
<td>Other Details</td>
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<tr>
<td>Patel M. et al. 2004 (42)</td>
<td>Every 3mo for 1y, then every 6mo</td>
<td>Sextant TRUS biopsy at 6 mo or upon abnormal PSA/DRE</td>
<td>RP or RT offered upon progression or request</td>
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<tr>
<td>Tosoian J. et al. 2011 (43-48)</td>
<td>Every 6mo</td>
<td>12- to 14-core TRUS biopsy every 1y</td>
<td>RP or RT offered upon progression</td>
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<tr>
<td>Soloway M. et al. 2010 (49, 50)</td>
<td>Every 3 to 4mo for first 2y, then every 6mo</td>
<td>10- to 12-core TRUS biopsy after 9 to 12mo, then every 1y or upon abnormal PSA/DRE</td>
<td>No other details</td>
<td></td>
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<tr>
<td>Hilton J. et al. 2012 (51)</td>
<td>Done but no details given</td>
<td>Biopsy every 12 to 18mo</td>
<td>No other details</td>
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<tr>
<td>Fujita K. et al. 2009 (52)</td>
<td>Every 6mo</td>
<td>10- to 12-core TRUS biopsy every 1y</td>
<td>No other details</td>
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<tr>
<td>Warlick C. et al. 2006 (53)</td>
<td>Every 6mo</td>
<td>Biopsy every 1y</td>
<td>Surgery offered if abnormal biopsy</td>
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<tr>
<td>Iremashvili V. et al. 2012 (54)</td>
<td>Every 3 to 4mo</td>
<td>Biopsy at 1y and then every 1 to 2y or upon abnormal PSA/DRE</td>
<td>Active treatment recommended upon progression</td>
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<tr>
<td>Sugimoto M. et al. 2010 (55)</td>
<td>Every 2mo for 6mo, then every 3mo</td>
<td>NR</td>
<td>Aggressive treatment recommended if PSAdt ≤2y</td>
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<tr>
<td>Zhang L. et al. 2006 (56)</td>
<td>Every 3mo for 2y, then every 6mo</td>
<td>NR</td>
<td>No other details</td>
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<tr>
<td>Stephenson A. et al. 2002 (57)</td>
<td>Every 3 to 6mo</td>
<td>Sextant biopsy every 1y</td>
<td>No other details</td>
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</tbody>
</table>

AS = active surveillance; DRE = digital rectal exam; mo = month(s); NR = not reported; PSA = prostate specific antigen; PSAdt = PSA doubling time; RP = radical prostatectomy; RT = radiation therapy; TP = total prostatectomy; TRUS = transrectal ultrasound; WW = watchful waiting; y = year(s)
**Outcomes**

Due to studies being either noncomparative or heterogeneous, pooled meta-analyses were not conducted. Studies were assessed individually. Similarly, only one RCT was found for the topic of 5ARIs and AS and therefore, no meta-analysis was done.

**Survival Rate**

Rates for OS, PCS, and treatment-free survival (TFS) in different studies can be found in Table 2. OS rates ranged from 68% to 100% in patients undergoing AS. One study showed that patients remaining on AS and patients who eventually received active treatment did not significantly differ for OS (13). PCS rates were generally higher than OS rates as most studies reported PCS rates of 100%. The hazard ratio (HR) for non-PC to PC mortality was 18.6 at 10 years and the risk of non-PC mortality was higher in men >70 years of age compared with men <70 years of age (HR 33.3 vs versus 8.76) (13). TFS rates were lower than PCS and OS rates and ranged from 77% to 85% at 2 years, 58% to 86% at 5 years, and 41% to 62% at 10 years.

In one study that analyzed a group of intermediate-risk (Gleason score 7) patients, OS was 68%, PCS was 100%, and TFS at 6 years was 59% (21). In another study that compared AS/WW with RP and with RT in intermediate-risk patients, PCS rates were 94.8%, 96.6%, and 96.2% respectively (16).
Table 2. Survival rate, disease progression, and active/deferred treatment in patients undergoing AS

<table>
<thead>
<tr>
<th>Reference*</th>
<th>OS (95%CI)</th>
<th>PCS (95%CI)</th>
<th>TFS</th>
<th>Disease progression or reclassification</th>
<th>Reasons for progression or reclassification</th>
<th>Receipt of active treatment</th>
<th>Reasons for active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz L 2012 (13)</td>
<td>79% 68% (62% to 74%) at 10y</td>
<td>97% at 10y</td>
<td>84% at 2y 72% at 5y 62% at 10y</td>
<td>30%</td>
<td>14% short PSAdt 8% Gleason upgrade 1% upstaged 0.9% volume progression</td>
<td>30% Of which, 26% RP 67% RT 7.4% HT</td>
<td>48% short PSAdt 27% Gleason upgrade 4% upstaged 3% volume increase 10% patient choice</td>
</tr>
<tr>
<td>Kravchick S et al. 2011 (14)</td>
<td>88%</td>
<td>100%</td>
<td>46% at mean 78.9mo</td>
<td>Unclear</td>
<td>25% PSA rose &gt;30% 10% Gleason upgrade 8% had more positive cores</td>
<td>42% Of which, 55% RP 25% RT 20% CB</td>
<td>50% Gleason upgrade, positive cores, PSA increase, or changes on DRE</td>
</tr>
<tr>
<td>Roemeling S. et al. 2006 (15)</td>
<td>86% 91% at 5y 85% at 8y</td>
<td>100% at 5y and 99% at 8y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>30% at median 40mo Of which, 10% RP 58% RT 21% HT 10% BT</td>
<td>PSA increase</td>
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<tr>
<td>Stattin P. et al. 2010 (16)</td>
<td>AS/WW 77% (74% to 79%) at 10y</td>
<td>AS/WW 97.6% (95.9% to 98.8%) at 10y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>van den Bergh R. et al. 2009 (20)</td>
<td>91% 77% at 10y</td>
<td>99.8% 100% at 10y</td>
<td>43% at 10y</td>
<td>Unclear</td>
<td>9.4% PSA &gt;10ng/mL 15% PSAdt &lt;3y</td>
<td>32% at mean 2.55y Of which, 43% RP</td>
<td>17% tumour changes on DRE</td>
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<td>Study</td>
<td>5-year</td>
<td>10-year</td>
<td>5-year</td>
<td>10-year</td>
<td>Events</td>
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<td>Ischia J. et al. 2012 (23)</td>
<td>99%</td>
<td>100%</td>
<td>62%</td>
<td>45%</td>
<td>17% Upstaged</td>
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<td>• 12% BT</td>
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<tr>
<td>Ercole B. et al. 2008 (24)</td>
<td>88%</td>
<td>100%</td>
<td>74%</td>
<td>NR</td>
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<td>• 33% RT</td>
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<td>• 22% HT</td>
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<td>PSA increase</td>
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<td>Gleason upgrade</td>
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<td>Anxiety</td>
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<tr>
<td>Bul M. et al. 2013 (26)</td>
<td>99%</td>
<td>100%</td>
<td>77%</td>
<td>68%</td>
<td>28% Upstaged</td>
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<td>• 21% Gleason upgrade</td>
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<td>• 51% positive cores</td>
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<td>• 28% had both</td>
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<td>• 21% at median 1.6y</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 48% RP</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 5% RT</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 1.5% HT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 0.8% HIFU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>73% Gleason upgrade</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>or positive cores, or PSA increase or changes on DRE/TRUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9% anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel M. et al. 2004 (42)</td>
<td>100%</td>
<td>100%</td>
<td>58%</td>
<td>41%</td>
<td>25% at median 44mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Gleason upgrade</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 35%</td>
<td></td>
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<td>Of which,</td>
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<td></td>
<td></td>
<td></td>
<td>• 55% RP</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 42% RT</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55% Gleason upgrade, volume increase, positive cores, PSA increase or</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>changes on DRE/TRUS</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22% anxiety</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22% had both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tosoian J. et al. 2011 (43)</td>
<td>98.2%</td>
<td>100%</td>
<td>81%</td>
<td>59%</td>
<td>31% Upstaged</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 45% Gleason upgrade</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 55% positive cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 33% at median 2.2y</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<td>Of which,</td>
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<td></td>
<td></td>
<td></td>
<td>• 50% RP</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• 50% RT</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26% patient choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74% Gleason upgrade or positive cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soloway M. et al. 2010 (49)</td>
<td>NR</td>
<td>NR</td>
<td>86%</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 14% at mean 33 mo</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Of which,</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 38% TP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 44% RT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 19% HT</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>26% patient choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74% Gleason upgrade or positive cores</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results from the most recent reference of each study are shown

AS = active surveillance; BT = brachytherapy; CB = cryoablation; DRE = digital rectal exam; HIFU = high intensity focused ultrasound; HT = hormone therapy; mo = month(s); NR = not reported; OS = overall survival rate; PCS = PC-specific survival rate; PSA = prostate specific antigen; PSAdt = PSA doubling time; RP = radical prostatectomy; RT = radiation therapy; TFS = treatment-free survival rate (likelihood of remaining on AS); TP = total prostatectomy; TRUS = transrectal ultrasound; WW = watchful waiting; y = year(s)

Comorbidity
Only one study reported on the comorbidity of patients after receiving AS. Compared with baseline, 32% more AS patients had increased comorbidity by a Charlson Comorbidity Index score ≥1 (14).

