INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

FINAL APPRAISAL DOCUMENT

ACTIVE SURVEILLANCE & RADICAL PROSTATECTOMY FOR THE MANAGEMENT OF LOW-RISK, CLINICALLY-LOCALIZED PROSTATE CANCER

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EXECUTIVE SUMMARY

Introduction

Prostate cancer is the second leading cause of cancer deaths and the seventh overall cause of death in men in the United States (Centers for Disease Control and Prevention, 2008). Given that most new cases are diagnosed at an early, localized stage, significant attention has been focused on understanding the risks and benefits of alternative management strategies for patients with low-risk disease. The major options include active surveillance and various forms of radiation therapy and surgery. Most men in the United States choose one of the definitive forms of treatment, but data to compare the long-term risks and benefits of active surveillance and each of the definitive treatment options are limited, placing great emphasis on the need for objective sources of guidance to help clinicians and patients engage in active shared decision-making.

ICER has previously appraised the comparative clinical effectiveness and value of 4 forms of radiation therapy: intensity-modulated radiation therapy (IMRT), low-dose-rate interstitial brachytherapy, proton beam therapy (PBT), and three-dimensional conformal radiation therapy (3D-CRT). This appraisal focuses on active surveillance as well as the major approaches to radical prostatectomy—namely, the traditional "open" approach, minimally invasive laparoscopic prostatectomy, and robot-assisted laparoscopic prostatectomy. It must be emphasized that this review is relevant only for considerations of the management of localized, low-risk disease; the evidence and clinical tradeoffs involved in the treatment of intermediate- or high-risk prostate cancer would differ substantially.

For active surveillance and radical prostatectomy there are several key questions that have served to frame this review:

1) The impact of active surveillance and radical prostatectomy on survival, freedom from disease progression/recurrence, and quality of life relative to alternative management options
2) The relative rates of symptom progression and treatment-related complications and side effects
3) The effects of variation in practice and surgeon experience, frequently called the "learning curve," on patient outcomes for the different versions of radical prostatectomy
4) The patient clinical characteristics and individual values that may influence the relative risks and benefits of these alternative management options
5) The cost-effectiveness and budget impact of active surveillance and radical prostatectomy relative to alternative management options

Because these management options represent very different pathways of care, with potentially important differences in short and long-term risks and benefits, all health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of active surveillance and the alternative surgical prostatectomy options for clinically-localized, low-risk prostate cancer.

Alternative Treatment Options

Active Surveillance

Because of the limited aggressiveness of many localized prostate cancers, active surveillance is viewed by most experts as a reasonable strategy for many men with low-risk prostate cancer (NCCN, 2008). Nonetheless, in the U.S. active surveillance is infrequently used; data from 1990-2006 in the CaPSURE registry suggest that active surveillance is employed in <10% of low-risk patients (Cooperberg, 2007).

The term 'watchful waiting' is sometimes used interchangeably with active surveillance. However, watchful waiting was first coined during an era when many men were first diagnosed with prostate cancer not through PSA screening but through presentation with obstructive urinary symptoms or a palpable nodule. It has been estimated that PSA screening detects prostate cancers an average of 9 years before clinical diagnosis in the absence of screening, and therefore patients with PSA-screen-detected disease will have a much more favorable outcome, even without treatment, than patients diagnosed clinically in earlier watchful waiting studies (Parker, 2004).

Following the publication of randomized controlled trials that showed a 10-year survival advantage for radical prostatectomy over this earlier form of watchful waiting (Bill-Axelson 2005, 2008), current practice has shifted away from a relatively passive watchful waiting approach towards what is a much more active program of surveillance via repeated PSA tests and prostate biopsies, with definitive treatment triggered by any sign of biochemical or pathological progression. The major differences between the older version of watchful waiting and the modern approach to active surveillance are illustrated in the graphic below, based on a prototypical set of criteria used in the UK (Parker, 2004).

Contrasts between active surveillance and watchful waiting.

	Active Surveillance	***Watchful Waiting***
Primary Aim	*To individualize treatment*	*To avoid treatment*
Patient Characteristics	*Fit for radical treatment; age 50-80*	*Age >70 or life expectancy <15 years*
Tumor Characteristics	*T1-T2, Gleason ≤7, Initial PSA <15*	*Any T stage, Gleason ≤7, Any PSA*
Monitoring	*Frequent PSA testing, Repeat biopsies*	*PSA testing unimportant, No repeat biopsies*
Indications for Treatment	*Short PSA doubling time, Upgrading on biopsy*	*Symptomatic progression*
Treatment Timing	*Early*	*Delayed*
Treatment Intent	*Curative*	*Palliative*

Source: Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol* 2004;5:101-6.

Professional guidelines have identified multiple criteria that define candidacy for AS; a common definition is based on a Gleason score (a measure of tumor aggression) of 6 or less, PSA levels 10 ng/ml or less, and a stage between T1c and T2a (NCCN, 2009). Patients with Gleason scores of 7 are also often considered eligible for active surveillance. Other criteria that may be used include 33% or fewer positive cores (biopsy samples), or 50% or fewer single-core involvement. When a patient opts for active surveillance, he is put on a regular monitoring schedule. While there is no universal standard protocol for active surveillance, monitoring schedules often include serial PSA blood tests every 3-6 months, digital rectal exams (DRE) every 3-6 months, and a repeat biopsy at one year followed by subsequent biopsies every 3-5 years thereafter (Klotz, 2008). Other monitoring tests that have been employed include bone scans and CT scans of the abdomen and pelvis to monitor for metastases, as well as transrectal ultrasounds in combination with DRE to assess for progression of local disease or urinary symptoms (Choo, 2002).

Thresholds to trigger definitive treatment in patients on active surveillance are also not universally agreed upon. A rapid rate of PSA increase, or the "PSA velocity", is used by some physicians as an indicator of aggressive disease. Others consider the doubling of a PSA level within 3-4 years (i.e., "PSA doubling time") to be the most reliable indicator of disease progression. Still others contend that results of repeat biopsies provide the best predictor of disease progression. Because the natural history of prostate cancer is poorly understood, clinicians often consider all of these potential triggers to judge when to advise patients that definitive treatment should be initiated.

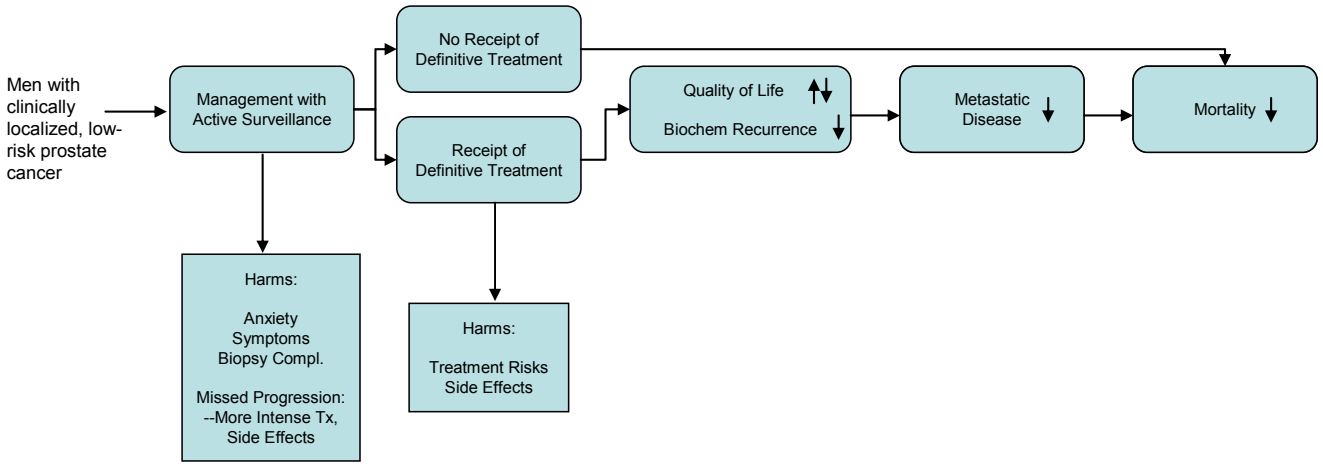
Radical Prostatectomy

Radical prostatectomy has long been an option for the treatment of prostate cancer. The procedure involves the surgical removal of the prostate gland, seminal vesicles, and, in some cases, lymph nodes under general anesthesia; an inpatient hospital stay of 1-4 days' duration is typical. Radical prostatectomy is usually performed when the cancer is localized to the prostate. Candidates for surgery are generally in good overall health with a life expectancy of at least 10 years. There are 3 major surgical approaches employed in radical prostatectomy: radical retropubic prostatectomy (i.e., the traditional "open" surgical approach), as well as two minimally-invasive surgical approaches, laparoscopic radical prostatectomy and robot-assisted laparoscopic prostatectomy. Modern applications of both open and minimally-invasive prostatectomy also involve the use of "nerve-sparing" techniques in an attempt to preserve post-surgical erectile function.

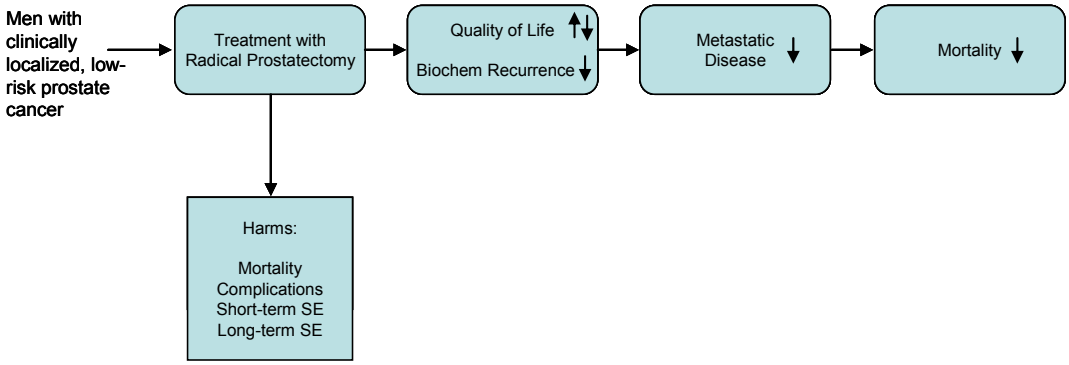
Utilization of laparoscopic and, in particular, of robot-assisted procedures have increased dramatically in recent years. Between 2003 and 2005, utilization of minimally-invasive techniques among Medicare beneficiaries grew from 12.2% to 31.4% (Hu, JCO, 2008), a change likely to have been driven primarily by growth in robot-assisted surgery (Blute, 2008). Advocates for these techniques cite potentially reduced blood loss as well as shorter hospital stays and recovery time as advantages over open prostatectomy (Berryhill, 2008). There is a steep learning curve associated with these procedures, however, as surgeons must adjust to reduced range of motion, discontinuity between real and visible movement, and reduced tactile feedback (Rassweiler, 2006).

Analytic Framework for Evaluation of Active Surveillance and Radical Prostatectomy
The analytic framework for this review is shown in two figures on the following page; one each for active surveillance and radical prostatectomy. There are little to no data directly demonstrating the impact of these therapies on overall patient survival, so judgments about the effectiveness of these interventions must rest almost exclusively upon consideration of the strength of surrogate endpoints as well as evaluation of treatment-associated risks. Note that the figures below are intended to convey the conceptual links involved in evaluating outcomes of these management options, and are not intended to depict a clinical pathway that all patients would transit through. A separate depiction of clinical pathways is available in the Economic Model section of this report (see Section 8).

Analytic Framework: Active Surveillance in Prostate Cancer Treatment



Analytic Framework: Radical Prostatectomy in Prostate Cancer Treatment



The link between biochemical evidence of disease recurrence and survival has been the subject of much debate. Because of the slow growth of most prostate cancers, and the consequent need for extremely long follow-up periods to measure survival accurately, biochemical recurrence, or "failure," as marked by changes in PSA levels following treatment, is widely used as a predictor of survival. Some evidence suggests that biochemical failure is an appropriate surrogate in certain subgroups, such as high-risk patients younger than 75 years (Kwan, 2003). 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.

Evidence on Comparative Clinical Effectiveness

Data Quality

A total of 111 studies met all entry criteria for review. Randomized controlled trials do not exist that compare measures of benefit and/or harm between active surveillance and radical prostatectomy. Randomized evidence is limited to the Scandinavian randomized controlled trial of radical prostatectomy vs. watchful waiting (Bill-Axelson, 2005) as well as a single-center study comparing open and laparoscopic prostatectomy (Guazzoni, 2006). The remaining studies included retrospective cohort studies of cancer registries or claims databases as well as case series predominantly from single academic sites. While some of the surgical case series included comparisons to historical or contemporaneous controls receiving an alternative surgical approach, comparisons between groups are problematic for multiple reasons, including selection bias, changes in surgical protocols over time, differential follow-up for newer vs. older approaches, and changes in measurement of prostate cancer severity.

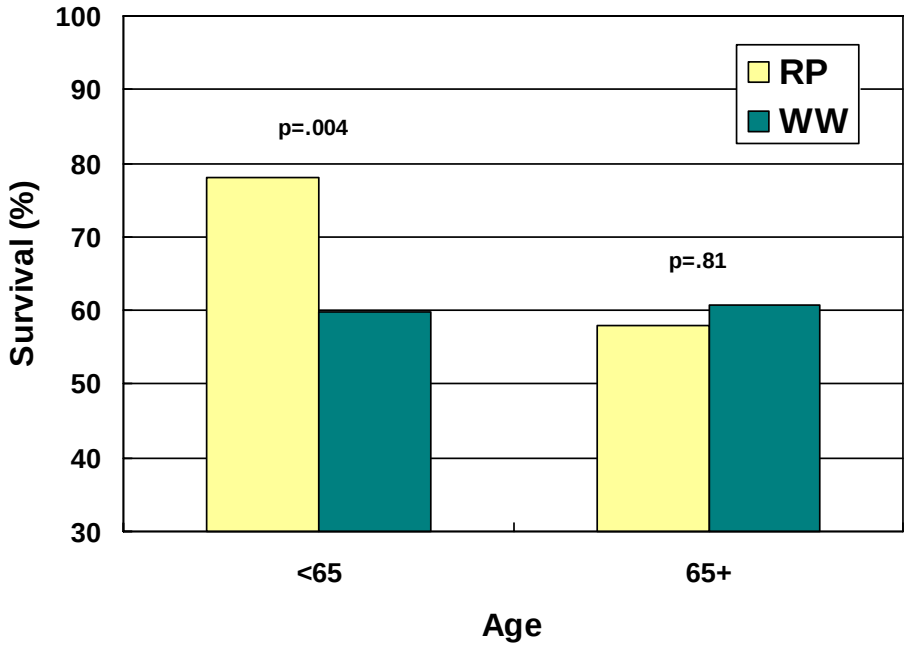
Data on active surveillance are also limited, given its relatively recent evolution from watchful waiting. The longest reported median follow-up is 7 years (vs. 20-30 years in some watchful waiting studies); in addition, only one active surveillance study involved a comparison to a treatment alternative, a contemporaneous comparison to a watchful waiting cohort (Hardie, 2005). 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.

Survival and Freedom from Biochemical Failure

There are no data available to directly compare the impact of active surveillance vs. radical prostatectomy on overall survival. Some articles draw inferences of a lower boundary for active surveillance from older randomized controlled data on watchful waiting vs.

prostatectomy, in which the results indicated a survival benefit for surgery in men under age 65, but not in those 65 and older (see Figure ES1 below).

Figure ES1. 12-year overall survival by age and treatment arm, SPCG-4 trial.
Source: Bill-Axelson, JNCI, 2008

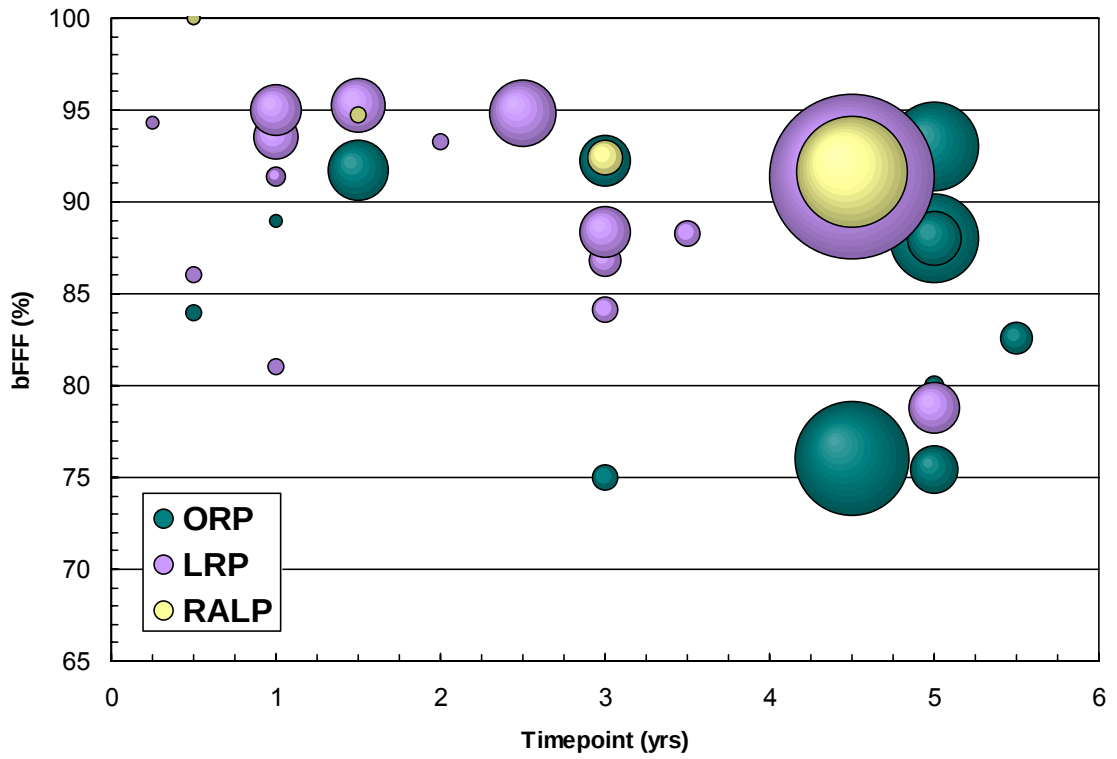


While there are no studies that directly compare active surveillance to radical prostatectomy, 5-year survival rates in published case series are comparable (range: 84-99%). No studies comparing the impact of different surgical approaches on overall survival have been published.

Similar evidence limitations characterize findings on disease-specific survival. No studies have directly compared active surveillance to radical prostatectomy, nor have any evaluated the impact of surgical approach on this outcome. However, published case series estimates of five-year disease-specific survival for both active surveillance and radical prostatectomy largely overlap in a range from 86-100%.

Comparisons of freedom from biochemical failure (bFFF) following prostatectomy is complicated by the use of variable definitions of biochemical failure, as well as differences in duration of follow-up, pathological tumor staging, and other patient and/or study characteristics. When studies were limited to those with sufficient follow-up to report 3-year or longer-term estimates, findings were similar across surgical approaches (see Figure ES2 on the following page).

Figure ES2. Biochemical freedom from failure, by surgical approach and timepoint.



ORP: Open prostatectomy; LRP: Laparoscopic prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy; NOTE: Bubble size used to illustrate study sample size

Treatment-Free Survival in Active Surveillance

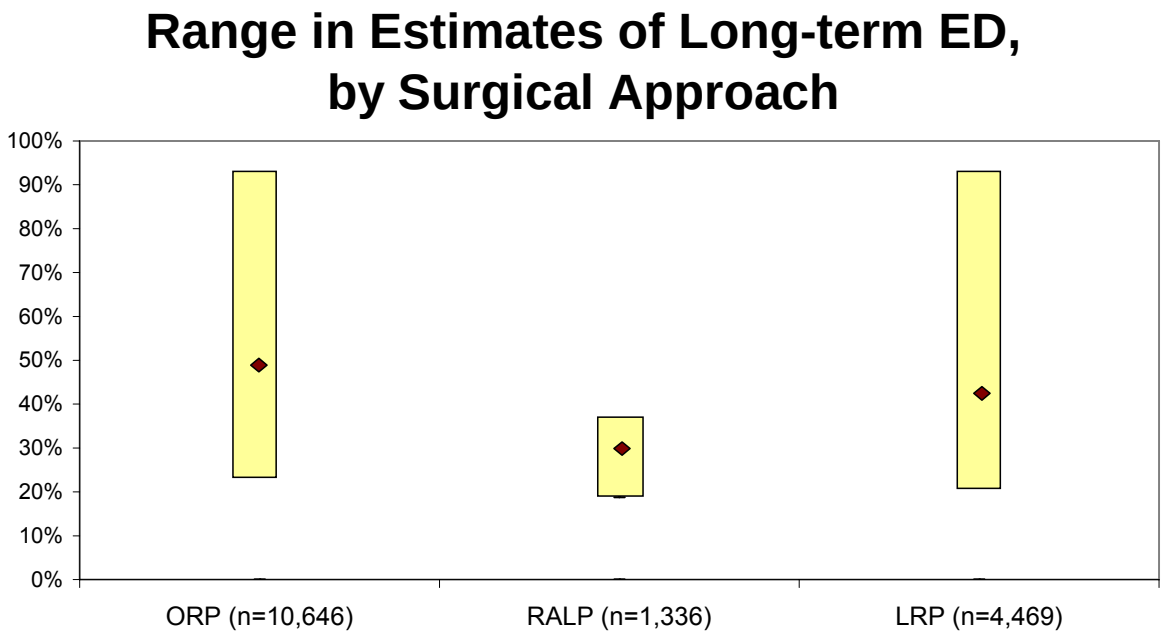
Approximately 25%-50% of patients who begin active surveillance will ultimately receive some form of treatment within 5-10 years. Very limited data suggest that approximately one-third to one-half of decisions to initiate definitive treatment are due to patient choice and not because of clinical or pathologic 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 (Dall'Era, 2008; Carter, 2007; Klotz, 2007). In addition, between 25%-65% of men are found to have a completely benign pathology on first re-biopsy (Soloway, 2008). The clinical significance of Gleason grade progression or regression on surveillance biopsies is unknown (Dall'Era, 2009). 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.

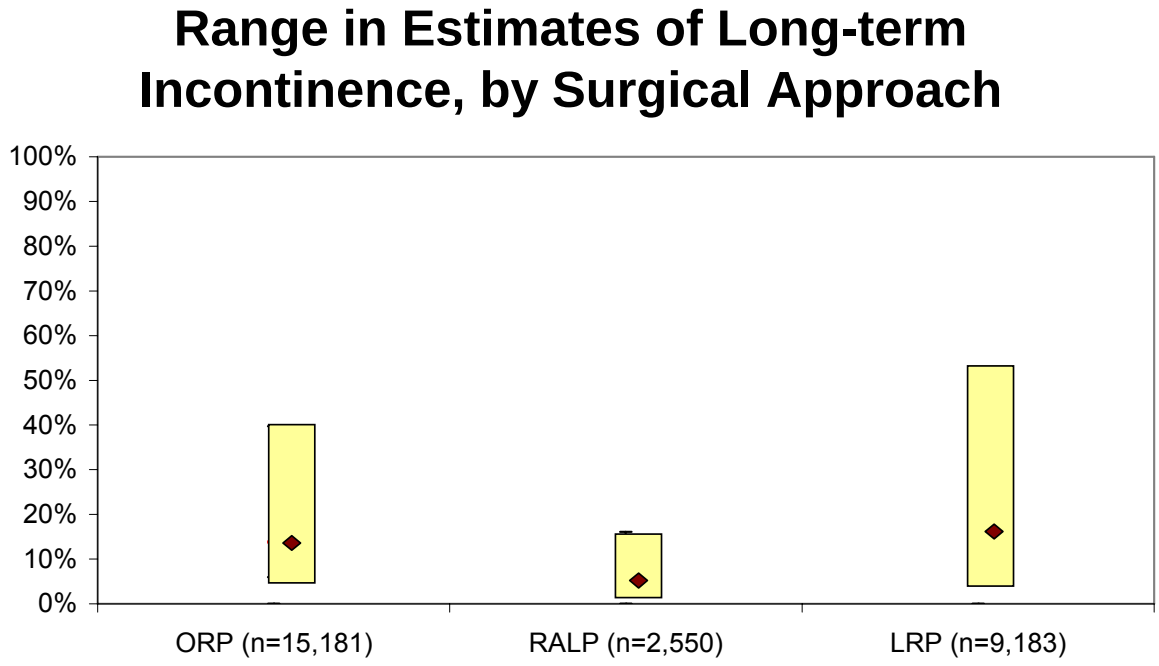
Potential Harms: Radical Prostatectomy

Nearly all information on potential harms of radical prostatectomy comes from individual case series, necessitating indirect comparisons across surgical practices and patient populations that differ in demographic and clinical characteristics, study timeframe, measurement of outcome, and other characteristics. Because of these concerns, the ICER

review assigns no degree of certainty to nominal differences in the published rates of harms by surgical approach. As examples, the variability in estimates for long-term erectile dysfunction and incontinence are illustrated below.

Pooled data on these harms are presented for informational purposes alone in Table ES1 on page 14.





NOTE: Diamonds represent pooled mean rate; rectangles represent full range of estimates

Peri-Operative Complications

Intra- or peri-operative mortality is rare across all surgical approaches to prostatectomy, with a risk of approximately 0.4% for 65 year-old men. While rates differ somewhat by patient age, the risk is well below 1% in all age groups, and does not differ materially by surgical approach.

Data on complications are extremely variable due to differences in measures, patient populations, surgeon experience, and other factors. A rough estimation based on pooled data suggest that the risk of major complications, including DVT/PE, MI, and stroke, is approximately 3-4% and does not appear to materially differ across surgical approaches. The risk of minor peri-operative complications such as UTI or wound infection is approximately 8-9%. The limited comparative data available suggest that minimally-invasive prostatectomy performed by experienced surgeons may be associated with lower rates of minor peri-operative complications, but interpretation of these data is complicated by the younger age of patients undergoing minimally-invasive techniques, and complication rates appear significantly higher among surgeons with limited experience with the newer techniques. Operative blood loss is lower in minimally-invasive approaches, as are associated transfusion requirements, but there is no evidence of a reduced risk of major hemorrhage.

Urethral Stricture, Incontinence, and Erectile Dysfunction

The risk of urethral stricture varies considerably in the published literature, with estimates ranging from less than 1% to 15%. Some evidence suggests that the risk of stricture has declined significantly over time, as all surgical techniques have evolved. Evidence is conflicting on the impact of minimally-invasive surgery on stricture rates; studies of employer and Medicare claims data have indicated reduced risk of stricture from minimally-invasive prostatectomy among younger patients, while for unclear reasons an increased risk was observed in older men (Hu, JCO, 2008; Hu, J Urol, 2008).

Incontinence remains a significant concern among patients undergoing radical prostatectomy, regardless of surgical approach. Approximately 40% of patients will have incontinence at 3 months post-surgery. This side effect appears to resolve in many patients 12 or more months after surgery, but our analysis suggests that between 10-15% of men will still require occasional or consistent pad use at 12-24 months. Evaluation of differences by surgical approach is problematic for many reasons, including differential follow-up and patient age; however, existing data do not suggest a substantial difference in the risk for acute or chronic incontinence by surgical approach.

Both short- and long-term erectile dysfunction (ED) are also significant concerns among men undergoing radical prostatectomy. Approximately 70% of men experience ED in the first three months following surgery. ED improves over the course of the year, but at 12 months following surgery approximately 35% of men who were potent prior to bilateral nerve-sparing surgery will still have ED. Rates of ED among men receiving unilateral or non nerve-sparing surgery are between 50-80%. Data are not sufficient to perform reliable comparisons of ED across different surgical approaches.

Table ES1. Reported harms of radical prostatectomy, by surgical approach.

Measure	ORP	LRP	RALP
Peri-Operative			
*Mortality**	Studies: 62 Pooled: 0.4% Range: 0.0-0.7%	Studies: 62 Pooled: 0.4% Range: 0.0-0.7%	Studies: 62 Pooled: 0.4% Range: 0.0-0.7%
Major Comp	Studies: 20 Pooled†: 4.7% (3.7%, 5.7%) Range: 2.1%-28.6%	Studies: 21 Pooled: 3.5% (2.4%, 4.6%) Range: 0.0%-36.6%	Studies: 12 Pooled: 2.5% (1.4%, 3.6%) Range: 0.0%-7.8%
Minor Comp	Studies: 20 Pooled: 9.5% (3.3%, 15.7%) Range: 0.3%-25.3%	Studies: 21 Pooled: 7.8% (6.1%, 9.4%) Range: 0.0%-23.5%	Studies: 12 Pooled: 5.3% (3.1%, 7.4%) Range: 0.5%-15.0%
Conversion	N/A	Studies: 22 Pooled: 0.4% (-0.1%, 0.9%) Range: 0.0%-3.7%	Studies: 14 Pooled: 0.1% (-0.1%, 0.3%) Range: 0.0%-2.3%
+ *Margins* *(pT2)* *(pT3)*	Studies: 14 Pooled: 16.8% (13.2%, 20.4%) Range: 6.0%-34.2% Pooled: 45.2% (35.5%, 55.0%) Range: 9.1%-84.6%	Studies: 25 Pooled: 13.9% (12.1%, 15.7%) Range: 4.7%-30.2%) Pooled: 39.3% (35.0%, 43.5%) Range: 16.7%-71.0%	Studies: 10 Pooled: 10.5% (8.1%, 12.8%) Range: 2.5%-20.0% Pooled: 35.4% (26.6%, 44.2%) Range: 13.0%-66.7%
Side Effects			
Urethral Stricture	Studies: 13 Pooled: 3.4% (2.5%, 4.4%) Range: 0.4%-19.8%	Studies: 16 Pooled: 0.3% (0.1%, 0.6%) Range: 0.0%-6.4%	Studies: 7 Pooled: 1.3% (0.3%, 2.4%) Range: 0.0%-2.3%
Urinary Incontinence	*Acute* Studies: 7 Pooled: 46.7% (25.1%, 68.2%) Range: 25.0%-90.2% *Long-term* Studies: 17 Pooled: 12.7% (9.6%, 15.8%) Range: 6.1%-39.5%	*Acute* Studies: 11 Pooled: 43.0% (23.9%, 62.0%) Range: 8.0%-89.8% *Long-term* Studies: 19 Pooled: 17.3% (13.7%, 20.8%) Range: 5.0%-52.2%	*Acute* Studies: 7 Pooled: 28.9% (13.6%, 44.2%) Range: 6.7%-65.2% *Long-term* Studies: 7 Pooled: 7.3% (2.9%, 11.7%) Range: 2.9%-16.0%
Erectile Dysfunction	*Acute* Studies: 5 Pooled: 76.8% (66.2%, 87.4%) Range: 62.5%-95.1% *Long-term* Studies: 16 Pooled: 45.3% (38.7%, 51.9%) Range: 24.0%-90.0%	*Acute* Studies: 10 Pooled: 71.4% (60.2%, 82.6%) Range: 57.7%-94.7% *Long-term* Studies: 17 Pooled: 41.4% (34.6%, 48.3%) Range: 21.9%-91.2%	*Acute* Studies: 3 Pooled: 59.1% (43.2%, 74.9%) Range: 46.9%-71.7% *Long-term* Studies: 7 Pooled: 26.3% (22.2%, 30.4%) Range: 18.8%-35.0%

*Meta-analysis of mortality data by surgical approach infeasible due to large number of zero values
NOTES: ORP: Open radical prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted radical prostatectomy
†From random-effects meta-analysis (with 95% confidence intervals)

Potential Harms: Active Surveillance

Biopsy-related Complications

Data are extremely limited on the incidence and severity of complications arising from initial or repeat prostate biopsy during active surveillance. In addition, measurement of the type and severity of complications varies greatly by study. Nevertheless, prostate biopsy appears to be a relatively safe procedure. The majority of complications reported are transient and self-limiting, such as pain, rectal bleeding, hematuria, and hematospermia.

Data from the largest of these studies, an examination of initial and repeat biopsy in over 1,000 men enrolled in a prospective study of prostate cancer detection (Djavan, 2001), indicated that the incidence of the two most serious complications requiring intervention, namely urosepsis and acute urinary retention, was 0.1% and 2.6% respectively.

Patient Anxiety

While the possibility exists that obstructive urinary symptoms and erectile dysfunction may worsen during active surveillance, data are available only from the Toronto cohort, where findings suggested a rate of symptomatic progression of approximately 3% at a median of 3.75 years of follow-up (Choo, 2004). Limited data on symptom progression are available from watchful waiting studies, but the evidence is not comparable due to the older age and advanced cancer characteristics of these cohorts.

Uncertainty regarding cancer progression while on active surveillance does have the potential to impact patient anxiety. While anxiety levels do appear to predict receipt of definitive treatment among men on surveillance programs, limited data from the active surveillance and watchful waiting literature suggest that overall anxiety levels do not differ between men who have selected these regimens and those who choose initial definitive treatment with radiation therapy or surgery.

Learning Curve: Radical Prostatectomy

There is a substantial learning curve for all forms of radical prostatectomy; cases performed by inexperienced surgeons tend to have higher rates of complications, side effects, disease recurrence, and need for subsequent treatment.

The impact of the learning curve can be observed across multiple measures of surgical outcomes. For example, the average rate of conversion from minimally-invasive to open prostatectomy due to failure of the minimally-invasive approach is less than 1%; however, rates as high as 14% have been observed among surgeons who are relatively inexperienced with the technique. Similarly, evidence from claims-based studies suggest that rates of salvage radiation or hormonal therapy after prostatectomy, treatments often indicative of positive surgical margins, are over 2 times greater among surgeons with a low volume of minimally-invasive surgeries vs. high-volume surgeons (Hu, JCO, 2008).

Given the strength of the data linking surgeon experience to broad ranges of complications and side effects, variability between surgeons and institutions is likely a more important

predictor of patient outcomes than any difference that might be due to the surgical approach selected. For example, if the ranges of side effects found in the ICER systematic review are assumed to arise solely from differences in surgical expertise, a surgeon performing at the 75th percentile among his or her peers would have a combined major complication rate of approximately 2-3%, with long-term rates of ED at 30-35% and incontinence at 5-7%. These complication and side effect rates would be significantly lower than those of surgeons operating at the 25th percentile, whose patients would suffer major complications at 10-12%, ED at 50-60%, and incontinence at 15-20%. Not all of the variation in published outcomes can be ascribed to surgical expertise, but the data do suggest that variation in surgical performance is a critical feature in any evaluation of the comparative effectiveness of radical prostatectomy to active surveillance or other interventions for localized prostate cancer.

Hospital Costs and Efficiency: Open vs. Robotic Prostatectomy

In the U.S., Medicare reimbursement for all 3 surgical approaches to prostatectomy is similar, with the only difference being a $500 higher payment for the CPT code associated with minimally-invasive approaches. However, costs to the hospital differ substantially, as acquisition, maintenance, and supply costs for laparoscopic guidance and robot systems add significantly to the costs of providing these services. For example, recent estimates of the cost of a robotic surgical system include acquisition costs of $1.6 million, annual maintenance costs of $100,000-$200,000 and disposables costs of $2,000-$3,000 per case (Lotan, 2004; Joseph, 2008; Quang, 2007). Minimally-invasive prostatectomy has been associated in the literature with reductions in the length of hospital stay of 2-3 days compared to open prostatectomy, but the use of clinical pathways in many institutions has also resulted in shortened length of stay and reduced transfusion requirements to levels that are indistinguishable by surgical approach (Farnham, 2006; Nelson, 2007). Published evidence indicates that operating-room time is longer with minimally-invasive surgery; findings from our systematic review indicated average operative time of approximately 3 hours for open prostatectomy, vs. 4-4.5 hours for minimally-invasive techniques. This is due to the technical complexity of minimally-invasive procedures; as with other operative outcomes, there is some evidence that operative times shorten as surgeons gain more experience with minimally-invasive techniques (Ficarra, 2009).

