Active Surveillance in Men With Localized Prostate Cancer

A Systematic Review

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Background: Active surveillance (AS) and watchful waiting (WW) have been proposed as management strategies for low-risk, localized prostate cancer.

Purpose: To systematically review strategies for observational management of prostate cancer (AS or WW), factors affecting their utilization, and comparative effectiveness of observational management versus immediate treatment with curative intent.

Data Sources: MEDLINE and Cochrane databases (from inception to August 2011).

Study Selection: Screened abstracts and reviewed full-text publications to identify eligible studies.

Data Extraction: One reviewer extracted data, and another verified quantitative data. Two independent reviewers rated study quality and strength of evidence for comparative effectiveness.

Data Synthesis: Sixteen independent cohorts defined AS, 42 studies evaluated factors that affect the use of observational strategies, and 2 evidence reports and 22 recent studies reported comparisons of WW versus treatment with curative intent. The most common eligibility criteria for AS were tumor stage (all cohorts), Gleason score (12 cohorts), prostate-specific antigen (PSA) concentration (10 cohorts), and number of biopsy cores positive for cancer (8 cohorts). For monitoring, studies used combinations of periodic PSA testing (all cohorts), digital rectal examination (14 cohorts), and rebiopsy (14 cohorts). Predictors of receiving no active treatment included older age, comorbid conditions, lower Gleason score, tumor stage, PSA concentration, and favorable risk group. No published studies compared AS with immediate treatment with curative intent. Watchful waiting was generally less effective than treatment with curative intent; however, applicability to contemporary patients may be limited.

Limitations: Active surveillance and WW often could not be differentiated in the reviewed studies. Published randomized trials have assessed only WW and did not enroll patients diagnosed by PSA screening.

Conclusion: Evidence is insufficient to assess whether AS is an appropriate option for men with localized prostate cancer. A standard definition of AS that clearly distinguishes it from WW is needed to clarify scientific discourse.

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In 2011, more than 240 000 men were projected to be diagnosed with prostate cancer and 33 000 to die of the disease in the United States (1). Currently, most cases of prostate cancer are detected with prostate-specific antigen (PSA) screening. Most prostate cancer detected with PSA screening is expected to be early-stage, low-risk tumors (2). Patients with low-risk prostate cancer are more likely to die of non–prostate cancer causes (3, 4).

Many immediate active treatment options are available for localized prostate cancer. Most commonly, radical prostatectomy (RP) or radiation therapy (RT), with or without androgen deprivation therapy, are offered with curative intent. However, many men who are treated probably receive no clinical benefit because of the slow progression of their tumors (2). Active treatments also result in substantial adverse events, including impotence, urinary or bowel dysfunction, and other complications. Thus, determination of the appropriate management strategy for early-stage, low-risk prostate cancer is an important public health concern.

Active surveillance (AS) and watchful waiting (WW) are 2 observational strategies that involve forgoing immediate therapy for patients with prostate cancer. Active surveillance is curative in intent, and WW is palliative. Active surveillance is appropriate in men with disease that is believed to be indolent who do not require immediate therapy. Patients are monitored closely, often with a multifactorial follow-up, including periodic PSA testing, digital rectal examination (DRE), prostate imaging, and prostate biopsy. These patients are treated with surgery or radiation on evidence of biochemical, histologic, or anatomical progression, or at the patient's discretion. In practice, AS is generally used in relatively younger men with low-risk cancer who are otherwise healthy and may benefit from and tolerate aggressive therapies that are offered with curative intent upon cancer progression. Watchful waiting is typically a more passive strategy, with interventions—often palliative—triggered by symptomatic progression. Watchful waiting is usually reserved for older men with localized cancer or major comorbid conditions who are not likely to benefit from or tolerate aggressive curative treatment.

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CME quiz (preview on page I-4)
Conversion of graphics into slides

The National Cancer Institute and the Centers for Disease Control and Prevention sponsored a National Institutes of Health State-of-the-Science Conference in December 2011 to examine the role of AS in the management of early-stage, low-risk prostate cancer. The National Institutes of Health tasked the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program to provide an evidence review for use in this conference. The objective of this report is to summarize the existing literature on the role of AS in the management of early-stage, low-risk prostate cancer.

Methods

With input from experts in the epidemiology and treatment of prostate cancer, we developed and followed a standard protocol for all review steps. An evidence report that provides a detailed description of our methods, including the detailed literature search strategies, results, and conclusions, is available at the Effective Health Care Program's Web site (www.effectivehealthcare.ahrq.gov) (5).

Key Questions

The National Institutes of Health State-of-the-Science Conference Planning Committee crafted 5 key questions for the conference (http://consensus.nih.gov/2011/prostate.htm), and this paper focuses on 3 of them (**Appendix Table 1**, available at www.annals.org). A fourth question about the natural history of prostate cancer is used as background information, and the fifth question about future research needs is incorporated into the Discussion section. This paper preferentially reports on AS over WW; additional information on WW is provided in the full report (5).

Data Sources and Selection

Literature searches were performed in MEDLINE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Randomized Controlled Trials, and the Health Technology Assessment Database, from inception to August 2011. We searched for prostate cancer, AS, WW, and other related management strategies. We also searched MEDLINE for studies of specific databases, such as SEER (Surveillance, Epidemiology, and End Results) and CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor). Full search strategies are published elsewhere (5). We performed targeted searches of the Cost-Effectiveness Analysis Registry to identify additional economic evaluations of AS; we considered only the cost components of cost-utility and cost-effectiveness analyses. We also reviewed reference lists of included studies and systematic reviews, and studies suggested by technical experts. For comparative effectiveness, we relied on 2 previous AHRQ evidence reports on prostate cancer, updating their findings. Additional details about the data sources and eligibility criteria for each question are detailed in **Appendix Table 2** (available at www.annals.org). We excluded unpublished data and non–English-language articles.