Disease Progression and Receipt of Active/Deferred Treatment
The proportion of patients whose disease progressed and the proportion that received active treatment are given in Table 2. In six studies, 17% to 31% of patients on AS had their disease reclassified to a higher risk group after some time (13, 23, 26, 42, 43, 58). The reasons for disease reclassification included upgraded Gleason score, upstaging, volume progression, rising PSA, faster PSA doubling times, and increasing number of positive cores.

In 11 studies, 14% to 42% of patients undergoing AS moved on to receive active treatment, whether because of disease reclassification, anxiety, patient choice, or other reasons (13-15, 20, 23, 24, 26, 42, 43, 49, 58). Most AS patients who moved on to active treatments received RP, RT, and/or hormone therapy (HT). Of patients receiving treatment, 10% to 68% had RP (13-15, 20, 23, 24, 26, 42, 43, 49, 58) 5% to 67% had RT (13-15, 20, 24, 26, 42, 43, 49, 58), and 1.5% to 22% had HT (13,15,20-26,49,58) In two studies, 9% and 20% of patients had both RT and HT (23, 58). Some of the less common active treatments were brachytherapy (23), cryoablation (14), and high-intensity focused ultrasound (HIFU) (26). More outcomes related to AS patients who moved on to have RP and RT are described in their own subsections below.

In a study reporting results for only intermediate-risk patients, 30% of them eventually moved on to receive active treatment, of which 20% had RP, 53% had RT, and 27% had HT (21). Another study reported that 42% of patients in the intermediate-risk group were eventually treated but treatment types were not specified (13).

Outcomes in AS Patients who Moved on to Receive RP
Several studies reported post-AS outcomes of patients who had RP and these are summarized in Tables 3 and 4. Four studies compared delayed RP with immediate RP and Table 3 shows the three that reported similar outcomes. Of those three studies, two found that more patients in the delayed RP group had a Gleason score upgrade than patients in the immediate RP group (54, 55). Patients in the delayed RP and immediate RP groups did not significantly differ for biochemical recurrence rate, positive surgical margins, and extraprostatic extension. The fourth study reported that the risk of noncurable cancer associated with delayed and immediate RP did not significantly differ (adjusted relative risk [RR] 1.08, confidence interval [CI] 0.55 to 2.12) (53).

### Table 3. Non randomized comparison of outcomes in patients having delayed versus immediate RP

<table>
<thead>
<tr>
<th>Reference</th>
<th>Groups</th>
<th>Gleason score upgrade</th>
<th>Biochemical recurrence rate (PSA failure)</th>
<th>Positive surgical margins</th>
<th>Extraprostatic extension (nonorgan confined disease)</th>
</tr>
</thead>
</table>

Section 2: Evidentiary Base
The studies in Table 4 were noncomparative studies of patients on AS who moved on to have RP. Two studies reported Gleason score upgrading after RP (25, 42). In four studies, there was no biochemical recurrence in AS patients who had RP (23, 24, 42, 49), whereas in three studies, biochemical recurrence rates ranged from 3.8% to 8.6% (20, 43, 58), and another study reported a 38% biochemical recurrence rate (13). Five studies reported positive surgical margins in 5.8% to 50% of patients (17, 22, 25, 42, 48). In six studies, the proportion of patients with extraprostatic extension ranged from 0% to 38% (15, 17, 22, 25, 42, 48). Four studies reported that 2.1% to 12% of patients had seminal vesicle invasion (17, 22, 42, 48) and four studies reported that 0% to 12% of patients had lymph node invasion (17, 22, 25, 48).

**Table 4. Post-RP outcomes in patients on AS who moved on to have RP**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Gleason score upgrade</th>
<th>Biochemical recurrence rate (PSA failure)</th>
<th>Positive surgical margins</th>
<th>Extraprostatic extension (nonorgan confined disease)</th>
<th>Seminal vesicle invasion</th>
<th>Lymph node invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz L 2012 (13)</td>
<td>NR</td>
<td>38% at 5y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Roemeling S. et al. 2006 (15)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Seiler D. et al. 2012 (17)</td>
<td>Unclear</td>
<td>NR</td>
<td>31%</td>
<td>13%</td>
<td>8.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>van den Bergh R. et al. 2009 (20)</td>
<td>NR</td>
<td>8.6% at median 3.4y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Grimaldi J. et al. 2002 (22)</td>
<td>NR</td>
<td>NR</td>
<td>50%</td>
<td>38%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Ischia J. et al. 2012 (23)</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ercole B. et al. 2008 (24)</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bul M. et al. 2012 (25)</td>
<td>31%</td>
<td>NR</td>
<td>24%</td>
<td>19%</td>
<td>NR</td>
<td>0%</td>
</tr>
<tr>
<td>Patel M. et al 2004 (42)</td>
<td>41%</td>
<td>0%</td>
<td>5.8%</td>
<td>18%</td>
<td>5.8%</td>
<td>NR</td>
</tr>
<tr>
<td>Tossoian J. et al. 2011 (43)</td>
<td>NR</td>
<td>4.2%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Duffield A. et al. 2009 (48)</td>
<td>NR</td>
<td>NR</td>
<td>15%</td>
<td>35%</td>
<td>2.1%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Soloway M. et al. 2010 (49)</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dall’Era MA. et al. 2008 (58)</td>
<td>NR</td>
<td>3.8% at 3y</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

AS = active surveillance; NR = not reported; PSA = prostate specific antigen; RP = radical prostatectomy; y = year(s)

**Outcomes in AS patients who Moved on to Receive RT**

Eight studies that reported post-AS biochemical recurrence rates in patients who had RT are summarized in Table 5. The proportion of patients with biochemical recurrence after
RT ranged from 0% to 57% (13, 14, 20, 23, 24, 42, 43, 58). One study reported a Gleason score upgrade after RT in one patient (14).

Table 5. Biochemical recurrence rate (PSA failure) in AS patients who moved on to have RT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Biochemical recurrence rate (PSA failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz L. et al. 2012 (13)</td>
<td>57% at 5y</td>
</tr>
<tr>
<td>Kravchick S et al. 2011 (14)</td>
<td>1 patient</td>
</tr>
<tr>
<td>van den Bergh R. et al. 2009 (20)</td>
<td>7.7% at median 4.4y</td>
</tr>
<tr>
<td>Ischia J. et al. 2012 (23)</td>
<td>0%</td>
</tr>
<tr>
<td>Ercole B. et al. 2008 (24)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Patel M. et al. 2004 (42)</td>
<td>7.7%</td>
</tr>
<tr>
<td>Tosoian J. et al. 2011 (43)</td>
<td>14.6%</td>
</tr>
<tr>
<td>Dall’Era MA. et al. 2008 (58)</td>
<td>0%</td>
</tr>
</tbody>
</table>

PSA = prostate specific antigen; y = year(s)

Adverse Events

The commonly reported adverse events in patients on AS were urinary incontinence and erectile dysfunction (28, 49, 52). Whereas serial biopsy was associated with erectile dysfunction in one study (52), another study reported no such association (51). One study reported more sexual activity in patients in the AS group compared with patients in the RP or RT treatment groups (P<0.001) (11).

A before-after comparison in one study found that before active treatment, 5.6% of AS patients had urinary incontinence whereas 29% had new-onset urinary incontinence after RP, and 2.4% had new-onset urinary incontinence after RT (28).

Beneficial Effect of 5ARIs on Patients Undergoing AS

One RCT compared patients undergoing AS with and without 5ARIs, specifically dutasteride at a dose of 0.5mg/d (12). The addition of dutasteride to the AS protocol significantly delayed time to progression at 3y (HR, 0.62; CI, 0.43 to 0.89), reduced disease progression at 18 months (HR, 0.56; 95% CI, 0.36 to 0.87). Groups did not significantly differ for adverse events. No RCTs were found for the other 5ARI, finasteride.

Predictors of Disease Reclassification to Higher Risk

Five studies evaluated PSA to predict disease reclassification in prostate cancer and the sensitivities, specificities, PPV, NPV, and accuracy of each are presented in Table 6. For PSA there was a wide range of sensitivities (38% to 100%), specificities (49% to 90%), PPVs (33% to 76%) and NPVs (78% to 85%) for disease progression (29, 46, 56, 57). One study concluded that PSA was not reliable for predicting adverse pathology (47). Another study reported that both PSA velocity (p<0.001) and PSA doubling time (p=0.019) were associated with adverse histology, but PSA velocity was more accurate than PSA doubling time (29).

Table 6. PSA studies that predicted risk for disease progression or reclassification

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disease progression (reclassification)</th>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ng M. et al. 2009 (29)</td>
<td>27% at 18 to 24mo</td>
<td>PSAdt at different thresholds</td>
<td>38% to 70%</td>
<td>49% to 78%</td>
<td>33% to 38%</td>
<td>78% to 82%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA velocity at different thresholds</td>
<td>38% to 75%</td>
<td>51% to 89%</td>
<td>36% to 56%</td>
<td>80% to 85%</td>
<td>NR</td>
</tr>
<tr>
<td>Khan L. et al. 2003</td>
<td>25.4% at 1st repeat biopsy</td>
<td>PSA velocity, % free PSA, and</td>
<td>65% for detecting</td>
<td>90% for detecting</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
One study evaluated MRI to predict disease reclassification and found that MRI did not detect cancer in 38% of patients while MRI and biopsy were concordant in 40% of patients (59). In this study, 32.1% of patients were reclassified and when no cancerous lesion was identified, MRI reclassified 3.5% of patients (59). MRI had a sensitivity of 55% (CI, 43 to 67), specificity of 95% (CI, 82 to 99), PPV of 83% (CI, 73 to 93), and NPV of 81% (CI, 71 to 91) for disease reclassification (59).