Analysis of Comparative Value

We used findings from our systematic review on clinical effectiveness to inform a primary cost-utility analysis of active surveillance and radical prostatectomy in 65-year-old men with localized prostate cancer. Due to the emphasis many clinicians place on age and life expectancy at the time of diagnosis, we also performed an analysis with a cohort of 55-year-old men, as well as multiple sensitivity analyses examining potential variations in relative differences in outcomes and costs between the various treatment strategies. Utilities (i.e., the value, between 0 and 1, placed on quality of life in a particular state of health) for patients with individual side effects or side-effect combinations were obtained from published literature. Costs of surveillance, surgery, complications, and side effects were based on national Medicare payment rates for relevant services; the costs of patient time

associated with these services were also estimated using national wage rates. Two alternative analyses were performed using actual third-party payer costs obtained from private health plans in the United States.

The "base case" economic model developed for this analysis was framed with the assumption that active surveillance and radical prostatectomy achieve comparable overall mortality rates in men with low-risk, localized prostate cancer. This assumption was based on the existing data on active surveillance which, through 5-7 years of follow-up, does not suggest any decrement in overall or cancer-specific survival for active surveillance compared to prostatectomy. However, because the existing data cannot exclude some chance of a survival benefit for prostatectomy in later years, an alternative scenario was created in which the prostate cancer-specific mortality of active surveillance patients is set at 2.5% higher than radical prostatectomy at 10 years (and persisting for the remainder of the patient's life). This survival advantage for prostatectomy reflects another assumption: that any possible survival advantage for prostatectomy over active surveillance will be, at most, approximately half of the absolute survival difference seen in earlier trials of watchful waiting, when patients were largely diagnosed clinically, as opposed to through PSA testing, and when the protocol did not involve close surveillance with the goal of initiating curative treatment for early biochemical or histological signs of progression (Bill-Axelson, 2005).

In the model, patients aged 65 or older starting on active surveillance who experience progression to intermediate-risk disease are assumed to receive intensity-modulated radiation therapy (IMRT) with short-term androgen deprivation therapy (ADT); patients over 65 who opt for definitive treatment for reasons other than grade progression receive IMRT alone. Radical prostatectomy was assumed as the definitive treatment of choice for all active surveillance patients if they are under age 65 at the time definitive treatment is begun.

Other key assumptions within the economic model are shown below in Table ES2 on the following page and are discussed more fully in the body of this review.

Table ES2. Major assumptions of the ICER economic model

ASSUMPTION	RATIONALE & SOURCE
• No men will die of prostate cancer within 6 months of diagnosis	Low prostate cancer specific mortality in low-risk patients -ICER Review
• All men who recur after treatment recur biochemically	Patients monitored closely by PSA after treatment -ICER Review
• Progression from recurrence to metastatic disease to death identical regardless of treatment	No proven disease-related benefit to one treatment over another -ICER Review
• Men on AS who receive treatment have = risk of CaP death as men treated initially	No studies with sufficient follow up to suggest mortality benefit or harm to AS -ICER Review
• Treatment after AS is RP if <65 or IMRT (w/ or w/o ADT) if ≥65	Mortality benefit to RP vs. WW limited to men <65 yo -Bill-Axelson, 2005
• No men treated with RP receive adjuvant/salvage XRT	<10% low-risk CaP have positive margins at RP -Louie-Johnsun, 2009; Griffin, 2007 Use of salvage XRT in men with low-risk disease <15% -Lu-Yao, 1996; Grossfeld, 1998

NOTES: AS: Active surveillance; RP: Radical prostatectomy; IMRT: Intensity-modulated radiation therapy; XRT: external beam radiation therapy; WW: Watchful waiting; CaP: Prostate cancer

Base Case Model Results

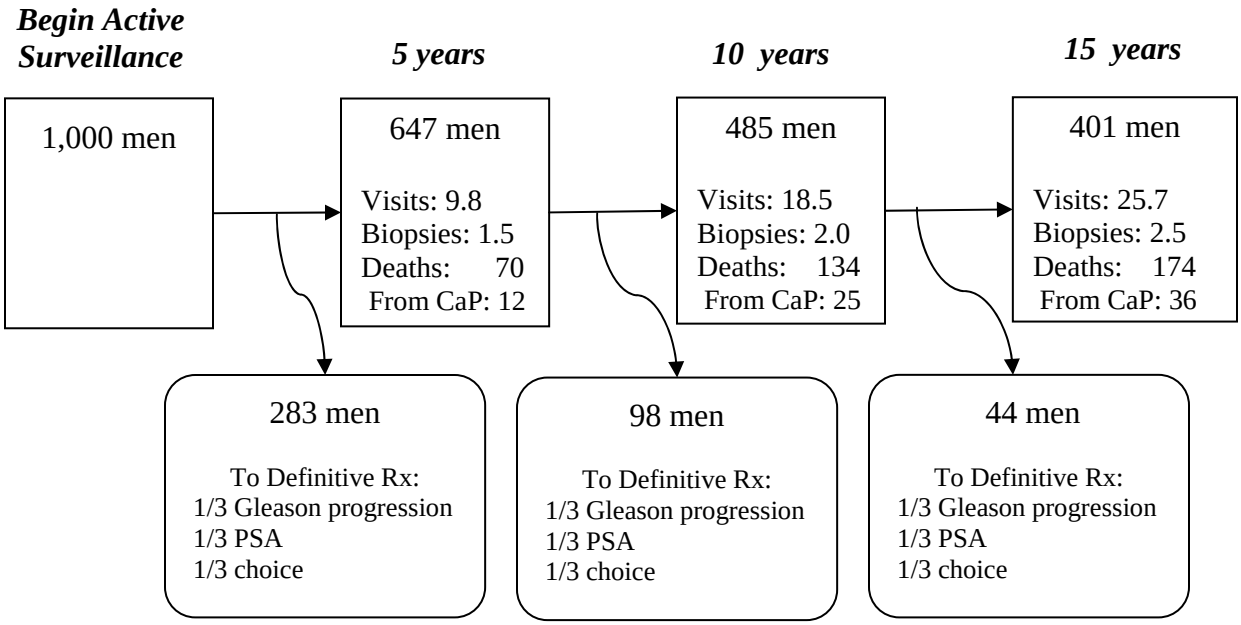
Clinical Outcomes

Under the assumption that active surveillance and prostatectomy confer equal survival, men at age 65 with low-risk prostate cancer have an additional life expectancy of approximately 16 years with either form of management. Complications and side effects reduce the final total of quality-adjusted life years.

A flowchart based on model results of the progression of visits, biopsies, and decisions to enter into definitive treatment for patients aged 65 beginning on active surveillance is displayed in Figure ES3 below. Among men on active surveillance, the likelihood of receiving definitive treatment is 28%, 45%, and 54% after 5, 10, and 15 years respectively, and 61% over a lifetime. Decisions to opt for definitive treatment are driven by approximately equal proportions of men with Gleason progression on surveillance biopsy,

increases in PSA doubling time or other PSA-related findings, and patient choice without objective findings of disease progression. By year 15, men on active surveillance will have had, on average, approximately 26 visits and 2.5 biopsies. These numbers reflect an average that includes the experience of the entire cohort; after adjustment for attrition due to mortality, more than 50% of patients originally on surveillance will have moved into definitive treatment by 15 years.

Figure ES3. Schematic flowchart of 5, 10- , and 15-year cumulative visits, biopsies, all-cause and disease-specific mortality, and treatment decisions of among a cohort of 65 year-old men beginning active surveillance for low-risk, clinically-localized prostate cancer. Data derived from ICER decision-analytic model.



For men treated with radical prostatectomy, the model results showed a risk of peri-operative death of 0.4%, reflecting the parameter input from the ICER systematic review. The risk of developing new ED following radical prostatectomy is 31%; the risk of urinary incontinence is 9%. These estimates are lower than those produced by the ICER review, as they reflect incidence over and above the underlying risk of these conditions due to age and comorbidity. Inclusion of higher estimates would likely magnify the quality-of-life effects already observed with active surveillance (see below). Among the men on active surveillance who ultimately receive IMRT, there are small increased risks for ED, incontinence, and proctitis. A table summarizing the key rates for both short-term and long-term side effects for radical prostatectomy and active surveillance in men aged 65 and 55 is shown in Table ES3 on the following page.

Table ES3. Comparative Value Evidence Table (CVET): Lifetime clinical outcomes for 65- and 55-year-old men with clinically-localized, low-risk prostate cancer.

Outcome (%, except where noted)	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
Age 65 Years			
Prog. to treatment	61.1%	100.0%	38.9%
Peri-operative death	N/A	0.4%	N/A
Minor complications	0.2%	9.5%	9.3%
Major complications	0.0%	4.8%	4.8%
Treatment-related SE			
Incontinence	3.6%	8.6%	5.0%
ED	5.3%	30.7%	25.4%
GI (from IMRT)	2.7%	N/A	N/A
Prostate cancer death	9.0%	9.0%	0.0%
Life years (mean)	16.0	16.0	0.0
QALYs (mean)	8.97	7.82	(1.2)
Age 55 Years			
Prog. to treatment*	72.1%	100.0%	28.0%
Peri-operative death	0.1%	0.4%	0.3%
Minor complications	2.8%	9.5%	6.7%
Major complications	1.1%	4.8%	3.7%
Treatment-related SE			
Incontinence	6.5%	10.4%	4.0%
ED	13.7%	35.7%	22.0%
GI (from IMRT)	2.0%	N/A	N/A
Prostate cancer death	16.0%	16.0%	0.0%
Life years (mean)	22.0	22.0	0.0
QALYs (mean)	11.54	10.33	(1.2)

NOTES: SE: side effects; ED: erectile dysfunction; GI: gastrointestinal; IMRT: intensity-modulated radiation therapy; QALYs: quality-adjusted life years
*In this younger-age population, 30% of treated patients receive radical prostatectomy

Costs

The initial cost of treatment with radical prostatectomy was $13,553, a figure that represents a Medicare payment rate based on the estimated proportion of cases that are uncomplicated (86%), and that are associated with minor (9.5%) or major (4.8%) complications. Active surveillance is less expensive than radical prostatectomy in the early years following diagnosis, but the results of pathway cost analyses provided by the model suggest that over a lifetime the average costs for active surveillance in 65-year-old men are estimated to be approximately $2,000 higher than for radical prostatectomy ($30,422 vs. $28,348). A breakdown of costs for each pathway is shown in Table ES4 on the following page. As can be seen, the similarity in total lifetime costs between active surveillance and radical prostatectomy is largely driven by the costs of definitive treatment with IMRT or radical prostatectomy ultimately received by over 60% of patients who start active surveillance. As

shown in alternative analyses in the body of the review, active surveillance becomes less costly overall compared to radical prostatectomy if less-expensive brachytherapy is used for definitive treatment in lieu of IMRT.

Table ES4. Comparative Value Evidence Table (CVET): Average lifetime costs for 65- and 55-year-old men with clinically-localized, low-risk prostate cancer.

Cost ($)	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
Age 65 Years			
Year 1 treatment	4,228	13,553	9,325
Services	4,809	4,624	(185)
Visits	3,382	4,624	1,241
Biopsies	1,427	N/A	N/A
Definitive Rx (IMRT)	14,327	N/A	N/A
Patient time	8,156	6,150	(2,006)
Short-term SE	270	1,477	1,207
Long-term SE	589	786	196
TOTAL			
Undiscounted	38,542	33,589	(4,953)
Discounted	30,422	28,348	(2,074)
Age 55 Years			
Year 1 treatment	3,796	14,496	10,700
Services	5,530	5,213	(317)
Visits	3,848	5,213	1,365
Biopsies	1,682	N/A	N/A
Definitive Rx (IMRT/RP)	13,986	N/A	N/A
Patient time	12,226	9,132	(3,094)
Short-term SE	647	1,468	821
Long-term SE	545	718	173
TOTAL			
Undiscounted	46,690	40,699	(5,991)
Discounted	33,642	31,440	(2,202)

NOTES: SE: side effects; IMRT: intensity-modulated radiation therapy; RP: radical prostatectomy
Component costs presented for illustrative purposes, and will not sum to discounted total

Incremental Cost-effectiveness

As shown on the following page in Table ES5 the model results demonstrated that the avoidance or delay of surgery-related harms afforded by active surveillance translates into a substantial net benefit in quality of life, as this strategy produces an additional 1.15 quality-adjusted years of life compared to immediate radical prostatectomy. Findings were similar for 55-year-old men as well, and for simplicity only the results for 65-year-old men are shown in Table ES5.

Active surveillance was thus found to have higher clinical effectiveness, as measured in quality-adjusted life years, than radical prostatectomy, at an additional lifetime cost of $2,074. The formal incremental cost-effectiveness ratio of active surveillance is $1,803 per QALY gained. For 55 year-old men, active surveillance remained substantially more effective, and cost differences were similar (incremental cost-effectiveness ratio: $1,820 per QALY gained).

Table ES5. Lifetime quality-adjusted life expectancy and costs for 65-year-old men with clinically-localized, low-risk prostate cancer, by treatment type.

Strategy	QALYs	Incremental QALYs	Cost	Incremental Cost	Cost/QALY
Open RP	7.82	Reference	$28,348	reference	
AS	8.97	1.15	$30,422	$2,074	$1,803

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

The findings noted above include estimates for reductions in quality-of-life from having undergone radical prostatectomy or remaining on active surveillance, even if no complications or side effects are encountered. When quality-of-life reductions were limited to those arising from side effects, complications, and symptoms only, QALY differences were not as pronounced (10.75 vs. 10.09 for active surveillance and radical prostatectomy respectively), resulting in approximately 8 additional months of quality-adjusted life expectancy for patients in active surveillance at an incremental cost-effectiveness ratio of $3,142 per QALY gained.

Under the alternative model framework in which there is an assumed absolute prostate cancer-specific mortality difference of 2.5% at 10 years in favor of radical prostatectomy, the model results indicated that active surveillance still produced substantially more QALYs on a population basis than prostatectomy, with an additional 0.99 QALYs per patient.

Uncertainty in the base-case model results was assessed through a probabilistic sensitivity analysis. Average costs and QALYs were determined from 100,000 individual-level runs of the model with a unique set of draws from distributions around costs, utilities, and probabilities. Average QALYs for radical prostatectomy were lower than the *lowest* estimates for active surveillance in approximately 30% of the runs; QALYs were higher than the *highest* estimates in another 16%. Formal results of the probabilistic sensitivity analysis are described and discussed in the body of this review.

Alternative Scenarios and Sensitivity Analyses

The body of the report includes the results of several other alternative scenarios, along with the results of numerous one-way sensitivity analyses. Among the key findings was that if the definitive treatment received by patients beginning active surveillance is changed from IMRT to brachytherapy, the active surveillance pathway retains its higher QALY

production but becomes approximately $4,000 less expensive than radical prostatectomy. In all alternative scenarios and sensitivity analyses, active surveillance generated higher QALYs than radical prostatectomy. And, even in scenarios in which costs were increased for active surveillance, such as when representative private payer costs were examined, the absolute lifetime cost difference between active surveillance and prostatectomy remained small, leading to cost savings for active surveillance or incremental cost-effectiveness ratios for active surveillance well below $10,000 per QALY.

Open radical prostatectomy vs. robot-assisted laparoscopic prostatectomy
The findings of the systematic review, and assumptions about costs in the economic model, meant that our base case analysis was not constructed to compare different surgical approaches for radical prostatectomy. We did perform an alternative analysis assuming "maximal" effectiveness for robotic vs. open prostatectomy--in other words, if all nominal differences of the pooled results in the systematic review were considered true differences. Using these estimates, an 8-week gain in QALYs would be realized for robot-assisted surgery from reduced rates of complications and side effects. In addition, lifetime cost savings of approximately $1,700 would be obtained with robotic prostatectomy. It is important to note that the cost estimates used in this analysis are based on Medicare payments for these surgical techniques, and do not take into account the substantial differences in acquisition cost, maintenance, and supplies between the surgical approaches.

Findings on Economic Impact
A summary of the economic impact of active surveillance and radical prostatectomy can be found in Table ES6 on the following page; for the purposes of simplicity, results are presented only for 65 year-old men. Along with the incremental cost-effectiveness ratio, the Table provides evidence on estimated budget impact for a cohort of 1,000 prostate cancer patients over a two-year period. In the first two-year period following diagnosis, a strategy of active surveillance would save nearly $8 million dollars under current Medicare reimbursement rates; a savings of over $13 million dollars would be expected under one of the private payer actual cost scenarios evaluated.

Table ES6 on the following page also presents a hypothetical "fixed budget tradeoff" suggesting potential annual incremental health system spending for doctors and nurses that could be afforded with the potential cost savings achievable by shifting care for 1,000 patients from radical prostatectomy to active surveillance. These figures ignore the downstream costs of definitive treatment for many patients started on active surveillance, and are presented primarily in the spirit of exploring different frameworks through which evidence on value can be presented to decision-makers.

Table ES6. Comparative Value Evidence Table (CVET): Additional findings on value for 65-year-old men with clinically-localized, low-risk prostate cancer.

Measure	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
1. Service Impact			
Visits	35.9	37.2	1.3
Biopsies	2.8	0.0	(2.8)
Pathway Total	38.8	37.2	(1.6)
2. Cost per Life-Year Saved	N/A		(equivalent survival)
3. Cost per QALY Gained	$1,803		
SA 1: 55 yo men	$1,820		
SA 2: Private-pay estimate A	$3,434		
4. Budget Impact (per 1,000, 2 years)	$5,809,000	$13,591,000	$7,782,000
Using Private-Pay Estimate A	$8,721,000	$22,028,000	$13,307,000
5. Fixed Budget Tradeoffs (Annual)		38.9	*Nurse FTEs @ $100K each*
		19.5	*MD FTEs @ $200K each*
		2.4	*Robotic Surgical System @ $1.6M each*

NOTES: QALY: Quality-adjusted life year; FTE: Full-time equivalent

ICER Evidence Review Group Deliberation

The ICER Evidence Review Group deliberation (see section starting on page 32 for membership and details) focused on many important issues regarding the evidence provided by the ICER review. Major points of discussion are shown in the numbered points below.

1) *Lack of comparative data on overall and disease-specific survival for active surveillance and radical prostatectomy is not a reason to assume NO mortality differences.* While it was recognized that candidate populations for active surveillance and watchful waiting differ in many important respects, including level of risk at diagnosis and intensity of monitoring, several clinicians suggested that the survival data currently available for AS are too premature to compare this approach to definitive treatment. The lack of longer-term data was viewed as particularly relevant for the level of certainty regarding the clinical effectiveness of active surveillance for patients under age 65. Others, however, felt confident that active surveillance's effectiveness would be no worse, and likely better, than watchful waiting, which appears to produce survival equivalent to surgery in older patients. Nevertheless, to explore this uncertainty, ICER created an alternative scenario for the model that assumes a disease-specific survival benefit for radical prostatectomy equivalent to approximately one-half that observed in the SPCG-4 trial (i.e., absolute difference of 2.5% at 10 years and persisting for life).

2) *Variability in surgical practice should receive greater emphasis in the report.* The report has been revised to further highlight (a) the lack of training and competency standards for

newer surgical approaches; (b) variability in outcomes by surgeon and institution; and (c) the impact of the learning curve on all potential surgical outcomes. An additional sensitivity analysis has also been conducted to explore the impact of complication and side-effect rates at the 25th vs. 75th percentile of the observed distribution.

3) *The review and economic model should include the harms of repeat biopsy among patients on active surveillance.* Consistent with the approach taken for complications and side effects of surgery, focus was placed on those outcomes that necessitated significant intervention—namely, cases of urosepsis and acute urinary retention. The costs and utility decrements associated with these complications have been added to the model.

4) *The assumption that active surveillance maintains a constant monitoring intensity over time is incorrect.* Most clinicians in the group felt that physician visits would certainly decrease in frequency as patients remain on surveillance. The model has been adjusted to decrease visit frequency from quarterly to semi-annually after one year.

5) *Any tabular display of nominal differences in outcomes by surgical approach carries the risk of these differences being perceived as "real", despite the presence of cautionary language in the text.* Presentation of these findings has been modified to include graphic displays of selected outcomes to illustrate the wide range and significant overlap observed. The presentation of nominal reported differences has been preserved; this does not imply superiority of any one technique over another, but was done to meet the stated goal of exploring all relevant outcomes of each surgical approach independently.

6) *The disutility estimates for health states defined by the absence of complications or side effects were called into question.* Many on the ERG felt that the original estimates of quality-of-life impact from simply having undergone radical prostatectomy or remaining on surveillance were too severe and imbalanced between management options. Utility estimates have been revised to use the same methodologic approach (i.e., time tradeoff) for both radical prostatectomy and active surveillance; in addition, alternative analyses have been conducted in which reductions in quality-of-life are estimated for side effects, complications, and symptoms alone.

7) *It was noted that presented data on differences in hospital length of stay and operative time between surgical approaches may be based on historical data for open surgery, and that improvements in clinical pathways have minimized differences between surgical approaches.* Further discussion of this issue has been added to the report.

8) *The current analysis has not considered the effects of undergrading of cancer severity and risk on prostate biopsy.*
The draft report has previously noted the phenomenon of Gleason progression on re-biopsy, with reported rates of 30-40% over time; to date, however, the long-term effects of such undergrading are unknown. In addition, several other studies have observed rates of *benign* pathology of 25-60% at re-biopsy, with future consequences that are again unknown. It is possible the improvements in biopsy techniques may reduce the

occurrence of these phenomena. In any event, sensitivity analyses were conducted in this appraisal with an assumed difference in cancer-specific mortality, with findings that did not materially differ from those of primary analyses.

Discussion of ICER Integrated Evidence Ratings

Background on the ICER rating methodology, including descriptions of the rating categories for comparative clinical effectiveness and comparative value, can be found on page 35 of this Executive Summary.

The discussions of the assignment of ICER ratings for comparative clinical effectiveness and for comparative value were conducted separately for comparisons of active surveillance to open radical prostatectomy and for robotic vs. open prostatectomy respectively. Surgery's status as the "reference" category for these ratings in no way implies that ICER considers it a more proven technology or the standard of care. Rather, the rating system is designed to make two-way comparisons, and it is standard practice to make the most frequently-employed or longest-standing therapy the "reference" intervention.

Seven of 15 participants felt that the evidence was sufficient to rate active surveillance's clinical effectiveness as at least "Comparable" to open prostatectomy, while 4 participants felt that the evidence base, while promising, was still too thin to label active surveillance at a level higher than "Unproven with Potential". Of the remaining participants, 2 were undecided between "U" and "C", while 2 others considered the evidence "Insufficient" to make a determination. With regard to comparative value, 6/13 and 4/13 participants rated active surveillance as definitively "High" and "Reasonable/Comparable" respectively, while the remainder were undecided between these two levels (note: Insufficient ratings do not carry a value designation).

Responses were more varied when robotic vs. open prostatectomy was the comparison of interest. Four of 15 participants rated the evidence on clinical effectiveness for robotic surgery to be "Insufficient", 3 rated the procedure as "Unproven with Potential", and 2 each rated the procedure as "Comparable" and "Incremental" respectively. The remainder of participants rated robotic surgery along the continuum between "Insufficient" and "Incremental". Based on a payer perspective that included patient time costs, the majority of participants rated robotic surgery's comparative value as "Reasonable/Comparable", although one participant allowed for a possible "High" designation, and another allowed for the possibility of a "Low" value designation.

The input of the ERG is advisory to ICER; the ultimate rating is made after independent discussion and reflection on the entirety of the review as well as associated meetings. The final ICER ratings are shown on the following pages. Further description of ICER's rationale for the ratings is provided after the figures.

ICER Integrated Evidence Rating™: Active Surveillance vs. Open Radical Prostatectomy for Clinically-Localized, Low-Risk Prostate Cancer

The Comparative Clinical Effectiveness of active surveillance among patients with clinically-localized, low-risk prostate cancer is rated as:

- ***C --- Comparable for patients aged 65 years*, based on similar survival in comparative studies of watchful waiting and radical prostatectomy and early data from active surveillance series showing similar or better outcomes in comparison to watchful waiting**
- ***U --- Unproven with Potential for patients aged 55 years*, based on differences in survival from the watchful waiting/radical prostatectomy studies and early data from active surveillance series showing similar outcomes to radical prostatectomy series**

The Comparative Value of active surveillance among patients with clinically-localized, low-risk prostate cancer is rated as:

- **a --- High**

The Integrated Evidence Ratings:

Ca for patients aged 65 years

Ua for patients aged 55 years

Comparative Clinical Effectiveness	a High	b Reasonable/Comp	c Low
Superior: A	Aa	Ab	Ac
Incremental: B	Ba	Bb	Bc
Comparable: C	AS=Ca (65 y)	Cb	Cc
Inferior: D	Da	Db	Dc
Unproven/Potential: U/P	AS=Ua (55 y)	Ub	Uc
Insufficient: I	I	I	I

Comparative Value

ICER Integrated Evidence Rating™: Robot-Assisted vs. Open Radical Prostatectomy for Clinically-Localized, Low-Risk Prostate Cancer

The Comparative Clinical Effectiveness of robot-assisted radical prostatectomy among patients with clinically-localized, low-risk prostate cancer is rated as:

- **U --- Unproven with Potential**

The Comparative Value of active surveillance among patients with clinically-localized, low-risk prostate cancer is rated as:

- **b --- Reasonable/Comparable***

The Integrated Evidence Rating = Ub

*** Based on current 3rd party reimbursement policy that does not materially distinguish between surgical approaches**

Comparative Clinical Effectiveness	a	b	c
Superior: A	Aa	Ab	Ac
Incremental: B	Ba	Bb	Bc
Comparable: C	Ca	Cb	Cc
Inferior: D	Da	Db	Dc
Unproven/Potential: U/P	Ua	RALP=Ub	Uc
Insufficient: I	I	I	I
	High	Reasonable/Comp	Low
		Comparative Value	

Description of Rationale for ICER Integrated Evidence Ratings

ICER opted to create two ratings in comparing active surveillance and radical prostatectomy: one for "younger" patients (aged 55), and one for "older" patients (aged 65). These are very rough categories meant to capture and reflect the different level of certainty ICER felt the evidence could support for different age cohorts given the relatively short-term data on active surveillance. The rating for patients aged 65 reflects a high level of certainty that the net health benefit of active surveillance is comparable to that provided by radical prostatectomy, as well as the possibility that active surveillance may in fact provide an incremental benefit once more mature data become available. The data from the randomized trial of watchful waiting did not show any significant difference in overall or prostate cancer-specific mortality for men over age 65, and the 5-7 year data available on active surveillance, combined with the "earlier" identification of prostate cancer through PSA testing, creates a persuasive argument that the comparative clinical effectiveness of active surveillance for older, low-risk, localized prostate cancer patients is very comparable to that of radical prostatectomy. In fact, these data would likely have resulted in a "comparable" rating even if the comparison was between *watchful waiting* and radical prostatectomy. Although the model suggested higher average QALYs for active surveillance, which might support a judgment of "incremental" comparative clinical effectiveness, ICER judged that the relative variation in many factors, including surgical expertise and individual patient utilities for various side effects, made "comparable" the most reasonable designation for comparative clinical effectiveness.

The rating for patients aged 55 reflects the lower, "moderate" certainty that ICER judged the evidence supported for a designation of a comparable or incrementally better net health benefit for active surveillance. The ICER rating reflects our judgment that, even though the data are limited, there is reasonable certainty that modern protocols for active surveillance produce mortality outcomes not substantially inferior to radical prostatectomy, while maintaining the quality-of-life advantages of having many patients never require definitive treatment.

The comparative value rating for active surveillance vs. radical prostatectomy reflects consideration of the model results showing low incremental cost-effectiveness ratios, significant near-term cost savings for patients opting for active surveillance, and the fact that under several alternative reimbursement and treatment scenarios, active surveillance appears to be both more effective and cost-saving. In particular, input from the ERG made it clear that many patients begun on active surveillance, even if aged 65 or older, would be treated with prostatectomy or brachytherapy instead of IMRT should they desire or require definitive treatment. The selection of less expensive definitive treatment is a key variable in the modeling of active surveillance, and one that ICER felt supported an overall judgment of a comparative value rating of "high value."

The ratings for the comparison of open and robot-assisted radical prostatectomy are based on the consideration that even though the data on outcomes of patients treated with the robot-assisted technique are extremely limited, the technique is a variation on radical

prostatectomy and not an entirely new modality of treatment; accordingly, ICER felt there was "moderate" certainty that the comparative clinical effectiveness of robot-assisted prostatectomy is at least comparable, and perhaps "incremental" to the traditional open procedure. Given that third-party payment for robot-assisted prostatectomy is currently set at essentially the same rate as that for open radical prostatectomy, it seemed most logical to rate the comparative value "reasonable/comparable." It is possible that the high acquisition cost and the increased marginal costs of robot-assisted surgery will be factored into reimbursements in the future; there is also the countervailing argument that, at least in some institutions, robot-assisted prostatectomy can aid progress toward a lower length of hospital stay. How these various costs play out for different stakeholders in the health care system is difficult to estimate, reinforcing our judgment that a suitable designation for comparative value at this time is "reasonable/comparable."

Sample Physician-Patient Script

Discussing the evidence on potential risks and benefits of active surveillance and immediate treatment options is a central element of shared decision-making between patients, clinicians, and families. ICER offers the script below as an example of how clinicians could initiate a conversation with a 65 year-old male with prostate cancer that would foster consideration of the findings of this evidence review. Conveying this amount of information in one conversation may not be practicable or appropriate for many patients; nor is the text intended to be prescriptive regarding any one management option. The intent is to foster discussion, and to suggest only one of many styles through which clinicians can empower their patients to share in the consideration of the evidence on reasonable clinical alternatives and to help them choose the option that will reflect their broader best interests.

"I know you've looked at your options, including surgery, radiation treatment, or what is called "active surveillance" for your prostate cancer. We've talked a little bit about these options already. Today let's go further. First, I'd like you to know that evidence reviews and national expert groups have concluded that – for men like you with low-risk prostate cancer – there is no evidence that any of these approaches is any better than the others at keeping you healthy and extending your life. Active surveillance is, therefore, a very reasonable option for you to consider, as it would allow you to delay, for many years in some circumstances, the discomfort and side effects that may occur with treatment. On the other, hand, some men do opt for treatment right away, so let's talk about the radiation options and surgery. We have had more years of experience with brachytherapy; IMRT has been in use for about 8 years; and proton beam therapy is fairly new for prostate cancer so we have far less data on its longer-term outcomes. Similarly, there is more evidence on traditional "open" prostatectomy, and less on laparoscopic and robotic approaches. These options have potential advantages and disadvantages with regard to possible side effects of treatment, which you should take some time thinking about. In addition, all of these options require differing amounts of procedure and monitoring time as well as numbers of visits to the doctor. And, some are more expensive than others, both for your own out-of-pocket costs and for your health plan. Before we run through some of these pros and cons together, let me stop here to see if you have any questions or if you've heard anything about any of these options that you'd like to discuss…."

Evidence Review Group Members
The Evidence Review Group (ERG) is an independent group brought together by ICER and composed of academic experts, patients, clinicians, epidemiologists, ethicists, and medical policy representatives of stakeholder groups including health plans and manufacturers.

The purpose of the ERG is to guide and help interpret the entire appraisal process. Members of the ERG are first convened to function as a "scoping committee" for the appraisal. During this phase the key questions for the appraisal are outlined, including elements such as the appropriate comparator technologies, patient outcomes of interest, patient subpopulations for which clinical and cost-effectiveness may vary systematically, time horizon for outcomes, and key aspects of the existing data that must be taken into account during the appraisal. The ERG may be divided into sub-committees that advise the ICER appraisal team at the mid-point of the appraisal on the early findings and challenges encountered. All of the ERG members listed below participated in scoping and/or mid-cycle activities, but not all were able to participate in the final ERG meeting.

At the final ERG meeting, members are asked to declare any interests in the technology or its comparator(s), or other potential influences on their expertise (listed below). The ERG meeting allows for in-depth deliberation on the findings of the ICER appraisal document and provides an opportunity for comment on the determination of the ICER integrated evidence rating. Although the ERG helps guide the final determination of the ICER Integrated Evidence Rating™, the final rating is ultimately a judgment made by ICER, and individual members of the ERG should not be viewed in any way as having endorsed this appraisal.

ERG Participant Name and Affiliation	Potential Influences on Expertise
Peter Albertsen, MD, MS Professor of Surgery, Chief and Program Director, Division of Urology University of Connecticut Health Center Director, Connecticut Institute for Clinical and Transitional Science	Member of Blue Cross/Blue Shield Technology Assessment Panel; member of steering committee for ProtecT trial (active surveillance vs. immediate surgery or radiation)
John Ayanian, MD, MPP Professor of Medicine & Health Care Policy Harvard Medical School & Brigham & Women's Hospital Professor of Health Policy & Management Harvard School of Public Health	None
Peter Carroll, MD Professor and Chair, Department of Urology Ken and Donna Derr-Chevron Distinguished Professor University of California, San Francisco	None

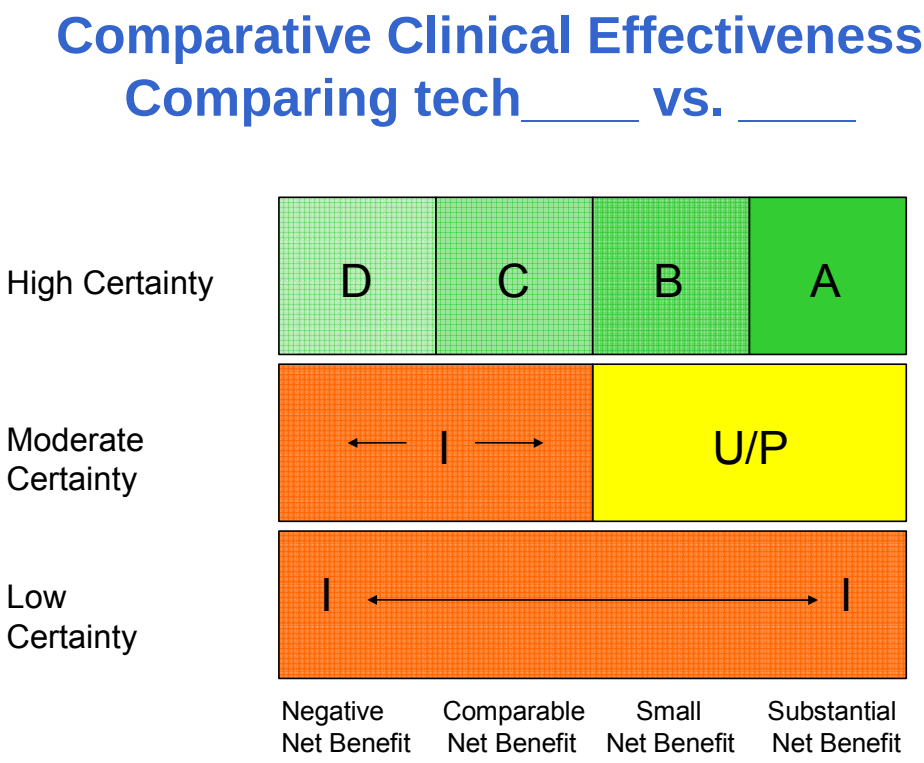
Richard Choo, MD, FRCPC, FACR Associate Professor of Radiation Oncology Mayo Clinic College of Medicine	None
Myriam Curet, MD, FACS Professor, Department of Surgery Stanford University Chief Medical Officer, Intuitive Surgical	Chief Medical Officer of Intuitive Surgical
Michele DiPalo Director, Health Services Evaluation Blue Cross & Blue Shield of Massachusetts	Employed by payer; involved in evaluation of new/emerging technology
Ted Ganiats, MD Chair, Department of Family & Preventive Medicine University of California at San Diego School of Medicine Executive Director, UCSD Health Services Research Center	No financial conflicts
G. Scott Gazelle, MD, MPH, PhD Director, Institute for Technology Assessment, Massachusetts General Hospital Professor of Radiology, Harvard Medical School Professor of Health Policy & Management, Harvard School of Public Health	None
Marthe Gold, MD Professor & Chair, Community Health and Social Medicine City College of New York	No financial conflicts, interested in strategies to trim healthcare budgets
Lou Hochheiser, MD Medical Director, Clinical Policy Development Humana, Inc.	Employed by payer; involved in clinical policy development
Jim C. Hu, MD, MPH Assistant Professor of Surgery, Harvard Medical School Director, Minimally Invasive Urologic Oncology Brigham & Women's Hospital	Perform open and robot-assisted prostatectomy
Phil Kantoff, MD Professor of Medicine Harvard Medical School Dana-Farber Cancer Institute	None

Terry Lindblom, MBA, PA-C Patient/Consumer Representative	Prostate cancer survivor
David Most, PhD Patient/Consumer Representative	Prostate cancer survivor
Lee Newcomer, MD Senior Vice President, Oncology UnitedHealthcare	Employed by payer
Catherine Tak Piech, MBA Vice President, Health Economics & Outcomes Research Centocor Ortho Biotech Services, LLC	Shareholder of Johnson & Johnson, which markets materials for minimally-invasive surgery through its Ethicon Endo-Surgery division
Alan B. Rosenberg, MD Vice President, Medical Policy, Technology Assessment, and Credentialing Programs Wellpoint, Inc.	Employed by payer, involved in coverage decisions; member, AHRQ Effective Health Care Stakeholder Group
Martin G. Sanda, MD Associate Professor of Surgery Harvard Medical School Beth Israel Deaconess Medical Center	Financial support from Beckman, Lilly, Amgen; involved in Phase II clinical trial of CyberKnife®
Ian Thompson, MD Professor and Chair, Department of Urology University of Texas HSC at San Antonio	Chair of AUA prostate cancer guideline committee; perform active surveillance and surgery; consultant to Veridex, a Johnson & Johnson company developing a biomarker for prostate cancer
Sean Tunis, MD, MSc Founding Director Center for Medical Technology Policy	No financial conflicts
David Veroff, PhD Vice President, Evaluation Services Health Dialog	Employed by patient information company

Methodology: ICER Integrated Evidence Rating™

Comparative Clinical Effectiveness

The ICER Integrated Evidence Rating™ combines a rating for comparative clinical effectiveness and a rating for comparative value. The clinical effectiveness rating arises from a joint judgment of the level of certainty provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



A = "Superior" [High certainty of a moderate-large net health benefit]
B = "Incremental" [High certainty of a small net health benefit]
C = "Comparable" [High certainty of a comparable net health benefit]
D = "Inferior" [High certainty of an inferior net health benefit]
U/P = "Unproven with Potential " [Moderate certainty of a small or moderate-large net health benefit]
This category is meant to reflect technologies whose evidence provides:

1) High certainty of *at least* comparable net health benefit
2) Moderate certainty suggesting a small or moderate-large net health benefit

I = "Insufficient" The evidence does not provide high certainty that the net health benefit of the technology is at least comparable to that provided by the comparator(s).

