TREATMENT OPTIONS FOR LOCALIZED PROSTATE CANCER: QUALITY-ADJUSTED LIFE YEARS AND THE EFFECTS OF LEAD-TIME

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ABSTRACT

Objectives. The purposes of this study were to estimate the difference in quality-adjusted life-years between conservative management and prostatectomy or radiotherapy (RT) by clinical Gleason score (2 to 4, 5 to 6, 7, and 8 to 10) for patients aged 55 years and older with clinically localized prostate cancer and to adjust for and explore the effects of lead-time. For localized prostate cancer, it is not known whether treatment (prostatectomy or RT) results in longer quality-adjusted survival than conservative management. Observed survival benefits after treatment may be biased by the lead-time resulting from early diagnosis with prostate-specific antigen screening.

Methods. A Markov simulation was developed, and transition probabilities were derived from a review of published studies. Utility weights were measured in male volunteers older than 60 years. Estimates of disease progression during conservative management were adjusted for lead-time. Sensitivity analyses were performed on all parameters (including estimates for lead-time).

Results. For Gleason score 2 to 4 cancer, conservative management yielded the greatest number of quality-adjusted life-years. For Gleason score 5 to 6 cancer, any of the options appeared beneficial, depending on the estimates for disease progression. For Gleason score 7 to 10 cancer, prostatectomy and RT resulted in more quality-adjusted life-years than conservative management; with a lead-time adjustment of greater than 10 years, the outcomes with conservative management and prostatectomy were similar. The choice between prostatectomy and RT was sensitive to estimates of disease progression after treatment.

Conclusions. Conservative management is a reasonable option for Gleason score 2 to 4 cancer and for some patients with Gleason score 5 to 6 cancer. Prostatectomy or RT is recommended for Gleason score 7 to 10 cancer. The survival benefits after treatment were not explained by the lead-time alone.

The management of prostate cancer remains controversial. Since the introduction of prostate-specific antigen (PSA) screening, prostate cancer is diagnosed at an earlier stage (potentially resulting in lead-time bias).¹ This shift has made it difficult to compare estimates of disease progression with conservative management from the pre-PSA era with the more recent estimates of disease progression after treatment (prostatectomy or radiotherapy [RT]) for patients diagnosed with prostate cancer by PSA screening.

A recently published trial found better disease-free survival among patients randomized to prostatectomy (versus conservative management) but little difference in overall survival. Moreover, both treatment and conservative management were associated with significant complications.² Only a small portion of these patients, however, were diagnosed by PSA screening. A number of studies published within the past decade have continued to suggest a survival ben-
e, fit after prostatectomy and RT for patients diagnosed as a result of PSA screening.3–7

Trials in the post-PSA era are being conducted, but the results will not be available for several years. In the interim, patients and clinicians have to make decisions under conditions of considerable uncertainty. Previous models have been developed but were based on studies in the pre-PSA era.8,9 To compare the outcomes for patients managed conservatively with those treated surgically (retropubic or perineal prostatectomy) or with RT (external beam RT or conformal external beam RT) in the post-PSA era, we designed a new model that adjusted for quality of life (QOL) and competing causes of death. Estimates of disease progression during conservative management were also adjusted for lead-time.

MATERIAL AND METHODS

THE MODEL

A Markov model simulated outcomes for patients between the ages of 55 and 75 years with a diagnosis of clinically localized prostate cancer (Fig. 1). Markov states (health states) were chosen to account for the impact of long-term treatment complications or cancer progression on QOL. Under conservative management, hypothetical patients remained well until the onset of metastases. Hormone-sensitive disease was followed by hormone-refractory disease.10,11 Disease progression after prostatectomy or RT sequenced biochemical failure (a rise in PSA of 0.2 to 0.4 ng/mL after prostatectomy or a sequential rise in PSA after RT) before metastatic disease.3–7,12,13 Permanent treatment complications included one, or a combination of, sexual dysfunction, urinary symptoms, and bowel dysfunction (after RT only).14–18

Patients could "exit" this simulation as a result of death from prostate cancer, treatment, or other causes (taken from U.S. Life Tables).19–21 A 1-year Markov cycle and a half-year cycle correction were used; the model was run until gains in quality-adjusted life years (QALYs) were less than 0.001. The model was developed and analyzed using DATA, version 4.0.22

