

A Decision Analysis for Treatment of Clinically Localized Prostate Cancer

Michael W. Kattan, PhD, Mark E. Cowen, MD, MSc, Brian J. Miles, MD

OBJECTIVE: To determine the preferred treatment of clinically localized prostate cancer.

DESIGN: Cancer grade, patient age, and comorbidities are considered in a Markov model with Monte Carlo sensitivity analyses. Large and recent pooled analyses and patient-derived utilities are included.

RESULTS: Principal findings suggest benefit for radical prostatectomy relative to watchful waiting for men under 70 years of age with low to moderate comorbidity. Men older than 70 with high comorbidity and disease of low to moderate grade do better with watchful waiting.

CONCLUSIONS: Cohort-level sensitivity analyses suggest a quality-adjusted treatment benefit for radical prostatectomy for younger men and treatment harm for older men. Tailored patient and clinician decisions remain necessary, especially for men older than 70 in good health but with aggressive cancers.

KEY WORDS: decision analysis; prostate cancer; watchful waiting; patient-derived utilities; radical prostatectomy.
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Adenocarcinoma of the prostate is the leading cause of cancer in American men, and the second leading cause of death from cancer.¹ In 1996, 317,000 new cases of prostate cancer and 41,400 deaths due to prostate cancer were expected.² The reason for the continued mortality increases are unclear, but the rise in incidence is largely due to the increased use of prostate-specific antigen (PSA) testing.³ The controversial aspect of prostate cancer is determining which patients need curative treatment, considering many more men die with prostate cancer than of it. A randomized clinical trial of watchful waiting (WW) versus

radical prostatectomy (RP) would help resolve the debate. The results of such a trial, however, are at least a decade away. In the meantime, we must rely on rational comparisons of the risks and benefits with either choice.

The purpose of this study is to compare WW and RP in a decision analysis in which the risks of adverse events and patients' feelings about those events are quantified. Our perspective is that of society; we analyzed the data to determine the preferred treatment for a hypothetical cohort of men with localized prostate cancer. Although cost-effectiveness is important, it is not included in this report. Our outcomes of interest are life expectancy, with and without adjustments for quality of life, for WW and RP patients who are between the ages of 60 and 75.

Two large pooled analyses of metastasis-free survival have recently been conducted: one on WW patients,⁴ and one on RP patients.^{5,6} In addition, a recent analysis by Albertsen et al. has illustrated the increased risk of death due to noncancerous chronic illnesses in the prostate cancer population.⁷ Recent studies have also examined treatment and complication impacts on quality of life^{8,9} and patient utilities.¹⁰ Our analysis incorporates all of these recent developments in an attempt to provide a comprehensive and current evaluation of the choice between RP and WW for localized prostate cancer.

METHODS

Decision Analysis Model

We build on a model of prostate cancer previously published by the Prostate Patient Outcomes Research Team (PORT).¹¹ We analyzed this model previously,¹² and we found it reasonably approximated the natural history of prostate cancers. In our Markov model (depicted in Fig. 1), all patients begin with localized prostate cancer with no evidence of metastases and are treated by WW or RP. Each 6 months, a fraction of the patients progress to hormonally controlled metastatic disease. In subsequent 6-month periods, a fraction of these patients progress to hormone-refractory metastatic disease and eventual death from prostate cancer. At every 6-month period, a fraction of the patients die from causes other than prostate cancer. The arrows in Figure 1 illustrate the permissible transitions of the cohort fractions. The probabilities of the initial transition to metastatic disease depend on disease grade and the two treatment options: RP or WW.

Probabilities

The metastatic progression probabilities (Table 1) of the model came from multiple sources and depended on

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Address correspondence and reprint requests to Dr. Kattan: Scott Department of Urology and Information Technology Program, Baylor College of Medicine, Fondren Building, Room 403, 6535 Fannin St., Houston, TX 77030.