Certainty

The vertical axis of the matrix is labeled as a degree of certainty with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of certainty thus is linked to but is not synonymous with the overall validity, consistency, and directness of the body of evidence available for the assessment. ICER establishes its rating of level of certainty after deliberation by the Evidence Review Group, and throughout ICER follows closely the considerations of evidentiary strength suggested by the Effective Health Care program of the Agency for Health Research and Quality (AHRQ) (www.effectivehealthcare.org) and the GRADE working group (www.gradeworkinggroup.org).

High Certainty:

An assessment of the evidence provides high certainty in the relative magnitude of the net health benefit of the technology compared to its comparator(s).

Moderate Certainty:

There is moderate certainty in the assessment of the net health benefit of the technology. Moderate certainty implies that the evidence is limited in one or more ways so that it is difficult to estimate the net health benefit with precision. ICER's approach considers two qualitatively different types of moderate certainty. First, there may be limited certainty in the magnitude of any net health benefit, but there is high certainty that the technology is *at least* as effective as its comparator(s). The second kind of moderate certainty applies to those technologies whose evidence may suggest comparable or inferior net health benefit and for which there is not high certainty that the technology is at least comparable. These two different situations related to "moderate certainty" are reflected in the matrix by the different labels of "Unproven with Potential" and "Insufficient."

Limitations to evidence should be explicitly categorized and discussed. Often the quality and consistency varies between the evidence available on benefits and that on harms. We follow the GRADE and AHRQ approaches in highlighting key types of limitations to evidence, including:

a. Internal validity
    i. Study design
    ii. Study quality
b. Generalizability of patients (directness of patients)
c. Generalizability of intervention (directness of intervention)
d. Indirect comparisons across trials (directness of comparison)
e. Surrogate outcomes only (directness of outcomes)
f. Lack of longer-term outcomes (directness of outcomes)
g. Conflicting results within body of evidence (consistency)

Low Certainty:
There is low certainty in the assessment of net health benefit and the evidence is insufficient to determine whether the technology provides an inferior, comparable, or better net health benefit.

Net Health Benefit
The horizontal axis of the comparative clinical effectiveness matrix is "net health benefit." This term is defined as the balance between benefits and harms, and can either be judged on the basis of an empiric weighing of harms and benefits through a common metric (e.g., Quality Adjusted Life-Years, or "QALYs"), or through more qualitative, implicit weightings of harms and benefits identified in the ICER appraisal. Either approach should seek to make the weightings as explicit as possible in order to enhance the transparency of the ultimate judgment of the magnitude of net health benefit.

Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, two blood pressure medications may both act to control high blood pressure and may have the same profile of toxicities such as dizziness, impotence, or edema. In such cases a comparison of benefits and harms is relatively straightforward. However, a second situation in comparative effectiveness is much more common: two interventions present a set of trade-offs between overlapping but different benefits and harms. An example of this second situation is the comparison of net health benefit between medical treatment and angioplasty for chronic stable angina. Possible benefits on which these interventions may vary include improved mortality, improved functional capacity, and less chest pain; in addition, both acute and late potential harms differ between these interventions. It is possible that one intervention may be superior in certain benefits (e.g. survival) while also presenting greater risks for particular harms (e.g. drug toxicities). Thus the judgment of "net" health benefit of one intervention vs. another often requires the qualitative or quantitative comparison of different types of health outcomes.

Since net health benefit may be sensitive to individual patient clinical characteristics or preferences there is a natural tension between the clinical decision-making for an individual and an assessment of the evidence for comparative clinical effectiveness at a population level. ICER approaches this problem by seeking, through the guidance of its scoping committee, to identify a priori key patient subpopulations that may have distinctly different net health benefits with alternative interventions. In addition, the ICER appraisal will also seek to use decision analytic modeling to identify patient groups of particular clinical characteristics and/or utilities which would lead them to have a distinctly different rating of comparative clinical effectiveness.

The exact boundary between small and moderate-large net benefit is subjective and ICER does not have a quantitative threshold. The rating judgment between these two categories is guided by the deliberation of the Evidence Review Group.

Comparative Value

There are three categories of value: high, reasonable or comparable, and low. The ICER rating for comparative value arises from a judgment that is based on multiple considerations. ICER does not employ a single measure of cost-effectiveness for assignment of comparative value, nor does it rely on a formal threshold for determination of the level of value. Instead, comparative value is informed by multiple measures of potential economic impact, including:

- Impact on service use (e.g., tests, hospitalizations)
- Cost to reduce adverse outcomes (e.g., cost per hospitalization averted)
- Cost to achieve clinical success (e.g., cost per curative outcome)
- Cost per life year gained
- Cost per quality-adjusted life year (QALY) gained
- Budget impact per 1,000 diseased individuals
- System issues (e.g., manpower tradeoffs to invest in new technology)

The advantages for evaluating the full list of economic measures are twofold. First, the importance of these measures varies for individual stakeholders. For example, payers may be most interested in expressions of the clinical value achieved for the additional investment provided (e.g., cost per QALY, cost per event averted), while integrated health systems may ascribe most importance to measures of budgetary or system impact, and patients may be most interested in differential rates of downstream testing or other service use. Second, sole reliance on traditionally-accepted measures of cost-effectiveness such as cost per QALY may mask important considerations in evaluating whether to adopt a new technology. Cost-effectiveness findings may appear to be "reasonable" based on widely-used thresholds (e.g., $50,000 per QALY gained), when in reality the incremental investment required is for an imperceptible clinical gain.

ICER has developed a method for presenting multiple measures of economic impact together in a format known as the Comparative Value Evidence Table (CVET), which allows for visualization of economic measures important to each healthcare stakeholder. Wherever feasible, the CVET has been designed for interactive modification of certain economic model parameters and visualization of how findings might change. Uncertainty in model results is also explored through "sensitivity analyses"— analyses of the robustness of the economic model to changes in certain probabilities and/or costs. Assignment of comparative value is made based on the performance of the technology in question across all of these measures, in consultation with the ICER Evidence Review Group. An example of the summary table from the CVET can be found on the following page.

Details on the methodology underpinning the design and presentation of cost-effectiveness analyses within ICER appraisals are available on the ICER website at www.icer-review.org.

ICER Comparative Value Evidence Table (CVET)

Measure	Technology A	Technology B	Difference (B-A)
1. Service Impact			
Tests	27.4	17.9	(9.5)
Visits	31.6	24.8	(6.8)
Hospitalizations	0.0	1.0	1.0
Hospital days	0.0	3.0	3.0
Days of missed work	4.7	5.9	1.2
Pathway Total	63.7	52.6	(11.1)
2. Cost-Consequences			
$ to Prevent 1 Case of X		$210,000	
$ per Cure		$350,000	
3. Cost per Life-Year Saved		N/A	(equivalent survival)
4. Cost per QALY Gained		$1,050,000	
% of Cost/QALY <$100,000		2.63%	
SA 1: Surg Compl. 50% of Basecase		$547,000	
SA 2: ED 50% of Basecase		$442,000	
5. Budget Impact (per 1,000, 2 years)		$1,425,000	
6. Fixed Budget Tradeoffs		19.0	*Nurse FTEs @ $75K each*
		11.4	*MD FTEs @ $125K each*

Integrated Ratings

The ICER Integrated Evidence Rating™ combines the individual ratings given for comparative clinical effectiveness and comparative value. The overall purpose of the integrated ratings is to highlight the separate considerations that go into each element but to combine them for the purposes of conveying that clinical benefits provided by technologies come at varying relative values based on their cost and their impact on the outcomes of care and the health care system.

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

APPRAISAL OVERVIEW

ACTIVE SURVEILLANCE & RADICAL PROSTATECTOMY FOR TREATMENT OF CLINICALLY-LOCALIZED, LOW-RISK PROSTATE CANCER

The overview is written by members of ICER's research team. The overview summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties.

Final Scope

Rationale for the Appraisal
Given the prevalence of prostate cancer and the increasing number of men who are diagnosed at an early, low-risk stage, a significant amount of attention has been placed on options for the management of low-risk prostate cancer. ICER has previously appraised the comparative clinical effectiveness and value of 4 radiation alternatives—intensity-modulated radiation therapy (IMRT), low-dose-rate, interstitial brachytherapy, proton beam therapy (PBT), and three-dimensional conformal radiation therapy (3D-CRT). To provide a complete set of evidentiary reviews on all the major management options for low-risk prostate cancer, this appraisal will focus on active surveillance as well as the major approaches to radical retropubic prostatectomy—namely, the traditional "open" approach, minimally invasive laparoscopic prostatectomy, and robot-assisted laparoscopic prostatectomy.

Because these management options represent very different pathways of care, with potentially important differences in short and long-term risks and benefits, all health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of active surveillance and the alternative surgical prostatectomy options for clinically-localized, low-risk prostate cancer.

Objective:
To appraise the comparative clinical effectiveness and comparative value of active surveillance and radical prostatectomy for men with clinically-localized, low-risk prostate cancer.

Key questions:

1) The impact of active surveillance and radical prostatectomy on survival, freedom from disease progression/recurrence, and quality of life relative to alternative management options

2) The relative rates of symptom progression and treatment-related complications and side effects

3) The effects of variation in practice and surgeon experience, frequently called the "learning curve," on patient outcomes for the different versions of radical prostatectomy

4) The patient clinical characteristics and individual values that may influence the relative risks and benefits of these alternative management options

5) The cost-effectiveness and budget impact of active surveillance and radical prostatectomy for low-risk prostate cancer relative to alternative management options

Key considerations highlighted by the Evidence Review Group:

1. Treatment variants: The radical prostatectomy modalities of primary interest to clinicians, payers, and other decision-makers are those that use bilateral nerve-sparing techniques via open, laparoscopic, and robot-assisted laparoscopic approaches. As for active surveillance, while there is some variability in the protocols currently in use, ERG members were in agreement that all protocols that included serial PSA and DRE testing and re-biopsy are relevant for evaluation.

2. Operator experience: ERG members noted the significance of surgeon experience on the risks and benefits of radical prostatectomy, and advised that evidence of differences in outcomes related to the surgical "learning curve" should be highlighted.

3. Risks: There was interest in evaluating the potential procedural complications and other adverse outcomes of the various forms of radical prostatectomy.

4. Patient subgroups: While age is an important differentiator for understanding the balance of benefits and harms of each treatment option, the point was raised that age by itself is a poor marker of the individual "valuation" of side effects and other tradeoffs. It was suggested that the analysis consider differing valuation "scenarios" (e.g., importance of sexual function) to more thoroughly explore these effects.

5. Costs: While Medicare facility payments do not currently distinguish reimbursement for prostatectomy by surgical approach, the need for documentation of the significant initial investment, maintenance, and disposable costs associated with robot-assisted prostatectomy should be considered.

6. Ethical considerations: There appear to be no distinctive ethical issues regarding the patient population or the interpretation of results from cost-effectiveness analyses.

1. Background

1.1 The Condition

Prostate cancer is the second leading cause of cancer deaths and the seventh overall cause of death in men in the United States (CDC, 2007). In 2008, approximately 186,320 new patients in the United States were diagnosed with prostate cancer and 28,660 men died of the disease (NCI, 2008). The advent of prostate-specific antigen (PSA) screening for prostate cancer diagnosis and monitoring in the late 1980's has led to a substantial increase in the proportion of men diagnosed with the disease at its earliest, low-risk stage (Stephenson, 2002). The age-adjusted incidence rate of prostate cancer has accordingly grown, from 119 to 159.5 per 100,000 men between the years 1986 and 2004, with approximately 50% of new cases identified as low-risk (Ries, 2007).

Formal diagnosis of prostate cancer is made via biopsy. The TNM 2002 classification scheme of the American Joint Committee on Cancer provides a framework for assigning clinical stage. As a result of widespread PSA testing, most patients are now diagnosed with asymptomatic, clinically localized cancer (NCCN, 2009). Clinically localized disease is subdivided into the following stages:

T1: Clinically unapparent tumor neither palpable nor visible by imaging
- T1a: tumor incidental histologic finding in 5% or less of tissue resected
- T1b: Tumor incidental histologic finding in more than 5% of tissue resected
- T1c: Tumor identified by needle biopsy (e.g. because of elevated PSA).

T2: Tumor confined within the prostate
- T2a: Tumor involves one half of one lobe or less
- T2b: Tumor involves more than on-half of one lobe but not both lobes
- T2c: Tumor involves both lobes

T3: Tumor extends through the prostatic capsule
- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumor invades the seminal vesicles

In addition, a pathologist assigns a Gleason grade to the biopsy specimen, which provides an estimate of the cancer's likelihood of growing and spreading (Gleason, 1977). Assessment of the full risk of tumor spread beyond the prostate and of recurrence involves a combination of stage classification, Gleason score, and PSA level. Several nomograms have been developed to help assess these risks (Partin, 2001). While definitions of low, intermediate, and high risk disease have varied slightly among approaches, the definition provided by the National Comprehensive Cancer Network (NCCN), has been well-validated and widely published (D'Amico, 1999). The NCCN guidelines define the risk levels as follows (NCCN, 2009):

- Low risk:
  T1-T2a and Gleason score 2-6 and PSA < 10 ng/ml

- Intermediate risk:
  T2b-T2c or Gleason score 7 or PSA 10-20 ng/ml

- High risk:
  T3a or Gleason score 8-10 or PSA > 20 ng/ml.

These risk categories are intended to help inform treatment decision-making but they do not predict with perfect accuracy the risks for metastases and cancer-specific death. New independent prognostic factors are being sought using molecular markers and other radiologic evaluations of the prostate (NCCN, 2009). However, these new prognostic factors remain investigational, and the basic risk categorization presented above is still the most widely accepted tool to define the risk of recurrence following initial therapy and therefore these risk categories serve as a guide to appropriate treatment strategies for clinically localized prostate cancer.

Although 40% of men older than 50 harbor prostate cancer, only 1 in 4 present clinically, and only 1 in 14 will die of a prostate cancer-specific death (NCCN, 2009). This has led to the oft-cited conclusion that "men are much more likely to die with, rather than from, prostate cancer" (Wilt, 2008). Low-risk disease is unlikely to metastasize prior to the development of signs or symptoms of local progression (Cornell Urology, 2008). Thus, in addition to early definitive treatment with surgery or radiation therapy, an approach of active surveillance has been considered an appropriate consideration for men with low-risk localized disease.

2. The Alternative Treatment Strategies

The primary goal of the treatment of prostate cancer is to prevent death and disability while minimizing complications and discomfort from interventions (Wilt, 2008). Factors such as tumor stage, age, pre-existing medical conditions, and patient values regarding the risks of potential complications and side effects, are taken into account in the determination of appropriate treatment options.

The list of common treatment options for prostate cancer includes:

1) Active surveillance
2) Surgery to remove the entire prostate gland and surrounding structures (radical prostatectomy)
3) Interstitial brachytherapy
4) Proton beam therapy
5) Intensity-modulated radiation therapy (IMRT)
6) Three-dimensional conformal radiation therapy (3D-CRT)
7) Freezing the prostate (cryotherapy)
8) Androgen deprivation therapy (ADT)

There is no single "gold standard" approach to treatment and little high-quality data with which to compare the relative effectiveness of these various options. Data suggest that many of these interventions have comparable cure rates but that rates of certain harms may differ (Jani, 2003). In such a situation, guidelines, clinical opinion, and patient choice are guided strongly by relevant information on the risks of complications and side effects among different treatments, and it is in this vein that the benefits of these treatment options have been most widely discussed. The most commonly-employed treatments are discussed below.

2.1 Active Surveillance

Because of the limited aggressiveness of many localized prostate cancers, active surveillance is a reasonable strategy for many men (NCCN, 2008). Active surveillance involves forgoing immediate treatment while monitoring closely for signs of progression of disease. If the patient shows signs or symptoms of advancing disease, the decision can be made to initiate treatment with the intention to cure the patient (Adolfsson, 2008). The term 'watchful waiting' is also sometimes used interchangeably with AS. However, watchful waiting was first coined during an era when many men were first diagnosed with prostate cancer not through PSA screening but through presentation with obstructive urinary symptoms or a palpable nodule. It has been estimated that PSA screening detects prostate cancers an average of 9 years before clinical diagnosis in the absence of screening, and therefore patients with PSA-screen-detected disease will have a much more favorable outcome, even without treatment, than patients diagnosed clinically in earlier watchful waiting studies. In addition, the older watchful waiting data came from studies in which active treatment was usually triggered not by rising biochemical findings on blood tests or by advancing pathological findings on repeated biopsies, but by progression of the

obstructive symptoms of localized cancer. As a result, many men who did eventually undergo active treatment in earlier studies had cancers that had spread beyond the capsule of the prostate, thereby progressing beyond the stage when treatment with curative intent could be provided.

Following the publication of randomized controlled trials that showed a 10-year survival advantage for radical prostatectomy over this earlier form of watchful waiting (Bill-Axelson 2005, 2008), current practice has shifted towards the adoption of active surveillance via repeated PSA tests and prostate biopsies, with definitive treatment triggered by any sign of biochemical or pathological progression. The major differences between the older version of watchful waiting and the modern approach to active surveillance are illustrated in the graphic on the following page, based on criteria typically used in the UK for active surveillance (Parker, 2004).

Professional guidelines have identified multiple criteria that define candidacy for AS; a common definition is based on a Gleason score (a measure of tumor aggression) of 6 or less, PSA levels 10 ng/ml or less, and a stage between T1c and T2a (NCCN, 2009). Other criteria that may be used include 33% or less positive cores (biopsy samples), or 50% or less single core involvement. When a patient opts for active surveillance, he is put on a regular monitoring schedule. While there is no universal standard protocol for active surveillance, monitoring schedules often include serial PSA blood tests every 3-6 months, digital rectal exams (DRE) every 3-6 months, and a repeat biopsy at one year followed by subsequent biopsies every 3-5 years thereafter (Klotz, 2008). Other monitoring tests that have been employed include bone scans and CT scans of the abdomen and pelvis to monitor for metastases, as well as transrectal ultrasounds in combination with DRE to assess for progression of local disease or urinary symptoms (Choo, 2002).

Thresholds to trigger definitive treatment in patients on active surveillance are also not universally agreed upon. A rapid rate of PSA increase, or the "PSA velocity", is used by some physicians as an indicator of aggressive disease. Others consider the doubling of a PSA level within 3-4 years (i.e., "PSA doubling time") to be the most reliable indicator of disease progression. Still others contend that results of repeat biopsies provide the best predictor of disease progression. Because the natural history of prostate cancer is poorly understood, clinicians must consider all of these potential triggers to judge when to advise patients that definitive treatment should be initiated.

Contrasts between active surveillance and watchful waiting.

	Active Surveillance	*Watchful Waiting*
Primary Aim	*To individualize treatment*	*To avoid treatment*
Patient Characteristics	*Fit for radical treatment; age 50-80*	*Age >70 or life expectancy <15 years*
Tumor Characteristics	*T1-T2, Gleason ≤7, Initial PSA <15*	*Any T stage, Gleason ≤7, Any PSA*
Monitoring	*Frequent PSA testing, Repeat biopsies*	*PSA testing unimportant, No repeat biopsies*
Indications for Treatment	*Short PSA doubling time, Upgrading on biopsy*	*Symptomatic progression*
Treatment Timing	*Early*	*Delayed*
Treatment Intent	*Curative*	*Palliative*

Source: Parker C. Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol* 2004;5:101-6.

Proponents of active surveillance argue that, for the increasing numbers of men diagnosed with low-risk, clinically-localized disease, delaying curative therapy and its associated toxicities for as long as possible should be the first option considered (Dall'Era, 2009). Others feel that the possibility of progression to a stage at which curative treatment is no longer possible, along with the residual anxiety that some patients will experience during active surveillance, makes this approach unwise for some patients, particularly younger men (Pickles, 2007; Latini, 2007).

The search for better prognostic indicators for local progression continues. Some researchers have employed so-called "prostate saturation biopsy", in which the number of core samples taken is far greater than in the traditional 12-core approach (i.e., 30-80 cores). However, the results of multiple studies and several systematic reviews suggest no material improvement in diagnostic or prognostic accuracy for saturation biopsy relative to traditional techniques (Eichler, 2006; Jones, 2006). Several prognostic tests (e.g., AltheaDx®, ProstatePx®, Epigenomics®) have also been developed to isolate morphologic features, genetic factors, and/or biomarkers that may be indicative of aggressive cancers and/or predictive of recurrence. Their use is not yet widespread, as evidence regarding improvements in survival or biochemical recurrence has not yet accumulated.

2.2 Radical Prostatectomy

Radical prostatectomy has long been an option for the treatment of prostate cancer. The procedure involves the surgical removal of the prostate gland, seminal vesicles, and, in some cases, lymph nodes under general anesthesia; an inpatient hospital stay of 1-4 days' duration is typical. Radical prostatectomy is usually performed when the cancer is localized to the prostate. Candidates for surgery are generally in good overall health with a

life expectancy of at least 10 years. There are 4 major approaches commonly employed in radical prostatectomy:

- **Open Prostatectomy**
  - ***Radical retropubic prostatectomy*:** first developed in the 1940's, this is now the most common form of open prostatectomy. The procedure involves an incision that begins below the navel and extends to the pubic bone to access the prostate gland. If warranted, lymph nodes may also be removed to test for cancer spread.
  - ***Radical perineal prostatectomy*:** involves an approach to the prostate via an incision from the anus to the base of the scrotum. The incision is smaller than with the retropubic approach; removal of lymph nodes requires that a separate incision be made, however.

- **Minimally-Invasive Prostatectomy**
  - ***Laparoscopic prostatectomy*:** first introduced in 1997, this technique requires several small incisions and is performed with surgical instruments that are inserted through the incisions, using a two-dimensional laparoscopic camera that allows the surgeon to view the surgical field in real time; a single robotic arm is sometimes used to manipulate the camera.
  - ***Robot-assisted prostatectomy*:** a type of laparoscopic technique in which the surgeon manipulates a set of 4 robotic arms to perform the procedure while seated at a viewing console nearby. A three-dimensional stereoscopic viewing system is employed. The robotic arms are manipulated by a set of "master arms" that provide basic force feedback to the surgeon; 3 of the arms are used for mounting and manipulating surgical instruments, while the fourth manipulates the camera. The first published robotic prostatectomy series appeared in 2001.

Modern applications of both open and laparoscopic prostatectomy also involve the use of "nerve-sparing" techniques in an attempt to preserve post-surgical erectile function. The perineal approach makes the use of bilateral nerve-sparing techniques or lymph node dissection during the same procedure problematic (Korman, 2009); as such, it is infrequently employed in the U.S. and will therefore not be a focus of this appraisal.

Utilization of laparoscopic and, in particular, of robot-assisted procedures have increased dramatically in recent years. Between 2003 and 2005, utilization of minimally-invasive techniques among Medicare beneficiaries grew from 12.2% to 31.4% (Hu, 2008), a change likely to have been driven primarily by growth in robot-assisted surgery (Blute, 2008). Advocates for these techniques cite potentially reduced blood loss as well as shorter hospital stays and recovery time as advantages over open prostatectomy (Berryhill, 2008). There is a steep learning curve associated with these procedures, however, as surgeons must adjust to reduced range of motion, discontinuity between real and visible movement, and reduced tactile feedback (Rassweiler, 2006). In addition, the results of a recent study of the correlation between surgeon volume and operative outcomes indicate that higher rates of complications and disease recurrence are observed among surgeons who switched from

open to minimally-invasive prostatectomy relative to those who were trained only in minimally-invasive techniques (Vickers, 2009).

Certain technical aspects of radical prostatectomy continue to evolve, regardless of surgical approach. For example, while the use of unilateral or bilateral nerve-sparing techniques is now commonplace during radical prostatectomy, the success of autologous nerve grafting during reconstructive surgery has led to the advent of bilateral sural nerve grafting to replace resected cavernous nerves. This procedure is largely considered experimental, however, as findings from the small, single-center studies that have been conducted to date largely suggest no material improvements in erectile function for nerve grafting relative to nerve-sparing techniques (Namiki, 2007; Mikhail, 2007).

2.3 Brachytherapy

Prostate brachytherapy refers to interstitial placement of radioactive seeds for clinically localized prostate cancer. The most common form of the procedure, "low-dose-rate" (LDR) brachytherapy, typically delivers a radiation dose of between 120-160 Gray (Gy) units. The procedure involves a dose planning visit, an ambulatory care or overnight visit for the procedure itself, recovery time, and a post-operative follow-up visit. Proponents of brachytherapy feel that the procedure exposes less normal tissue to radiation in comparison to other forms of external beam radiation (EBRT) while providing a higher radiation dose to the target (American Brachytherapy Society, 2008). The procedure is not indicated for patients with large prostate size or those with a history of urethral stricture, as the procedure results in short-term inflammation and swelling of the gland (Mayo, 2008). Other potential risks of brachytherapy include infection, injury, and anesthesia-related complications from the procedure, migration of radioactive seeds to other parts of the anatomy, acute urinary retention, other acute and late-onset urinary incontinence or irritative symptoms, rectal morbidity (e.g., proctitis, hemorrhage), and sexual dysfunction.

2.4 Intensity Modulated Radiation Therapy (IMRT)

IMRT is a form of EBRT developed in the mid-late 1990s that uses multiple beam angles and computed tomography (CT) based computer planning to conform the dose to the target organ as closely as possible in an attempt to spare normal adjacent structures. IMRT is typically performed as an outpatient procedure at a dose of 75-82 Gy; patients will typically have a dose planning visit, followed by 37-45 brief (15-20 minutes) daily treatments. Proponents of IMRT feel that the technology is able to deliver escalated doses of radiation while maintaining acceptable levels of toxicity (Esiashvili, 2004). Patients must be completely immobilized during the procedure to prevent radiation to normal tissue. Potential treatment-related toxicities include early- and late-onset urinary incontinence and/or obstructive symptoms, rectal toxicity, and sexual dysfunction.

2.5 Proton Beam Therapy (PBT)

Clinical use of proton radiation, either alone or as a boost to photon therapy, was first employed at 2 major US centers (Loma Linda, CA and Boston, MA) in the 1970s, and has grown steadily over time. PBT is performed in a similar setting and schedule to that of IMRT (see above), with an equivalent range in dose. Proponents of PBT argue that protons are better suited for targeted radiation than photons because they deposit the bulk of their radiation energy at the target (Larsson, 1958). Potential treatment-induced toxicities from PBT are similar to those of brachytherapy (with the exception of acute urinary retention) and IMRT, and include early and late-onset urinary incontinence and/or obstructive symptoms, rectal toxicity, and sexual dysfunction. Finally, the dose distribution from the most commonly-used proton scanners deposits a significant amount of radiation in the femoral heads, raising concerns about a possible increased risk of hip fracture.

3. Clinical Guidelines & Competency Standards

3.1 Active Surveillance

Clinical Guidelines

- American Urological Association (2007):
  http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf
  The AUA has concluded that active surveillance is considered one of the viable monotherapy options for clinically localized, low-risk prostate cancer, along with radical prostatectomy, external beam radiotherapy, and interstitial brachytherapy, and that "study outcomes data do not provide clear-cut evidence for the superiority of any one treatment."

- National Comprehensive Cancer Network (2008):
  http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf
  The NCCN Prostate Cancer Panel Members stated that "patients with clinically localized cancer who are candidates for definitive treatment and choose active surveillance should have regular follow up" of PSA as often as every 3 months and at least every 6 months, DRE as often as every 6 months and at least every 12 months, and needle biopsy as often as annually for patients with life expectancy >10 years (less often for patients with life expectancy <10 years).

- American Cancer Society (2008):
  http://www.cancer.org/docroot/CRI/content/CRI_2_4_4X_Expectant_Therapy_Watching_and_Waiting_36.asp?sitearea=
  In an online guide on prostate cancer, active surveillance is suggested as a possible treatment for men who are older or have other health problems, but not for younger, healthy patients with fast-growing cancer. The pros and cons of watchful waiting and active surveillance are described as not well understood.

- National Institute for Health and Clinical Excellence (NICE, UK) (2008):
  http://www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline.pdf
  In the NICE guidance on the diagnosis and treatment of prostate cancer, active surveillance is recommended to be the first option presented to patients with low-risk, localized cancer who are eligible for radical treatment.

- Association of Comprehensive Cancer Centres, Dutch Urological Association (2007):
  http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=575
  The ACCC's guidelines for treatment of localized prostate cancer indicate that "active monitoring is preferred for patients with low risk disease (T1c-2a, Gleason <7, PSA <10 ng/mL) with advanced age (>75 years). With this approach, the patient should be informed that life expectancy is not determined by the prostate cancer and that each treatment is associated with a risk of adverse effects. Active monitoring may also be considered for patients with moderate or high risk disease if they have

obvious comorbidity and advanced age, which negatively influences life expectancy."

- European Association of Urology (2007):
  http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf
  Active surveillance is indicated for younger patients with localized stage T1a prostate cancer with a life expectancy of >10 years and for asymptomatic patients with stage T1b-T2b cancer. Re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended.

Competency Standards

To date, no training or competency standards specific to active surveillance have been published.

3.2 Radical Prostatectomy

Clinical Guidelines

- American Urological Association (2007):
  http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/proscan07/content.pdf
  The AUA has concluded that radical prostatectomy is considered one of the viable monotherapy options for clinically localized, low-risk prostate cancer, along with active surveillance, external beam radiotherapy, and interstitial brachytherapy, and that "study outcomes data do not provide clear-cut evidence for the superiority of any one treatment."

- National Comprehensive Cancer Network (2008):
  http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf
  The NCCN Prostate Cancer Panel Members determined that radical prostatectomy is appropriate for "any patient with clinically localized prostate cancer that can be completely excised surgically, who has a life expectancy of 10 years or more and no serious co-morbid conditions that would contraindicate an elective operation." It is also stated that laparoscopic and robot-assisted procedures are common and that results can be similar to the open surgical procedure in experienced hands.

- National Institute for Health and Clinical Excellence (2008):
  http://www.nice.org.uk/nicemedia/pdf/CG58NICEGuideline.pdf
  NICE released official guidelines on radical prostatectomy in which it was recommended that radical prostatectomy should be offered to patients with localized prostate cancer at intermediate or high risk. Evidence is not currently sufficient to recommend any one surgical approach over another.

- European Association of Urology (2007):
  http://www.uroweb.org/fileadmin/user_upload/Guidelines/07_Prostate_Cancer_2007.pdf
  Patients with a T1b, T1c, or T2 stage tumors and life expectancy of over 10 years can be recommended to undergo radical prostatectomy. Laparoscopic and robot assisted laparoscopic procedures seem to have similar short-term outcomes as compared to high volume centers for open radical prostatectomy; however, long term outcomes are unknown.

Competency Standards

- British Association of Urological Surgeons (BAUS, UK) (2007):
  http://www.bauslibrary.co.uk/PDFS/BSEND/Guidelines for training in laparoscopy.pdf
  Surgeons wishing to become competent in laparoscopic approaches to complex procedures (including radical prostatectomy) should fulfill the following criteria:
  - Attend a designated procedure specific 'wet lab' course.
  - Watch live procedures in the context of demonstrations, i.e. a master class.
  - Attend a high-volume center to watch designated cases. The proposed theatre team should visit a high-volume center to learn all aspects of the surgery.
  - Identify a mentor.
  - Start doing complex procedures with mentor.
  - At the end of the training period, perform several procedures independently observed by an experienced laparoscopic surgeon.
  - Audit results. Submit results to BAUS annual laparoscopic audit.

- In the USA, fellowships in minimally-invasive and robot-assisted surgery, as well as criteria for determining procedure competency, are the responsibility of individual institutions. The Society for Laparoendoscopic Surgeons (SLS) has also established a supplementary training program for graduating fellows that is currently being piloted at Florida Hospital, Orlando.
  http://www.sls.org/i4a/pages/index.cfm?pageid=3332

- An example of competency-based robotic surgery privileges is available from Stony Brook University Medical Center, Stony Brook, NY.
  http://www.stonybrookmedicalcenter.org/workfiles/house_staff/RoboticSurgery.pdf
  Privilege level is determined based on:
  - Prior year robotic surgical volume
  - Minimum number of current-year robotic cases
  - Number of proctored/monitored cases
  - Current privileges to perform open prostatectomy
  - Satisfactory quality assurance reviews

4. Medicare and Representative Private Insurer Coverage Policies

4.1 Active Surveillance

No specific policies on active surveillance, active monitoring, or watchful waiting were identified from the Centers for Medicare and Medicaid Services or private health plans.

4.2 Radical Prostatectomy

- Centers for Medicare and Medicaid Services (CMS): CMS does not have a National Coverage Decision on radical prostatectomy (open, laparoscopic, or robot-assisted). Local coverage decisions indicate that robot-assisted laparoscopic prostatectomy is a covered service, and that reimbursement is identical to that for general laparoscopic prostatectomy.

- CIGNA: Radical prostatectomy is covered for the treatment of prostate cancer. CIGNA stipulates that no additional reimbursements are provided for the use of robotic-assisted surgical techniques.

