Supplementary Online Content


eTables 2, 3, 5-8 updated online April 4, 2011.

eAppendix. Systematic Review and References
eFigure 1. Decision Tree Schema
eFigure 2. QUORUM Flow Chart Showing Results of Literature Search
eFigure 3. Overall Survival, by Management Approach and Timepoint
eTable 1. Reported Short- and Long-Term Adverse Effects, by Treatment Type
eTable 2. Sensitivity Analysis: Discounting
eTable 3. Sensitivity Analysis: Patient-Derived Utilities
eTable 4. Non-patient and Patient-Derived Utilities
eTable 5. Sensitivity Analysis of Probability of Disease Progression or Symptoms With Active Surveillance
eTable 6. Sensitivity Analysis of Adverse Effects of Treatment
eTable 7. Sensitivity Analyses of Utility of Being on Active Surveillance, Utility of Experiencing Erectile Dysfunction on Active Surveillance, and Utility of Experiencing Urinary Obstructive Symptoms on Active Surveillance
eTable 8. Sensitivity Analysis of Utility of Being Post-treatment Without Adverse Effects
eTable 9. Prospective Studies of Active Surveillance

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Systematic Review and References

Probabilities used in the model were drawn from the literature, primarily from 3 previously-performed systematic reviews. The purpose of these systematic reviews was to characterize the available evidence and to populate decision analytic models. These analyses included treatment modalities not analyzed in this model: the description below is an abridged version of the final reports of the Institute for Clinical and Economic (ICER) analyses modified to reflect only the data used in the model presented in this manuscript. For a complete description of the previous reviews, please see the websites below:

Active Surveillance/Radical Prostatectomy:  

Brachytherapy:  

Intensity-Modulated Radiation Therapy:  

All probabilities used in this model were drawn from meta-analysis performed as described below other than the probabilities of 1) progression from biochemical recurrence to metastatic disease, 2) death after development of metastatic disease, and 3) probability of progressive disease on active surveillance. In the case of active surveillance, this probability was derived by calculating a weighted annual probability of progression due to the unsuitability of the few studies available for meta-analysis. This probability was tested extensively in sensitivity analysis (see article body and eTable 5).

Systematic Review: Methods

The systematic reviews included primary studies as well as prior systematic reviews and health technology assessments. Studies were identified from electronic databases as well as manual citation review and had a study population of adult males who received one of the management options of interest. The search timeframe spanned from January 1996 to June 2010. Major eligibility criteria included

- Exclusion of other variants of treatment (e.g., high-dose-rate brachytherapy)
- Preponderance of patients met criteria for low-risk disease, or data presented for subpopulation meeting low-risk criteria
- Sample size \( \geq 50 \) patients
- English-language only

eFigure 2 shows a flow chart of the results of all searches for included primary studies (n=309).

When there were at least 3 studies available, meta-analyses were conducted to generate pooled estimates of complications and side effects for each treatment approach. Because no difference in biochemical recurrence was assumed across treatments, overall pooled estimates of these measures were generated. Due to variability in study population demographics, prevalence of low-risk disease, definition of outcomes, and other factors, random-effects models were employed using the DerSimonian-Laird method with inverse variance weighting; effect estimates were generated along with 95% confidence intervals.

Given the high potential for publication or other evidence dissemination bias from the type of evidence reviewed, estimates were subjected to multiple tests of such bias. Specifically, rank correlation-tau and Egger’s regression were performed and assessed for significance; if either result was significant, the trim-and-fill method was employed to adjust the pooled estimate. Meta-analyses were conducted using MIX software version 1.73.

Data Quality

A total of 309 studies were evaluated in three separate appraisals of the technologies of interest: IMRT (n=32 studies); brachytherapy (n=152 studies); and active surveillance and radical prostatectomy (n=105 studies).
Randomized controlled trials do not exist that compare measures of benefit and/or harm between brachytherapy, radical prostatectomy, IMRT, and active surveillance. Randomized evidence is limited to the Scandinavian randomized controlled trial of radical prostatectomy vs. watchful waiting\(^6\) and one report from a randomized trial of the addition of the androgen receptor inhibitor bicalutamide to watchful waiting\(^7\). Nearly all of the remaining treatment studies were relatively small single-center case series of a single modality as well as comparative series with historical or contemporaneous controls, a body of evidence further limited by considerable variability in population age and other demographics, treatment selection processes, follow-up duration, number of patients with low-risk disease, and definitions and measurement of treatment outcomes, making both direct and indirect comparisons across treatments highly problematic.

Information on active surveillance performed with intensive patient follow-up protocols is also somewhat limited given its relatively recent evolution from more conservative management strategies. The longest reported median follow-up for active surveillance is 7 years (vs. 20-30 years in some watchful waiting studies). In addition, only one active surveillance study involved a comparison to a treatment alternative, a contemporaneous comparison to a watchful waiting cohort in the UK\(^8\). The lack of a substantive body of data on active surveillance outcomes beyond 5-7 years limits the level of certainty that can be achieved in comparisons of clinical effectiveness, particularly for younger patients (<65 years old) who would be expected to live an additional 20 years or more.

**Comparative Clinical Effectiveness**

**Overall Survival**

There are no data available from randomized controlled trials to compare directly the impact of different management options on the overall survival of patients with low-risk prostate cancer. While direct comparisons of rates of overall survival across active surveillance and all the immediate treatment options are unavailable, 5-year survival rates in published case series are comparable (range: 77-99%); as noted above, rates are influenced by differences in population demographics, proportion of subjects with low-risk disease, and other factors (see eFigure 3). Overall survival of patients following radical prostatectomy has also been infrequently reported (7 studies)\(^6, 9-13\). Reports of newer technologies such as IMRT have been based on relatively short follow-up durations and have largely not documented the effects of these modalities on survival, relying instead on measures of biochemical control as a surrogate.

