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Observation Versus Initial Treatment for Men With Localized, Low-Risk Prostate Cancer A Cost-Effectiveness Analysis

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Abstract

Background—Observation is underused among men with localized, low-risk prostate cancer.

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Contribution

This analysis used recent trial data to show that observation slightly improves quality-adjusted life expectancy and is less expensive than treatment after diagnosis for men aged 65 and 75 years with localized prostate cancer. Treatment would have to be markedly more effective than current data suggest for the conclusion to be overturned.

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Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available to approved individuals after discussion with Dr. Hayes (Julia_Hayes@dfci.harvard.edu). *Data set:* Available from Dr. Hayes (Julia_Hayes@dfci.harvard.edu).

Context

Most men with localized, low-risk prostate cancer are treated soon after diagnosis.

Caution

The model was based on many assumptions given the scarcity of data for outcomes with treatment and observation.

Implication

Compared with treatment after diagnosis, observation is cost-effective for men aged 65 to 75 years under a wide range of clinical scenarios. —The Editors

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Objective—To assess the costs and benefits of observation versus initial treatment.

Design—Decision analysis simulating treatment or observation.

Data Sources—Medicare schedules, published literature.

Target Population—Men ages 65 and 75 years with newly diagnosed low-risk prostate cancer (prostate-specific antigen level <10 μg/L, stage ≤T2a, Gleason score ≤3+3).

Time Horizon—Lifetime.

Perspective—Societal.

Intervention—Treatment (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) or observation (active surveillance [AS] or watchful waiting [WW]).

Outcome Measures—Quality-adjusted life expectancy, costs.

Results of Base-Case Analysis—Observation was more effective and less costly than initial treatment. Compared with AS, WW provided 2 additional months of quality-adjusted life expectancy (9.02 vs. 8.85 years) at a savings of $15 374 ($24 520 vs. $39 894) in men aged 65 years and 2 additional months (6.14 vs. 5.98 years) at a savings of $11 746 ($18 302 vs. $30 048) in men aged 75 years. Brachytherapy was the most effective and least expensive initial treatment.

Results of Sensitivity Analysis—Treatment became more effective than observation when it led to more dramatic reductions in prostate cancer death (hazard ratio, 0.47 vs. WW and 0.64 vs. AS). Active surveillance became as effective as WW in men aged 65 years when the probability of progressing to treatment on AS decreased below 63% or when the quality of life with AS versus WW was 4% higher in men aged 65 years or 1% higher in men aged 75 years. Watchful waiting remained least expensive in all analyses.

Limitation—Results depend on outcomes reported in the published literature, which is limited.

Conclusion—Among these men, observation is more effective and costs less than initial treatment, and WW is most effective and least expensive under a wide range of clinical scenarios.

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The optimal management of men with low-risk, clinically localized prostate cancer is controversial. In the prostate-specific antigen (PSA) era, up to 70% of these men have low-risk disease (stage ≤T2a, PSA level <10 μg/L, Gleason score ≤3+3) and less than 6% risk for prostate cancer–specific death at 15 years (1-4). More than 90% of these men are currently treated with radical prostatectomy (RP), external beam radiation, or brachytherapy (BT) (5), but as many as 60% may not have required therapy in their lives (6). Most men who undergo treatment have at least 1 long-term adverse effect (7-9).

The cost of unnecessary treatment is not limited to adverse effects. In 2000, diagnosis and treatment was estimated to cost $1.3 billion in the United States, an increase of 30% since 1994 (10). A recent analysis estimated that the cost of diagnosis and treatment is just more than $5 million to prevent 1 prostate cancer death (11).

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Observation is an alternative to treatment of men with localized, low-risk disease and takes the form of active surveillance (AS) and watchful waiting (WW). With AS, men are followed closely—typically with serial PSA tests, digital rectal examinations, and biopsies—and treated with curative intent if the disease progresses. In the most mature series, 30% of men were ultimately treated, and prostate cancer–specific survival was 97.2% at 10 years (12).

With WW, men are observed without monitoring and given palliative treatment when the disease becomes symptomatic. Traditionally, this approach has been reserved for men expected to die with, not of, prostate cancer, usually because of advanced age or comorbid conditions. However, in subgroup analyses of PIVOT (Prostate Cancer Intervention Versus Observation Trial), which followed 731 men (median age, 67 years) who had been randomly assigned to RP or WW for a median of 10 years (13), men with low-risk prostate cancer derived no benefit from RP compared with WW in all-cause mortality (hazard ratio [HR], 1.15 [95% CI, 0.80 to 1.66]) or prostate cancer–specific mortality (HR, 1.48 [CI, 0.42 to 5.24]). The PRoTECT (Prostate Testing for Cancer and Treatment) trial (14), comparing active monitoring, RP, and radiotherapy, will also yield useful information about the relative benefits of observation with monitoring but will not close enrollment until 2015.

We recently did a decision analysis suggesting that quality-adjusted life expectancy (QALE) improves with AS compared with initial treatment (15), and previous cost analyses have suggested that observation is less expensive than initial treatment (16-17) but did not formally estimate cost-effectiveness. Therefore, we did a cost-effectiveness analysis of AS and WW compared with initial treatment of low-risk, clinically localized prostate cancer in men aged 65 and 75 years.

Methods

We developed a state transition model using TreeAge software (TreeAge Software, Williamstown, Massachusetts) and did a Monte Carlo simulation to estimate the costs and health benefits for men with low-risk, clinically localized prostate cancer treated with intensity-modulated radiation therapy (IMRT), BT, open RP (in men aged 65 years only; robotic prostatectomy was not modeled), AS, or WW (Supplement 1, available at www.annals.org). Health benefits were described in months or years of QALE (15). Costs were derived from Medicare reimbursements and average wages for age-matched men. Men were aged 65 or 75 years on model entry, and they exited at death. Costs and health benefits were discounted at 3% annually. We used a societal perspective, in accordance with the Panel on Cost-Effectiveness in Health and Medicine (18).

Treatment Strategies

The AS strategy comprised PSA tests every 3 months, digital rectal examinations every 6 months, and biopsies at 1 year and every 3 years thereafter (12). Men who progressed to more aggressive disease (Gleason histology score of 7 on repeated biopsy, clinical or biochemical progression) or selected treatment received IMRT; in the base case, BT and RP were not modeled in men treated with AS. Ten percent of men who developed a Gleason

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score of 7 had “unfavorable risk” disease and received 6 months of androgen-deprivation therapy with IMRT (19).

The WW strategy reproduced the PIVOT experience. Men were followed with visits and PSA tests every 6 months and bone scans every 5 years, and 20.4% of men were treated over 10 years (49% with RP, 39% with IMRT, and 12% with BT) (13).

Model Inputs

Model inputs were generated from a systematic review updated through June 2012 and from PIVOT; probabilities were estimated using random-effects meta-analysis (13, 15) (Table 1, Appendix Table 1, and Appendix 1 [available at www.annals.org]).<20-30> The model was calibrated to ensure that its performance was consistent with assumptions. Internal validation was done to ensure that model outputs were consistent with model inputs; external validation demonstrated that model outputs were consistent with outcomes reported in the literature (Appendix 1).