Five reviewers participated in abstract screening and study selection. An iterative screening process was used for training and to ensure consistency in application of eligibility criteria. Abstracts were screened once, using a low threshold for inclusion. During full-text screening, equivocal articles were rescreened by at least 2 team members; and disagreements were resolved by consensus.

Data Extraction and Quality Assessment

Data from each study were extracted by 1 of 5 reviewers. Quantitative data were verified by another reviewer. We extracted information on study design features, enrollment years, patient and disease characteristics, interventions or predictors of interest, outcome effect sizes, and relevant qualitative findings.

For the comparative effectiveness question, we used predefined criteria to grade study quality as A (good), B (fair), or C (poor). We also rated the strength of the overall body of evidence for this question as high, moderate, low, or insufficient. Because of the descriptive nature of the reported information, we did not rate study quality and strength of evidence for other questions addressed in this review. Criteria for study quality and strength of evidence followed standard AHRQ practice (5–7). The quality assessment was rated by 1 reviewer and confirmed by at least 1 other. Disagreements were resolved by consensus. The strength of the evidence was determined by consensus.

Data Synthesis and Analysis

Study data were tabulated into summary tables (available in the full evidence report [5]) and synthesized qualitatively. An evidence map for studies on offer of, acceptance of, or adherence to AS was drawn using a weighted scatterplot. Meta-analysis was not performed due to clinical heterogeneity, potentially selective reporting, and substantial population overlap between studies using the same databases.

Role of the Funding Source

This project was funded under contract from the AHRQ, U.S. Department of Health and Human Services. The AHRQ did not participate in the literature search; determination of study eligibility criteria; data analysis or interpretation; or preparation, review, or approval of the manuscript for publication.

Results

Our literature search yielded 2175 citations. Of these, 914 articles were considered potentially eligible for inclusion on the basis of the titles and abstracts. An additional 66 citations from reference lists, expert recommendations, and targeted searches were also reviewed. After full-text screening, 195 papers, 2 evidence reports (8, 9) and their associated articles (10, 11), and 2 economic assessments (12, 13) were included in the evidence report. Of these, 121 unique publications were relevant to the questions ad-

dressed in the current article (**Appendix Figure 1**, available at www.annals.org).

Definitions of AS and Other Observational Management Strategies

Investigators have used the terms AS, WW, and others to denote observational management strategies, both with and without curative intent. We classified the identified protocols into those having curative intent (AS) and those in which intent was palliative (WW). We also extracted information from randomized, controlled trials (RCTs) where 1 group was assigned to observational management. Our review of the patient selection criteria in RCTs should be interpreted with caution. Trial eligibility criteria are based on patients' appropriateness for all interventions being tested. Thus, patients who meet eligibility criteria for a trial of active treatment versus observational management are likely to differ from the natural cohort of patients who are on AS or WW.

Patient Selection Criteria in AS Cohorts

Sixteen unique cohorts (**Appendix Table 3**, available at www.annals.org) reported eligibility criteria and monitoring protocols for AS in men with low-risk or clinically localized prostate cancer (T1 or T2). The most commonly used eligibility criteria were based on Gleason score (12 cohorts), PSA concentration (10 cohorts), and number of biopsy cores positive for cancer (8 cohorts). Less commonly, criteria were based on age and imaging findings. The reported cutoff for Gleason scores was generally a score of 6 or less (no pattern 4 or 5). Prostate-specific antigen concentration thresholds included 10 μg/L or less (7 cohorts), 15 μg/L or less (3 cohorts), and 20 μg/L or less (2 cohorts); some cohorts reported using more than 1 cutoff value. For cohorts that used the maximum number of biopsy cores positive for cancer, 5 permitted 2 or fewer cores and 3 permitted 3 or fewer.

Follow-up Protocols and Triggers for Intervention in AS Cohorts

All 16 cohorts included regular PSA testing in the follow-up protocol, and 14 used DRE. Routine prostate rebiopsy was performed in 14 cohorts. Frequency of PSA testing ranged from every 3 to every 6 months. Frequency of DRE ranged from every 3 to every 6 to 12 months. Rebiopsy was performed within 6 to 18 months after enrollment. One cohort performed a bone scan annually for the first 2 years and biennially thereafter. Another cohort selectively performed prostate magnetic resonance imaging every 1 to 3 years.

Twelve cohorts included Gleason score among their monitoring criteria for disease progression. Disease progression was generally defined as a Gleason score or pattern greater than those used in the eligibility criteria for AS. Nine cohorts included the minimum number of biopsy cores positive for cancer as part of their monitoring criteria. Two cutoffs were used: 3 or more positive biopsy cores in 6 cohorts, or 4 or more in 3 cohorts. Criteria for recommending curative treatments varied across the cohorts. The recommended treatments were not standardized and were generally left to the discretion of patients and their treating physicians.

Observational Strategies With Delayed Treatment of Palliative Intent

Thirteen cohorts reported follow-up protocols for patients who initially received no treatment and who were subsequently treated only upon symptomatic progression (14–26). Compared with AS cohorts, the 13 WW cohorts were less likely to use Gleason score thresholds or the number and percentage of cores positive for cancer as inclusion criteria. Both strategies used PSA-based criteria, but the thresholds in AS cohorts were lower (10 to 15 μg/L) than those used in other strategies (15 or 50 μg/L). Active surveillance protocols had more clearly defined follow-up processes than protocols with palliative intent. Further details are provided in the evidence report (5).

