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Decision Analysis of the Benefits and Costs of Screening for Prostate Cancer

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(adopted from Hayes et al, Annals of Internal Medicine, June 2013) PURPOSE/SCOPE: Observation has emerged as a strategy to avoid overtreatment in men with screen-detected low-risk prostate cancer (CaP). This analysis examines the cost-effectiveness of observation with watchful waiting (WW) as experienced in the PIVOT study or active surveillance (AS), radical prostatectomy (RP), radiation therapy (IMRT), and brachytherapy (BT) in these men. METHODS: A Markov Monte Carlo model was constructed. Main outcomes were costs (2012US$) and quality-adjusted life-years (QALYs) for men aged 65 and 75 years. RESULTS: Observation was more effective and less costly than initial treatment. Compared with AS, WW provided 2 additional months of QALE (9.02 vs. 8.85 y) at a savings of $15374 ($24520 vs. $39894) in men aged 65 and 6.14 vs. 5.98y at a savings of $11746 ($18302 vs. $30048) in men aged 75. BT was the most effective and least expensive initial treatment. Treatment became more effective than observation when it led to greater reductions in CaP death (hazard ratio, 0.47 vs. WW; 0.64 vs. AS). AS became as effective as WW in men aged 65 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. WW remained least expensive in all analyses. CONCLUSIONS: In this model, observation with WW and AS is a cost-effective strategy.

Prostate cancer, screening, cost-effectiveness analysis
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INTRODUCTION

This annual report details the progress that has been made between August 2012 and August 2013, the fourth year of the Physician Research Training Award entitled “Decision analysis of the benefits and costs of screening for prostate cancer”. The goal of the proposed research is to develop a decision analytic model of PSA screening for prostate cancer. This model will permit the analysis of the effect of various PSA screening strategies on life expectancy (LE), quality-adjusted LE (QALE), and the cost-effectiveness of screening. The comparator will be a natural history model of unscreened, conservatively-treated prostate cancer based on primary data. It is hypothesized that the optimal screening strateg(ies) for prostate cancer will be dependent not only upon mortality benefit, but also upon the value patients place on health states and costs.

This report will summarize the accomplishments that have been made in undertaking the tasks outlined in the Statement of Work. Due to difficulties that have arisen in conducting Task 1, previously reported, the majority of the work conducted to date has been on Task 3. The portion of the model described in Task 3 assesses the life expectancy, quality-adjusted life expectancy, and cost-effectiveness of treatment in screened vs. unscreened men with prostate cancer. Over the past four years, a model has been constructed comparing first the effectiveness, then the cost-effectiveness of treatment strategies for low-risk, clinically localized prostate cancer. In the initial iteration of this model, the strategies studied included active surveillance, radical prostatectomy, brachytherapy, intensity-modulated radiation therapy, and proton beam therapy. It was found that active surveillance is the most effective strategy of these, or associated with the greatest quality-adjusted life expectancy, but brachytherapy is the least expensive treatment. Active surveillance remained cost-effective under all scenarios constructed in men 65 years of age. Results of this model were published in the Journal of the American Medical Association², presented at annual meetings of professional societies, discussed in a teleconference sponsored by the Institute for Healthcare Improvement and JAMA, and discussed at the Cancer Intervention and Surveillance Modeling Network’s (CISNET) Annual Conference at the National Institutes of Health. A second manuscript, incorporating data published in 2012 from the PIVOT trial³, compares watchful waiting to active surveillance, brachytherapy, IMRT, and radical prostatectomy was recently published in Annals of Internal Medicine¹, and a third is being written.

This report will also summarize the training accomplishments achieved over the past year. As planned, I have continued to receive training in the construction and population of a Markov Monte Carlo model, and I have participated and presented in institutional conferences. I have participated in meetings with my mentors as planned.

Although the order in which the work is being conducted has changed due to circumstances beyond my control, the tasks outlined in the original statement of work will be performed as originally planned, and I am pleased to report that new sources of patient data that have become available to me will improve the model’s validity. I look forward to the opportunity to continue working on this timely and important work.
**TASK 1: Develop a Markov Monte Carlo disease model of the natural history of prostate cancer.**

**Methods.** We will create a Markov Monte Carlo disease model of the natural history of prostate cancer. Individuals will progress from a disease-free state to preclinical disease to clinically-detectable prostate cancer; each individual will have a PSA value and, in those with prostate cancer, a Gleason score. Men with disease will progress from clinically localized to regional to metastatic disease and death of prostate cancer; they may also progress between Gleason scores. Death of other causes can occur from any health state.

