Published in final edited form as:

Curr Opin Oncol. 2012 May ; 24(3): 243–250. doi:10.1097/CCO.0b013e3283527f99.

Active surveillance for prostate cancer: past, present and future

Eric A. Singer[a], **Aradhana Kaushal**[b], **Baris Turkbey**[c], **Anna Couvillon**[d], **Peter A. Pinto**[a], **Howard L. Parnes**[e]

[a]Urologic Oncology Branch, Bethesda, Maryland, United States

[b]Radiation Oncology Branch, Center for Cancer Research, Bethesda, Maryland, United States

[c]Molecular Imaging Program, Bethesda, Maryland, United States

[d]Medical Oncology Branch, Cancer Research Center, Bethesda, Maryland, United States

[e]Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland, United States

Abstract

Purpose of review—This article reviews recent developments in the use of active surveillance for localized prostate cancer.

Recent findings—The treatment of localized prostate cancer continues to be a major challenge for urologic oncologists. Screening with prostate-specific antigen has resulted in increased numbers of low-risk prostate cancers being detected. Aggressive whole-gland therapy with surgery, or radiation therapy is associated with potentially life-altering treatment-related side effects such as urinary incontinence, bowel toxicity and erectile dysfunction. The goal of active surveillance is to avoid or delay the adverse events associated with prostate cancer therapy while still allowing for curative intervention in the future, if needed.

Summary—Active surveillance is a reasonable treatment option for many men with low-risk, and some men with intermediate-risk, prostate cancer. Additional research is needed to determine the optimal active surveillance inclusion criteria, monitoring schedule, and treatment triggers. It is hoped that advances in prostate imaging, biomarkers, and focal therapy will foster greater use of active surveillance in appropriately selected men to optimize quality-of-life without compromising cancer outcomes.

Keywords

active surveillance; focal ablation; multiparametric MRI; prostate cancer; prostate-specific antigen; screening; watchful waiting

Correspondence to Howard L. Parnes, MD, Chief, Prostate and Urologic Cancer, Research Group, Division of Cancer Prevention, National Cancer Center, National Cancer Institute, Bethesda, MD, United States. Tel: +1 301 402 3606; fax: +1 301 435 1564; parnesh@mail.nih.gov.

Conflicts of interest

The authors have no conflicts of interest to disclose.

INTRODUCTION

Prostate cancer continues to be a significant burden on men's health. Globally, more than 900000 new cases of prostate cancer are diagnosed and over 250000 deaths are expected annually from the disease [1]. Among men in developed nations, prostate cancer has the highest incidence and third highest mortality rate of any malignancy [1]. Within the United States, prostate cancer affects more men than any other noncutaneous malignancy with an estimated 240890 new cases and 33720 deaths anticipated in 2011 [2].

The therapeutic landscape of prostate cancer has improved dramatically in the past few years with the approval of several agents that have been shown to prolong the lives of men with advanced, castration-resistant disease [3–5]. However, for men with localized prostate cancer, who constitute the vast majority of men diagnosed with the disease, the traditional treatments of surgical excision or radiation therapy, and their attendant side-effects, remain largely the same [6,7].

The widespread use of prostate-specific antigen (PSA)screeninginthe1990s led to a marked increase in prostate cancer detection [2]. Although the effect of screening on prostate cancer mortality was not known, early detection was intuitively felt to be advantageous by many in the medical community [8–13]. Subsequently, two major prospective clinical trials, one in the United States and one in Europe, were performed to assess the risks and benefits of prostate cancer screening.

The prostate, lung, colorectal and ovarian screening trial (PLCO), a randomized clinical trial of prostate cancer screening in more than 75000 men (aged 55–74), sponsored by the National Cancer Institute, did not show a mortality benefit for annual screening after 7–10 years of follow-up [relative risk(RR)1.13; 95% confidence interval(CI), 0.75–1.70] [14].

With three additional years of follow-up, the results were essentially unchanged (RR 1.09, 95% CI 0.87-1.36) [15■]. Despite the fact that more than half of the men in the control group received PSA testing as part of their routine medical care outside of the trial (contamination), significantly more cancers (about 20%) were still detected in the screened arm. Nevertheless, PLCO can be viewed as a comparison of regular screening versus less regular screening, rather than as a comparison of screening versus no screening.

In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC), with a median follow-up of 9 years, reported a 20% reduction (95% CI 0.65-0.98) in prostate cancer mortality associated with PSA testing every 2–4 years in 162243 men aged 55–69. This trial had a much lower rate of contamination and consequently an even greater increase in prostate cancer diagnoses (about 70%) on the screened arm than was seen in the PLCO trial. However, the ERSPC investigators estimated that 1410 men had to be screened and 48 treated for every prostate cancer death averted [16]. Although the number needed to treat might decrease with longer follow-up, these findings underscore the potential risk of overtreatment associated with prostate cancer screening [17]. Interestingly, as many as 30% of the men with screen-detected cancer in the Goteborg cohort of the ERSPC, which had the greatest prostate cancer mortality reduction among all the ERSPC sites (RR 0.56, 95% CI 0.39-0.82), were still on active surveillance as of the most recent follow-up [18].