No studies were found that evaluated DRE or the PCA3 marker and reported diagnostic outcomes for disease reclassification.

After reviewing the already-included studies that met the criteria for other research questions, it was found that two studies also evaluated the predictors of disease reclassification or progression by using univariate or multivariate analysis. Since the assessment of disease reclassification is an important component of AS, the results of these two studies are reported in Table 7. Baseline PSA was found to predict disease reclassification/progression in both studies but conflicting results were found for some of the other factors including number of positive cores and PSA density (26, 42). Both studies found that clinical stage did not predict reclassification or progression (26, 42).

Table 7. Studies identified post hoc that used univariate or multivariate analysis to report factors that predicted disease reclassification or progression

<table>
<thead>
<tr>
<th>Reference</th>
<th>Analysis</th>
<th>Predictors of disease reclassification or progression</th>
<th>Factors not associated with reclassification or progression</th>
</tr>
</thead>
</table>
| Bul M. et al. 2013 (26) | Multivariate | • PSA density (OR, 2.5; CI, 1.9 to 3.4)  
• 2 positive cores (OR, 2.1; CI, 1.7 to 2.7)  
• PSAdt <3y (OR, 1.7; CI, 1.3 to 2.3) and 3-10y (OR, 1.3; CI, 1.01 to 1.7)  
• PSA at baseline (OR, 0.9; CI, 0.84 to 0.96)  
• Age at baseline (OR, 1.02; CI, 1.0 to 1.04) | • Total biopsy cores  
• Clinical stage T2 |
| Patel M. et al. 2004 (42) | Univariate | • Positive biopsy (p=0.004)  
• PSA at baseline (p=0.01) | • Clinical stage  
• Number of positive cores  
• PSAdt  
• Gleason score at baseline  
• PSA density at baseline |

CI = 95% confidence interval; OR = odds ratio; p = p-value; PSA = prostate specific antigen; PSAdt = PSA doubling time; y = year(s)
Factors that Affect Adherence or Compliance of Patients Undergoing AS

One study found that men who had greater anxiety were less likely to continue AS than men who were less anxious (p<0.01) (60). Another study found that men on AS taking 5ARIs were more likely to continue AS than men on AS alone (p=0.006) (27).

Factors that Affect the Offer of AS, Receipt of AS, or the Choice to Undergo AS

Several patient factors including older age (61-63), obesity (Body Mass Index >35kg/m²) (64), unmarried status, and fewer positive cores were found to be significantly associated with the choice to undergo AS over other active treatments, (61). One study found that patients from multidisciplinary clinics were more likely to choose AS than patients under the care of individual practitioners (61). The offer and receipt of AS were also shown to be associated with older age, lower tumour stage, lower grade, lower Gleason score (62, 65) and increased comorbidity (16, 61, 63).

While one study found that lower PSA was associated with receipt of AS (62), another study found no association (61). Factors not associated with receipt or choice of AS were ethnicity (61, 66), income, family history, and number of physicians seen (61).

No studies were found that evaluated the effects of the AS protocol, social support or geographic variables on the offer, receipt, or choice to undergo AS.

Effect of the Care Provider or Care Setting on Clinical Outcomes of AS

No studies were found that evaluated the association between type of care provider (e.g., physician, specialist, clinician, or other human resources) or clinical setting (e.g., hospital or clinic) and clinical outcomes of AS.

Ongoing, Unpublished, or Incomplete Studies

Three unpublished ongoing trials about AS were identified and are detailed in Appendix VI.

DISCUSSION

This systematic review did not find RCTs comparing AS with immediate active treatments (e.g., RP, RT, HT, etc.) for prostate cancer. The majority of included studies are noncomparative. One study reported survival rates in AS and immediate treatment patients from a registry (16). Unlike a previous systematic review on the same topic that opted to evaluate comparative studies of other observational management strategies for prostate cancer (2), this systematic review focused only on the noncomparative studies of AS. The members of the Working Group believe that it would be more meaningful to base recommendations on comparative AS studies.

From a methodological perspective, this means that the quality of existing evidence is considered weak. Understandably, the lack of comparative studies such as randomized controlled trials (RCTs) on AS may be attributed to AS being a newer management strategy, as well as the slow progressive nature of prostate cancer, which would give such studies a very long maturation time. Another reason would be the lack of participants in such trials, as demonstrated in the START trial (clinicaltrials.gov ID: NCT00499174) that was terminated early due to insufficient accrual, and in which many patients were unwilling to be randomized because of their preference to undergo AS. However, should RCTs become available in future, they would provide the best evidence for clinical recommendations in this field.

In clinical practice, AS is a management strategy for prostate cancer that has been applied to both low-risk and intermediate-risk patients. However, this systematic review did
not find many studies evaluating intermediate-risk patients as a separate group and thus, most of the existing evidence supports recommendations for low-risk patients.

Congruent with a recent review (2), survival rate outcomes from the studies included in this review indicated that prostate cancer mortality is rare and men are more likely to die of other causes. In support of the feasibility for an AS program in low-risk patients, the TFS rates in these studies were shown to be lower than PCS or OS rates. However, some patients eventually moved on to active treatment during the course of AS. The receipt of active treatment administered only when necessary logically minimized serious adverse events in these patients. These findings are consistent with the results of a study that reported survival rates in intermediate-risk patients (21).

The most common active treatments that AS patients received were RP, RT, and HT. Compared with immediate RP, AS patients who moved on to have delayed RP were more likely to have Gleason score upgrading, however, other post-RP outcomes did not significantly differ between groups. This suggests that there is fairly low risk associated with undergoing AS and waiting to have RP, further supporting an AS management strategy for low-risk prostate cancer. For post-RT outcomes, most of the noncomparative studies found that the rate of biochemical recurrence was fairly low.

The commonly reported adverse events in AS studies are urinary incontinence and erectile dysfunction (28, 49, 52). These are similarly reported in the literature for immediate active treatments such as RP (3, 67). It has also been reported that rates of urinary incontinence in AS patients are not different from those in patients receiving immediate active treatments (28).

No consistent AS protocol was found across the AS studies identified in this systematic review. Most studies included PSA testing, DRE, and multicore repeat biopsies in the AS protocol, however, the frequency of these tests varied from one study to another. One study challenged the current biopsy technique with a newer biopsy technique, TPM (30); however, more evidence would be needed before recommendations could be made to change the gold standard. The addition of dutasteride, a 5ARI, to the AS management strategy was found to be beneficial because it delayed disease progression, improved quality of life (12) and improved patient adherence to the AS protocol (27).

The development of an AS protocol should also take into account the measures that can predict disease progression or reclassification because such measures will help determine whether a patient should move on to receive active treatment. In this review, the results were conflicting as to whether PSA is a good measure of predicting disease progression/reclassification in prostate cancer. Differences were also found in the ability of different measures of PSA such as PSA velocity, PSA density, and PSA doubling time for predicting progression or reclassification (26, 29, 42, 46, 47, 56, 57). MRI was found to have a high yield in predicting disease reclassification; however, this is based on evidence from one study (59). No evidence was found for the ability of DRE and PCA3 to predict disease progression/reclassification.

Patients from multidisciplinary clinics were more likely to receive AS than patients under the care of individual practitioners (61) and this can be explained by the nature of AS: involving multifactorial follow-up and referrals to different doctors as necessary. A multidisciplinary clinic provides the convenient infrastructure for patients to access different types of care in one place. No studies were found that evaluated the effects of clinical setting or care provider on clinical outcomes of AS but should such studies be available in future, it would further support the advantage of a multidisciplinary clinic for care of patients with prostate cancer undergoing AS.

Another objective of this guideline was to see if any patient, clinical or socio-environmental factors were associated with the offer, receipt or choice of treatment for...
prostate cancer. Some patient factors that were associated with a patient’s choice to receive AS included lower tumour stage, lower grade, lower Gleason score (62, 65), and fewer positive cores (61). These factors are consistent with the profile of a patient at low risk for prostate cancer. Since WW and AS are management strategies that avoid immediate active treatment, it is not surprising that other factors such as older age (61-63), obesity (64), and baseline comorbidity (16, 61, 63), that are typically associated with the receipt of WW (2), were also associated with AS. One study reported an increase in comorbidity from baseline after the course of AS (14).

CONCLUSIONS

Although this systematic review does not provide the highest quality of evidence, due to the nature of prostate cancer as a slow progressive disease and to AS being a management strategy with few adverse events, the evidence is sufficient on which to base the recommendations for the province of Ontario in Section 1 for AS in patients at low risk for prostate cancer. Since AS is becoming a more common choice for prostate cancer management, and one that clinical practitioners are more commonly offering to their patients today, it is important to develop recommendations for a standardized protocol that can be applied consistently across the province.

Every few years, the PEBC conducts a review and assessment of its guidelines to update the evidence and any new relevant studies identified will be taken into consideration to evaluate whether the guideline recommendations are still valid.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

JOURNAL REFERENCE


ACKNOWLEDGEMENTS AND AUTHORSHIP

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• Janet Rowe for copy editing.