All men treated initially were assumed to have the HR point estimate of 1.48 reported in PIVOT for prostate cancer–specific death compared with WW (13). We assumed as a base case that AS would provide 25% additional benefit compared with WW in preventing prostate cancer–specific death and used an HR for prostate cancer–specific death for treatment compared with AS of 1.85 (15). We changed 2 probabilities from the previous decision analysis to reflect the publication of updated results of AS cohorts (12, 22, 23, 25-28): The annual probability of Gleason progression on AS decreased to 2.3% from 2.7%, and the annual probability of developing other signs of disease progression increased to 5.2% from 2.7% (Table 1) (15).

We classified adverse effects of treatment as short-term (occurring and resolving within 90 days) and long-term (occurring or persisting at least 90 days after treatment and persisting for life) (Tables 1 to 3 and Appendix Table 1).

Utilities—Utilities for health states were elicited using a time-tradeoff method from men without prostate cancer (range, 0 [deceased] to 1 [perfect health]) (15). For men in more than 1 health state simultaneously (for example, on AS with urinary obstructive symptoms), we multiplied utilities (Table 2 and Appendix Table 1).

Costs—We input costs in 2012 U.S. dollars for initial treatment of prostate cancer, ongoing treatment of erectile dysfunction and urinary obstructive symptoms existing before treatment, surveillance, treatment of short- and long-term adverse effects, and patient time costs (Table 3, Appendix 1, and Supplement 2 [available at www.annals.org]) (31). We included inpatient and outpatient direct and indirect medical costs derived from the Centers for Medicare & Medicaid Services Hospital Outpatient Prospective Payment System (32). We valued patient time at $165 per day, assuming an 8-hour workday at the 2012 U.S. median wage, for men 65 years or older (33).

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Sensitivity, Alternative, and Threshold Analyses

We did 1-way sensitivity analyses on key parameters, including the PIVOT-based HRs for prostate cancer–specific death (13) (Appendix Table 2, available at www.annals.org); the probability of progressing to treatment on WW and AS (Appendix Table 3, available at www.annals.org); the probability of progressing to the PIVOT distribution of treatments (RP, IMRT, or BT) among men receiving AS (Appendix Table 4, available at www.annals.org); the utility of being on observation; and treatment, surveillance, and patient time costs and discounting rates (Appendix Tables 5 to 9, available at www.annals.org). In threshold analyses, we identified parameter values at which strategy rankings changed (Table 5). In probabilistic sensitivity analyses (analyses done simultaneously on all model parameters [probabilities, costs, and utilities] to quantify the cumulative effect of uncertainty on the results), we simulated 100 000 individuals for each of 500 samples drawn from independent distributions representing the uncertainty surrounding estimates of probabilities, utilities, and costs for each strategy (Appendix 2, Appendix Figures 2 and 3, and Appendix Table 10, available at www.annals.org).

Role of Funding Source

This study was funded by the National Cancer Institute, U.S. Department of Defense, Prostate Cancer Foundation, and Blue Shield of California Foundation. The funding source had no role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Results

In this model comparing observation using WW or AS with initial treatment, the lifetime risk for death from prostate cancer was 4.8% for men on AS, 6.0% for men on WW, and 8.9% for men treated initially (Table 4). Life expectancy was similar among the strategies: 81.6 years for men on AS, 81.4 years for men on WW, and 81.2 years for men treated initially. Among men aged 65 years, 78% on AS were treated over their lifetimes compared with 34% on WW, at a median of 6.8 and 12.4 years after diagnosis, respectively. Among men aged 75 years, 61% on AS and 23% on WW were treated a median of 5.4 and 8.4 years after diagnosis, respectively.

Among all strategies in men aged 65 years, WW offered the most QALE at the lowest cost (Table 4) and was cost-saving compared with AS, providing 2 additional months of QALE for $15 374 less. Both observational strategies were more effective than initial treatment, but AS was more expensive than BT (by $4520) and RP (by $1714). Brachytherapy was the most effective therapy at 8.14 years of QALE but cost an additional $10 854 compared with WW. Intensity-modulated radiation therapy was similar to BT for effect but, at $48 699, was the most expensive strategy. Quality-adjusted life expectancy was poorest with RP (7.95 years).

Estimates were qualitatively similar in men aged 75 years. Watchful waiting was most effective and least expensive, providing 6.08 years of QALE at a cost of $18 302. Active

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surveillance provided 2 months less QALE but cost an additional $11 746 compared with WW.

Brachytherapy was again the most effective and least expensive initial treatment (less expensive than AS by $1238). Intensity-modulated radiation therapy was the least effective and most expensive strategy.

For all but WW, the largest cost was treatment of prostate cancer (including the average cost of the procedure and patient time costs) (Appendix Table 11, available at www.annals.org). For men aged 65 years, RP was least expensive ($12 199) and IMRT was most expensive ($25 569). The cost of treatment for men in the AS cohort overall (with IMRT) was $15 688. On WW, the greatest costs were associated with treating underlying erectile dysfunction and urinary symptoms. The cost of surveillance of men diagnosed with prostate cancer (before and after treatment) was highest in those on AS for men aged 65 and 75 years.

Sensitivity Analysis of Disease-Related Parameters

When we changed the HR for prostate cancer–specific death to the lower confidence bound of the PIVOT point estimate for the comparison of treatment and observation, the scenario least favorable to observation, both WW and AS became less effective than any initial treatment in men aged 65 years; WW remained least expensive (Appendix Table 2). The HR for prostate cancer–specific death at which the QALE with observation was equal to the most effective treatment, BT, was 0.47 for WW and 0.64 for AS, meaning that treatment would have to be 53% better than WW and 36% better than AS to overcome the QALE advantage of observation.

Results were qualitatively similar in men aged 75 years. Watchful waiting was less effective than AS under the base case (5.76 vs. 5.98 years of QALE) when the HR for prostate cancer–specific death for treatment compared with WW was reduced to the lower confidence bound, but it remained less expensive. Active surveillance was less effective than WW with the same change (5.57 v. 5.76 years of QALE), and the rankings of costs did not change. The HR for prostate cancer–specific death at which QALE on WW was equal to initial treatment was 0.31 in men aged 75 years; for AS, it was 0.42.

When the HR for prostate cancer–specific death for treatment versus AS was doubled from baseline (HR for treatment of 3.7 relative to AS), AS remained less effective than WW and the ranking of costs did not change (Appendix Table 2). The HR for prostate cancer–specific death for treatment versus AS would have to be 7.71 in men aged 65 years and 4.3 in men aged 75 years for AS to be equal to WW (Table 5).

