



Evidence-Based Series 17-9 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Active Surveillance for the Management of Localized Prostate Cancer

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and the Active Surveillance Guideline Development Group*

Report Date: December 10, 2014

An assessment conducted in November 2024 indicated that Evidence-based Series (EBS) 17-9 REQUIRES UPDATING. It is still appropriate for this document to be available while this process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

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

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PEBC Report Citation (Vancouver Style): Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J, et al. and the Active Surveillance Guideline development Group. Active surveillance for the management of localized prostate cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario; 2014 Dec 10 [Requires Updating 2024 Nov]. Program in Evidence-based Care Guideline No.: 17-9 REQUIRES UPDATING.

Journal Citation (Vancouver Style): Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J, et al. Active surveillance for the management of localized prostate cancer: guideline recommendations. Can Urol Assoc J. 2015;9(5-6):171-8.

IN REVIEW

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A Quality Initiative of the
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**Active Surveillance for the Management of
Localized Prostate Cancer: Guideline Recommendations**

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

Report Date: December 10, 2014

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 (2) 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 \leq 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.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Updating

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at:

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**Active Surveillance for the Management of
Localized Prostate Cancer: Evidentiary Base**

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Report Date: December 10, 2014

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 1. Differences between watchful waiting and active surveillance

	Watchful waiting	Active surveillance
Purpose and intent	<ul style="list-style-type: none">• Palliative disease management strategy that initiates	<ul style="list-style-type: none">• Curative disease management strategy that initiates curative treatment

	interventions to relieve symptoms of disease progression	when disease progresses
Eligibility criteria	<ul style="list-style-type: none"> Any-stage nonmetastatic prostate cancer, allows for PSA >10 ng/mL and includes men with more chronic illness Suitable for older men or those who cannot receive curative treatment due to comorbidity 	<ul style="list-style-type: none"> Stage T1c to T2a low risk clinically localized prostate cancer, PSA <10 ng/mL, Gleason score ≤6 Suitable for men with indolent disease
Follow-up protocol	<ul style="list-style-type: none"> Passive follow-up strategy; follow-up only when symptoms arise 	<ul style="list-style-type: none"> Regular, multifactorial follow-up with PSA, DRE, prostate imaging, and repeat biopsy
Indicators for treatment	<ul style="list-style-type: none"> Development of symptoms such as urinary obstruction, pain or bony fractures 	<ul style="list-style-type: none"> 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

- 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)?
- In patients with localized prostate cancer undergoing AS, which findings of the following tests predict increasing risk of reclassification to a higher-risk disease state? What are

their test characteristics (i.e., positive and negative predictive values, sensitivities, specificities, and likelihood ratios)?

- PSA kinetics (e.g., velocity or doubling time)
 - DRE
 - Imaging (e.g., magnetic resonance imaging [MRI] or ultrasound [US])
 - Prostate cancer antigen3 (PCA3)
3. In patients with localized prostate cancer undergoing AS, how does supplementation with 5-alpha reductase inhibitors (5ARIs) (e.g., finasteride or dutasteride) compare with no supplementation?
 4. In patients with localized prostate cancer undergoing AS, how do clinical outcomes differ if treatment is managed by a:
 - Single doctor versus a multidisciplinary team of clinicians?
 - Urologist versus another oncologist (e.g., a radiation oncologist)?
 - University/teaching hospital versus a community or private clinic/hospital?
 5. In patients with localized prostate cancer who are candidates for or who are undergoing AS, how does the offer, receipt, or choice of treatment and patient compliance or adherence differ based on (but not limited to) the following factors:
 - AS protocol: order of and frequency of tests (PSA, DRE, imaging), and other test/clinical factors?
 - Care provider(s): single versus team of doctors; urologist versus other oncologist?
 - Care setting: clinic versus hospital?
 - Patient factors: clinical, psychosocial?
 - Social support: family or community?
 - Socioeconomic or geographic variables?

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.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any associated programs are editorially independent from the Ministry.

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 $n \geq 30$ 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.