A complete list of the members of the Active Surveillance Guideline Development Group (Working Group and Expert Panel), with their affiliations and conflict of interest information, is provided in Section 3, Appendix VII.
REFERENCES


APPENDICES

Appendix I. Details of the environmental scan to identify practice guidelines and systematic reviews about active surveillance

<table>
<thead>
<tr>
<th>Database (Acronym)</th>
<th>Website URL</th>
<th>Date of search</th>
<th>Search Terms or Section Browsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standards and Guidelines Evidence (SAGE)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| cancerview.ca     | 12 Mar 2012           | • search 1  
|                    |                        | - title word: prostate  
|                    |                        | - ICG: genitourinary OR early stage OR adult OR active surveillance  
|                    |                        | • search 2  
|                    |                        | - title word: prostate AND active surveillance  
|                    |                        | • search 3  
|                    |                        | - title word: (localized OR localised) AND prostate cancer  
| National Guideline Clearinghouse |
| guideline.gov     | 13 Mar 2012           | • search: prostate active surveillance OR localized prostate cancer OR localized prostate cancer  
|                    |                        | • age: adult (19 to 44), middle age (45 to 64), aged (80+ )  
|                    |                        | • clinical specialty: urology  
|                    |                        | • sex: male  
| National Health and Medical Research Council (NHMRC), Australia |
| nhmrc.gov.au      | 13 Mar 2012           | search: prostate  
| Canadian Medical Association (CMA) Infobase |
| cma.ca            | 9 Mar 2012            | search, title word: prostate cancer  
| National Institute for Health and Clinical Excellence (NICE) |
| nice.org.uk       | 9 Mar 2012            | section: urogenital cancer  
| Scottish Intercollegiate Guidelines Network (SIGN) |
| sign.ac.uk        | 9 Mar 2012            | section: cancer  
| American Society of Clinical Oncology (ASCO) Guidelines |
| asco.org          | 9 Mar 2012            | section: genitourinary cancer  
| National Comprehensive Cancer Network (NCCN) |
| nccn.org          | 9 Mar 2012            | section: prostate cancer  
| New Zealand Guidelines Group (NZGG) |
| nzgg.org.nz       | 9 Mar 2012            | section: prostate cancer  
| Cochrane Database of Systematic Reviews |
| thecochranelibrary.com | 2012, issue 1 | section: health topics → cancer → prostate  
| Agency for Healthcare Research and Quality (AHRQ) evidence reports and technology reports |
| ahrq.gov          | 14 Mar 2012           | section: EPC evidence reports → topic index: A-Z  
| International prospective register of systematic reviews (PROSPERO) |
| www.crd.york.ac.uk/prospero | 13 Mar 2012 | search, title word: prostate AND cancer |

Appendix II. Complete search strategy for the primary literature systematic review

Database: EMBASE <1996 to 2012 week 37>, OVID MEDLINE(R) without revisions <1996 to September week 1 2012>, OVID MEDLINE(R) in-process and other nonindexed citations <September 14, 2012>

1. watchful waiting.mp.
2. active surveillance.mp.
3. conservative management.mp.
4. expectant management.mp.
5. deferred treatment.mp.
6. ((expectant$ adj5 manage$) or (expectant$ adj5 treatment) or (conservative$ adj5 manage$) or (active adj5 surveillance) or (watchful adj5 waiting) or (watch adj5 wait) or (watchful adj5 observation) or (active$ adj5 monitor$) or (defer$ adj5 treatment)).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. prostate cancer.mp. or exp Prostatic Neoplasms/
9. ((prostat$ adj5 neoplas$) or (prostat$ adj5 cancer$)).tw.
10. 8 or 9
11. 7 and 10
12. limit 11 to english language
13. limit 12 to yr="1987-current"
14. remove duplicates from 13

Appendix III. Details of the search for conference abstracts about active surveillance from 2010-2012

<table>
<thead>
<tr>
<th>Database (Acronym)</th>
<th>Website URL</th>
<th>Search terms or Section browsed</th>
</tr>
</thead>
</table>
| American Society of Clinical Oncology (ASCO) and ASCO’s Genitourinary Cancers Symposium via Journal of Clinical Oncology | jco.ascopubs.org | • search 1
  o title word: prostate AND cancer
  o title or abstract word: surveillance OR waiting OR observation OR expectant OR conservative
• search 2
  o title word: prostate AND active AND surveillance |
• section 7.8 Prostate Cancer: Nonsurgical Management of Localised Tumours (2011)
• section 7.8 Prostate Cancer: Nonsurgical Management of Localised Tumours (2010) |
| American Urological Association (AUA) via Journal of Urology | jurology.com | search, title word: prostate cancer AND (surveillance OR waiting OR observation OR expectant OR conservative OR monitor) |
| Canadian Urological Association (CUA) via CUA Journal | cuaj.ca | section: all meeting abstracts |
| American Society for Radiation Oncology (ASTRO) via International Journal of Radiation Oncology Biology Physics | redjournal.org | search, title word: prostate cancer AND (surveillance OR waiting OR observation OR expectant OR conservative OR monitor) |

Appendix IV. Details of the search for ongoing studies about active surveillance

<table>
<thead>
<tr>
<th>Database (Acronym)</th>
<th>Website URL</th>
<th>Date</th>
<th>Search terms</th>
</tr>
</thead>
</table>
| National Institutes of Health (NIH) | clinicaltrials.gov | 15 Mar 2012 | • condition: prostate cancer
• intervention: active surveillance OR watchful waiting OR observation OR expectant
• gender: male
• age: adult (18 to 65) OR senior (66+)

| National Cancer Institute (NCI) | cancer.gov | 13 Mar 2012 | • cancer type/condition: prostate
• stage/subtype: stage I prostate cancer OR stage II prostate cancer OR stage IIA prostate cancer OR stage IIB prostate cancer
• trial type: treatment
• keywords/phrases: active surveillance OR watchful waiting OR observation |
| European Organisation for Research and Treatment of Cancer (EORTC) | eortc.org | 13 Mar 2012 | title word: prostate |
### Appendix V1. Quality assessment for non-RCT study designs

<table>
<thead>
<tr>
<th>Reference*</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Baseline patient Characteristics</th>
<th>Length of Follow-up</th>
<th>Follow-up Rate</th>
<th>Funding and Support</th>
</tr>
</thead>
</table>
| van den Bergh R. et al. 2012 (11) | Comparison of 2 cohorts from different studies | 266 | • Mean age 65y  
• AS patients had Gleason 6, PSA ≤10ng/mL, stage ≤T2  
• RP or RT patients had Gleason 6 to 8 | Range 6 to 18mo | 38% to 100% response rate on questionnaire | PCRF |
| Klotz L. 2012 (13) | Prospective cohort | 450 | • 99% stage T1a-2c; 0.9% T3  
• Gleason 3 to 7  
• Median age 70y  
• Low- and intermediate-risk PC | Median 6.8y  
Range 1 to 16y | 100% accounted for | Prostate Cancer Canada |
| Kravchick S. et al. 2011 (14) | Prospective cohort | 48 | • Age 60 to 75y  
• Low-risk PC  
• Stage T1a-c  
• PSA ≤10ng/mL  
• Gleason ≤6 | Mean 81.1mo | NR | NR |
| Roemeling S. et al. 2006 (15) | Retrospective cohort | 64 (WW), 136 (RP), 91 (RT) | • Patients retrospectively met AS criteria  
• Mean age 68y  
• Stage T1c-2  
• Mean PSA 4.1ng/mL | Median 79.4mo  
Mean 80.8mo  
Range 6.8 to 129.8mo | 100% accounted for | DCS, NOHRD, EU, BCH |
| Stattin P. et al. 2010 (16) | Retrospective cohort | 8304 | • Low- or intermediate-risk PC, localized PC  
• Age ≤70y  
• Stage T1-2, N0/X, M0/X  
• Gleason ≤7  
• PSA ≤20ng/mL | Median 8.2y | 82.5% included in the analysis | Swedish Research Council, Swedish Cancer Foundation, Västerbotten County Council |
| Seiler D. et al. 2011 (17) | Case series | 61 had RP (from 283 AS patients) | • Age 49 to 72y  
• PSA 2.4-26ng/mL  
• Gleason 6 | For patients who had RP  
• Median 68.8mo  
• Range: 1 to 139mo | NR | Messerli Foundation, Horten Foundation, Aargau Cancer League, Swiss Cancer League, Health Department of Canton and Aargau, PCRF, Baugarten Foundation |
| Dall’Era M. et al. 2010 (19) | Case-control | 33 delayed RP (of 233 AS patients), 278 immediate RP | • Mean age 59y  
• Low-risk PC  
• Gleason 6  
• Stage cT1-2 | Postoperative follow-up  
• For delayed RP: median 12mo, range <1 to 60mo  
• For immediate | NR | NR |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>N</th>
<th>Characteristics</th>
<th>RP: median 27mo, range &lt;1 to 162mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>van den Bergh R. et al. 2009 Eur Urol. (20)</td>
<td>Retrospective study of 4 cohorts</td>
<td>616</td>
<td>Patients retrospectively met AS criteria</td>
<td>Mean 4.35y, Median 3.91y Range 0 to 11.63y</td>
</tr>
<tr>
<td>van den Bergh R. et al. 2009 BJU Int. (21)</td>
<td>Case series</td>
<td>50</td>
<td>Age 59 to 76y, Gleason 7 (88% 3+4; 12% 4+3), Stage T1c-2, PSA 5.7 ng/mL</td>
<td>Median 2.6y, IQR 0.8 to 5y, 86% included in the analysis</td>
</tr>
<tr>
<td>Grimaldi J. et al. 2002 (22)</td>
<td>Prospective cohort</td>
<td>8 had RP (from 38 offered radical treatment out of 200 AS patients)</td>
<td>Age 49 to 84y, Gleason ≤5-7, PSA 0.3 to 14.6ng/mL</td>
<td>NR</td>
</tr>
<tr>
<td>Ischia J. et al. 2012 (23)</td>
<td>Retrospective record review</td>
<td>154</td>
<td>Age 36 to 81y, Mean PSA 6.5ng/mL, 95% Gleason ≤5 to 7; 5% unknown</td>
<td>Median duration of AS 1.9y, Range 0.1 to 16.6y, 2 patients followed &gt;10y</td>
</tr>
<tr>
<td>Ercole B. et al. 2008 (24)</td>
<td>Retrospective case series</td>
<td>40</td>
<td>Stage T1c-2a, Gleason ≤6, PSA &lt;10ng/mL, Median age 68y</td>
<td>For 31 patients, Median duration of AS 48mo, Range 12 to 168mo, 100% accounted for</td>
</tr>
<tr>
<td>Bul M. et al. 2012 (25)</td>
<td>Prospective cohort</td>
<td>189 had RP (from 2079 AS patients)</td>
<td>Median age 63y, Median PSA 5.8ng/mL, Gleason ≤6, Stage T1c-2a</td>
<td>For those remaining on AS, Median 1.6y, Range 0.8 to 2.8y, 88.4%</td>
</tr>
<tr>
<td>Bul M. et al.</td>
<td>Prospective</td>
<td>2494</td>
<td>Median age 66y</td>
<td>Median 1.6y, 98.3%</td>
</tr>
</tbody>
</table>