The publication of the initial mortality data from the PLCO and ERSPC led the United States Preventive Services Task Force (USPSTF) to update their 2008 report on the benefits and harms of PSA-based screening [19■]. They subsequently issued a draft report (posted on-line for public comment until November 2011) giving PSA screening a 'D' rating, indicating moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. This would broaden the USPSTF's previous recommendation against PSA-based screening in men 75 years of age or older [20]. Although many professional groups such as the American Urological Association, American Association of Clinical Urologists, and Society of Urologic Oncology issued rebuttals supporting various PSA-based screening strategies, the USPSTF analysis served to focus attention on the problem of over treatment. This has led to renewed interest in active surveillance for the management of localized prostate cancer [21■■].

ACTIVE SURVEILLANCE: PAST

Observational management strategies are not new to prostate cancer. Watchful waiting, a term sometimes confused with active surveillance, is a treatment strategy that is often used for older men with significant comorbidities. Men on watchful waiting have been diagnosed with prostate cancer and are not treated until their disease becomes symptomatic, which is usually associated with locally advanced or metastatic disease. Once symptomatic, palliative interventions such as androgen deprivation therapy via surgical or medical castration, focal radiation to alleviate bone pain, or transurethral resection of the prostate to relieve bladder outlet obstruction are often utilized.

In contrast, active surveillance does not delay therapy until a man is symptomatic and no longer curable. The goal is to closely monitor men for changes in the aggressiveness of their cancer via serial biopsies and PSA measurements and, if an unfavorable change is detected, to offer definitive local therapy with curative intent. The Scandinavian Prostate Cancer Group-4 (SPCG-4) and the Prostate Cancer Intervention Versus Observation Trial (PIVOT) are reassuring in this regard. The SPCG-4 compared radical prostatectomy with watchful waiting in a 95% nonscreen-detected cohort in Sweden. Despite substantially delayed intervention by current practice standards, surgery still produced significant improvements in overall and prostate cancer-specific survival [22]. This suggests that the window of curability is relatively wide following a diagnosis of low-risk, screen-detected disease. PIVOT compared radical prostatectomy with watchful waiting in men with screen-detected, localized prostate cancer. With a median follow-up of 10 years (range 7.3–12.6 years), surgery did not reduce overall or prostate-cancer specific mortality compared with a purely palliative expectant management approach, at least among men with PSA values 10ng/ml or less or in men with low-risk prostate cancer [21■■,23].

Randomized clinical trials of active surveillance appear to be infeasible in North America as evidenced by the recent closure of the Surveillance Therapy Against Radical Treatment (START) for favorable risk prostate cancer trial – a US Intergroup trial sponsored by National Cancer Institute (NCI) Canada – for failure to meet its accrual goals. In contrast, the Prostate Testing for Cancer and Treatment (ProtecT) trial, a randomized comparison of

active monitoring versus treatment in approximately 3000 men in the United Kingdom, is expected to report major outcomes in 2016 [24].

Although it is clear that active surveillance has a vital role to play in reducing the harms associated with overtreatment of prostate cancer, several challenges remain [6,7]. These include elucidating the optimal inclusion criteria, surveillance regimen and triggers for intervention. Although these issues are not currently being addressed by randomized trials, several academic centers have published single-arm, cohort studies, providing a framework for future research comparing different active surveillance strategies [21■■].

ACTIVE SURVEILLANCE: PRESENT

A recent National Institutes of Health State-of-the-Science meeting concluded that active surveillance is a viable option that ‘should be offered’ to patients with low-risk prostate cancer [21■■]. However, fewer than 10% of low-risk prostate cancer patients pursue a delayed intervention approach despite the known side effects and uncertain benefits of definitive therapy in this setting [7,25]. The absence of clear evidence regarding the treatment options for low-risk prostate cancer requires that the pros and cons of the available approaches be presented in an unbiased manner [21■■].

Selection criteria

Although selection criteria for active surveillance have not been compared in randomized trials, epidemiological data and prospective case series provide a reasonable basis upon which to identify appropriate candidates for this approach [26–28]. The health professional follow-up study, a large prospective cohort study recently reported on the outcome of delayed prostate cancer intervention in 342 (10.3%) of 3331 cohort participants diagnosed with prostate cancer between 1986 and 2007. About 50% of these men were ultimately treated at a median follow-up of 8.6 years. Age less than 70 years, clinical stage more than T1, Gleason score above 6 and PSA more than 20 were all significantly associated with progression to treatment on multivariate analysis [27].