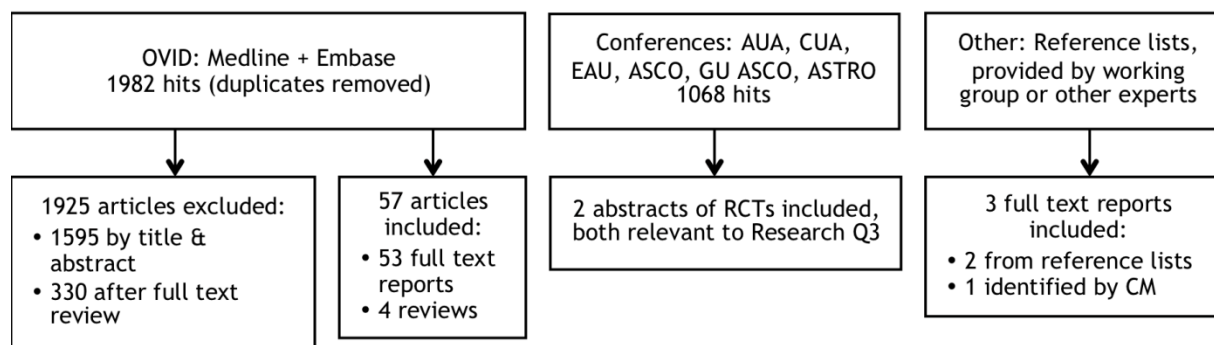


Figure 1. Schematic diagram showing results from the primary literature search.

Literature Search Results

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 2 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

Reference(s)	Sample size	PSA test	DRE	Biopsy	Other details
Fleshner N. et al. 2012 (12)	302	Every 3mo for 1y, then every 6mo	At screening, 18mo and 3y	12-core TRUS biopsy at 18mo and 3y, or upon abnormal PSA/DRE	No other details
Choo R. et al. 2002 (41) (13, 31-41)	450	Every 3mo for 2y, then every 6mo	Every 3mo for 2y, then every 6mo	8- to 14-core biopsy at 6 to 12mo, then every 3 to 4y	Definitive intervention offered if PSA _{Adt} <3y, Gleason >4+3, or clinical progression
Kravchick S et al. 2011 (14)	48	Every 3mo	Every 3mo	TRUS biopsy every 18mo or upon abnormal PSA/DRE	No other details
Roemeling S. et al. 2006 (15)	64 (WW), 136 (RP), 91 (RT)	Every 3mo for 1y, then every 6mo	Every 3mo for 1y, then every 6mo	Sextant biopsy upon abnormal PSA/TRUS/DRE	TRUS was also done but no details provided
Stattin P. et al. 2010 (16)	8304	Every 3mo	Every 3mo	NR	No other details
Seiler D. et al. 2012 (17)	61 had RP (from 283 AS patients)	Every 6mo	NR	TRUS biopsy every 1y	Physical exam every 6mo
Dall'Era M. et al. 2010 (19)	33 had delayed RP (from 233 AS patients), 278 had immediate RP	Every 3mo	Every 3mo	12-core biopsy every 12 to 24mo	TRUS every 6 to 12mo
van den Bergh R. et al. 2009 (20, 21)		Every 2 to 4y	Every 2 to 4y	Sextant to 10- to 12-core biopsy upon abnormal PSA/TRUS/DRE	TRUS every 2 to 4y
Grimaldi J. et al. 2002 (22)	8 had RP (from 38 offered radical treatment out of 200 AS patients)	Every 3mo for 2y, then every 6mo	Every 3mo for 2y, then every 6mo	TRUS biopsy at 12 to 18mo	<ul style="list-style-type: none"> • Clinical exam every 3mo for 2y, then every 6mo • TRUS every 6mo • Bone scan every 1y for 12y • Radical therapy offered upon progression
Ischia J. et al. 2012 (23)	154	Every 3mo	Every 6mo	6- to 17-core biopsy at 12 to 18mo, then every 3y	Clinical exam every 6mo
Ercole B. et al. 2008 (24)	40	Every 3 to 6mo	Every 6 to 12mo	Repeat TRUS biopsy every 2y or upon abnormal PSA/DRE	No other details
Bul M. et al. 2012 (25, 26)	2494	Every 3mo for 2y, then every 6mo	Every 6mo for 2y, then every 1y	8- to 12- core, volume dependent biopsy at 1, 4, 7y or every 1y if PSA _{Adt} =3 to 10y	Radical treatment offered upon reclassification to higher risk
Finelli A. et al. 2011 (27)	288	Every 3mo for 2y, then every 6mo	Every 6mo	6-16 core biopsy at 1y, then every 2-3y or upon abnormal PSA/DRE	No other details
Radomski L. et al. 2012 (28)	443	Every 3mo for 2y, then every 6mo	Every 6mo	6- to 16-core biopsy at 1y, then every 2 to 3y or upon abnormal PSA/DRE	No other details
Ng M. et al. 2008	NR	Every 1 to 3mo for 1y,	NR	Octant TRUS biopsies at 18 to	No other details