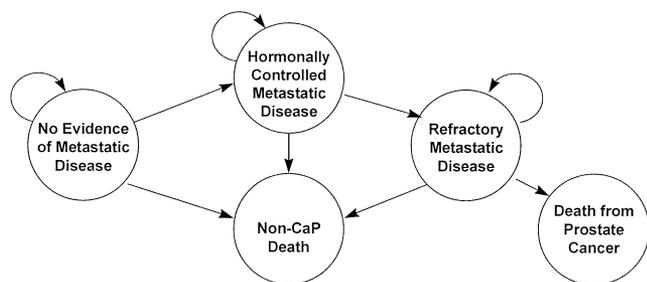


FIGURE 1. Markov model of prostate cancer.

biopsy Gleason grade of the cancer, one of the best preoperative predictors of prostate cancer progression.¹³ For WW patients, a pooled analysis of more than 800 men from several treatment centers was utilized.⁴ The corresponding source for metastatic progression in RP patients was that of Gerber,^{5,6} which was a pooled analysis of 3,500 men, also from several treatment centers. Our metastatic progression probabilities are constant over time. Previous decision analyses have modeled the impact of treatment based on capsular penetration.^{11,12,14} Capsular penetration, however, cannot be determined in the WW patient. Rather, we have chosen to model treatment efficacy using actual treatment data, pooled and analyzed in the same manner as the WW data. The 10-year metastatic-free survival figures were used from both series.

Because most patients with prostate cancer die of causes other than their disease, comorbidity needs to be included in the model. The risk of death from comorbidity was obtained from a large study over several years on Connecticut prostate cancer patients.⁷ This study provided the hazard ratios for men with advanced comorbidity: the greater the number of comorbidities, the higher the risk of death due to noncancer causes.

As RP introduces potential complications, especially impotence and incontinence, these need modeling as well. Complication rates were obtained from a large structured review by Wasson.¹⁵ Wasson's reported rates for impotence and incontinence were chosen over those reported by Fowler et al.,⁸ because patients in the latter series were generally older (80% of patients over 70 years, 30% over 75 years) than the age group considered in this analysis, and potency and continence recovery are age-related,^{16,17} resulting in complication rates higher than we would ex-

pect in younger men. Nevertheless, we examined the effects of Fowler's probabilities in sensitivity analyses. Probabilities of other RP complications such as operative mortality, bladder neck contracture, and bowel damage were preserved from the original PORT analysis.¹¹

Utilities

The relative value patients assign to potential health states is represented as a utility. Utilities typically vary between 0, the utility or value of being dead, and 1.0, the utility of living in perfect health.¹⁸ Most of the utilities used in this analysis were obtained from interviewing 31 men between the ages of 55 and 75, all outpatients from a general internal medicine practice, and none of whom had been diagnosed with prostate cancer (Table 2).¹⁰ Descriptions of the health states of interest (living with prostate cancer managed by WW, living with metastatic prostate cancer responsive or refractory to hormonal therapy, post-treatment impotence, and severe incontinence) were read to the participants. Each man participated in the time trade-off assessment^{19,20} to determine the amount of remaining life expectancy he would give up if he were living in a particular health state because of prostate cancer. The number of "healthy" years without direct consequence from prostate cancer divided by the years of remaining life expectancy yielded a utility value for each health state. The higher the utility, the more preferred the health state. Men treated with radical prostatectomy without the adverse sequelae of disease progression, incontinence, or impotence might still not be in a state of "perfect health" by virtue of their age and coexisting health conditions.²¹ In this case, instead of 1.0, we assigned a utility value of 0.84, the mean for men age 65 to 74 in the population-based Beaver Dam study,²¹ a large longitudinal cohort study of health states for a random selection of adults.