Not surprisingly, given the longer period of follow-up available, more studies have evaluated the impact of watchful waiting on overall survival than have done so for active surveillance. Generally, survival rates for watchful waiting across all published studies were highly variable (range: 61-92.7% at 5 years)\(^6, 7, 13-38\). Survival rates were correlated with the percentage of patients whose cancer exhibited low-risk characteristics (i.e., PSA <10 ng/ml, Gleason ≤6, stage T1-T2a). Among patients in the study reporting the lowest survival\(^22\), only 60% had low-risk cancer, whereas nearly 90% of patients had low-risk cancer in the study with the highest survival estimate\(^39\).

Survival rates in the literature for active surveillance are higher than those for watchful waiting, albeit after shorter follow-up durations. Five-year rates range from 85-100%\(^8, 30-45\); as noted previously, men in active surveillance programs tend to be younger, asymptomatic, and have lower-risk tumors than those in the previous watchful waiting cohorts. While there are no studies that actually compared active surveillance to radical prostatectomy, 5-year survival rates were generally comparable to those observed for active surveillance (range: 84-99%)\(^6, 9-13\).

The most widely-cited comparative data on overall survival come from the Scandinavian randomized controlled trial of radical prostatectomy and watchful waiting\(^6\). At 12 years, a 7-percentage-point difference was noted in overall survival (67.3% vs. 60.2% for radical prostatectomy and watchful waiting respectively, \(p=.09\)). This gap was driven, however, by a substantial and significant difference among men who were <65 years of age at randomization; no differences in survival were observed among older men.

In studies evaluating overall survival after brachytherapy, survival rates varied substantially, as there was considerable variation in population demographics, proportion of patients with low-risk disease, duration of followup, and other factors. At 5 years post-treatment initiation, the most commonly-reported timepoint in these studies, survival ranged from 77-97% in the brachytherapy reports\(^46-64\). As evidence of the effects of differences in study populations on this outcome, a retrospective analysis using data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program, found that 10-year survival differed significantly by age among men undergoing brachytherapy: 92.1% among men aged <60 years at time of treatment vs. 62.9% among those aged 60 years or more\(^46\).
Disease-Specific Survival

Similar evidence limitations characterize findings on disease-specific survival. Published case series estimates of 5-year disease-specific survival for all management options largely overlap in a tight range from 95-100%. As with overall survival, disease-specific survival is reported infrequently in studies of IMRT.

Given the long duration needed to assess impact on overall or cancer-specific survival, many studies of radiation therapy treatments and radical prostatectomy use biochemical failure as an intermediate outcome. The link between biochemical evidence of disease recurrence and survival has been the subject of much debate. Questions remain, however, regarding biochemical failure’s prognostic ability for other patients. Nonetheless, biochemical failure has gained broad consensus among clinicians and researchers as a valid surrogate outcome. Clinicians use it as a trigger for decisions to employ adjuvant or salvage therapy following prostatectomy, and its role as a surrogate measure in research will endure due to the practical barriers to conducting large-scale trials of sufficient duration to measure disease-specific and overall mortality.

However, any comparison of rates of biochemical failure across treatment modalities is complicated not only by the study differences previously noted (e.g., duration of follow-up, pathological tumor staging, proportion of low-risk subjects), but also by the use of several different definitions of biochemical failure. Within the limits of the available evidence, no findings support a distinct difference in biochemical failure rates at 5 or 10 years across brachytherapy, IMRT, or radical prostatectomy.

Biochemical Freedom from Failure (bFFF) Following Radical Prostatectomy

Measurement of biochemical recurrence is an important surrogate endpoint for treatment outcome, as it is the major factor in determining requirements for salvage therapy following definitive treatment. Interpretation of studies reporting on bFFF is complicated by the use of variable definitions of failure; for example, while the AUA recommends the use of 0.2 ng/mL as the PSA threshold for biochemical recurrence, this measure was utilized in only 4 of the 12 studies evaluated. The range of biochemical freedom from failure in these studies was 75-93% at 5 or more years of follow-up.

Biochemical Freedom from Failure (bFFF) Following Radiation Therapy

For brachytherapy and IMRT, we found a total of 27 studies with median follow-up of 5 years or longer that reported freedom from biochemical failure (bFFF). However, most of the accumulated evidence was for brachytherapy (23 of 27 studies); we identified only 3 IMRT studies with sufficient follow-up.

As with the other measures of survival, significant overlap was observed in measures of bFFF across treatments, and variability was observed in population demographics, definition of and prevalence of low-risk disease, and detail in reporting of adjuvant therapies received. Rates of bFFF in the brachytherapy studies ranged from 61-99% at between 5 and 12 years of follow-up. These included a large, multi-institutional case series of approximately 2,700 patients who received I125 or Pd103 brachytherapy between 1988-1998 and were followed for a median of 63 months: the 8-year rate of bFFF among low-risk patients (n=1,444) was 74%. No discernable trends of bFFF were observed when estimates were examined by year of study publication, biochemical failure definition, duration of follow-up, or proportion of patients with low-risk disease. The 3 IMRT studies included estimated bFFF at different timepoints (3, 5, and 8 years) and varied in duration of follow-up between a median of 5 and 7 years, but generated rates that were similar (85%, 91.5%, and 89% at 3, 5, and 8 years respectively) in subgroups that were identified as low or favorable risk.

