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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

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

An assessment conducted in January 2024 deferred the review of Evidence-based Series (EBS) 17-9. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 17-9 is comprised of 3 sections. You can access the summary and full report here:
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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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Evidence-Based Series 17-9: Section 1

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

Active Surveillance for the Management of Localized Prostate Cancer: Guideline Recommendations

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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 ≤ 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 ≤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.
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FURTHER QUALIFYING STATEMENTS

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

FUTURE RESEARCH

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

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Updating

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