Original Article

A Decision Analysis Comparing 3 Active Surveillance Protocols for the Treatment of Patients With Low-Risk Prostate Cancer

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BACKGROUND: Active surveillance (AS) is a viable management option for approximately 50% of men who are newly diagnosed with prostate cancer. To the authors' knowledge, no direct comparisons between the different variants of AS protocols have been conducted to date. The authors developed a microsimulation decision model to evaluate which of 3 alternative AS protocols is optimal for men with low-risk prostate cancer, and compared each of these with immediate treatment. **METHODS:** Men who were diagnosed with low-risk prostate cancer at age 65 years were modeled as having been treated with either immediate therapy or via each of 3 AS protocols. Modeled AS protocols represent those in the literature; a modified AS protocol was included in a sensitivity analysis. Immediate therapy included radical prostatectomy, external-beam radiotherapy, or brachytherapy. Outcome measures were quality-adjusted life-years (QALYs) and costs. Cost-effectiveness analysis and deterministic and probabilistic sensitivity analyses were performed. **RESULTS:** Immediate therapy produced fewer QALYs than all variants of AS. Of the AS protocols evaluated, biennial biopsy was found to be the only efficient option, with an incremental cost-effectiveness ratio of $3490 per QALY compared with immediate therapy. It delayed the need for curative therapy by a mean of 56 months, and was found to be preferred in >86.9% of cases in probabilistic sensitivity analysis. A modified version of low-intensity AS dominated all other options. **CONCLUSIONS:** For a 65-year-old man with low-risk prostate cancer, AS with biennial biopsy appears to be highly cost-effective compared with common alternatives. An AS protocol using triennial biopsy was found to dominate all other strategies and should be considered for men who are comfortable with a longer period between biopsies. The optimal strategy depends on a patient's tolerance for periodic biopsies and comfort with delaying radical treatment. Physicians should incorporate these patient preferences into decision making. ***Cancer* 2018;0:1-11**. *© 2018 American Cancer Society.*

KEYWORDS: active surveillance, cost analysis, cost-effectiveness, decision analysis, decision model, low risk, prostate biopsy, prostate cancer.

INTRODUCTION

In the early 1990s, prostate-specific antigen (PSA) screening led to the increased detection of early-stage prostate cancer.[1,2] Approximately 50% of newly diagnosed patients are diagnosed with low-risk prostate cancer, defined as organ-confined disease (classified as T1/T2a), a PSA level <10 ng/mL, and a Gleason score ≤6 on prostate biopsy.[3] Due to this increased detection of low-risk cancers, clinicians have developed less aggressive management algorithms.[4] Traditional therapies such as radical prostatectomy, brachytherapy, and external-beam radiotherapy frequently cause side effects such as erectile dysfunction and urinary and bowel incontinence, the risk of which may outweigh the benefits of immediate treatment. Despite the increased use of less aggressive strategies, to the best of our knowledge no definitive protocol currently exists.[5,6]

For men with an initial diagnosis of low-risk disease, disease progression often is slow enough that the side effects of radical treatment can be delayed, and occasionally avoided, without reducing the patient's survival.[7,8] The term "active surveillance" (AS) suggests a treatment plan whereby the intention is to cure the patient, but in which radical treatment may be avoided permanently because the cancer's rate of progression is slow enough that patients are likely to die of other causes.[7]

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TABLE 1. Existing Studies Reporting AS Protocols and Their Eligibility Criteria

Institution	AJCC TNM Staging	GS	PSA	PSAD, ng/mL/mL	Positive Core Needle Biopsies	Cancer per Core Needle Biopsy
Johns Hopkins	1c	≤6		≤0.15	≤2	≤50%
Miami	≤T2a	≤6	≤10		≤2	≤20%
Aarau, Switzerland		≤6		≤0.15	≤2	≤50%
McGill University	<2b	≤6			≤2	≤50%
UCSF	≤2	≤6	≤10		≤33%	≤20%
Dana-Farber	1c-2c	≤6			<3	≤50%
Chicago/MSKCC	1-2a	≤6	≤10		≤3	
Royal Marsden Hospital, UK	1-2	≤6[a]	≤15		≤50%	
Cleveland Clinic	1c-2a	≤6	<10			
Princess Margaret Hospital, UK	1c-2a	≤6	≤10		≤3	≤50%
MSKCC	≤2a	≤6	≤10		≤3	≤50%
Monash and Southern		≤7	6.5[b]		≤2	
PRIAS	1c-2	≤6	≤10	≤0.2	≤2	
Toronto	1	≤6[c]	≤10[d]			
Connecticut	1-2a	≤6	≤10		≤2	<50%

Abbreviations: AS, active surveillance; GS, Gleason score; MSKCC, Memorial Sloan Kettering Cancer Center; PRIAS, Prostate Cancer Research International Active Surveillance; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; UCSF, University of California at San Francisco.
[a]For patients aged >65 years this was relaxed to ≤7.
[b]This study did not provide a threshold. The number reported is a median Gleason sum.
[c]Until January 2000, this was relaxed to ≤7 for patients aged >70 years.
[d]Until January 2000, this was relaxed to ≤15 for patients aged >70 years.

AS Protocols

There is a wide range of intensity in the monitoring regimens of AS protocols, from digital rectal examination (DRE) and PSA measurements every 3 months with yearly biopsies to semiannual DRE and PSA with biopsies performed every 3 to 4 years (Table 1).[3,9-14] More intense monitoring may not necessarily confer better outcomes because it brings its own set of problems, such as lower compliance and the risk of protocol abandonment, and imposes burdens of patient pain and suffering and emotional and financial costs.[15-18] To our knowledge, no published study to date has compared multiple active surveillance protocols.