Active surveillance became favored over WW if the probability of having treatment on AS decreased below 63% in men aged 65 years and 42% in men aged 75 years (Table 5 and Appendix Table 3). If the probability of having treatment on AS or WW doubled, the rankings did not change. In an analysis in which men having AS progressed to a distribution of RP, IMRT, and BT identical to that in PIVOT, the QALE did not change substantially. Active surveillance remained more expensive than WW by $10 500 in men aged 65 years

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and $7900 in men aged 75 years, but it became less expensive than BT by $289 in men aged 65 years and $2633 in men aged 75 years.

Sensitivity Analysis of Utility of Being on Observation—In men aged 65 years, the QALE of AS and WW became equal when the utility of being on AS increased from 0.83 to 0.87. In men aged 75 years, the QALE of AS and WW became equal when the utility of being on observation increased from 0.83 to 0.84 (Table 5).

Sensitivity Analyses of Costs—In all analyses varying costs, WW remained least expensive (Appendix Tables 5 to 8). For AS to be equal to WW in cost, we had to set the cost of treatment equal to that of BT, the least expensive treatment; reduce costs of surveillance and treating short- and long-term adverse effects of treatment by 50%; and decrease the probability of being treated by 40%.

Probabilistic Sensitivity Analysis—The ranking of strategies and magnitude of effect difference between strategies was unaltered in probabilistic sensitivity analyses that incorporated uncertainty in estimates for men aged 65 and 75 years (Appendix Figures 2 and 3 and Appendix Table 10). However, overlapping CIs surrounding both costs and QALE reflect the collective uncertainty surrounding all of the model inputs (Appendix 2).

Discussion

Mounting evidence suggests that many men with localized, low-risk prostate cancer are treated unnecessarily at substantial personal and societal cost. In this study, we demonstrated that both WW and AS are associated with improved QALE compared with initial treatment and that WW is cost-saving compared with any other strategy in men aged 65 and 75 years at diagnosis. Watchful waiting was more effective than AS or initial treatment in all but 3 scenarios modeled (Table 5) and remained less expensive in every 1-way sensitivity analysis conducted.

The QALE advantage of WW was lost if treatment became associated with substantial improvements in prostate cancer–specific death. Because of variability in patient selection, surveillance protocols, and the dearth of data in the WW literature after PSA screening, we based our WW simulation on PIVOT (13, 34), the first randomized trial comparing observation with initial treatment in a screened population. In the base case, we assumed that the HR for prostate cancer–specific death for treatment versus WW was the point estimate reported in the low-risk subset of PIVOT. No trials have compared AS with WW: Given its emphasis on intervention and curative treatment, we assumed that AS would perform 25% better in preventing prostate cancer–specific death than WW and then varied this HR over a wide range. For treatment to yield a higher QALE, it would have to provide a survival benefit at least 50% better than WW and 36% better than AS.

The QALE advantage of WW was also lost when we varied the probability of progression to treatment with AS. In the absence of long-term follow-up of studies of observation, we assumed constant rates of conversion from observation to treatment. Active surveillance

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became favored over WW if the probability of progressing to treatment on AS decreased by more than 15% in men aged 65 years and more than 19% in men aged 75 years.

Active surveillance also yielded a higher QALE than WW when AS increased quality of life. As previously reported, utilities are key to the QALE advantage associated with AS versus initial treatment (15). In the base case, we assumed no difference in utility between AS and WW in the absence of literature values. Sensitivity analyses found that increasing the quality of life with AS from 0.83 to 0.87 in men aged 65 years or to 0.84 in men aged 75 years made AS equivalent to WW.

Watchful waiting remained the least expensive in all but the most extreme scenario modeled as a result of the magnitude of difference in cost in the number of men treated, treating adverse effects of treatment, and surveillance. The high cost of AS was primarily due to the cost of curative treatment and surveillance. In the base case, men on AS who convert to treatment receive IMRT, the most expensive method. Active surveillance remained substantially more expensive than WW in the sensitivity analysis in which the same treatment distribution was used for AS as for WW, although its cost was slightly less than that of initial treatment with BT.

In a recent decision analysis, Keegan and colleagues (17) compared the costs of AS with initial treatment with RP, radiation therapy, BT, and primary androgen-deprivation therapy. Active surveillance was associated with a per-patient cost savings of $16 042 (CI, $16 039 to $16 046) after 5 years and $9944 (CI, $9941 to $9948) after 10 years of follow-up (17). This study used hospital costs at a single institution, and costs were lower because it did not incorporate the costs of symptoms on AS or the costs of treatment of adverse effects, in contrast to our study.

Corcoran and colleagues (35) compared a combination of WW and AS with RP and found that RP was more expensive, at $15 235 versus $6558 to $11 992 for WW and AS (depending on the rate of conversion to RP and surveillance schedule). However, this analysis used a 15-year time horizon and an annual conversion rate between 5% and 7%. Our annual rate of conversion to treatment of 9% in the base case of AS reflects the more current data used in our analysis, and our lifetime horizon results in higher costs for AS and WW in our study. One recent analysis has modeled the prostate cancer–specific mortality rate of AS compared with AS followed by RP and found that RP was associated with 1.8 months of additional life expectancy (36), but no studies to date have done cost-effectiveness analyses for WW and AS compared with initial treatment.

The limitations of our study reflect, in part, limitations in the literature. We used point estimates from a subgroup analysis in PIVOT, a study criticized for being underpowered. Although the estimate of the HR for prostate cancer–specific death for treatment versus AS is a reasonable assumption, no data exist to compare AS with WW or with treatment, although we calibrated our model to PIVOT and validated it using the published literature (Appendix 1). We assumed a constant rate of conversion from observation to treatment, but it may diminish with time. The rates of progression to treatment in our model are similar to those reported in the literature (34% in men aged 75 years and 37% in men aged 65 years

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after 5 years) (12, 22, 23, 25-28), but to date, most Gleason score upgrading on biopsy has occurred within several years of diagnosis (37-39). In the absence of data in the literature, men who progressed on AS received IMRT in our base case because most men are eligible for this treatment in contrast to BT or RP, for which eligibility is limited by prostate volume and comorbid conditions, respectively, thus biasing results against AS in terms of cost. Utilities are central to any analysis of QALE, and the lack of a standardized catalog of prostate cancer health states is a hindrance to modeling cost-effectiveness in this disease. We have attempted to address all of these concerns in sensitivity and probabilistic sensitivity analyses. We have not included a cost-effectiveness acceptability curve to illustrate uncertainty surrounding the willingness-to-pay threshold. However, given the debate surrounding the existence of an accepted threshold in this country, we believe that the probabilistic sensitivity analysis conveys the uncertainty and magnitude of our results in a transparent way (40). Despite the considerable uncertainty surrounding inputs in this model and the limitations of this study, one may conclude that observation is a reasonable and, in some situations, cost-saving alternative to initial treatment.