Treatment-Free Survival in Active Surveillance

Approximately 25-50% of patients who begin active surveillance will ultimately receive some form of treatment within 5-10 years. Very limited data suggest that approximately one-third to one-half of decisions to initiate definitive treatment are due to patient choice and not because of clinical or pathologic progression. Sparse data show that Gleason grade progression occurs in 5-40% of men over time, with nearly all grade change from 3+3 at diagnosis to 3+4 disease after re-biopsy. In addition, between 25-65% of men are found to have a completely benign pathology on first re-biopsy. The clinical significance of Gleason grade progression or regression on surveillance biopsies is unknown. Because active surveillance differs fundamentally from watchful waiting in its inclusion of the possibility of treatment with curative intent, the proportion of patients ultimately receiving treatment cannot be directly compared across these two approaches.
Rates of definitive treatment among all active surveillance studies ranged from 8-54%; however, a tighter range of 24%-34% was observed in the largest of these studies40, 41, 44, 45, 93. In the UCSF active surveillance registry of 328 patients, 24% of men underwent active treatment after a median time of 3.6 years of surveillance, with grade progression as the greatest driver of treatment40. With a median follow-up of 5.8 years, Klotz reported that 34% of men were treated, primarily after a finding of a short PSA doubling time41, 92.

Some men elect definitive treatment in the absence of clinical progression. The UCSF series shows a low rate of active surveillance “attrition” of 8%40, whereas other centers describe higher rates of 12% and 23% (from the Toronto and Memorial Sloan-Kettering series, respectively41, 44). Results from another study indicate that approximately half of men received definitive treatment within 2 years93. Of 197 men receiving deferred treatment, 110 (56%) did so despite a favorable PSA and PSA doubling time. Re-biopsy results were known only for 27 of these patients, and in none of these patients was Gleason progression the reason for active treatment. Analyses showed that men opting for treatment were significantly younger than those who remained without treatment, although older age has been associated with treatment in other cohorts44.

Evidence on PSA changes and tumor grade progression while on active surveillance is sparse. Data from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) show that for men on active surveillance primarily within community practices, rising PSA is the greatest predictor of treatment receipt21. A PSA doubling time of <3 years was the most common indication for active treatment in the Toronto experience, occurring in nearly half of patients receiving treatment41.

In other series employing a re-biopsy strategy, an increase in Gleason grade occurs in a significant number of men. In over 300 men on active surveillance in the UCSF series, 38% had a rise in Gleason score on surveillance biopsy over time40. The Johns Hopkins active surveillance series described a similar rate of 30%, whereas the Toronto series reported a lower rate of 4%. A certain percentage of Gleason progression is not surprising, as the Gleason score has been found to differ between prostate biopsy and removal of the prostate in 20-30% of men receiving immediate radical prostatectomy44. In addition, a number of men are found with completely benign pathology on surveillance biopsies. Performing an initial surveillance biopsy 6-12 months after diagnosis, investigators in Miami report a negative biopsy rate of 63% in their series of men65. Other series have reported lower negative rates of approximately 25% with immediate re-biopsy.

Although the natural history of PSA, digital rectal exams, and biopsy results may be relevant to patients and clinicians in forecasting the possible outcomes for patients on active surveillance, it is important to note that the clinical significance of these findings is difficult to interpret. Ultimately, however, experience at multiple clinical sites suggests that current practice will lead to approximately 25-50% of men receiving active treatment within 5-10 years, of whom approximately one-third to one-half will do so purely by patient choice and not by specific signs indicating clinical progression.

**Potential Harms**

*Risks Common to More Than One Treatment*

Reported rates of side effects common to all forms of radiation and radical prostatectomy (i.e., urinary adverse effects and erectile dysfunction) are displayed in eTable 1 on the following page, as are rates of gastrointestinal adverse effects for radiation treatments. For radiation modalities, adverse effect rates are classified as moderate-to-severe based on a Radiation Therapy Oncology Group (RTOG) or Common Toxicity Criteria (CTC) score of 2 or higher95, 96. For surgery, classification systems are rarely used, so the literature synthesis focused on strict definitions of incontinence (any pad use) and erectile dysfunction (no erections or erections insufficient for intercourse). It is important to note that only studies reporting adverse effects of nerve-sparing radical prostatectomy were included.

**Urinary Adverse Effects**

Incontinence is a significant adverse effect of radical prostatectomy; adverse effects of radiation therapies include irritative voiding symptoms and more uncommonly incontinence. In all cases, the rates of “short-term” incontinence (i.e., within 90 days after treatment) are relatively high (30-50%), particularly for surgery, with some resolution over time; by 2 years following treatment, rates of “long-term” incontinence have declined to 5-15%. Evidence is not sufficiently robust to distinguish rates of urinary adverse effects by radiation modality.

**Radical Prostatectomy**

We evaluated outcomes in the literature related to urinary incontinence by recording whether there was continued pad use (occasional or consistent) among patients who were considered to be continent at baseline. Incontinence was
considered both as an acute outcome (i.e., at 3 months post-surgery), and again as a chronic outcome (from 12-24 months post-surgery, typically 12 months).

The pooled estimate for acute incontinence was 46.7% (95% CI, 25.1%, 68.2%)\(^9\), \(^68-74\), \(^97-104\). As with the other measures of harms, there was substantial variation in results across studies. Our analyses estimate the risk of chronic incontinence following radical prostatectomy at 12.7% (95% CI, 9.6%, 15.8%). As above, estimates by study and population varied substantially. Measurement differences may again assist in explaining the range.

**Radiation Therapy**

Acute urinary toxicity was reported in 11 brachytherapy and 4 IMRT studies using RTOG-grading in our review. The pooled estimate for acute RTOG ≥2 toxicity in brachytherapy studies was 28.7% (95% CI, 17.1%, 40.4%), varying widely from 10-65%\(^9\), \(^84\), \(^105-113\). It is important to note, however, that some of these studies separately report cases of acute urinary retention, a complication specific to brachytherapy (please see discussion below), while it is unclear in other studies whether urinary retention is being considered as part the overall urinary toxicity analysis.