Concerns Regarding Disease Progression

Several studies of patients with low-risk prostate cancer have indicated that the risk of metastasis is low, and that prostate cancer–specific survival rates are high for patients with disease that has not yet metastasized.[3,19-25] Data from the recent Prostate Testing for Cancer and Treatment (ProtecT) trial indicate that after a median follow-up of 10 years, only 1% of patients had died due to their cancer compared with 9% of patients who died of other causes, and that there was no significant difference noted with regard to overall survival between men undergoing radical treatment and those under AS.[8] It is interesting to note that the ProtecT trial implemented an "active monitoring" strategy that included only PSA testing and no biopsy, which is less "intense" than all AS protocols we modeled.

Although there may never be a prospective randomized trial comparing the effectiveness of various AS protocols, we now have sufficient data to predict what might be the optimal monitoring intensity for patients with low-risk prostate cancer. We reviewed reported AS protocols and then modeled their clinical effectiveness and cost-effectiveness to make appropriate recommendations regarding monitoring intensity that balance oncologic outcomes against patient mortality, morbidity, and cost.

MATERIALS AND METHODS

We created a Markov state transition patient-level microsimulation model with a monthly cycle length in TreeAge Pro 2015 (version 15.1.0.0-v20150223; TreeAge Software Inc, Williamstown, Massachusetts) to model the effects of alternative strategies for treating patients with low-risk prostate cancer (PSA level ≤10 ng/mL and Gleason score ≤7). All other statistical analyses were undertaken in R statistical software (version 3.1.1; R Foundation, Vienna, Austria). A model schematic is shown in Figure 1 and in more detail in Supporting Figures S1 to S4.

In the base case analysis, we simulated 3 variants of AS protocols, each of which resembles a protocol that has been reported on in the published literature (the search terms and results of the economic literature review can be found in the Supporting Materials;

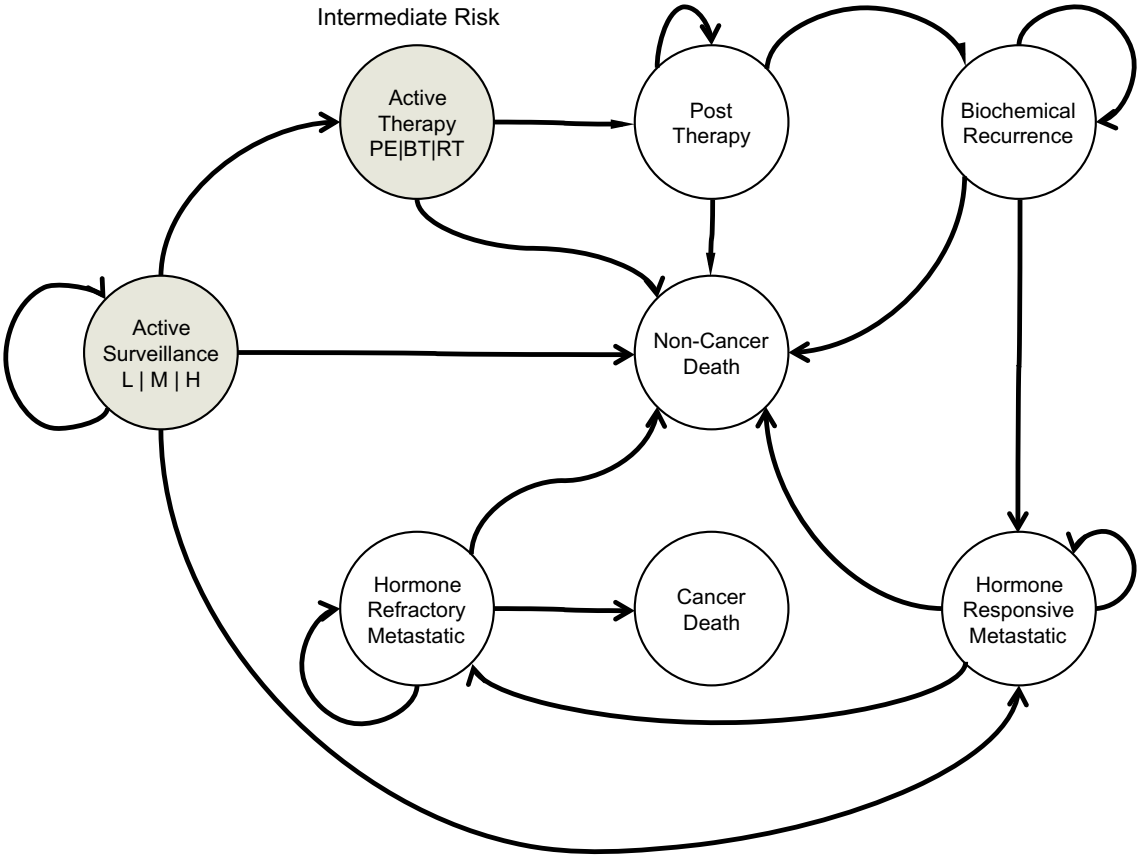

Figure 1. Conceptual model structure. BT indicates brachytherapy; H, high intensity; L, low intensity; M, medium intensity; PE, Prostatectomy; RT, radiotherapy.

the review was undertaken to find parameters for the model, and was in addition to the literature review for AS protocols we report on within the current study), and a nationally representative immediate curative treatment strategy. In the model, men were diagnosed at age 65 years, and outcomes from each of the 3 strategies were simulated. Each man entered the model with a PSA level and PSA velocity that were assigned randomly from within a plausible range taken from the literature.[26,27] Men then were tracked until death from cancer or background causes. US Social Security Administration 2009 life tables were used to model background mortality risk and discounted utilities and costs at an annual rate of 3%. To reflect parameter uncertainty, we ran our model 1000 times, each time with 10,000 patients using a unique parameter set sampled from the defined distributions. We averaged over all simulations to determine the mean effectiveness and cost for each strategy. For each strategy, total quality-adjusted life-years (QALYs) and costs per patient were reported. Probabilistic sensitivity analyses were performed based on the distribution of costs and QALYs across the 1000 randomly selected parameter sets.