(29)		every 3mo on 2 nd y, then every 6mo		24mo, then every 2y	
Patel M. et al. 2004 (42)	88	Every 3mo for 1y, then every 6 mo	Every 3mo for 1y, then every 6 mo	Sextant TRUS biopsy at 6 mo or upon abnormal PSA/DRE	RP or RT offered upon progression or request
Tosoian J. et al. 2011 (43-48)	769	Every 6mo	Every 6mo	12- to 14-core TRUS biopsy every 1y	RP or RT offered upon progression
Soloway M. et al. 2010 (49, 50)	230 (AS) 219 (TP)	Every 3 to 4mo for first 2y, then every 6mo	Every 3 to 4mo for first 2y, then every 6mo	10- to 12-core TRUS biopsy after 9 to 12mo, then every 1y or upon abnormal PSA/DRE	No other details
Hilton J. et al. 2012 (51)	427	Done but no details given	Done but no details given	Biopsy every 12 to 18mo	No other details
Fujita K. et al. 2009 (52)	333	Every 6mo	Every 6mo	10- to 12-core TRUS biopsy every 1y	No other details
Warlick C. et al. 2006 (53)	38 had delayed surgery (from 320 AS patients), 150 had immediate surgery	Every 6mo	Every 6mo	Biopsy every 1y	Surgery offered if abnormal biopsy
Iremashvili V. et al. 2012 (54)	22 had delayed RP (from 207 AS patients), 38 had immediate RP	Every 3 to 4mo	Every 3 to 4mo	Biopsy at 1y and then every 1 to 2y or upon abnormal PSA/DRE	Active treatment recommended upon progression
Sugimoto M. et al. 2010 (55)	28 had delayed RP (from 117 AS patients), 14 had immediate RP	Every 2mo for 6mo, then every 3mo	NR	Rebiopsy after 1y	Aggressive treatment recommended if PSAdt ≤2y
Zhang L. et al. 2006 (56)	231	Every 3mo for 2y, then every 6mo	NR	NR	No other details
Stephenson A. et al. 2002 (57)	104	Every 3 to 6mo	Every 3 to 6mo	Sextant biopsy every 1y	No other details

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

Reference*	OS (95%CI)	PCS (95%CI)	TFS	Disease progression or reclassification	Reasons for progression or reclassification	Receipt of active treatment	Reasons for active treatment
Klotz L 2012 (13)	<ul style="list-style-type: none"> • 79% • 68% (62% to 74%) at 10y 	97% at 10y	<ul style="list-style-type: none"> • 84% at 2y • 72% at 5y • 62% at 10y 	30%	<ul style="list-style-type: none"> • 14% short PSAdt • 8% Gleason upgrade • 1% upstaged • 0.9% volume progression 	<ul style="list-style-type: none"> • 30% <p>Of which,</p> <ul style="list-style-type: none"> • 26% RP • 67% RT • 7.4% HT 	<ul style="list-style-type: none"> • 48% short PSAdt • 27% Gleason upgrade • 4% upstaged • 3% volume increase • 10% patient choice
Kravchick S et al. 2011 (14)	88%	100%	46% at mean 78.9mo	Unclear	<ul style="list-style-type: none"> • 25% PSA rose >30% • 10% Gleason upgrade • 8% had more positive cores 	<ul style="list-style-type: none"> • 42% <p>Of which,</p> <ul style="list-style-type: none"> • 55% RP • 25% RT • 20% CB 	<ul style="list-style-type: none"> • 50% Gleason upgrade, positive cores, PSA increase, or changes on DRE
Roemeling S. et al. 2006 (15)	<ul style="list-style-type: none"> • 86% • 91% at 5y • 85% at 8y 	100% at 5y and 99% at 8y	NR	NR	NR	<ul style="list-style-type: none"> • 30% at median 40mo <p>Of which,</p> <ul style="list-style-type: none"> • 10% RP • 58% RT • 21% HT • 10% BT 	<ul style="list-style-type: none"> • PSA increase
Stattin P. et al. 2010 (16)	AS/WW	AS/WW	NR	NR	NR	NR	NR
	<ul style="list-style-type: none"> • 77% (74% to 79%) at 10y 	<ul style="list-style-type: none"> • 97.6% (95.9% to 98.8%) at 10y 					
	RP	RP					
	<ul style="list-style-type: none"> • 89% (87% to 90%) at 10y 	<ul style="list-style-type: none"> • 99.6% (99.0% to 99.9%) at 10y 					
	RT	RT					
	<ul style="list-style-type: none"> • 82% (79% to 84%) at 10y 	<ul style="list-style-type: none"> • 98.2% (96.0% to 99.4%) at 10y 					
van den Bergh R. et al. 2009 (20)	<ul style="list-style-type: none"> • 91% • 77% at 10y 	<ul style="list-style-type: none"> • 99.8% • 100% at 10y 	43% at 10y	Unclear	<ul style="list-style-type: none"> • 9.4% PSA >10ng/mL • 15% PSAdt <3y 	<ul style="list-style-type: none"> • 32% at mean 2.55y <p>Of which,</p> <ul style="list-style-type: none"> • 43% RP 	<ul style="list-style-type: none"> • 17% tumour changes on DRE