The pooled estimate for acute urinary toxicity for IMRT was 30.0% (95% CI, 13.2%, 46.7%)\(^91\), \(^111\), \(^114\), \(^115\). A high degree of variability in estimates of acute toxicity also was observed in the IMRT studies (7-49%). Consideration of all presented findings (including acute urinary retention, discussed below) yields an estimate that is moderately higher for brachytherapy\(^48\), \(^84\), \(^105-113\) as compared to IMRT\(^91\), \(^111\), \(^114\), \(^115\) (~40% vs. ~30% respectively). In the Eade comparative study\(^111\), the rate of acute urinary toxicity was significantly (p<.01) greater among patients in the brachytherapy group (26.6% vs. 6.9% for IMRT); no multivariate analysis was performed on acute toxicity measures, however.

Rates of late urinary toxicity were reported in 12 brachytherapy studies and 5 IMRT studies. As with other toxicities reported above, use of modified RTOG scales as well as variability in actuarial estimation and timepoints complicated our review across studies. The reported ranges of late RTOG ≥2 urinary toxicity were 16.7% (95% CI, 7.7%,25.7%) for brachytherapy\(^48\), \(^55\), \(^84\), \(^85\), \(^105\), \(^106\), \(^108\), \(^111-113\), \(^116\), \(^117\) and 13.4% (95% CI, 7.5%,19.2%) for IMRT\(^91\), \(^111\), \(^115\), \(^118\). Rates varied widely in studies of both modalities, with similar estimates when considered on an overall basis (13-16%). The comparative data from Eade suggested a fivefold higher rate of late urinary toxicity with brachytherapy (19.2% vs. 3.5% for IMRT, p<.01), a difference that remained significant after multivariate adjustment rates for other treatments (in which rates of late urinary toxicity were generally lower than rates of acute toxicity)\(^111\).

**Erectile Dysfunction**

Information on both short- and long-term erectile dysfunction (ED) is available from the literature on radical prostatectomy. Rates of short-term ED following surgery are quite high, even with the use of “nerve-sparing” surgical techniques; approximately 70% of previously potent men will have ED within 90 days after surgery. As with urinary incontinence, resolution does occur over time, but long-term ED following surgery remains a substantial concern, affecting about 40% of men at 12-24 months.

**Radical Prostatectomy**

ED following radical prostatectomy was assessed in our systematic review based on reported rates of complete inability to have an erection or erections insufficient for intercourse. ED was measured at both acute (3-month) and chronic (12-month) timepoints.

Published evidence on ED following radical prostatectomy is limited by differential follow-up and differing age and comorbidities across patient cohorts. In addition, interpretation of the results of many studies is further complicated by the use of adjuvant androgen deprivation therapy which may result in short-term ED in many patients\(^119\). The pooled estimate for acute ED across all studies was 76.8% (95% CI, 66.2%, 87.4%)\(^9\), \(^68-70\), \(^72-74\), \(^98-101\), \(^103\), \(^104\), \(^120\). Findings for the acute measure were generally not stratified by use of nerve-sparing techniques. A high degree of variability across studies was observed for findings of chronic ED. Pooled results provided an overall estimate of chronic ED of 45.3% (95% CI, 38.7%, 51.9%)\(^9\), \(^68-70\), \(^72-74\), \(^98-101\), \(^103\), \(^104\), \(^120\).

**Radiation Therapy**

Available evidence on ED following radiation treatment is very limited and is characterized by lack of data on baseline potency, use of different survey instruments to measure potency, and adjuvant receipt of androgen deprivation therapy (which may result in at least short-term ED in many patients)\(^119\). Only long-term ED has been reported in these series and has primarily been studied for brachytherapy only. A total of 7 brachytherapy and 2 IMRT studies measured the rate of ED in patients deemed to be potent at baseline. In the brachytherapy studies, the rate of ED ranged from 14-43%\(^63\), \(^84\), \(^105\), \(^106\), \(^109\), \(^121\), \(^122\). Rates in the 2 IMRT studies were very consistent (48-49%); both studies represented patient series from the same institution\(^113\), \(^114\). These limited data suggest rates of long-term ED similar to that of surgery.
Gastrointestinal Toxicity

All forms of radiation therapy are also associated with gastrointestinal (GI) toxicity, primarily in the form of proctitis (inflammation of the anus and lining of the rectum). Rates of moderate-to-severe GI toxicity range from approximately 5-15% and appear to be somewhat higher with IMRT relative to brachytherapy, both in the short and long term; again, however, evidence is limited, particularly with the newer radiation modalities.

Rates of acute GI toxicity were reported in 9 brachytherapy studies and 4 IMRT studies. Among patients receiving brachytherapy, rates of RTOG ≥2 toxicity ranged from 0-10%; 3 of the 10 studies reported no observed cases of moderate-severe acute toxicity. Rates were more variable in the IMRT studies, ranging from 2-50%. It should be noted that in the two studies with the highest reported rates, a “modified” RTOG scale was employed; however, the modification used was not clearly described. When all findings are considered together, rates of acute GI toxicity are nominally lower for brachytherapy in comparison to IMRT.

The one comparative study mentioned above compared patients receiving IMRT (n=216) in 2001-2004 and brachytherapy (n=158) during 1998-2004 at a single institution; IMRT recipients were treated to 74-78 Gy, and brachytherapy patients received I125 implants at a median dose to 90% of the prostate of 153.6 Gy. Treatment groups differed significantly by age, tumor stage, prostate size, baseline AUA score, and prior TURP. The rates of acute GI toxicity (within 3 months following treatment) did not significantly differ between IMRT and brachytherapy (2.3% vs. 1.9%, p=1.0). Note that, while bFFF was calculated in this study, the median duration of follow-up (43 months) did not meet our minimum criteria; therefore, only comparisons of toxicity rates are reported.

We found a greater number of reports of late gastrointestinal toxicity in our review: 15 brachytherapy and 6 IMRT studies. Rates of late GI toxicity were similar in the brachytherapy and IMRT studies, ranging from 0-13% in the former and 2-24% in the latter; when all rates are considered, the overall rate was similar (4-6%) in both groups. It is important to note that, while most estimates of late toxicity were calculated on an “actuarial” (i.e., Kaplan-Meier) basis, detail on the methods and/or timepoints employed was lacking in many articles.