Factors Affecting the Offer of, Acceptance of, or Adherence to Observational Management

Twenty-five studies reported multivariable analyses of the association between different physician or patient factors or delivery system characteristics and the offer of, acceptance of, or adherence to observational management strategies (27–51). Most analyses were conducted on the CaPSURE or SEER-linked databases (in 12 and 4 studies, respectively). Sixteen additional studies explored similar associations by using qualitative research methods or surveys (52–67). An evidence map of studies considered for this question is presented in **Appendix Figure 2** (available at www.annals.org). No experimental study specifically examined factors addressing the offer of, acceptance of, or adherence to observational management. One systematic review detailed the use of decision-making tools and aids in managing men with prostate cancer (68).

Only 2 studies exclusively assessed AS (42, 43); other studies did not distinguish between AS and WW. Only findings pertaining to physician or patient factors are summarized here. Findings relevant to delivery system characteristics are described in the full evidence report (5). Of note, the outcomes of many examined studies were either actual management with an observational strategy (that is, a composite of the offer of, acceptance of, and adherence to such a strategy) or interruption (or cessation) of observational management. Thus, studies often did not differentiate between lack of adherence and other reasons for treatment change, such as disease progression.

Clinical Factors

Many multivariable analyses found that receipt of observational management strategies was predicted by older age (27, 29, 30, 34, 36, 40, 41, 44, 45, 47, 49, 50), more comorbid conditions (27, 32–34, 36, 40), lower Gleason score (40, 41, 50), well-differentiated tumors (27, 34), lower-stage disease (41, 47, 69), lower PSA concentration

(40, 41, 47), or lower risk on the D'Amico scale (29, 36). Multivariable analyses also found that interruption of observational management strategies was predicted by higher-stage disease (37, 45, 46), higher PSA concentration at diagnosis (37, 45), lower free–total PSA ratio (42), or more rapid PSA increase (32, 44) but not comorbid conditions (32, 45, 46) or Gleason score (37, 42, 44–46); 2 (37, 45) of 4 studies (32, 37, 45, 46) found an association with younger age; and 1 (35) of 3 studies (32, 35, 37) found an association with higher D'Amico risk score.

One survey of New Zealand general practitioners found that 45% would offer observational management if the patient's life expectancy was less than 10 years, but only 3% would do so for patients with a longer life expectancy (55). One survey of 1063 urologists and radiation oncologists reported that 10% to 20% would recommend observational management strategies for a 65-year-old man with a low PSA concentration, a Gleason score of 4 or 5, good health, a negative DRE result, and no evidence of nonlocalized disease (59). Few would recommend observational management strategies for men with higher PSA concentrations or Gleason scores.

Patient Factors

Four multivariable analyses reported that not being married or in a permanent relationship was associated with an increased probability of receiving observational management (28, 34, 40, 50), and 1 found that marital status was not a factor in predicting use of WW (47). Three multivariable analyses found that predictors of choosing observational management strategies included the desire to avoid adverse effects and having current bowel problems (48), urinary dysfunction (47), or other urinary conditions (33). Sexual dysfunction was predictive of choosing RT over observational management strategies (47). One multivariable analysis reported that increased anxiety was associated with an increased probability of interruption of observational management (32). One multivariable analysis reported that marital status was not associated with time to interruption of observational management strategies (32). One analysis compared 180 men who declined to be randomly assigned (that is, did not participate in the trial) and instead selected AS, versus 138 men in the trial who were randomly assigned to AS (43). It found that lower baseline anxiety (and not being randomly assigned) was associated with choosing AS.

Two qualitative research studies (sample sizes of 25 [54] and 50 [60]) and 2 surveys (sample sizes of 185 [52] and 768 [66]) reported that concern for adverse effects of treatment was 1 reason for choosing observational management. Adverse effects included impotence (44%), incontinence (48%) (52), and unspecified effects (11%) (66). A survey of 102 men reported that fear of consequences was the most common reason for not selecting observational management (58). In 2 surveys, advice from family and friends was the most influential factor in deciding treatment of 19% of 654 men (56) and 9% of 231 men surveyed (61). In a focus group of 44 men, one half reported relying on influential persons to make a treatment decision (62). In an open-ended interview of 102 men with localized disease, 4% reported that family opinions were a reason for not choosing observational management (58). One set of interviews of 25 men with low-risk prostate cancer reported that physician description of prostate cancer affected treatment choice (54). One survey of men with early-stage prostate cancer reported that men who chose RP over RT or observational management strategies perceived prostate cancer as a more serious disease (56).

Physician Factors

Two qualitative research studies (sample sizes of 25 [54] and 102 [58]) and 1 survey (sample size of 185 [52]) reported that recommendation of a physician (urologist or radiation oncologist) was the most influential factor in a patient's choosing or not choosing AS (for 30% [58] and 73% [52]; no quantitative data were available in the smaller study [54]). Two surveys of men with prostate cancer (sample sizes of 654 [56] and 231 [61]) reported that a recommendation from a urologist, radiation oncologist, or other physician was most influential in the treatment decision (for 51% [56] and 57% [61] of patients).

Comparative Effectiveness

AS Versus Immediate Treatment

To understand the effectiveness of AS relative to immediate treatment with curative intent, studies of AS need a control group for comparison; therefore, we did not include single-group AS cohort studies. However, no study reported clinical outcomes specifically for AS management strategies versus immediate definitive treatment. Therefore, evidence is insufficient to evaluate the comparative effectiveness of AS management versus immediate definitive treatment in men with localized prostate cancer.

We did not find studies comparing the actual economic cost of AS with that of active treatments. Results from model-based economic evaluations (12, 13, 70, 71) of AS using U.S. prices to estimate treatment costs have been summarized in the full evidence report (5).