						<ul style="list-style-type: none"> • 48% RT • 9% HT 	
Ischia J. et al. 2012 (23)	99%	100% at 10y	<ul style="list-style-type: none"> • 62% at 5y • 45% at 10y 	17%	Upstaged	<ul style="list-style-type: none"> • 16% <p>Of which,</p> <ul style="list-style-type: none"> • 68% RP • 20% RT+HT • 12% BT 	<ul style="list-style-type: none"> • 96% upstaged • 4% patient choice
Ercole B. et al. 2008 (24)	88%	100%	74% at 5y	NR	NR	<ul style="list-style-type: none"> • 22% <p>Of which,</p> <ul style="list-style-type: none"> • 44% RP • 33% RT • 22% HT 	<ul style="list-style-type: none"> • PSA increase • Volume increase • Gleason upgrade • Anxiety
Bul M. et al. 2013 (26)	99%	100%	<ul style="list-style-type: none"> • 77% at 2y • 68% at 4y 	28%	<ul style="list-style-type: none"> • 21% Gleason upgrade • 51% positive cores • 28% had both 	<ul style="list-style-type: none"> • 21% at median 1.6y <p>Of which,</p> <ul style="list-style-type: none"> • 48% RP • 5% RT • 1.5% HT • 0.8% HIFU 	<ul style="list-style-type: none"> • 73% Gleason upgrade, positive cores, or PSAdt <3y • 9% anxiety •
Patel M. et al. 2004 (42)	100%	100%	<ul style="list-style-type: none"> • 58% at 5y • 41% at 10y 	25% at median 44mo	<ul style="list-style-type: none"> • Gleason upgrade 	<ul style="list-style-type: none"> • 35% <p>Of which,</p> <ul style="list-style-type: none"> • 55% RP • 42% RT 	<ul style="list-style-type: none"> • 55% Gleason upgrade, volume increase, positive cores, PSA increase or changes on DRE/TRUS • 22% anxiety • 22% had both
Tosoian J. et al. 2011 (43)	98.2%	100%	<ul style="list-style-type: none"> • 81% at 2y • 59% at 5y • 41% at 10y 	31%	<ul style="list-style-type: none"> • 45% Gleason upgrade • 55% positive cores 	<ul style="list-style-type: none"> • 33% at median 2.2y <p>Of which,</p> <ul style="list-style-type: none"> • 50% RP • 50% RT 	<ul style="list-style-type: none"> • 26% patient choice • 74% Gleason upgrade or positive cores
Soloway M. et al. 2010 (49)	NR	NR	86% at 5y	NR	NR	<ul style="list-style-type: none"> • 14% at mean 33 mo <p>Of which,</p> <ul style="list-style-type: none"> • 38% TP • 44% RT • 19% HT 	NR

*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; PSA_{dt} = 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

Reference	Groups	Gleason score upgrade	Biochemical recurrence rate (PSA failure)	Positive surgical margins	Extraprostatic extension (nonorgan confined disease)

Dall'Era M. et al. 2010 (19)	Delayed RP	NS	NR	NS	NS
	Immediate RP				
Iremashvili V. et al. (54)	Delayed RP	• 32%	• 18%	41%	14%
	Immediate RP	• 11%	• 13% NS	37% NS	16% NS
Sugimoto M. et al. (55)	Delayed RP	• 68%	• 25%*	NR	NS
	Immediate RP	• 43%	• 21%*		

*Statistical significance unclear.

NR = not reported; NS = not significant; PSA = prostate specific antigen; RP = radical prostatectomy.

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

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

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

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

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

Reference	Disease progression (reclassification)	Test	Sensitivity	Specificity	PPV	NPV	Accuracy
Ng M. et al. 2009 (29)	27% at 18 to 24mo	PSAdt at different thresholds	38% to 70%	49% to 78%	33% to 38%	78% to 82%	NR
		PSA velocity at different thresholds	38% to 75%	51% to 89%	36% to 56%	80% to 85%	NR
Khan M. et al. 2003	25.4% at 1 st repeat biopsy	PSA velocity, % free PSA, and	65% for detecting	90% for detecting	NR	NR	NR