A population-based study in the United Kingdom, where PSA screening and definitive therapy is less common than in the United States, examined the factors associated with long-term outcome among men treated conservatively for localized prostate cancer. Of 1176 men with untreated disease, the most powerful predictor of prostate cancer death was Gleason score. Baseline PSA level was the second most important factor, although it had only about one-fourth the predictive value of Gleason score in this regard. Together, Gleason score and PSA separated men into three prognostic groups with very different outcomes. Age, extent of disease and clinical stage were of limited additional prognostic value [28].

Patient characteristics

A patient’s age and comorbidities are central to the active surveillance decision-making process; more restrictive eligibility criteria should generally be required for men with longer life expectancies [29]. At the NCI, we offer active surveillance to selected men, regardless of age, provided they are willing to accept the uncertainties and close follow-up associated with this approach. Of course, there are also uncertainties, and a need for periodic follow-up, after

definitive therapy. Notably, the SPCG-4 randomized trial comparing surgery with watchful waiting, found no differences in anxiety and depression between the two groups [30]. In a recent decision analysis using a simulation model, active surveillance was associated with the greatest quality-adjusted life expectancy in men with low-risk prostate cancer, although individual preferences were important factors in this regard [31■].

Ultimately, treatment decisions for men with early stage prostate cancer must balance age, health status and personal preferences against estimates of disease aggressiveness coupled with the potential risks and benefits of definitive intervention [32]. These decisions should reflect the importance a man assigns to the possible outcomes associated with each treatment approach and his attitude towards risk [33].

Tumor characteristics

The tumor characteristics used to identify appropriate candidates for inclusion in the three largest, single-institution series of active surveillance are shown in the Table 1. The similarities in the eligibility criteria utilized are more apparent than the differences; however, they do represent a range of inclusiveness reflecting underlying attitudes towards the fundamental challenge in active surveillance, which is to avoid overtreatment without compromising cure.

As shown, the eligibility criteria utilized by the University of Toronto were most inclusive from 1995 to 1999, during which they allowed men with Gleason score 3+4=7 disease and PSA levels up to 15, depending on age and comorbidities. Beginning in January 2000, they restricted eligibility to more favorable risk men [34■■]; however, as of their most recent update, 29% of the entire cohort were D'Amico intermediate risk based on Gleason score 3+4=7 or PSA greater than 10ng/ml [35]. Notably, stage and Gleason score, but not baseline PSA levels, were significantly associated with progression to definitive intervention [34■■].

The Johns Hopkins University cohort represents a more highly selected case series requiring a PSA density less than 0.15ng/ml per ml, Gleason score less than 7, less than three involved cores and at least 50% involvement of any one core [36■■]. These criteria have a more than 90% positive predictive value (PPV) for identifying organ-confined disease [37,38]. The University of California, San Francisco (UCSF) eligibility criteria are similar to those used at Johns Hopkins, with the exception of the PSA density requirement. Although their formal criteria require low-risk disease on the basis of clinical stage, Gleason score, and PSA, they do offer active surveillance to 'strongly motivated' men with higher risk disease [39■■]. As this case series matures, it will provide increasingly useful data on the potential role of active surveillance in men with low-volume, intermediate-risk disease.

Monitoring

The goal of monitoring during active surveillance is to identify the subset of patients with biologically aggressive prostate cancer, although, their disease is still curable. The monitoring guidelines and triggers for intervention utilized by Toronto, Johns Hopkins, and UCSF are summarized in the Table 1. As shown, PSA levels are monitored on a 3–6 month basis in all three cohorts, with or without a digital rectal examination (DRE). The major difference is the frequency of surveillance biopsies. Follow-up biopsies are performed yearly

at Johns Hopkins. In Toronto, they are routinely done every 3–4 years, with additional biopsies performed based on PSA kinetics, change in clinical stage or for evidence of progression on imaging studies. Given the risk of urosepsis due to antibiotic-resistant organisms and the more than twofold increased risk in hospitalizations following standard, multicore prostate biopsies, strategies to reduce this procedure are clearly needed [40,41■]. Therefore, many active surveillance programs have begun to incorporate imaging into their monitoring protocols, reflecting recent advances in MRI and PET [42].

Triggers for intervention

The Toronto group utilized PSA kinetics to guide treatment recommendations from the inception of their active surveillance program in 1995–2008. They used a PSA doubling time (PSADT) of less than 2 years as a trigger for intervention until 2000, at which time they lowered their threshold for intervention to a PSADT of less than 3 years [34■■,43]. However, given concerns regarding the reliability of PSA kinetics and the emerging role of imaging in the active surveillance setting, starting in 2008, they began using PSA kinetics as an indication for further evaluation with MRI and/or repeat prostate biopsy rather than as a trigger for intervention [21■■,44,45]. This change in protocol is supported by a recent analysis of the Hopkins cohort showing no association between PSADT and progression on biopsy [46■].