TRANSITION PROBABILITIES

Transition probabilities (probabilities of moving from one health state to another) were derived from studies identified through a PubMed search for reports published in the past 15 years. Estimates for disease progression under conservative management (the annual probability of metastases) were only available from the pre-PSA era.10,11 To estimate disease progression after treatment (annual probabilities of biochemical failure and metastases after biochemical failure) in the post-PSA era, studies that followed patients diagnosed after the late 1980s were selected. Outcome measures from these studies also had to be determined from patients with clinically localized cancer and had to include the probabilities required for the model stratified by Gleason score or grade (Table I). The ranges for these estimates were also derived from the literature review3–7,19 (Table I). Because prostate cancer is often restaged after surgery (this generally biases the results in favor of surgery), the estimates of disease progression after surgery were based on a study that included outcomes by clinical stage.3 The ranges, however, were adjusted to include the estimates of disease progression derived from other studies.3,4

The risks (and ranges) for treatment complications were derived from several institutional and population-based studies14–19 (Table II). Because about 20% of patients may develop sexual dysfunction independent of treatment, the literature-derived risk of sexual dysfunction was decreased by 20%.14
Because estimates for transition probabilities were uncertain, one-way sensitivity analyses (changing estimates for one variable) were done on all model parameters. This was done to determine whether the model outcomes were sensitive (or changed as a result of) the uncertainty surrounding a particular estimate.

**ADJUSTMENT FOR LEAD-TIME**

Estimates for disease progression under conservative management were adjusted for lead-time. Lead-time ranged from 3.5 to 5.5 years for Gleason score 8 to 10 and Gleason score 2 to 4 cancers, respectively (Table I). To determine whether the model was sensitive to estimates for lead-time, the model was run at the age of 65 years (about the median age of diagnosis for prostate cancer) to determine how rapid or slow disease progression under conservative management had to be to approximate the outcomes after prostatectomy. For Gleason score 2 to 4 (and 5 to 6) cancers, we questioned whether smaller estimates of lead-time (resulting in faster disease progression under conservative management) would favor treatment. Thus, estimates for lead-time started at zero (no adjustment for lead-time). For Gleason score 7 and 8 to 10 cancers, we examined whether greater lead-time estimates (resulting in slower disease progression under conservative management) would favor conservative management over treatment. The lead-time estimates for higher grade cancers, therefore, ranged up to 10 years.

**UTILITY WEIGHTS (QALYS), DISCOUNT RATE, AND MEDIAN SURVIVAL**

The time spent in each health-state (Markov state) was assigned a standard gamble utility weight measured in 162 men aged 60 years and older (one half of whom had prostate cancer), using a computer-based utility assessment program (http://preferences.ucsd.edu). This study was designed specifically to measure the health states within the model, including combinations of urinary, sexual, and bowel dysfunction. Utility weights adjusted the survival time for QOL. For example, the utility weight for bowel symptoms was 0.71; thus, each year with bowel symptoms was equal to 0.71 QALYs. Utility weights were varied by ± 1 standard deviation in the sensitivity analyses. (The main utility weights and standard deviations are also shown in the bottom left of Table II.) Future health outcomes were discounted at an annual rate of 3% (range 1% to 5% for the sensitivity analyses). The approximate median survival was calculated by running the model without adjusting for QOL and without discounting.

**RESULTS**

**QALYS AND MEDIAN SURVIVAL**

The differences between QALYs after treatment and conservative management are shown in Figure 2. Conservative management yielded more QALYs than treatment for patients with Gleason score 2 to 4 and 5 to 6 cancers. In contrast, treatment appeared beneficial for patients with Gleason score 7 and 8 to 10 cancers. The median survival was greater than the quality-adjusted survival because of treatment complications. However, for Gleason score 2 to 4 cancer, only a marginal difference was found in median survival between conservative management and treatment. Patients with Gleason score 5 to 6 cancer gained about 0.5 year after treatment. Patients with Gleason score 8 to 10 cancer at age 55, 65, and 75 gained approximately 4.5, 3, and 2 years, respec-

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**TABLE I. Estimates for probabilities of disease progression**

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Annual Probability of Developing Metastases Under Conservative Management (With and Without Lead-Time Adjustment)</th>
<th>Annual Probability of Rising PSA After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Prostatectomy</td>
</tr>
<tr>
<td>2–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.02 (0.005–0.04)</td>
<td></td>
<td>0.02 (0–0.03)</td>
</tr>
<tr>
<td>5–6</td>
<td></td>
<td>0.04 (0.02–0.09)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>0.09 (0.04–0.1)</td>
</tr>
<tr>
<td>8–10</td>
<td></td>
<td>0.1 (0.09–0.2)</td>
</tr>
</tbody>
</table>

**Annual Probability of Metastases After PSA Rise†**

<table>
<thead>
<tr>
<th></th>
<th>Conservative Management</th>
<th>Prostatectomy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gleason scores</td>
<td>0.08 (0.06–0.17)</td>
<td>0.12 (0.06–0.17)</td>
<td></td>
</tr>
</tbody>
</table>

**Annual Probability of Death After Metastases§**

<table>
<thead>
<tr>
<th></th>
<th>Conservative Management</th>
<th>Prostatectomy</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Gleason scores</td>
<td>0.23 (0.13–0.50)</td>
<td>0.23 (0.13–0.50)</td>
<td>0.23 (0.13–0.50)</td>
</tr>
</tbody>
</table>

Key: PSA = prostate-specific antigen.
Data in parentheses are the range.
‡ Range derived from median time to metastases after PSA rise, Gleason score 5–7 and 8–10 cancers.
† Upper bound assigned.
§ Median time to death after metastases. 3 yr (range 1–5).
tively. Similar gains were seen for Gleason score 7 cancer.