- United Healthcare: "Laparoscopic radical prostatectomy is proven for the treatment of localized prostate cancer. Robotic-assisted radical prostatectomy is proven non-preferentially as a form of laparoscopic radical prostatectomy for the treatment of localized prostate cancer. Coverage for robotic-assisted radical prostatectomy is not differentiated from laparoscopic radical prostatectomy."

- Humana: Members may be eligible for indicated robot-assisted surgery (including prostatectomy) using FDA-approved devices; however, "robotic-assisted surgery is considered integral to the primary procedure and is not separately reimbursable."

- Blue Cross/Blue Shield of Massachusetts: Robot-assisted laparoscopic radical prostatectomy is covered for treatment of prostate cancer; no additional reimbursements are provided for use of the robotic technique.

5. Previous Systematic Reviews/Tech Assessments

5.1 Active Surveillance

- Agency for Healthcare Research and Quality (2008):
  http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=9&DocID=79#section4
  In an analysis of the comparative risks, benefits, and outcomes of therapeutic options for clinically-localized prostate cancer, including radiation therapy, radical prostatectomy, and active surveillance, AHRQ concluded that "no one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects."

- The National Institute for Health and Clinical Excellence (NICE, UK) has not performed a distinct technology assessment on active surveillance methods, but does recommend the approach as the initial management option for patients with clinically-localized disease who are eligible for radical treatment (see Section 3).

5.2 Radical Prostatectomy

- Agency for Healthcare Research and Quality (2008):
  http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=9&DocID=79#section4
  In an analysis of the comparative risks, benefits, and outcomes of therapeutic options for clinically-localized prostate cancer, including radiation therapy, radical prostatectomy, and active surveillance, AHRQ concluded that "no one therapy can be considered the preferred treatment for localized prostate cancer due to limitations in the body of evidence as well as the likely tradeoffs an individual patient must make between estimated treatment effectiveness, necessity, and adverse effects."

- The National Institute for Health and Clinical Excellence (NICE, UK) (2006):
  http://www.nice.org.uk/nicemedia/pdf/IPG193Guidance.pdf
  In an update to guidance initially published in 2003, NICE concludes that "current evidence on the safety and efficacy of laparoscopic radical prostatectomy (including robot-assisted surgery) appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance", and further highlights the need for specialized training in individuals performing these procedures.

- California Technology Assessment Forum (2008):
  http://www.ctaf.org/content/assessment/detail/872
  Robotic assisted laparoscopic radical prostatectomy did not meet CTAF criteria, as it was deemed that evidence was insufficient to conclude any of the following:

  1. The technology must improve net health outcomes.

2. The technology must be as beneficial as any established alternatives.
3. The improvement must be attainable outside of the investigational setting.

- Medical Services Advisory Committee (MSAC, Australia) (2006): http://www.msac.gov.au/internet/msac/publishing.nsf/Content/app1091-1 Robotic-assisted laparoscopic radical prostatectomy is at least as safe as and possibly safer than open radical prostatectomy. It is as effective as open surgery and may have additional advantages. The cost-effectiveness compared to open surgery is unknown.

- Canadian Agency for Drugs and Technologies in Health (CADTH, Canada): CADTH has not recently reviewed open, laparoscopic, or robot-assisted radical prostatectomy.

6. Ongoing Clinical Studies

Trial Sponsor /Title	Design	Primary Outcomes	Populations	Variables	Comments
Dep. of Veterans Affairs, NCI, AHRQ (NCI high priority trial) NCT00007644 "PIVOT Trial"	RCT	▪ All cause mortality ▪ CAP mortality ▪ Survival – disease free and progression free ▪ Quality of life ▪ Cost effectiveness	▪ N = 1,050 ▪ Age < 75	Radical prostatectomy vs. Palliative expectant management	Final data collected November 2009.
National Cancer Institutes of Canada and United States NCT00499174 "START Trial"	RCT	▪ Disease-specific survival ▪ QOL ▪ Overall survival ▪ Progression after radical intervention ▪ ADT initiation ▪ Biomarkers and PSA doubling-time	▪ N=2,130 o Age o PSA level of ▪ 10 ng/mL or less and Gleason score 6 or less	Standard treatment (surgery, brachytherapy, EBRT, vs. active surveillance)	Final data collection 2023
Oxford Radcliffe Hospital NCT00632983 "ProtecT Study"	RCT	▪ Survival ▪ Disease progression ▪ Complications ▪ Quality of life	▪ N=2050	Active surveillance vs. radical prostatectomy vs. radiation	Multi-center study. Final data collection 2013.
Memorial Sloan-Kettering, NCT00578123	RCT	▪ Potency after 2 years ▪ Recovery of continence	▪ N=450 ▪ Clinical stage T1-3a, NX or N0, Mx or M0	Open vs. robot assisted vs. laparoscopic prostatectomy	Final data to be collected July 2010.
William Beaumont Hospital NCT00442000	Retrospective Observational	▪ Perioperative outcomes ▪ Postoperative outcomes	▪ N=1000 ▪ Age > 18	Robotic, Retropubic, and Perineal Prostatectomy	Ongoing, but no longer recruiting. Final data collection was November 2008.
MD Anderson Cancer Center NCT00490763	Prospective Observational	▪ 5-year disease progression ▪ Psychosocial adjustment and QoL ▪ 10-year disease progression	▪ N=650 ▪ Low-risk pts who choose active surveillance	Active surveillance	Final data collection 2020
European Organization for Research and Treatment of Cancer NCT00027794	Interventional, Open Label	▪ Success rate for locally advanced pts ▪ Toxic event rates ▪ pN status of patients ▪ 2-year PSA survival ▪ Surgical morbidity	▪ N = 32 to 74 ▪ Age <70 ▪ Locally advanced cancer	Radical prostatectomy	Study began in 2001. This is multicenter study.

7. The Evidence

7.1 Systematic Literature Review

Objectives
The primary objectives of the systematic review were to:

- Evaluate and compare the published evidence on the overall mortality and disease-specific mortality associated with active surveillance and radical prostatectomy as treatments for clinically-localized, low-risk prostate cancer; and

- Evaluate and compare the potential harms of these therapies, including:

    - Radical prostatectomy
        - Peri-operative mortality
        - Major and minor procedure-related complications (e.g., bowel injury)
        - Urethral stricture
        - Acute (3 mo) and late (12 mo or more) urinary incontinence
        - Acute and late erectile dysfunction

    - Active surveillance
        - Progression of obstructive urinary symptoms
        - Progression of erectile dysfunction
        - Surveillance-related anxiety

While it is recognized that practice has recently shifted to more aggressively monitor low-risk patients who are not immediately treated, there is no formal or universally-accepted approach to such monitoring. In addition, several early watchful waiting studies involved substantial proportions of low-risk patients who received treatment with curative attempt. We therefore felt it important to include for consideration all of these studies as representing the full "spectrum" of active surveillance. Nevertheless, an attempt was made to determine the intent and approach for each of these studies. Active surveillance and watchful waiting were distinguished from each other based on the use of a monitoring protocol and treatment intent. Those studies that involved periodic monitoring with the intent to provide curative treatment once certain thresholds were crossed were considered to be active surveillance, while those that involved palliative treatment alone with or without any active monitoring, and reports of patients receiving no definitive treatment, were considered to represent watchful waiting. Details of all studies considered, including our designation of active surveillance vs. watchful waiting, are available in Table 1 at the end of this section.

Potential harms of radical prostatectomy included "peri-operative" deaths occurring during surgery or within 30 days following; major (e.g., bowel injury) and minor (e.g., UTI) procedural complications; urethral stricture; and both acute (within 90 days following surgery) and late (12-24 months following surgery) rates of urinary incontinence and

erectile dysfunction. We also examined procedural outcomes for difference by surgical approach, including operating room time, hospital length of stay, and blood loss or requirements for intra-operative transfusion.

While active surveillance does not involve the immediate use of any radical treatment, age- and disease-related symptoms (i.e., obstructive urinary symptoms and erectile dysfunction) may still worsen during the surveillance period. These data were gleaned from active surveillance and watchful waiting reports wherever feasible. In addition, studies that measured anxiety associated with ongoing surveillance were also evaluated.

We also examined the literature on the "learning curve" associated with the three major surgical approaches to prostatectomy to examine the potential effects of the learning process on the clinical outcomes of primary interest. Finally, published studies of the economic impact of these management options are also summarized to provide additional context for the ICER economic model (see Section 8).

Methods

This review included studies of the benefits and harms of active surveillance and radical prostatectomy in the treatment of clinically-localized, low-risk prostate cancer. Low-risk disease is typically identified as follows:

- Stage T1-T2a
- Gleason score 6 or lower
- PSA <10 ng/mL

Both active surveillance and radical prostatectomy are also recommended approaches for patients with intermediate-risk prostate cancer (i.e., Stage T2b-T2c, Gleason 7, PSA 10-20 ng/ml), provided that life expectancy exceeds 10 years (NCCN, 2009). Therefore, while studies were sought with a preponderance of low-risk subject, patients at intermediate risk were not excluded from any analyses.

Guidance from the ICER Evidence Review Group suggested that the three major forms of radical retropubic prostatectomy—open, laparoscopic, and robot-assisted—were of primary interest to healthcare stakeholders. As such, the perineal approach to prostatectomy was not considered in this appraisal.

Electronic databases searched included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies were also searched. The search strategies used for MEDLINE, EMBASE, and *The Cochrane Library* are shown in Appendix A.

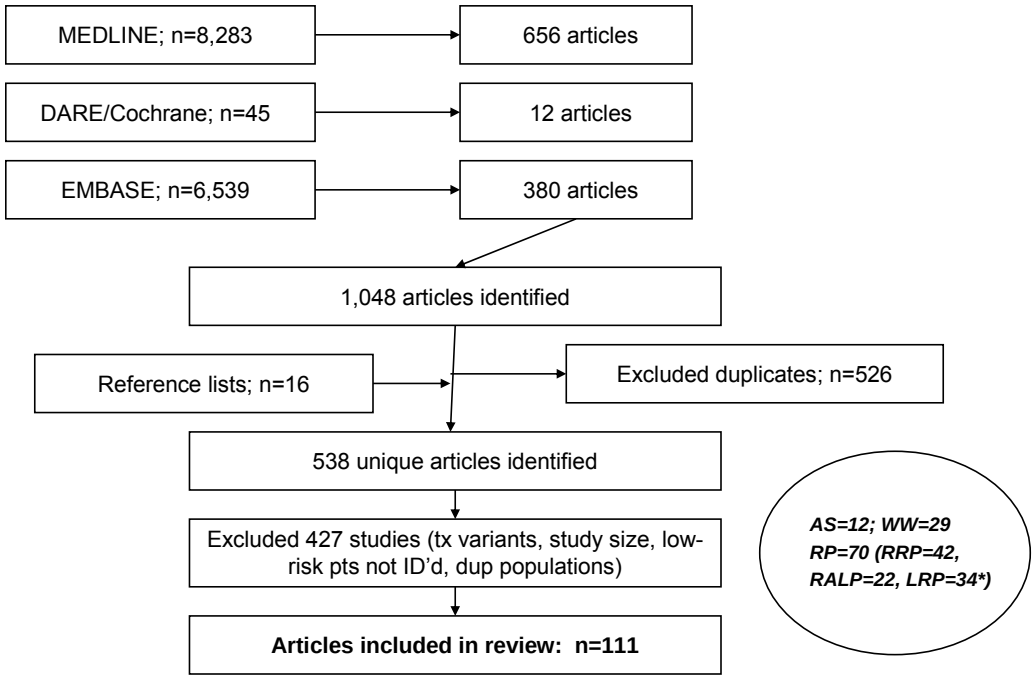
Included studies had a study population of adult males who received one of the management options of interest. The search included studies published during the period

January 1996 – May 2009; this timeframe was felt by the ERG to be generally consistent with the time frame during which PSA screening was prevalent enough to provide low-risk populations comparable to those in practice today. Other major eligibility criteria included:

- Exclusion of other variants of treatment (e.g., perineal prostatectomy)
- Preponderance of patients met criteria for low-risk disease, or data presented for subpopulation meeting low-risk criteria
- Sample size ≥50 patients
- English-language only

Studies were not restricted by instrumentation or manufacturer, outcome measurement technique, surveillance protocol, or surgical training thresholds. Figure 1 below shows a flow chart of the results of all searches for included primary studies (n=111).

Figure 1. QUORUM flow chart showing results of literature search



AS=Active surveillance; WW=Watchful waiting; RP=Radical prostatectomy; RRP=Radical retropubic prostatectomy; RALP=Robot-assisted radical prostatectomy; LRP=Laparoscopic radical prostatectomy
*NOTE: Numbers of studies by prostatectomy approach sum to greater than 70; 31 of 70 studies involved comparisons of two or more surgical approaches

7.2 Data Analyses

Survival
Data were collected where reported on both overall and prostate cancer-specific survival. Survival rates were only abstracted if clearly reported using either Kaplan-Meier or actuarial techniques, or if all subjects met certain timepoint thresholds.

Freedom from Biochemical Failure
Reported rates of freedom from biochemical failure (bFFF, also described as disease-free survival, biochemical no evidence of disease (bNED), or freedom from biochemical recurrence) were recorded as reported from studies of radical prostatectomy. As described previously, there is no universally-employed definition of biochemical failure following prostatectomy; the definitions employed were reported in evidence tables along with other relevant study data.

Treatment-Free Survival
The analogue surrogate endpoint to bFFF in active surveillance studies is treatment- or clinical progression-free survival. This was recorded if reported using Kaplan-Meier or actuarial techniques, and was supplemented by data on median time to treatment, clinical or other reasons for treatment, and the type of treatment selected.

Potential Harms
Peri-operative deaths were classified as those occurring during radical prostatectomy or within 30 days following the procedure. Surgery-related complications were recorded as "major" or "minor" based on a discrete list of complication types, and were developed with clinical input from the ERG; a specific classification scheme (e.g., Clavien) was *not* used, as such schemes were infrequently employed in the studies we evaluated. Major complications were those that were felt to require re-exploration of the surgical site or a significant new clinical intervention, and included:

- Major hemorrhage
- Deep vein thrombosis and/or pulmonary embolism
- Major and/or systemic infection
- Myocardial infarction and/or stroke
- Bowel injury

Minor complications were recorded as a single category based on classification as "minor" or "not requiring invasive treatment" in comparative or other case series. While a discrete set of minor complications was not analyzed, a representative list of the most frequently reported minor complications can be found below:

- Urinary tract infection
- Lymphocele
- Ileus
- Wound abscess

- Transient fever
- Anastomotic leakage
- Hematoma

The presence of urethral stricture was recorded separately based on reported rates of stricture or other relevant terms (e.g., "bladder neck contracture"). Data on urinary incontinence was recorded among individuals continent at baseline, and was based strictly on rates of full continence or absence of use of security pads. Information on erectile dysfunction was recorded among persons potent at baseline; patients were considered to have erectile dysfunction based on reported rates of complete inability to have an erection or erections insufficient for intercourse. Rates were stratified where feasible by the use of nerve-sparing techniques (i.e., bilateral, unilateral, or none). For both incontinence and erectile dysfunction, information on both acute (typically within 90 days of treatment) and late (12-24 months following treatment) effects were recorded.

While active surveillance does not involve the use of any radical treatment, age- and disease-related symptoms (i.e., obstructive urinary symptoms and erectile dysfunction) may still worsen during the surveillance period. These data were gleaned from active surveillance and watchful waiting reports wherever feasible, and were supplemented with age-matched non-cancer data as a reference. In addition, there are clinical risks associated with repeat biopsy in men continuing on surveillance. Finally, studies that measured anxiety associated with ongoing surveillance were also captured, both in terms of the effect on the timing and choice of radical treatment as well as the impact on patient quality of life.

Conversion
While not a classical surgical complication *per se*, technical difficulties in minimally-invasive surgical approaches may require conversion to the open procedure if resolution is not feasible with the initial approach. We evaluated reported rates of conversion for both laparoscopic and robot-assisted prostatectomy.

Positive Surgical Margins
Comparisons across studies of the rate of positive surgical margins--tissue evidence of remaining cancer cells after surgery--is problematic for several reasons. As with other surgical outcomes, this rate may be heavily influenced by surgeon training, skill, and competence. In addition, the rate of positive surgical margins is influenced by the distribution of the pathological stage of the cancer, as more extensive tumors are typically subject to a higher rate of positive surgical margins (Khan, 2005). The prognostic significance of positive surgical margins is also open to debate. While their adverse impact on biochemical recurrence has been reasonably-well established (Swindle, 2007), no association with overall or disease-specific survival has been documented (Stephenson, 2009). Guidance from the ERG suggested that comparisons of the rates of positive surgical margins be made for cancers with similar pathological staging; rates were compared across approaches for pT2 and pT3 tumors respectively.

Learning Curve
Literature specific to the issue of "learning curve" for radical prostatectomy was analyzed to determine the potential effects of the learning process on surgical complications, long-term side effects, biochemical recurrence, and survival. In addition, comparative and individual prostatectomy series that report data stratified according to the learning curve were also assessed.

Economic Impact
As described above, studies of the economic impact of these treatments were not evaluated systematically; instead, the available literature on the costs and cost-effectiveness of these strategies were summarized in part to set a context for the economic evaluation.

Data Synthesis
In contrast to the approach taken by many systematic reviewers, ICER seeks to formally synthesize collected data wherever feasible, for a twofold purpose: (1) to go beyond documenting the presence of statistical heterogeneity by exploring its possible root causes; and (2) to provide information on the possible differences in outcome between treatment alternatives, even if the quality of data do not allow for firm conclusions on comparative clinical effectiveness. In addition, the systematic review is often used to produce estimates for the economic model, as pooled values may offer improved precision over data from a single study.

When there were at least 3 studies available, meta-analyses were conducted to generate pooled estimates of effect for each therapeutic strategy. 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 (DerSimonian, 1986) with inverse variance weighting; effect estimates were generated along with 95% confidence intervals. Heterogeneity was assessed via the tau-squared statistic, a quantification of the variance in effect size between studies, as well as observations regarding overlap in the estimates by treatment type and the width of the analysis-generated confidence interval.

Given the high potential for publication or other evidence dissemination bias from the type of evidence reviewed (i.e., mostly single-center case series), 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 1.7 (Bax, 2006).

7.3 Results

The most abundant data are available on the outcomes of patients undergoing open radical prostatectomy (42 studies; N=132,402), followed by the laparoscopic (34 studies; N=19,324) and robot-assisted (22 studies; N=6,819) approaches. A total of 12 studies of active

surveillance were available (N=2,377), along with 29 studies of watchful waiting (N=52,402). Overall, patients undergoing open prostatectomy were older than those receiving minimally-invasive treatment (weighted mean age 67.7 years vs. 63.3 and 60.5 years for laparoscopic and robot-assisted surgery, respectively). Patients in watchful waiting cohorts were the oldest, with a mean age at the start of management of 71.7; patients on active surveillance protocols averaged 66.7 years old. Study characteristics and data on specific outcomes are summarized in evidence tables in Appendix B.

Evidence Quality

Of the 111 studies identified via systematic review, a total of 4 RCT reports were included: one randomized, within-surgeon comparison of open vs. laparoscopic radical prostatectomy (Guazzoni, 2006); two reports from the Scandinavian Prostate Cancer Group (SPCG) randomized trial of open radical prostatectomy vs. watchful waiting (Bill-Axelson, 2005/2008; Steineck, 2002); and one report from a randomized trial of the addition of the androgen receptor inhibitor bicalutamide to watchful waiting (McLeod, 2005). All of the remaining articles represented single- or multi-center case series, with close to half of these articles comparing one or more surgical approaches with contemporaneous or historical controls. The lone RCT of two surgical approaches mentioned above did *not* measure oncologic or functional outcomes; the scope of this trial was limited to procedure-related measures (e.g., operative time, blood loss) and complications only.

The interpretation of the articles comparing surgical techniques to historical or contemporaneous controls is problematic for multiple reasons. First, in studies with contemporaneous cohorts there is significant potential bias introduced by the clinician-driven selection of patients for alternative surgical approaches. As for comparisons of contemporary surgical case series with historical controls, interpretation is clouded by potential temporal differences in patient selection and ancillary care; many of the open prostatectomy series, for example, were conducted in an earlier era relative to laparoscopic or robot-assisted surgery.

Post hoc comparisons or explicit matching based on stage, PSA, and other clinical factors are often made to try to demonstrate that patients are clinically comparable, and that any difference in outcomes can therefore be ascribed to the treatment modality. There are specific problems, however, with this approach. First, patients from earlier time periods will have had, on average, longer follow-up periods within which to demonstrate long-term side effects, biasing the results in favor of the new treatment (Peschel, 2003). Indeed, follow-up for open prostatectomy series averaged 32.2 months in this review, vs. 18.4 months for laparoscopic series and 12.9 months for patients receiving robot-assisted surgery. Second, there is evidence that Gleason scoring has changed over time, and subtle changes in scoring may have caused an "upshift" in Gleason scores that will make the outcomes of patients in more recent years appear superior relative to those with comparable Gleason scores from earlier periods (Chism, 2003).

While there is a general preference among researchers for use of contemporaneous over historical controls (Guyatt, 1986), these may in fact have greater risk for confounding in this

setting. For example, most of the contemporaneous comparative studies evaluated in this review were conducted in a single institution. However, little to no detail is provided on how patients were selected for each surgical approach. In situations where both types of procedures were performed by the same surgeon or surgical group, selection bias remains a highly likely confounder of any differences in outcomes. In situations where the procedures were performed by different groups, study results may be influenced by differences in surgeon training, competence, or level of experience.

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 (Hardie, 2005). 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.

Key Studies

Despite the overall low quality of available data, several studies appear to have been particularly influential in informing clinical opinion on relative risks and benefits of alternative treatment options. These studies are notable either for the intrinsic rigor of their study design and/or the representativeness of their patient population. Summaries of their key findings are provided below.

Watchful waiting/Active surveillance

Bill-Axelson (2005, 2008): This was a randomized clinical trial in Sweden, Finland, and Iceland in which a total of 695 men with clinically-detected prostate cancer, aged 64.7 years on average, were assigned to immediate radical prostatectomy or a watchful waiting protocol that included semi-annual clinical exams and blood work as well as annual bone scans. At 10 years, the rates of prostate cancer mortality (9.6% vs. 14.9%, p=.01) and overall mortality (27.0% vs. 32.0%, p=.04) were lower in the radical prostatectomy arm, as were the rates of distant metastases and local progression. Differences in prostate cancer mortality were more pronounced among men aged <65 years (8.5% vs. 19.2%, p<.01). The 2008 update to the initial trial report showed similar findings, but no further widening of differences in outcomes. However, further stratifications by age suggested that the clinical benefits of radical prostatectomy were primarily seen in men <65 years of age.

Carter (2007): In the largest US-based active surveillance cohort assessed to date, a total of 407 men with a median age of 65.7 years were enrolled at Johns Hopkins Medical Center and were followed for a median of 3.4 years (range: 0.4-12.5 years). Entry criteria were based primarily on PSA density ≤0.15 ng/mL/cm^3, Gleason ≤6, no more than 2 positive biopsy cores, and no more than 50% of any one core positive for cancer. Nearly all

participants had T1c disease at diagnosis. Twenty-five percent of patients have been treated; variables significantly associated with the decision to treat in multivariate analyses included older age at diagnosis and earlier year of diagnosis. When analyses were restricted to men meeting all entry criteria, change in PSA density and slope of the PSA velocity curve were also significant predictors of treatment. Five-year overall and disease-specific survival were estimated to be 98% and 100% respectively.

Hardie (2005): This study represents the only published comparison of men on an active surveillance protocol (n=80, median age 70.5 years) to those receiving a watchful waiting regimen (n=32, median age 77 years). The AS and WW cohorts were contemporaneous at a single institution, with selection determined by clinicians and patients based largely on age, comorbidities, other "prognostic characteristics," and patient preference. After approximately 4 years of follow-up, 80% of men begun on active surveillance had avoided active treatment, 14% had received radical treatment with curative intent, and 6% had died, all from causes other than prostate cancer. In contrast, among men begun on watchful waiting, 63% remained free of active treatment after 4 years, 25% had received palliative hormonal therapy, and 12% had died, including one death from metastatic prostate cancer.

Klotz (2007): This is the longest-standing active surveillance protocol reported on to date, from Sunnybrook Health Sciences Center in Toronto, Ontario. A total of 331 patients have been followed for a median of 5.8 years (range: 2-10.5 years). Eligibility was based on D'Amico low-risk criteria for patients aged 70 years and younger; for older patients, criteria were expanded to include Gleason score ≤7 and PSA ≤15 ng/ml. Median patient age was 70 years; 80% of patients had low-risk cancer. Thirty-four percent of patients have received definitive treatment; the leading reasons for treatment included rapid PSA doubling time (15%) and patient preference (12%). Overall and disease-specific survival were estimated to be 85% and 99% respectively at 7 years.

van den Bergh (2009): Data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) study included information on 616 men with screen-detected prostate cancer who met criteria for active surveillance (PSA ≤10 ng/ml, PSA density <0.2 ng/ml per ml, stage T1c-T2, Gleason ≤6, and ≤2 positive biopsy cores). Patients were enrolled at 4 European centers, were a mean age of 66.3 years, and were followed for a median of 3.9 years (range 0-11.6 years). Definitive treatment was triggered in 197 men (32%) at a mean of 2.6 years after diagnosis. In contrast to the Johns Hopkins experience, *younger* age at diagnosis was significantly associated with the decision to treat. Fifty-six percent of treated men received therapy despite favorable PSA and PSA doubling time; this was explained by DRE and re-biopsy findings in only a small percentage of cases. Ten-year overall and disease-specific survival estimates were 77% and 100% respectively.

<u>Open vs. minimally invasive radical prostatectomy</u>

Guazzoni (2006): This study randomized 120 consecutive and age-matched men with low-intermediate risk prostate cancer to receive open vs. laparoscopic prostatectomy at a single center in Italy. Patients were followed for a variety of intra- and peri-operative outcomes.

Operative time was significantly longer for men undergoing laparoscopic surgery (235 vs. 170 minutes for open prostatectomy, p<.001), and the rate of use of bilateral nerve-sparing was significantly lower (41.6% vs. 51.6%, p<.02). However, operative blood loss (853.3 cc vs. 257.3 cc for laparoscopic surgery, p<.001) and transfusion rate (45.0% vs. 13.3%, p<.001) were significantly greater among men receiving open surgery. Rates of peri-operative complications and post-operative pain were comparable between the two groups.

Hu (JCO, 2008): This was a Medicare claims-based comparison of a national sample of approximately 2,700 patients undergoing minimally-invasive (i.e., laparoscopic or robot-assisted) or open prostatectomy between 2003 and 2005. Men undergoing minimally-invasive surgery had fewer peri-operative complications (29.8% vs. 36.4%, p = 0.002) and shorter lengths of stay (1.4 vs. 4.4 days, p < 0.001); however, they were more likely to receive salvage therapy suggesting the failure of curative treatment (27.8% vs. 9.1%, p < 0.001). These differences persisted after adjustment for age, race, comorbidity, and geographic region. Adjusted analyses also showed a higher risk for urinary stricture with minimally-invasive surgery (OR 1.40; 95% CI: 1.04, 1.87). Increasing surgeon volume was associated with a modest decrease in the risk for urinary stricture and salvage therapy.

Hu (J Urol, 2008). A similar claims-based analysis, this time on a large employer-based administrative data set, provided outcomes of minimally-invasive vs. open prostatectomy in a younger cohort of over 14,000 men. Minimally-invasive surgery was again found to be associated with fewer 30-day complications (14.2% vs. 17.5%, p = 0.001) and blood transfusions (2.2% vs. 9.1%, p < 0.001), as well as shorter lengths of stay (1 vs. 4 days, p < 0.001). The findings on urethral stricture were opposite those of the Medicare cohort, however, with minimally-invasive surgery associated with a lower rate (6.8% vs. 12.9%, p < 0.001). Rates of salvage therapy were not evaluated in this study, nor were outcomes related to continence or potency.

Rassweiler (2006): In the largest minimally-invasive prostatectomy series reported to date, nearly 6,000 men underwent laparoscopic prostatectomy at 18 centers in Germany, Austria, and Switzerland and were followed for a median of 12.2 months. Findings revealed substantial variability in peri-operative and functional outcomes by center. For example, the rate of conversion to open surgery was 2.4% overall, but ranged between 0% and 14.1%. Similarly, the rate of peri-operative complications averaged 8.9%, and ranged from 1.8-10.8%. The prevalence of incontinence at 12 months was 15.1% (range: 6-28%), while that of new erectile dysfunction was 47.5% among patients undergoing bilateral nerve-sparing surgery (range: 33-65%).

Clinical Effectiveness

Overall Survival

There are no data available to directly compare the impact of active surveillance vs. radical prostatectomy on overall survival. Inferences must be drawn from randomized controlled data on watchful waiting vs. prostatectomy, combined with evidence from case

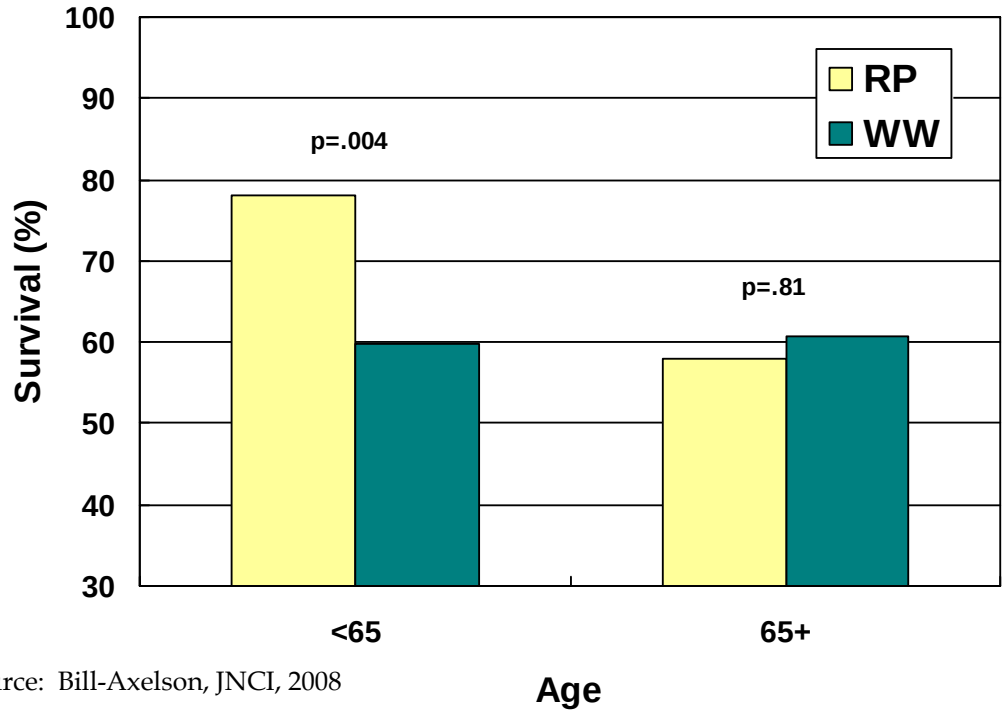
series of active surveillance and watchful waiting. While there are no studies that directly compare active surveillance to radical prostatectomy, 5-year survival rates in published case series are comparable (range: 84-99%). No studies comparing the impact of different surgical approaches on overall survival have been published.

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 (18 vs. 7, respectively). Overall survival of patients following radical prostatectomy has also been infrequently reported (7 studies); 6 of these studies focused on open prostatectomy alone.

The most widely-cited comparative data on overall survival come from the Scandinavian RCT of radical prostatectomy and watchful waiting (Bill-Axelson, 2008). At 12 years, a 7-percentage-point difference was noted in overall survival (67.3% vs. 60.2% for RP and WW respectively, p=.09). This gap was driven, however, by a substantial and significant difference among men who were <65 years of age at randomization (see Figure 2 below); no differences in survival were observed among older men.

Generally, survival rates for watchful waiting across all published studies were highly variable (range: 61-92.7% at 5 years). 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 (Merglen, 2007), only 60% had low-risk cancer, whereas nearly 90%of patients had low-risk cancer in the study with the highest survival estimate (Carter, 2003).

Figure 2. 12-year overall survival by age and treatment arm, SPCG-4 trial.



Source: Bill-Axelson, JNCI, 2008

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%; 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 actively compared active surveillance to radical prostatectomy, 5-year survival rates were generally comparable to those observed for active surveillance (range: 84-99%). No studies comparing the impact of different surgical approaches on overall survival have been published.

Disease-specific Survival

There are no data available to directly compare the impact of active surveillance vs. radical prostatectomy on disease-specific survival. Inferences must be drawn from randomized controlled data on watchful waiting vs. prostatectomy, combined with evidence from case series of active surveillance. While there are no studies that directly compare active surveillance to radical prostatectomy, 5-year disease-specific survival rates in published case series are comparable (range: 86-100%). No studies comparing the impact of different surgical approaches on disease-specific survival have been published.

Available evidence and findings for disease-specific survival parallel that of overall survival. Data were available from 3 times as many watchful waiting studies (N=21) as active surveillance or radical prostatectomy studies (6 and 5 respectively); all prostatectomy studies were of the open approach only. At 12 years, disease-specific survival in the Scandinavian RCT was higher for RP than WW (87.5% vs. 82.1%, p=.03); as with overall survival, this difference was driven entirely by the <65 cohort (88.1% vs. 76.9%, p=.014).

The predominance of low-risk disease in active surveillance studies equates to minimal death due to prostate cancer in published studies with follow-up less than 10 years; at 5 years, disease-specific survival was 100% in 5 studies and 99% in the remaining study. Findings from a cohort of men on active surveillance from Toronto, Canada with a median follow-up of 8 years, the longest follow-up of any published study, showed very few prostate cancer related events. After 7 years, overall survival is 85% and disease-specific survival is 99%, with 3 reported deaths from prostate cancer (Klotz, 2007). A recently published article with pooled results from the multi-center European EPSPC trial found a 100% calculated (Kaplan-Meier) 10-year disease-specific survival for patients managed on active surveillance (van Den Bergh, 2009). Findings for patients undergoing radical prostatectomy from long-term cancer registry studies echo those of the Scandinavian trial, with disease-specific survival rates ranging from 86-98% at between 5 and 10 years of follow-up (Barry, 2001; Aus, 2005; Lai, 2001).

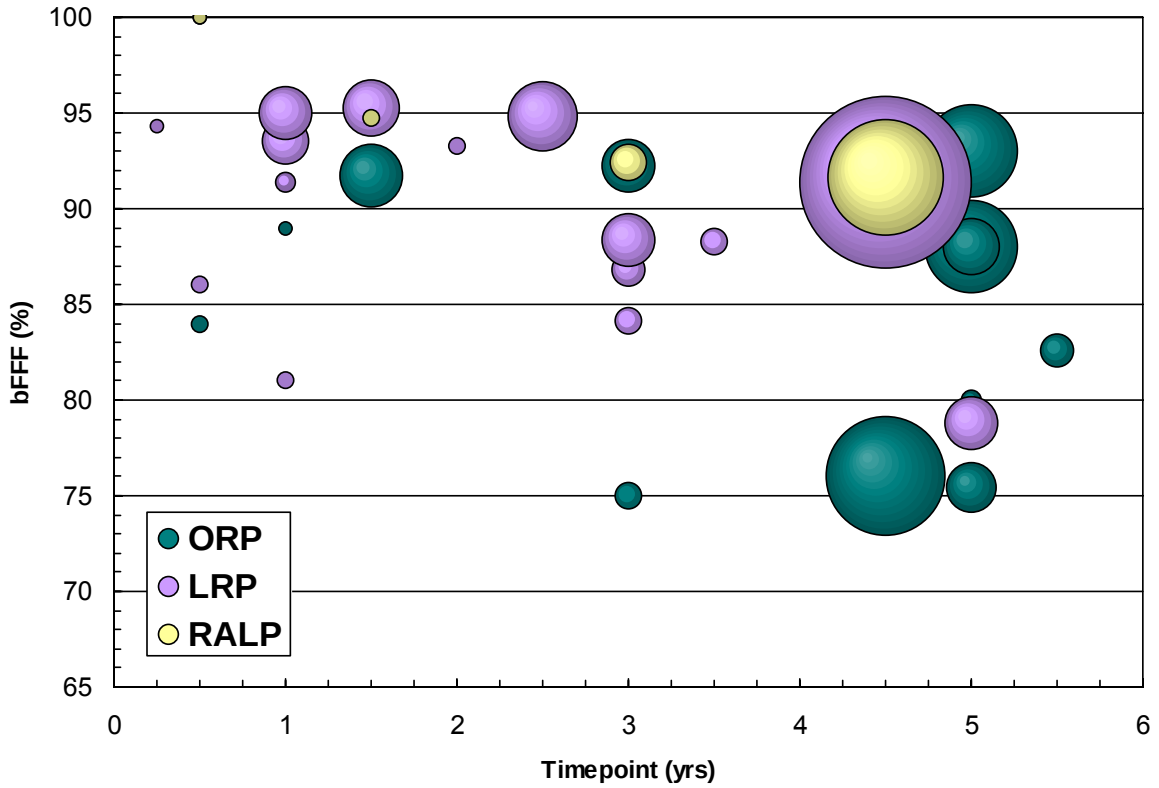
Biochemical Freedom from Failure (bFFF) Following Radical Prostatectomy

There are inadequate data on which to base a judgment of potential differences among the 3 major surgical approaches on freedom from biochemical failure after surgery, due to differences in techniques used to measure this outcome, duration of follow-up, pathological tumor staging, and other patient and/or study characteristics.