Monte Carlo Analyses

Several of the input parameters for this analysis were estimated from sample data that lack the conclusiveness of a randomized clinical trial. Chief among those are the progression rates for both RP and WW and the patient health-state utilities. For all of these factors, baseline es-

Table 1. Influential Baseline Probabilities in the Decision Analysis*

	Clinical Category (Differentiation)			Reference Number
	Well	Moderate	Poor	
Metastasis, annual				
Watchful waiting	0.021	0.055	0.135	4
Radical prostatectomy	0.014	0.039	0.065	5,6
Impotence	0.31	0.31	0.31	15
Incontinence	0.06	0.06	0.06	15

*The model contains more than 50 probabilities. These are the most influential.¹²

Table 2. Baseline Utilities in the Decision Analysis

Health State	Utility	Reference Number
No recurrence (radical prostatectomy)	0.84	21
Living with prostate cancer (watchful waiting)	0.72	10
Impotence	0.69	10
Incontinence	0.57	10
Metastatic cancer	0.42	10
Refractory cancer	0.13	10

timates and their 95% confidence intervals (CIs) are presented in Table 3. To determine whether the preferred treatment approach would differ with the value of the parameter used, sensitivity analyses are usually performed by varying the progression rates and utilities. However, in this analysis there are two progression rates (WW and RP) and five utilities (from Table 3), and varying more than three factors at a time makes it difficult to interpret the results.²² Furthermore, systemically varying these factors across their ranges does not appropriately consider that values in the middle of the range are more likely than values at the extremes. For these two reasons, we used a second-order Monte Carlo sensitivity analysis²² to determine if the results were consistent when the utilities and progression rates were varied. This type of analysis runs the decision model multiple times, each time randomly choosing probabilities and utilities from values within their expected ranges based on (but not limited by) their 95% CIs, and assuming a logistic normal distribution.²² This approach allows collection of multiple modeled outcomes with computation of summary statistics, e.g., mean quality-adjusted life expectancy (QALE) and its variance,

and it allows tests for statistical significance between therapies.

Statistical significance is partially dependent on the number of model runs performed in the Monte Carlo analysis. A very large number of runs may result in very small confidence intervals, so that a very slight clinical difference between therapies would be statistically significant. Conversely, too few runs could result in a lack of statistical significance owing to low statistical power despite a true difference between therapies. To determine the appropriate number of model runs is analogous to calculating the sample size for a randomized clinical trial. The first step of sample size calculation would be to decide what minimum difference between therapies would be clinically significant. As Cohen has suggested, a "moderate" effect (a difference in means equal to half the standard deviation) is a reasonable starting point.²³ In addition, attempting to detect a smaller effect would most likely compel a cost-effectiveness analysis to determine the value of such a difference. We therefore conducted a power analysis to determine the minimum number of model runs necessary to detect an 80% chance of obtaining a significant test result (two-tailed, 5% level) if there were a true "moderate" difference between therapies. Our power calculations indicated that 67 model runs were needed in order to detect this level of difference using a nonparametric test.

RESULTS

Baseline Model

Figure 2 illustrates the years of benefit of RP relative to WW with and without quality-of-life adjustments for various age and cancer grade combinations. For the left side of Figure 2, the QALE of the WW cohort was subtracted from the QALE of the RP cohort. Because the QALE of the RP cohort was larger at every age-grade com-

Table 3. Parameters Varied in the Monte Carlo Sensitivity Analyses

Parameter	Baseline	95% Confidence Interval*
Freedom of metastasis (% at 10 yr)		
Watchful waiting		
Well differentiated	81	75–86
Moderately differentiated	58	49–66
Poorly differentiated	26	13–41
Radical prostatectomy		
Well differentiated	87	78–92
Moderately differentiated	68	62–73
Poorly differentiated	52	38–64
Utilities		
Life with untreated prostate cancer	0.72	0.63–0.80
Impotence	0.69	0.61–0.77
Incontinence	0.57	0.46–0.68
Metastatic prostate cancer	0.42	0.33–0.51
Refractory prostate cancer	0.13	0.08–0.17

*Note that these confidence intervals are not necessarily the limits used in the sensitivity analyses. Rather, the actual limits are computed and based on these intervals.