Section 2: Evidentiary Base
<table>
<thead>
<tr>
<th>Year</th>
<th>Study Type</th>
<th>Cohort Details</th>
<th>Evidentiary Base</th>
</tr>
</thead>
</table>
| 2013 (26)  | cohort              | • Low-risk PC  
• Stage T1c-2  
• PSA ≤10ng/mL  
• Gleason ≤6 | • IQR 1 to 2.8y  
• Association |
| Finelli A. et al. 2011 (27) | Retrospective cohort | 288  
• Mean age 64y  
• Low-risk PC  
• Stage T1c-2a  
• Gleason ≤6  
• PSA <10ng/mL | • For men stopping AS, median 32.3mo (IQR 17.3 to 52.9mo)  
• For men continuing AS, median 43.2mo (IQR 25.2 to 60.9mo)  
69%  
None |
| Radomski L. et al. 2012 (28) | Cohort, data from retrospective records | 443  
• Age 40 to 80y  
• PSA 0.21 to 36ng/mL  
• Gleason 4 to 8 | NR  
NR  
NR |
| Patel M. et al. 2004 (42) | Retrospective review of a prospective database | 88  
• Stage T1a-2c, NX0, M0  
• Mean PSA 5.9ng/mL  
• Gleason 2 to 7  
• Mean age 65y  
• 88% low-risk PC; 12% intermediate-risk PC | • Median 44mo  
• Range 7 to 172mo  
98.9%  
NCI, Leon Lowenstein Foundation |
| Tosoian J. et al. 2011 (43) | Prospective cohort | 769  
• Age 45 to 92y  
• Stage T1c  
• Very low-risk PC | • Median 2.7y  
• Range 0.01 to 15y  
89.3%  
Patrick C Walsh Prostate Cancer Research Fund, Prostate Cancer Foundation |
| Duffield A. et al. 2009 (48) | Prospective cohort | 51 had RP  
(from 470 AS patients)  
• Age 52 to 70y | NR  
94% slides available for review for the RP cases  
NR |
| Soloway M. et al. 2010 (49) | Comparison of 2 cohorts, data from retrospective database | 230 (AS), 219 (TP)  
• Mean age 63y  
• Mean PSA 5.07ng/mL | • Mean 44mo  
• Median 32mo  
• Range 12 to 208mo  
100% accounted for  
none |
| Hilton J. et al. 2012 (51) | Retrospective record review | 427  
• Median age 61y  
• Stage T1c  
• Median PSA 5.2ng/mL  
• 93% Gleason 4 to 6; 7% Gleason 7 to 8 | • Median 3.2y  
• IQR 1.9 to 5.1y  
85%  
NIH/NCI |
<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Characteristics</th>
<th>Follow-up</th>
<th>5-Year OS</th>
<th>Funding Sources</th>
</tr>
</thead>
</table>
| Fujita K. et al. 2009 (52) | Retrospective chart review | 333         | • Age 51 to 83y  
• Mean PSA 4.7ng/mL | NR        | 69%       | Ministry of Health, Labor and Welfare of Japan, Foundation for Promotion of Cancer Research, Japanese Urological Association |
| Warlick C. et al. 2006 (53) | Case-control | 38         | • Median age 61y  
• Median PSA 4.9 to 5.0ng/mL | NR        | NR        | NIH |
| Iremashvili V. et al. 2012 (54) | Case-control | 22         | • Median age 61y  
• Stage T1-2  
• Mean PSA 4.8 to 5ng/mL | Postoperative follow-up  
• For delayed RP: median 2.1y  
• For immediate RP: median 3.5y | NR        | NR        | Ministry of Health, Labor and Welfare of Japan, Foundation for Promotion of Cancer Research, Japanese Urological Association |
| Sugimoto M. et al. 2010 (55) | Prospective cohort | 28         | • Age 54 to 80y  
• Mean PSA 7.1 to 7.2ng/mL  
• Gleason 5 to 6 | Range 1 to 78mo | 92.5% for entire cohort, including those who did not have RP | Ministry of Health, Labor and Welfare of Japan, Foundation for Promotion of Cancer Research, Japanese Urological Association |
| Dall’Era MA. et al. 2010 (58) | Retrospective database review | 321         | • Mean age 63y  
• Mean PSA 6.5ng/mL  
• Gleason 5 to 8  
• 71% low-risk PC; 26% intermediate-risk PC; 3% high-risk PC | Median 3.6y  
• Range 1 to 17y | NR        | NIH |
| Latini D. et al. 2007 (60) | Prospective database | 105         | • Age: 32% <75y; 68% ≥75y  
• Men with localized PC choosing AS  
• 99% stage T1 and T2; 1% T3  
• 97% Gleason ≤7; 3% Gleason 8 to 10  
• 94% PSA <20ng/mL; 6% PSA >20ng/mL | 3y       | NR        | TAP Pharmaceutical Products; NIH/NCI; Department of Defense Congressionally Directed Medical Research Program in PC; American Cancer Society |
| Aizer A. et al. 2012 (61) | Retrospective registry review | 701         | • Mean age 61y  
• Low-risk PC  
• Stage T1c-2a  
• Gleason ≤6 | NR        | NR        | Massachusetts General Hospital |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample Size</th>
<th>Baseline Patient Characteristics</th>
<th>Gold Standard</th>
<th>Details of Test Administration</th>
<th>Blinding</th>
<th>Outcomes</th>
<th>Length of Follow-up</th>
<th>Funding and Support</th>
</tr>
</thead>
</table>
| Ng M. et al. 2008 (29) | Prospective case series | 243 | • Age 50 to 80y  
• Stage T1/T2a, N0/X, M0/X  
• Gleason ≤7 (≤3+4) | Biopsy | NR | NR | Sensitivity, specificity, PPV, NPV | ≥2y | 98% but 82% included in analysis | NR |
| Stattin P. et al. 2008 (62) | Retrospective cohort | 8304 | • PSA ≤10ng/mL  
• Incident PC  
• Age ≤70y  
• Stage T1-2, N0/X, M0/X  
• Gleason ≤7  
• PSA ≥20ng/mL | Median 4y | 96% | Swedish Cancer Foundation, Vasterbotten County Council |
| Cooperberg M. et al. 2010 (63) | Prospective database | 11892 | • Age <50 to >75y  
• 36% low-risk PC; 36% intermediate-risk PC; 15% high-risk PC; 12% unknown | NR | NR | AP, Takeda Pharmaceutical; NIH/NCI |
| Davies B. et al. 2008 (64) | Prospective database | 5041 | • Newly diagnosed localized PC  
• Age <55 to ≥75y  
• 36% low-risk PC; 36% intermediate-risk PC; 15% high-risk PC; 12% unknown | NR | NR | TAP Pharmaceutical Products |
| Ananadadas C. et al. 2010 (65) | Prospective cohort | 768 | • Age 44 to 76y  
• Stage T1/T2  
• PSA <20ng/mL  
• Gleason ≤7 | 2y | NR | AstraZeneca |
| Moses K. et al. 2010 (66) | Prospective database | 4284 | • Age 39 to 92y  
• 80% low- to intermediate risk PC; 20% high-risk PC | Mean 38 to 42mo | NR | TAP Pharmaceutical Products; NIH/NCI |

*If a study had more than one publication, then the quality assessment was only done on the latest publication.