In this analysis, observation was associated with improved QALE compared with initial treatment in men with low-risk prostate cancer. Watchful waiting provided greater QALE benefit compared with initial treatment than AS, but this finding was dependent on several model assumptions. As has been demonstrated, preferences are central to the QALE advantage of observation, and the decision about which strategy to pursue must be an individual one. Using our results, we estimated that if the number of newly diagnosed men with low-risk prostate cancer who selected observation with WW increased from 10% to 50%, it would result in a cost savings of more than $1 billion; if one half of the men who chose observation opted for WW and one half for AS, it would save $500 million. As we better classify men as low risk by adding molecular and imaging techniques currently in development to standard clinical parameters, prospective studies should determine whether less surveillance than is typically done on AS is safe for men who select observation for low-risk prostate cancer. These findings provide further support for WW and AS as reasonable and underused options for men with low-risk prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix 1

Methods

Systematic Review

We searched MEDLINE; EMBASE; and the Cochrane Library, including the Database of Abstracts of Reviews of Effects, for English-language studies published between January 1996 and June 2012. Search terms included *prostatic neoplasms*; *prostate cancer*; *radical prostatectomy*; *prostatic neoplasms* and *active surveillance*; *prostatic neoplasms* and *watchful waiting*; *prostatic neoplasms* and *active management*; *prostatic neoplasms* and *conservative management*; *prostatic neoplasms* and *deferred treatment*; *brachytherapy*; *radiosurgery*; *radiotherapy*, *high-energy radiotherapy*, and *intensity-modulated*; and *high-energy radiation therapy*. Health technology assessments, systematic reviews, and primary studies were included, and we also searched reference lists of all eligible studies. Additional eligibility criteria included most patients with low-risk disease or subgroup analysis focused on low-risk patients and a sample size of more than 50 patients.

As previously described, effect estimates and associated CIs were created using the DerSimonian–Laird method with inverse variance weighting. Results were subjected to several tests of bias, including rank correlation and Egger regression tests. If either proved significant, we used the trim-and-fill method to adjust the pooled estimate. Meta-analyses were done using MIX, version 1.7 (BiostatXL, Sunnyvale, California) (7-9, 13, 15,).

Model Calibration and Validation

We calibrated only 1 parameter in this model because only 1 parameter was “unobservable” (not taken directly from the literature) (44). This parameter, the probability of developing metastatic disease on AS or WW, was adjusted iteratively until the lifetime HR for prostate cancer–specific death for RP was 1.48 relative to WW and 1.85 relative to AS, an assumption made in the model. The HR for treatment versus WW was taken from the PIVOT point estimate at 12 years, and we assumed that this HR would remain constant for the life of the men (13). The lifetime risk for prostate cancer–specific death that our model produced was 4.8% for men on AS, 6.0% for men on WW, and 8.9% for men treated initially, consistent with the HR from PIVOT and our assumptions.

We did internal validation to ensure that the model produced results that were consistent with model inputs, ensuring the accuracy and predictability of the model. External validation was done by comparing outputs of the model with model inputs and the literature. For example, in our model, the 12-year risk for prostate cancer–specific death is 3.0% after initial treatment (with any method) and 2.8% on WW. In PIVOT, the 12-year point estimate of prostate cancer–specific death for the low-risk subset of men was 2.7% for WW and 4.1% for RP (13). In another study, in men aged 66 to 74 years, the 10-year prostate cancer–specific mortality rate for those with Gleason scores of 5 to 7 and stage T1c disease who were managed conservatively was 2% (4). In a third study in Sweden, the 10-year risk for prostate cancer–specific death in men with low-risk prostate cancer was 2.4% (CI, 1.2% to 4.1%) in an observation cohort and 0.7% (CI, 0.3% to 1.4%) in the curative treatment cohort

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(2). In this way, we have ensured that our model results are consistent with outcomes in the literature.

Costs

Costs were inflated to 2012 U.S. dollars from 2008 U.S. dollars using the U.S. Consumer Price Index for medical care, as provided by the U.S. Bureau of Labor Statistics (31).

Direct Medical Costs—Inpatient costs were estimated from the Centers for Medicare & Medicaid Services, based on average national payment estimates from the 2008 Hospital Inpatient Prospective Payment System, along with Current Procedural Terminology (CPT) codes and American Society of Anesthesiologists units.

Outpatient costs were estimated using CPT codes and ambulatory payment codes and relative value units from the 2008 Hospital Outpatient Prospective Payment System (32), with the professional component in the hospital outpatient setting from the Physician Fee Schedule. Costs of medications were obtained from the 2008 Red Book (43). Additional treatment costs were estimated from the Clinical Laboratory Fee Schedule (42) and Durable Medical Equipment, Prostetics/Orthotics & Supplies Fee Schedule (41) from the Centers for Medicare & Medicaid Services. Total relative value units included work- and facility-related components, with both technical and professional components where applicable.

Costs of managing treatment-related adverse effects are weighted averages representing typical case mixes. All related office visits are included. In the case of long-term adverse effects, both 1-time and ongoing costs are included, the former often reflecting procedural interventions. The sources of these case-mix estimates include literature review and expert opinion (7-9).

Patient Time Costs—Patient time was valued at $165 per day, assuming an 8-hour workday at the 2012 U.S. median wage (33). Estimates of the number of hours required for each intervention were derived from literature sources (45), online patient guides, and interviews with clinicians (7-9).<46-48>

Appendix 2

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis permits us to assess the degree to which uncertainty surrounding estimates of probabilities, utilities, and costs plays a role in the results of the model. Each time the model is run, each probability, utility, and cost is drawn from a distribution of possible values, thereby accounting for uncertainty surrounding all estimates simultaneously. We simulated 100 000 individual life histories for each of 500 samples drawn from independent distributions around each parameter. We used β distributions around probabilities and utilities with the exception of the probability of developing metastatic disease on AS (uniform); γ distributions were used for costs.

This probabilistic sensitivity analysis, therefore, reflects the uncertainty surrounding each parameter in the model, including costs, utilities, symptoms on observation, adverse effects

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of treatment, and risk for prostate cancer–specific death. As seen in Appendix Figures 2 and 3 and Appendix Table 10, the ranking of strategies and magnitude of effect difference between strategies is unaltered when uncertainty is incorporated in men aged 65 and 75 years. However, the wide and overlapping CI surrounding both costs and QALE reflect the collective uncertainty of all of the model inputs.

Appendix

Appendix Table 1

Additional model inputs including Adverse Effects of Treatment and Utilities associated with adverse effects of treatment (adapted from (15)).