AS Protocols

Each variant of AS modeled involved DRE, PSA, and biopsy. Low-intensity AS included DRE and PSA testing quarterly for 24 months and then semiannually thereafter, confirmatory biopsy at 12 months and then triennially thereafter, and bone scans for any man whose PSA increased to >20 ng/mL. This protocol modeled that used in the Prostate Cancer Research International Active Surveillance (PRIAS) study. Medium-intensity AS included PSA and DRE testing semiannually and biopsy biennially, whereas high-intensity AS involved PSA and DRE testing semiannually and biopsy annually. Table 2 lists the bases for each of these intensity classifications.

TABLE 2. Study Protocols and Intensity Classifications

Institution	PSA	DRE	Biopsy	Intensity Classification
Johns Hopkins	q6	q6	q12	High
Miami	q3	q3	q12	High
Aarau, Switzerland	q6	q6	q12	High
McGill University	q3	q3	q12	High
UCSF	q3-6	q3-6	q12-24	Medium
Dana-Farber	q6	q6	q12-18	Medium
Chicago/MSKCC	q6-12	q6-12	q12-36	Medium
Royal Marsden Hospital, UK	q3-6	q3-6	q18-24	Medium
Cleveland Clinic	q6-12		q24[a]	Medium
Princess Margaret Hosp	q3-6	q6	q24-36[b]	Low
MSKCC	q6	q6	q24-36[c]	Low
Monash and Southern	q3	q6	q36[d]	Low
PRIAS	q3-6[e]	q3-6[e]	q36[f]	Low
Toronto	q3-6[d]		q36-48[g]	Low
Connecticut	q6m	q6-12	q24[h]	Low

Abbreviations: DRE, digital rectal examination; MSKCC, Memorial Sloan Kettering Cancer Center; PRIAS, Prostate Cancer Research International Active Surveillance; PSA, prostate-specific antigen; UCSF, University of California at San Francisco.
[a]Initial Confirmatory Biopsy is undertaken.
[b]Until 80 years old.
[c]Initial biopsy at 12-18 months, then subsequent at 24-36 months.
[d]Initial biopsy at 12 months, then subsequent at 36 month intervals.
[e]q3 months for first 2 years, then q6 months.
[f]Initial follow up at q12, then q36 following. If PSA doubles between years 3-10, q12 month.
[g]Initial confirmatory biopsy undertaken at 6-12 months, then q36-48 until 80 years old.
[h]Additional biopsy can be triggered by increase in PSA of 0.75ng/dl or based on DRE findings.

In an additional analysis, we included a fourth AS protocol, which was a modified version of the low-intensity protocol. Unlike the low-intensity protocol modeled on PRIAS, which used a confirmatory biopsy at 12 months after diagnosis, the modified low-intensity protocol did not require its first (postdiagnosis) biopsy until the third year of monitoring. It also specified semiannual (rather than quarterly) DRE and PSA for the first 2 years as specified in the low-intensity AS protocol. This protocol is not commonly practiced but may be of interest to physicians seeking a low-intensity monitoring regimen.

Any man under AS who no longer satisfied the eligibility criteria for any AS protocol was treated with a brachytherapy (BT) regimen that was identical to that used in the immediate treatment strategy. We used modified probabilities for these men due to the fact that men who no longer were eligible for AS had a greater chance of having progressed to an intermediate disease classification. For the purposes of the current analysis, we did not consider the use of endorectal coil magnetic resonance imaging because it is not part of the standard of care of published AS protocols.

Immediate Treatment

Our immediate treatment strategy applied the age-specific, nationally representative distribution of radical prostatectomy, external-beam radiotherapy, and BT.[28] We excluded strategies for primary androgen deprivation therapy and cryotherapy due to their infrequent use as first-line treatment options in patients considered to be at low risk.

Men undergoing treatment may incur morbidities related to bowel, urinary, or sexual function. After treatment, patients continued until death from other causes or until biochemical disease recurrence. After treatment, men were monitored via PSA testing and DRE annually. If biochemical disease recurrence occurred, men were presumed to have hormone-responsive disease and were treated with hormone therapy until such time as their disease became refractory and they developed metastases. Men with refractory metastases were treated palliatively until death.

Model Inputs

Probabilities

All probabilities were estimated from secondary sources (Table 3). When possible, multiple values for the same parameter were aggregated via meta-analysis (see Supporting Figs. 5 and 6). In cases in which data were insufficient for this, we modeled the data using a beta distribution.

For probabilities regarding frequency of metastases, we performed survival analysis. Using data from several studies, we generated multiple beta distributions that fit the data. We then used these parameter sets to generate a beta distribution that would identify the probability at any given time point for this parameter.