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. Evidence from an analysis of Medicare claims suggest that rates of bFFF may differ by surgical approach, as the use of salvage therapy post-prostatectomy was significantly higher for minimally-invasive surgery vs. the open technique (Hu, JCO, 2008).

However, long-term data specifically on bFFF are extremely limited for minimally-invasive surgery; indeed, 5-year or longer estimates were generally only available in studies of open prostatectomy. In addition, 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 7 of the 25 studies evaluated. Results are presented by treatment, timepoint, and sample size (as approximated by bubble size) below.

Figure 3. Biochemical freedom from failure, by surgical approach and timepoint.



ORP: Open prostatectomy; LRP: Laparoscopic prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy
NOTE: Bubble size used to illustrate study sample size

The reported range of bFFF in the 4 robot-assisted studies was higher (92-100%) than for laparoscopic or open surgery; however, the highest reported rates came from 2 studies with less than 2 years of follow-up. When estimates were restricted to those reported at 3 years or more, results for all surgical approaches were generally in the range of 88-92% (see Figure 3 above). When we examined studies with similar characteristics (e.g., same

biochemical failure definition, study timeframe, tumor characteristics), no advantage could be determined for any one surgical approach.

While differences in bFFF by surgical approach could not be adequately assessed, patient age was found to be a significant predictor of biochemical recurrence in several studies. For example, in a comparison of older (≥71 years) vs. younger (≤59 years) men undergoing laparoscopic prostatectomy (Poulakis, 2006), 6-month estimates of bFFF were 86% in older men vs. 95% in the younger cohort.

Treatment-Free Survival in Active Surveillance

Approximately 25%-50% of patients who begin active surveillance will ultimately receive some form of treatment within 3-7 years. Very limited data suggests 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 should not 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 studies (Klotz, 2007; Carter, 2007; Dall'Era, 2008; Roemeling, 2007; van den Bergh, 2009). 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 treatment (Dall'Era, 2008). 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 time (Klotz, 2007).

Some men elect definitive treatment in the absence of clinical progression. The UCSF series shows a low rate of active surveillance "attrition" of 8% (Dall'Era, 2008), whereas other centers describe higher rates of 12% and 23% from the Toronto and Memorial Sloan-Kettering series, respectively (Klotz, 2007; Patel, 2004). Results from the European ERSPC study indicate that approximately half of men received definitive treatment within 2 years (van den Bergh, 2009). 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 cohorts (Carter, 2007).

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 receipt (Meng, 2003). 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 treatment (Klotz, 2007).

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 time (Dall'Era, 2008). 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 prostatectomy (Griffin, 2007). 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 men (Soloway, 2008). 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 (Dall'Era, 2009). 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 Associated With Radical Prostatectomy

While there is relatively abundant data from case series on the short and intermediate-term risks associated with radical prostatectomy, there are very limited data available with which to compare these potential harms across the different surgical approaches. The single published RCT of open vs. laparoscopic prostatectomy (Guazzoni, 2006) examined peri-operative complications alone, and did not assess the rate of short- or long-term incontinence or ED. Much of the comparison of harms between these treatment options must therefore be made indirectly across populations that differ in demographic and clinical characteristics, study timeframe, measurement of outcome, and other characteristics as noted previously. Not surprisingly, these study differences give rise to a range of estimates that vary widely, regardless of surgical approach. Two examples of the variability in these estimates as well as the degree of overlap between surgical approaches can be found on the following page for long-term erectile dysfunction and incontinence respectively. Pooled data on all potential harms by surgical approach is nevertheless presented for informational purposes alone in on page 75.

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 (Choo, 2004). 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 as well as the effects of patient anxiety.

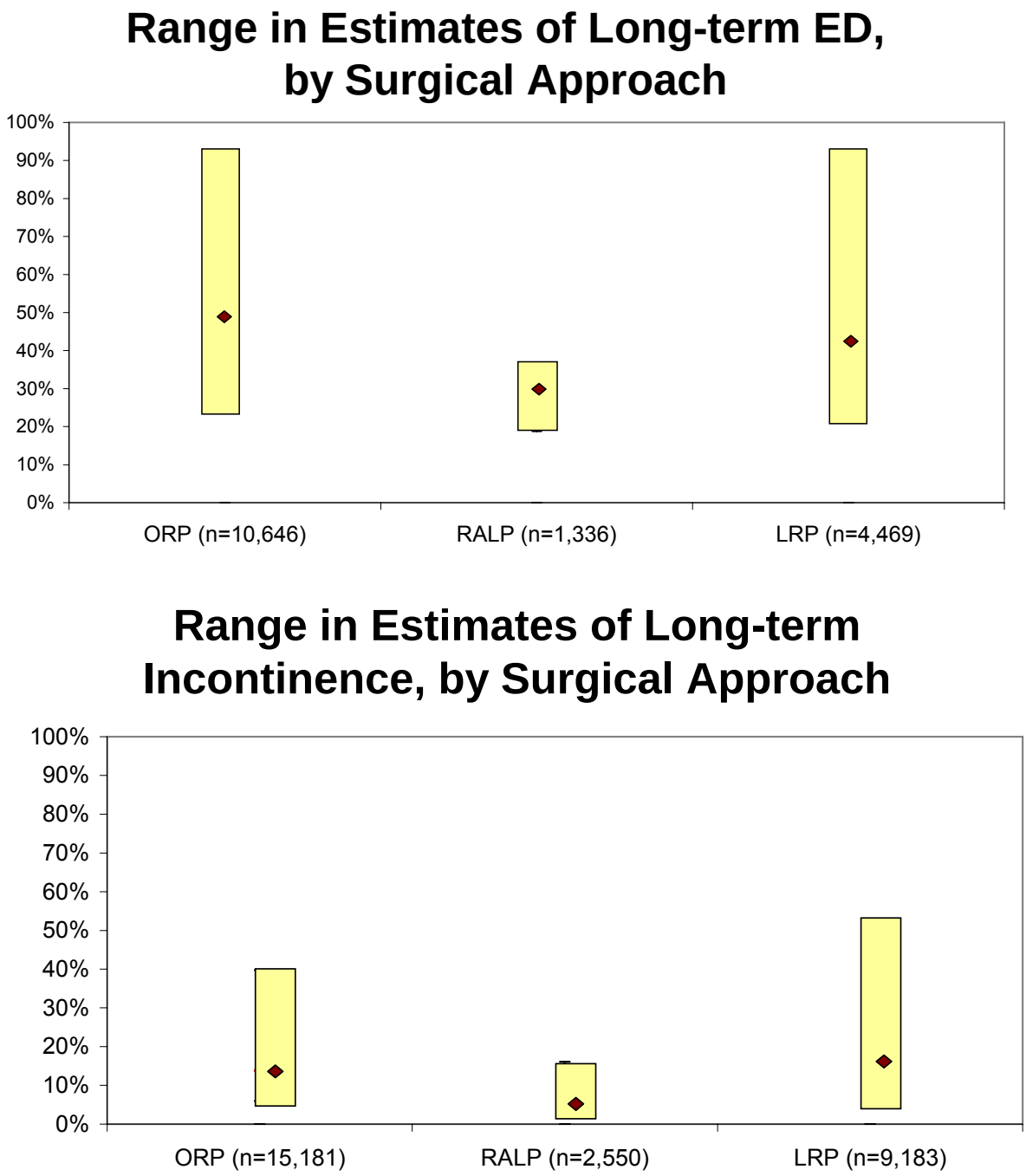
Peri-Operative Mortality

Intra- or peri-operative mortality is rare across all surgical approaches to prostatectomy, with a risk of approximately 0.4%.

Intra- or peri-operative mortality was extremely rare for all surgical approaches; among a total of nearly 30,000 patients evaluated in the single or comparative case series that reported peri-operative mortality, only 11 deaths were reported (0.04%). In the RCT comparing open and laparoscopic prostatectomy, no deaths were reported in either arm (Guazzoni, 2006). Findings from a large observational study of Medicare claims (Lu-Yao, 1999) indicated that, among nearly 94,000 patients examined, 526 peri-operative deaths occurred (0.56%). 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.

Not surprisingly, some differences in peri-operative mortality were noted by patient age, although the risk appears to be minimal at all ages. In a retrospective analysis of over 11,000 men in the Ontario Cancer Registry who underwent radical prostatectomy (Alibhai, 2005), a total of 53 (0.48%) died within 30 days of surgery; rates ranged from 0.19% among men aged <60 years to 0.66% among those aged 70-79 years.

Figure 4. Variability in estimates of long-term side effects, by surgical approach.



NOTE: Diamonds represent pooled mean rate; rectangles represent full range of estimates

Table A. Reported harms of radical prostatectomy, by surgical approach.

Measure	ORP	LRP	RALP
Peri-Operative			
*Mortality**	Studies: 62 Pooled†: 0.4% Range: 0.0-0.7%	Studies: 62 Pooled: 0.4% Range: 0.0-0.7%	Studies: 62 Pooled: 0.4% Range: 0.0-0.7%
Major Comp	Studies: 20 Pooled: 4.7% (3.7%, 5.7%) Range: 2.1%-28.6%	Studies: 21 Pooled: 3.5% (2.4%, 4.6%) Range: 0.0%-36.6%	Studies: 12 Pooled: 2.5% (1.4%, 3.6%) Range: 0.0%-7.8%
Minor Comp	Studies: 20 Pooled: 9.5% (3.3%, 15.7%) Range: 0.3%-25.3%	Studies: 21 Pooled: 7.8% (6.1%, 9.4%) Range: 0.0%-23.5%	Studies: 12 Pooled: 5.3% (3.1%, 7.4%) Range: 0.5%-15.0%
Conversion	N/A	Studies: 22 Pooled: 0.4% (-0.1%, 0.9%) Range: 0.0%-3.7%	Studies: 14 Pooled: 0.1% (-0.1%, 0.3%) Range: 0.0%-2.3%
+ *Margins* *(pT2)* *(pT3)*	Studies: 14 Pooled: 16.8% (13.2%, 20.4%) Range: 6.0%-34.2% Pooled: 45.2% (35.5%, 55.0%) Range: 9.1%-84.6%	Studies: 25 Pooled: 13.9% (12.1%, 15.7%) Range: 4.7%-30.2%) Pooled: 39.3% (35.0%, 43.5%) Range: 16.7%-71.0%	Studies: 10 Pooled: 10.5% (8.1%, 12.8%) Range: 2.5%-20.0% Pooled: 35.4% (26.6%, 44.2%) Range: 13.0%-66.7%
Side Effects			
Urethral Stricture	Studies: 13 Pooled: 3.4% (2.5%, 4.4%) Range: 0.4%-19.8%	Studies: 16 Pooled: 0.3% (0.1%, 0.6%) Range: 0.0%-6.4%	Studies: 7 Pooled: 1.3% (0.3%, 2.4%) Range: 0.0%-2.3%
Urinary Incontinence	*Acute* Studies: 7 Pooled: 46.7% (25.1%, 68.2%) Range: 25.0%-90.2% *Long-term* Studies: 17 Pooled: 12.7% (9.6%, 15.8%) Range: 6.1%-39.5%	*Acute* Studies: 11 Pooled: 43.0% (23.9%, 62.0%) Range: 8.0%-89.8% *Long-term* Studies: 19 Pooled: 17.3% (13.7%, 20.8%) Range: 5.0%-52.2%	*Acute* Studies: 7 Pooled: 28.9% (13.6%, 44.2%) Range: 6.7%-65.2% *Long-term* Studies: 7 Pooled: 7.3% (2.9%, 11.7%) Range: 2.9%-16.0%
Erectile Dysfunction	*Acute* Studies: 5 Pooled: 76.8% (66.2%, 87.4%) Range: 62.5%-95.1% *Long-term* Studies: 16 Pooled: 45.3% (38.7%, 51.9%) Range: 24.0%-90.0%	*Acute* Studies: 10 Pooled: 71.4% (60.2%, 82.6%) Range: 57.7%-94.7% *Long-term* Studies: 17 Pooled: 41.4% (34.6%, 48.3%) Range: 21.9%-91.2%	*Acute* Studies: 3 Pooled: 59.1% (43.2%, 74.9%) Range: 46.9%-71.7% *Long-term* Studies: 7 Pooled: 26.3% (22.2%, 30.4%) Range: 18.8%-35.0%

*Meta-analysis of mortality data by surgical approach infeasible due to large number of zero values
NOTES: ORP: Open radical prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted radical prostatectomy
†From random-effects meta-analysis (with 95% confidence intervals); for informational purposes only

Peri-Operative Complications

The types of complications deemed to be "major" are listed in Figure 5 below. In addition, while only a summary "minor" complication category was used, a representative list of the most commonly-observed minor complications is also included.

Figure 5. Major and minor complications of radical prostatectomy.

Major	Minor*
Major hemorrhage	UTI
DVT/PE	Lymphocele
Major/systemic infection	Ileus
MI/stroke	Wound abscess
Bowel injury	Transient fever
	Anastomotic leakage
	Hematoma

DVT: Deep vein thrombosis; PE: Pulmonary embolism; MI: Myocardial infarction; UTI: Urinary tract infection
*Minor complications assigned to single category; representative list of most commonly-observed complications is presented

- ***Major Complications:***
  Data on major complications is extremely variable due to differences in measures, patient populations, surgeon experience, and other factors. A rough estimation based on pooled data suggest that the risk of major complications, including DVT/PE, MI, and stroke, is approximately 3-4% and does not appear to materially differ across surgical approaches.

Absolute rates of major complications were as follows: DVT/PE (1.0%); major hemorrhage (0.8%); systemic infection (0.7%); and 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.

While the pooled data by surgical approach suggest some nominal differences in favor of minimally-invasive surgery (Table A), comparisons of these rates are problematic for several reasons. First, as previously noted, patients undergoing minimally-invasive surgery are younger than those in open prostatectomy series; age is a known risk factor for nearly all of the major complications of interest. Second, data on major complications from the key reports of minimally-invasive surgery are incomplete or missing altogether. The largest

series of laparoscopic prostatectomy (n=5824) does not report rates of MI/stroke or systemic infection (Rassweiler, 2005); rates of major hemorrhage (2.2%) and bowel injury (1.7%) in this study are higher than the pooled estimates above, while the rate of DVT/PE (0.6%) is somewhat lower. The largest published series of robot-assisted prostatectomy (n=2652) does not provide information on major complications by type, reporting only on the rate of complications requiring surgical intervention (0.8%) (Menon, 2007).

- ***Minor Complications:***

The risk of minor peri-operative complications such as UTI or wound infection is approximately 8-9%. The limited comparative data available suggest that minimally-invasive prostatectomy performed by experienced surgeons may be associated with lower rates of minor peri-operative complications, but interpretation of these data is complicated by the younger age of patients undergoing minimally-invasive techniques, and complication rates appear significantly higher among surgeons with limited experience with a new technique. Operative blood loss is lower in minimally-invasive approaches, as are associated transfusion requirements; neither of these benefits has consistently been shown to translate to a reduced risk of major hemorrhage, however.

The rates of minor complications ranged from 0.3-25.3% (pooled estimate: 8.4%; 95% CI: 5.0%, 11.7%). Guazzoni, 2006 found nominal differences in the rates of minor complications in favor of laparoscopic prostatectomy relative to open surgery (there were no reported major complications in either arm), but did not test for the significance of these differences and concluded that complication rates were "comparable". As with major complications, the remaining evidence does not permit conclusions to be drawn regarding whether differences based on pooled mean results would be realized in a truly comparative setting due to differences in patient characteristics and incomplete measurement and/or reporting of complications.

In the operating room, minimally-invasive surgery results in substantially lower levels of blood loss relative to open surgery. In our sample of studies, blood loss averaged 992 cc for open prostatectomy vs. 352 and 168 cc for laparoscopic and robot-assisted surgery respectively. This also translates to fewer requirements for intra-operative blood transfusion; data from our systematic review indicate a rate of transfusion of approximately 30% for open prostatectomy, vs. 2-6% for minimally-invasive surgery. However, rates range widely (e.g., from 0-67% for open surgery); this is not surprising, as rates of intra-operative bleeding are influenced by surgeon skill, institution, and hemostasis protocols (Nutall, 2002; Koch, 1996). In addition, our analysis indicated no differences by surgical approach in the rate of post-operative major hemorrhage (see Major Complications above).

Data from analyses of both Medicare and employer claims (Hu, JCO, 2008; Hu, J Urol, 2008) suggest that the overall rate of complications is 3-5 percentage points lower among patients receiving minimally-invasive surgery relative to open prostatectomy. While these studies did not distinguish complications by severity, significant reductions were observed for minimally-invasive surgery in cardiac, respiratory, wound, and genitourinary complications. Among Medicare beneficiaries, however, the likelihood of urethral stricture

(OR: 1.40; 95% CI: 1.04, 1.87) and salvage radiation or hormonal therapy (OR: 3.67; 95% CI: 2.81, 4.81) was *higher* among patients receiving minimally-invasive surgery (Hu, JCO, 2008). While this was partially explained by the level of surgeon experience with minimally-invasive surgery, rates of salvage therapy among even the most experienced surgeons remained higher than for open prostatectomy.

In any event, rates of peri-operative complications, particularly major complications, are generally low, even in men of advanced age; overall complication rates ranged from 17.5% to 26.9% in men aged <60 years v. those aged 70-79 years in the Ontario Cancer Registry study (Alibhai, 2005); however, levels of comorbidity had 4-8 times the explanatory power of age alone in predicting the likelihood of any surgical complication.

Urethral Stricture, Incontinence, and Erectile Dysfunction

- ***Urethral Stricture:***
  The risk of urethral stricture varies considerably in the published literature, with estimates ranging from less than 1% to 15%. Some evidence suggests that the risk of stricture has declined significantly over time, as all surgical techniques have evolved.

The incidence of urethral stricture was generally low across all surgical approaches; for example, in a large study of Medicare claims, of 94,000 men undergoing open prostatectomy only 790 (0.8%) received treatment for stricture (Lu-Yao, 1999). The overall pooled estimate for the frequency of urethral stricture across all studies in our database was 1.6% (1.2%, 2.0%), which is similar to reported rates in multiple prostatectomy reviews (Gettman, 2006; Ficarra, 2009).

Rates of stricture were 15% and 7%, respectively, in two large Medicare and employer-based claims analyses (Hu, JCO, 2008, Hu, J Urol, 2008). Because these studies are based on broad databases more representative of general community practice, these somewhat higher rates of urethral stricture may be more generalizable to results outside of academic centers in which surgeons may have greater experience. In the two Hu studies, use of minimally-invasive surgery was associated with a *lower* rate of stricture vs. open prostatectomy in the younger, employed population, but in the older Medicare cohort minimally-invasive surgery had a *higher* comparative rate of stricture. The discussion section of the latter article suggests that higher urethral stricture rates may be due to the learning curve for minimally-invasive approaches, but does not explain the discrepancy in risks found between cohorts of older and younger men.

There is also some evidence that the rate of stricture has declined over time. Among case series published in the first 6 years of our analysis timeframe, the crude pooled rate was 5.3%; the rate in studies published in 2005 or later was 1.7%. This decline over time in the rate of stricture post-prostatectomy has been observed for the open technique as well as for minimally-invasive surgery.

- ***Urinary Incontinence:***
  Short-term incontinence remains a significant concern among patients undergoing radical prostatectomy, regardless of surgical approach. Approximately 40% of patients will have incontinence at 3 months post-surgery. This side effect appears to resolve in many patients 12 or more months after surgery, but our data suggest that between 10-15% of men will still require occasional or consistent pad use at 12-24 months. Evaluation of differences by surgical approach is problematic for many reasons, including differential follow-up and patient age. Existing data do not suggest a substantial difference in the risk for acute or chronic incontinence by surgical approach.

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 across all studies in our database was 40.1% (95% CI: 28.5%, 51.6%). As with the other measures of harms, there was substantial variation in results across studies, with high degrees of overlap for different surgical approaches. The overall range was 8-92%; at the low end of this spectrum was a small, single-center comparative study of laparoscopic and robot-assisted prostatectomy (50 patients in each group); pad use was self-reported (Joseph, 2005). At the high end was a larger single-center comparative study of open and laparoscopic prostatectomy, in which a subset of enrolled men (N=214 and 193 respectively) agreed to undertake formal health-related quality of life evaluations every 3 months for 48 months (Touijer, 2008); incontinence was estimated at multiple timepoints using Kaplan-Meier techniques.

Our analyses estimate the risk of chronic incontinence following radical prostatectomy at 13.6% (95% CI: 11.5%, 15.7%). As above, estimates by study and population varied substantially (range: 2.9-52.2%). Measurement differences may again assist in explaining the range. The lowest reported rate was obtained in a prospective, comparative study of open and robot-assisted prostatectomy in which 208 patients completed a well-known continence questionnaire (ICIQ-UI) at 12 months (Ficarra, 2009); however, those reporting "occasional" leakage were considered continent in this study. The highest reported rate was obtained in the Touijer study described above. Consistent with our findings for acute and chronic incontinence, the largest quality-of-life evaluation following definitive treatment for prostate cancer conducted to date, in which over 1,200 men and 600 spouses responded to serial surveys at multiple timepoints reported a rate of post-prostatectomy pad use that dropped from 67% at 2 months to 24% at 12 months (Sanda, 2008).

In comparing the data on incontinence between open radical prostatectomy and minimally-invasive approaches, the effects of truncated follow-up must be considered. As mentioned previously, the average duration of follow-up in studies of minimally-invasive surgery was one-third to one-half that of open prostatectomy, which renders comparisons across

approaches essentially impossible. Also, comparisons of surgical approaches are confounded by the younger age of patients undergoing minimally-invasive surgery. Age is a well-documented risk factor for incontinence following radical prostatectomy; for example, at 12 months following open surgery, 2.5% of men aged <60 years reported no urinary control vs. 13% of men aged 75-79 years in the SEER-based Prostate Cancer Outcomes Study (PCOS) (Stanford, 2000).

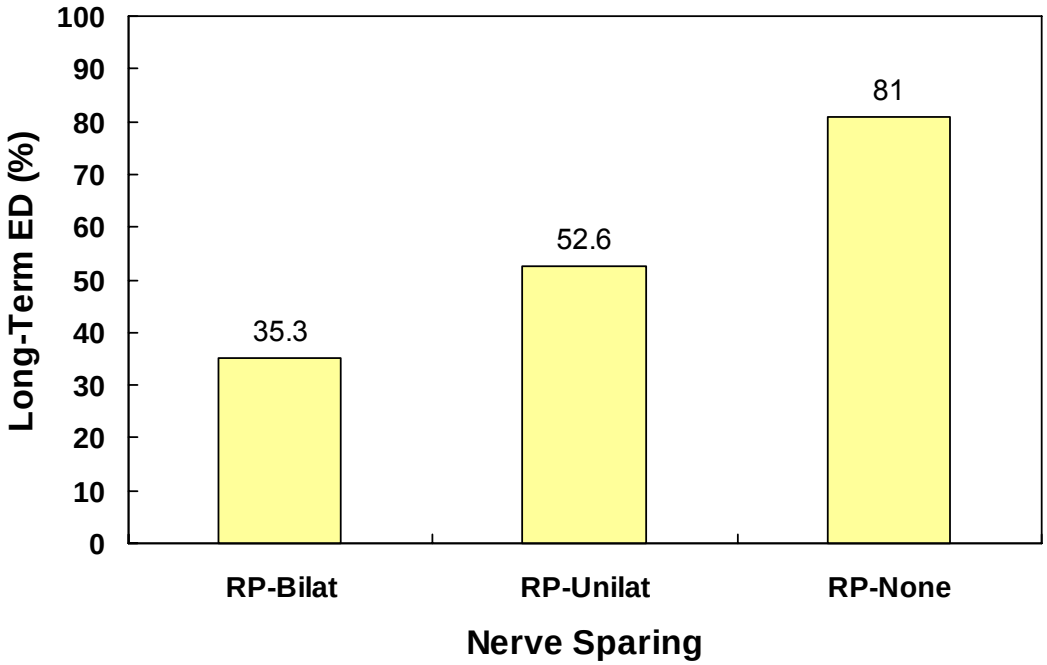
- ***Erectile Dysfunction:***
  Both short- and long-term ED remain a significant concern among men undergoing radical prostatectomy, regardless of approach. Approximately 70% of men experience ED in the first three months following surgery. ED improves over the course of the year, but at 12 months following surgery approximately 35% of men who were potent prior to bilateral nerve-sparing surgery will still have ED. Rates of ED among men receiving unilateral or non nerve-sparing surgery are between 50-80%.

As described in the Methods section, ED was assessed in our systematic review based on reported rates of complete inability to have an erection or erections insufficient for intercourse. As with urinary incontinence, 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 (Lubeck, 2001).

The pooled estimate for acute ED across all studies was 70.7% (95% CI: 63.0%, 78.4%). Findings for the acute measure were generally not stratified by use of nerve-sparing techniques. While not as variable as urinary incontinence, the range of reported estimates was nevertheless wide, ranging from 47-92%. A high degree of variability across studies was observed for findings of chronic ED (19-91%). Pooled results provided an overall estimate of chronic ED of 40.3% (95% CI: 36.1%, 44.5%), with the rate for patients undergoing bilateral nerve-sparing techniques at 35% (see Figure 6 on the following page). Higher rates of ED were reported in the Sanda quality-of-life evaluation (90% at 2 months, 75% at 12 months) (Sanda, 2008).

Figure 6. Rates of erectile dysfunction at a minimum of 12 months of follow-up, by use of nerve-sparing techniques.



RP: Radical prostatectomy; Bilat: Bilateral nerve-sparing; Unilat: Unilateral nerve-sparing: None: No nerve-sparing

<u>Conversion from Laparoscopic or Robot-assisted to Open Prostatectomy:</u>
On an overall basis, conversion from minimally-invasive to open surgery is less than 1%; however, rates as high as 14% have been found among surgeons who are earlier in the learning curve.

The incidence of conversion was extremely rare in the sampled studies, as 24 of 36 studies reported a zero rate, and incidence was quite low in the remaining studies. It was only feasible therefore to develop a pooled estimate that combined the reported rates for both types of minimally-invasive procedures. The pooled rate of open conversion was estimated to be 0.3% (95% CI: 0.0%, 0.7%).

There is evidence to suggest, however, that conversion is more frequently a problem for surgeons who are earlier in their learning curve for minimally-invasive surgery (see also "Learning Curve" section below). For example, data from the initial experience with minimally-invasive prostatectomy at a single center in Canada indicated that conversions were required in 3 of the first 4 cases seen (Chin, 2007). In addition, findings from a large multi-center series of 5,824 laparoscopic prostatectomy patients indicated an overall conversion rate of 2.4%, but a range by center of 0-14.1% (Rassweiler, 2006).

<u>Positive Surgical Margins</u>
For a given tumor stage, limited evidence suggests that there is no substantial intrinsic difference in the rate of positive surgical margins by surgical approach. One large study of the use of subsequent radiation and hormonal treatment following prostatectomy, markers

for positive surgical margins, found that the most important factor in differences between open radical prostatectomy and minimally-invasive techniques is the level of experience with the technique.

To provide a common platform for comparison of positive surgical margins, estimates were derived for both pathological stage 2 (pT2a, pT2b, or pT2c) and 3 (pT3a or pT3b) tumors. The overall pooled estimate of positive surgical margins in our sample among pT2a, pT2b, or pT2c tumors was 14.6% (95% CI: 13.1%, 16.0%). Small differences were noted in pooled estimates by surgical approach (13.9% and 10.5% for laparoscopic and robot-assisted vs. 16.8% for open prostatectomy. Not surprisingly, the overall rate of positive margins among pT3 tumors was higher (40.0%; 95% CI: 36.5%, 43.6%). Again, nominal differences were observed by surgical approach (39.3% and 35.4% for laparoscopic and robot-assisted vs. 45.2% for open prostatectomy).

While differences have been reported by surgical approach, rates of positive margins are heavily influenced by surgeon experience and operative technique. For example, findings from an initial series of laparoscopic prostatectomy in Germany indicated an overall rate of positive margins of 78% (Weber, 2001). In addition, an analysis of US Medicare claims found that the rate of subsequent radiation or hormonal therapy was 3 times *higher* in patients receiving minimally-invasive vs. open prostatectomy (Hu, 2008). These treatments are commonly employed when positive margins are identified, suggesting that minimally-invasive techniques may, in the community, be associated with higher rates of positive surgical margins. However, adjusted analyses from this study also showed that the patients of high-volume minimally-invasive surgeons experienced slightly lower odds of receiving subsequent therapy compared to patients undergoing open radical prostatectomy (OR, 0.92; 95% CI 0.88 to 0.98).

Learning Curve

There is a substantial and flattened learning curve for all forms of radical prostatectomy; cases performed by inexperienced surgeons tend to have higher rates of complications, side effects, disease recurrence, and need for subsequent treatment. Prior training with the open technique does not necessarily prepare the surgeon for success with minimally-invasive approaches.

Case series-based evidence on the impact of the surgical "learning curve" for minimally-invasive surgery on measures of oncologic and functional outcome is extremely limited and highly variable. The threshold for declaring the learning curve complete ranged from 10-200 cases in these studies. In most situations, "early" cases were excluded from consideration completely (Ahlering, 2004; Remzi, 2005; Joseph, 2005; Smith, 2007; Laurila, 2008; Ficarra, 2009; Rozet, 2005).

In relatively few studies outcomes were compared for "early" vs. "late" case experience. In a single center comparative evaluation of laparoscopic vs. open prostatectomy in Germany (Rassweiler, 2003), 438 laparoscopic patients were divided equally into 2 groups representing early vs. late experience. Significant reductions in operative time, blood loss,

open conversions, and peri-operative complications were observed in the late cohort relative to both early laparoscopic and open prostatectomy. No differences in positive margins, PSA relapse, or long-term side effects were observed. Peri-operative outcomes also were compared for the first and second sets of 50 patients treated laparoscopically in the United Kingdom (Eden, 2006). A significant reduction in operative time was noted among patients in the second series (219 vs. 268 minutes, $p<.05$); however, blood loss, complication rates, and rates of margin positivity were statistically similar between the cohorts.

In addition to Hu's analysis of Medicare claims, formal study of the learning curve was undertaken in several other large-volume studies. Vickers and colleagues reported the results of retrospective analysis of nearly 8,000 patients treated with open prostatectomy by 72 surgeons at 4 academic centers in the US (Vickers, 2007). Findings from multivariate analyses indicated a long and "flattened" learning curve; the 5-year rate of biochemical freedom from failure did not plateau until 250 surgeries were performed. There was a 67% increase in recurrence risk among surgeons with 10 vs. 250 prior procedures. Findings from a follow-up study of laparoscopic prostatectomy (Vickers, 2009) suggested that, in comparison to the previous study, benefits of increased laparoscopic experience accrued more slowly than for open procedures; similar freedom-from-failure rates were not observed until after 750 laparoscopic procedures. Interestingly, prior open prostatectomy experience was associated with a more than twofold increase in the risk of recurrence relative to laparoscopic-only training, suggesting that open surgical skills do not necessarily translate when surgeons shift to minimally-invasive approaches.

Given the strength of the data linking surgeon experience to broad ranges of complications and side effects, variability between surgeons and institutions is likely a more important predictor of patient outcomes than any difference that might be due to the surgical approach selected. For example, if the ranges of side effects found in the ICER systematic review are assumed to arise solely from differences in surgical expertise, a surgeon performing at the 75th percentile among his or her peers would have a combined major complication rate of approximately 2-3%, with long-term rates of ED at 30-35% and incontinence at 5-7%. These complication and side effect rates would be significantly lower than those of surgeons operating at the 25th percentile, whose patients would suffer major complications at 10-12%, ED at 50-60%, and incontinence at 15-20%. Not all of the variation in published outcomes can be ascribed to surgical expertise, but the data do suggest that variation in surgical performance is a critical feature in any evaluation of the comparative effectiveness of radical prostatectomy to active surveillance or other interventions for localized prostate cancer.

The extreme variability in estimates of surgical outcome may in part be the result of the lack of formal training and/or competency standards for radical prostatectomy, particularly the newer surgical approaches. There is documented evidence that extended training produces superior outcomes relative to shorter training regimens (Verdaasdonk, 2007), yet procedure training for minimally-invasive surgery may be as short as 1-2 days in duration. In addition, despite data suggesting great interest in robotic surgery among a majority of

surgical residents, findings from a recent survey suggested that access to robotic techniques was available in only 20% of residency programs (Patel, 2003).

Potential Harms Associated with Active Surveillance

Biopsy-related Complications

Data are extremely limited and variable on the incidence and severity of complications arising from initial or repeat prostate biopsy during active surveillance. Nevertheless, prostate biopsy appears to be a relatively safe procedure. Most complications, such as pain and rectal bleeding, are transient and self-limiting. 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%.

Evidence of complications arising from transrectal prostate biopsy is very limited; we could identify only 2 studies that have been published within the past 3 years (Lee, 2006; Sieber, 2007). 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 (Presti Jr., 2007).

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 (Djavan, 2001).

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 (Djavan, 2001). 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 (Crundwell, 1999; Enlund, 1997; Lee, 2006).

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 (Sieber, 2007). 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).

Patient Anxiety

Limited data from the active surveillance and watchful waiting literature suggest that anxiety levels do not substantially differ between men on these regimens and those

receiving radiation or surgery. However, it appears that anxiety levels do predict receipt of treatment for patients on a surveillance regimen.

Explicit measurement of anxiety is available in only one published report of active surveillance (Burnet, 2007). Anxiety was measured using the Hospital Anxiety and Depression Scale (HADS) in 100 patients undergoing surveillance, and compared to 81 men who were receiving radical treatment and 148 patients who were in post-treatment status. While there were nominal crude differences in the rate of anxiety (21% for surveillance vs. 15% and 10% for post- and on-treatment respectively), treatment group was not significantly associated with either anxiety or depression in multivariate analyses.

In the watchful waiting literature, the most comprehensive assessment of anxiety was measured in a subset analysis of the Scandinavian SPCG-4 trial (Steineck, 2002). At a mean of 4 years following randomization, moderate-high anxiety was reported in approximately one-third of survey participants, and did not differ significantly between those in the radical prostatectomy and watchful waiting groups. Findings from an analysis of 310 CaPSURE participants undergoing watchful waiting (Arredondo, 2004) indicate significant declines over time in physical, social, and symptom quality-of-life scores; however, no material changes in either emotional or mental health scores were observed. A separate CaPSURE analysis also reported unchanged HRQOL scores for watchful waiting patients on the mental health, emotional, vitality, and social function scales of the RAND survey (Litwin, 2002).