For patients with a baseline Gleason score of 3+3=6, the Toronto group has used a two-step increase in Gleason score to 4+3=7 as a trigger for intervention. At UCSF, treatment is recommended for a Gleason score of 4+3=7 in patients with a baseline score of 3+4=7, or the presence of any pattern 4 in men with baseline scores of 3+3=6. PSA kinetics and evidence of progression on biopsy, DRE or MRI are also used to prompt treatment recommendations. At Johns Hopkins, the presence of any pattern 4 disease, more than two involved biopsy cores or more than 50% involvement of any one core, are triggers for intervention.

Outcomes

Nearly 3000 men have been entered on single institution and multicenter active surveillance protocols [47]. Whereas the median follow-up of these case series is still relatively short, ranging from about 2 to 7 years, more than 200 patients have been followed for over 10 years. Although one-third of the men being followed in these case series have progressed to definitive therapy, the overall cancer-specific survival for the cohort is 99.7% [34■■].

The most mature case series is that of the University of Toronto, where 450 men have been followed for a median of 8 years (range 1–16 years). Although 29% of the men in this cohort had intermediate-risk disease due to a Gleason score 3+4=7 or PSA more than 10ng/ml, the 10-year actuarial cancer-specific survival for the entire group is 97.2% [34■■]. At 5 and 10 years, 72 and 62% of patients remained on active surveillance. Overall, 135 of the 450 (30%) men in this cohort have progressed to intervention. Of these 450 men, 65 (14%) met criteria for short PSADT and 36 (8%) for progression of tumor grade. Only 14 patients (3%) stopped active surveillance because of personal preference. Although the biochemical failure rate at 5 years was 53% among the 125 men who underwent definitive therapy, this

represents 13% of the overall 450 patient cohort, which is similar to that expected for favorable-risk patients receiving immediate therapy [34■■].

The UCSF cohort is comprised of 376 patients meeting low-risk criteria and 90 intermediate-risk criteria. Overall, 129 (34%) men in this cohort had an increase in Gleason score on follow-up biopsy [48■■]. At 3–4 years, about half of the men in each risk group remain progression-free.

Of 769 active surveillance participants in the Johns Hopkins cohort, which now has a median follow-up of 2.7 years, 603 (78.4%) satisfied all of the Epstein criteria for very low-risk disease. Patients who did not fulfill all of these criteria were significantly more likely to undergo definitive intervention. However, compliance with these criteria was not significantly associated with Gleason score upgrading on subsequent biopsies [36■■].

The overall median time to intervention at Hopkins was 6.5 years. For the 33.2% of men who have been definitively treated, the median time to intervention was 2.2 years [36■■]. Only 106 men or 13.8% of the total cohort had an increase in Gleason score on follow-up biopsy. This contrasts with the experiences of UCSF and Toronto, which reported Gleason score upgrading in approximately one-third of men [39■■,49]. The majority of upgrading in all three case series occurred within the first 2 years, suggesting that the change in Gleason score was more likely to reflect misclassification of tumor grade due to variable sampling of the gland than progression (dedifferentiation) of existing disease.

Population-based studies provide further evidence for Gleason score misclassification on prostate biopsy. Freedland *et al.* [50] reported an upgrading rate of 27% among 1113 patients treated with immediate prostatectomy. Higher baseline PSA values, more biopsy cores with cancer and obesity were associated with upgrading at surgery, whereas, a biopsy Gleason score of 3+4=7 and having at least an eight core biopsy were inversely correlated with upgrading. Suardi *et al.* [51] compared biopsy to prostatectomy in 4885 men meeting various criteria for active surveillance. They found upgrading rates of 39–56% depending on the criteria utilized.

ACTIVE SURVEILLANCE: FUTURE

In order to further refine the inclusion factors and treatment triggers discussed above, researchers are looking to advances in biomarkers, imaging, and focal therapy to optimize active surveillance regimens and improve patient outcomes. In addition, men on active surveillance represent an important cohort for discovery and implementation of prostate cancer prevention strategies.

Biomarkers

Numerous studies are examining potential replacements for or adjuncts to serum PSA. For example, in a prospective study of 106 men with low-risk prostate cancer on biopsy who subsequently underwent radical prostatectomy, a significant linear correlation was observed between urinary prostate cancer antigen 3 and tumor volume, suggesting that this biomarker

could be used to justify active surveillance in some men who would otherwise be excluded on the basis of standard biopsy criteria [52].