*Task 1.1 Utilizing data from the published literature, create a model of the preclinical development of prostate cancer.* Estimates of age-specific prevalence of preclinical prostate cancer, correlation of the presence of preclinical disease with serum PSA, and evaluation of PSA rise in the serum of patients subsequently diagnosed with prostate cancer will be obtained from the published literature. This data will be combined using regression analysis to estimate the preclinical incidence and progression of disease based on Gleason score and PSA.

*Task 1.2 Utilizing data from the control arm of the ERSPC, create a model of the characteristics of prostate cancer at diagnosis in a contemporary, unscreened population.* We will utilize data provided by investigators from the ERSPC to model tumor and patient characteristics of clinically-diagnosed prostate cancer in the modern era, including age, stage at diagnosis, and Gleason score,

*Task 1.3 Utilizing data from a database of men diagnosed in the pre-PSA era, create a model of the progression of clinically localized, conservatively-treated prostate cancer.* We have created a database of such men in collaboration with investigators from Örebro, Sweden, that will be used to develop transition probabilities between model health states described in Task 1.1. We will collaborate with Dr. D’Amico in interpretation and analysis of the data, particularly with regard to modeling PSA kinetics.

*Task 1.4 Calibrate the model using data from published studies of the natural history of conservatively-treated prostate cancer and recent clinical trials.* We will calibrate the model to reproduce target outputs within 5% of pre-selected values. Sources of calibration data for our model will include incidence data from the control arm of the ERSPC and the published literature.

**Timeline:** The collection and analysis of data from the ERSPC and the Örebro cohort and from the published literature will take 9 months. Construction and calibration of the natural history model will take 15 months. Two manuscripts will be generated: the first will reflect findings from the primary data, and the second will describe the natural history model. I will also take a course during the fall of the first year in order to acquire skills necessary to develop transition probabilities from the published literature.

**Outcomes:** This task will result in the creation of a natural history model of unscreened, conservatively-treated prostate cancer that will provide data on characteristics of patients at clinical diagnosis and at progression, rates of progression, and prostate cancer specific- and all cause mortality.

**Progress report:**
An important feature of this model as originally designed was that it was to have been able to trace the natural history of prostate cancer in men diagnosed in the pre-PSA era whose prostate cancer had been regraded in the modern era, hence avoiding the concern raised by the fact that Gleason scores have shifted higher over the past 20 years. The construction of this portion of the model was therefore crucially dependent upon data obtained from the Örebro cohort, as outlined in Task 1.3. However, as described in previous progress reports, during analysis of the data from Örebro, I realized that in our cohort, Gleason score did not correlate with prostate cancer-specific survival. This finding is at odds with the published literature and prompted me to question the accuracy of the Gleason grading performed. A representative selection of pathologic samples was obtained from Örebro and regraded by a pathologist at Massachusetts General Hospital. It was realized that serious errors in Gleason scoring had been made and that as a result, this data was unusable.
At this time last year, I was hopeful that it would be possible to locate and regrade these samples and to include more samples identified through collaboration with investigators at the Harvard School of Public Health. However, it proved impossible to coordinate the considerable regrading efforts between investigators in several countries in a timely manner for this project. I have therefore turned to other possible sources of long term outcomes data on men who were diagnosed with prostate cancer in the pre-PSA era. I have been in communication with Dr. Lars Holmberg, a colleague and investigator on the SPCG-4 trial, who has presented my request for data to the steering board of that study. The SPCG-4 trial was a randomized controlled trial initiated in 1989 that compared watchful waiting to radical prostatectomy in men diagnosed in Sweden in the pre-PSA era; results following this cohort for a median of 12.8 years have been published. Although the follow-up will not be as long as in our Örebro cohort, this cohort is a reasonable and well-recognized replacement. I currently await their response to my application (made at the start of the summer; Dr. Holmberg has been away and has just returned, so I anticipate a response in the near future).

Since the discovery of this complication, my research efforts have therefore been primarily focused on Task 3, as described below.