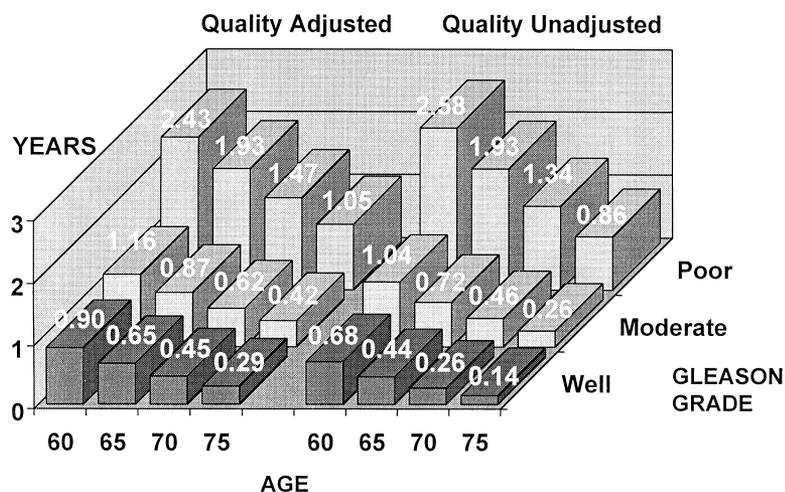


FIGURE 2. Years of benefit of radical prostatectomy versus watchful waiting.

combination, all values are positive, indicating that RP is the preferred therapy owing to the longer net life expectancies. The right-hand side of Figure 2 represents the same analysis with quality-of-life modifiers (utilities) removed and thus represents the quality-unadjusted life years of benefit of RP relative to WW. As with the quality-adjusted figures, all values are positive, indicating greater life expectancy for the RP patients.

Monte Carlo Sensitivity Analyses

Because the Monte Carlo analyses provide more than a single point estimate, the variability of the results should be illustrated, and we have used boxplots for this purpose. (See Fig. 3A for patients with low grade, Fig. 3B for moderate grade, and Fig. 3C for high grade.) Each boxplot highlights the median result near the center (white area), surrounded by 95% CIs (illustrated by an adjacent darker area). Solid areas indicate the center quartiles of the data. The full range of the data is indicated by the vertical "whiskers" (ending brackets). The CIs for each age-matched pair of boxplots do not overlap; therefore the apparent difference between therapies is unlikely to have resulted from chance alone. Figure 3D illustrates boxplots using no utilities in the analysis of selected age-grade combination. Again, CIs fail to overlap, indicating it is unlikely that the median QALEs for the therapies are equal.

Other Sensitivity Analyses

Discount Rate

Because this study is strictly a treatment-effectiveness analysis, and not a cost-effectiveness analysis, the baseline analysis assumed a 0% discount rate, which values later years of life the same as immediate years if utilities are constant. For potential comparison with other studies, this discount rate was varied to 5% per annum, so that later years were valued as less important. This modification reduced the degree of benefit for RP to 1.36 years for a 60-year-old man with poorly differentiated cancer and to 0.18 years for a 75-year-old man with well-

differentiated cancer. However, at no age-grade combination was WW preferred.

Comorbidity

The Index of Coexistent Disease (ICED) comorbidity index was varied from its baseline of 0 to a high of 3. At the second level of comorbidity (ICED = 1), RP remained preferred but only by 0.21 QALY (quality-adjusted life years) for 75-year-old men with well-differentiated cancer. At the next level of comorbidity (ICED = 2), the same conclusion was obtained, but RP exceeded WW only by 0.08 QALY (quality-adjusted life years) for the 75-year-old, well-differentiated cohort. At the highest level of comorbidity (ICED = 3), the QALE for the RP cohort is smaller than the QALE for WW for older men with well-differentiated cancer, indicating WW is the preferred approach in this circumstance.