We included a parameter in the model to represent the probability that patients drop out from an AS

TABLE 3. Model Parameters

Probabilities	Value	Distribution (SD)	Source
BCR: intermediate risk	0.0453		31-34
BCR: low-risk brachytherapy	0.0159		32,35
BCR: low-risk prostatectomy	0.0230		31,35,36
BCR: low-risk radiotherapy	0.0230		35
Metastases during BCR	0.050 (0.01)	Beta	23,31,37
Metastases while under AS	0.00138 (0.000037)	Beta	7,9,22,23,37-40
Death due to prostatectomy	0.00383 (0.000018)	Beta	41-43
Refractory metastases	0.28		44
Complications due to biopsy (major)	0.009		19,21,28
Complications due to biopsy (minor)	Varies	Table	28
Long-term GI AEs: brachytherapy	0.04		37
Long-term sexual AEs: brachytherapy	0.323		37,44
Long-term urinary AEs: brachytherapy	0.167		37,40,44
Long-term GI AEs: prostatectomy	0.00		37
Long-term sexual AEs: prostatectomy	0.453		37
Long-term urinary AEs: prostatectomy	0.127		37,43
Long-term GI AEs: radiotherapy	0.066		37
Long-term sexual AEs: radiotherapy	0.48		37
Long-term urinary AEs: radiotherapy	0.134		37
Exit protocol due to anxiety or psychological reasons	0[a]		
Utilities			
Age-specific baseline utility	Varies	Table	45
Utility for active surveillance	0.817 (0.0484)	Beta	25-27
Utility while in BCR	0.731 (0.030)	Beta	25,32,37
One-time disutility from prostate biopsy	−0.00274		46
One-time disutility from biopsy complications	−0.003		19,46
One-time disutility from prostatectomy	−0.0959		46
Metastatic prostate cancer	0.364 (0.067)	Beta	3,25,26,40
GI complications	0.74 (0.1982)	Beta	25
Sexual complications	0.831 (0.0614)	Beta	3,25,27,37
Sexual and GI complications	0.706 (0.0888)	Beta	3,25,27,40
Urinary complications	0.860 (0.286)	Beta	3,25,37
Urinary and GI complications	0.743 (0.059)	Beta	3,25,37
Urinary and sexual complications	0.825 (0.032)	Beta	3,25,37
Urinary, sexual, and GI complications	0.516 (0.081)	Beta	3,25,37
Costs			
Treatment of BCR	$2565		32
Prostate biopsy	$2557		47
Complications of biopsy (major)	$13,479 ($11,800)	LogNormal	48
Complications of biopsy (minor)	$122		47,49
Brachytherapy	$12,600 ($7,360)	LogNormal	48
Prostatectomy	$12,141 ($5,391)	LogNormal	48,50,51
Radiotherapy	$20,607 ($4,544)	LogNormal	24,32,33,40,51,52
Follow-up office visit	$122		47
Long-term bowel complications (initial costs)	$810.61		40
Long-term urinary complications (initial Costs)	$741.45		40
Long-term sexual complications (initial Costs)	$831.49		37
Treatment of metastatic hormone-refractory PC	$2212		32
Treatment of metastatic hormone-responsive PC	$3172		32

Abbreviations: AE, adverse event; AS, active surveillance; BCR, biochemical disease recurrence; GI, gastrointestinal; SD, standard deviation.
[a]Zero was used for this parameter in the base case to model a situation in which patients remain on the AS protocol as long as they are eligible. The robustness of the results was tested by undertaking sensitivity analysis on this parameter over a range of plausible values.

protocol due to anxiety or other reasons. The base case model used a value of zero, but literature regarding the appropriate value for this parameter is to our knowledge inconclusive. Given this uncertainty, we conducted deterministic sensitivity analysis on the parameter.

Utilities

Utilities are numeric values ranging from 0 for death to 1 for perfect health and are used to indicate preferences for a given health state; the summation of each year multiplied by its utility weight is used to determine total QALYs. Utilities were estimated for all complications and all health states. For those patients on any of the AS protocols, a value of 0.817 was used (based on a pooled estimate of several studies).[29-31] We modeled health state utilities as beta distributions to allow for patient-level variability of preferences in the population. For transient procedure-related disutilities, we applied a fixed utility decrement to each patient's current utility in each model cycle for the duration of the procedure.

TABLE 4. Base Case Analysis: Selected Key Results Generated by the Model for Men Aged 65 Years With Low-Risk Disease

Outcome	Immediate Treatment	Low-Intensity AS	Medium-Intensity AS	High-Intensity AS
Lifetime metastases	10.94%	7.98%	6.30%	6.64%
Prostate cancer death	7.56%	6.97%	5.48%	5.70%
ATFS	0 mo	52.73 mo	56.16 mo	54.91 mo
Life expectancy (SD), y	81.87 (0.08)	81.97 (0.15)	82.08 (0.15)	82.07 (0.15)

Abbreviations: AS, active surveillance; ATFS, active treatment-free survival, a measure of how long patients remain free of any active treatment for prostate cancer; SD, standard deviation.

Costs

Costs were determined from the published literature, the Centers for Medicare & Medicaid Services fee schedule, the fee schedule at a major academic hospital, and the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) database. We used cost analyses by prior authors for selected costs, such as the cost of complications due to treatment. For costs associated with BT, radical prostatectomy, and radiotherapy, we modeled a log-normal distribution to represent the possibility of a small group of high-cost patients. We fit distributions based on either the median and mean hospital costs as reported in the HCUP or, in the case of radiotherapy, fit a log-normal distribution.