Probabilities of Adverse Effects of Treatment	**Base Case (SD)***
Short-term adverse effects of treatment	
Radical prostatectomy(8)	
Perioperative death	0.0044(0.00001)
Major complications**	0.0472(0.0168)
Minor complications***	0.0948(0.0019)
Urinary toxicity	0.47(0.0578)
Erectile dysfunction	0.77(0.0384)
Urethral stricture	0.0344 (0.002)
IMRT	
Urinary toxicities****	0.3(0.0835)
Gastrointestinal toxicities	0.18 (0.0506)
Brachytherapy(7,9)	
Urinary toxicities****	0.29 (0.058)
Acute urinary retention	0.1 (0.021)
Gastrointestinal toxicities	0.02 (0.001)
Active surveillance (biopsy)(40)	
Urosepsis	0.001 (0.0001)
Acute urinary retention	0.026 (0.0049)
Long-term adverse effects of treatment	
Radical prostatectomy(8)	
Urinary toxicity	0.127 (0.011)
Erectile dysfunction	0.453 (0.021)
IMRT(7,9)	
Urinary toxicities****	0.04 (0.009)
Gastrointestinal toxicities	0.03 (0.01)
Erectile dysfunction	0.124 (0.028)
Secondary malignancy	0.0003 (1% lifetime risk beginning 10 y after treatment) (0.00008)
Brachytherapy(7,9)	
Urinary toxicities****	0.06 (0.039)

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Probabilities of Adverse Effects of Treatment	**Base Case (SD)** *
Gastrointestinal toxicities	0.01 (0.008)
Erectile dysfunction	0.124 (0.028)
Secondary malignancy	0.00015 (0.5% lifetime risk beginning 10 y after treatment) (0.000038)
Baseline and interim development of erectile dysfunction, urinary symptoms	
Erectile dysfunction(41)	
Baseline probability, age 65	0.3 (0.075)
Development of symptoms (increasing with age)	0.015 (0.004)
Urinary obstruction(42)	
Baseline probability, age 65	0.3 (0.075)
Development of symptoms (increasing with age)	0.011 (0.003)
Health States(38)	**Utility (SD)**
Treatment of Adverse Effects	
Impotence	0.88(0.20)
Urinary difficulty	0.88(0.16)
Urinary incontinence	0.81(0.30)
Bowel problems	0.63 (0.32)
Impotence and urinary difficulty	0.77(0.24)
Impotence and urinary incontinence	0.84(0.23)
Urinary incontinence and bowel	0.64(0.33)
Impotence and bowel	0.55(0.35)
Impotence, urinary incontinence and bowel	0.38(0.30)
Major complications of RP	0.96(0.012)
Minor complications of RP	1.00 (N/A)
Other Health States	
Treatment with RP	0.46(0.36)
Treatment with radiation therapy	1.0(N/A)

Beta distribution (real number form)

Formula: $\mathrm{f}\,(\mathrm{x}) = x^{(a-1)}(1-x)^{(b-1)}\,\frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}$

Domain: $0 < x < 1$

Parameters: $a > 0$, $b > 0$

Details: $Mean = \frac{a}{(a+b)}$

The parameters a and b can be approximated from a mean μ and standard deviation σ:

$$\mathrm{a} = \mu\left(\frac{\mu(1-\mu)}{\sigma^2} - 1\right)$$

$$b = (1-\mu)\left(\frac{\mu}{\sigma^2}(1-\mu) - 1\right)$$

* Where standard deviations are provided, the parameter was varied (range 0,1) in probabilistic sensitivity analysis using a beta distribution function in TreeAge Pro parameterized with approximations of a and b (range 0,1) based on the mean and standard deviation (sd) using the following formulas:

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** Major complications include major bleeding, deep vein thrombosis/pulmonary embolus, myocardial infarction/stroke, bowel injury, and major/systemic infection.

*** Minor complications represent those outcomes not typically requiring re-exploration or invasive intervention (e.g., UTI, hematoma, ileus)

**** Urinary toxicities include irritative voiding symptoms and incontinence.

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Appendix Table 2

Costs of One-Time and Recurrent Treatments of Adverse Effects

Cost per 3-month cycle of one-time plus recurrent costs	Adverse Effects	Coding	Intervention	RVUs/medication amount	Payment ($)	Weighting*	Charges per 3-month cycle	Cost per cycle	Patient Days, Weighted	Comments
Urinary Incontinence	Chronic management of urinary incontinence		anticholinergic agent (tolteridine)	60 tablets (1mg)	140.20	100%	3	$ 420.59		60 tabs per month
	One-time costs	APC 0126	level I Urinary and Anal Procedures	1.0356	74.63	74%	1	$ 55.23	0.74	Includes CPT 51736 (urodynamics/ uroflowmetry) & 53601 (dilate urethra stricture)
		APC 0164	level II Urinary and Anal Procedures	2.0077	144.69	25%	1	$ 36.17	0.50	Includes CPT 0084T (temporary prostate urethral stent) and CPT 53621 (dilate urethra stricture)
		APC 0150	level V Anal/Rectal Procedures	30.1606	2.173.55	1%	1	$ 21.74	0.10	Includes CPT 46762 (artificial sphincter)
		CPT 99214	Office/outpatient visit, estimated	1.91	82.31	100%	2	$ 164.62	1.00	
								$ 698.35	**2.34**	
Erectile Dysfunction (ED)	Chronic management of ED		sidenafil citrate 50mg tab/week	30 tablets (50mg)	408.34	97%	0.4	$ 63.37		Assuming 1 tablet/week
	One-time costs**	HCPCS	vacuum erection device		546.41	10%	1	$ 21.86		
		CPT 54405	prosthesis (insert multi-comp penis pros)	144.1246	10.386.45	5%	1	$ 207.73	0.10	
			Caverject pens, intracavernous injections	2 pens	65.57	5%	26	$ 34.09		Assuming 2.2 uses/week
		CPT 99214	Office/outpatient visit, estimated	1.91	82.31	100%	2	$ 65.85	1.00	
								$ 392.90	**1.10**	
Gastrointestinal Adverse Effects	Chronic management of GI bleeding		6 months anti-inflammatory enema: 3g/day sulfazine	91.2g per month	101.50	100%	6	$ 609.01	11.00	
	One-time costs	APC 0143	colonoscopy for bleeding	8.8486	637.68	30%	1	$ 191.30	0.30	
			sigmoidoscopy/ablation		637.68	30%	3	$ 573.91	0.45	
			6 months anti-inflammatory enema for refractory cases	91.2g per month	101.50	30%	6	$ 182.70	3.00	
								$ 1.556.92	**14.75**	
Urinary Obstruction	Chronic management urinary obstruction		Tamsulosin	1 30-day supply	94.64	100%	3	$ 283.93		
	One-time costs	CPT 99214	office/outpatient visit, estimated	1.91	82.31	100%	2	$ 164.62	1.00	
		APC 0163	level IV Cystourethroscopy & other Genitourinary Procedures	36.0774	2.599.94	2%	1	$ 52.00	0.04	
		CPT 52000	Cystoscopy	5.97	430.49	100%	1	$ 430.49	2.00	

