



OVERVIEW

Active Surveillance

Introduction

The widespread use of prostate-specific antigen (PSA) blood tests for prostate cancer screening has resulted in a substantial increase in the numbers of patients diagnosed with early-stage disease who are at low risk for disease progression. In such patients, immediate aggressive surgical or radiation-based treatment may not be deemed necessary. A reasonable alternative in these circumstances may be active surveillance (AS), which allows the patient to defer treatment while monitoring for signs of disease progression; once these signs do appear, treatment is then initiated with the intention to cure the patient. The terms 'active management', 'expectant management', and 'conservative management' are often used to refer to AS. The term 'watchful waiting' is also sometimes used interchangeably with AS, but these approaches are now understood to differ in intent and process. In contrast to the expectation that curative treatment will be triggered that is inherent in AS, watchful waiting refers to the practice of delaying any type of intervention and initiating treatment only for palliative (i.e., non-curative) purposes after significant disease progression.

Multiple criteria define candidacy for AS; a common definition is based on a Gleason score (a measure of tumor aggression) of 6 or less, PSA levels 10 ng/ml or less, and a stage between T1c and T2a. Other criteria that may be used include 33% or less positive cores (biopsy samples), or 50% or less single core involvement. Active surveillance can also be an option for patients for whom prostate cancer is unlikely to be the cause of death; for example, patients with short life expectancy or other significant illnesses.

When a patient opts for active surveillance, he is put on a regular monitoring schedule. While there is no universal standard protocol for active surveillance, monitoring schedules often include serial PSA blood tests every 3 months to one year, digital rectal exams every 6 months to one year, and repeat biopsies as often as every year. Some providers also use bone or CT scans to monitor for metastases, complete blood counts to monitor for anemia, and examination of other physical symptoms such as fatigue, weight loss, or weakness. Thresholds to trigger definitive treatment in patients on active surveillance are also not universally agreed upon. A

rapid rate of PSA increase, or the “PSA velocity”, is used by some physicians as an indicator of aggressive disease. Others consider the doubling of a PSA level within 3-4 years (i.e., “PSA doubling time”) to be the most reliable indicator of disease progression. Still others contend that results of repeat biopsies provide the best predictor of disease progression. Because the natural history of prostate cancer is poorly understood, clinicians must rely on these triggers to determine when definitive treatment should be initiated.

As with all management options for prostate cancer, the long term effects of active surveillance on patient survival as well as cancer progression have not been definitively determined, although large-scale clinical trials examining these issues are currently underway. The primary advantage of the strategy is that it allows the patient to defer any side effects or discomfort from more aggressive forms of treatment. The main risk is undetected disease progression and/or metastases. Key areas of uncertainty, many of which this appraisal seeks to address, include:

- 1) The disease-specific and overall mortality of patients managed on active surveillance.
- 2) Evidence on the relative performance of varying protocols for active surveillance.
- 3) Variability in practice (e.g., measurement of progression, frequency of monitoring, triggers for therapy) by individual clinicians and/or treatment centers.
- 4) Clinical and cost-effectiveness of active surveillance relative to other management alternatives (i.e., surgery, radiation therapy modalities).
- 5) How best to share existing evidence and remaining uncertainties with patients and families to inform decision-making.

Professional Organization and Agency Recommendations

- American Urological Association (2007):
<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf>
The AUA has concluded that active surveillance is considered one of the viable monotherapy options for clinically localized, low-risk prostate cancer, along with radical prostatectomy, external beam radiotherapy, and interstitial brachytherapy, and that “study outcomes data do not provide clear-cut evidence for the superiority of any one treatment.”
- National Comprehensive Cancer Network (2008):
http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf
The NCCN Prostate Cancer Panel Members stated that “patients with clinically localized cancer who are candidates for definitive treatment and choose active surveillance should have regular follow up” of PSA as often as every 3 months and at least every 6 months, DRE as often as every 6 months

and at least every 12 months, and needle biopsy as often as annually for patients with life expectancy >10 years (less often for patients with life expectancy <10 years).