WW Versus Immediate Treatment

In reviewing studies of WW versus immediate treatment, we hypothesized that studies comparing WW with active treatment could provide a lower bound of the comparative effectiveness of AS (that is, represent a worst-case scenario), with all other factors being equal. We revisited 2 completed AHRQ reports (8, 9) that compared observational management strategies with immediate treatment and updated them with more recent studies. A summary of these studies is presented in **Appendix Table 4** (available at www.annals.org).

For the comparison of WW with RP, we identified updated results for 1 RCT (2 publications [72, 73]) and 3 prospective (74–76) and 9 retrospective (77–85) cohort studies, in addition to studies included in previous reviews (8, 9). In total, 2 RCTs of WW versus RP (72, 86) reported long-term follow-up. The larger RCT reported statistically significant survival benefits from RP compared with WW (72). The applicability of RCT findings to contemporary patients with prostate cancer is limited because most enrolled patients were not diagnosed with PSA screening. Results from nonrandomized comparative studies were generally consistent with those from RCTs and suggested that RP was more effective than WW. Quality of life was reported in 1 RCT (73) and 4 nonrandomized comparative studies (74–76, 82); the results varied across domains of quality measures.

For the comparison of WW with RT, in addition to studies identified in a previous systematic review of RT for localized prostate cancer (9), we reviewed 1 RCT (87) and 7 nonrandomized comparative studies (74, 75, 78, 80–82, 88). The RCT found no statistically significant differences in quality of life between the treatments at 10 years (87). No published RCT has reported information on mortality outcomes. Observational studies generally suggested that men treated with RT have lower mortality rates than men on WW (78, 81). For quality of life, results varied across domains (74, 82, 87, 88).

We identified 4 studies comparing the actual treatment costs of WW versus immediate treatment (27, 89–91). These studies included few patients receiving observational management and have been summarized in the full evidence report (5).

Discussion

Since the introduction of PSA testing, the epidemiology of prostate cancer in the United States has changed substantially. The increase in prostate cancer incidence has been accompanied by an increase in the proportion of cancer diagnosed at an earlier stage and with a lower tumor grade (2). Patients diagnosed with prostate cancer are more likely to die of non–prostate cancer causes (4), suggesting that some patients receiving surgery or radiation therapy may be exposed to treatment-related morbidity with no long-term survival advantage. Therefore, observational management strategies, including AS, have been proposed as potential alternatives to immediate active treatment. However, we found that AS protocols were not standardized across centers, and evidence on treatment effectiveness was limited by the lack of comparative studies. Studies of factors that influence the implementation of observational management strategies were hampered by the lack of clear definitions of these strategies and the limited information that is available in existing data sets.

Definitions of AS and WW

The terms AS and WW have been used interchangeably in the literature. Although the different intents (curative or palliative) of the applied strategies can often be deduced, we suggest that the term AS be reserved for protocols of curative intent and WW be reserved for protocols of palliative intent. This will improve clarity in scientific discourse.

Interpretation of future studies would be best served if observational management strategies were clearly defined. Definitions will need to include the goal or intent of the intervention, criteria for determining which patients should be managed observationally, a complete description of the monitoring protocol (including the timing of each assessment), and the triggers for stopping observational management to seek definitive treatment. Currently, there is little consistency among studies in who is eligible for AS or WW and how patients are monitored.

Research on AS strategies implicitly assumes that it is possible to identify men who are at sufficiently low risk for progression of their prostate cancer for whom AS can be a safe and appropriate option. Basic and clinical research to uncover better molecular, clinical, or imaging markers of indolent versus aggressive disease (particularly potentially fatal biological forms of newly diagnosed prostate cancer among patients with low-risk disease, according to current criteria) are necessary to better inform which patients are most likely to benefit from observational management versus active treatment. Combining such markers into predictive scores can improve our ability to identify patients who are most likely to benefit from immediate active treatment (92).

Factors Affecting the Offer of, Acceptance of, or Adherence to Observational Management

Few studies specifically examined factors related to men who were enrolled in AS protocols. Most currently available databases collect information only about what treatment patients received and when. Therefore, existing data cannot be used to identify the factors that influence the offer of treatment options and lead patients to accept one of those options, or to study predictors of adherence to these initial treatment choices. Even the best analysis of predictors of received treatment cannot adequately address this question. It was notable, however, that fear was a common factor in choosing treatment strategy. For some, fear of adverse effects was a reason to avoid treatment; for others, fear of consequences was a reason to avoid surveillance. However, full exploration of factors that affect the implementation of observational management strategies will require the prospective collection of data, specifically about which interventions were offered to each patient, which treatments the patients accepted, and when they chose to receive curative treatment despite lack of evidence of progression.

AS Versus Definitive Treatments

No study provided results from direct comparisons of AS with RP or RT in men with localized disease. Two RCTs comparing RP with WW suggested that surgery improves survival (although only 1 reported a statistically significant effect on mortality). One RCT comparing WW with RT found few differences in quality of life between groups at 10 years. Randomized studies were mostly conducted before PSA screening and, thus, may now have limited applicability. Nonrandomized comparative studies (mostly retrospective) were generally consistent with the RCTs; however, they are susceptible to confounding bias. Further evaluation is also needed to analyze competing risks for morbidity and mortality in elderly men with low-risk disease who are at elevated risk for death from other causes. Results from the recently completed PIVOT (Prostate Cancer Intervention Versus Observation Trial: WW vs. RP in PSA-detected cancer; NCT00007644 [23]) and the ongoing ProtecT (Prostate Testing for Cancer and Treatment: AS vs. RP or RT; NCT00632983 [93]) trial will provide valuable information for the treatment of men with low-risk prostate cancer. Preliminary results from PIVOT have been presented (94). Preliminary 15-year results of the Scandinavian trial of external beam radiation therapy versus WW have also been presented (95). The published reports will need to be evaluated to assess their conclusions.