AP = Abbot Pharmaceuticals; AS = active surveillance; BCH = Beckman Coulter Hybritec; CSF = Cancer Society of Finland; DCS = Dutch Cancer Society; EU = European Union; FFC = Foundation for Finnish Culture; HSCF = Helsingin Sanomat Centenarian Fund; IQR = interquartile range; mo = month(s); NCI = National Cancer Institute; NIH = National Institutes of Health; NOHRD = Netherlands Organization for Health Research and Development; NR = not reported; PC = prostate cancer; PCRF = Prostate Cancer Research Foundation; PSA = prostate specific antigen; RP = radical prostatectomy; RT = radiation therapy; SCS = Swedish Cancer Society; SJF = Sigrid Juselius Foundation; TP = total prostatectomy; WOH = Wallach Oy Hybritech; WW = watchful waiting; y = year(s)

Appendix V2. Quality assessment for diagnostic study designs
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Sample Size</th>
<th>Age/Stage/PSA</th>
<th>Biopsy Method</th>
<th>Follow-up</th>
<th>Sensitivity, Specificity, Accuracy</th>
<th>PPV, NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barzell W. et al. 2012 (30)</td>
<td>Prospective cohort</td>
<td>124</td>
<td>Mean age 69y, Mean PSA 5.6ng/mL; Men at low risk for PC</td>
<td>TPM (because gold standard was index test)</td>
<td>Biopsy done before TPM in a single sitting by same surgeon</td>
<td>NR</td>
<td>Sensitivity, specificity, PPV, NPV</td>
</tr>
<tr>
<td>Khan M. et al. 2003 (46)</td>
<td>Prospective cohort</td>
<td>78</td>
<td>Age 50 to 74y, Stage T1c, PSA &lt;0.15ng/mL</td>
<td>TRUS biopsy</td>
<td>Biopsy</td>
<td>Sensitivity, specificity</td>
<td>≥1y NR</td>
</tr>
<tr>
<td>Ross A. et al. 2010 (47)</td>
<td>Prospective cohort</td>
<td>290</td>
<td>Mean age 65y, Stage T1c, Gleason ≤6, no pattern ≥4, PSA ≤15ng/mL</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>Sensitivity, specificity</td>
<td>Median 2.9y, Range 0.5 to 12y 100% Peter Jay Sharp Foundation</td>
</tr>
<tr>
<td>Zhang L. et al. 2006 (56)</td>
<td>Prospective cohort</td>
<td>231</td>
<td>Median age 71y (range 49 to 84y), Stage T1b-2b, N0M0, Gleason ≤7, PSA ≤15ng/mL</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>Sensitivity, specificity, accuracy</td>
<td>8y, Mean 3.4y, Median 3y, Range 0.55 to 9y 100%</td>
</tr>
<tr>
<td>Stephenson A. et al. 2002 (57)</td>
<td>Retrospective cohort</td>
<td>104</td>
<td>Localized PC, Age 51 to 86y, 96% stage T1a-2b; 4% T3, 80% Gleason 2-6; 20% Gleason 7 to 10 or unknown</td>
<td>Biopsy</td>
<td>Biopsy</td>
<td>PPV, NPV</td>
<td>Median 33mo 90% NR</td>
</tr>
<tr>
<td>Margel D. et al. 2012 (59)</td>
<td>Prospective cohort</td>
<td>60</td>
<td>Mean age 63y, Low-risk localized PC, Stage T1c-2a, Gleason ≤6, no pattern 4, PSA ≤10ng/mL</td>
<td>TRUS biopsy</td>
<td>MRI ≤6wks from biopsy and reviewed by same uroradiologist</td>
<td>Biopsy</td>
<td>Cancer detection and reclassification rates, Sensitivity, specificity, PPV, NPV</td>
</tr>
</tbody>
</table>
Appendix V3. Quality assessment for the one included randomized controlled trial

<table>
<thead>
<tr>
<th>Reference</th>
<th>Trial Design and Analysis</th>
<th>Sample Size and Power</th>
<th>Baseline Patient Characteristics</th>
<th>Blinding</th>
<th>Length of Follow-up</th>
<th>Follow-up Rate</th>
<th>Funding and Support</th>
</tr>
</thead>
</table>
| Fleschner N. et al. 2012 (12) | Centrally randomized, multicentre Phase 4 trial, intention-to-treat analysis (final report) | 147 (dutasteride), 155 (placebo) 150 per group needed for 96% power | • Age 48 to 82y  
• Low-risk localized PC  
• Stage T1c-2a  
• Gleason ≤6, no pattern ≥4  
• PSA ≤11ng/mL  
• Groups balanced | Sponsor, site personnel, and participants masked to treatment allocation | 3y | 91% had final biopsy assessment | GlaxoSmithKline |

PC = prostate cancer; PSA = prostate specific antigen; y = year(s)

Appendix VI. Unpublished ongoing trials on active surveillance

<table>
<thead>
<tr>
<th>Name of Trial</th>
<th>National Clinical Trial Number</th>
<th>Brief Description and Status</th>
</tr>
</thead>
</table>
| START         | NCT00499174                    | • active surveillance versus radical prostatectomy or radiation  
• started in 2007 but closed early in 2011 due to insufficient accrual |
| ProtecT       | NCT00632983                    | • active surveillance versus radical prostatectomy or radiation  
• estimated completion date after December 2013 |
| PCM301        | NCT01310894                    | • active surveillance versus drug (TOOKAD)  
• estimated completion date June 2015 |
A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Active Surveillance for the Management of Localized Prostate Cancer:
Development Methods, Recommendations Development and External Review Process

C. Morash, C. Agbassi, L. Klotz, T. McGowan, J. Srigley, A. Evans, and the Active Surveillance Guideline Development Group

Report Date: December 10, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). (1) The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is produces evidence-based and evidence-informed guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- **Section 3: Development Methods, Recommendations Development, and External Review Process.** Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

**FORMATION OF WORKING GROUP**

The Surgical Oncology Program asked the PEBC to develop a guideline on active surveillance (AS) for the management of localised prostate cancer. In consultation with the Surgical Oncology Program, a Working Group was identified from Ontario. This Working Group consisted of two urologists, two pathologists, one radiation oncologist, and one methodologist. The Working Group and Surgical Oncology Program also formed the Active Surveillance Guideline Development Group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as an Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

**OBJECTIVES AND RESEARCH QUESTIONS**

The Working Group developed the following objectives for this guideline in consultation with the Surgical Oncology Program. The intention is to make recommendations that aim:

- To describe the role of AS as a management strategy for patients with localized prostate cancer.
- To identify patients with prostate cancer that would most benefit from AS.
- To develop an evidence-based protocol for AS in localized prostate cancer and identify the factors affecting the offer of, acceptance of, and adherence to AS.
- To understand the role of 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) in patients with localized prostate cancer undergoing AS.
- To identify which physician is responsible for managing the AS protocol and if any other human resources required to offer AS (e.g., a genitourinary pathologist, psychosocial specialist, etc.) would need specific training.

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives.

- How does AS compare with immediate active treatments (e.g., radical prostatectomy, radiation therapy, 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)?

- 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)?
  - Prostate-specific antigen (PSA) kinetics (e.g., velocity or doubling time)
  - Digital rectal examination (DRE)
  - Imaging (e.g., magnetic resonance imaging [MRI] or ultrasound)
  - Prostate cancer antigen 3 (PCA3)

- In patients with localized prostate cancer undergoing AS, how does supplementation with 5ARIs (e.g., finasteride or dutasteride) compare with no supplementation?
- 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?

- 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?

GUIDELINE REVIEW
Almost all PEBC projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as “the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context” (3). This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with de novo recommendations development.

For this document, a search was conducted of the SAGE Directory of Cancer Guidelines (www.cancerview.ca/sage), the National Guidelines Clearinghouse (guideline.gov), and the National Health and Medical Research Council, Australia (nhmrc.gov.au). In addition, the websites of several known high-quality guideline developers were searched. Only guidelines published after 1996 were considered. Two guidelines from the environmental scan received a full text review but the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument was not used to evaluate them because they did not meet the criteria for guideline inclusion.

EVIDENTIARY BASE DEVELOPMENT
Using the research questions described above, a search for existing systematic reviews and a systematic review of the primary literature were conducted, as described in Section 2 of this EBS.

INITIAL RECOMMENDATIONS
Using the evidentiary base in Section 2, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality, the potential for bias in the evidence and the likely benefits and harms of AS for the management of localized prostate cancer. The members of the Working Group considered the values they used in weighing benefits compared with harms, and then made a considered judgment. This process is described in detail for each topic area described below.
Role of AS in Localized Prostate Cancer

Key Evidence for Benefits and Harms
Although no randomized controlled trial (RCT) comparing AS with immediate active treatment was found, a 100% prostate cancer survival rate was reported by eight noncomparative studies of low risk patients undergoing AS. A 100% survival rate was also recorded for intermediate-risk prostate cancer patients undergoing AS. When AS/watchful waiting (WW) was compared with radical prostatectomy (RP) or radiotherapy (RT) in a nonrandomized study, the survival rates were similar. Two other studies reported high survival rates of 97% and 98%. In another study, urinary incontinence occurred in 5.6% of patients on AS, 29% of those who moved on to RP and 2.4% in those who moved on to RT (12). In studies comparing immediate RP with delayed RP in patients undergoing AS, no differences in biochemical recurrence rate, positive surgical margins, extraprostatic extension and risk of noncurable cancer were found.

Aggregate Evidence Quality and Potential for Bias
AS is a management strategy for intermediate-risk and low-risk patients. However, there is no consistent AS protocol across the studies. The members of the Working Group decided to focus on low-risk patients because the systematic review did not find many studies evaluating intermediate-risk patients. Because of lack of comparative studies, the quality of existing evidence for AS in low-risk patients is considered weak. Several patient factors such as age, weight, marital status, and tumour characteristics were found to be associated with the choice of AS over active treatment. Ethnicity and income are among the factors that are not associated with patient’s choice of management strategy.

Values of the Working Group
For intermediate-risk patients undergoing AS, survival rates were shown to be similar to those on active treatments. The Working Group placed high values on evidence which shows that AS does not present new or different harms when compared with immediate active treatment. The rates of commonly reported adverse events in AS studies are similar to those in active treatment. The survival rates in several studies also confirmed that the use of AS in low-risk patients is worthwhile. The consensus opinion of the members of the Working Group is that patients can be considered for AS based on age and number of focal pathology.