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Cost per 3-month cycle of one-time plus recurrent costs	Adverse Effects	Coding	Intervention	RVUs/medication amount	Payment ($)	Weighting*	Charges per 3-month cycle	Cost per cycle	Patient Days, Weighted	Comments
		APC 0126	level I Urinary and Anal Procedures	1.0356	74.63	50%	1	$ 37.31	1.00	Includes CPT 51736 (urodynamics/ uroflowmetry) & 53601 (dilate urethra stricture)
								$ 968.36	**4.04**	
Recurrent costs only										
Urinary Incontinence	Chronic management of incontinence		anticholinergic agent (tolteridine)	60 tabs (1mg)	140.20	100%	3	$ 420.59		
		CPT 99214	Office/outpatient visit, estimated	1.91	82.31	100%	1	$ 82.31	0.50	
								$ 502.90	**0.50**	
Erectile Dysfunction	Chronic management of ED		sidenafil citrate 50mg tab/week	30 tabs (50mg)	408.34	97%	0.4	$ 63.37		Assuming 1 tablet/week
			Caverject pens, intracavernous injections	2 pens	65.57	5%	6	$ 7.87		Assuming 1 use every 2 weeks
		CPT 99214	Office/outpatient visit, estimated	1.91	82.31	100%	1	$ 82.31	0.50	
								$ 153.55	**0.50**	
Gastrointestinal Adverse Effects	Chronic management of GI bleeding		6 months anti-inflammatory enema: 3g/day sulfazine	91.2g per month	101.50	10%	1.5	$ 15.23	0.55	
		APC 0143	colonoscopy for bleeding	8.8486	637.68	5%	0.025	$ 0.80	0.00125	
			s igmoidoscopies/ablation		637.68	5%	0.075	$ 2.39	0.0005625	
			6 months anti-inflammatory enema for refractory cases	91.2g per month	101.50	5%	1.5	$ 7.61	0.3	
								$ 26.03	**0.85**	
Urinary Obstruction	Chronic urinary obstruction		Tamsulosin	1 30-day supply	94.64	100%	3	$ 283.93		
		CPT 99214	Office/outpatient visit, estimated	1.91	82.31	100%	1	$ 82.31	0.50	
								$ 366.25	**0.50**	

ABBR: RVU: Relative value units: CPT: Current procedural terminology: APC: Ambulatory Payment Codes; HCPCS: Health Care Common Procedure Coding System

*Weighting: Weighted averages of costs represent typical case mixes (severity, treatment modality) derived from structured interviews with clinicians

**For the purposes of this model it is assumed that 40% of men with erectile dysfunction seek treatment

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Appendix Table 3

Sensitivity analysis of probability of prostate cancer specific death

	Range	Base Case		2 × base HR WW: 2 × 1.48 = 2.96 AS: 2 × 1.85 = 3.7		0.42 HR	
		Cost	QALE(y)	Cost	QALE(y)	Cost	QALE(y)
65 year old men							
WW	3.0% - 21.1%	$24,520	9.02	$24,806	9.21	$22,567	7.97
AS	2.4% - 21.1%	$39,894	8.85	$40,117	8.90	$34,752	7.60
75 year old men							
WW	1.3% - 9.3%	$18,302	6.14	$18,563	6.18	$17,707	5.76
AS	1.1% - 9.3%	$30,048	5.98	$30,251	6.02	$28,335	5.57

ABBR: WW: watchful waiting; AS: active surveillance

Appendix Table 4

Sensitivity analysis of probability of undergoing treatment on observation

	Range	Base Case		50% base case		200% base case	
		Cost	QALE(y)	Cost	QALE(y)	Cost	QALE(y)
65 year old men							
WW	0.35%-1.4%	$24,520	9.02	$21,748	9.14	$28,708	8.88
AS	1.4%-5.8%	$39,894	8.85	$35,260	9.08	$43,607	8.58
75 year old men							
WW	0.35%-1.4%	$18,302	6.14	$16,446	6.17	$21,325	6.03
AS	1.4%-5.8%	$30,048	5.98	$25,818	6.12	$34,567	5.84

ABBR: WW: watchful waiting; AS: active surveillance

Appendix Table 5

Sensitivity analysis of treatment costs of adverse effects of treatment (costs of all adverse effects modified simultaneously from 50% to 200% of base case value)

	Base Case	50% Base Case	200% Base Case
65 year old men			
WW	$24,520	$21,980	$29,778
BT	$35,374	$30,822	$44,305
RP	$38,180	$32,038	$52,229
AS	$39,894	$36,582	$46,363
IMRT	$48,699	$44,112	$57,927
75 year old men			
WW	$18,302	$16,384	$22,410
BT	$28,810	$23,260	$35,099
AS	$30,048	$27,955	$34,832
IMRT	$42,286	$38,909	$49,113

ABBR: WW: watchful waiting; BT: brachytherapy; AS: active surveillance; RP: radical prostatectomy; IMRT: intensity-modulated radiation therapy

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Appendix Table 6

Sensitivity analysis of procedure costs (Range 50%-200% of cost of treated, weighted by treatment distribution in the case of WW and AS)

	50%	200%	Base Case	50% Base Case	200% Base Case
65 year old men					
WW	8,746	34,981	$24,520	$22,173	$29,223
BT	6,168	24,672	$35,374	$29,231	$47,611
RP	6,151	24,602	$38,180	$32,139	$50,444
AS	12,840	51,359	$39,894	$32,487	$54,349
IMRT	12,837	51,348	$48,699	$35,849	$74,141
75 year old men					
WW	8,746	34,981	$18,302	$16,656	$21,644
BT	6,168	24,672	$28,810	$22,733	$41,048
AS	12,840	51,359	$30,048	$24,429	$41,791
IMRT	12,837	51,348	$42,286	$29,489	$67,652

ABBR: WW: watchful waiting; BT: brachytherapy; AS: active surveillance; RP: radical prostatectomy; IMRT: intensity-modulated radiation therapy

Appendix Table 7

Sensitivity analysis of surveillance costs (average annual cost pre-treatment)

	50%	200%	Base Case	50% base case	200% base case
65 year old men					
WW	$263	$1,053	$24,520	$22,280	$29,056
AS	$543	$2,170	$39,894	$37,569	$30,925
75 year old men					
WW	$263	$1,053	$18,302	$16,529	$21,913
AS	$543	$2,170	$30,048	$28,435	$33,511

ABBR: WW: watchful waiting; AS: active surveillance

Appendix Table 8

Sensitivity analysis of patient time costs (Range 50%-200% or $83-$330)

	Base Case	50% Base Case	200% Base Case
65 year old men			
WW	$24,520	$21,617	$30,323
BT	$35,374	$31,594	$42,724
RP	$38,180	$34,444	$45,549
AS	$39,894	$35,400	$48,343
IMRT	$48,699	$44,105	$57,385
75 year old men			
WW	$18,302	$16,184	$22,647
BT	$28,810	$26,054	$34,454
AS	$30,048	$26,813	$36,537

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	Base Case	50% Base Case	200% Base Case
IMRT	$42,286	$38,827	$49,224

ABBR: WW: watchful waiting; BT: brachytherapy; AS: active surveillance; RP: radical prostatectomy; IMRT: intensity-modulated radiation therapy

Appendix Table 9

Sensitivity analysis of discounting rate (Range 0%-6%)

	Base Case (3%)	0%	6%
65 year old men			
WW	$24,520	$32,657	$19,381
BT	$35,374	$43,242	$30,223
RP	$38,180	$46,536	$32,897
AS	$39,894	$50,993	$32,168
IMRT	$48,699	$56,314	$43,662
75 year old men			
WW	$18,302	$22,305	$15,501
BT	$28,810	$32,595	$26,145
AS	$30,048	$35,988	$25,931
IMRT	$42,286	$45,913	$39,632

ABBR: WW: watchful waiting; BT: brachytherapy; AS: active surveillance; RP: radical prostatectomy; IMRT: intensity-modulated radiation therapy

Appendix Table 10

Sensitivity analysis of AS with men progressing to the same treatment distribution as WW (49% RP, 39% IMRT, 12% BT)

	Base Case		AS with PIVOT treatment	
	Cost	QALE	Cost	QALE
65 year old men				
WW	$24,520	9.02		
AS	$39,894	8.85	$35,085	8.85
75 year old men				
WW	$18,302	6.14		
AS	$30,048	5.98	$26,177	6.03

ABBR: WW: watchful waiting; AS: active surveillance

Appendix Table 11

Breakdown of Average Lifetime Costs for Each Strategy in 65 and 75 year old men (values include patient time costs).