In lieu of RCTs, adequate information may be obtained from long-term, prospective, nonrandomized comparative studies. These studies should also use a priori criteria for eligibility and AS protocols that undergo minimal change over time or between centers. They will also need to use appropriate methods to control for the broad range of factors that affect the decision to use AS and influence clinical outcomes. Confounding bias, particularly confounding by indication, is always a concern for nonrandomized studies of therapeutic interventions. A priori–specified subgroup analyses of both RCTs and prospective nonrandomized comparative studies should be conducted to look for particular sets of men who may benefit most from each approach. Given the heterogeneity of protocols used for WW and AS and the lack of comparative data, for the time being clinicians need to consider how relevant each proposed observational management strategy is to their patients. The variability of existing strategies can be expected to result in heterogeneity of treatment effects in studies comparing observational management versus immediate treatment with curative intent.

Limitations

Because of the nonstandardized uses of the terms AS and WW and the commonly mixed treatment objectives (both curative and palliative) thereof, it was often difficult to determine which patients received active monitoring for triggers to initiate curative treatment, and which patients had observation for clinical symptoms to initiate palliative treatment. Even among studies that clearly used either AS or WW, interpretation was complicated by the wide range of protocols.

In addition, we may not have captured all relevant studies, because we restricted our searches to English-language articles. We also may not have captured all studies of observational management that did not use appropriate keywords in the abstracts. Broad searches of the psychosocial literature about treatment offer, acceptance, or adherence were beyond the scope of this review.

Conclusion

Since the introduction of PSA screening, more men have been diagnosed with early-stage, low-risk prostate cancer. The comparative effectiveness of AS versus immediate active treatment remains unclear. A standard, universally accepted use of the term AS that clearly distinguishes it from WW and other observational management strategies is needed to promote scientific discourse in this field. Future clinical studies are needed to determine the optimal AS protocol and provide information on the comparative effectiveness of AS versus immediate active treatment. These studies will require large sample sizes and long-term follow-up.

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Appendix Table 1. Key Questions Guiding This Review*

How are AS and other observational management strategies defined?
- Common metrics: age, Gleason score, number of cores, percentage of cores, PSA (velocity, doubling time) imaging, behavioral indicators
- Follow-up protocols: Gleason score, number of cores, percentage of cores, PSA imaging, behavioral indicators

What factors affect the offer of, acceptance of, and adherence to AS?
- Physician factors: primary care, diagnosing physician, consultant second opinion, clinical factors
- Patient factors: family involvement, personal preferences, risk perceptions, family history, social support
- Delivery system: economic incentives and disincentives (insurance type [HMO, military, private], availability of technology), geographic location (small-area variation, regional variation, urban vs. rural), academic centers vs. private practice
- Communication strategies: risk assessment, predictive models, decision-making tools and aids

What are the comparative short- and long-term outcomes of AS versus immediate treatment with curative intent for localized prostate cancer?
- Prostate-specific and all-cause mortality
- Morbidity from primary treatment decision
- Incidence of metastatic disease
- Quality of life
- Costs

AS = active surveillance; PSA = prostate-specific antigen.
* The National Institutes of Health Conference Planning Committee developed 5 key questions (see http://consensus.nih.gov/2011/prostate.htm). A question on the natural history of prostate cancer is not included in the present article, but relevant evidence is used as background information. Similarly, information on a fifth question about future research needs has been incorporated into the Discussion section.

Appendix Table 2. **Data Sources and Study Eligibility Criteria for Each Review Question**

Source or Study Selection Criterion	How Are AS and Other Observational Management Strategies Defined?	What Factors Affect the Offer of, Acceptance of, or Adherence to AS?	What Are the Comparative Short- and Long-Term Outcomes of AS Versus Immediate Treatment With Curative Intent for Localized Prostate Cancer?
Principal data source(s)*	MEDLINE, HTA database, CCRCT, and CDSR	MEDLINE, HTA database, CCRCT, and CDSR	MEDLINE, HTA database, CCRCT, CDSR, CEA Registry, prior systematic reviews†
Populations of interest	Men with prostate cancer considered for observational management	Men with prostate cancer considered for observational management	Men with clinically localized prostate cancer (T1–T2) without known lymph nodes (N0–X) or metastases (M0–X); <20% of study sample could have more advanced disease
Intervention or predictors	Protocols for observational management (that is, no immediate curative treatment)‡	Any predictor analyzed or any tool (e.g., decision aid) tested to affect the offer of, acceptance of, or adherence to observational management strategies	Observational management strategies (no active treatment, including ADT)
Comparators (when appropriate)	NA	NA	Active treatment (RP, EBRT, or BT, each with or without ADT); not ADT monotherapy
Outcomes	NA	Offer of, acceptance of, or adherence to AS or WW (excluding ADT), as defined by study authors	Prostate cancer mortality, all-cause mortality, morbidity from primary treatment, metastatic disease, quality of life, and costs
Study design and additional selection criteria	Any primary study or study protocol reporting information on selection criteria and describing the monitoring strategy was considered eligible. When multiple publications were available on the same cohort, we used the publication that provided the most complete information on eligibility criteria and follow-up protocols as the primary source of information for this review. We considered additional publications from the same cohort when they reported changes in the study protocol that affected the definition of the observational strategy. When all articles from the same center or research team used the same observational strategy (that is, when the same definition was consistently used in all publications), we generally referenced the article with the earliest publication date.	Cohort studies or database analyses with multivariable analyses adjusting for a minimum of age and tumor stage (if the analysis was not limited to localized cancer) or using other multivariable-adjustment methods (e.g., propensity score) Cohort studies using qualitative research methods (e.g., focus groups, surveys). Eligible studies must have used a predefined approach to collect information. Cohort or comparative studies evaluating any tool	Longitudinal comparative studies conducted in a multicenter setting; randomized or nonrandomized; prospective or retrospective Nonrandomized studies had to use multivariable or other methods to adjust for possible confounding (specifically including age and tumor stage)