Considered Judgement
Although no RCT comparing AS with immediate active treatment was found, noncomparative studies have shown that AS is a feasible management strategy in low-risk patients. The rates of adverse events such as urinary incontinence are low in patients undergoing AS. Studies comparing immediate RP with delayed RP in patients on AS detected no significant differences. For intermediate-risk patients with higher Gleason score, active treatment is deemed appropriate but AS is considered feasible for those with lower Gleason score since the studies showed prostate cancer survival rates were similar to active treatment. As such, the Working Group recommended that AS be preferred to other immediate active treatments in patients with low-risk prostate cancer. Due to lack of evidence, no recommendations were made for intermediate-risk patients.

Initial (DRAFT) Recommendation 1
For patients with low-risk (Gleason score ≤6) localized prostate cancer, AS is the preferred disease management strategy.
Initial (DRAFT) Recommendation 2
Active treatments (RP or RT) are appropriate for patients with intermediate-risk (Gleason score 7) localized prostate cancer. For select patients with low-volume intermediate-risk (Gleason score 3+4=7) localized prostate cancer, AS can be considered.

Components of an AS Protocol and Predictors of Disease Reclassification

Key Evidence for Benefits and Harms
PSA, DRE, transrectal ultrasound (TRUS) and biopsy were included as components of AS protocol in the studies that reported the details of their AS protocol. DRE and PSA were carried out on the patients every 3 months in the first 2 years and every 6 months beyond 2 years. In some studies annual or biannual multicore biopsies were also included as part of AS protocol. In one study, MRI was shown to be a good predictor of disease reclassification.

Aggregate Evidence Quality and Potential for Bias
No AS protocol was found to be consistent across the studies that reported the details of their AS protocol. PSA testing was included in most of the studies and the frequency ranged from every 2 to 6 months; more frequently in the first 2 years and less frequently thereafter. DREs were conducted every 3 to 6 months. One study conducted PSA tests and DRE every 2 to 4 years. Multicore (6- to 17-core) biopsies, with or without TRUS, were typically conducted every 6 months to 1 year and a few studies conducted repeat biopsies every 2 to 3 years.

Seven studies evaluated the ability of PSA to predict disease progression. In two of the studies, clinical stage did not predict reclassification. Baseline PSA was found to predict disease progression but the results of other studies were not conclusive for PSA as a good measure for predicting disease progression or reclassification. One study found that MRI has a high yield in predicting disease reclassification. No evidence was found for DRE or PCA3 having a predictive value. These measures are taken into consideration because they help to identify patients that require active treatment.

Values of the Working Group
No AS protocol was found to be consistent across the studies that reported the details of their AS protocol. Since most studies included PSA testing, DRE, and multicore biopsy in their protocol, these are considered the three most important components of an AS protocol. The members of the Working Group feel that reducing the frequency of biopsy will reduce the risk of complication since the survival rates (97% to 100%) were found to be similarly high in studies that opted for reduced biopsy frequency.

Considered Judgement
To develop an AS protocol, it is important that the components are taken into consideration. Appropriate measures to predict disease progression and reclassification should be taken into account. These would help to assess whether a patient should move on to active treatment or continue with AS. Although no AS protocol was found to be consistent across the studies, PSA, DRE, and multicore biopsy are considered the most important components. With the evidence supporting the frequency of administration for each component, the Working Group recommended PSA, DRE, biopsy, and MRI as components of an AS protocol. The role of MRI in AS is evolving. It is useful when there is discordance between the clinical course and pathologic findings of a patient.
Initial (DRAFT) Recommendation 3

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, then serial biopsy every 3 to 5 years thereafter.

The AS protocol may include the following test:
- Multiparametric MRI (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 tumour progression in patients at risk.

Supplementation with 5-alpha reductase

Key Evidence for Benefits and Harms
Dutasteride delays disease progression and improves quality of life in very low-risk patients with prostate cancer when used to supplement an AS protocol.

Aggregate Evidence Quality and Potential for Bias
In one RCT, the addition of dutasteride was demonstrated to be beneficial to patients with prostate cancer who are on AS. This RCT reported a short follow-up period and detected no survival rate benefits.

Values of the Working Group
The available evidence for the use of 5ARIs in patients undergoing AS is of high quality. The members of the Working Group are aware of the the U.S. Food and Drug Administration warning on the use of 5ARIs, but considering the evidence from one study finding that patients on 5ARIs are more likely to adhere to their AS routine, the members believe that the benefit outweighs the risk.

Considered Judgement
Although no RCT was found for finasteride, the benefits of dutasteride in patients with low-risk prostate cancer on AS shows that the addition of 5ARIs to AS can improve quality of life and adherence to AS. The members of the Expert Panel believe that this is a drug class effect and that finasteride may also have a role in men on AS.

Initial (DRAFT) Recommendation 4
Daily 5ARIs may have a role in men on AS

Proceeding to Active treatment

Key Evidence for Benefits and Harms
An RCT found that RP compared with WW reduced mortality rates and risk of distance metastases. The patients on AS who were reclassified to higher risk received active RP or RT, and Gleason score or biopsy are the recommended indicators for disease reclassification.

Aggregate Evidence Quality and Potential for Bias
Fourteen noncomparative studies reported the outcomes of patients on AS that moved on to receive RP or RT. Most patients moved to receive active treatment because of disease
reclassification to higher risk, anxiety, and patient choice. Comparison of immediate versus delayed RP in some studies found no significant differences in biochemical recurrence rate, positive surgical margins, and extraprostatic extension.

_Values of the Working Group_

Disease reclassification is an important step in identifying who moves on to receive active treatment. The most common active treatments reported in the studies are RP and RT. Other less common active treatments are brachytherapy, cryoblation, and high-intensity focused ultrasound. Considering that the biopsy is a gold standard in measuring disease state and that Gleason score is widely used in disease classification, the Working Group based this recommendation on consensus opinion.

_Considered Judgement_

Different types of active treatment for patients on AS who are reclassified to higher risk were reported in the studies included in this document, but RP is the most commonly reported procedure. Evidence showed that RP is better than WW at reducing mortality rates and risk of distant metastases. For the purposes of disease reclassification, the Working Group recommends using Gleason score and biopsy as indicators.

<table>
<thead>
<tr>
<th>Initial (DRAFT) Recommendation 5</th>
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<tbody>
<tr>
<td>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 tumour, consideration should be given to active therapy (e.g., RP or RT).</td>
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</tbody>
</table>

INTERNAL REVIEW

Almost all PEBC documents undergo internal review before the external review. The internal review for this document was conducted by the Report Approval Panel and the Expert Panel. The feedback from the members of both panels was reviewed by the Working Group and the required changes were incorporated into the document. The Working Group obtained the Panels’ final approval of the document before sending it for External Review.

Expert Panel Review and Approval

The CCO Surgical Oncology Group and some other clinical experts from Ontario acted as the Expert Panel for this document. The members of this panel were required to submit conflict of interest declarations prior to reviewing and approving the document. In order for this document to be considered approved, 75% of the Expert Panel membership must cast a vote or abstain from voting and 75% of those that voted must approve the document. In April 2014, the Expert Panel convened in Toronto to review the first draft of the document. During this meeting, the Expert Panel provided the following key feedback.

- **Background:**
  - A paragraph on the favourable outcomes of low-grade prostate cancer should be added to the background information. This should include information about the pathology Gleason grading shift.
  - A comment should be added that this guideline supports screening.
  - This guideline should reference the U.S. task force report to quote harms from overtreatment as this would help support the role of AS.
- Recommendation 1: Patient preference should be considered and added in recommendation 1 to highlight patient-centred care.
- Recommendation 3: The Expert Panel suggested that the MRI recommendation be reworded to include the statement that “Depending on individual patient’s risk of reclassification, age, etc., the interval between serial biopsies should be evaluated carefully and may need to be decreased.”

In response to this feedback, the Working Group made the following changes.

- Modified the background section and referenced the U.S. task force article. A more detailed description of the difference between AS and WW was added to the second paragraph. The importance of Gleason scoring system in low-grade prostate cancer and the benefits of its modifications in recent years were also discussed. However, the members of the Working Group did not think that there is a need to indicate that this document supports or does not support screening.
- The Working Group did not add the patient-centred statement to recommendation 1 as suggested by the Expert Panel because it is mentioned in the qualifying statement for recommendation 1.
- Explicit information about the use of MRI in AS was added to the aspect of recommendation 3 that pertains to MRI, and to the qualifying statement section as well.

A draft of the document incorporating the changes described above was circulated to the Expert Panel members by email. On June 3 2014, the Expert Panel provided additional feedback during a teleconference. The Working Group incorporated the changes and the final draft of the document was sent to the panel members for a formal approval vote. Fourteen members (77%) of the 18-member Expert Panel responded; 13 (72%) members voted and 1 member abstained from voting. 100% of those that voted approved the document. At the time of the voting, some Expert Panel members suggested additional minor changes that did not require altering the recommendations. The Working Group, after thorough consideration, made the required changes.

Report Approval Panel Review and Approval
The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. These RAP reviewers do not have any involvement in the development of the guideline prior to internal review. RAP members must approve the document before external review. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with PEBC’s Assistant Director of Quality and Methods making a final determination that the RAP’s concerns have been addressed.