Data do suggest, however, that anxiety plays a role in patient selection of radical treatment while in active surveillance when there is no sign of clinical progression. A total of 105 men from the CaPSURE registry who elected active surveillance were assessed using a 3-item anxiety questionnaire semi-annually (Latini, 2007). Thirty-four percent of men received treatment a median of 40 months following diagnosis. Increasing anxiety scores were an independent and significant predictor of treatment.

Hospital Costs and Efficiency: Open vs. Minimally-Invasive Prostatectomy
In the U.S., reimbursement of all 3 surgical approaches to prostatectomy is similar. However, costs to the hospital differ substantially, as acquisition, maintenance, and supply costs for laparoscopic guidance and robot systems add significantly to the costs of providing these services. Minimally-invasive prostatectomy is associated with shorter hospital length of stay relative to open prostatectomy; however, operating-room time remains longer with minimally-invasive surgery.

There are substantial differences between surgical approaches in their cost to the institution providing these services. Purchase costs for laparoscopic positioning and robot systems have been estimated to be as high as $200,000 and $1.6 million, respectively (Lotan, 2004; Joseph, 2008; Quang, 2007). In addition, annual maintenance costs for robotic systems range from $100,000-$200,000, and the costs of disposables range from $2,000-$3,000 per case (Lotan, 2004).

Operating-room time remains longer for minimally-invasive surgery, even in cases where improvement has been noted along the learning curve. OR time in our sample was shorter for open prostatectomy (191 minutes) as compared to both laparoscopic (264 minutes) and robot-assisted (223 minutes) respectively. On the other hand, minimally-invasive surgery appears to be associated with significantly shorter hospital length of stay relative to open prostatectomy. With a focus on US-based studies in our sample, length of stay averaged 2.2 and 1.1 days for laparoscopic and robot-assisted prostatectomy respectively, vs. 4.0 days for open prostatectomy. Because reimbursement in the U.S. does not generally differ substantially for each surgical approach, there is considerable pressure on institutions to recover acquisition, maintenance, and procedural costs for minimally-invasive surgery based on a combination of procedure volume, shorter hospital length of stay, reduced laboratory and blood bank use, and cost-shifting to other cases (Klotz, 2007).

Formal evidence on the comparative cost-effectiveness of different surgical approaches to prostatectomy is limited. Lotan and colleagues developed an economic model to compare the institutional costs to the hospital of open, laparoscopic, and robot-assisted prostatectomy (Lotan, 2004). Costs were estimated for the inpatient surgical stay only; robot-assisted costs were calculated alternatively with and without the estimated $1.2 million initial purchase cost. Total inpatient costs were estimated to be $5,554, $6,041, and $7,280 for open, laparoscopic, and robot-assisted prostatectomy ($6,709 without initial purchase cost); in threshold analyses, there were no modifications in length of stay, disposables cost, purchase or maintenance cost, or case volume that would result in equivalent costs for robot-assisted and open surgery, whereas a 20% reduction in operative time (from 200 to 160 minutes) would introduce cost-neutrality between open and laparoscopic surgery. Similar findings were observed in a 3-way comparison of academic medical center operating-room costs (Joseph, 2008); laparoscopic costs were twice as high as those for open surgery ($3,876 vs. $1,870), while costs of robot-assisted surgery were 3 times higher ($5,410).

In contrast, findings from a study of facility and professional costs at the Duke Prostate Center (Mouraviev, 2007) suggest higher operative costs for robotic prostatectomy relative to open retropubic or perineal approaches, but total hospital costs that were somewhat lower ($10,047 vs. $10,704 and $10,536 respectively) due to shorter length of stay and fewer laboratory and transfusion requirements. The authors discuss the possibility that completion of the learning curve for minimally-invasive surgery is a partial explanation for why these findings differ from those of other economic studies.

While differences in resource utilization between surgical approaches have been observed in these studies, there is also evidence that hospital and clinical efficiency has improved to similar levels for *all* surgical approaches. For example, multiple case series observed at Vanderbilt University Medical Center suggest clinically similar transfusion requirements for open and robot-assisted prostatectomy when standardized hemostasis protocols are employed (Farnham, 2006; Koch, 1996).

In addition, hospital length of stay for open radical prostatectomy has decreased dramatically through the use of clinical pathways (Smith Jr., 1996), which may in turn mitigate differences between surgical approaches. For example, findings from a recent comparative series of over 1,000 open and robot-assisted prostatectomies, also at Vanderbilt, indicate essentially identical mean lengths of stay for these two approaches (1.25 vs. 1.17 days respectively, p=.27), as well as statistically similar rates of unscheduled clinic/ER visits and hospital readmissions (Nelson, 2007).

8. Economic Model

8.1 Objective

The primary objective of the economic model was to assess the comparative clinical outcomes and cost-effectiveness of active surveillance and radical prostatectomy as treatment options for patients with low-risk, clinically localized prostate cancer. (NOTE: while not a focus of this appraisal, the model also allows for evaluation of the most common options for radiation therapy: brachytherapy, IMRT and PBT).

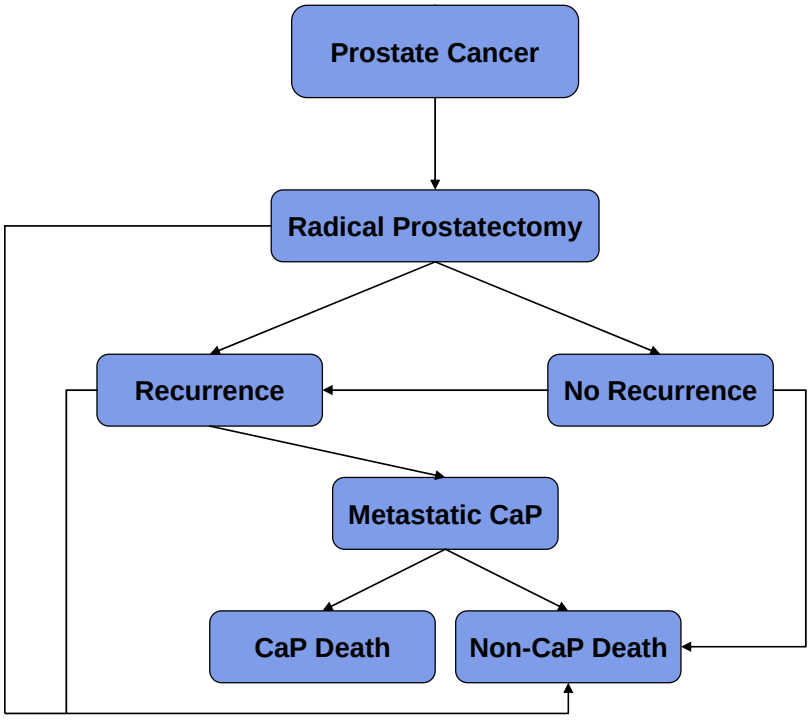
Our systematic review of the evidence on clinical effectiveness found no evidence to support differential survival or rates of biochemical recurrence among these treatment strategies, so the model focuses on differences in procedural complications, and short- and long-term side effects of treatment. However, because survival differences between radical prostatectomy and *watchful waiting* have been noted, the potential for a survival benefit for surgery relative to active surveillance was explored in an alternative analysis.

8.2 Methods

Overview of Model

The model was constructed to track movement of men from diagnosis through subsequent states of health (i.e., a Markov state-transition model). The primary model simulated lifetime histories of 100,000 men (i.e., Monte Carlo analyses) to estimate outcomes and costs among those diagnosed at age 65. The general structure and flow for patients undergoing immediate definitive treatment is shown in Figure 1 below.

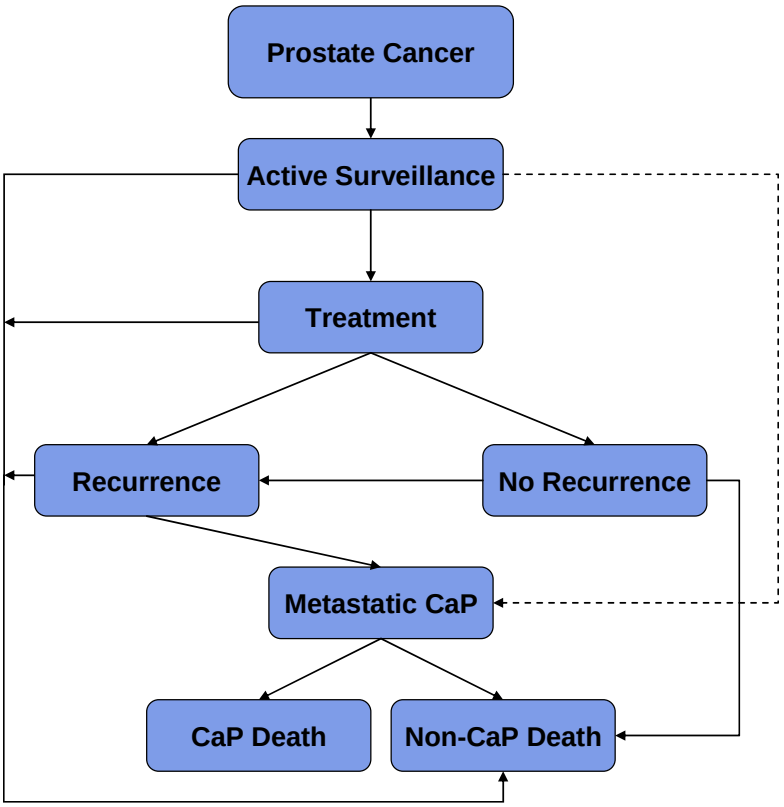
Figure 1. Model of immediate definitive treatment for low-risk prostate cancer.



Men enter the model and are immediately assigned to treatment with radical prostatectomy. Once treated, men may biochemically recur or not; those who recur may progress to metastatic disease and death due to prostate cancer or other causes. Men may die of non-prostate cancer causes from any health state. Because the results of our systematic review indicated no differences in major outcomes among the surgical approaches to prostatectomy, the model primarily focused on open prostatectomy, with consideration of minimally-invasive surgery in alternative analyses. The use of salvage or adjuvant radiation among men undergoing radical prostatectomy was not modeled (see Key Assumptions).

The model structure and flow for men who initially are assigned to active surveillance can be seen in Figure 2 below. Progression to treatment may be triggered by Gleason progression (i.e., to Gleason 7 or higher disease), other measures of local progression (e.g., PSA doubling time), or patient preference in the absence of any clinical measure of progression. It is assumed that men with Gleason progression are treated with IMRT and 6 months of androgen deprivation therapy (ADT), regardless of age. Men treated for other reasons receive radical prostatectomy if under 65 years of age at treatment initiation, and IMRT if aged 65 years or older. The active surveillance structure is identical to that of immediate treatment from the point of treatment forward; however, in addition to a risk of metastatic disease following biochemical recurrence, the active surveillance arm includes the possibility that metastases can develop *prior* to definitive treatment, as indicated by the dotted line in Figure 2.

Figure 2. Model of active surveillance for low-risk prostate cancer.



The active surveillance protocol included (a) quarterly physician visits in the first year, visits every 6 months thereafter; (b) quarterly PSA testing; (c) digital rectal exams (DRE) every 6 months; (d) re-biopsy at 1 year following diagnosis; and (e) re-biopsy every 3 years thereafter. In our base case analysis, we assumed that men on AS would not have obstructive urinary symptoms or erectile dysfunction attributable to their disease, but that they would develop these symptoms at an age-related rate similar to men without prostate cancer. Men receiving AS were also at risk of major complications of repeat biopsy, including urosepsis and acute urinary retention.

Men receiving radical prostatectomy were at risk of peri-operative death as well as major (e.g., DVT/PE) and minor (e.g., UTI) complications and urethral stricture; the rates of short- and long-term urinary incontinence and erectile dysfunction were modeled in these men. Finally, because treatment with IMRT with or without ADT is an option for older men on active surveillance, we also modeled the short- and long-term side effects of these treatments, including erectile dysfunction as well as urinary and gastrointestinal side effects. Patients could experience all possible combinations of the presence or absence of these effects. We used the available literature to assign utilities to health states, including utilities for major surgical complications, disease-related symptoms, short- and long-term side effects, and the general physical and emotional impact of treatment and active surveillance.

Major categories of costs included treatment costs, costs for management of complications, toxicities, side effects and symptoms, and patient time costs while in treatment. Base case treatment costs were estimated by using 2008 Medicare payments and patient time costs were based on 2008 US wages of age-matched men. The primary outcomes are costs and quality-adjusted life expectancy, both discounted at a 3% annual rate.

Key Assumptions
Major assumptions of the model as well as relevant sources and justification are presented in Table 1 on the following page. Assumptions were made based on review of the literature as well as discussions with clinical and economic expert members of the ERG, and were subject to testing in sensitivity analyses.

Type of Analysis
This study is a cost-utility analysis (CUA). Incremental cost-effectiveness ratios (ICERS) are presented with costs in 2008 U.S. dollars, and effectiveness in quality-adjusted life-years (QALYs).

Perspective
We followed most recommendations of the Panel on Cost-Effectiveness in Health and Medicine (Gold, 1996) but since we were not addressing societal questions of the full return on investment in various treatment strategies, we adopted a public payer perspective for the base case which includes capital expenditures in its reimbursement framework and took

patient time in therapy into account. Note that 1st-copy costs for installation of an IMRT facility or robotic surgery system were excluded. Sensitivity analyses were performed in which we examined alternative perspectives. Specifically, we performed analyses that (a) excluded patient time costs from consideration; and (b) used private payer perspectives (i.e., no adjustment for capital expenditures, reimbursement estimates from private insurers).

Table 1. Major assumptions of Markov model of active surveillance and radical prostatectomy for low-risk, clinically-localized prostate cancer.

ASSUMPTION	RATIONALE & SOURCE
• No men will die of prostate cancer within 6 months of diagnosis	Low prostate cancer specific mortality in low-risk patients -ICER Review
• All men who recur after treatment recur biochemically	Patients monitored closely by PSA after treatment -ICER Review
• Progression from recurrence to metastatic disease to death identical regardless of treatment	No proven disease-related benefit to one treatment over another -ICER Review
• Men on AS who receive treatment have = risk of CaP death as men treated initially	No studies with sufficient follow up to suggest mortality benefit or harm to AS -ICER Review
• Treatment after AS is RP if <65 or IMRT (w/ or w/o ADT) if ≥65	Mortality benefit to RP vs. WW limited to men <65 yo -Bill-Axelson, 2005
• No men treated with RP receive adjuvant/salvage XRT	<10% low-risk CaP have positive margins at RP -Louie-Johnsun, 2009; Griffin, 2007 Use of salvage XRT in men with low-risk disease <15% -Lu-Yao, 1996; Grossfeld, 1998

NOTES: AS: Active surveillance; RP: Radical prostatectomy; IMRT: Intensity-modulated radiation therapy; XRT: external beam radiation therapy; WW: Watchful waiting; CaP: Prostate cancer

Target Population

We conducted our base case analysis for 65 year-old men with clinically localized prostate cancer and a low risk of cancer recurrence. Patients at low-risk for recurrence have stage T1 to T2a lesions, Gleason scores between 2 and 6, and PSA levels less than 10 ng/mL (D'Amico, 1999). Alternative analyses were conducted for cohorts of men aged 55 years (see Alternative Cohorts).

Strategies
Possible definitive treatment options for patients receiving active surveillance varied based on patient age and type of disease progression, as follows:

- Radical prostatectomy (if under age 65 at time of progression)
- IMRT (if age 65+ at time of progression)
- IMRT + ADT (for progression to Gleason 7 disease)

As described previously, our primary comparison was between active surveillance and open radical prostatectomy. Radical prostatectomy was performed using bilateral nerve-sparing technique. Subsequent treatment with IMRT involved 39 daily fractions at a total dose of 75-81 Gy; ADT treatment lasted 6 months.

Time Horizon
A lifetime horizon was adopted to capture prostate cancer-related costs and health effects. We discounted future costs and QALYs at 3% annually.

Prevalence of Complications, Side Effects, and Symptoms
Patients were at risk of developing symptoms related to complications or side effects of treatment (see Table A at the end of this section). The development of one type of symptom did not predict the development of any other type; in other words, patients could have a single adverse effect or all possible adverse effects, as well as any possible combination. In addition, because the focus was primarily on moderate-to-severe side effects, all adverse effects were assumed to be treated.

Natural History of Symptoms While on Active Surveillance
In this model, patients who undertake a program of active surveillance experience progressive urinary and sexual symptoms associated with their age. Data on the prevalence and rate of progression of these symptoms specifically among men on active surveillance are unavailable. Because of the low-risk and localized nature of disease in our target population, we therefore assumed that the prevalence of these symptoms and their progression during active surveillance would be similar to that experienced by men of the same age in the general population based on review of the literature (Andersson, 2004; Bacon, 2003). However, we also conducted sensitivity analysis around these parameters to examine whether a higher incidence of urinary obstructive symptoms and erectile dysfunction would materially affect our results (see Sensitivity Analyses).

Complications of Biopsy during Active Surveillance
Patients on active surveillance who are re-biopsied may experience significant complications of this procedure, including urosepsis and acute urinary retention. We modeled these risks based on data from a large series of men undergoing initial and repeat biopsy as part of a prostate cancer screening program (Djavan, 2001). Other complications of biopsy (e.g., hematuria, rectal bleeding) were felt to be transient and self-limiting, and were therefore not modeled.

Complications and Side Effects of Radical Prostatectomy
We modeled peri-operative complications of radical prostatectomy occurring within 30 days of surgery, including mortality as well as major and minor complications. Complications deemed to be major included major bleeding, DVT/PE, MI/stroke, bowel injury, and major or systemic infection. Minor complications represented those outcomes not typically requiring re-exploration or invasive intervention (e.g., UTI, hematoma, ileus). Data on the rates of mortality and peri-operative complications were obtained based on the results of the ICER systematic review (Table A).

Other side effects included urethral stricture, urinary incontinence, and erectile dysfunction. A single figure for a risk of stricture within 9 months of surgery was estimated based on findings from the ICER systematic review; in contrast, because risks of urinary incontinence and erectile dysfunction are known to be initially high and then diminish over time following prostatectomy, both short-term (occurring within 90 days post-procedure) and long-term (occurring within 12 months post-procedure) estimates were modeled; the ICER systematic review also served as the source for these estimates. Short-term effects were limited to 3 months' duration, while long-term effects were assumed to persist for life.

Side effects of Radiation Therapy
Only side effects that met or exceeded grade 2 on the RTOG or CTC toxicity scales were considered, as these are the effects that typically require treatment (National Cancer Institute, 1999; Radiation Therapy Oncology Group, 2008). Estimated risks of side effects of IMRT included genitourinary and gastrointestinal side effects as well as erectile dysfunction, and were based on the results of the prior ICER systematic review of radiation options for low-risk prostate cancer (ICER, 2008). Short-term side effects were defined as those occurring within 90 days following treatment; long-term side effects included those with a duration longer than 90 days as well as those occurring up to 2 years after radiation.

The time course of erectile dysfunction following radiation is different than that for surgery; rather than a sharp increase followed by decline and stabilization following surgery, incidence steadily increases following radiation until a plateau is reached approximately 2 years following treatment (Talcott, 2003). Therefore, only a long-term estimate was made for patients undergoing radiation, based on findings from the prior ICER systematic review. All men treated with IMRT in combination with androgen deprivation therapy (i.e., for Gleason 7 or higher disease) were assumed to have erectile dysfunction for one year following treatment.

Finally, several studies have documented a small but non-zero potential risk of a second primary cancer attributable to the dose of radiation received during IMRT (Abdel Wahab, 2008; Brenner, 2000; Kry, 2005; Schneider, 2008; Schneider, 2006; Chung, 2008; Bostrom, 2007). In the model, a 1% lifetime risk of a second fatal cancer was assumed to emerge 10 years after IMRT and be constant for remaining years of life (see Table A).

Disease Outcomes

Men Immediately Treated with Radical Prostatectomy or IMRT
Consistent with findings from our systematic reviews, it was assumed that radical prostatectomy and IMRT are associated with similar disease-related outcomes. Therefore, rates of biochemical recurrence, subsequent development of metastatic disease, and death due to prostate cancer in men with metastatic disease were the same after any immediate treatment of low-risk disease.

Men Receiving Active Surveillance
In our active surveillance scenarios, treatment may be triggered due to progression to higher risk disease (i.e., progression to Gleason 7 or higher disease on subsequent biopsy), other progression unrelated to biopsy findings (e.g., rapid PSA doubling time, clinical progression), or patient preference. Based on data from modern active surveillance series, approximately one-third of patients who receive definitive treatment have evidence of Gleason 7 or higher disease on re-biopsy; another third have evidence of progression through measures such as PSA doubling time; and the remaining third choose to be treated with no evidence of disease progression.

As discussed above, men who experience progression to Gleason 7 or higher disease are treated with IMRT and 6 months of ADT. We elected to add 6 months of ADT to definitive IMRT to create a "worst-case scenario", in which the consequences of AS include more aggressive therapy. Their subsequent risk of biochemical recurrence (and accordingly, metastatic disease and prostate cancer death) is higher than in men with low-risk disease (D'Amico, 1999). The remainder of treated men receive radical prostatectomy if aged less than 65 years, and IMRT (without ADT) if aged 65 years or older. Subsequent risks for these men are identical to those for men treated immediately after diagnosis.

Age-specific risks of death from causes other than prostate cancer were based on the 2004 US life tables (US Centers for Disease Control, 2009).

Health-related Quality of Life
Health state utilities were based primarily on the work of Stewart et al. (Stewart, 2005; personal communication, 2009), who elicited preferences from men over 60 years of age, half of whom had been diagnosed with prostate cancer. Utilities were obtained using the time-tradeoff method and included utilities for urinary, gastrointestinal, and sexual side effects of treatment alone or in any possible combination. Utilities for men without symptoms but with untreated, recurrent, and metastatic disease were also reported.

Utilities for major complications of surgery were derived based on data from a national catalogue of utilities measured on the EQ-5D for multiple chronic conditions (Sullivan, 2006). Conditions were matched to the major complications of interest; a weighted average was derived based on the relative proportions of each complication as measured during the ICER systematic review. Because minor complications did not involve significant treatment, no decrement in utility was assigned to these effects.

Men who developed side effects or complications of treatment were assigned a disutility corresponding to their disease state and the effects they experienced. Patients were assumed to maintain their post-treatment health state and utility until death, with 2 exceptions: (1) health state utilities related to short-term side effects, which were adjusted to be proportionate to a 3 month-duration; and (2) erectile dysfunction attributed to ADT, which was assumed to last only for the year during which such treatment was given.

Treatment Costs

Costs for treatments are provided in Table B. In addition to primary treatment, treatment costs included those of drugs, supplies, tests, and follow-up visits. Base case direct medical costs were assumed to equal the national average Medicare payment rates in a hospital setting (except where noted), and drug costs were derived from the 2008 Red Book (Thomson Reuters, 2008). Medicare outpatient payments were estimated using current procedural terminology (CPT) codes, 2008 ambulatory payment codes (APCs) and relative value units (RVUs) from the 2008 Hospital Outpatient Prospective Payment System (OPPS), with the professional component in the hospital outpatient setting from the Physician Fee Schedule. Costs of additional treatment components were estimated from the 2008 Lab Fees and Durable Medical Equipment Schedules from the Centers for Medicare & Medicaid Services (CMS) (CMS, 2008). Total RVUs included work-related and facility-related components, with both technical and professional components where applicable. Medicare inpatient payments were based on national payment estimates from the 2008 Hospital Inpatient Prospective Payment System (IPPS), along with the 2008 Anesthesia Conversion Factor and American Society of Anesthesiologists (ASA) units for anesthesiologist payments.

Open radical prostatectomy was estimated to cost $10,479, $17,779, and $27,879 for uncomplicated cases, cases with minor complications, and cases with major complications, respectively, based on national payment rates for these cases based on CMS' Medicare-Severity Diagnosis Related Groups (MS-DRGs), surgeon payment (i.e., CPT) codes for open prostatectomy, and anesthesiologist (ASA) payments based on an average of 191 minutes of operative time (calculated from the systematic review). Corresponding estimates for laparoscopic and robot-assisted prostatectomy (which share the same codes) were $10,970, $18,270, and $28,370 respectively based the above MS-DRGs, CPT codes for laparoscopic prostatectomy, and ASA payments based on an average of 253 minutes of operative time.

IMRT was estimated to cost $21,050, based on delivery of 39 fractions and CPT codes for office consultation, IMRT treatment planning and delivery, immobilization and beam modifying devices, dosimetry calculations, port films, and a special physics consultation and treatment procedure. The base case cost estimate was a "blended" rate based on differential payments to hospitals and free-standing radiation therapy centers; two-thirds of IMRT cases were assumed to occur in hospitals, with the remaining one-third of treatment in free-standing centers, based on expert opinion. Androgen deprivation therapy (as a 6-month adjunct to IMRT for intermediate risk patients) was estimated to cost $8,034 based on 2 injections of leuprolide, daily bicalutamide, and associated office visits and monitoring of liver function tests.

Active surveillance costs were estimated at $995 in the first year based on codes for quarterly visits and PSA tests as well as biopsy. Surveillance costs (PSA tests and visits) for subsequent years would total $300, as only bi-annual physician visits were assumed after the first year. Post-treatment monitoring costs were estimated to be $248 annually, based on physician visits for PSA testing every 6 months.

We did not consider the cost of medical care for conditions other than prostate cancer or for terminal care. Because we assume that all treatment modalities are equally effective in terms of survival benefits, the incorporation of these costs would merely add a constant to each year of life and would not change incremental cost-effectiveness ratios. Similarly, costs for any diagnostic tests common to all patients entering the model were not included.

Costs of Management of Toxicities, Side Effects, and Symptoms
Costs of managing treatment-related adverse effects were derived from CPT codes, published studies, and structured interviews with clinicians. Costs in Table B are weighted averages representing typical case mixes (severity, treatment modality) described in more detail below. All related office visits are included. Note that the costs of peri-operative complications of radical prostatectomy are included in the prospective inpatient payments, and as such, no separate management costs were estimated.

An estimated 40% of patients experiencing erectile dysfunction pursue treatment, with weekly Viagra as the first line of therapy in 97% of treated cases. An estimated 10% of treated cases receive a vacuum device, another 5% of treated cases receive prostheses and another 5% of treated cases receive intracavernous injections for their impotence.

Men who experience urinary symptoms while on active surveillance are assumed to undergo cystoscopy and are treated with daily Flomax®. An estimated 50% of these patients undergo dilation, and a small proportion (2%) undergo TURP. Patients experiencing acute urinary retention undergo catheterization (90% of cases), cystoscopy (10% of cases), or transurethral resection of the prostate (TURP) (1% of cases). Other types of acute GU toxicity are treated with 1 month of Flomax, with approximately 10% of patients also undergoing cystoscopy and another 5% of patients requiring antibiotic treatment of infection. Incontinence is diagnosed with uroflowmetry and treated with an anticholinergic agent for urinary frequency and urgency. Approximately 25% of patients require temporary stenting and 1% require an artificial sphincter. Finally, all patients who experience urethral stricture are assumed to undergo cystoscopy and dilation.

Patients experiencing acute GI toxicity following radiation were assumed to undergo a colonoscopy and a 6-month course of an anti-inflammatory enema. Patients experiencing late GI toxicity were first treated with a 6 month course of an anti-inflammatory enema that effectively controls bleeding in 70% of cases. The remainder were assumed to undergo a colonoscopy followed by an average of three sigmoidoscopy procedures with ablation for intractable bleeding, followed by an additional 6 month course of enemas.

Cases of urosepsis following prostate biopsy were assumed to be admitted to hospital but not to require mechanical ventilation or have major complications. As such, a DRG payment for uncomplicated septicemia was employed and estimated to total $11,804 in 2008 dollars.

Patient Time Costs

Patient time required to undergo treatment and seek care for management of adverse effects was valued at $151 per day, assuming an 8-hour work day at the 2008 U.S. median wage for men aged 65 and older (US Bureau of Labor Statistics, 2008). Estimates of the number of hours required for each intervention were derived from literature sources (Yabroff, 2007), online patient guides, and interviews with clinicians.

Briefly, office visits were estimated to require 4 hours (including travel) and daily visits for radiation therapy were assumed to require 2 hours. Time in hospital for radical prostatectomy ranged from 2.7 days (uncomplicated) to 12.2 days (major complications); time in hospital for urosepsis was estimated to be 5.7 days. Colonoscopies and cystoscopies were assumed to require 1 day. Estimates of total patient time per condition were weighted by case mix as above.

Alternative Analyses and Cohorts

In order to evaluate how our results would vary in different patient populations, we performed multiple alternative analyses. We also conducted sensitivity analyses on certain key probabilities and assumptions in order to determine the effect of the uncertainty surrounding these estimates on our base case results.

RP survival benefit. The first alternative analysis assumed that a disease-specific survival benefit for open radical prostatectomy vs. active surveillance would be observed; the assumed benefit was an absolute difference of 2.5% at 10 years and persisting for life, which is approximately one-half that observed in the SPCG-4 trial of radical prostatectomy vs. watchful waiting (Bill-Axelson, 2005).

Cohort of 55 year-old men. This alternative analysis populated the base case scenario with an alternative cohort of 55-year-old men, with corresponding changes in all-cause mortality, baseline (pre-treatment) rates and development of symptoms, and wage rate.

Alternative definitive treatments for men on active surveillance. We conducted two analyses varying the treatment men on active treatment received when they either progressed or chose to be treated. In the first analysis, we assumed that men who progressed biochemically or clinically (except those with Gleason progression) as well as those who chose treatment would receive brachytherapy rather than IMRT. In the second alternative analysis, men who progressed by Gleason score were treated with IMRT *without* ADT.

Private payer cost scenarios. Estimates of non-Medicare reimbursements for radical prostatectomy, IMRT, brachytherapy, and ADT were derived from private-pay sources.

Varying disutilities associated with symptoms and health states. We next varied the disutility associated with various health states. We first created a scenario in which no disutility was included for erectile dysfunction; in a second alternative scenario, only disutilities associated with side effects, and none associated with the psychological or emotional states associated with active surveillance or radical prostatectomy, were included.

Omitting patient time costs. In this analysis, we omitted patient time costs in order to simulate the standard payer perspective.

Maximal assumption of effectiveness of robot-assisted vs. open prostatectomy. We also compared alternative techniques of radical prostatectomy, assuming that the nominal differences in complications and side effects observed in the systematic review represented true differences that were supported by definitive research.

Sensitivity Analyses: Active Surveillance. We conducted sensitivity analyses around the probabilities of (a) progressing to Gleason 7 or higher disease; (b) experiencing any form of progression; (c) electing treatment without objective evidence of progression; and (d) developing urinary and/or sexual symptoms while on active surveillance. Base case estimates were varied over a broad range.

Probabilistic Sensitivity Analysis

Uncertainty around estimates of costs was represented by using gamma distributions both to disallow negative costs and to account for the skewness typically found in cost data. Parameters of the gamma distributions were derived by defining the base case value as the mean and assuming a 95% confidence interval roughly spanning the range of 50% to 200% of the base case value, or

$$\text{standard deviation} = [\ (2*\text{base case value} - 0.5*\text{base case value}) / 4\ ]$$

Uncertainty around event probabilities was represented using beta distributions (range [0,1]), choosing parameters that allowed wide ranges for rates of biochemical recurrence and toxicity incidence. Uniform distributions were assigned to represent uncertainty around utilities.

8.3 Results

Base Case Results

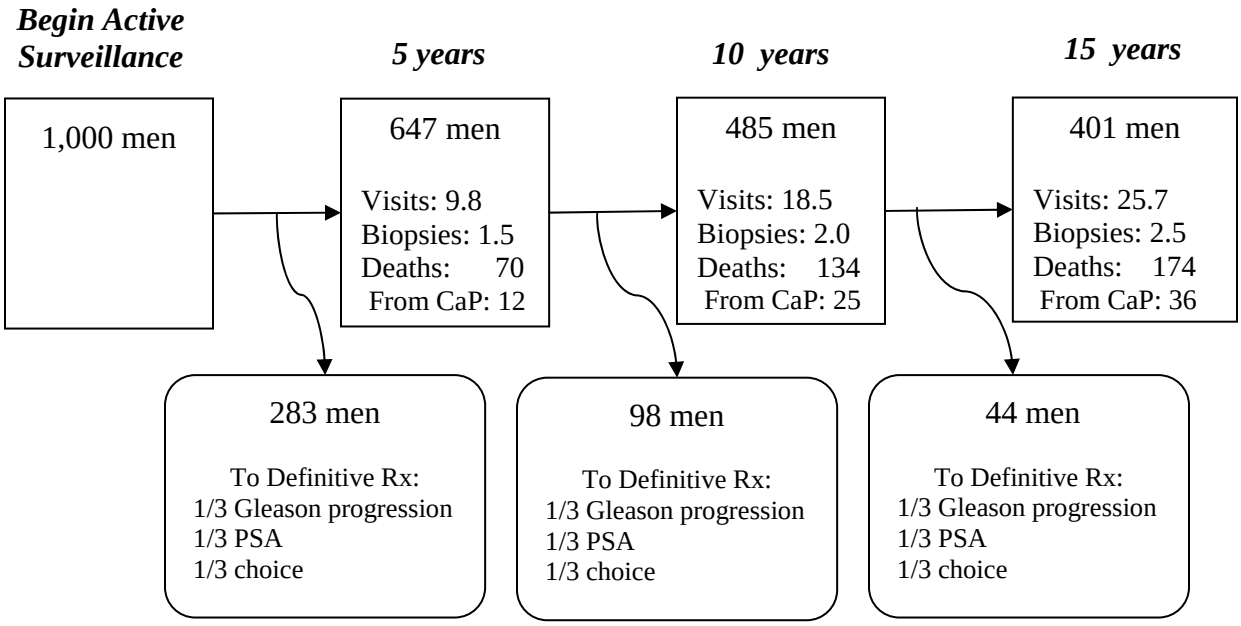
Our base case analysis followed a cohort of men either treated with a) open radical prostatectomy at diagnosis or b) active surveillance followed by definitive treatment at progression or at patient request. This comparison attempts to balance the benefits and harms of immediate treatment vs. a strategy of close observation. Whereas surgery carries the benefit of probable cure soon after diagnosis, it is also associated with significant side effects; active surveillance offers men an opportunity to avoid treatment, but carries the risk of possible "escape from cure" and the expense and inconvenience of more frequent visits. Our model attempted to quantify the benefits and costs of these alternative strategies.

If treated at age 65, the strategy of open radical prostatectomy is associated with an average of 37 visits over the lifetime of the patient. The risk of developing ED attributable to this procedure is 31%; the risk of incontinence is 9%. These estimates are lower than those produced by the ICER systematic review, as they reflect incidence over and above the underlying risk of these conditions due to age and comorbidity. The undiscounted cost of treatment is $10,410, and the cost of visits thereafter is $3,655. The patient time cost associated with this approach is estimated to be $6,150.

Progression through active surveillance is illustrated in Figure 3 on the following page. If a man elects active surveillance, the lifetime risk he will progress to treatment is 61%. He will undergo 36 visits and on average, 2.8 biopsies over this period. The chance of his developing incontinence due to subsequent treatment is 4%; he also has a 5% chance of ED and 3% risk of GI side effects as a result of treatment. The cost of this approach includes $4,809 for visits and biopsies, and $8,156 in patient time costs. The average cost of definitive treatment is $14,327 over the entire cohort.

We assumed that men who underwent active surveillance would not be at an added risk of death due to prostate cancer or any other cause as a result of having elected this approach. Therefore, the life expectancy of 16 years for these patients is equivalent to that of radical prostatectomy.

Figure 3. Schematic flowchart of 5, 10- , and 15-year cumulative visits, biopsies, all-cause and disease-specific mortality, and treatment decisions of among a cohort of 65 year-old men beginning active surveillance for low-risk, clinically-localized prostate cancer. Data derived from ICER decision-analytic model.