(46)		gland volume	favourable pathology	favourable pathology			
	16.7% at 2 nd repeat biopsy	PSA velocity, % free PSA, and gland volume	100% for identifying patients who should have a 3 rd biopsy	70% for identifying patients who should have a 3 rd biopsy	NR	NR	NR
Ross A. et al. 2010 (47)	35% at median 2.9y	PSA velocity and PSA _{dt}	No cut point had both high sensitivity and specificity for disease progression on biopsy		NR	NR	NR
Zhang L. et al. 2006 (56)	40% at high risk for progression	PSA _{dt} and repeat biopsy	61%	72%	NR	NR	68%
Stephenson A. et al. 2002 (57)	53%	PSA _{dt}	NR	NR	76%	60%	NR

mo = month(s); NPV = negative predictive value; NR = not reported; PPV = positive predictive value; PSA = prostate specific antigen; PSA_{dt} = PSA doubling time; y = year(s)

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

Reference	Analysis	Predictors of disease reclassification or progression	Factors not associated with reclassification or progression
Bul M. et al. 2013 (26)	Multivariate	<ul style="list-style-type: none"> PSA density (OR, 2.5; CI, 1.9 to 3.4) 2 positive cores (OR, 2.1; CI, 1.7 to 2.7) PSA_{dt} <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) 	<ul style="list-style-type: none"> Total biopsy cores clinical stage T2
Patel M. et al. 2004 (42)	Univariate	<ul style="list-style-type: none"> Positive biopsy (p=0.004) PSA at baseline (p=0.01) 	<ul style="list-style-type: none"> Clinical stage Number of positive cores PSA_{dt} Gleason score at baseline PSA density at baseline

CI = 95% confidence interval; OR = odds ratio; p = p-value; PSA = prostate specific antigen; PSA_{dt} = 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 $> 35 \text{ kg/m}^2$) (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

Morash C, Tey R, Agbassi C, Klotz L, McGowan T, Srigley J, et al. Active surveillance for the management of localized prostate cancer: guideline recommendations. *Can Urol Assoc J*. 2015;9(5-6):171-8.

ACKNOWLEDGEMENTS AND AUTHORSHIP

The Active Surveillance Guideline Development Group and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Rodney Breau, Melissa Brouwers, Laurie Elit, Andrew Feifer, Neil Fleshner, Sarah Kellet, Donna Maziak, Leigh McKnight, Robin McLeod, and Sheila McNair.
- Hans Messersmith, Linda Sugar, Kiril Trpkov, and Cindy Walker-Dilks for providing feedback on draft versions.
- Kashem Esaba for conducting a data audit.
- 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.

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APPENDICES

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

Database (Acronym)	Website URL	Date of search	Search Terms or Section Browsed
Standards and Guidelines Evidence (SAGE)	cancerview.ca	12 Mar 2012	<ul style="list-style-type: none"> search 1 <ul style="list-style-type: none"> - title word: prostate - ICG: genitourinary OR early stage OR adult OR active surveillance search 2 <ul style="list-style-type: none"> - title word: prostate AND active surveillance search 3 <ul style="list-style-type: none"> - title word: (localized OR localised) AND prostate cancer
National Guideline Clearinghouse	guideline.gov	13 Mar 2012	<ul style="list-style-type: none"> 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/prospere	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

Database (Acronym)	Website URL	Search terms or Section browsed
American Society of Clinical Oncology (ASCO) and ASCO's Genitourinary Cancers Symposium via Journal of Clinical Oncology	jco.ascopubs.org	<ul style="list-style-type: none"> search 1 <ul style="list-style-type: none"> title word: prostate AND cancer title or abstract word: surveillance OR waiting OR observation OR expectant OR conservative search 2 <ul style="list-style-type: none"> title word: prostate AND active AND surveillance
European Association of Urology (EAU) Congress	uroweb.org	<ul style="list-style-type: none"> section 7.7.1 Prostate Cancer: Management of nonmetastatic disease: Active Surveillance (2012) 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	urology.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

Database (Acronym)	Website URL	Date	Search terms
National Institutes of Health (NIH)	clinicaltrials.gov	15 Mar 2012	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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

Reference*	Study Design	Sample Size	Baseline patient Characteristics	Length of Follow-up	Follow-up Rate	Funding and Support
van den Bergh R. et al. 2012 (11)	Comparison of 2 cohorts from different studies	266	<ul style="list-style-type: none"> Mean age 65y AS patients had Gleason 6, PSA $\leq 10\text{ng/mL}$, stage $\leq \text{T2}$ 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	<ul style="list-style-type: none"> 99% stage T1a-2c; 0.9% T3 Gleason 3 to 7 Median age 70y Low- and intermediate-risk PC 	<ul style="list-style-type: none"> Median 6.8y Range 1 to 16y 	100% accounted for	Prostate Cancer Canada
Kravchick S. et al. 2011 (14)	Prospective cohort	48	<ul style="list-style-type: none"> Age 60 to 75y Low-risk PC Stage T1a-c PSA $\leq 10\text{ng/mL}$ Gleason ≤ 6 	Mean 81.1mo	NR	NR
Roemeling S. et al. 2006 (15)	Retrospective cohort	64 (WW), 136 (RP), 91 (RT)	<ul style="list-style-type: none"> Patients retrospectively met AS criteria Mean age 68y Stage T1c-2 Mean PSA 4.1ng/mL 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Low- or intermediate-risk PC, localized PC Age $\leq 70\text{y}$ Stage T1-2, N0/X, M0/X Gleason ≤ 7 PSA $\leq 20\text{ng/mL}$ 	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)	<ul style="list-style-type: none"> Age 49 to 72y PSA 2.4-26ng/mL Gleason 6 	For patients who had RP <ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Mean age 59y Low-risk PC Gleason 6 Stage cT1-2 	Postoperative follow-up <ul style="list-style-type: none"> For delayed RP: median 12mo, range <1 to 60mo For immediate 	NR	NR