Cohort Costs	Cost($)	Cost ($)
Age	65	75
Active Surveillance		
Surveillance Costs		
Total Pre-treatment	6081	4886

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Cohort Costs	Cost($)	Cost ($)
PSA	2859	2299
Biopsies	1832	1474
Visits	1390	1112
Total Post-treatment	3204	1714
Total	9285	6599
Procedure Costs		
Total	15688	12475
Radical Prostatectomy (if applicable)	0	0
IMRT	15212	12084
IMRT+ADT	476	391
Symptoms and Adverse Effect Treatment Costs		
Underlying symptoms		
Total	12758	9817
While on AS	896	489
After treatment	11862	9327
Surveillance biopsy complications	55	44
Treatment of adverse effects of treatment		
Total	2108	1113
Short Term		
RP	0	0
IMRT	308	242
IMRT+ADT	1	1
Total	310	243
Long Term		
RP	0	0
IMRT	1756	849
IMRT+ADT	42	21
Total	1798	870
Radical Prostatectomy		
Procedure Cost	12199	12118
Symptoms and Adverse Effect Treatment Costs		
Underlying symptoms	11761	9334
Treatment of adverse effects of treatment		
Total	7824	5325
Short Term	1802	1762
Long Term	6022	3563
Surveillance Costs	6396	4287
IMRT		
Procedure Cost	25569	25417
Symptoms and Adverse Effect Treatment Costs		
Underlying symptoms	12235	9550
Treatment of adverse effects of treatment		

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Cohort Costs	Cost($)	Cost ($)
Total	4481	3010
Short Term	687	692
Long Term	3794	2317
Surveillance Costs	6413	4308
BT		
Procedure Cost	12283	12213
Symptoms and Adverse Effect Treatment Costs		
Underlying symptoms	12067	9469
Treatment of adverse effects of treatment		
Total	4619	2807
Short Term	196	199
Long Term	4423	2608
Surveillance Costs	6406	4321
Watchful Waiting		
Surveillance Costs		
Total Pre-treatment	4517	3664
PSA	1860	1486
Biopsies	0	0
Visits	1844	1473
Bone Scans	814	706
Total Post-Treatment	1501	799
Total	6018	4463
Procedure Costs		
Total	4617	3319
Radical Prostatectomy	1596	1148
IMRT	2643	1889
BT	379	282
Symptoms and Adverse Effect Treatment Costs		
Underlying symptoms		
Total	12656	9871
While on WW	1812	854
After treatment	10844	9017
Treatment of adverse effects of treatment		
Total	1228	648
Short Term		
RP	228	171
IMRT	52	38
BT	6	4
Total	280	209
Long Term		
RP	547	251
IMRT	320	151

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Cohort Costs	Cost($)	Cost ($)
BT	81	38
Total	948	440

ABBR: AS: active surveillance; RP: radical prostatectomy; BT: brachytherapy; IMRT: intensity-modulated radiation therapy; WW: watchful waiting; ADT: androgen deprivation therapy

Appendix Table 12

Probabilistic Sensitivity Analysis Results for 65 and 75 year old men

Strategy	Cost ($)	95% CI ($)	QALE (years)	95%CI
Age 65				
WW	23,054	16,348 – 29,761	9.06	5.44 - 12.67
BT	34,831	23,374 – 46,288	8.13	3.9 - 12.36
RP	38,076	26,556 – 49,597	7.83	3.36 - 12.31
AS	39,611	26,328 – 52,894	8.92	5.65 - 12.18
IMRT	47,893	29,099 – 66,686	8.04	3.76 - 12.32
Age 75				
WW	17,544	12,486 – 22,603	6.07	3.29 - 8.86
BT	28,380	18,310 – 38,450	5.56	2.49 - 8.63
AS	29,959	19,728 – 40,190	6.05	3.71 - 8.39
IMRT	42,033	23,658 – 60,408	5.53	2.55 - 8.52

ABBR: QALE: quality-adjusted life expectancy; AS: active surveillance; RP: radical prostatectomy; BT: brachytherapy; IMRT: intensity-modulated radiation therapy; WW: watchful waiting

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Table 1

Model inputs: key probabilities, utilities, and costs. For further detail, please see Appendix Table 1(adapted from (15)).

Annual probabilities	**Base Case Estimate (SD*)**	**Range used in Sensitivity Analysis**
Disease-related probabilities		
Disease-related probabilities: Low-risk prostate cancer		
Biochemical recurrence after treatment (7-9)	0.01 (year 1; lifetime risk 0.45)	Not varied
Progression from biochemical recurrence to metastatic disease (36)	0.05	Not varied
Death of prostate cancer after development of metastatic disease (37)	0.22	Not varied
Disease-related probabilities: Active surveillance		
Progressing to Gleason 7 disease(12,22,23,26)	0.023(0.006)	0.012-0.046
Other progression (PSA, DRE)(12, 20-26)	0.052(0.013)	0.026-0.104
Electing treatment	0.018(0.005)	0.009-0.036
Development of metastatic disease prior to treatment	.00003**	Not varied
Disease-related probabilities: Watchful waiting		
Progression to treatment (13)	0.02 (0.005)	0.01-0.04
Disease-related probabilities: Intermediate- risk prostate cancer (Gleason≥7)		
Biochemical recurrence after treatment(19)	0.01 (year 1; lifetime risk 0.60)	Not varied
Progression from biochemical recurrence to metastatic disease(36)	0.05	Not varied
Health State	**Utility (SD)**	**Range**
Prostate Cancer		
Active Surveillance(15,38)	0.83(0.24)	0.42-1
Watchful Waiting(38)	0.83(0.24)	0.42-1
Biochemical recurrence	0.68(0.26)	Not varied
Metastatic cancer	0.12(0.18)	Not varied
Post treatment without side effects(39)	0.80(0.24)	0.4-1
Costs	**Base Case Estimate ($)**	**50%-200% used for all costs**
Direct Costs* **		
Surveillance Costs		
Physician visit with PSA	140	
Incremental cost of biopsy with prophylactic antibiotics	688	
PSA only	29	
Bone scan	320	
Procedure Costs		
Radical prostatectomy (open)	11,856	
IMRT	23,817	
Brachytherapy	11,511	
Androgen Deprivation Therapy	9,090	