**TASK 2: Compare the clinical effectiveness, cost and cost-effectiveness of PSA screening strategies.**

*Methods.* Task 2.1 Vary the biopsy threshold for screening PSA, the interval between screening events, and establish the effect of PSA kinetics prior to diagnosis on screening strategies. We will first assess the effect of annual screening varying PSA biopsy thresholds. We will then vary the interval between PSA screening events using these thresholds. These two variables will then be modified simultaneously to identify the screening strategy that maximizes LE. Subsequent analyses will focus on identifying the optimal screening strategy once a PSA velocity has been established. The model will vary PSA velocity, biopsy threshold, and subsequent screening interval simultaneously. Similar analyses will be performed using PSA doubling time.

**Task 2.2 For each strategy, establish the lead time and effect on prostate cancer incidence.** To quantitate lead time, the difference in time between screen diagnosis and clinical diagnosis of prostate cancer will be calculated. To estimate incidence and overdiagnosis rates, incidence in the presence and absence of screening will be compared.

**Task 2.3 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the clinical effectiveness, cost, and cost-effectiveness of each screening strategy.**

We will run the model using both community and patient-elicited utilities from the published literature and unpublished results provided by Dr. Susan Stewart. Dr. Swan will assist in analysis of these utilities and their incorporation into the model. Costs will be estimated from a societal perspective. Costs and QALYs will be discounted. Total cost will be the sum of direct medical costs. Costs will be calculated using data from the medical literature or local institutional cost data and will be expressed in 2012 dollars. The model will estimate the QALE and costs associated with each screening strategy. The model results will estimate the magnitude of benefit for intermediate and long-term outcomes, costs of care, and incremental cost-effectiveness.

**Task 2.4 Identify model parameters likely to cause a shift in model results using sensitivity analysis.** We will perform sensitivity analysis on parameters likely to have a significant effect on LE in our model. The model will be run across a literature-derived plausible range of probabilities for selected variables.

**Timeline:** Modification of the model to assess screening strategies, model calibration, and the calculation of lead time, incidence, and overdiagnosis rates will take approximately one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months. I will take several courses at HSPH during the first two years to acquire the skills necessary for this task. One manuscript will be generated after completion of the screening model to describe the effect of
screening on LE in conservatively-treated patients and the lead time and overdiagnosis associated with screening; the second at the completion of the CEA.

Outcomes: This task entails the creation of a PSA screening model that will compare outcomes in screened versus unscreened conservatively-treated men. Outcomes will include LE, QALE, and cost-effectiveness for each strategy and identification of the strategy that maximizes each of these outcomes; secondary outcomes will include lead time, incidence, and overdiagnosis rates for each strategy.

Progress report:
This task, originally planned to be undertaken during months 18-42, will be conducted months 52-60.

TASK 3: Modify the model created in Task 2 to include modern treatment practices to evaluate the clinical effectiveness, cost, and cost-effectiveness of the PSA screening strategies described above.

Methods. Task 3.1 Extend the model created in Task 2 to include modern treatment practices. We will incorporate modern treatment practices into the model to determine the effect of screening and treatment of screen-diagnosed disease on LE, QALE, and its cost-effectiveness. Treatments and outcomes will be obtained from the published literature and expert opinion, and sensitivity analysis will be performed. Task 3.2 Extend the model to include quality of life adjustments (utilities) and costs and use the model to estimate the effectiveness, cost, and cost-effectiveness of each screening strategy. In treated men, utilities and costs will be calculated, and effectiveness and cost-effectiveness of each screening strategy will be estimated, as described in Task 2.3. Task 3.3 Explore the role of future, as-yet-undeveloped diagnostic tests in screening for prostate cancer to establish the test characteristics required in order to identify men with clinically significant disease. The creation of a natural history model will enable us to identify the characteristics of prostate cancer most predictive of outcomes. Decision analytic modeling will highlight predictors of adverse outcomes in our model and will enable us to use them to characterize an “ideal” screening test.

Timeline: Modification of the model to include modern treatment practices and its calibration will take one year. Identification of costs, analysis and incorporation of utilities, cost-utility analysis and sensitivity analysis are projected to take nine months; analysis and comparison of these results with those obtained in Task 2 will take 3 months. Two manuscripts will be produced: the first describing the effect of screening on LE in treated vs. untreated men, the second at the completion of the CEA. Courses I will take to acquire skills necessary for this task will be taken during the second and third years. I will attend seminars and national meetings and continue clinical work with prostate cancer patients throughout the award period.

Outcomes: Outcomes for this task will include LE, QALE, and cost-effectiveness for each screening strategy in men treated for prostate cancer and identification of the screening strategy that maximizes each of these outcomes.