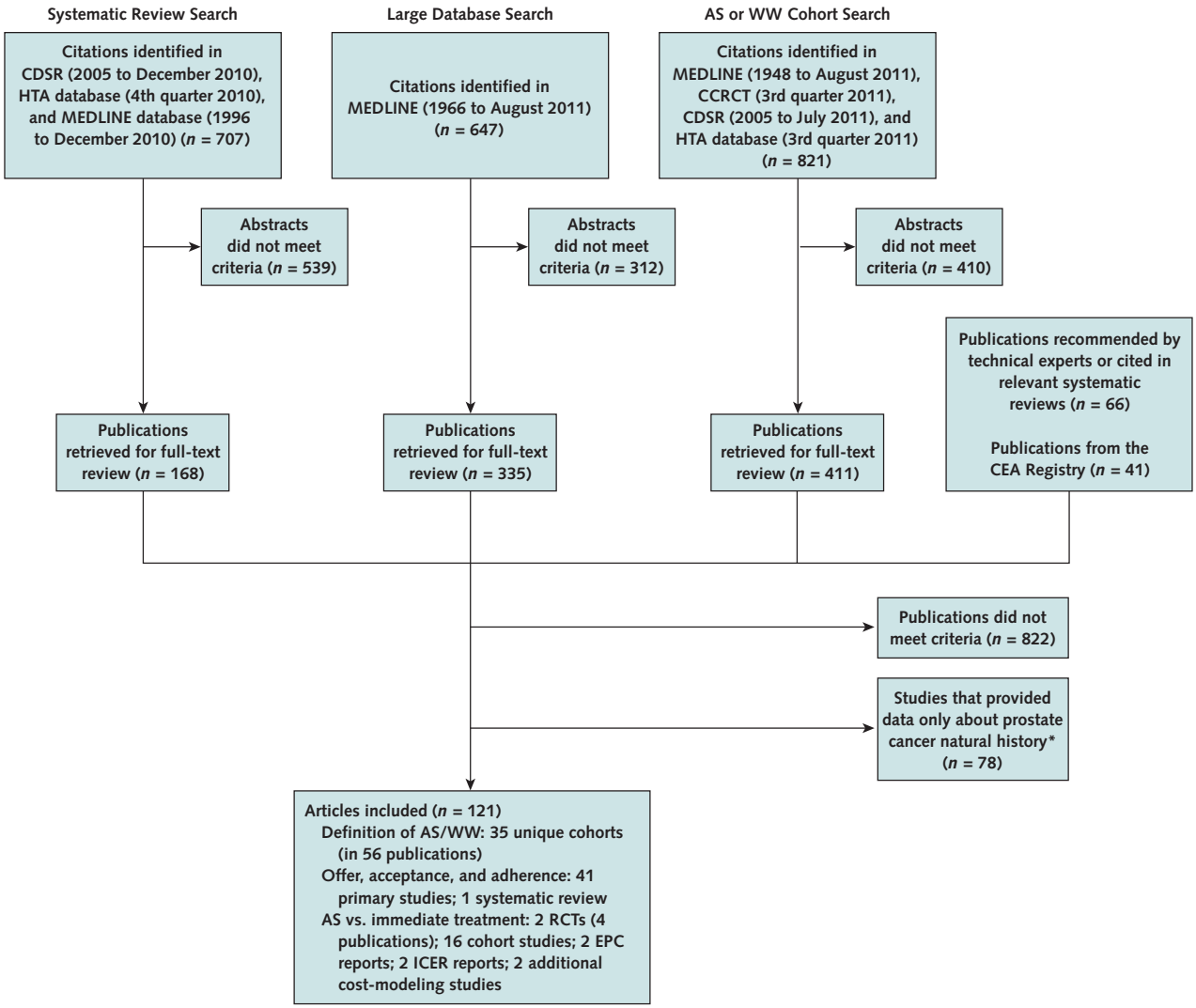
ADT = androgen deprivation therapy; AS = active surveillance; BT = brachytherapy; CCRCT = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CEA = Cost-Effectiveness Analysis; EBRT = external beam radiation therapy; HTA = Health Technology Assessment; NA = not applicable; RP = radical prostatectomy; WW = watchful waiting.

* Searches were supplemented with studies recommended by the Technical Expert Panel, reference lists of eligible primary studies and relevant review articles, and targeted searches for economic evaluations.

† Conducted through the Agency for Healthcare Research and Quality Evidence-based Practice Center program (8, 9).

‡ The goal of observation could be either to identify disease progression indicative of the need for curative treatments or to determine the need for palliative treatment.

Appendix Figure 1. **Summary of evidence search and selection.**



AS = active surveillance; CCRCT = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; CEA = Cost-Effectiveness Analysis; EPC = Evidence-based Practice Center; HTA = Health Technology Assessment; ICER = Institute for Clinical and Economic Reviews; RCT = randomized, controlled trial; WW = watchful waiting.

* These studies were relevant to "Key Question 1" in the main report (5) but are not covered here. The numbers of studies for each question do not add up to the total number of included studies because some studies addressed many questions.