The rate of late gastrointestinal toxicity in the comparative IMRT-brachytherapy study described above was significantly higher among patients receiving brachytherapy (7.9% vs. 2.4% for IMRT, p=.03), primarily due to proctitis. This difference did not remain significant, however, in multivariate analyses controlling for patient characteristics.

Radiation-induced Malignancies

The risk of secondary malignancy from the radiation exposure of brachytherapy and IMRT is very difficult to assess but is assumed by most experts to be approximately 0.5%-1%. The literature is limited to registry-based observational studies of cancer prevalence among patients receiving older-generation radiation technologies, and dose-extrapolation studies for newer-generation radiation modalities. Given that EBRT modalities such as IMRT involve greater radiation exposure outside the prostate than brachytherapy, this model assumes a lifetime attributable risk of 1% for IMRT and 0.5% for brachytherapy. Since other treatment options for localized prostate cancer involve no radiation, these risks may be particularly relevant for some patients, particularly younger men.

Risks Specific to Particular Treatments

Brachytherapy

Brachytherapy has a unique risk of acute urinary retention due to swelling of the prostate gland in reaction to the local inflammation caused by the seeds. A total of nine studies separately report the incidence of acute urinary retention, or the sudden and complete inability to urinate. Reported rates ranged across a fairly tight spectrum between 2% and 17%, with a pooled estimate of 9.7% (95% CI, 1.7%, 17.1%), and generally reflected the requiring urethral catheterization for between 4 and 10 weeks following onset.

Radical Prostatectomy

There is relatively abundant data from case series on the short and intermediate-term risks associated with radical prostatectomy.

Peri-Operative Mortality

Intra- or peri-operative mortality was extremely rare for all surgical approaches; among a total of nearly 30,000 patients evaluated in the studies that reported peri-operative mortality, only 11 deaths were reported (0.04%). Findings from a large observational study of Medicare claims indicated that, among nearly 94,000 patients examined, 526 peri-operative...
deaths occurred (0.56%)\textsuperscript{136}. The overall pooled estimate of mortality among all studies was 0.44%; a confidence interval could not be constructed because of the large number of zero observations.

**Peri-Operative Complications**

**Major Complications:** The types of complications deemed to be “major” include major/systemic infection, MI/stroke, major hemorrhage, deep vein thrombosis/pulmonary embolus (DVT/PE), and bowel injury. Data on major complications is extremely variable due to differences in measures, patient populations, surgeon experience, and other factors. An estimate based on pooled data suggest that the risk of major complications is 4.7% (95% CI, 3.7%, 5.7%) across 20 studies\textsuperscript{14, 66-71, 74, 97-100, 136-142}. Absolute rates of major complications were as follows: DVT/PE (1.0%); major hemorrhage (0.8%); systemic infection (0.7%); and myocardial infarction (MI)/stroke and bowel injury (0.6% each). The overall pooled estimate was 3.7% (95% CI, 3.1%, 4.3%). Significant variation was observed in reported rates of major complications across all studies, ranging from 0-36.6%; the reasons for this variation are unclear, as the majority of studies described no criteria for tracking complications or measuring their severity.

**Minor Complications:** Minor complications include hematoma, anastomotic leakage, transient fever, wound abscess, ileus, lymphocele, and urinary tract infection. In this systematic review, the rate of minor complications was 9.5% (95% CI, 3.3%, 15.7%) across 20 studies\textsuperscript{14, 66-71, 74, 97-100, 136-142}.

**Urethral Stricture**

The incidence of urethral stricture was low, at 3.4% (95% CI, 2.5%-4.4%) over 13 studies\textsuperscript{67, 68, 70, 71, 74, 98-100, 102, 136, 139, 141, 143}. For example, in a large study of Medicare claims, of 94,000 men undergoing open prostatectomy, only 790 (0.8%) received treatment for stricture\textsuperscript{136}.

**Potential Harms: Active Surveillance**

Prostate biopsy appears to be a relatively safe procedure, although measurement of the type and severity of complications varies greatly by study. However, the majority of complications reported are transient and self-limiting, such as pain, rectal bleeding, hematuria, and hematospermia. The incidence of the two complications requiring major intervention is low; urosepsis has been reported to occur in <1% of patients, while acute urinary retention has been reported in 1-3%.

We could identify only 2 studies that have been published within the past 3 years\textsuperscript{144, 145}. Findings from older studies may not be as relevant, as the technique has evolved from the original 6-core sextant scheme to 10- and 12-core schemes as well as saturation approaches\textsuperscript{146}. In addition, as with measures of surgical complications, there is substantial variability in the types of complications reported as well as their definition. For example, there remains significant variation on what constitutes “infectious complications”. In some studies, the presence of fever and/or chills suffices; in others, only overt and definitive infections are reported\textsuperscript{147}.

Nevertheless, the incidence of major complications following prostate biopsy appears to be low. Djavan and colleagues reported on safety findings on initial and repeat biopsy in a total of 1,051 men who were evaluated prospectively as part of the European Prostate Cancer Detection Study\textsuperscript{147}. While minor complications such as hematuria and rectal bleeding were frequent, occurring in nearly 70% of cases, only two major complications (both cases of urosepsis) were observed in 1,871 biopsies performed. The only other complication requiring significant intervention was acute urinary retention, occurring in 2.6% of initial biopsies and 2.2% of repeat biopsies. Findings were similar in smaller series of between 92-415 men\textsuperscript{145, 148, 149}.

In another large series, Sieber and colleagues evaluated complication rates in 1,000 men undergoing 10- to 12-core biopsy and compared findings to their previous study using the 6-core technique\textsuperscript{144}. Findings indicated that, while the rates of “significant” urinary tract infections and rectal bleeding increased nominally relative to the previous study, they remained rare (0.3% and 0.7% respectively).