Progress report:
In a previous progress report, we described the Markov Monte Carlo model comparing active surveillance to treatment at diagnosis with radical prostatectomy or radiation therapy using brachytherapy, intensity-modulated radiation therapy, or proton beam therapy. Briefly, a societal perspective was taken with a lifetime horizon. A systematic review of the literature was performed to establish transition probabilities for disease outcomes and for the probabilities of incurring complications of surgery and adverse effects (erectile dysfunction, urinary incontinence, gastrointestinal dysfunction). Utilities were obtained from literature review and from personal communication, (personal communication, Stewart). Outcomes included QALEs, used for comparative effectiveness analysis, previously described and published in JAMA.
The model has also been utilized to produce cost-effectiveness data. Costs for the model have been obtained from Medicare reimbursement schedules and include costs of initial treatment, treatment of side effects, and patient time costs. We submitted a manuscript of our cost-effectiveness analysis to *Annals of Internal Medicine* and after extensive revision and expanding the manuscript to incorporate a watchful waiting strategy based on the results of the PIVOT study comparing watchful waiting to radical prostatectomy in a screened population and published in the summer of 2012\(^3\), this manuscript was accepted for publication and published in June 2013. This analysis compares the cost-effectiveness of watchful waiting, active surveillance, brachytherapy, intensity-modulated radiation therapy, and radical prostatectomy.

In this study, we found that watchful waiting is both more effective and less expensive than either active surveillance or initial treatment. Compared with active surveillance, watchful waiting provided 2 additional months of QALE (9.02 vs. 8.85 years) at a cost 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. Treatment became more effective than observation when it led to more dramatic reductions in prostate cancer death (hazard ratio, 0.47 vs. watchful waiting and 0.64 vs. active surveillance). Active surveillance became as effective as watchful waiting in men aged 65 years when the probability of progressing to treatment on active surveillance decreased below 63% or when the quality of life with active surveillance versus watchful waiting was 4% higher in men aged 65 years or 1% higher in men aged 75 years. Watchful waiting remained least expensive in all analyses\(^1\).

The model described above is specific to men with low-risk prostate cancer (Gleason \(\leq 3+3; \) clinical stage \(\leq T2a, \) PSA <10 ng/mL). Modifications necessary to generalize this model to all men treated after screening include establishing prostate cancer-specific outcomes for men with intermediate and high-risk disease, outcomes that are expected to be reflected in shorter life expectancies for men with higher-risk disease. It is anticipated that these modifications to the model will require 6 months to complete and will take place from months 54-60 of the grant period, as originally planned.

The source of data for this portion of Task 3 is very exciting. As part of a project that is evolving out of this model – assessing the cost-effectiveness of adjuvant therapies for prostate cancer – I will have access to a database currently being assembled at DFCI as part of an international collaboration that will combine primary data on patient information and outcomes for over 16,000 men (projected) with primarily intermediate- and high-risk, clinically localized prostate cancer who underwent treatment for their disease as part of a clinical trial. I will apply for funding to support the modeling component of this larger effort this year. Access to this data will enrich the model immeasurably, as we will be able to develop probabilities directly from the data as opposed to extrapolating from published results of multiple different trials with varying endpoints. This database is currently under construction, and it is anticipated will be available for my use in the treatment model within 3 months.

In addition, this year we continued to analyze practice patterns for the treatment of men with biochemical recurrence of prostate cancer after definitive treatment and with metastatic disease
using our institutional CRIS (Prostate Cancer Research Information System) database at Dana-Farber Cancer Institute\textsuperscript{11}. A manuscript containing some of these analyses has been written and published in Cancer\textsuperscript{12} this summer. The next step in this project will be to analyze the costs of these treatments. This analysis will provide information regarding costs incurred by patients from recurrence of their disease after treatment to death for use to address Task 3.2.

Completed abstracts and manuscripts are listed in the Reportable Outcomes section of this report.
KEY RESEARCH AND TRAINING ACCOMPLISHMENTS

Research Accomplishments:

In summary, work completed on this grant proposal to date has demonstrated that
a) in screen-detected men with low-risk prostate cancer, active surveillance is a
cost-effective alternative to initial treatment with radical prostatectomy or
radiation therapy (with brachytherapy, intensity-modulated radiation
therapy, or proton beam therapy), for men between 55 and 75 years of age
at diagnosis.
b) the quality-adjusted life expectancy benefit of active surveillance seen in these
men is robust but depends upon the patient preferences, or utilities,
associated with being on active surveillance and with having been treated.
c) observation with watchful waiting as practiced in the PIVOT study is
associated with improved QALE and is cost saving compared to either
active surveillance or initial treatment in men 65 and 75 years of age.