- American Cancer Society (2008):
http://www.cancer.org/docroot/CRI/content/CRI_2_4_4X_Expectant_Therapy_Watching_and_Waiting_36.asp?sitearea=
In an online guide on prostate cancer, active surveillance is suggested as a possible treatment for men who are older or have other health problems, but not for younger, healthy patients with fast-growing cancer. The pros and cons of watchful waiting and active surveillance are described as not well understood.
- National Institute for Clinical Excellence (2008):
<http://www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline.pdf>
In the NICE guidance on the diagnosis and treatment of prostate cancer, active surveillance is recommended to be the first option presented to patients with low-risk, localized cancer who are eligible for radical treatment.
- Association of Comprehensive Cancer Centres, Dutch Urological Association (2007):
http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=575
The ACCC's guidelines for treatment of localized prostate cancer indicate that "active monitoring is preferred for patients with low risk disease (T1c-2a, Gleason <7, PSA <10 ng/mL) with advanced age (>75 years). With this approach, the patient should be informed that life expectancy is not determined by the prostate cancer and that each treatment is associated with a risk of adverse effects. Active monitoring may also be considered for patients with moderate or high risk disease if they have obvious comorbidity and advanced age, which negatively influences life expectancy."
- European Association of Urology (2007):
http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf
Active surveillance is indicated for younger patients with localized stage T1a prostate cancer with a life expectancy of >10 years and for asymptomatic patients with stage T1b-T2b cancer. Re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended.

Recent Technology Assessments

- Agency for Healthcare Research and Quality (2008):
<http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=9&DocID=79#section4>

In an analysis of the comparative risks, benefits, and outcomes of therapeutic options for clinically-localized prostate cancer, including radiation therapy, radical prostatectomy, and active surveillance, AHRQ concluded that “no one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects.”

Coverage Policies

No specific policies on active surveillance, active monitoring, or watchful waiting were identified from the Centers for Medicare and Medicaid Services or private health plans.

Ongoing Research (from www.clinicaltrials.gov)

Trial Sponsor /Title	Design	Primary Outcomes	Populations	Variables	Comments
Dep. of Veterans Affairs, NCI, AHRQ (NCI high priority trial) NCT00007644 "PIVOT Trial"	RCT	<ul style="list-style-type: none"> ▪ All cause mortality ▪ CAP mortality ▪ Survival – disease free and progression free ▪ Quality of life ▪ Cost effectiveness 	<ul style="list-style-type: none"> ▪ N = 1,050 ▪ Age < 75 	Radical prostatectomy vs. Palliative expectant management	Final data collected November 2009.
Oxford Radcliffe Hospital NCT00632983 "ProtecT Study"	RCT	<ul style="list-style-type: none"> ▪ Survival ▪ Disease progression ▪ Complications ▪ Quality of life 	<ul style="list-style-type: none"> ▪ N=2050 	Watchful waiting vs. radical prostatectomy vs. radiation	Multi-center study. Final data collection 2013.
National Cancer Institutes of Canada and United States NCT00499174 "START Trial"	RCT	<ul style="list-style-type: none"> ▪ Disease-specific survival ▪ QOL ▪ Overall survival ▪ Progression after radical intervention ▪ ADT initiation ▪ Biomarkers and PSA doubling-time 	<ul style="list-style-type: none"> ▪ N=2,130 ▪ Age ▪ PSA level of 10 ng/mL or less and Gleason score 6 or less 	Standard treatment (surgery, brachytherapy, EBRT, vs. active surveillance)	Final data collection 2023
MD Anderson Cancer Center NCT00490763	Prospective Observational	<ul style="list-style-type: none"> ▪ 5-year disease progression ▪ Psychosocial adjustment and QoL ▪ 10-year disease progression 	<ul style="list-style-type: none"> ▪ N=650 ▪ Low-risk pts who choose active surveillance 	Active surveillance	Final data collection 2020