It should be noted that, while the possibility exists that disease-related symptoms (chiefly obstructive urinary symptoms and erectile dysfunction) may worsen during active surveillance, the progression of these symptoms has only been studied in the Toronto cohort, where findings suggested a rate of symptomatic progression of approximately 3% at a median of 3.75 years of follow-up\textsuperscript{150}. In addition, while limited data on symptom progression are available from watchful waiting studies, information is not comparable due to the older age and advanced cancer characteristics of these cohorts. As such, symptom progression was not evaluated systematically for active surveillance, and evaluation of “harms” was limited to complications related to initial and repeat biopsy for the purposes of generating model probabilities.
REFERENCES


© 2010 American Medical Association. All rights reserved.


© 2010 American Medical Association. All rights reserved.


eFigure 1. Decision Tree Schema
eFigure 2. QUORUM Flow Chart Showing Results of Literature Search

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

MEDLINE; n=11,231 → 1,485 articles
DARE/Cochrane; n=76 → 30 articles
EMBASE; n=8,356 → 607 articles

2,122 articles identified

Reference lists; n=27 → Excluded duplicates; n=873

1,276 unique articles identified

Excluded 967 studies (treatment variants, study size, low-risk patients not identified, duplicate populations)

Articles included in review: n=309*

*AS/WW=61
Brachytherapy=152
IMRT=32
RP=64

ABBR: AS=active surveillance; WW=watchful waiting; IMRT=intensity-modulated radiation therapy; RP=radical prostatectomy
eFigure 3. Overall Survival, by Management Approach and Timepoint

AS: Active surveillance; RP: Radical prostatectomy; BT: brachytherapy; IMRT: Intensity-modulated radiation therapy

NOTE: Bubble size illustrates study sample size
**eTable 1.** Reported Short- and Long-Term Adverse Effects, by Treatment Type

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Brachytherapy</th>
<th>IMRT</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Short-term** | Studies: 9  
  High: 9.6%  
  Low: 0.0%  
  Pooled<sup>†</sup>: 2.1% (0.0%, 4.1%) | Studies: 4  
  High: 50.3%  
  Low: 2.3%  
  Pooled: 18.4% (8.3%, 28.5%) | N/A |
| **Long-term** | Studies: 18  
  High: 12.8%  
  Low: 0.0%  
  Pooled: 4.0% (2.5%, 5.4%) | Studies: 7  
  High: 24.1%  
  Low: 1.6%  
  Pooled: 6.6% (3.9%, 9.4%) | N/A |
| **Urinary** | | | |
| **Short-term** | Studies: 11  
  High: 64.8%  
  Low: 9.7%  
  Pooled: 28.7%  
  (17.1%, 40.4%) | Studies: 4  
  High: 49.0%  
  Low: 6.9%  
  Pooled: 30.0%  
  (13.2%, 46.7%) | Studies: 7  
  High: 46.7%  
  Low: 6.6%  
  Pooled: 46.7% (25.1%, 68.2%)  
  Range: 25.0%-90.2% |
| **Long-term** | Studies: 12  
  High: 40.3%  
  Low: 0.0%  
  Pooled: 16.7%  
  (7.7%, 25.7%) | Studies: 5  
  High: 28.3%  
  Low: 3.5%  
  Pooled: 13.4% (7.5%, 19.2%) | Studies: 17  
  High: 43.0%  
  Low: 14.3%  
  Pooled: 32.3%  
  (25.7%, 38.9%)  
  Range: 6.1%-39.5% |
| **Sexual** | | | |
| **Short-term** | N/A | N/A | Studies: 5  
  High: 43.0%  
  Low: 14.3%  
  Pooled: 32.3%  
  (25.7%, 38.9%)  
  Range: 24.0%-90.0% |
| **Long-term** | Studies: 7  
  High: 49.0%  
  Low: 48.0%  
  Pooled: NR | Studies: 2  
  High: 49.0%  
  Low: 48.0%  
  Pooled: NR | Studies: 16  
  High: 45.3%  
  Low: 38.7%  
  Pooled: 45.3% (38.7%, 51.9%)  
  Range: 24.0%-90.0% |

*As measured on RTOG or NCI-CTC toxicity scales for radiation modalities  
†From random-effects meta-analysis (with 95% confidence intervals)
eTable 2. Sensitivity Analysis: Discounting (data updated online April 4, 2011)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>8.49</td>
<td>-</td>
</tr>
<tr>
<td>BT</td>
<td>8.05</td>
<td>-0.44</td>
</tr>
<tr>
<td>IMRT</td>
<td>8.02</td>
<td>-0.03</td>
</tr>
<tr>
<td>RP</td>
<td>7.83</td>
<td>-0.19</td>
</tr>
</tbody>
</table>


In this analysis, discounting was performed using a discount rate of 3%/year, in accordance with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. Discounting decreases the value of future years relative to the present; this analysis is included to facilitate comparison of our results to previous cost-effectiveness models. In this analysis, active surveillance remained most effective, although the magnitude of effectiveness was decreased from 6.2 months of QALE in the base case to 5.3 months.
eTable 3. Sensitivity Analysis: Patient-Derived Utilities (data updated online April 4, 2011)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>12.29</td>
<td>-</td>
</tr>
<tr>
<td>BT</td>
<td>11.86</td>
<td>-0.43</td>
</tr>
<tr>
<td>IMRT</td>
<td>11.83</td>
<td>-0.03</td>
</tr>
<tr>
<td>RP</td>
<td>11.70</td>
<td>-0.13</td>
</tr>
</tbody>
</table>