Appendix Table 3. Eligibility Criteria and Follow-up Protocols in Studies of AS*

AS Cohort or Center	Country	Year Enrollment Began	Term Used in Original Article	Eligibility Criteria			Follow-up Protocol		
				Age, *y*	Gleason Score†	PSA Level, μg/L	PSA Level or PSA Kinetics	DRE	Rebiopsy
Baylor College of Medicine and Memorial Sloan-Kettering Cancer Center (96)	United States	1984	EM, deferred therapy	NR	<7	NR	PSAV >0.75 μg/L/y	Used	Used
McGill University (97, 98)	Canada	1987	WW, AS	NR	NR	NR	Used but not specified	Used	Used
University of Connecticut Health Center (99)	United States	1990	AS	NR	NR	NR	Used but not specified	Used	Used
Four tertiary care academic medical centers (100)	United States	1991	AS	≤75	≤6	≤10	Used but not specified	Used	Used
University of Miami (52, 101–103)	United States	1991	WW, AS	≤80 (52)	≤6 (101)	≤15 (101) ≤10 (52, 102)	PSA increase of 25%–50%/y (103)	Used (101)	Used (101)
University of California, San Francisco (104–108)	United States	After 1991	AS	NR	≤6 A trial (107) in the same institution reported additional a priori–defined exceptions‡	<10 A trial (107) in the same institution reported additional a priori–defined exceptions‡	PSAV >0.75 μg/L/y PSADT <1 y (107)	Used	Used
Royal Marsden Hospital (22, 109–111)	United Kingdom	1993	AS	NR	<3 + 4	≤20 (22) ≤15 (109)	PSADT <4 years (109) PSAV >1 μg/L/y (110, 111)	Used	Not routine (22)
Johns Hopkins University (112)	United States	1994	AS, EM with curative intent	NR	≤6	PSAD ≤0.15 μg/L/cm^3	PSA kinetics were not used as part of triggers for intervention	Used	Used
Toronto–Sunnybrook Regional Cancer Center (113–116)	Canada	1995	WW, AS	NR	≤6 ≤3 + 4 (if age ≥70 y) (114)	≤10 <15 (if age ≥70 y) (114)	PSA DT <2 y Protocol changes in PSADT assessment or calculation in 1999 and after 2002. In 2005, the group developed a general linear mixed model as a clinical decision-making aid§ (116)	Used	Used
Memorial Sloan-Kettering Cancer Center (117)	United States	1997	AS	NR	No Gleason score 4 or 5	<10	>10 μg/L	Used	Used
ProtecT (118)	United Kingdom	2000	Active monitoring	NR	NR	NR	Used but not specified	Used	Not routine
Dana-Farber Cancer Institute (119)	United States	2000	AS	NR	≤6 with no pattern 4	NR	Used but not specified	Used	Used
Kagawa Medical University§ (120)	Japan	2002	AS	50–80	≤6	≤20	PSADT <2 y	NR	Used
Cleveland Clinic (121)	United States	2004	Surveillance	NR	No Gleason score 4 or 5	≤10	Used but not specified	NR	Used
PRIAS (122)	Multinational	2006	AS	NR	≤3 + 3	≤10; PSAD ≤0.2 μg/L/cm^3	PSADT 0–3 y	Used	Used
PASS (123)	United States	2008	AS	NR	NR	NR	PSADT <3 y	Used	Used

AS = active surveillance; DRE = digital rectal examination; EM = expectant management; NR = not reported; PASS = Prostate Active Surveillance Study; PRIAS = Prostate Cancer Research International: Active Surveillance; ProtecT = Prostate Testing for Cancer and Treatment; PSA = prostate-specific antigen; PSAD = prostate-specific antigen density; PSADT = prostate-specific antigen doubling time; PSAV = prostate-specific antigen velocity; WW = watchful waiting.

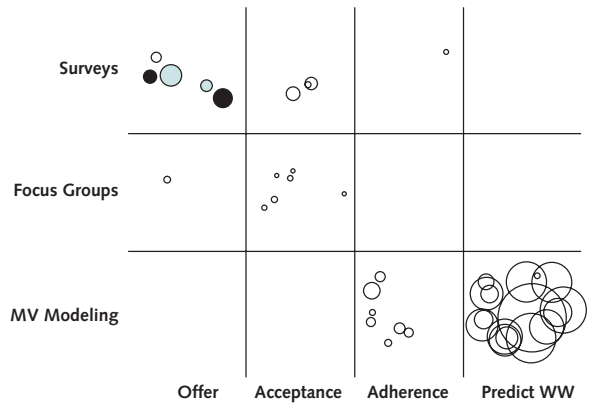
* Numbers in parentheses indicate reference citations.

† The Gleason patterns range from 1 to 5, with 5 being the least differentiated pattern. A Gleason score of 4 + 3 (primary + secondary grade) = 7 is different from 3 + 4 = 7. Therefore, it is more informative to give both patterns than to provide only the sum (that is, the Gleason score).

‡ A trial of nutrition supplements conducted at the University of California, San Francisco, among men with "low-burden prostate cancer, choosing AS for disease management." This trial used the same eligibility criteria as the University of California, San Francisco, AS cohort but explicitly reported the following a priori exceptions: PSA <15 μg/L for men with concurrent benign prostatic hyperplasia or prostatitis, having a Gleason score of 4 reported only in a microfocus of tumor (defined as ≤2-mm length) and having >33% positive biopsy cores due to a tumor microfocus. The authors reported that "these criteria were consistent with the clinical standards of our institution for determining the candidates for AS."

§ The model generates 2 reclassification curves (high and low risk) that, when overlaying PSA data of each patient, defines 3 risk zones of high, intermediate, and low risk for reclassification. Patients with a PSA consistently in the high-risk zone are recommended for active treatment.