Impotence and Incontinence Probabilities

The Fowler Medicare probabilities were substituted for the Wasson probabilities to determine whether the therapy decision was sensitive to these figures. These probabilities had a strong effect on the QALEs; RP was preferred only for high-grade cancers.

DISCUSSION

A conclusive randomized clinical trial would suggest the preferred treatment strategy for clinically localized prostate cancer. In the meantime, a decision analysis comparing radical prostatectomy and watchful waiting was performed to estimate the QALE for men aged 60 to 75 years under these two treatment protocols. Baseline analyses suggested a survival benefit for RP patients. Monte Carlo sensitivity analysis indicated these differences were insensitive to the uncertainty in the data ($p < .05$). These findings held for men aged 60 to 75 years with any biopsy grade, although age and grade affect the degree of benefit achieved with aggressive therapy.

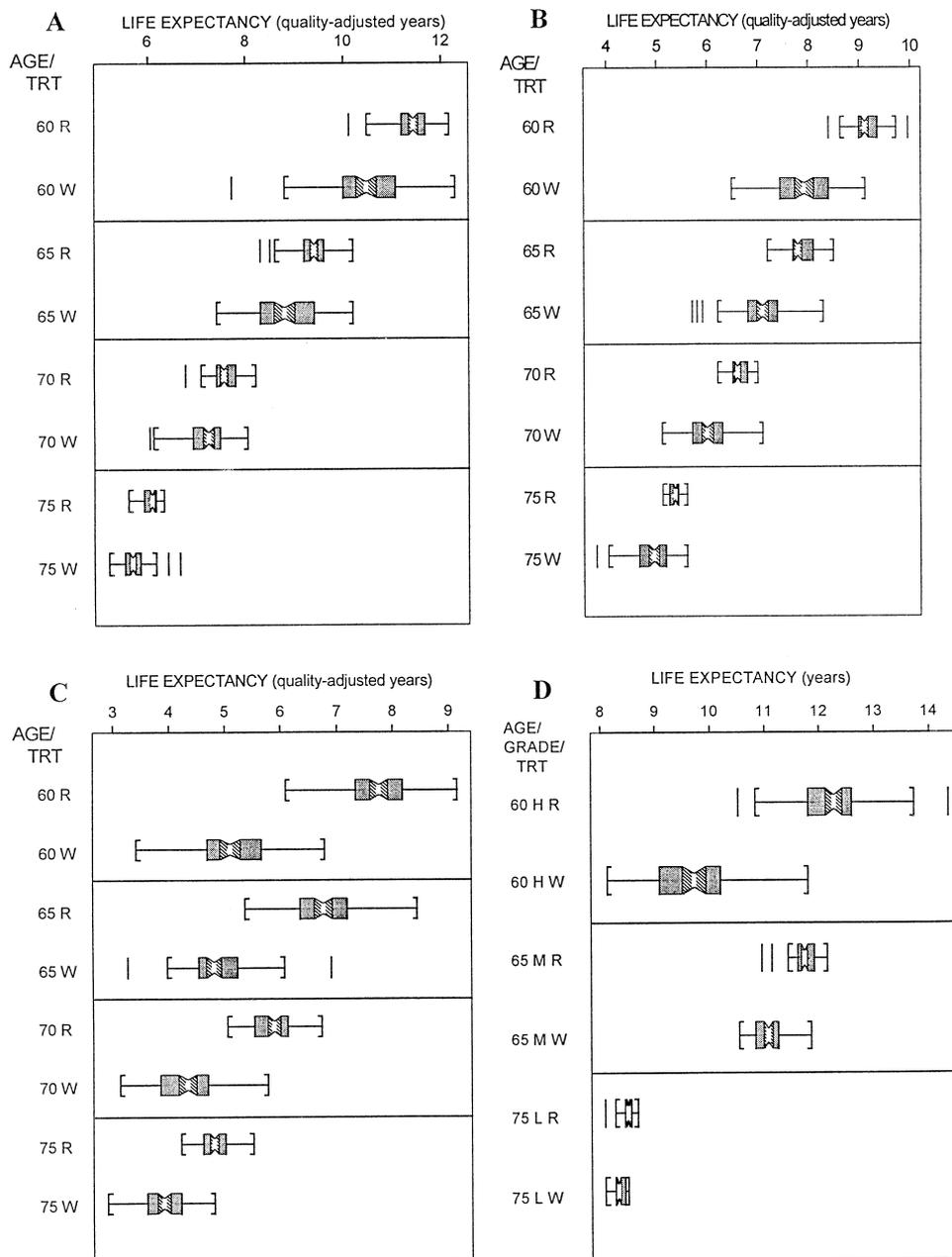


FIGURE 3. Monte Carlo results by cancer grade: (A) low; (B) moderate; (C) high; (D) no quality adjustments. TRT indicates treatment; R, radical prostatectomy; W, watchful waiting. For panel D, H indicates high grade; M, medium grade; L, low grade. White area near the center is the median. Hash marks and indentation indicate 95% confidence intervals for the median. Solid areas indicate center quartiles of the data. Vertical whiskers show the range of the data as well as outliers.

Other sensitivity analyses varied the conclusions by removing the utilities, increasing the discount rate to 5%, and increasing comorbidity. Each of these conditions affected the degree of benefit, and WW was the preferred approach for elderly men with high comorbidity and well-differentiated disease by virtue of the greater net QALE. When quality-of-life adjustments were considered, the benefit of RP increased. At first, this would seem counter-intuitive. However, the reason for this may be that the psychological impact of living with untreated cancer has more of an effect (on the WW patients) than the discom-

fort associated with treatment-related impotence and incontinence (affecting the RP patients). This phenomenon was noted in all cases except the relatively young man with high-grade disease who, if he selected WW, would spend a smaller fraction of his remaining life expectancy in the metastatic-free health state. That is, he would be expected to progress rapidly out of the localized stage, in which the psychological penalty of living with an untreated cancer is imposed, and therefore the disturbing impact of living with untreated and localized cancer lasts a short time. It might be expected that a WW patient who