**Sensitivity Analyses**

*Progression to Metastases Under Conservative Management and Adjustment for Lead-Time.* Prostatectomy resulted in more QALYs than conservative management for patients with Gleason score 2 to 4 cancer if the annual progression to metastases under conservative management was significantly greater (around 0.04) than the baseline probability (0.01). With Gleason score 5 to 6 cancer, the model also suggested that prostatectomy would be beneficial if the probability of metastases were slightly greater (around 0.03) than baseline (0.02). For Gleason score 7 and 8 to 10 cancers, the QALYs remained greater after treatment even at the lower estimates of disease progression under conservative management.

If the lead-time adjustment for Gleason score 2 to 4 cancer was less than 0.5 year (resulting in much faster disease progression under conservative management), prostatectomy would result in more QALYs than would conservative management. Prostatectomy also resulted in more QALYs if the lead-time adjustment was less than 3 years for Gleason score 5 to 6 cancer. In contrast, the model only began to favor conservative management for patients with Gleason score 7 and 8 to 10 cancers if a lead-time adjustment of greater than 10 years (resulting in much slower disease progression under conservative management) was used.

*Transition Probabilities After Treatment: Biochemical Failure, Progression to Metastases, and Long-Term Complications.* More effective treatment results in lower risks of disease progression after treatment (progression to biochemical failure and then to metastases). However, conservative management continued to yield more QALYs with Gleason score 2 to 4 cancer even at lower estimates of disease progression after treatment. Conservative management also remained preferred at lower estimates of treatment complications. The model suggested that prostatectomy for Gleason score 5 and 6 cancers.

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**TABLE II. Treatment complications and utility weights**

<table>
<thead>
<tr>
<th>Treatment Complications (Main Health States) with Utility Weights</th>
<th>Probability of Treatment Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual dysfunction</td>
<td>0.89 (0.74–1)</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>0.87 (0.71–1)</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>0.71 (0.45–0.97)</td>
</tr>
<tr>
<td>Death from treatment</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Prostatectomy</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>0.47 (0.15–0.6)</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>0.2 (0.03–0.4)</td>
</tr>
<tr>
<td>Bowel dysfunction</td>
<td>0.07 (0.04–0.09)</td>
</tr>
<tr>
<td>Death from treatment</td>
<td>0.003 (0.001–0.1)</td>
</tr>
</tbody>
</table>

Data in parentheses are the range.
to 6 cancer may be preferred if lower estimates of disease progression after prostatectomy were used. Prostatectomy also yielded more QALYs than conservative management with lower risks of sexual dysfunction as a result of treatment.

The choice between prostatectomy and RT for Gleason score 7 and 8 to 10 cancers was also sensitive to the estimates for treatment efficacy. For Gleason score 8 to 10 cancer, RT appeared preferable over prostatectomy if the risk of death after surgery was greater than approximately 0.06 and 0.02 at the age of 55 and 75 years, respectively. This choice was not otherwise sensitive to the risks of treatment complications (within the ranges tested).

Utility Weights and Discount Rate. The model was not sensitive to utility weights for patients with Gleason score 2 to 4 cancer. For Gleason score 5 to 6 cancer, prostatectomy began to yield more QALYs (than conservative management) when significantly greater weights (greater than 0.94) were used for sexual dysfunction. For older (age 75) patients with Gleason score 7 and 8 to 10 cancers, either prostatectomy or RT could yield the most QALYs, depending on the utility weights. The model was not sensitive to the discount rate.

COMMENT

Conservative management resulted in the most QALYs for patients with Gleason score 2 to 4 cancer. Less of a difference was observed between conservative management and treatment for patients with Gleason score 5 to 6 cancers; the model was, therefore, sensitive to the uncertainty surrounding many of the model parameters. For higher grade cancers, either prostatectomy or RT could be preferred. The choice between the two options was sensitive to the estimates of disease progression after treatment (treatment efficacy).