				RP: median 27mo, range <1 to 162mo		
van den Bergh R. et al. 2009 Eur Urol. (20)	Retrospective study of 4 cohorts	616	<ul style="list-style-type: none"> • Patients retrospectively met AS criteria • Age 51 to 76y • Stage T1c-2c • PSA 1.2 to 9.9 ng/mL • Gleason ≤6 	<ul style="list-style-type: none"> • Mean 4.35y • Median 3.91y Range 0 to 11.63y 	94%	DCS, NOHRD, EU, BCH, SCS, WOH, AP, CSF, SJF, HSCF, FFC, Europe against Cancer, Schering-Plough, Academy of Finland
van den Bergh R. et al. 2009 BJU Int. (21)	Case series	50	<ul style="list-style-type: none"> • Age 59 to 76y • Gleason 7 (88% 3+4; 12% 4+3) • Stage T1c-2 • PSA 5.7 ng/mL 	<ul style="list-style-type: none"> • Median 2.6y • IQR 0.8 to 5y 	86% included in the analysis	DCS, NOHRD, EU, BCH, SCS, WOH, AP, CSF, SJF, HSCF, FFC, Europe against Cancer, Schering-Plough, Academy of Finland, Gunvor and Ivan Svensson Foundation, Af Jochnick Foundation
Grimaldi J. et al. 2002 (22)	Prospective cohort	8 had RP (from 38 offered radical treatment out of 200 AS patients)	<ul style="list-style-type: none"> • Age 49 to 84y • Gleason ≤5-7 • PSA 0.3 to 14.6ng/mL 	NR	NR	NR
Ischia J. et al. 2012 (23)	Retrospective record review	154	<ul style="list-style-type: none"> • Age 36 to 81y • Mean PSA 6.5ng/mL • 95% Gleason ≤5 to 7; 5% unknown 	<ul style="list-style-type: none"> • Median duration of AS 1.9y • Range 0.1 to 16.6y • 2 patients followed >10y 	NR	NR
Ercole B. et al. 2008 (24)	Retrospective case series	40	<ul style="list-style-type: none"> • Stage T1c-2a • Gleason ≤6 • PSA <10ng/mL • Median age 68y 	For 31 patients, <ul style="list-style-type: none"> • Median duration of AS 48mo • Range 12 to 168mo 	100% accounted for	NR
Bul M. et al. 2012 (25)	Prospective cohort	189 had RP (from 2079 AS patients)	<ul style="list-style-type: none"> • Median age 63y • Median PSA 5.8ng/mL • Gleason ≤6 • Stage T1c-2a 	For those remaining on AS <ul style="list-style-type: none"> • Median 1.6y • Range 0.8 to 2.8y 	88.4%	PCRF, Dutch Urological Association, NutsOhra
Bul M. et al.	Prospective	2494	<ul style="list-style-type: none"> • Median age 66y 	<ul style="list-style-type: none"> • Median 1.6y 	98.3%	PCRF, Dutch Urological

2013 (26)	cohort		<ul style="list-style-type: none"> Low-risk PC Stage T1c-2 PSA \leq10ng/mL Gleason \leq6 	<ul style="list-style-type: none"> IQR 1 to 2.8y 		Association
Finelli A. et al. 2011 (27)	Retrospective cohort	288	<ul style="list-style-type: none"> Mean age 64y Low-risk PC Stage T1c-2a Gleason \leq6 PSA <10ng/mL 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Median 44mo Range 7 to 172mo 	98.9%	NCI, Leon Lowenstein Foundation
Tosoian J. et al. 2011 (43)	Prospective cohort	769	<ul style="list-style-type: none"> Age 45 to 92y Stage T1c Very low-risk PC 	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> Mean age 63y Mean PSA 5.07ng/mL 	<ul style="list-style-type: none"> Mean 44mo Median 32mo Range 12 to 208mo 	100% accounted for	none
Hilton J. et al. 2012 (51)	Retrospective record review	427	<ul style="list-style-type: none"> Median age 61y Stage T1-2 Median PSA 5.2ng/mL 93% Gleason 4 to 6; 7% Gleason 7 to 8 	<ul style="list-style-type: none"> Median 3.2y IQR 1.9 to 5.1y 	85%	NIH/NCI