The decision whether to employ utilities obtained from individuals with the condition of interest or to obtain these values from members of the community is central to any decision analysis. Our decision to use utilities from community members reflects our desire to present a decision analysis from the societal perspective, rather than the individual. In doing so, we are following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine. The purpose of this approach is to present results that reflect the public interest. However, we recognize that many hold the view that only patients can assess the impact of a particular health state on quality of life. We also recognize that in the setting of an effectiveness analysis comparing alternative therapeutic strategies for a single condition, the use of patient preferences may provide valuable insight into the most effective way to “create health.” eTable 4 compares non-patient and patient-derived utilities.
### eTable 4. Non-patient and Patient-Derived Utilities

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility (non-patient)</th>
<th>SD</th>
<th>Utility (patient)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate Cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Surveillance*</td>
<td>0.83</td>
<td>0.24</td>
<td>0.90</td>
<td>0.15</td>
</tr>
<tr>
<td>Biochemical recurrence</td>
<td>0.68</td>
<td>0.26</td>
<td>0.80</td>
<td>0.21</td>
</tr>
<tr>
<td>Metastatic cancer</td>
<td>0.12</td>
<td>0.18</td>
<td>0.31</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Treatment Adverse Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impotence</td>
<td>0.88</td>
<td>0.20</td>
<td>0.91</td>
<td>0.18</td>
</tr>
<tr>
<td>Urinary difficulty</td>
<td>0.88</td>
<td>0.16</td>
<td>0.88</td>
<td>0.14</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>0.81</td>
<td>0.30</td>
<td>0.84</td>
<td>0.20</td>
</tr>
<tr>
<td>Bowel problems</td>
<td>0.63</td>
<td>0.32</td>
<td>0.66</td>
<td>0.31</td>
</tr>
<tr>
<td>Impotence and urinary difficulty</td>
<td>0.77</td>
<td>0.24</td>
<td>0.81</td>
<td>0.23</td>
</tr>
<tr>
<td>Impotence and urinary incontinence</td>
<td>0.84</td>
<td>0.23</td>
<td>0.78</td>
<td>0.24</td>
</tr>
<tr>
<td>Urinary incontinence and bowel</td>
<td>0.64</td>
<td>0.33</td>
<td>0.63</td>
<td>0.28</td>
</tr>
<tr>
<td>Impotence and bowel</td>
<td>0.55</td>
<td>0.35</td>
<td>0.59</td>
<td>0.29</td>
</tr>
<tr>
<td>Impotence, urinary incontinence and bowel</td>
<td>0.38</td>
<td>0.30</td>
<td>0.44</td>
<td>0.34</td>
</tr>
<tr>
<td>Major complications of RP**</td>
<td>0.96</td>
<td>0.012</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Minor complications of RP***</td>
<td>1.00</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Other Health States</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post treatment without side effects****</td>
<td>0.80</td>
<td>0.24</td>
<td>0.87</td>
<td>N/A</td>
</tr>
<tr>
<td>Treatment with RP</td>
<td>0.46</td>
<td>0.36</td>
<td>0.64</td>
<td>0.28</td>
</tr>
<tr>
<td>Treatment with radiation therapy</td>
<td>1.0</td>
<td>N/A</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

*The non-patient derived utility for active surveillance is from Dale et al\(^{157}\). The patient-derived utility for active surveillance in this table is from Dr. Stewart (personal communication) (see discussion below).

**This utility was taken from a national catalogue of community-based utilities, weighted to reflect the incidence of post-radical prostatectomy complications\(^{158}\). No patient-derived equivalent is available in the literature, to our knowledge, so non-patient utilities were used in the sensitivity analysis.

***Because minor surgical complications did not involve significant treatment, no decrement in utility was assigned to these complications.

****This value was taken from patients in a biopsy clinic\(^{157}\). No similar utility has been elicited from patients with a diagnosis of prostate cancer elsewhere in the literature, to our knowledge. The value provided has been generated as described in the discussion.

One difficulty in performing this sensitivity analysis is that patient-derived utilities are not available for every health state used in our model. For example, the “post treatment without side effects” utility was elicited from patients in a biopsy clinic but is unique in the literature to our knowledge. For the purposes of this sensitivity analysis, we have made the assumption that the patient-derived utility will rise proportionally similarly to the utility for active surveillance (in active surveillance, the non-patient utility was 0.83 from Dale et al\(^{157}\), the patient-derived utility was 0.9 from Dr. Stewart [personal communication]). We have therefore increased the utility for post-treatment without side effects from 0.80 to 0.87.
eTable 5. Sensitivity Analysis of Probability of Disease Progression or Symptoms With Active Surveillance (data updated online April 4, 2011)

In these analyses, neither doubling the probability of any disease progression on active surveillance nor doubling the probability of developing symptoms on active surveillance changed the ranking of active surveillance as the most effective strategy. When the rate of disease progression on active surveillance was doubled from 5.3%/year to 10.6%/year, active surveillance provided 10.82 QALYs, or 3.8 additional months of QALE (quality-adjusted life expectancy) compared to brachytherapy, the initial treatment associated with the highest QALE in the base case (10.5 QALYs). Active surveillance was associated with 11.02 QALYs in the base case analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Probability Range Tested</th>
<th>QALYs: 50% base case probability</th>
<th>QALYs: 200% base case probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of any progression on AS</td>
<td>50%-200%</td>
<td>11.15</td>
<td>10.82</td>
</tr>
<tr>
<td>Probability of any symptoms on AS</td>
<td>50%-200%</td>
<td>11.04</td>
<td>10.94</td>
</tr>
</tbody>
</table>

ABBR: AS=active surveillance; QALY=quality-adjusted life year
**eTable 6. Sensitivity Analysis of Adverse Effects of Treatment (data updated online April 4, 2011)**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>11.12</td>
<td>-</td>
</tr>
<tr>
<td>BT</td>
<td>10.64</td>
<td>-0.48</td>
</tr>
<tr>
<td>IMRT</td>
<td>10.60</td>
<td>-0.04</td>
</tr>
<tr>
<td>RP</td>
<td>10.42</td>
<td>-0.18</td>
</tr>
</tbody>
</table>