Appendix Figure 2. **Evidence map for studies of factors affecting the offer of, acceptance of, or adherence to observational management strategies.**



MV = multivariable; WW = watchful waiting.
Two studies (43, 51) are not depicted in the graph because they assessed different outcomes (consent to randomization and decisional conflict, respectively).

Appendix Table 4. Comparative Studies of Observational Management Versus Immediate Treatment*

Comparison, by Study Design and Outcome	Studies	Methodological Quality Grade†	Trial Name or Database(s)	Key Findings: Adjusted RR (95% CI)
RP vs. WW				
RCTs				
Prostate-specific mortality	1 RCT	1 A	SPCG-4 (72)	0.62 (0.44–0.87)
All-cause mortality	2 RCTs	1 A, 1 C	SPCG-4 (72)	0.75 (0.61–0.92)
			VACURG (86)	No difference in mortality (HR not reported; $P = 0.39$)
Distant metastasis	1 RCT	1 A	SPCG-4 (72)	0.59 (0.45–0.79)
Quality of life	1 RCT	1 A	SPCG-4 (73)‡	Erectile dysfunction: 1.8 (1.3–2.6) Urinary incontinence: 2.3 (1.3–3.9)
Nonrandomized comparative studies				
Prostate-specific mortality	3 retrospective cohorts	3 B	SEER-Medicare (77)	0.63 (0.55–0.70) (using a propensity score analysis) 1.37 (0.15–12.5) (using an instrumental variable analysis)
			NCRSFS (81)	0.49 (0.34–0.71)
			Connecticut Tumor Registry (79)	0.29 (0.17–0.52)
All-cause mortality	5 retrospective cohorts	4 B, 1 C	SEER-Medicare (77)	0.65 (0.62–0.68) (using a propensity score analysis) 0.92 (0.39–2.17) (using an instrumental variable analysis)
			SEER-Medicare (78)	0.50 (0.47–0.53)
			NCRSFS (81)	0.49 (0.41–0.57)
			POCS (83)	0.43 (0.32–0.59)
			CPDR (85)	0.52 (0.32–0.84) (WW with secondary treatment)
Morbidity from primary treatment	2 retrospective cohorts	1 B, 1 C	CaPSURE (80)	Urethral stricture: 10.4 (3.3–33)
			SEER-Medicare (84)	Bladder irrigation/cystostomy: 1.71 (1.33–2.20) TURP/bladder neck incision: 2.63 (2.08–3.33) Urethral dilation: 0.71 (0.61–0.84)
Quality of life	1 retrospective; 3 prospective cohorts	1 B, 3 C	CaPSURE (2 studies) (75, 82); HPFS (76); Wisconsin hospitals (74)	General quality of life: Better in SF-36 social function domain, not other domains (1 study); better SF-36 scores from immediately after treatment to 2-y follow-up (1 study); no difference in any domain or overall quality-of-life scores (1 study) Disease-specific: Worse in urinary and sexual function (1 study)
RT vs. WW				
RCTs				
Quality of life	1 RCT	1 C	Ancillary investigation from Umea University trial (87)	After 10-y follow-up, the study reported no statistically significant differences in health-related quality-of-life function or symptom scales. The authors stated that the complete trial data are not yet ready for publication.
Nonrandomized comparative studies				
Prostate-specific mortality	1 retrospective cohort	1 B	NCRSFS (81)	0.70 (0.45–1.09)
All-cause mortality	2 retrospective cohorts	2 B	SEER-Medicare (78)	0.81 (0.78–0.85)
			NCRSFS (81)	0.68 (0.57–0.82)
Morbidity from primary treatment	1 retrospective cohort	1 B	CaPSURE (80)	Urethral stricture: BT vs. WW: 1.68 (0.46–6.14) EBRT vs. WW: 1.77 (0.48–6.55)
Quality of life	4 retrospective cohorts	2 B, 2 C	CaPSURE (2 studies) (75, 82); ECR (88); Wisconsin hospitals (74)	General quality of life: Better in SF-36 social function domain, not other domains (1 study); worse in physical functioning and bodily pain domains (1 study) Disease-specific: No difference (1 study) One study only reported temporal changes for each treatment group without reporting formal statistical comparisons.
RP and RT vs. WW				
Nonrandomized comparative studies				
Prostate-specific mortality	1 retrospective cohort	1 B	SEER-Medicare (78)	0.67 (0.58–0.77)
All-cause mortality	1 retrospective cohort	1 B	SEER-Medicare (78)	0.69 (0.66–0.72)
Morbidity from primary treatment	1 retrospective cohort	1 B	CaPSURE (80)	Urethral stricture: 4.39 (0.72–26.7)

BT = brachytherapy; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; CPDR = Center for Prostate Disease Research; EBRT = external beam radiation therapy; ECR = Eindhoven Cancer Registry; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NCRSFS = National Cancer Register of Sweden Follow-up Study; POCS = Patterns of Care Study; RCT = randomized, controlled trial; RP = radical prostatectomy; RR = relative risk; RT = radiation therapy; SEER = Surveillance, Epidemiology, and End Results; SF-36 = 36-Item Short-Form Health Survey; SPCG-4 = Scandinavian Prostate Cancer Group Study 4; TURP = transurethral resection of the prostate; VACURG = Veterans Administration Cooperative Urological Research Group; WW = watchful waiting.

* Numbers in parentheses indicate reference citations. This table summarizes the findings from the most recent publications of all relevant randomized trials (including those identified in previous reviews), but only includes nonrandomized comparative studies identified through update searches.

† A = good quality, low risk of bias; B = fair/moderate quality, intermediate risk of bias; C = poor quality, high risk of bias. The criteria for assigning these grades are presented in the full evidence report (available at www.effectivehealthcare.ahrq.gov).

‡ Updated results on quality of life from this study were published after our systematic review was completed (124).