Identification of the molecular alterations that drive tumor development and progression could have profound implications for active surveillance patient selection. For example, the TMPRSS2-ERG gene fusion transcript, which can be detected in urine, has been associated with prostate cancer aggressiveness. However, it has also been associated with less aggressive disease. Large population-based studies will be required to determine whether this gene rearrangement confers prognostic value, after controlling for Gleason score and PSA [52–55].

Imaging

The utility of active surveillance is dependent upon accurate assessment of disease grade and extent [45]. Imaging, specifically multiparametric MRI, has garnered significant attention for its ability to guide transrectal prostate biopsies, allowing for a more accurate assessment of a man's disease burden and reducing misclassification [56■,57■]. The ability of MRI to depict zonal anatomy facilitates the diagnosis of anterior tumors, which are difficult to detect by DRE and are often missed on TRUS-guided biopsy [58,59■]. The MRI characteristics of prostate lesions have also been shown to correlate with D'Amico risk stratification [60]. Although imaging is not expected to obviate the need for histologic confirmation, it is likely to help decrease the frequency of surveillance biopsies, thereby reducing an important source of morbidity for men on active surveillance [58,61].

An important caveat is that diagnostic information obtained from increasingly sensitive imaging modalities is likely to add to the stage and grade migration that has occurred in prostate cancer over the past 25 years [62]. Ever-increasing detection of micro foci of 'high-grade' disease will necessitate ongoing reassessments of risk categories to avoid excluding patients who may benefit from this approach.

Focal ablation

Using MRI to target prostate tumors has also furthered interest in focal ablation. Rather than treating the whole gland with surgery or radiation, destroying the dominant lesion may provide adequate cancer control while avoiding bowel, bladder, and sexual function sequelae[63].The benefits of focal ablation, and specifically whether it will improve cancer outcomes compared with active surveillance, remain to be determined in well designed, prospective studies. A recently opened feasibility study at the NCI is using laser energy to ablate biopsy-confirmed tumors (Gleason 3+3 or 3+4) visible on multiparametric MRI in men who would otherwise be candidates for active surveillance (NCT01377753) [64].

Chemoprevention

The term 'chemoprevention' refers to the administration of natural or synthetic agents to reverse, inhibit, slow or prevent the development of cancer [65]. Given that approximately one-third of men on active surveillance are likely to progress over 5 years, many would benefit from an intervention to slow the transformation of their prostate cancer from an indolent to a more aggressive phenotype [47]. In addition, active surveillance presents an

opportunity to evaluate potential chemopreventive agents. For example, in a placebo-controlled trial in 302 men with low-risk prostate cancer being managed expectantly, treatment with dutasteride (a drug that inhibits the conversion of testosterone to the more potent androgen, dihydrotestosterone) increased the likelihood of having a negative surveillance biopsy [66]. Additional NCI-sponsored chemoprevention trials in men on active surveillance are currently being planned.

CONCLUSION

Active surveillance is a good option for many men with localized prostate cancer, although research is needed to optimize inclusion criteria, monitoring protocols and treatment triggers. The influence of imaging, biomarkers, and focal therapy on the implementation of active surveillance is expected to grow in the coming years. The use of MRI to improve the accuracy of biopsies, thereby minimizing the risk of misclassification, and to reduce the frequency of surveillance biopsies, is likely to increase the acceptance of active surveillance in the community. However, patient and physician education will be needed if this approach is to receive the consideration it deserves as an alternative to immediate therapy.

Men on active surveillance represent an important cohort for discovery of agents to prevent or slow the progression of prostate cancer, and many could potentially benefit from such an approach. The discovery of relevant biomarkers to facilitate the development of chemopreventive agents and to reduce overtreatment brought on by the two-edged sword of increasingly powerful diagnostic technology remains a major unmet need.

Acknowledgements

The authors thank Debbie McNally, RN, Luz Giodano, PA, and Arlene del Mundo, RN, Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda.

This research was funded by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research, Bethesda, MD.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 349).

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69–90. [PubMed: 21296855]
2. Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61:212–236. [PubMed: 21685461]
3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364:1995–2005. [PubMed: 21612468]

4. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376:1147–1154. [PubMed: 20888992]
5. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363:411–422. [PubMed: 20818862]
6. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. JAMA 2011; 306:1205–1214. [PubMed: 21934053]
7. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008; 358:1250–1261. [PubMed: 18354103]
8. Shibata A, Ma J, Whittemore AS. Prostate cancer incidence and mortality in the United States and the United Kingdom. J Natl Cancer Inst 1998; 90:1230–1231. [PubMed: 9719085]
9. Lu-Yao G, Albertsen PC, Stanford JL, et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ 2002; 325:740–745. [PubMed: 12364300]
10. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. Urology 2001; 58:417–424. [PubMed: 11549491]
11. Concato J, Wells CK, Horwitz RI, et al. The effectiveness of screening for prostate cancer: a nested case-control study. Arch Intern Med 2006; 166:38–43. [PubMed: 16401808]
12. Kopec JA, Goel V, Bunting PS, et al. Screening with prostate specific antigen and metastatic prostate cancer risk: a population based case-control study. J Urol 2005; 174:495–499; discussion 499. [PubMed: 16006879]
13. Labrie F, Candas B, Dupont A, et al. Screening decreases prostate cancer death: first analysis of the 1988 Quebec prospective randomized controlled trial. Prostate 1999; 38:83–91. [PubMed: 9973093]
14. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009; 360:1310–1319. [PubMed: 19297565]
15. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up. J Natl Cancer Inst 2012; 104:125–132. [PubMed: 22228146] ■This is an update to the 2009 PLCO prostate cancer screening trial results with three additional years of follow-up.
16. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009; 360:1320–1328. [PubMed: 19297566]
17. Gulati R, Mariotto AB, Chen S, et al. Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates. J Clin Epidemiol 2011; 64:1412–1417. [PubMed: 22032753]
18. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol 2010; 11:725–732. [PubMed: 20598634]
19. Lin K, Croswell JM, Koenig H, et al. Prostate-specific antigen-based screening for prostate cancer: an evidence update for the U.S. Preventive Services Task Force, U.S.D.o.H.a.H. Services. Rockville: Agency for Healthcare Research and Quality; 2011 pp. 1–56.■AHRQ Publication No. 12–05160-EF-1. USPSTF update that gave PSA testing for prostate cancer screening a ‘grade D’ draft recommendation.
20. Calonge N, Petitti DB, DeWitt TG, et al. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008; 149:185–191. [PubMed: 18678845]
21. NIH, National Institutes of Health State-of-the-Science Conference: Role of Active Surveillance in the Managment of Men with Localized Prostate Cancer, U.S.D.o.H.a.H. Services. Bethesda: National Center for Biotechnology Information (US); 2011 pp. 1–127.■■State-of-the-science conference on active surveillance for localized prostate cancer featuring many of the thought leaders in the field.
22. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl JMed 2011;364:1708–1717. [PubMed: 21542742]
23. Wilt TJ, Brawer MK, Barry MJ, et al. The prostate cancer intervention versus observation trial:VA/NCI/AHRQ cooperative studies program #407 (PIVOT): design and baseline results of a

randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. Contemp Clin Trials 2009; 30:81–87. [PubMed: 18783735]

24. Lane JA, Hamdy FC, Martin RM, et al. Latest results from the UK trials evaluating prostate cancer screening and treatment: the CAP and ProtecT studies. Eur J Cancer 2010; 46:3095–3101. [PubMed: 21047592]
25. Harlan SR, Cooperberg MR, Elkin EP, et al. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. J Urol 2003; 170:1804–1807. [PubMed: 14532780]
26. Lawrentschuk N, Klotz L. Active surveillance for low-risk prostate cancer: an update. Nat Rev Urol 2011; 8:312–320. [PubMed: 21519351]
27. Shappley WV 3rd, Kenfield SA, Kasperzyk JL, et al. Prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort. J Clin Oncol 2009; 27:4980–4985. [PubMed: 19720918]
28. Cuzick J, Fisher G, Kattan MW, et al. Long-term outcome among men with conservatively treated localised prostate cancer. Br J Cancer 2006; 95:1186–1194. [PubMed: 17077805]
29. Klotz L. Active surveillance for prostate cancer: a review. Curr Urol Rep 2010; 11:165–171. [PubMed: 20425623]
30. Steineck G, Helgesen F, Adolfsson J, et al. Quality of life after radical prostatectomy or watchful waiting. N Engl J Med 2002; 347:790–796. [PubMed: 12226149]
31. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. JAMA 2010; 304:2373–2380. [PubMed: 21119084] ■This article demonstrated that active surveillance produces higher quality-adjusted life expectancy scores than other therapies for clinically localized prostate cancer.
32. Smith MR. Effective treatment for early-stage prostate cancer—possible, necessary, or both? N Engl J Med 2011; 364:1770–1772. [PubMed: 21542749]
33. Barry MJ. Health decision aids to facilitate shared decision making in office practice. Ann Intern Med 2002; 136:127–135. [PubMed: 11790064]
34. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol 2010; 28:126–131. [PubMed: 19917860] ■■This is the most recent update on the University of Toronto active surveillance experience.
35. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998; 280:969–974. [PubMed: 9749478]
36. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011; 29:2185–2190. [PubMed: 21464416] ■■This is the most recent update to the Johns Hopkins Medical Institute active surveillance experience.
37. Bastian PJ, Mangold LA, Epstein JI, et al. Characteristics of insignificant clinical T1c prostate tumors. A contemporary analysis. Cancer 2004; 101:2001–2005. [PubMed: 15372478]
38. Lee MC, Dong F, Stephenson AJ, et al. The Epstein criteria predict for organ-confined but not insignificant disease and a high likelihood of cure at radical prostatectomy. Eur Urol 2010; 58:90–95. [PubMed: 19875227]
39. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol 2011; 29:228–234. [PubMed: 21115873] ■■This is the most recent update to the UCSF active surveillance experience.
40. Hadway P, Barrett LK, Waghorn DJ, et al. Urosepsis and bacteraemia caused by antibiotic-resistant organisms after transrectal ultrasonography-guided prostate biopsy. BJU Int 2009; 104:1556–1558. [PubMed: 20053186]
41. Loeb S, Carter HB, Berndt SI, et al. Complications after prostate biopsy: data from SEER-Medicare. J Urol 2011; 186:1830–1834. [PubMed: 21944136] ■This study determined that the hospitalization rate of medicare beneficiaries undergoing prostate biopsy was significantly higher than that of an un-biopsied control population.
42. Turkbey B, Albert PS, Kurdziel K, et al. Imaging localized prostate cancer: current approaches and new developments. AJR Am J Roentgenol 2009; 192:1471–1480. [PubMed: 19457807]