Complications

We used recent literature regarding the rates of complications due to repeat prostate biopsies to create a tabular distribution concerning this parameter as a function of the number of biopsies performed (see Supporting Table 1).[32] Major complications of biopsy can lead to hospitalization. We modeled costs to account for this based on our own analysis of the Agency for Healthcare Research and Quality's HCUPNet data set (https://hcupnet.ahrq.gov/#setup) for hospitalizations associated with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure code 60.11.[16,32]

We modeled the frequency of complications due to each of the treatments as both short-term and long-term adverse effects. We presumed that short-term adverse effects persist for 3 months and long-term adverse effects persist for the patient's lifetime.

RESULTS

Base Case

In the cohort of men diagnosed at age 65 years, medium-intensity AS was found to be the most effective strategy, yielding 10.169 QALYs. This was followed by high-intensity AS (10.137 QALYs) and then low-intensity AS (10.053 QALYs). Immediate curative treatment offered the fewest QALYs (9.574 QALYs), but at a lower cost ($22,988) compared with any of the AS strategies. Among AS strategies, medium-intensity AS had the lowest cost ($25,065) and also yielded the most QALYs. The lifetime risk of developing metastatic cancer was 6.64%, 6.30%, 7.98%, and 10.94%, respectively, for high-intensity AS, medium-intensity AS, low-intensity AS, and immediate treatment (Table 4). The lifetime risk of death from prostate cancer was 5.70%, 5.48%, 6.97%, and 7.56%, respectively, for high-intensity AS, medium-intensity AS, low-intensity AS, and immediate treatment. We found medium-intensity AS to be a highly cost-effective strategy, with an incremental cost-effectiveness ratio of $3490 per QALY (Table 5).

TABLE 5. Base Case Analysis: Results for Men Aged 65 Years With Low-Risk Disease

Protocol	Cost	QALY	ICER ($/QALY)	Dominance
Immediate treatment	22,988	9.574	–	–
Low-intensity AS	~~24,890~~	~~10.053~~	–	Extended
Medium-intensity AS	25,065	10.169	3490	None
High-intensity AS	~~36,638~~	~~10.137~~	–	Absolute

Abbreviations: AS, active surveillance; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Costs and QALYs were discounted at 3% per year.

Sensitivity Analysis

In probabilistic sensitivity analysis, medium-intensity AS was found to have an 86.9% probability of being the most cost-effective strategy at a willingness-to-pay (WTP) criterion of $50,000 per QALY. Considering cost minimization only (WTP of $0/QALY), immediate treatment was preferred with near certainty.

For the parameters of "frequency of metastases," "utility for being in an AS protocol," or "departure from protocol due to anxiety," we undertook 1-way sensitivity analyses to determine threshold values. We found the model results were insensitive to changes in anxiety dropout rates for all possible values. Medium-intensity AS was found to be the most cost-effective option for values of the utility for AS >0.75 (Fig. 2 Top). For any values of metastases