In this analysis, the probability of incurring any adverse effects of treatment (short- and long-term) was reduced by 50% for all approaches. Active surveillance remained the most effective strategy.
eTable 7. Sensitivity Analyses of Utility of Being on Active Surveillance, Utility of Experiencing Erectile Dysfunction on Active Surveillance, and Utility of Experiencing Urinary Obstructive Symptoms on Active Surveillance  (data updated online April 4, 2011)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Utility Range Tested (50%-1.0)</th>
<th>QALYs: 50% Base Case Utility</th>
<th>QALYs: Utility=1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of being on active surveillance</td>
<td>0.42-1</td>
<td>7.85</td>
<td>12.29</td>
</tr>
<tr>
<td>Utility of erectile dysfunction on active surveillance</td>
<td>0.44-1</td>
<td>10.81</td>
<td>11.08</td>
</tr>
<tr>
<td>Utility of urinary obstructive symptoms on active surveillance</td>
<td>0.44-1</td>
<td>10.87</td>
<td>11.05</td>
</tr>
</tbody>
</table>

In these analyses, only reducing the utility of being on active surveillance by 50% resulted in active surveillance having a lower QALE than the most effective initial treatment, brachytherapy. Please see text for further discussion. In the base case, active surveillance was associated with 11.02 QALYs and brachytherapy with 10.5 QALYs.
eTable 8. Sensitivity Analysis of Utility of Being Post-treatment Without Adverse Effects

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Utility Range Tested (50%-1.0)</th>
<th>QALYs: 50% Base Case Utility</th>
<th>QALYs: Utility=1</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>0.4-1</td>
<td>9.18</td>
<td>11.93</td>
</tr>
<tr>
<td>BT</td>
<td>0.4-1</td>
<td>6.0</td>
<td>12.65</td>
</tr>
<tr>
<td>IMRT</td>
<td>0.4-1</td>
<td>6.0</td>
<td>12.61</td>
</tr>
<tr>
<td>RP</td>
<td>0.4-1</td>
<td>5.83</td>
<td>12.45</td>
</tr>
</tbody>
</table>


In this analysis, the utility of being post-treatment without side effects but with fear of recurrence was varied from 50%-1. When the utility was increased to 1, active surveillance became less effective than any initial treatment. In the base case, the utility for active surveillance was 0.83, and active surveillance was associated with 11.02 QALYs. Please see text for further discussion.
**eTable 9. Prospective Studies of Active Surveillance**

<table>
<thead>
<tr>
<th>Study</th>
<th>Entry Criteria</th>
<th>Number of patients</th>
<th>Median Age</th>
<th>Follow up (median)</th>
<th>Trigger for treatment</th>
<th>PCSS</th>
<th>Non-prostate cancer mortality</th>
<th>Patients treated</th>
<th>Progressive disease/reason for treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klotz 201032</td>
<td>Gleason &lt;6; PSA&lt;10 ng/mL (until 1999, included men &gt;70 with PSA &lt;15 ng/mL or Gleason 3+4)</td>
<td>450</td>
<td>70.3</td>
<td>6.8 y</td>
<td>Palpable nodule; histologic progression; PSADT&lt;3 years</td>
<td>10 y actuarial OS 78.6%</td>
<td>10 y actuarial OS 97.2%</td>
<td>30% (135)</td>
<td>Progressive disease: 25% (113) Patient preference: 3.0% (14)</td>
</tr>
<tr>
<td>Carter39</td>
<td>T1c-2a; PSADT 0.15 ng/mL; &lt;2 cores positive; Gleason &lt; 6; &lt;50% any single core involved</td>
<td>407</td>
<td>65.7</td>
<td>2.8 y</td>
<td>Gleason 4 or 5 on repeat biopsy; &gt;2 biopsy cores positive or &gt;50% involvement of any one core</td>
<td>100%</td>
<td>2% (8)</td>
<td>25% (103)</td>
<td>NR</td>
</tr>
<tr>
<td>Hardie8</td>
<td>T1/T2; PSA &lt;20 ng/mL; Gleason ≤7</td>
<td>80</td>
<td>70.5</td>
<td>42 mo</td>
<td>PSA velocity at physician/patient discretion</td>
<td>100%</td>
<td>6% (5)</td>
<td>14% (11)</td>
<td>Progressive disease: 11.3% (9) Patient Preference: 2.5% (2)</td>
</tr>
<tr>
<td>Van As159</td>
<td>T1-T2a; Gleason &lt;3+4; PSA&lt;15 ng/mL; &lt;50% total core involvement</td>
<td>326</td>
<td>67</td>
<td>22 mo</td>
<td>PSA velocity &gt; 1 ng/ml/yr or histological progression (primary Gleason grade &gt; 4, or % biopsy core positive &gt; 50%)</td>
<td>100%</td>
<td>2% (7)</td>
<td>20% (65)</td>
<td>Progressive disease: 18.5% (60) Patient Preference: 1.5% (5)</td>
</tr>
<tr>
<td>Van den Bergh93</td>
<td>T1c/T2, PSA ≤ 10.0 ng/mL, PSA density of&lt;0.2 ng/mL/mL, Gleason ≤3+3; ≤2 positive biopsy cores</td>
<td>500</td>
<td>66.0</td>
<td>1.02 y</td>
<td>PSA-DT 0–3 years, clinical stage ≥ T2; histologic progression ( &gt; two positive cores or Gleason &gt;6)</td>
<td>NR</td>
<td>NR</td>
<td>73% (at 2 y)</td>
<td>Progressive disease: 13.6% (68) Patient choice: 2.4% (12)</td>
</tr>
</tbody>
</table>

**ABBR:** PCSS: Prostate cancer-specific survival; PSADT: PSA doubling time; PSAV: PSA velocity

© 2010 American Medical Association. All rights reserved.