43. Choo R, Klotz L, Danjoux C, et al. Feasibility study: watchful waiting for localized low to intermediate grade prostate carcinoma with selective delayed intervention based on prostate specific antigen, histological and/or clinical progression. J Urol 2002; 167:1664–1669. [PubMed: 11912384]
44. Vickers AJ, Savage C, O'Brien MF, et al. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. J Clin Oncol 2009; 27:398–403. [PubMed: 19064972]
45. Raz O, Haider M, Trachtenberg J, et al. MRI for men undergoing active surveillance or with rising PSA and negative biopsies. Nat Rev Urol 2010; 7:543–551. [PubMed: 20930867]
46. Ross AE, Loeb S, Landis P, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. J Clin Oncol 2010; 28:2810–2816. [PubMed: 20439642] ■The authors conclude that postdiagnosis PSA changes are not predictive of adverse changes in tumor histology.
47. Cooperberg MR, Carroll PR, Klotz L. Active surveillance for prostate cancer: progress and promise. J Clin Oncol 2011; 29:3669–3676. [PubMed: 21825257]
48. Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. J Clin Oncol 2011; 29:2795–2800. [PubMed: 21632511] ■■Some men on active surveillance experience a Gleason score upgrade on repeat biopsy; early upgrades are often due to tumor undersampling while late upgrades may represent tumor dedifferentiation.
49. Choo R, Danjoux C, Morton G, et al. How much does Gleason grade of follow-up biopsy differ from that of initial biopsy in untreated, Gleason score 4–7, clinically localized prostate cancer? Prostate 2007; 67:1614–1620. [PubMed: 17823923]
50. Freedland SJ, Kane CJ, Amling CL, et al. Upgrading and downgrading of prostate needle biopsy specimens: risk factors and clinical implications. Urology 2007; 69:495–499. [PubMed: 17382152]
51. Suardi N, Capitanio U, Chun FK, et al. Currently used criteria for active surveillance in men with low-risk prostate cancer: an analysis of pathologic features. Cancer 2008; 113:2068–2072. [PubMed: 18792067]
52. Ploussard G, Durand X, Xylinas E, et al. Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance. Eur Urol 2011; 59:422–429. [PubMed: 21156337]
53. Auprich M, Chun FK, Ward JF, et al. Critical assessment of preoperative urinary prostate cancer antigen 3 on the accuracy of prostate cancer staging. Eur Urol 2011; 59:96–105. [PubMed: 20980098]
54. Auprich M, Haese A, Walz J, et al. External validation of urinary PCA3-based nomograms to individually predict prostate biopsy outcome. Eur Urol 2010; 58:727–732. [PubMed: 20619529]
55. Rubin MA, Maher CA, Chinnaiyan AM. Common gene rearrangements in prostate cancer. J Clin Oncol 2011; 29:3659–3668. [PubMed: 21859993]
56. Pinto PA, Chung PH, Rastinehad AR, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol 2011; 186:1281–1285. [PubMed: 21849184] ■MRI/ultrasound fusion-guided prostate biopsies increased cancer detection compared with standard transrectal ultrasound with 12 core biopsy.
57. Turkbey B, Mani H, Shah V, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol 2011; 186:1818–1824. [PubMed: 21944089] ■Multiparametric endorectal MRI of the prostate provides a positive predictive value for detecting prostate cancer approaching 100%.
58. Turkbey B, Bernardo M, Merino MJ, et al. MRI of localized prostate cancer: coming of age in the PSA era. Diagn Interv Radiol 2012; 18:34–45. [PubMed: 21922459]
59. Lawrentschuk N, Haider MA, Daljeet N, et al. 'Prostatic evasive anterior tumours': the role of magnetic resonance imaging. BJU Int 2010; 105:1231–1236. [PubMed: 19817743] ■MRI of the prostate is especially helpful for diagnosing unpalpable, anterior tumors, which are often found in men with elevated PSAs and previous negative biopises.