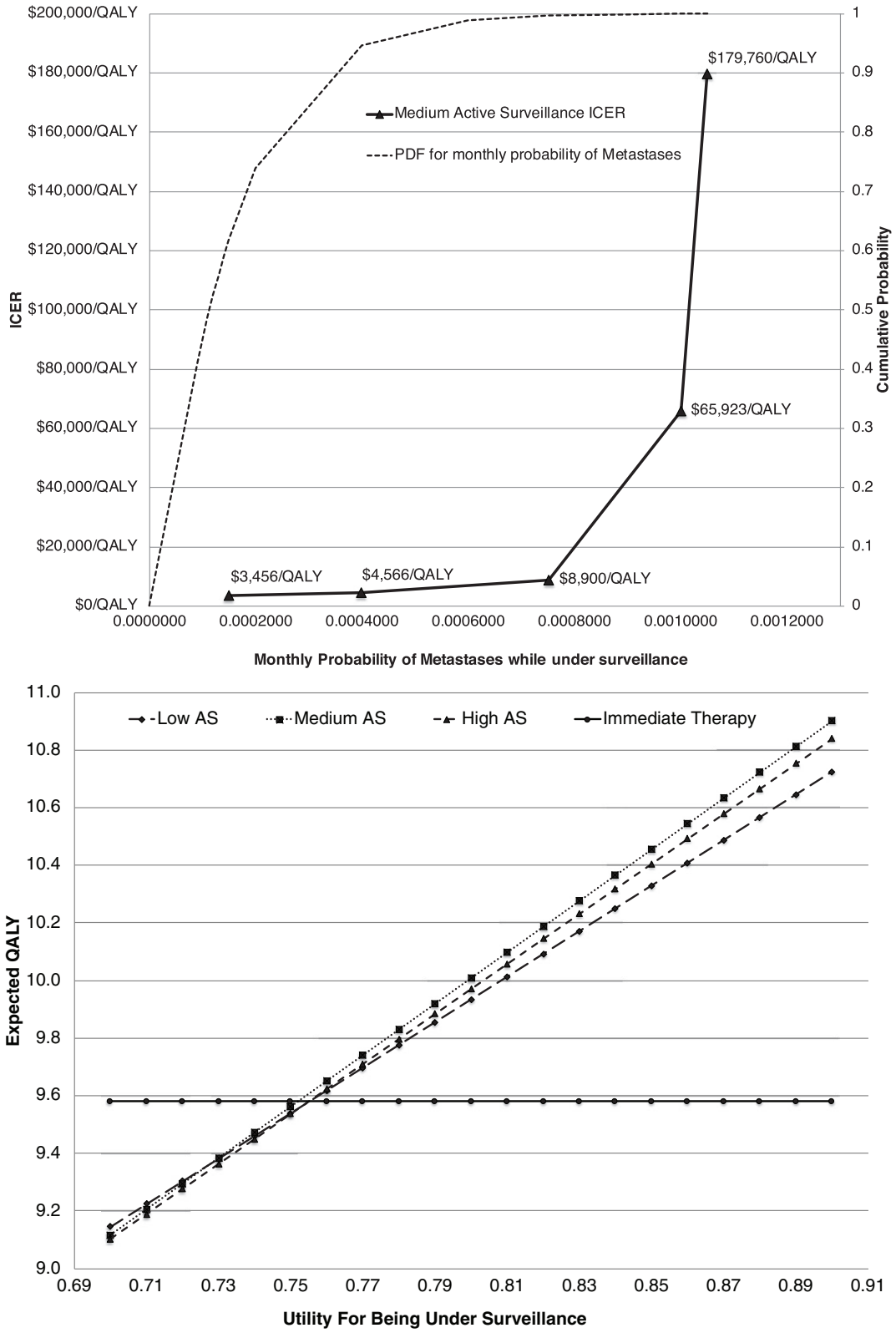

Figure 2. (*Top*) Sensitivity analysis of the incremental cost-effectiveness ratio (ICER) for medium-intensity active surveillance (AS) at varying levels of frequency of metastases. (*Bottom*) Sensitivity analysis of utility while under AS. PDF indicates probability density function; QALY, quality-adjusted life-year.

TABLE 6. Analysis With the Modified Low-Intensity Protocol Included: Results for Men Aged 65 Years With Low-Risk Disease

Protocol	Cost	QALY	ICER ($/QALY)	Dominance
Immediate treatment	22,988	9.574	–	Dominated
Low-intensity AS	24,890	10.053	–	Dominated
Modified low-intensity AS	21,399	10.194	–	Dominant
Medium-intensity AS	~~25,065~~	~~10.169~~	–	Dominated
High-intensity AS	~~36,638~~	~~10.137~~	–	Dominated

Abbreviations: AS, active surveillance; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
Costs and QALYs were discounted at 3% per year.

within 99.97% of the modeled distribution of expected probabilities of metastases while under AS (ie, <1.241% per year, a value that was >7-fold higher than best existing estimates for the rate of metastases while under AS), medium-intensity AS still was found to be a cost-effective strategy at a WTP of $150,000 per QALY (Fig. 2 Bottom).

The results noted when the fourth AS protocol (modified low-intensity) was included in the comparison were quite different from those of the base case. It is interesting to note that the removal of the confirmatory biopsy at 12 months after the initiation of the protocol and a change to a consistent semiannual (rather than quarterly) DRE and PSA test specified in the modified low-intensity protocol increased efficiency. With these changes, the modified low-intensity protocol appears to be the dominant strategy, offering greater QALY (10.194 QALYs) at a lower cost ($21,399) compared with any other protocol (Table 6).

DISCUSSION

Approximately one-half of patients newly diagnosed with prostate cancer have low-volume tumors of Gleason score 6, or so-called "low-risk" disease, which often can be managed effectively with AS. Although there is evidence to suggest that these cancers present very little risk of metastasis and that delaying treatment does not increase this risk appreciably, to our knowledge fewer than 20% of men are treated with AS. Studies of men with Gleason score ≤6 disease identified only 22 individuals with lymph node metastases from 14,123 men, and a prostate cancer mortality rate of only 0.2% to 1.2% at 15 years in a population of 11,521 men.[33,34]

The recent results for the ProtecT study indicate that treatment appears to have little impact on overall survival over a median follow-up of 10 years, even when biopsy is excluded from the AS protocol, as it was in the ProtecT study. The model in the current study, when run over 10 years, was found to generate rates of metastases (approximately 2%) and death due to cancer (approximately1%) for patients treated with AS that were similar to those found in the ProtecT trial. This suggests that AS is effective at identifying patients with progressive disease while it still is early enough to intervene.

To the best of our knowledge, there is no consensus to date regarding the appropriate intensity of AS. Both American Urological Association and European Association of Urology guidelines recommend AS in patients with low-risk disease, but to our knowledge neither specifies a protocol. The potential health benefits that would accrue from identifying the most appropriate surveillance protocol are considerable. The challenge is to select the least intense and costly AS protocol without compromising potential curability.

The analysis in the current study illustrated that all 3 commonly reported AS protocols offer superior quality-adjusted outcomes and expected survival outcomes compared with immediate treatment.

The model in the current study demonstrated that medium-intensity AS offers an improvement in quality-adjusted life-days of 217 days over current practice at an incremental cost of $2077. The majority of this gain in quality-adjusted survival arises because the average patient initiating medium-intensity AS will delay treatment for 56 months, thereby deferring any adverse effects of treatment. If individual preferences are such that utility while under AS is <0.75, immediate treatment becomes the preferred strategy. We believe that the slightly higher lifetime rates of metastases and cancer death shown in the current model for patients undergoing immediate treatment are a facet of both a misalignment of treatments and the lower intensity and annual PSA and DRE monitoring that occur after treatment. This finding may suggest that more frequent follow-up is warranted for these patients.

The results of the model in the current study suggested that improvements to the low-intensity AS protocol may be achieved by decreasing its intensity further, in turn making it the optimal strategy in terms of quality-adjusted survival and cost. This arises because the

disutility from an increased rate of complications from more frequent biopsies outweighs the gains achieved through the small number of cancers that are prevented from metastasizing in the interval between biopsies. The inefficiency of the low-intensity AS protocol noted in the current study is eliminated and reversed when the frequent monitoring in the first 2 years after diagnosis is eliminated. These protocol modifications may need to be applied on a patient-specific basis because not all clinicians or their patients may be comfortable with extended waiting until the first surveillance biopsy. The results of the model in the current study suggested that this uncommon protocol deserves further consideration by clinicians who favor a low-intensity approach.