progresses could suffer regret,²⁴ and have a lower quality of life than a patient who pursued aggressive therapy, but whose disease still progressed.

Conversely, it is also possible that the low utility value which patients assigned to the WW state was influenced by how that state was described, a framing effect. As an example, it is plausible that presenting information about the lack of a difference in cancer survival between RP and WW patients and the risk of treatment complications would influence patient utilities. If so, clinicians need to pay particular attention to how they present the treatment alternatives. Watchful waiting patients may regret not acting, and RP patients who fail may regret undergoing the procedure in vain.

In addition, the disutility of a rising PSA level following definitive treatment needs measuring and modeling, as does the disutility of RP itself. The short-term inconvenience of the treatment may subtract part of 1 month from the QALE of RP.

In order to test the effect of the psychological disutility of living with untreated cancer, this disutility was varied from a low of that obtained by time trade-off to a high of that of our cured RP patient. For well-differentiated cancer, WW becomes the preferred strategy when the utility of living with untreated cancer exceeds 0.76 for 75-year-old or .78 for a 60-year-old. With moderately differentiated cancer, the threshold ranged from 0.78 to 0.82 across the same ages. No threshold between the baseline utilities (0.72 and 0.84) was found for poorly differentiated cancers. These results strongly suggest that management of the psychological or social needs of watchful waiting patients deserves attention.

Even though our model suggests a treatment benefit associated with RP, our results do not imply that screening by PSA or other means is beneficial. One reason for this is that the utilities associated with the screening process are largely unknown. Indeed, the sensitivity analysis of the psychological disutility of living with untreated cancer underscores the risk imposed by routine prostate cancer screening, since avoiding knowledge of prostate cancer increases QALE. Our model assumes men already know they have prostate cancer, and captures the apparent disutility associated with that knowledge. It is unclear what the appropriate policy should be before diagnosis.