In our cost-effectiveness model, active surveillance followed by IMRT was more effective but marginally more expensive than initial open radical prostatectomy. Table 2 provides estimated costs and QALYs from each strategy.

Table 2. Base Case Results

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	7.82	Reference	Reference
AS	$30,422	$2074	8.97	1.15	$1,803

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

Active surveillance followed by IMRT was more effective, providing an additional 13.8 months of quality-adjusted life expectancy, at an additional cost of $2,074, yielding an incremental cost-effectiveness ratio of $1,803 per QALY. The added expense of AS is due principally to the greater amount of patient time required and to the cost of IMRT for men who are treated, which was estimated to be approximately twice that of radical prostatectomy.

Despite the higher lifetime cost for active surveillance, the short-term budgetary impact to a payer or integrated health system is higher for radical prostatectomy, as all patients are immediately treated with this strategy. Using Medicare reimbursements as the basis, in the

first two-year period following diagnosis of cancer in a cohort of 1,000 patients, a strategy of active surveillance would save nearly $8 million dollars under current Medicare reimbursement rates; a saving of over $13 million dollars would be expected under one of the private payer actual cost scenarios evaluated. Figures are shown in the Comparative Value Evidence Table (CVET) in Appendix C.

Alternative Perspectives and Cohorts

Cost-Utility Analysis Among 55-Year-Old Men

We modeled the cost effectiveness of active surveillance as compared to open radical prostatectomy in a cohort of men aged 55 years. Younger men have lower baseline rates and annual probability of developing erectile dysfunction and urinary symptoms; therefore the probability of these events was modified accordingly. In addition, the patient time costs of men below age 65 years are higher than those of men of retirement age; these costs were also age-adjusted. Results are displayed in Table 3.

Table 3. Model Results for 55-Year Old Men

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$31,440	Reference	10.33	Reference	Reference
AS	$33,642	$2,202	11.54	1.21	$1,820

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

In this younger cohort, active surveillance remained more effective than initial prostatectomy, yielding 14.7 months of QALE at an incremental cost of $2,202. Incremental benefits and costs were similar to those observed among 65-year old men, yielding an incremental cost-effectiveness ratio of $1,820 per QALY gained. The incremental benefits of AS over ORP in this setting arise from the fact that more men develop side effects attributable to treatment, rather than to age, in both cohorts. However, men on AS develop proportionally more side effects of treatment as a result of the fact that younger men on AS are treated with RP rather than IMRT at progression to treatment (30% of all men treated). An additional 10% of 55 year-old men on AS will develop side effects as a result of treatment relative to 65 year old men; the corresponding increase in men receiving initial ORP is 7%.

Treatment costs for AS are lower among younger men, based on the fact that 30% of patients will undergo less costly definitive treatment (i.e., ORP as opposed to IMRT), and to the delay in definitive treatment relative to 65 year-old men; treatment costs incurred later are discounted more heavily. However, this reduction is offset by higher visit and patient time costs due to the extended period of surveillance in this cohort.

Potential Survival Benefit for Radical Prostatectomy

We examined the effects of an assumed absolute difference of 2.5% at 10 years in prostate-cancer specific mortality at in favor of radical prostatectomy over active surveillance, a rate approximately one-half that observed in the SPCG-4 trial of surgery and watchful waiting (Bill-Axelson, 2005, 2008). Findings are presented in Table 4 below.

Table 4. Assumed Disease-Specific Survival Benefit for Radical Prostatectomy.

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	7.82	Reference	Reference
AS	$29,948	$1,600	8.81	0.99	$1,616

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

The additional disease-specific mortality for AS patients results in an overall reduction of 8 weeks in average QALE for the cohort. However, the cost differences between AS and ORP are also reduced, as more AS patients die from prostate cancer over time. As a result, the incremental cost-effectiveness ratio generated ($1,648 per QALY gained) is similar to those for the overall cohorts of older and younger men.

Alternative Scenarios Varying Utilities

We also examined the effect of varying the utility associated with certain health states. First, we conducted an analysis including only the disutility associated with side effects: in other words, this analysis did not take into account the disutility of "living with cancer" in the case of active surveillance or of "having been treated in the past with ORP without side effects". This analysis allows us to quantify the quality of life difference between the two approaches that is attributable to side effects alone.

Table 5. Model Results, Disutility of Side Effects Only

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	10.09	Reference	Reference
AS	$30,422	$2,074	10.75	0.66	$3,142

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

Elimination of all but side-effect disutilities resulted in improved QALE for both management options. AS remained associated with improved effectiveness in this scenario, generated approximately 8 additional months of QALE relative to ORP. In comparison to base case findings, these results suggest that approximately 60% of the QALE benefit for AS is attributable to the impact of side effects alone.

Second, we eliminated the disutility associated with erectile dysfunction (ED) for both treatment approaches in order to simulate the experience for a hypothetical cohort of men

whose perception of health state is unaffected by the presence of this side effect as well as to assess the contribution of this disutility to the overall results, which are presented in Table 6 below.

Table 6. Model Results, Excluding Disutility Associated with ED

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	8.45	Reference	Reference
AS	$30,422	$2,074	9.40	0.95	$2,183

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

AS again remained associated with higher QALE in this scenario, which increased for both management alternatives. In the case of ORP, QALE increased from 7.82 to 8.45 QALYs and from 8.97 to 9.4 QALYs in the case of AS, at an additional cost of $2,074, or $2,183/QALY. However, this approach improved the QALE of ORP to a greater extent than for AS: ORP gained an additional 2.4 months of QALE relative to AS, reflecting the higher incidence of ED in men treated with ORP.

Active Surveillance: Varying the Definitive Treatment Received

In order to evaluate the effect the treatment received at progression had on the cost-effectiveness of AS relative to ORP, we performed two further analyses. In the first, we estimated the cost and effectiveness of AS if the men who progressed were treated with brachytherapy as opposed to IMRT. The costs of treatment and patient time associated with treatment are significantly lower for brachytherapy than for IMRT: for brachytherapy, treatment costs are $10,174 and patient time costs $755, as compared to $21,050 and $1,699 respectively for IMRT. In addition, the side effect profile of brachytherapy is slightly different, including an added risk of acute urinary retention, as outlined in our previous analysis. The results of this analysis are summarized in Table 4.

We also performed an analysis in which men who progressed to Gleason 7 or above disease were treated with IMRT alone, as opposed to IMRT with 6 months of ADT as in our base case scenario. The choice of whether to add ADT to IMRT can be influenced by many factors, including the characteristics of the patient's disease and the baseline health of the patient. In our base case scenario, we assumed the "worst case" scenario regarding characteristics of the patients' disease. In this analysis, we assume ADT is not deemed necessary or advisable. These results are also summarized in Table 7 on the following page.

Table 7. Active Surveillance: Varying the Treatment Modality Received

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	7.82	Reference	Reference
AS→BT	$24,350	-$3,998	8.98	1.16	N/A*
AS→IMRT no ADT	$28,930	$582	9.05	1.23	$473

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years
BT: brachytherapy; IMRT: intensity-modulated radiation therapy; ADT: androgen deprivation therapy
*Strategy is less costly and more effective; no ICER is generated

If AS is followed by brachytherapy, AS provides a QALY benefit of 14.1 months, similar to our base case estimate, but at a cost savings of $3,998. If AS is followed with IMRT without ADT, AS provides an additional 15 months of QALE at an incremental cost of $582; the incremental cost-effectiveness ratio is $473 per QALY gained. These analyses emphasize the importance of the cost of definitive treatment in the overall cost-effectiveness of an AS strategy as well as the fact that AS remains more effective than ORP regardless of subsequent treatment received.

Private Pay Treatment Costs

We estimated the cost-effectiveness of the AS and ORP approaches using two non-Medicare private pay treatment cost schedules obtained from large private health plans in the United States. In scenario A, treatment with IMRT costs $42,000, as opposed to $21,050 in our base case. Similarly, ORP costs $19,000, as opposed to $10,479 in our base case. The results are summarized in Table 8 below. In this case, doubling the cost of both ORP and IMRT results in an additional cost for AS of $4,018, yielding an ICER of $3,494/QALY.

Table 8. Private Pay Treatment Costs – COSTS A

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$36,807	Reference	7.82	Reference	Reference
AS	$40,825	$4,018	8.97	1.15	$3,494

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

In scenario B, treatment with IMRT costs $25,000 and ORP $15,000. The results are summarized in Table 9 on the following page. Increasing the cost of IMRT by 25% and ORP by 50% results in AS both costing less, at a cost savings of $540, and providing a clinical benefit as compared to ORP. These analyses again emphasize the importance of the relative cost of ORP vs. IMRT on model results.

Table 9. Private Pay Treatment Costs – COSTS B

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$32,900	Reference	7.82	Reference	Reference
AS	$32,360	-$540	8.97	1.15	N/A*

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years
*Strategy is less costly and more effective; no ICER is generated

Omitting Patient Time Costs

This model excluded patient time costs in order to simulate a standard payer perspective. The results of this model are summarized in Table 10.

Table 10. Omitting Patient Time Costs

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$23,325	Reference	7.82	Reference	Reference
AS	$24,027	$702	8.97	1.15	$610

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

In this scenario, AS produces an incremental cost of $702 for the same clinical benefit seen in the base case, 13.8 months of QALE; incremental cost-effectiveness is estimated to be $610 per QALY gained. This result reflects the substantial patient time cost of IMRT compared to ORP as well as the cost of more frequent visits while undergoing AS.

Assuming Maximal Effectiveness of Robot-Assisted vs. Open Prostatectomy

We also conducted an alternative analysis to examine the impact of RP technique on QALE and cost. Our systematic review concluded that the evidence in the literature was not sufficient to infer real differences in the incidence of complications and side effects between the different techniques, and we therefore used ORP in our base case analysis. However, we wished to evaluate the magnitude of effect on cost and QALE should the differences in side effect and complication rates reported to date be supported once more evidence has accumulated.

Table 11. Model Results Comparing Open to Robot-Assisted Radical Prostatectomy

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Open RP	$28,348	Reference	7.82	Reference	Reference
Robot-Assisted RP	$26,608	-$1,740	7.97	0.15	N/A*

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years
*Strategy is less costly and more effective; no ICER is generated

In this case, robot-assisted RP is both less expensive and more effective than open RP, yielding an additional 7.8 weeks of QALE at a cost savings of $1,740. The cost of the robot-assisted approach is slightly higher than open RP due to higher surgeon payments and anesthesia reimbursement, but the costs of subsequent visits for treatment of complications and side effects are lower based on the nominally lower rates of these outcomes as observed in the ICER review. Despite these lower rates, the QALE benefit observed in this analysis is relatively modest.

Sensitivity Analyses: Active Surveillance

Probability of Progressive Disease

There is considerable uncertainty surrounding the clinical outcomes of patients on active surveillance. In our base case estimates, we based our probability of progression to treatment on the evidence provided by the relatively few papers employing active surveillance protocols. These papers have variable definitions of progression and level of detail in reporting. In most cases, progression was defined as an increased PSA velocity or decreased PSA doubling time, new clinical findings, or progression to Gleason 7 or higher-risk disease on re-biopsy. However, in only two papers was the proportion of men who progressed to higher Gleason disease quantified. Anticipating the importance of estimates of the proportion of men who were treated on the outcomes of our model, we performed multiple sensitivity analyses to attempt to examine these uncertainties.

We first varied the probability of men who developed a component of higher Gleason score disease on biopsy while on active surveillance. The results may be seen in Table 12 on the following page.

In our base case, approximately one-third of men who are treated on AS are treated as a result of developing a higher Gleason score on re-biopsy. In this scenario, increasing this probability does not eliminate the QALE benefit of AS over ORP (the benefit ranges from 7.9 months of QALE using the highest probability of progression to 15.5 months using the lowest). Incremental costs range between $302 at the lowest probability of progression to $8,683 at the highest probability, yielding incremental cost-effectiveness ratios that range between $238 and $13,359/QALY; these costs are driven by the need for expensive IMRT and ADT therapy in patients with Gleason 7 or higher disease.

In the second sensitivity analysis, we varied the probability of any progression, including Gleason progression and progression due to change in clinical exam or PSA kinetics. In this analysis, AS was again more effective than ORP in both analyses. Halving the probability of disease progression leading to treatment increased the QALE from 8.97 in our base case to 9.15 at a cost savings of $1,246 compared to ORP. Doubling the probability of progression decreased the benefit from 8.97 QALYs to 8.40 at an additional cost of $9,646, yielding an ICER of $16,631/QALY.

Table 12. Active Surveillance Sensitivity Analyses

Strategy	Base case estimate	Range for SA	Cost	Incremental Cost of AS	QALYs	ICER ($/QALY)
Base case ORP			$28,348	Reference	7.82	Reference
Base case AS			$30,422	$2,074	8.97	$1,803
1. Active surveillance - Varying probability of Gleason 7 disease	0.026	50%-200%	50%: $28,650 200%: $33,417	50%: $302 200%: $5,069	50%: 9.09 200%: 8.78	$238 $5,280
2. Active surveillance - Probability of any progression	0.053	50%-200%	50%: $27,102 200%: 34,533	50%: -$1,246 200%: $6,185	50%: 9.15 200%: 8.71	N/A* $6,949
3. Active surveillance - Probability of electing treatment	0.02	0%-200%	0%: $29,615 200%: $31,680	0%: $1,267 200%: $3,332	0%: 9.02 200%: 8.91	$1,056 $3,057

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years
*Strategy is less costly and more effective; no ICER is generated

Probability of Electing Treatment

Our third sensitivity analysis varied the probability of patients electing to undergo treatment without signs of progression. Again, we varied the probability from 50%-200% of our base case estimate, and the results are summarized in Table 12 above. Doubling the number of men who elect to undergo treatment reduced the QALE benefit by 2.7 months, and more than doubled the incremental cost of AS (from $2,074 in our base case to $4,965). Assuming that no men elected treatment, AS increased costs by $1,267 as compared to ORP, with a gain of 14.6 months of QALE.

All of these analyses emphasize that active surveillance remains more clinically effective than ORP regardless of the proportion of men who progress or who are treated. The number of patients who progress by Gleason, clinically, and by PSA kinetics would have to be increased 10-fold to obviate the clinical benefit of AS compared to ORP.

Active Surveillance: Sensitivity Analysis of Symptoms on AS

Given the low-volume disease of men in the AS cohort, our base case assumption was that these men would have no symptoms of urinary obstruction or erectile dysfunction beyond that of the general population. In order to assess whether this assumption would significantly affect the results of our model, we conducted sensitivity analysis around this parameter, increasing the probability of developing these symptoms by 200% (see Table 13 on the following page). Of note, this probability is approximately double that seen in men on the watchful waiting arm of the SPCG-4 trial (Steineck, 2002).

Table 13. Model Results of Sensitivity Analysis of Symptoms on AS

Strategy	Range for SA	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Base case Open RP		$28,348	Reference	7.82	Reference	
Base case active surveillance		$30,422	$2,074	8.97	1.15	$1,803
Active surveillance - Varying probability developing symptoms on AS	200%	$31,572	$3,224	8.85	1.03	$3,130

NOTES: RP: radical prostatectomy; AS: active surveillance; QALY: quality-adjusted life years

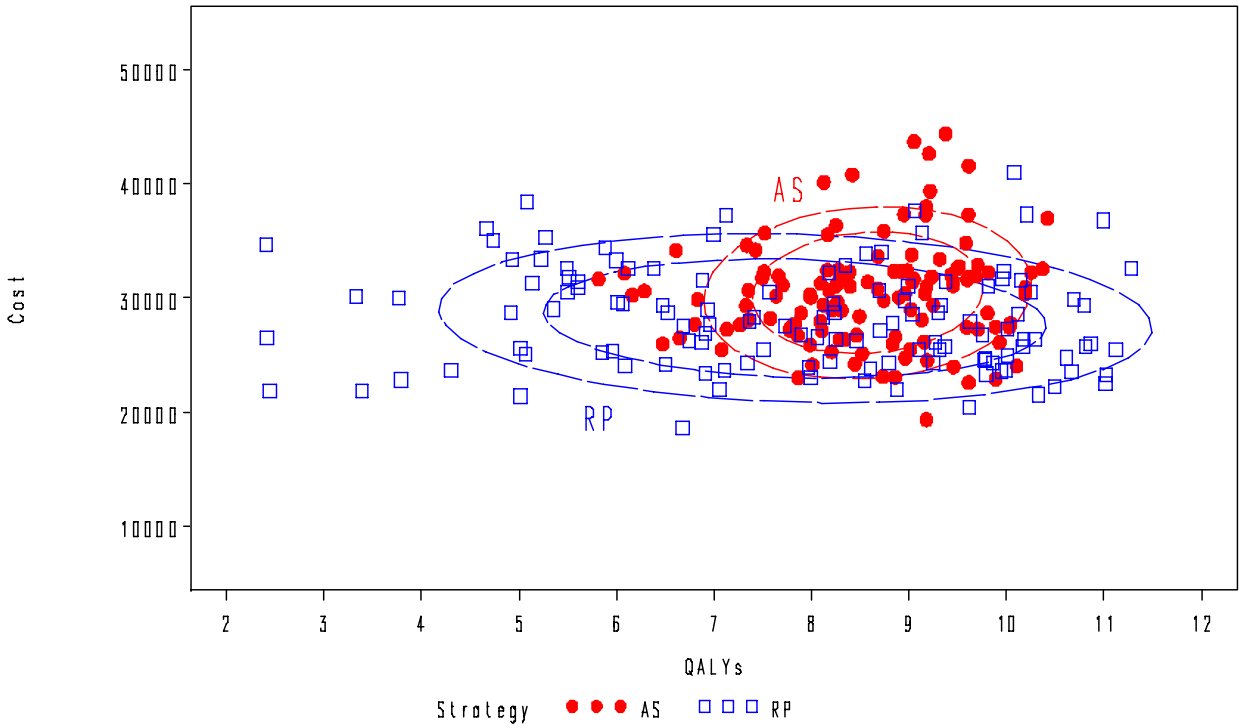
As seen in Table 13, increasing the probability of developing ED and urinary obstructive symptoms on AS does not significantly affect the benefit of AS relative to open RP: AS remains more effective, providing 12.5 months of additional QALE at an additional cost of $3,224, yielding an ICER of $3,130/QALY.

Probabilistic Sensitivity Analysis

Figure 4 on the following page shows discounted costs and discounted effectiveness (QALYs) from 125 samples (100,000 trials each) drawn from distributions around 65 parameters (complications, side effects, utilities, and costs).

As is evident in Figure 4, the uncertainty surrounding the QALYs from initial treatment with ORP (blue) was significantly greater than that from AS (red). Approximately 30% of the ORP trials resulted in QALY estimates that were lower than the lowest AS estimates (5th percentile). At the same time, 16% of the ORP trials produced QALY estimates that were higher than the highest AS estimates (95th percentile). The greater variability in QALE for ORP is not surprising, given the number of potential harms and associated disutilities patients could experience relative to AS. In contrast, the confidence ellipses indicate that *costs* of the strategies were not substantially different.

Figure 4. Cost-effectiveness Analysis: Probabilistic Sensitivity Analysis



Bivariate normal confidence ellipses drawn at 50% and 75% confidence.
Each point (n=125) represents average costs and QALYs from 100,000 individual-level trials run with a unique set of draws from distributions around costs, utilities, and probabilities as in Tables A and B.

8.4 Comparison of Results to Prior Health Economic Evaluations

To the best of our knowledge, there are only two published studies in which an economic model has been developed to assess the comparative cost-effectiveness of watchful waiting or AS and radical prostatectomy. Both come from the UK, and both consider only watchful waiting, basing mortality outcomes largely on the basis of the results of the SPCG-4 randomized controlled trial (Bill-Axelson, 2005).

The first economic evaluation, by Calvert (Calvert, 2003), compared policies of watchful waiting with radical prostatectomy in 60-year-old men with Gleason scores of 5-7. Costs were considered from the perspective of the National Health Service and the analysis was based on a Markov model. The baseline results of the analysis suggested that watchful waiting was less costly and more effective than radical prostatectomy. However, the number of QALYs gained per patient was almost equivalent for the two management options, demonstrating that gains in survival attributable to radical prostatectomy were offset by decrements in quality of life due to post-operative complications and long-term side effects.

A second economic evaluation was commissioned as part of the NICE clinical guideline on the diagnosis and treatment of prostate cancer (NICE, 2008). This work benefited from the 2005 publication of the results of the SPCG-4 RCT, but otherwise was similarly structured as a Markov model evaluating costs from the health service perspective. As with the earlier article, and largely consistent with the findings of our analysis, watchful waiting was shown to be the less costly and more effective option. Radical prostatectomy did provide a small improvement in life expectancy, but quality of life decrements related to complications and side effects produced a QALY advantage of approximately 0.3 overall for watchful waiting when selected for men aged 60.

Even though our analysis modeled the outcomes of active surveillance rather than watchful waiting, our findings are largely consonant with these earlier evaluations. Our base case results found AS to be slightly more expensive than radical prostatectomy, largely on the basis of the use of IMRT and sometimes ADT for the 60%of men estimated to receive delayed definitive treatment. But our findings of a relatively large QALY advantage for AS over radical prostatectomy derives from the same basic construct that AS reduces the number of men who suffer the quality of life decrements from surgical complications and long-term side effects.

Table A. Probabilities for decision-analytic model of prostate cancer treatment.

Annual probabilities	Base Case Estimate	Standard Deviation for PSA	Source(s)
Disease-related Probabilities			
Disease-related probabilities: low-risk prostate cancer			
Biochemical recurrence after treatment	0.01 (year 1; lifetime risk 0.45)	50%-200%	ICER Review
Progression from biochemical recurrence			
to metastatic disease	0.05	NA	Horwitz, 2005
Death of prostate cancer after development			
of metastatic disease	0.22	NA	Alibhai, 2003
Probability of developing metastatic disease on AS	.007		
Disease-related probabilities: intermediate-risk prostate cancer (Gleason≥7)			
Biochemical recurrence after treatment	0.01 (year 1; lifetime risk 0.60)	50%-200%	D'Amico, 2004
Progression from biochemical recurrence			
to metastatic disease	0.05	NA	
Side Effects of Treatment			
Short-term side effects of treatment			
Open RP (base case)			ICER review
Peri-operative death	0.0044	0.00001	
Major complications	0.0472	0.0168	
Minor complications	0.0948	0.0019	
Urinary toxicity	0.47	0.0578	
Erectile dysfunction	0.77	0.0384	
Urethral stricture	0.0344	0.002	
Robot-Assisted RP			ICER review
Peri-operative death	0.0044	NA	
Major complications	0.0250		
Minor complications	0.0525		
Urinary toxicities	0.289		
Erectile dysfunction	0.591		
Urethral stricture	0.0131		
IMRT			
Urinary toxicity	0.3	.075	ICER review
Gastrointestinal toxicity	0.18	0.045	
Active surveillance (biopsy)			
Urosepsis	.001	0.0001	Djavan, 2001
Acute urinary retention	.026	0.0049	Djavan, 2001
Long-term side effects of treatment			
Open RP			ICER review
Urinary toxicity	0.127	0.011	
Erectile dysfunction	0.453	0.021	

Long-term side effects of treatment (cont'd)					
Robot-Assisted RP					ICER review
Urinary toxicity	0.073		NA		
Erectile dysfunction	0.263				
IMRT					ICER review
Urinary toxicities		0.04		0.02-0.06	
Gastrointestinal toxicities		0.02		0.01-0.03	
Erectile dysfunction		0.064		0.016	ICER review, expert opinion
Baseline and interim development of erectile dysfunction, urinary symptoms					
Erectile dysfunction					Bacon, 2003
Baseline probability, age 65		0.3		0.075	
Development of symptoms, age 65-70 (increasing with age)		0.015		0.004	
Urinary obstruction					Andersson, 2004
Baseline probability, age 65	0.3		0.075		
Development of symptoms, age 65-70 (increasing with age)	0.011		0.003		
Utilities					
Asymptomatic men					
On active surveillance low risk disease		0.84		0.19	Stewart 2005
Biochemical recurrence		0.67		0.24	
Metastatic disease		0.25		0.11	
Undergoing radical prostatectomy	0.67		0.29		
Having undergone treatment without SE	0.8		0.24		Dale 2008
Men with single side effect					
Urinary toxicities		0.83		0.21	Stewart 2005
Gastrointestinal toxicities		0.71		0.26	
Sexual toxicities		0.89		0.16	
Men with more than one side effect					
Urinary and gastrointestinal toxicities		0.7		0.24	
Sexual and gastrointestinal toxicities		0.57		0.26	
Urinary and sexual toxicities		0.79		0.23	
Urinary, gastrointestinal, and sexual toxicities		0.45		0.31	
Men on active surveillance					
Utility of obstructive urinary symptoms	0.88		0.13		
Utility of major complication after RP	0.96		0.012		Sullivan 2006

Table B. Costs for decision-analytic model of prostate cancer treatment.

Category	Intervention	Cost (2008$)	Details, Source(s)	Values in Sensitivity Analyses and/or 95% CI for Prob. SA (2008$)
Outpatient Surveillance	Single visit with PSA	$124	{CPT 84152 + 99214}, PFS and LabFS	50%, 200%
	Incremental cost of biopsy w/antibiotic prophylaxis	$499	+ {CPT 55700, 76872, 76942, urologist-performed} + ciprofloxacin, 3d, 500 mg bid {Red Book}	50%, 200%
	PSA exam only (no physician visit)	$26	CPT 84152	50%, 200%
Inpatient Treatments	RP (open) – no complications	$10,479	DRG 665, ASA 00865, CPT 55840, HOPPS, AnesFS, PFS	50%, 200% $19,000 (private pay A) $15,000 (private pay B)
	minor complications - additional v. none	$7,300	incremental for DRG 666	50%, 200%
	major complications - additional v. none	$17,400	incremental for DRG 667	50%, 200%
	LRP or RALP - no complications	$10,970	DRG 665, ASA 00865, CPT 55866	50%, 200%
	minor complications - additional v. none	$7,300	incremental for DRG 666	50%, 200%
	major complications - additional v. none	$17,400	incremental for DRG 667	50%, 200%
	Sepsis post-biopsy	$11,804	DRG 872 (no mech. ventilation or major complications)	50%, 200%
Outpatient Treatments	ADT	$8,034	CPT and Red Book	50%, 200%
	IMRT	$21,050	39 fractions, blended hospital/non-facility, HOPPS/PFS	50%, 200% $16,958 (HOPPS) $29,235 (Non-facility, PFS) $42,000 (private pay A) $25,000 (private pay B)
	Brachytherapy	$10,174	100 sources per patient	50%, 200% $8,000 (private pay A) $10,000 (private pay B)
	management ST GU SE except AUR	$195	see text	50%, 200%
	management of AUR	$186	see text	50%, 200%
	management of ED	$491	see text	50%, 200%
	management of incontinence	$922	see text	50%, 200%
	management of ST GI SE	$1,154	see text	50%, 200%

Continued next page

Table B. Costs for decision-analytic model- continued.

Category	Intervention	Cost (2008$)	Details, Source(s)	Values in Sensitivity Analyses and/or 95% CI for Prob. SA (2008$)
Outpatient Treatments *(continued)*	management of GI SE	$1,444	see text	50%, 200%
	management of long-term urinary obstruction	$813	see text	50%, 200%
	management of stricture	$519	see text	50%, 200%
Patient Time Costs	*daily patient wage (men age 65+)*	*$151*	*BLS.gov, series ID LEU0252891700 if 5 work days/week*	*$189/day for ages 55-64*
	PSA test/MD visits	$76	half-day per visit	50%, 200% / $0
	Visit with TRUS-guided biopsy	$151	1 day per visit with biopsy	50%, 200% / $0
	Brachytherapy	$755	5 days per treatment	50%, 200% / $0 $412 for 3 recovery days
	IMRT	$1,699	11.25 days per treatment	50%, 200% / $0
	IMRT + ADT	$1,850	12.25 days per treatment	50%, 200% / $0
	ADT alone	$151	1 extra day for ADT	50%, 200% / $0
	management ST GU SE except AUR	$106	0.7 days	50%, 200% / $0
	management AUR	$139	0.92 days	50%, 200% / $0
	management of ED	$76	0.5 days	50%, 200% / $0
	management of incontinence	$195	1.29 days	50%, 200% / $0
	management of ST GI SE	$1,812	12 days	50%, 200% / $0
	management of GI SE	$2,227	14.75 days	50%, 200% / $0
	management of stricture	$151	1 day	50%, 200% / $0
	management of long-term urinary obstruction	$533	3.54 days	50%, 200% / $0
	RP no complications	$407	2.7 days (median LOS)	50%, 200% / $0
	RP minor complications	$542	median LOS increased to 6.3 days	50%, 200% / $0
	RP major complications	$1,431	median LOS increased to 12.2 days	50%, 200% / $0
	Biopsy complication (sepsis)	$858	median LOS for DRG 872 of 5.7 days	50%, 200% / $0

9. Recommendations for Future Research

As documented in this appraisal, there are notable areas of uncertainty regarding both the comparative clinical effectiveness and comparative value of active surveillance and alternative surgical approaches to prostatectomy among patients with clinically-localized, low-risk prostate cancer. This appraisal found no evidence to suggest any differences in overall or disease-specific survival between these management approaches. Much of the prior data gleaned from older studies of watchful waiting cohorts is not applicable to modern surveillance approaches. Finally, the evidence base on which to compare major surgical outcomes is weakened by major differences in study design, patient populations, measurement of outcomes, and duration of follow-up.

Data from 3 major ongoing trials should assist in understanding not only the progression of prostate cancer and its symptoms under active surveillance, but the impact of active surveillance on disease-specific and overall survival as well as local progression, symptoms and toxicity, and quality of life relative to radical prostatectomy and/or radiation therapy. These studies, which include the Prostate Cancer Intervention versus Observation Trial (PIVOT) trial in the U.S., the Prostate testing for cancer and Treatment (ProtecT) study in the U.K., and the Surveillance Therapy Against Radical Treatment (START) trial in Canada, all involve randomization of patients to active surveillance vs. radical prostatectomy, external beam radiation, or a combined treatment arm involving both modalities. Data collection for the PIVOT trial (731 men aged <75 years randomized to active surveillance or radical prostatectomy) is expected to be completed by November 2009; however, recruitment is still ongoing for the ProtecT and START trials, with final data collection still 5-15 years away.

Although the clinical and patient communities are anxiously awaiting the results of these 3 trials, a number of uncertainties remain that would be addressed by additional research. These uncertainties include:

- Better understanding of the natural history of prostate cancer
- Further documentation of the length of the learning curve for radical prostatectomy and radiation therapy with correlated development of competency standards
- Exploration of the long-term effects of Gleason under- and over-grading on initial biopsy
- Additional information on the effects of surveillance, treatment decisions, and definitive treatment on health-related quality of life
- Standardization of key outcome measures to better compare multiple treatment alternatives

- Identification of additional biomarkers and other determinants of prostate cancer outcome

- Development of appropriate vehicles for conveying uncertainty in current estimates of treatment effectiveness and harms to patients

ICER recommends that a number of studies be conducted to address these uncertainties; brief explanations of the study designs and primary outcomes are described below.

1. *Multi-center, long-term prospective cohort study.* This study would seek to capture patients at the point of prostate cancer diagnosis and follow them for a substantial period of time, and would ideally be conducted in a multi-disciplinary fashion; urologists, radiation oncologist, medical oncologists, and general internists would be involved in study conception and design. Receipt of active surveillance or some form of definitive treatment would be at patient and physician discretion. Patients would be assessed at multiple timepoints for a variety of clinical measures, including disease-related symptoms, tumor stage, grade, and PSA, and health-related quality of life; such a cohort would also present the opportunity to test the prognostic ability of additional biomarkers, molecular/genetic testing, and other clinical factors. In addition, this study would allow for the development of standard outcome definitions that could be used across all management alternatives, such as biochemical recurrence, treatment complications and side effects, and quality-of-life impacts. This study design would be ideal to measure the long-term effects of current approach to management and treatment (e.g., Gleason over- and under-grading, surgical technique, etc.).

2. *Multi-site retrospective "learning curve" study.* The information currently available for the prostatectomy learning curve has not suffered so much for lack of data as it has the relative crude approaches to analyzing it. Studies of individual case series have used arbitrary thresholds and relatively crude statistical analyses to evaluate progression along the curve. This retrospective study would glean both automated and medical record data from multiple sites, and then test various analytic approaches that are better suited to the complex nature of the data, such as Bayesian hierarchical models. Findings from this study would be used to develop minimum training and competency standards that better reflect the nature of the learning curves for both open and minimally-invasive approaches to prostatectomy.

3. *Psychometric study of methods of conveying uncertainty of outcome data for prostate cancer.* The absence of useable data from direct comparisons of treatment alternatives and the high degree of variability in estimates of outcome from the current evidence can be problematic for patients seeking to make an informed decision regarding the relative benefits and harms of each option. A psychometric study would be undertaken to examine patient response to a variety of graphic and textual displays of information on the variability, overlap, and non-standardized format inherent of most available comparative data on treatment outcome. Additional data on the key

influences on patient treatment decisions (e.g., perceptions of physician preference, experiences of friends and relatives, sources of data on treatment) could also be obtained. If warranted, multiple types of decision aids could be developed based on study findings and tested in a randomized clinical trial; outcomes of interest in this trial would include the factors involved in selection of treatment, patient satisfaction with the decision aid and the information provided, and the impact of the aids on mental and emotional health-related quality of life.

Finally, concerns regarding the relatively long wait for findings from the 3 ongoing clinical trials could be mitigated somewhat by the design of a separate clinical trial with a focus on shorter-term endpoints only. For example, limiting the endpoints of interest to symptom progression, treatment-related complications and side effects, and health-related quality of life would allow for the conduct of a trial with a maximum 2-3 year follow-up. This trial could incorporate some of the same features as above-described study designs, such as standardized outcome measures and the involvement of multiple disciplines, and would be conducted in a variety of academic and community settings.

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APPENDIX A:
LITERATURE SEARCH STRATEGY

The search strategy for radical prostatectomy was:

1 prostatic neoplasms (sh)
2 (robot* and radical prostatectomy)tw
3 (laparoscop* and radical prostatectomy) tw
4 (radical prostatectomy)tw
5 2 or 3 or 4
6 1 and 5
7 limit to humans and english and 1996-2009
8 limit to review articles
9 7 not 8 (exclude review articles)
10 (t1$ or t2a or local$)tw
11 9 and 10
12 (survival or mortality or died or death* or disease-specific)tw
13 11 and 12
14 high-risk (ti)
15 13 and 14
16 13 not 15
17 protein (ti)
18 16 not 17
19 case reports (limit)
20 18 not 19

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21 robot* or laparoscop* (tw)
22 20 and 21
23 20 not 21
24 salvage radical (ti)
25 23 not 24
26 advanced (ti)
27 26 not 26
28 DNA (ti)
29 27 not 28

The search strategy for active surveillance was:

1	Prostatic neoplasms (Mesh) and active surveillance
2	prostatic neoplasms (Mesh) and watchful waiting
3	prostatic neoplasms (Mesh) and active management
4	prostatic neoplasms (Mesh) and conservative management
5	Prostatic neoplasms (Mesh) and deferred treatment
6	1 or 2 or 3 or 4 or 5
7	limit 6 to "review articles"
8	6 not 7 (exclude review articles)
9	limit 8 to english language and humans
10	(t1$ ot t2a or local$)tw
11	9 and 10
12	limit 11 to comment
13	11 not 12
14	(survival or mortality or died or death* or disease-specific)(tw)
15	13 and 14
16	13 not 14
17	gene* (ti)
18	15 not 17

The Cochrane Library was searched using all relevant keywords for radical prostatectomy and active surveillance, as above.

APPENDIX B

SYSTEMATIC REVIEW EVIDENCE TABLES

Table 1. Characteristics of studies categorized as active surveillance or watchful waiting.