To the best of our knowledge, currently available studies for the most part report on watchful waiting to identify probabilities for metastases, which we believe can be misleading. The goal of watchful waiting is the palliation of symptomatic disease, and therefore it is very likely that should a man live long enough, disease progression and metastases will occur.

Due to uncertainty regarding the rates of metastases in men under AS, we modeled the probability of metastatic disease using a time-varying, nonlinear risk distribution derived from a meta-analysis of studies (in the case of the probability of metastases while in an AS protocol, we used several studies reporting the frequency of metastases at different time points [in different untreated populations] to fit a beta distribution for survival free from metastases; we then used this survival curve to draw metastasis-free probability values from at time [t=x] for time-dependent parameters for a beta distribution, similar to time-dependent hazard ratios used by other authors). The results of the current analysis were consistent with the published literature in their finding that metastatic disease is infrequent among patients with low-risk disease. Furthermore, our deterministic sensitivity analysis found that the actual probability of metastases would have to be 7-fold higher than the expected value of our meta-analysis regarding the parameter for medium-intensity AS to no longer be cost-effective. We are confident that the results of the current study are robust to changes in the frequency of metastases while patients are under AS (Fig. 2 Bottom).

CONCLUSIONS

The substantial gains in QALYs identified in the model in the current study lend support to the case for medium-intensity AS with biennial biopsy as the preferred treatment in this population given average preferences, or for a modified low-intensity protocol for those patients who are comfortable waiting a longer period between biopsies. This offers guidance to clinicians in the selection of appropriate monitoring strategies.

Future analyses should focus on further elucidating the advantages and disadvantages of extended intervals between surveillance biopsies, and to understanding patient preferences at the time a treatment choice is being made. Such preferences should be elicited on an ongoing basis in the case of AS.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Conception and design: **Craig White**, **Tony Nimeh**, and **Kevin R. Loughlin**. Acquisition of data: **Craig White** and **Tony Nimeh**. Analysis and interpretation of data: **Craig White** and **Tony Nimeh**. Drafting of the article: **Craig White**, **Tony Nimeh**, **G. Scott Gazelle**, **Milton C. Weinstein**, and **Kevin R. Loughlin**. Critical revision of the article for important intellectual content: **Craig White**, **Tony Nimeh**, **G. Scott Gazelle**, **Milton C. Weinstein**, and **Kevin R. Loughlin**. Statistical analysis: **Craig White**. Obtaining funding: **G. Scott Gazelle**. Administrative, technical, or material support: **Craig White**. Supervision: **G. Scott Gazelle**, **Milton C. Weinstein**, and **Kevin R. Loughlin**.

REFERENCES

1. Ip S, Dahabreh IJ, Chung M, et al. An evidence review of active surveillance in men with localized prostate cancer. *Evid Rep Technol Assess (Full Rep)*. 2011;204:1-341.
2. Shao YH, Demissie K, Shih W, et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst*. 2009;101: 1280-1283.
3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64:9-29.
4. Slomski A. Expert panel advocates surveillance for men with low-risk prostate cancer. *JAMA*. 2012;307:133.
5. Thompson I, Thrasher JB, Aus G, et al. AUA Prostate Cancer Clinical Guideline Update Panel. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007;177:2106-2131.
6. National Institutes of Health, US Department of Health and Human Services. NIH State-of-the-Science Conference: role of active surveillance in the management of men with localized prostate cancer. http://consensus.nih.gov/2011/prostatefinalstatement.htm. Accessed May 12, 2014.
7. Klotz L. Active surveillance for prostate cancer: a review. *Curr Urol Rep*. 2010;11:165-171.
8. Hamdy FC, Donovan JL, Lane JA, et al. ProtecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415-1424.
9. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol*. 2011;29:2185-2190.

10. Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA. Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. *J Urol*. 2008;180:1964-1967:discussion 1967-1968.
11. Seiler D, Randazzo M, Klotz L, et al. Pathological stage distribution in patients treated with radical prostatectomy reflecting the need for protocol-based active surveillance: results from a contemporary European patient cohort. *BJU Int*. 2012;110:195-200.
12. Ischia JJ, Pang CY, Tay YK, Suen CF, Aw HC, Frydenberg M. Active surveillance for prostate cancer: an Australian experience. *BJU Int*. 2012;109(suppl 3):40-43.
13. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol*. 2013;63:597-603.
14. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol*. 2013;64:981-987.
15. Williamson DA, Barrett LK, Rogers BA, Freeman JT, Hadway P, Paterson DL. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant Escherichia coli. *Clin Infect Dis*. 2013;57:267-274.
16. Nam RK, Saskin R, Lee Y, et al. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol*. 2010;183:963-969.
17. Fujita K, Landis P, McNeil BK, Pavlovich CP. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. *J Urol*. 2009;182:2664-2669.
18. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. *Urology*. 2002;60:826-830.
19. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med*. 2014;370:932-942.
20. Hardie C, Parker C, Norman A, et al. Early outcomes of active surveillance for localized prostate cancer. *BJU Int*. 2005;95:956-960.
21. Chodak GW, Thisted RA, Gerber GS, et al. Results of conservative management of clinically localized prostate cancer. *N Engl J Med*. 1994;330:242-248.
22. Wilt TJ. The Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy with watchful waiting for men with clinically localized prostate cancer. *J Natl Cancer Inst Monogr*. 2012;2012:184-190.
23. Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. *BJU Int*. 2008;101:165-169.
24. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer*. 2008;112:1650-1659.
25. Dall'Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer*. 2008;112:2664-2670.
26. Iremashvili V, Manoharan M, Lokeshwar SD, Rosenberg DL, Pan D, Soloway MS. Comprehensive analysis of post-diagnostic prostate-specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. *BJU Int*. 2013;111:396-403.
27. Raaijmakers R. Prostate Cancer Screening: The Role of Biopsy, PSA, PSA Dynamics and Isoforms. Rotterdam, the. Netherlands: Erasmus University; 2009.
28. Wilson LS, Tesoro R, Elkin EP, et al. Cumulative cost pattern comparison of prostate cancer treatments. *Cancer*. 2007;109:518-527.
29. Stewart ST, Lenert L, Bhatnagar V, Kaplan RM. Utilities for prostate cancer health states in men aged 60 and older. *Med Care*. 2005;43:347-355.
30. Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. *J Gen Intern Med*. 1997;12:299-305.
31. Klotz L. Active surveillance: the Canadian experience with an "inclusive approach." *JNCI Monogr*. 2012;2012:234-241. doi:10.1093/jncimonographs/lgs042.
32. Cooperberg MR, Ramakrishna NR, Duff SB, et al. Primary treatments for clinically localised prostate cancer: a comprehensive lifetime cost-utility analysis: cost-utility analysis of primary treatments for clinically localised prostate cancer. *BJU Int*. 2013;111:437-450. doi:10.1111/j.1464-410X.2012.11597.x.
33. Shah C, Lanni TB, Ghilezan MI, et al. Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer. *Brachytherapy*. 2012;11:441-445. doi:10.1016/j.brachy.2012.04.002.
34. Krishnan V, Delouya G, Bahary J-P, Larrivée S, Taussky D. The Cancer of the Prostate Risk Assessment (CAPRA) score predicts biochemical recurrence in intermediate-risk prostate cancer treated with external beam radiotherapy (EBRT) dose escalation or low-dose rate (LDR) brachytherapy: Capra predicts outcome. *BJU Int*. April 2014:n/a-n/a. doi:10.1111/bju.12587.
35. D'Amico AV. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969. doi:10.1001/jama.280.11.969.
36. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol*. 2003;169:517-523. doi:10.1016/S0022-5347(05)63946-8.
37. Hayes JH, Ollendorf DA, Pearson SD, et al. Active surveillance compared with initial treatment for men with low-risk prostate cancer: a decision analysis. *JAMA*. 2010;304:2373. doi:10.1001/jama.2010.1720.
38. Carter CA. Temporarily deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. *J Clin Oncol*. 2003;21:4001-4008. doi:10.1200/JCO.2003.04.092.
39. van den Bergh RCN, Roemeling S, Roobol MJ, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. *Eur Urol*. 2009;55:1-8. doi:10.1016/j.eururo.2008.09.007.
40. Hayes JH, Ollendorf DA, Pearson SD, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. *Ann Intern Med*. 2013;158:853-860. doi:10.7326/0003-4819-158-12-201306180-00002.
41. Ansari MZ, Costello AJ, Jolley DJ, Ackland MJ, Carson N, McDonald IG. Adverse events after prostatectomy in Victorian public hospitals. *ANZ J Surg*. 1998;68:830-836. doi:10.1111/j.1445-2197.1998.tb04697.x.
42. Dillioglugil O, Leibman BD, Leibman NS, Kattan MW, Rosas AL, Scardino PT. Risk factors for complications and morbidity after radical retropubic prostatectomy. *J Urol*. 1997;157:1760-1767. doi:10.1016/S0022-5347(01)64856-0.
43. Bianco F, Riedel E, Begg C, Kattan M, Scardino P. Variations among high volume surgeons in the rate of complications after radical prostatectomy: further evidence that technique matters. *J Urol*. 2005;173:2099-2103. doi:10.1097/01.ju.0000158163.21079.66.
44. Hummel S, Paisley S, Morgan A, Currie E, Brewer N. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. *Health Technol Assess Winch Engl*. 2003;7:iii, ix-x, 1-157.
45. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Mak Int J Soc Med Decis Mak*. 1993;13:89-102.
46. Krahn MD, Mahoney JE, Eckman MH, Trachtenberg J, Pauker SG, Detsky AS. Screening for prostate cancer. A decision analytic view. *JAMA J Am Med Assoc*. 1994;272:773-780.
47. Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. *Cancer*. 2012;118:3512-3518. doi:10.1002/cncr.26688.
48. *AHRQ HCUPNet NIS Database*. AHRQ. http://hcupnet.ahrq.gov/.
49. CMS Fee Schedule 2013.

50. Yu H, Hevelone ND, Lipsitz SR, Kowalczyk KJ, Hu JC. Use, costs and comparative effectiveness of robotic assisted, laparoscopic and open urological surgery. *J Urol*. 2012;187:1392-1399. doi:10.1016/j.juro.2011.11.089.
51. Eldefrawy A, Katkoori D, Abramowitz M, Soloway MS, Manoharan M. Active surveillance vs. treatment for low-risk prostate cancer: a cost comparison. *Urol Oncol Semin Orig Investig*. 2013;31:576-580. doi:10.1016/j.urolonc.2011.04.005.
52. Parthan A, Pruttivarasin N, Davies D, et al. Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol*. 2012;2. doi:10.3389/fonc.2012.00081.