Fujita K. et al. 2009 (52)	Retrospective chart review	333	<ul style="list-style-type: none"> • Age 51 to 83y • Mean PSA 4.7ng/mL 	NR	69%	NR
Warlick C. et al. 2006 (53)	Case-control	38 delayed surgery (of 320 AS patients), 150 immediate surgery	<ul style="list-style-type: none"> • Median age 61y • Median PSA 4.9 to 5.0ng/mL 	NR	NR	NR
Iremashvili V. et al. 2012 (54)	Case-control	22 delayed RP (of 207 AS patients), 38 immediate RP	<ul style="list-style-type: none"> • Median age 61y • Stage T1-2 • Mean PSA 4.8 to 5ng/mL 	Postoperative follow-up <ul style="list-style-type: none"> • For delayed RP: median 2.1y • For immediate RP: median 3.5y 	NR	NR
Sugimoto M. et al. 2010 (55)	Prospective cohort	28 delayed RP (from 117 AS patients), 14 immediate RP	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Mean age 63y • Mean PSA 6.5ng/mL • Gleason 5 to 8 • 71% low-risk PC; 26% intermediate-risk PC; 3% high-risk PC 	<ul style="list-style-type: none"> • Median 3.6y • Range 1 to 17y 	NR	NIH
Latini D. et al. 2007 (60)	Prospective database	105	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Mean age 61y • Low-risk PC • Stage T1c-2a • Gleason ≤6 	NR	NR	Massachusetts General Hospital

Stattin P. et al. 2008 (62)	Retrospective cohort	8304	<ul style="list-style-type: none"> • PSA $\leq 10\text{ng/mL}$ • Incident PC • Age $\leq 70\text{y}$ • Stage T1-2, N0/X, M0/X • Gleason ≤ 7 • PSA $\leq 20\text{ng/mL}$ 	Median 4y	96%	Swedish Cancer Foundation, Vasterbotten County Council
Cooperberg M. et al. 2010 (63)	Prospective database	11892	<ul style="list-style-type: none"> • Age <50 to $\geq 75\text{y}$ • 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	<ul style="list-style-type: none"> • Newly diagnosed localized PC • Age <55 to $\geq 75\text{y}$ • 82.5% low- to intermediate risk PC; 17.5% high-risk PC • Stage T1-3a, N0M0 	NR	NR	TAP Pharmaceutical Products
Ananadadas C. et al. 2010 (65)	Prospective cohort	768	<ul style="list-style-type: none"> • Age 44 to 76y • Stage T1/T2 • PSA <20ng/mL • Gleason ≤ 7 	2y	NR	AstraZeneca
Moses K. et al. 2010 (66)	Prospective database	4284	<ul style="list-style-type: none"> • 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

Reference	Study Design	Sample Size	Baseline Patient Characteristics	Gold Standard	Details of Test Administration	Blinding	Outcomes	Length of Follow-up	Follow-up Rate	Funding and Support
Ng M. et al. 2008 (29)	Prospective case series	243	<ul style="list-style-type: none"> • Age 50 to 80y • Stage T1/T2a, N0/X, M0/X • Gleason ≤ 7 ($\leq 3+4$) 	Biopsy	NR	NR	Sensitivity, specificity, PPV, NPV	$\geq 2\text{y}$	98% but 82% included in analysis	NR