Disease Progression

Estimates of disease progression were the main variables in the model. Either treatment could yield more QALYs (than conservative management) for patients with Gleason score 5 to 6 cancer at higher estimates of disease progression under conservative management. This is important because Gleason score 6 cancer may progress faster than Gleason 5 (and, therefore, treatment may be preferred for Gleason score 6 cancer). Following a PSA rise after treatment, low and moderate-grade cancers may also progress to metastases more slowly than higher grade cancers; for Gleason score 5 to 6 cancers, the model favored treatment at these lower estimates. Conservative management remained beneficial for patients with Gleason score 2 to 4 cancer even with the best estimates for treatment efficacy after prostatectomy and RT. For higher grade cancers, the most beneficial treatment option (prostatectomy or RT) depended on the estimates for treatment efficacy. Because the model was quite sensitive to these estimates, we can only conclude that the outcomes after prostatectomy and RT are similar.

Lead-Time

By exploring the effects of lead-time, we were able to address some of the controversy surrounding treatment outcomes. It is not known whether the benefit of treatment in the post-PSA era (compared with conservatively managed patients in the pre-PSA era) is the result of cancer diagnosis at an earlier stage (lead-time bias). Based upon our model, however, the lead-time for Gleason score 7 and 8 to 10 cancers would have to be greater than 10 years (ie, disease progression with conservative management would have to be much slower) before the outcomes for conservative management become similar to outcomes after prostatectomy. This would be unlikely for an aggressive cancer; thus, the benefit of treatment is probably not attributable to lead-time alone. Alternatively, with Gleason score 2 to 4 cancer, prostatectomy appeared to be beneficial compared with conservative management with small (up to approximately 0.5 year) lead-time adjustments. Thus, because the lead-time for slow-growing cancers is probably greater than 0.5 year, it is possible that lead-time may explain the treatment effects observed in some studies for Gleason score 2 to 4 cancers.

Median Survival, Treatment Complications, and Utility Weights

Without adjusting for QOL and without discounting, the model approximates median survival. In this case, median survival was greater than survival adjusted for QOL because of treatment complications. Other interventions may not prolong life (or increase median survival) but may improve QOL. As determined by our model for patients with Gleason score 2 to 4 cancer, only a marginal difference was found in median survival between conservative management and treatment; patients gained only about 0.5 year after treatment for Gleason score 5 to 6 cancer. In contrast, patients with higher grade cancers gained up to 2 additional years (over QALYs).

QOL, however, is an important issue for patients considering treatment for prostate cancer. To integrate QOL, estimates of treatment complications and their corresponding utility weights are required. Because estimates for treatment complications vary within and between studies, relatively wide ranges for complication risks were used. The utility weights for these symptoms were also directly measured for all health states in the model and were comparable to the weights found in other studies. These weights were lower than the utility
weights used in the Fleming model, which were derived from expert opinion.\textsuperscript{8} If greater utility weights for sexual dysfunction were used in the model, prostatectomy would be preferred for Gleason score 5 to 6 cancer; prostatectomy would also appear to be more beneficial for patients with Gleason score 7 and 8 to 10 cancers.

**Comparison with Other Models**

In addition, our results suggested stronger treatment effects for men with high-grade cancer compared with the Fleming model\textsuperscript{9} (and a reanalysis of this model by Kattan \textit{et al.}\textsuperscript{9}). This comparison, however, is problematic because of differences in model design and assumptions used to determine estimates for disease progression. Our estimates of disease progression after treatment were also derived from studies in the post-PSA era. Although this biased outcomes in favor of treatment, we addressed this by adjusting for, and exploring the effects of, lead-time on our results.

**Study Limitations**

This analysis did not deal with the issue of PSA screening. Androgen ablation with a rise in PSA also was not included, because our overall conclusions were unlikely to change.\textsuperscript{29} The publications used to derive the transition probabilities were limited to retrospective observational and cross-sectional studies. Finally, this analysis focused on the difference between management options and exploring the effects of lead-time on these outcomes. Individual patient risks and preferences, however, need to be considered to make individual recommendations. Because of this, future analyses will detail outcomes stratified by more specific risks and preferences.

**Conclusions**

Pending the completion of large randomized trials, this analysis should help to clarify some of the controversy surrounding treatment outcomes for clinically localized prostate cancer.\textsuperscript{30} Conservative management is reasonable for patients with Gleason score 2 to 4 cancer. Patients (between 55 and 75 years old) with Gleason score 7 and 8 to 10 cancers, however, benefit from either prostatectomy or RT. The outcomes are similar for both treatments, and survival after treatment did not appear to be explained by lead-time alone. Most patients, however, will be diagnosed with Gleason score 5 to 6 cancer\textsuperscript{1}; informed decision-making is especially important for these patients because, in some cases, treatment appeared to be marginally beneficial.

**References**