Author	Year	Sample Size	Median Age (yrs)	% Low Risk	PSA/DRE Protocol	Biopsy Protocol	Other Protocol	% Treated	Type
Eggener	2009	262	64.0	100	6-12 mo	18 mo	MRI 12-36 mo	16.4%	AS
Soloway	2007	99	66.0	100	3-6 mo	6-12 mo (1st)		8.1%	AS
Klotz	2007	331	70.0	80	Unk	Unk		34.1%	AS
Carter	2007	407	65.7	100	6 mo	12 mo		25.3%	AS
Hardie	2005	80	70.5	91	3-6 mo	None	Imaging PRN	13.8%	AS
Patel	2004	88	65.3	88	3-6 mo	6 mo		35.2%	AS
Dall'Era	2008	321	64.0	71	3 mo	12-24 mo	TRUS 6-12 mo	24.3%	AS
Roemeling	2007	278	69.8	94	Unk	Unk		29.5%	AS
Tewari	2004	467	67.0	85				NR	WW
Adolfsson	2007	119	68.0	63				56.3%	WW
Arai	2001	64	75.0	57				NR	WW
Bill-Axelson	2008	348	64.5	61				14.4%	WW
Burnet	2007	100	67.1	Unk	3-6 mo	None	Imaging PRN	NR	AS
Carter	2003	313	65.4	87				68.7%	WW
deVries	2004	191	68.6	93				15.7%	WW
El-Geneidy	2004	187	71.0	70				20.3%	WW
Hruby	2001	174	Unk	100	3-6 mo	12-18 mo	TRUS 6-12 mo	16.1%	AS
Johannson	2004	223	72.0	80				NR	WW
Kekehi	2008	118	Unk	80	2-3 mo	12 mo		54.2%	AS
McLeod	2005	2285	Unk	Unk				NR	WW
Meng	2003	457	Unk	40				NR	WW
Merglen	2007	378	71.0	60				NR	WW
Neulander	2000	54	76.4	70	3-4 mo		Voiding fx PRN	51.9%	WW
Postma	2005	108	68.6	94				16.7%	WW
Ross	2004	142	69.0	Unk	3-6 mo	PRN	Imaging PRN	28.2%	WW
Siegel	2001	64	66.0	Unk				NR	WW
Venkitaraman	2007	119	66.0	87	1-6 mo	18-24 mo		27.7%	AS
Wu	2004	1158	69.8	72				39.1%	WW
Zietman	2001	198	71.0	80	Serial			31.8%	WW
Albertsen	2005	767	69.0	72				NR	WW
Liu	2008	970	Unk	40				NR	WW
Lu-Yao	1997	19898	70.7	89				NR	WW
McLaren	1998	113	75.0	89				25.7%	WW
Wong	2006	12608	72.9	55				NR	WW
Zhou	2009	2306	Unk	70				NR	WW
Nicholson	2002	7496	Unk	100				NR	WW
Sandblom	2000	274	74.0	59				NR	WW
Jonsson	2006	104	73.0	100				NR	WW
Carter C	2003	313	65.4	85				68.7%	WW
Hoffman	2006	290	75-84	51				NR	WW
Steineck	2002	160	64.8	40				24.4%	WW

Table 2. Overall survival among patients treated for prostate cancer, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Location	Median F/U (mos)	Timepoint (Years)	Overall Survival (%)
Active Surveillance	Eggener	2009	262	64.0	100	N. America	29.0	5	98.9%
	Klotz	2007	331	70.0	80	Canada	85.2	7	85.0%
	Carter	2007	407	65.7	100	US	34.1	5	98.0%
	Hardie	2005	80	70.5	91	UK	42.0	5	94.0%
	Patel	2004	88	65.3	88	US	44.0	5	100.0%
	Dall'Era	2008	321	64.0	71	US	43.8	5	100.0%
	Roemeling	2007	278	69.8	94	Netherlands	41.4	5	89.0%
Radical Prostatectomy									
ORP	Bill-Axelson*	2005	347	64.6	61	Sweden	131.4	5	92.2%
	Bianco	2005	1746	Unk	40	US	73.0	5	89.0%
	Aus	2005	546	<75	Unk	Sweden	Unk	5	95.0%
	Barry	2001	1063	Unk	70	US	Unk	10	69.0%
	Lai	2001	11429	65.3	Unk	US	Unk	10	75.8%
	Liu	2008	2567	Unk	87	US	141.6	5	93.6%
LRP	Eden	2006	100	62.0	78	UK	45.0	3	99.0%
RALP	None								

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy
*Results from RP arm of SPCG-4 randomized controlled trial (vs. watchful waiting)

Table 3. Prostate cancer-specific survival among patients treated for prostate cancer, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Location	Median F/U (mos)	Timepoint (Years)	Disease-specific Survival (%)
Active Surveillance	Eggener	2009	262	64.0	100	N. America	29.0	5	100.0%
	Soloway	2007	99	66.0	100	US	45.3	5	100.0%
	Klotz	2007	331	70.0	80	Canada	85.2	7	99.0%
	Carter	2007	407	65.7	100	US	34.1	5	100.0%
	Hardie	2005	80	70.5	91	UK	42.0	5	100.0%
	Patel	2004	88	65.3	88	US	44.0	5	100.0%
	Dall'Era	2008	321	64.0	71	US	43.8	5	100.0%
	Roemeling	2007	278	69.8	94	Netherlands	41.4	5	100.0%
Radical Prostatectomy									
ORP	Bill-Axelson*	2005	347	64.6	61	Sweden	131.4	5	97.7%
	Bianco	2005	1746	Unk	40	US	73.0	5	94.0%
	Aus	2005	546	<75	Unk	Sweden	Unk	5	98.0%
	Barry	2001	1063	Unk	70	US	Unk	10	86.0%
	Lai	2001	11429	65.3	Unk	US	Unk	10	95.8%
LRP	None								
RALP	None								

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy
*Results from RP arm of SPCG-4 randomized controlled trial (vs. watchful waiting)

Table 4. Biochemical freedom from failure among patients treated for prostate cancer, by surgical approach.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Location	Median F/U (mos)	Failure Definition	Timepoint (Years)	bFFF (%)
ORP	Salomon	2002	145	65.1	80	France	54.8	PSA >0.2	3	75.0%
	Artibani	2003	50	64.3	90	Italy	10.2	PSA >0.3	1	89.0%
	Poulakis	2006	70	74.0	68	Germany	12.2	PSA >0.1	0.5	84.0%
	Touijer	2008	818	59.0	65	US	18.0	PSA >0.1	1.5	91.7%
	Roumeguere	2003	77	63.9	75	Belgium	12.2	Any PSA	1	93.1%
	Krambeck	2008	588	61.0	75	US	15.8	PSA >0.4	3	92.2%
	Rassweiler	2003	219	65.0	45	Germany	67.0	PSA inc. >0.2	5.5	82.6%
	Graefen	2006	1755	Unk	100	Germany	Unk	PSA >0.1	5	93.0%
	Bianco	2005	1746	Unk	40	US	73.0	PSA > 0.4, 0.2	5	88.0%
	Saranchuk	2005	647	58.0	79	US	15.0	PSA ≥0.2	5	88.0%
	Carini	2008	488	64.5	45	Italy	49.0	Unk	5	75.4%
	Stokes	2000	88	65.5	100	US	77.9	Any PSA	5	80.0%
	Amling	2000	2782	66.0	68	US	Unk	PSA ≥0.4	5	76.0%
LRP	Salomon	2002	137	64.1	90	France	9.7	PSA >0.2	3	84.1%
	Artibani	2003	71	63.1	77	Italy	10.3	PSA >0.3	1	81.0%
	Poulakis	2006	72	74.1	65	Germany	12.2	PSA >0.1	0.5	86.0%
	Touijer	2008	612	60.0	70	US	18.0	PSA >0.1	1.5	95.3%
	Roumeguere	2003	85	62.5	78	Belgium	12.2	Any PSA	1	91.4%
	Joseph	2005	50	61.8	40	US/UK	5.3	Unk	0.5	100.0%
	Rassweiler	2003	219	64.0	54	Germany	30.0	PSA inc. >0.2	3	86.8%
	Hakimi	2009	75	59.6	59	US	24.3	PSA >0.2	2	93.3%
	Lein	2006	1000	62.0	Unk	US	28.8	PSA inc >0.1	2.4	94.8%
	Eden	2006	100	62.0	78	UK	45.0	PSA >0.2	3	88.0%
	Guillonneau	2002	550	Unk	Unk	France	10.0	PSA >0.1	3	88.4%
	Rassweiler	2005	5824	64.0	100	Germany	12.2	Unk	5	91.4%
	Goeman	2006	550	62.4	97	France	Unk	PSA ≥0.2	5	78.8%
	Galli	2006	150	64.0	Unk	Italy	43.0	PSA >0.2	3.5	88.3%
	Curto	2005	425	62.0	89	France	11.0	Unk	1	93.5%
	Rozet	2005	600	62.0	97	France	12.2	PSA ≥0.2	1	95.0%
	Bollens	2001	50	63.3	Unk	Belgium	Unk	Unk	0.25	94.3%
RALP	Joseph	2005	50	59.6	44	US/UK	5.3	Unk	0.5	100.0%
	Krambeck	2008	294	61.0	73	US	15.8	PSA >0.4	3	92.4%
	Hakimi	2009	75	59.8	45	US	17.0	PSA >0.2	1.5	94.7%
	Menon	2007	2652	60.2	69	US	Unk	Unk	5	91.6%

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy
bFFF: Biochemical freedom from failure; PSA: Prostate-specific antigen
*Results from RP arm of SPCG-4 randomized controlled trial (vs. watchful waiting)

Table 5. Treatment-free survival and other statistics among patients managed by active surveillance for prostate cancer.

Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Location	Median F/U (mos)	Timepoint (Years)	Tx-Free Survival (%)	% Treated	Tx Reason*		
										Gleason	Oth Prog	Pt Choice
Eggener	2009	262	64.0	100	N. America	29.0	5	75.0%	16.4%	34.9%	27.9%	14.0%
Soloway	2007	99	66.0	100	US	45.3	5	85.0%	8.1%	---	---	---
Klotz	2007	331	70.0	80	Canada	85.2	7	---	34.1%	20.4%	44.2%	35.4%
Carter	2007	407	65.7	100	US	34.1	5	73.0%	25.3%	---	---	---
Hardie	2005	80	70.5	91	UK	42.0	5	79.2%	13.8%	---	---	---
Patel	2004	88	65.3	88	US	44.0	5	58.0%	35.2%	35.5%	19.4%	45.2%
Dall'Era	2008	321	64.0	71	US	43.8	5	67.0%	24.3%	43.6%	23.1%	33.3%
Roemeling	2007	278	69.8	94	Netherlands	41.4	5	70.8%	29.5%	---	---	---
Hruby	2001	174	Unk	100	Canada	21.0	Unk	---	16.1%	---	---	---
Kekehi	2008	118	Unk	80	Japan	54.0	3	48.9%	54.2%	25.0%	28.1%	46.9%
Venkitaraman	2007	119	66.0	87	UK	20.9	Unk	---	27.7%	---	---	---

NOTES: One surveillance study focusing only on quality of life (Burnet, 2007) not included in table
*Represent major reasons for treatment selection, may not sum to 100%; other reasons include metastases, voiding symptoms, etc.

Table 6. Major and minor peri-operative complications of radical prostatectomy, by surgical approach.

Surgery	Author	Year	Sample Size	Median Age (yrs)	Location	Major Complications (%)						Minor Complications (%)
						Maj Bleed	DVT/PE	Maj Infection	MI/Stroke	Bowel Inj	Total	
ORP	Tewari	2003	100	63.1	US	4.0%	1.0%	5.0%	1.0%	1.0%	12.0%	7.0%
	Ahlering	2004	60	62.7	US	0.0%	5.0%	0.0%	0.0%	0.0%	5.0%	5.0%
	Salomon	2002	145	65.1	France	2.1%	4.8%	2.1%	0.0%	2.8%	11.7%	13.1%
	Artibani	2003	50	64.3	Italy	0.0%	0.0%	16.0%	0.0%	0.0%	16.0%	4.0%
	Guazzoni	2006	60	62.9	Italy	8.3%	0.0%	5.0%	0.0%	0.0%	13.3%	10.0%
	Poulakis	2006	70	74.0	Germany	18.6%	4.3%	1.4%	4.3%	0.0%	28.6%	24.3%
	Brown	2004	60	59.0	US	0.0%	3.3%	0.0%	0.0%	0.0%	3.3%	15.0%
	Touijer	2008	818	59.0	US	0.4%	0.6%	0.0%	0.1%	0.0%	1.1%	5.9%
	Roumeguere	2003	77	64	Belgium	0.0%	0.0%	7.8%	0.0%	0.0%	7.8%	22.1%
	Krambeck	2008	588	61.0	US	1.7%	1.9%	0.2%	0.5%	0.0%	4.3%	0.3%
	Nelson	2007	374	59.9	US	0.0%	2.1%	1.1%	0.0%	0.0%	3.2%	1.6%
	Rassweiler	2003	219	65.0	Germany	2.3%	2.3%	2.7%	0.0%	1.4%	8.7%	9.6%
	Ficarra	2009	105	65.0	Italy	6.7%	0.0%	1.0%	1.9%	0.0%	9.5%	1.0%
	Kundu	2004	3477	61.0	US	0.0%	1.3%	0.7%	0.1%	0.0%	2.1%	7.1%
	Augustin	2003	1243	62.1	Germany	0.2%	1.4%	0.5%	0.1%	0.2%	2.5%	5.6%
	Lepor	2001	1000	60.3	US	0.4%	0.4%	0.4%	0.5%	0.5%	2.2%	4.3%
	Constantinides	2008	995	63.2	Greece	5.3%	1.4%	2.4%	0.0%	1.0%	10.2%	16.8%
	Carini	2008	488	64.5	Italy	1.0%	1.2%	0.0%	0.2%	0.6%	3.1%	11.3%
	Lu-Yao	1999	93986	69.6	US	0.6%	1.2%	0.8%	0.9%	0.8%	4.2%	25.3%
	Catalona	1999	1870	63.0	US	0.0%	2.1%	0.8%	0.1%	0.1%	3.0%	3.6%
LRP	Salomon	2002	137	64.1	France	0.7%	1.5%	0.7%	0.0%	1.5%	4.4%	13.9%
	Artibani	2003	71	63.1	Italy	11.3%	0.0%	22.5%	0.0%	2.8%	36.6%	0.0%
	Guazzoni	2006	60	62.3	Italy	0.0%	0.0%	1.7%	0.0%	1.7%	3.3%	8.3%
	Poulakis	2006	72	74.1	Germany	2.8%	1.4%	1.4%	1.4%	0.0%	6.9%	15.3%
	Brown	2004	60	58.8	US	0.0%	0.0%	0.0%	0.0%	1.7%	1.7%	23.3%
	Touijer	2008	612	60.0	US	1.0%	0.7%	0.0%	0.2%	0.0%	1.8%	2.1%
	Roumeguere	2003	85	62.5	Belgium	0.0%	0.0%	0.0%	0.0%	1.2%	1.2%	12.9%
	Joseph	2005	50	61.8	US/UK	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	2.0%
	Rozet	2007	133	62.5	France	0.0%	0.8%	1.5%	0.0%	0.0%	2.3%	4.5%
	Rassweiler	2003	219	64.0	Germany	3.2%	0.5%	0.5%	0.0%	1.4%	5.5%	6.8%
	Hakimi	2009	75	59.6	US	0.0%	1.3%	1.3%	0.0%	0.0%	2.7%	12.0%
	Hu	2006	358	63.7	US	2.2%	0.0%	0.0%	0.0%	2.0%	4.2%	23.5%
	Lein	2006	1000	62.0	US	2.2%	1.1%	0.4%	0.0%	4.1%	7.8%	5.0%
	Eden	2006	100	62.0	UK	0.0%	1.0%	0.0%	0.0%	1.0%	2.0%	9.0%
	Hoznek	2001	134	64.8	France	3.0%	0.7%	0.0%	0.7%	1.5%	6.0%	6.0%
	Rassweiler	2005	5824	64.0	Germany	2.2%	0.6%	0.0%	0.0%	1.7%	4.5%	4.4%
	Teber	2009	55	65.6	Germany	0.0%	0.0%	0.0%	0.0%	1.8%	1.8%	9.1%
	Goeman	2006	550	62.4	France	2.2%	0.0%	0.4%	0.2%	0.5%	3.3%	7.3%
	Rozet	2005	600	62.0	France	0.0%	0.2%	0.0%	0.0%	0.7%	0.8%	10.3%
	Stolzenburg	2005	700	63.4	Germany	0.9%	0.9%	0.1%	0.0%	0.6%	2.4%	8.9%
	Tuerk	2001	125	59.9	Germany	1.6%	2.4%	0.0%	0.0%	3.2%	7.2%	5.6%
RALP	Tewari	2003	200	59.9	US	0.5%	0.5%	1.0%	0.0%	0.0%	2.0%	# 0.5%
	Ahlering	2004	60	62.9	US	0.5%	0.5%	0.0%	0.0%	0.0%	1.0%	1.0%
	Joseph	2005	50	59.6	US/UK	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%
	Rozet	2007	133	62.0	France	1.5%	0.0%	1.0%	0.0%	0.0%	2.5%	10.0%
	Krambeck	2008	294	61.0	US	5.0%	1.0%	0.0%	1.5%	0.0%	7.5%	4.0%
	Nelson	2007	629	59.3	US	0.5%	2.0%	0.0%	0.0%	0.5%	3.0%	19.5%
	Hakimi	2009	75	59.8	US	0.5%	0.5%	1.0%	0.0%	0.0%	2.0%	2.0%
	Ficarra	2009	103	61.0	Italy	3.5%	0.0%	0.0%	0.0%	0.5%	4.0%	1.0%
	Hu	2006	322	62.1	US	2.5%	1.0%	0.0%	0.0%	0.0%	3.5%	20.0%
	Zorn	2006	300	59.4	US	2.5%	1.0%	3.0%	1.0%	0.0%	7.5%	5.0%
	Patel	2007	500	63.2	US	0.0%	0.0%	0.0%	0.0%	1.0%	1.0%	0.0%
	Joseph	2006	325	60.0	US	1.5%	2.5%	0.0%	1.5%	0.5%	6.0%	10.0%

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy

Table 7. Rates of urethral stricture among patients undergoing radical prostatectomy, by surgical approach.

Surgery	Author	Year	Sample Size	Median Age (yrs)	Location	Urethral Stricture
ORP	Poulakis	2006	70	74.0	Germany	4.3%
	Touijer	2008	818	59.0	US	0.4%
	Krambeck	2008	588	61.0	US	1.0%
	Rassweiler	2003	219	65.0	Germany	16.0%
	Ficarra	2009	105	65.0	Italy	5.7%
	Kundu	2004	3477	61.0	US	2.7%
	Augustin	2003	1243	62.1	Germany	1.7%
	Lepor	2001	1000	60.3	US	1.0%
	Kao	2000	857	64	US	19.8%
	Sacco	2006	985	64.5	Italy	5.1%
	Carini	2008	488	64.5	Italy	0.4%
	Lu-Yao	1999	93986	69.6	US	0.8%
	Catalona	1999	1870	63.0	US	3.8%
LRP	Poulakis	2006	72	74.1	Germany	0.0%
	Touijer	2008	612	60.0	US	0.2%
	Joseph	2005	50	61.8	US/UK	2.0%
	Rozet	2007	133	62.5	France	2.3%
	Rassweiler	2003	219	64.0	Germany	6.4%
	Hakimi	2009	75	59.6	US	1.3%
	Hu	2006	358	63.7	US	2.5%
	Lein	2006	1000	62.0	US	0.2%
	Guillonneau	2002	550	Unk	France	0.2%
	Teber	2009	55	65.6	Germany	1.8%
	Goeman	2006	550	62.4	France	0.4%
	Galli	2006	150	64.0	Italy	4.7%
	Curto	2005	425	62.0	France	0.0%
	Rozet	2005	600	62.0	France	0.2%
	Stolzenburg	2005	700	63.4	Germany	0.3%
	Tuerk	2001	125	59.9	Germany	1.6%
RALP	Joseph	2005	50	59.6	US/UK	0.5%
	Rozet	2007	133	62.0	France	0.5%
	Krambeck	2008	294	61.0	US	0.0%
	Hakimi	2009	75	59.8	US	1.5%
	Ficarra	2009	103	61.0	Italy	5.0%
	Hu	2006	322	62.1	US	0.5%
	Costello	2005	122	61.2	Australia	0.5%

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy

Table 8. Rates of short- and long-term urinary incontinence among patients undergoing radical prostatectomy, by surgical approach.

Surgery	Author	Year	Sample Size	Continent at Baseline (N)	Median Age (yrs)	Location	Incontinence 3 mo	Incontinence ≥12 mo
ORP	Ahlering	2004	60	60	62.7	US	25.0%	---
	Anastasiadis	2003	70	70	64.8	US	57.1%	32.9%
	Artibani	2003	50	14	64.3	Italy	---	21.4%
	Bianco	2005	1746	1288	Unk	US	---	9.0%
	Carini	2008	488	488	64.5	Italy	38.9%	5.9%
	Catalona	1999	1870	1325	63.0	US	---	7.7%
	Ficarra	2009	105	105	65.0	Italy	---	12.4%
	Graefen	2006	1755	1755	Unk	Germany	---	8.0%
	Krambeck	2008	588	490	61.0	US	---	6.1%
	Kundu	2004	3477	2737	61.0	US	---	7.1%
	Loeb	2008	3433	3433	61.0	US	---	7.0%
	Rassweiler	2003	219	219	65.0	Germany	---	10.0%
	Roumeguere	2003	77	56	63.9	Belgium	37.5%	16.1%
	Sacco	2006	985	985	64.5	Italy	31.8%	13.1%
	Saranchuk	2005	647	647	58.0	US	---	7.0%
	Stanford	2000	1291	1291	Unk	US	---	39.5%
	Touijer	2008	818	214	59.0	US	90.2%	25.2%
	Walsh	2000	64	64	Unk	US	45.3%	6.3%
LRP	Anastasiadis	2003	230	230	64.1	US	42.2%	28.3%
	Artibani	2003	71	20	63.1	Italy	---	40.0%
	Curto	2005	425	202	62.0	France	24.3%	5.0%
	Eden	2006	100	100	62.0	UK	---	16.0%
	Galli	2006	150	150	64.0	Italy	26.7%	8.7%
	Goeman	2006	550	550	62.4	France	---	17.1%
	Guillonneau	2002	550	341	Unk	France	---	18.0%
	Hakimi	2009	75	75	59.6	US	45.3%	10.7%
	Hoznek	2001	134	29	64.8	France	40.4%	13.8%
	Joseph	2005	50	50	61.8	US/UK	8.0%	---
	Lein	2006	1000	952	62.0	US	---	24.1%
	Link	2005	73	73	58.3	US	83.7%	32.9%
	Rassweiler	2003	219	219	64.0	Germany	---	9.6%
	Rassweiler	2005	5824	4992	64.0	Germany	---	15.1%
	Roumeguere	2003	85	52	62.5	Belgium	49.3%	19.2%
	Rozet	2005	600	498	62.0	France	---	16.1%
	Stolzenburg	2005	700	420	63.4	Germany	---	8.1%
	Teber	2009	55	55	65.6	Germany	38.2%	9.1%
	Touijer	2008	612	186	60.0	US	89.8%	52.2%
	Tuerk	2001	125	125	59.9	Germany	24.8%	8.0%
RALP	Ahlering	2004	60	60	62.9	US	23.3%	---
	Costello	2005	122	49	61.2	Australia	65.2%	---
	Ficarra	2009	103	103	61.0	Italy	---	29.1%
	Hakimi	2009	75	75	59.8	US	34.7%	6.7%
	Joseph	2005	50	50	59.6	US/UK	10.0%	---
	Joseph	2006	325	179	60.0	US	6.7%	4.5%
	Krambeck	2008	294	251	61.0	US	---	8.0%
	Menon	2007	2652	1142	60.2	US	---	16.0%
	Patel	2007	500	500	63.2	US	11.0%	3.0%
	Zorn	2006	300	300	59.4	US	53.0%	10.0%

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy

Table 9. Rates of short- and long-term erectile dysfunction among patients undergoing radical prostatectomy, by surgical approach.

Surgery	Author	Year	Sample Size	Potent at Baseline (N)	Median Age (yrs)	Location	Erectile Dysfunction 3 mo	Erectile Dysfunction ≥12 mo	Nerve Sparing (≥12 mo only) Bilateral	Nerve Sparing (≥12 mo only) Unilateral	Nerve Sparing (≥12 mo only) None
ORP	Anastasiadis	2003	70	70	64.8	US	70.0%	70.0%	57.1%	75.0%	---
	Artibani	2003	50	40	64.3	Italy	---	90.0%	---	---	---
	Bianco	2005	1746	785	Unk	US	---	36.9%	---	---	---
	Carini	2008	488	302	64.5	Italy	---	38.1%	30.4%	61.3%	---
	Catalona	1999	1870	858	63.0	US	---	33.4%	32.0%	53.3%	---
	Ficarra	2009	105	41	65.0	Italy	---	51.2%	51.2%	---	---
	Graefen	2006	1755	524	Unk	Germany	---	47.1%	---	---	---
	Krambeck	2008	588	417	61.0	US	---	37.2%	---	---	---
	Kundu	2004	3477	1834	61.0	US	---	24.8%	24.0%	46.9%	---
	Loeb	2008	3433	3433	61.0	US	---	37.0%	37.0%	---	---
	Marien	2009	634	634	57.0	US	---	41.0%	39.0%	53.0%	86.0%
	Roumeguere	2003	77	33	63.9	Belgium	66.7%	45.5%	45.5%	---	---
	Saranchuk	2005	647	647	58.0	US	82.0%	63.1%	63.1%	---	---
	Stanford	2000	1291	939	Unk	US	---	56.0%	54.0%	58.6%	65.6%
	Touijer	2008	818	164	59.0	US	95.1%	41.5%	---	---	---
	Walsh	2000	64	64	Unk	US	62.5%	26.6%	26.6%	---	---
LRP	Anastasiadis	2003	230	230	64.1	US	62.2%	47.0%	46.8%	54.5%	---
	Artibani	2003	71	57	63.1	Italy	---	91.2%	---	---	---
	Curto	2005	425	137	62.0	France	70.0%	41.6%	41.6%	---	---
	Eden	2006	100	64	62.0	UK	---	40.6%	40.6%	---	---
	Goeman	2006	550	506	62.4	France	59.1%	41.1%	---	---	---
	Guillonneau	2002	550	47	Unk	France	---	34.0%	---	---	---
	Hakimi	2009	75	63	59.6	US	84.1%	30.2%	28.9%	60.0%	---
	Hoznek	2001	134	25	64.8	France	---	44.0%	---	---	---
	Joseph	2005	50	50	61.8	US/UK	78.0%	---	---	---	---
	Link	2005	73	50	58.3	US	64.0%	22.0%	---	---	---
	Rassweiler	2005	5824	2912	64.0	Germany	---	47.5%	47.5%	---	---
	Roumeguere	2003	85	26	62.5	Belgium	57.7%	34.6%	34.6%	---	---
	Rozet	2005	600	89	62.0	France	---	36.0%	---	---	---
	Stolzenburg	2005	700	100	63.4	Germany	94.0%	76.0%	52.9%	87.9%	---
	Su	2004	177	61	Unk	US	67.4%	58.2%	23.8%	---	---
	Teber	2009	55	55	65.6	Germany	---	45.5%	21.9%	50.0%	93.3%
	Touijer	2008	612	132	60.0	US	94.7%	43.2%	---	---	---
	Tuerk	2001	125	44	59.9	Germany	---	40.9%	---	40.9%	---
RALP	Ficarra	2009	103	64	61.0	Italy	---	18.8%	18.8%	---	---
	Hakimi	2009	75	60	59.8	US	71.7%	35.0%	23.5%	42.9%	---
	Joseph	2005	50	50	59.6	US/UK	60.0%	---	---	---	---
	Joseph	2006	325	150	60.0	US	---	30.0%	10.9%	12.5%	100.0%
	Krambeck	2008	294	203	61.0	US	---	30.0%	---	---	---
	Menon	2007	2652	480	60.2	US	---	30.0%	29.0%	41.0%	60.0%
	Patel	2007	500	200	63.2	US	---	22.0%	---	---	---
	Zorn	2006	300	258	59.4	US	46.9%	26.0%	20.1%	39.2%	---

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy

Table 10. Rates of positive pT2 and pT3 surgical margins among patients undergoing radical prostatectomy, by surgical approach.

Surgery	Author	Year	Sample Size	Median Age (yrs)	Location	+Margins pT2 (%)	+Margins pT3 (%)
ORP	Ahlering	2004	60	62.7	US	9.0%	50.0%
	Salomon	2002	145	65.1	France	19.0%	52.7%
	Artibani	2003	50	64.3	Italy	6.0%	46.2%
	Guazzoni	2006	60	62.9	Italy	18.2%	31.3%
	Fromont	2002	139	64.3	France	21.0%	41.2%
	Terakawa	2008	220	69.1	Japan	17.3%	34.6%
	Silva	2007	89	63.0	Brazil	34.2%	84.6%
	Poulakis	2006	70	74.0	Germany	12.0%	36.7%
	Jurczok	2007	240	65	Germany	12.6%	30.5%
	Roumeguere	2003	77	63.9	Belgium	7.3%	72.2%
	Smith	2007	200	61.1	US	24.0%	60.0%
	Rassweiler	2003	219	65.0	Germany	17.0%	35.5%
	Laurila	2008	98	59.8	US	15.1%	9.1%
	White	2009	50	64.7	US	34.0%	66.7%
LRP	Salomon	2002	137	64.1	France	22.0%	48.5%
	Artibani	2003	71	63.1	Italy	14.0%	43.5%
	Guazzoni	2006	60	62.3	Italy	24.4%	33.3%
	Fromont	2002	139	63.5	France	10.0%	23.1%
	Terakawa	2008	132	67.3	Japan	30.2%	71.0%
	Silva	2007	90	62.0	Brazil	20.9%	55.6%
	Poulakis	2006	72	74.1	Germany	12.0%	31.3%
	Jurczok	2007	163	62.9	Germany	9.8%	29.6%
	Roumeguere	2003	85	62.5	Belgium	7.8%	51.4%
	Rozet	2007	133	62.5	France	15.5%	16.7%
	Rassweiler	2003	219	64.0	Germany	17.0%	31.8%
	Hakimi	2009	75	59.6	US	12.7%	25.0%
	Lein	2006	1000	62.0	US	14.8%	54.4%
	Eden	2006	100	62.0	UK	16.0%	25.0%
	Hoznek	2001	134	64.8	France	16.8%	48.5%
	Guillonneau	2002	550	Unk	France	11.8%	38.5%
	Rassweiler	2005	5824	64.0	Germany	10.6%	39.4%
	Teber	2009	55	65.6	Germany	7.5%	33.3%
	Goeman	2006	550	62.4	France	17.9%	44.1%
	Galli	2006	150	64.0	Italy	11.3%	49.1%
	Curto	2005	425	62.0	France	21.8%	43.3%
	Rozet	2005	600	62.0	France	14.6%	26.2%
	Stolzenburg	2005	700	63.4	Germany	10.8%	31.2%
	Su	2004	177	Unk	US	4.7%	44.8%
	Bollens	2001	50	63.3	Belgium	7.4%	42.9%
RALP	Ahlering	2004	60	62.9	US	4.5%	50.0%
	Rozet	2007	133	62.0	France	20.0%	13.0%
	Smith	2007	200	60.3	US	9.4%	50.0%
	Laurila	2008	94	58.8	US	10.0%	37.5%
	Hakimi	2009	75	59.8	US	10.9%	18.2%
	White	2009	50	62.0	US	19.1%	66.7%
	Zorn	2006	300	59.4	US	15.1%	52.2%
	Patel	2007	500	63.2	US	2.5%	28.0%
	Joseph	2006	325	60.0	US	10.6%	32.7%
	Mottrie	2007	184	62.0	Belgium	2.5%	37.1%

NOTES: ORP: Radical retropubic prostatectomy; LRP: Laparoscopic radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy; pT2: Pathological stage T2a, T2b, or T2c; pT3: Pathological stage T3a or T3b

APPENDIX C

COMPARATIVE VALUE EVIDENCE TABLES

Table 1. Estimated clinical outcomes for selected interventions for low-risk prostate cancer.

Outcome (%, except where noted)	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
Age 65 Years			
Prog. to treatment	61.1%	100.0%	38.9%
Peri-operative death	N/A	0.4%	N/A
Minor complications	0.2%	9.5%	9.3%
Major complications	0.0%	4.8%	4.8%
Treatment-related SE			
Incontinence	3.6%	8.6%	5.0%
ED	5.3%	30.7%	25.4%
GI (from IMRT)	2.7%	N/A	N/A
Prostate cancer death	9.0%	9.0%	0.0%
Life years (mean)	16.0	16.0	0.0
QALYs (mean)	8.97	7.82	(1.2)
Age 55 Years			
Prog. to treatment*	72.1%	100.0%	28.0%
Peri-operative death	0.1%	0.4%	0.3%
Minor complications	2.8%	9.5%	6.7%
Major complications	1.1%	4.8%	3.7%
Treatment-related SE			
Incontinence	6.5%	10.4%	4.0%
ED	13.7%	35.7%	22.0%
GI (from IMRT)	2.0%	N/A	N/A
Prostate cancer death	16.0%	16.0%	0.0%
Life years (mean)	22.0	22.0	0.0
QALYs (mean)	11.54	10.33	(1.2)

NOTES: SE: side effects; ED: erectile dysfunction; GI: gastrointestinal; IMRT: intensity-modulated radiation therapy; QALYs: quality-adjusted life years

*In this younger-age population, 30% of treated patients receive radical prostatectomy

Table 2. Estimated lifetime costs for selected interventions for low-risk prostate cancer, by cost component.

Cost ($)	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
Age 65 Years			
Year 1 treatment	4,228	13,553	9,325
Services	4,809	4,624	(185)
Visits	3,382	4,624	1,241
Biopsies	1,427	N/A	N/A
Definitive Rx (IMRT)	14,327	N/A	N/A
Patient time	8,156	6,150	(2,006)
Short-term SE	270	1,477	1,207
Long-term SE	589	786	196
TOTAL			
Undiscounted	38,542	33,589	(4,953)
Discounted	30,422	28,348	(2,074)
Age 55 Years			
Year 1 treatment	3,796	14,496	10,700
Services	5,530	5,213	(317)
Visits	3,848	5,213	1,365
Biopsies	1,682	N/A	N/A
Definitive Rx (IMRT/RP)	13,986	N/A	N/A
Patient time	12,226	9,132	(3,094)
Short-term SE	647	1,468	821
Long-term SE	545	718	173
TOTAL			
Undiscounted	46,690	40,699	(5,991)
Discounted	33,642	31,440	(2,202)

NOTES: SE: side effects; IMRT: intensity-modulated radiation therapy; RP: radical prostatectomy
Component costs presented for illustrative purposes, and will not sum to discounted total

ICER Comparative Value Evidence Table (CVET)

Measure	Active Surveillance	Open Radical Prostatectomy	Difference (ORP-AS)
1. Service Impact			
Visits	35.9	37.2	1.3
Biopsies	2.8	0.0	(2.8)
Pathway Total	38.8	37.2	(1.6)
2. Cost per Life-Year Saved	N/A		(equivalent survival)
3. Cost per QALY Gained	$1,803		
SA 1: 55 yo men	$1,820		
SA 2: Private-pay estimate A	$3,434		
4. Budget Impact (per 1,000, 2 years)	$5,809,000	$13,591,000	$7,782,000
Using Private-Pay Estimate A	$8,721,000	$22,028,000	$13,307,000
5. Fixed Budget Tradeoffs (Annual)		38.9	*Nurse FTEs @ $100K each*
		19.5	*MD FTEs @ $200K each*
		2.4	*Robotic Surgical System @ $1.6M each*

NOTES: QALY: Quality-adjusted life year; FTE: Full-time equivalent