Barzell W. et al. 2012 (30)	Prospective cohort	124	<ul style="list-style-type: none"> PSA <15ng/mL Mean age 69y Mean PSA 5.6ng/mL Men at low risk for PC considering AS 	TPM (because gold standard was index test)	Biopsy done before TPM in a single sitting by same surgeon	NR	Sensitivity, specificity, PPV, NPV	NR	NR	NIH Research, Medical Research Council, Pelican Cancer Foundation, Prostate Action and St. Peters Trust
Khan M. et al 2003 (46)	Prospective cohort	78	<ul style="list-style-type: none"> Age 50 to 74y Stage T1c PSA <0.15ng/mL 	TRUS biopsy	NR	NR	Sensitivity, specificity	≥1y	NR	NIH/National Cancer Institute
Ross A. et al. 2010 (47)	Prospective cohort	290	<ul style="list-style-type: none"> Mean age 65y Stage T1c Gleason ≤6, no pattern ≥4 PSA <15ng/mL 	Biopsy	NR	NR	Sensitivity, specificity	<ul style="list-style-type: none"> Median 2.9y Range 0.5 to 12y 	100%	Peter Jay Sharp Foundation
Zhang L. et al. 2006 (56)	Prospective cohort	231	<ul style="list-style-type: none"> Median age 71y (range 49 to 84y) Stage T1b-2b, N0M0 Gleason ≤7 PSA ≤15ng/mL 	Biopsy	NR	NR	Sensitivity, specificity, accuracy	<ul style="list-style-type: none"> 8y Mean 3.4y Median 3y Range 0.55 to 9y 	100%	NR
Stephenson A. et al. 2002 (57)	Retrospective cohort	104	<ul style="list-style-type: none"> Localized PC Age 51 to 86y 96% stage T1a-2b; 4% T3 80% Gleason 2-6; 20% Gleason 7 to 10 or unknown 	Biopsy	NR	NR	PPV, NPV	Median 33mo	90%	NR
Margel D. et al. 2012 (59)	Prospective cohort	60	<ul style="list-style-type: none"> Mean age 63y Low-risk localized PC Stage T1c-2a Gleason ≤6, no pattern 4 PSA ≤10ng/mL 	TRUS biopsy	MRI ≤6wks from biopsy and reviewed by same urologist	NR	<ul style="list-style-type: none"> Cancer detection and reclassification rates Sensitivity, specificity, PPV, NPV 	NR	93% included in analysis	Prostate Cancer Canada

AS = active surveillance; mo = month(s); MRI = magnetic resonance imaging; NIH = National Institutes of Health; NPV = negative predictive value; NR = not reported; PC = prostate cancer; PPV = positive predictive value; PSA = prostate specific antigen; TPM = Transperineal prostate mapping; TRUS = transrectal ultrasound; wks = weeks; y = year(s)

Appendix V3. Quality assessment for the one included randomized controlled trial

Reference	Trial Design and Analysis	Sample Size and Power	Baseline Patient Characteristics	Blinding	Length of Follow-up	Follow-up Rate	Funding and Support
Fleshner N. et al. 2012 (12)	Centrally randomized, multicentre Phase 4 trial, intention-to-treat analysis (final report)	<ul style="list-style-type: none"> 147 (dutasteride), 155 (placebo) 150 per group needed for 96% power 	<ul style="list-style-type: none"> 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

Name of Trial	National Clinical Trial Number	Brief Description and Status
START	NCT00499174	<ul style="list-style-type: none"> active surveillance versus radical prostatectomy or radiation started in 2007 but closed early in 2011 due to insufficient accrual
ProtecT	NCT00632983	<ul style="list-style-type: none"> active surveillance versus radical prostatectomy or radiation estimated completion date after December 2013
PCM301	NCT01310894	<ul style="list-style-type: none"> active surveillance versus drug (TOOKAD) estimated completion date June 2015

Evidence-Based Series 17-9: Section 3

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

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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 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 (eg, 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 judgement. 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.

Initial (DRAFT) 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).

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 not 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.

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

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.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	1(2%)	1(2%)	1(2%)	21(48%)	19 (44%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1(2%)	1(2%)		16(36%)	25(57%)
3. I would recommend this guideline for use in practice.	1(2%)	1(2%)	1(2%)	13(30%)	26(59%)

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 $\geq 10\%$ 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.

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Appendix VII: Members of the Working Group and Expert Panel

Name	Affiliation	COI Declared
Working Group		
Christopher Morash	University of Ottawa	No
Rovena Tey		No
Chika Agbassi	McMaster University	No
Laurence Klotz	Sunnybrook Health Sciences Centre	Yes
Tom McGowan	Credit Valley Hospital	Yes
John Srigley	Trillium Health Partners	No
Andrew Evans	University Health Network	No
Expert Panel		
Antonio Finelli	Princess Margaret Hospital	No
Arthur Grabowski	University of Toronto	No
Bish Bora	Northern Urology Centre	No
Chris Davidson	Kingston General Hospital	No
Eric Belanger	Ottawa Hospital	No
Glenn Bauman	London Health Sciences Centre	Yes
Ilias Cagiannos	Ottawa Hospital	Yes
Julie Bowen	Sudbury Regional Hospital	No
Ken Newell	Grey Bruce Health Services	No
Louis Fenkell	Stronach Regional Cancer Centre	No
Madeleine Moussa	London Health Sciences Centre	No
Masoom Haider	Sunnybrook Health Sciences Centre	Yes
Nick Schieda	Ottawa Hospital	No
Robert Siemens	Kingston General Hospital	Yes
Roland Sing		No
Tariq Aziz	St. Joseph Healthcare Hamilton	No
Rajiv Singal	Toronto East General Hospital	No