This document was reviewed by three RAP members, the PEBC Director, and two research methodologists. The RAP approved the document for external review in July 2014. The first draft sent to the Panel in February 2014 was not approved and the key issues raised were as follows:

The overall objectives: The RAP reviewers were concerned with the number and structure of the objectives, with the major issue being that the objectives had too many concepts that did necessarily connect with the recommendations. In response to the RAP
feedback regarding the objectives, the members of the Working Group revised the objective statements, ensuring that the key concepts were not eliminated.

The recommendations: The RAP reviewers did not disagree with the recommendations. However one reviewer believed that there was a tendency to oversell the recommendations based on the definitiveness of available evidence.

Recommendation 1: One of the RAP reviewers was of the opinion that since there are no RCTs or comparative studies to suggest that AS is a preferred management strategy, making such a statement in recommendation 1 is an overstatement.

The members of the Working Group considered this concern and decided not to make any changes to recommendation 1 because they believe that with expert judgement and with available evidence from the noncomparative studies, it is better to state that AS is a preferred management strategy than to state that it is a standard strategy.

Recommendation 2: One of the RAP members suggested that recommendation 2 seems to contradict itself. Another RAP reviewer recommended that a definition of “low volume” as stated in recommendation 2 and a definition of “active treatment” should be included. In response to these suggestions, the Working Group expanded the background information to include these definitions.

Recommendation 3: Listing DRE as one of the components of an AS protocol without any evidence was brought up as a concern by one RAP reviewer, but the Working Group had to include DRE because it is a generally accepted practice in prostate cancer management and it has little or no risk.

External Review by Ontario Clinicians and Other Experts
The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Surgical Oncology Expert Panel circulated the draft document with recommendations to external review participants for review and feedback.

Methods
Targeted Peer Review: During the guideline development process, eight targeted peer reviewers from Ontario and Alberta considered to be clinical and/or methodological experts on the topic of AS were identified by the Working Group and/or the DSG/clinical program. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations, and items evaluating whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on September 3, 2014. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Surgical Oncology Expert Panel reviewed the results of the survey.
**Professional Consultation**: Feedback was obtained through a brief online survey of healthcare professionals who are the intended users of the guideline. All urologists and radiation oncologists—including experts in brachytherapy, prostate biopsy, and MRI—in the PEBC database were contacted by email to inform them of the survey. Participants were directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). They were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. The notification email was sent on September 3, 2014 to over 200 participants and the consultation period ended on October 10, 2014. The Guideline Working Group and the Surgical Oncology Expert Panel reviewed the results of the survey.

**Results**

**Targeted Peer Review**: Three responses were received from five reviewers. Key results of the feedback survey are summarized in Table 8.

Table 8. Responses to nine items on the targeted peer reviewer questionnaire.

<table>
<thead>
<tr>
<th>Question</th>
<th>Reviewer Ratings (N=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest Quality (1)</td>
</tr>
<tr>
<td>1. Rate the guideline development methods.</td>
<td>3</td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
<td>1 2</td>
</tr>
<tr>
<td>3. Rate the guideline recommendations.</td>
<td>3</td>
</tr>
<tr>
<td>4. Rate the completeness of reporting.</td>
<td>1 2</td>
</tr>
<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
<td>3</td>
</tr>
<tr>
<td>6. Rate the overall quality of the guideline report.</td>
<td>1 2</td>
</tr>
<tr>
<td></td>
<td>Strongly Disagree (1)</td>
</tr>
<tr>
<td>7. I would make use of this guideline in my professional decisions.</td>
<td>3</td>
</tr>
<tr>
<td>8. I would recommend this guideline for use in practice.</td>
<td>3</td>
</tr>
</tbody>
</table>

9. What are the barriers or enablers to the implementation of this guideline report?
   One reviewer wrote: "This is a very much needed guideline for clinicians but one of the barriers is that it lacks high-quality evidence and may need a more explicit clarification for intermediate-risk (Gleason 3+4=7) cancers."

**Summary of Written Comments**

No major additional comments were made by the targeted peer reviewers.

**Professional Consultation**: 44 responses were received and the key results of the feedback survey are summarized in Table 9.

Table 9. Responses to four items on the professional consultation survey.
4. What are the barriers or enablers to the implementation of this guideline report?

Considering that AS is becoming a widely adopted management option, a standardized approach is essential. Some of the positive feedback received from the professional consultation indicates that the guideline report is clearly articulated and there are minimal barriers to implementing its recommendations in clinical routines. Patients’ acceptance of AS is more likely with evidence showing that more conservative management does not put them at risk. Reviewers said that these guideline recommendations are based on practical interpretation of the evidence and allows sufficient flexibility for patient-specific decision-making. Proper dissemination of the guideline to its target users, especially general practitioners and urologists, will be necessary.

The following barriers to implementation were identified in the professional consultation process:

- The main concern is the limitations of the supporting evidence, due to the relative scarcity of high-quality trials in this topic area. The limitations of the available data and the rapidly changing evidence base in this field need to be highlighted.

- There may be a need for further discussion on using a change in PSA levels as a trigger for therapeutic intervention, because the trigger point for starting active treatment has not been established. If clinicians use a quality of life (QOL) assessment, they may need to look into psychological QOL and not only the urological QOL.

- Understanding the role of mpMRI in AS will depend on the expertise and experience of the imaging centre and the interpreting radiologist. Since mpMRI for prostate cancer is not readily available in every centre with an MRI unit, more research into the utility and cost effectiveness of mpMRI is needed to facilitate a broader implementation. Perhaps the guideline should specify that mpMRI in AS in prostate cancer should be offered only in centres that can also offer the necessary expertise and experience.

- Nonacademic urologists and community urologists in rural settings may have difficulty implementing these guidelines. These physicians will need adequate resources/support to implement the AS strategy. Ideally, Ontario would implement a province-wide program that can standardize and provide support for this strategy.

- Patients may not choose AS due to factors such as having an expectation of treatment. In addition, with the concerns that a biopsy (even a confirmatory biopsy) does not accurately characterize cancer risk, the need for repeated biopsy may deter some patients. The AS approach may also result in AS fatigue - a situation in which patients get tired of follow-up and opt for treatment despite there being no change in their clinical picture. A patient engagement plan may be necessary to convey the information in the guideline.
- Financial incentives that favour active treatment are deemed the largest barrier to implementation of this guideline. It is well documented that physicians who counsel patients on treatment, especially outside of multidisciplinary clinics, are more likely to advise radical treatment over AS. Consideration should be given to creating a fee code for AS or insisting that all patients who qualify for AS must be seen in a multidisciplinary clinic before going for radical treatment.

Summary of Written Comments
The comments received from the professional consultation acknowledged the relevance and timeliness of the guideline and also reflected a general endorsement of the guideline with the following suggestions for improvement.
- PSA tests every 3 or 6 months may be too frequent in practice and the use of the “Age greater than 75 years” criterion may also be criticized as being ageist. “Less than 10 years life expectancy” would be a preferred definition.
- It will be worthwhile to define “high-volume Gleason 6 cancer” because it is not clear if it represents a certain number of positive cores or a percentage of positive cores. Should Gleason score (3+4) be differentiated from Gleason Score (4+3)?
- The guideline should add a section on prostate imaging for AS including 18F-fluorocholine or 11C-choline PET/CT or PET/MRI. When finalized, the Canadian Urological Association should e-mail a copy to urologists on its list. It is an excellent document.

Modifications/Actions
After reviewing the feedback from the external review, the members of the Working Group decided to make the following minimal changes:
- The phrase “intermediate-risk” was removed in recommendation 2 where it originally stated: “For select patients with low-volume intermediate-risk (Gleason 3+4=7) localized prostate cancer, AS can be considered.
- In response to the concern of being criticized as ageist, the phrase “or age greater than 75 years” was removed from one of the qualifying statements for recommendation 2, which initially stated that 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 less than 10% total tumour, or age greater than 75 years (consensus opinion of the Expert Panel).
- To define Gleason 7 in the justification for recommendation 5, the Working Group added the phrase “4+3 pattern or 3+4 with Gleason pattern 4 pathology accounting for ≥10% total tumour” in parentheses.

Conclusion
This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Surgical Oncology Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Conflict of Interest
In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, the Expert Panel members, and the internal and targeted external reviewers were asked to disclose potential COI. The RAP members and the external targeted reviewers declared no
conflict of interest. The PEBC Assistant Director (HM) and two research methodologists (CW and SK) also declared no conflicts of interest.

Out of the seven guideline authors, five (CM, CA, RT and JS) declared no financial and/or professional conflicts of interests. One author (TM) declared having a managerial responsibility in a department that received about $5000 for site visitations from Varian Medicals. Another author (LK) declared being a principal investigator for the START Study. He has provided guidance in news commentaries and has many journal publications in this topic area. AE has published an editorial in this topic area.

For the Expert Panel, 12 members declared no conflicts of interest, and four (MH, GB, IC, and RS) declared a competing interest. MH received a grant from Sentinelle Medical for the investigation of an endotracheal coil in prostate imaging. She has also been a principal investigator for a clinical trial investigating the value of multispectral 3-Tesla MRI in AS of prostate cancer and for the Active Surveillance Magnetic Resonance Imaging study. Her professional income could substantially increase by over $10000 per annum as a result of an increase in the use of prostate MRI. As a principal/co-investigator, GB received a $4-million grant from the Canadian Institutes of Health Research (in 2008 and a $2-million grant from the Ontario Institute for Cancer Research in 2012. His professional income could also increase substantially if there are fewer referrals for active treatments compared with AS. RS received a grant from Nometics Inc and IC received $5000 from AbbVie in the role of a consultant speaker.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.
REFERENCES

Appendix VII: Members of the Working Group and Expert Panel

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