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Annual probabilities	Base Case Estimate (SD*)	Range used in Sensitivity Analysis
Short-term Adverse Effects and Complications		
Minor complications of radical prostatectomy	8259	
Major complications of radical prostatectomy	19687	
Septicemia after biopsy	13355	
Urinary symptoms of treatment	221	
Acute urinary retention (brachytherapy)	210	
Bowel symptoms of treatment	1306	
Urethral stricture (radical prostatectomy)	587	
Long-term Adverse Effects and Symptoms		
Incontinence: including one-time costs	698	
Incontinence: recurrent costs	503	
Bowel effects: including one-time costs	1557	
Bowel effects: recurrent costs	26	
Erectile dysfunction: including one-time costs	393	
Erectile dysfunction: recurrent costs	154	
Underlying urinary obstruction	968	
Underlying erectile dysfunction	366	
Patient Time Costs		
Daily patient wage	165	
Surveillance Costs		
PSA test/provider visits	83	
Visit with TRUS-guided biopsy	165	
Bone scan	83	
Procedure Costs		
Radical prostatectomy (open)	445	
Brachytherapy	825	
IMRT	1,857	
Androgen Deprivation Therapy	165	
Short-term Adverse Effects and Complications		
Minor complications of radical prostatectomy	592	
Major complications of radical prostatectomy	1,564	
Septicemia after biopsy	938	
Urinary symptoms	115	
Acute urinary retention (brachytherapy)	152	
Bowel symptoms	1,975	
Urethral stricture (radical prostatectomy)	165	
Long-term Adverse Effects and Symptoms		
Incontinence: including one-time costs	386	
Incontinence: recurrent costs	83	

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Annual probabilities	Base Case Estimate (SD*)	Range used in Sensitivity Analysis
Bowel effects: including one-time costs	2,434	
Bowel effects: recurrent costs	140	
Erectile dysfunction: including one-time costs	182	
Erectile dysfunction: recurrent costs	83	
Underlying urinary obstruction	667	
Underlying erectile dysfunction	83	

Beta distribution (real number form)

Formula: $\mathrm{f}\left(\mathrm{x}\right)=x^{(a-1)}(1-x)^{(b-1)}\frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)}$

Domain: 0 < x < 1

Parameters: $a > 0$, $b > 0$

Details: $Mean=\frac{a}{(a+b)}$

The parameters a and b can be approximated from a mean μ and standard deviation σ:

$$\mathrm{a}=\mu\left(\frac{\mu(1-\mu)}{\sigma^2}-1\right)$$

$$b=(1-\mu)\left(\frac{\mu}{\sigma^2}(1-\mu)-1\right)$$

*Where standard deviations are provided, the parameter was varied (range 0,1) in probabilistic sensitivity analysis using a beta distribution function in TreeAge Pro parameterized with approximations of a and b (range 0,1) based on the mean and standard deviation (sd) using the following formulas:

**Uniform distribution used in probabilistic sensitivity analysis

***For sources of costs, please see Methods section and Appendix 1.

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Table 2

Base Case Average Lifetime Costs and QALE for men aged 65 and 75

	Cost ($)	Incremental Cost ($)	QALE(y)	Incremental QALE	% Treated	% Died Prostate Cancer
Age 65						
WW	24,520		9.02		34%	6.0%
BT	35,374	10,854	8.14	−0.88	100%	8.9%
RP	38,180	13,660	7.95	−1.07	100%	8.9%
AS	39,894	15,374	8.85	−0.17	78%	4.8%
IMRT	48,699	24,179	8.10	−0.92	100%	8.9%
Age 75*						
WW	18,302		6.14		23%	2.6%
BT	28,810	10,508	5.56	−0.58	100%	3.9%
AS	30,048	11,746	5.98	−0.16	61%	2.1%
IMRT	42,286	23,984	5.52	−0.62	100%	3.9%

ABBR: WW: watchful waiting; BT: brachytherapy; RP: radical prostatectomy; AS: active surveillance; IMRT: intensity-modulated radiation therapy

*Radical prostatectomy not modeled in 75 year olds

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Table 3

Threshold analyses of scenarios in which the QALE of AS is equal to/better than WW. WW remains less expensive than AS under every reasonable scenario modeled (please see text).

Model parameter	Base case (AS)	Threshold value at which AS' QALE is equal to/ better than WW's
65 year old men		
Hazard ratio prostate cancer-specific death for treatment vs. AS	1.85	≥7.71
Lifetime probability of being treated on AS	78%	≤63%
Utility of AS at which AS favored over WW	0.83	≤0.87
75 year old men		
Hazard ratio prostate cancer-specific death for treatment vs. AS	1.85	≥4.30
Lifetime probability of being treated on AS	61%	≤42%
Utility of AS at which AS favored over WW	0.83	≥0.84

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Table 4

Threshold Analyses of Scenarios in Which the QALE of AS if Equal to or Better Than That of WW*

Model Parameter	AS Base Case	Threshold Value at Which AS QALE is Equal to or BETTER Than WW QALE
Men aged 65 y		
HR for prostate cancer-specific death for treatment vs. AS	1.85	≥7.71
Lifetime probability of being treated on AS, %	78	≤63
Utility of AS at which AS if favored over WW	0.83	≥0.87
Men aged 75 y		
HR for prostate cancer-specific death for treatment vs. AS	1.85	≥4.30
Lifetime probability of being treated on AS, %	61	≤42
Utility of AS at which AS if favored over WW	0.83	≥0.84

AS = active surveillance; HR = hazard ratio; QALE = quality-adjusted life expectancy; WW = watchful waiting.

* WW remains less expensive than AS under every reasonable scenario modeled.

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Table 5

Base-Case Average Lifetime Costs and QALE for Men Aged 65 and 75 Years

Strategy	Cost, $	Incremental Cost, $	QALE, y	Incremental QALE, y	Men Treated, %	Died of Prostate Cancer, %
Men aged 65 y						
WW	24 520	-	9.02	-	34	6.0
BT	35 374	10 854	8.14	−0.88	100	8.9
RP	38 180	13 660	7.95	−1.07	100	8.9
AS	39 894	15 374	8.85	−0.17	78	4.8
IMRT	48 699	24 179	8.10	−0.92	100	8.9
Men aged 75 y *						
WW	18 302	-	6.14	-	23	2.6
BT	28 810	10 508	5.56	−0.58	100	3.9
AS	30 048	11 746	5.98	−0.16	61	2.1
IMRT	42 286	23 984	5.52	−0.62	100	3.9

AS = active surveillance; BT = brachytherapy; IMRT = intensity-modulated radiation therapy; QALE = quality-adjusted life expectancy; RP = radical prostectomy; WW = watchful waiting.

* RP not modeled in men aged 75 y.