Training accomplishments:

a) I have built a Markov Monte Carlo model, acquiring skills including model
design, the derivation of probabilities to populate the model, utilities, and
costs through regular instruction by my mentor Dr. Michael Barry, Dr.
James E. Stahl, Dr. Pamela McMahon.
b) Completion of the Society for Medical Decision Making’s Meta-Analysis
Course, October 2010
c) Attendance at
   ITA Core Seminar, a weekly seminar at ITA with didactic lectures focusing on
   study design, analysis, and grant-writing, and presentations of ongoing research
   including decision analysis, cancer outcomes, technology and quality of life
   assessment.
   Lank Center for GU Oncology Seminar, a bi-monthly lecture series during
   which basic research and recent developments in the diagnosis and treatment of
   GU cancers are presented.
   Lank Center for GU Oncology Journal Club, a monthly presentation of critical
   articles in genitourinary cancer basic and clinical research.
   Dana-Farber/Harvard Cancer Center Outcomes Research Seminar, a weekly
   seminar at DFCI focusing on study design and analysis and critical review of
   work in progress.
d) I have continued my clinical training under the guidance of Dr. Philip Kantoff
   through seeing patients 1.5 days/week and case discussions in both formal and
   informal settings.
REPORTABLE OUTCOMES

Manuscripts:


*Co-first authors
Data from this analysis will be used in the model under construction, as described above.

An analysis evaluating the cost-effectiveness of alternative surveillance strategies for observation in men with low-risk prostate cancer is in progress.

Abstracts:


Presentations:

Juried Poster Presentation

Oral presentation, Society for Medical Decision Making Annual Meeting, October 2010


Patents and licenses applied for/issued:

None

Degrees obtained that are supported by this training grant:

None

Development of cell lines, tissue or serum repositories:

None

Informatics such as databases and animal models:

None

Funding applied for based on work supported by this award:

Prostate Cancer Foundation Young Investigators Award.
Applied for and received, grant period July 2010 to July 2013.
The funds from this award are used to pay the salary of a computer programmer who is assisting in the development of the natural history model.

NIH/NCI R01CA183958-01. “Opening the Black Box of Cancer Policy Models”. Co-PI. Funding requested for 2014-2017. Applied June 2013; review date October 2013. Utilizing existing models of cancer, this project will develop a software platform that will address modeling’s black box reputation and allow policymakers to interact more fully with the model predictions, capabilities and limitations.

Employment or research opportunities applied for and/or received based on experience/training supported by this grant

None
CONCLUSIONS

In screen-detected men with low-risk prostate cancer, observation is a safe and effective alternative to initial treatment. In our model comparing active surveillance (AS) to initial treatment, the quality of life advantage associated with AS is robust, reflecting the deferred and substantially lower incidence of side effects of treatment experienced by men on AS. AS is associated with significant improvements in QALE even in analyses in which the probability of dying of prostate cancer or of developing progressive disease on AS is increased. However, our finding that the optimal strategy is sensitive to utility weights is evidence that the decision whether to pursue AS must be individualized. In future, models incorporating individual patient utilities may be available to assist patients and their caregivers to estimate the risks and potential benefits of AS prior to making this decision.

In particular after the publication of the PIVOT trial demonstrated no survival benefit to radical prostatectomy in men with low-risk prostate cancer, watchful waiting has gained attention as an intriguing alternative both to initial treatment and to the more interventionist active surveillance. When we modeled the results of the PIVOT study, it was found that watchful waiting was both more effective and less expensive than either active surveillance or initial treatment, even if the risk of dying of prostate cancer on active surveillance is half that of watchful waiting. Again, however, patient preferences were central to the quality of life advantage seen with observation.

Observation for low-risk prostate cancer is a promising strategy both on an individual and on a societal level, and increasingly media and professional attention is making it a more recognized alternative to initial treatment. However, the optimal approach for surveillance is not yet known – how little intervention is both safe and acceptable to patients and health care providers has yet to be determined, and we will analyze this question among others in the next months. However, it is hoped that increasing utilization of this approach will counteract the overtreatment resulting from PSA screening.
REFERENCES