60. Rastinehad AR, Baccala AA Jr, Chung PH, et al. D'Amico risk stratification correlates with degree of suspicion of prostate cancer on multiparametric magnetic resonance imaging. J Urol 2011; 185:815–820. [PubMed: 21239006]

61. Turkbey B, Xu S, Kruecker J, et al. Documenting the location of systematic transrectal ultrasound-guided prostate biopsies: correlation with multiparametric MRI. Cancer Imaging 2011; 11:31–36. [PubMed: 21450548]

62. Albertsen PC, Hanley JA, Barrows GH, et al. Prostate cancer and the Will Rogers phenomenon. J Natl Cancer Inst 2005; 97:1248–1253. [PubMed: 16145045]

63. Hou AH, Sullivan KF, Crawford ED. Targeted focal therapy for prostate cancer: a review. Curr Opin Urol 2009; 19:283–289. [PubMed: 19357510]

64. NCI. MR Image Guided Therapy in Prostate Cancer. (2011) http://www.clinicaltrials.gov/ct2/show/NCT01377753?term=prostate+cancer+ablation&recr=Open&no_unk=Y&type=Intr&state1=NA%3AUS%3AMD&rank=2.

65. Sporn MB, Suh N. Chemoprevention of cancer. Carcinogenesis 2000; 21:525–530. [PubMed: 10688873]

66. Fleshner N, Lucia MS, Melich K, et al. Effect of dutasteride on prostate cancer progression and cancer diagnosis on rebiopsy in the REDEEM active surveillance study. J Clin Oncol 2011; 29(Suppl 7):Abstract 2.

67. Klotz L. Active surveillance for prostate cancer: for whom? J Clin Oncol 2005; 23:8165–8169. [PubMed: 16278468]

68. Warlick C, Trock BJ, Landis P, et al. Delayed versus immediate surgical intervention and prostate cancer outcome. J Natl Cancer Inst 2006; 98:355–357. [PubMed: 16507832]

KEY POINTS

- Active surveillance is a good option for many men with localized prostate cancer and should not be restricted to men with limited life expectancies.
- Research is needed to optimize inclusion criteria, monitoring protocols, and treatment triggers for active surveillance.
- Multiparametric MRI improves the accuracy of prostate biopsies, reducing the risk of misclassifying Gleason score at diagnosis, and can help reduce the frequency of surveillance biopsies.
- Men on active surveillance represent an important cohort for the development of agents to slow or inhibit progression of prostate cancer (chemoprevention) and may benefit from such interventions.

Table 1.

Active surveillance strategies

Cohort	Eligibility criteria	Monitoring		Triggers for intervention
		PSA/DRE	Biopsy	
University of Toronto [21■■,34■■,43,67]	T1b-T2b, GS ≤7, PSA ≤15 (1995–1999); T1c-T2a, GS ≤ 6, PSA ≤ 10, ≤2 cores positive and <50% involvement of any core (2000-present)	Every 3 months X 2, then every 6 months	Confirmatory 8–14 core biopsy within one year; then surveillance biopsy every 3–4 years (or more frequently as needed to evaluate suspicious findings on MRI or for borderline PSADT)	GS ≥4 + 3 = 7 or clinical progression confirmed by biopsy; PSADT <2 years (1995–1998); PSADT <3 years (1999–2008)[a]
Johns Hopkins [36■■,46■,68]	T1c, GS ≤6, PSA density<0.15 ng/ml per ml, ≤2 cores positive, ≤50% involvement of any core	Every 6 months	Every 12 months (including transition zone)	GS >6 or >2 cores positive or >50% involvement of any core
University of California, San Francisco [39■■,48■■]	T1 or T2a, GS ≤6, PSA <10, <33% of biopsy cores positive	Every 3 months	Every 12–24 months (including anterior gland)	GS >6 or increase PSAV >0.75 ng/ml per year or increase in volume of disease on biopsy, DRE or MRI

DRE, digital rectal examination; GS, Gleason score; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; T1, tumor is not palpable on digital rectal exam; T1c, cancers identified by biopsy performed because of an elevated PSA; T2, tumor is palpable but confined within the prostate gland; T2a, tumor involves no more than half of one lobe of the prostate; T2b, tumor involves more than half of one lobe, but not both lobes.

[a]Since 2008, PSADT has been used to prompt further evaluation with MRI or repeat biopsy, not intervention.