Sensitivity analysis with Fowler's higher probabilities of impotence and incontinence dramatically affected the results for preferred treatment for prostate cancer. Radical prostatectomy in this case was preferred only for high-grade disease. However, the utility for incontinence treats this problem as total incontinence, with no utility for occasional or moderate stress urinary incontinence. Similarly, the utility value for impotence does not take into account the phenomenon of habituation, which indicates that individuals become more tolerant of a health state and do not discount the value of life in that state after a period of time. Furthermore, these probabilities are more reflective of an older population, may not be applicable to

a younger population, and do not consider the number of men who returned to normal continence by mechanical or pharmacological means. It is important to realize that the article by Fowler et al. was a quality-of-life study and not designed to derive utilities,⁸ and their definition of incontinence was less severe than ours, to the extent that most of the incontinent patients in the Fowler study were not bothered by their incontinence. Interestingly, of the 30% of men reporting incontinence (defined as moderate or severe), requiring one or more pads per day for control, only half considered their incontinence as a moderate to severe problem. As a result, Fowler's probabilities represent a worst-case scenario. Nevertheless, our results suggest that a RP for men over 75 years of age requires further justification.

Our findings extend the results of previous decision analyses of clinically localized prostate cancer. Fleming's analysis¹¹ lacked the large multicenter pooled studies of WW and RP patients, control for comorbidity, actual patient-derived utilities, and Monte Carlo sensitivity analyses. Beck's analysis¹² added the WW data to Fleming's analysis. In our analysis the baseline results for RP are substantially better than results presented by Fleming,¹¹ and slightly below those of Beck.¹² We feel our choice of using the metastatic rates from the two large pooled analyses was both necessary and unbiased for or against treatment. Although time until metastasis may be a soft end point, the calculated 10-year disease-specific survival estimates for WW (well, 91%; moderate, 80%; and poor, 61%) are within the 95% CIs published in the Chodak analysis except for the poorly differentiated grade. In poorly differentiated cancer, predicted survival by the model was higher than reported by Chodak, suggesting modeled disease to be less aggressive than reported, which would bias the model results in favor of WW.

There are important limitations to this study. First, the pooled analyses used to obtain the transition probabilities are not randomized trials, although these are large series. Selection of patients for treatment or WW was based on the suspected nature of their disease, their comorbidities, and their preferences guided by the informed consent process. Our model is sensitive to a selection bias associated with time until metastasis, and it is difficult to speculate whether such bias is present. Only a randomized trial can definitively answer this treatment question, but the results are more than 10 years away. Second, our utilities are based on a sample of 31 men without prostate cancer. A larger sample is needed for more precise estimates and to measure probable interactions with age. This sample is nonetheless superior to previous analyses that used physician consensus panels. We chose men without prostate cancer because those are men who will confront the treatment decision. Although utilities from actual prostate cancer patients should be compared, especially to examine possible change over time, the Panel on Cost-Effectiveness in Health and Medicine has argued against using patient-derived utilities in the reference case.²⁵ Our analysis was conducted at the cohort level (a

second-order Monte Carlo analysis), and more variability would be observed if individual patients were the unit of analysis. Therefore, our result may be useful at the societal level but not at that of the individual patient. The patient still has to decide, with the help of his clinician, the most appropriate strategy for himself. Individual patients have different utilities.

This analysis suggests that radical prostatectomy is preferred to watchful waiting for men under 70 years of age. Men older than 70 appear to face a toss-up unless they have high comorbidity coupled with disease of low to moderate grade, in which case watchful waiting becomes the preferred therapy. When a preferred treatment is not clearly indicated, treatment choice should be tailored to a patient's age, grade of prostate cancer, comorbidity, and utility profiles. Because of the limitations discussed above, our findings should not be regarded as definitive. We have used the best available data in conjunction with powerful modeling techniques to provide insight on an important but poorly understood question. While we await more definitive studies, these results may increase our understanding of the complex treatment decision facing men with prostate cancer today.

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