Management Options for Low-Risk Prostate Cancer:

A Report on Comparative Effectiveness and Value

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Management Options for Low-Risk Prostate Cancer: A Report on Comparative Effectiveness and Value

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This report represents a summary of three prior technology appraisals of management options for clinically-localized, low-risk prostate cancer. These appraisals are posted on the web site of the Institute for Clinical and Economic Review (ICER), and can be found at the links below:

- Intensity-modulated radiation therapy (IMRT) (November 2007)
  http://www.icer-review.org/index.php/imrt.html

- Brachytherapy and proton beam therapy (December 2008)
  http://www.icer-review.org/index.php/bt-pbt.html

- Active surveillance and radical prostatectomy (September 2009)
  http://www.icer-review.org/index.php/as-rp.html

While findings on comparative clinical effectiveness were informed by separate systematic reviews of the published literature for each appraisal, the search strategies, study entry criteria, and target patient populations were identified using a uniform approach across appraisals. In addition, all management options were evaluated in an updated decision-analytic model developed in 2009.

This summary report was written by members of ICER's research team. The report summarizes the evidence and views that have been considered by ICER and highlights key issues and uncertainties. The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of organizations providing financial support to ICER, other stakeholder organizations, or members of the advisory panels for the relevant technology appraisals.

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ABOUT ICER

The Institute for Clinical and Economic Review (ICER) provides independent evaluation of the comparative clinical effectiveness and comparative value of new and emerging technologies. ICER is based at the Massachusetts General Hospital's Institute for Technology Assessment (ITA), an affiliate of Harvard Medical School. ICER develops its assessments in collaboration with faculty and staff from the ITA and Harvard Medical School as well as with researchers and clinical experts from around the country. All ICER assessments are performed in conjunction with an external Evidence Review Group comprised of patients, clinical experts, independent methodological experts, and policy experts from the payer and manufacturer community who serve a longitudinal peer review function throughout, culminating in a public meeting to discuss the findings of the assessment and the assignment of ratings of clinical effectiveness and comparative value.

ICER has been purposely structured as a fully transparent organization able to engage with all key stakeholders in its appraisals while retaining complete independence in the formulation of its conclusions and the drafting of its reviews. ICER's academic mission is funded through a diverse combination of sources; funding is not accepted from manufacturers or private insurers to perform reviews of specific technologies. Since its inception, ICER has received funding from the following sources:

- The Agency for Healthcare Research & Quality (AHRQ)
- America's Health Insurance Plans (AHIP)
- Aetna Foundation
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TABLE OF CONTENTS

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SUMMARY OF KEY FINDINGS

- This review focuses on key considerations in the management of localized, low-risk prostate cancer; the evidence and clinical tradeoffs involved in the treatment of intermediate- or high-risk disease would differ substantially and are not addressed in these analyses. Primary management options for low-risk disease evaluated included active surveillance, open and robotic/laparoscopic radical prostatectomy, brachytherapy, intensity-modulated radiation therapy (IMRT), and proton beam therapy. All except proton beam therapy are listed by national guidelines as reasonable options for low-risk prostate cancer.

- There are no published reports of randomized controlled trials directly comparing these treatment options. Evidence from individual case series reports indicates comparable rates of disease recurrence as well as overall and cancer-specific mortality for all forms of surgery and radiation therapy.

- The evidence on the comparative effectiveness and harms of proton beam therapy is limited to relatively small, highly selective case series of short duration, making any judgments about its relative benefit or inferiority to other options premature. The uncertainty regarding proton beam therapy is accentuated because this technology involves delivery of a novel form of radiation, and there remain important questions about the full spectrum of possible effects.

- Robot-assisted laparoscopic prostatectomy represents a change in the method of delivery of an existing surgical treatment, traditional open prostatectomy. However, data on the comparative outcomes of robotic prostatectomy are also relatively short-term and arise from case series, limiting the certainty with which any judgment can be made on clinical benefits compared to open prostatectomy.

- Active surveillance is a relatively recent evolution of "watchful waiting," and entails enhanced monitoring to retain the goal of curative treatment should clinical progression occur. Findings from older studies of watchful waiting suggest a modest survival benefit for surgery among younger men but equivalent disease-specific and overall survival outcomes for men aged >65 years. More recent studies of active surveillance are primarily case series with outcomes limited to 5-7 years. Approximately 30% of patients on active surveillance progress to or choose definitive treatment within 5 years, and disease-specific and overall survival rates within this time frame are comparable to those patients who opt for immediate radical prostatectomy.

- ICER's economic model suggests that approximately 40% of patients aged 65 and older who begin active surveillance will die of other causes before their cancer progresses to require definitive treatment. The model findings also show that, even if a survival benefit of immediate surgery or other definitive treatment is assumed, the lower risk of complications and side effects associated with an active surveillance strategy produces more quality-adjusted life years for an entire population.

Therefore, despite the limitations in available data, ICER concludes that there can be high confidence that active surveillance is at least as effective, and likely more effective, than watchful waiting; and, that current evidence also allows high confidence in a judgment that for patients aged ≥65 the average net health benefit of active surveillance is comparable to immediate definitive treatment for patients with low-risk localized prostate cancer.

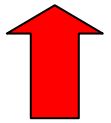
- For men younger than 65 and/or for patients who have a life expectancy greater than 20 years, the limitations in longer-term outcome data from active surveillance reduce the certainty to "moderate" that modern protocols for active surveillance produce mortality outcomes not substantially inferior to radical prostatectomy. However, the quality-of-life advantages of having many patients never require definitive treatment are maintained in this younger population.

- Comparison of the short-term complications and longer-term side effects of the different definitive therapies is challenging because of the lack of head-to-head trials, the role of clinician training and experience, and differences in the way patient outcomes have been measured in published studies. Nonetheless, the data do suggest some general distinctions. Radiation treatment has a higher rate of short- and long-term bowel side effects than surgery, and, among radiation options, IMRT has a higher rate than brachytherapy. Conversely, surgery has higher risks than radiation therapy of causing short-term (0-3 months) urinary incontinence and sexual dysfunction, with longer-term sexual dysfunction data very hard to interpret. The data on robotic-assisted prostatectomy are too preliminary to be able to make a judgment of any differences in clinical outcomes compared to traditional open prostatectomy.

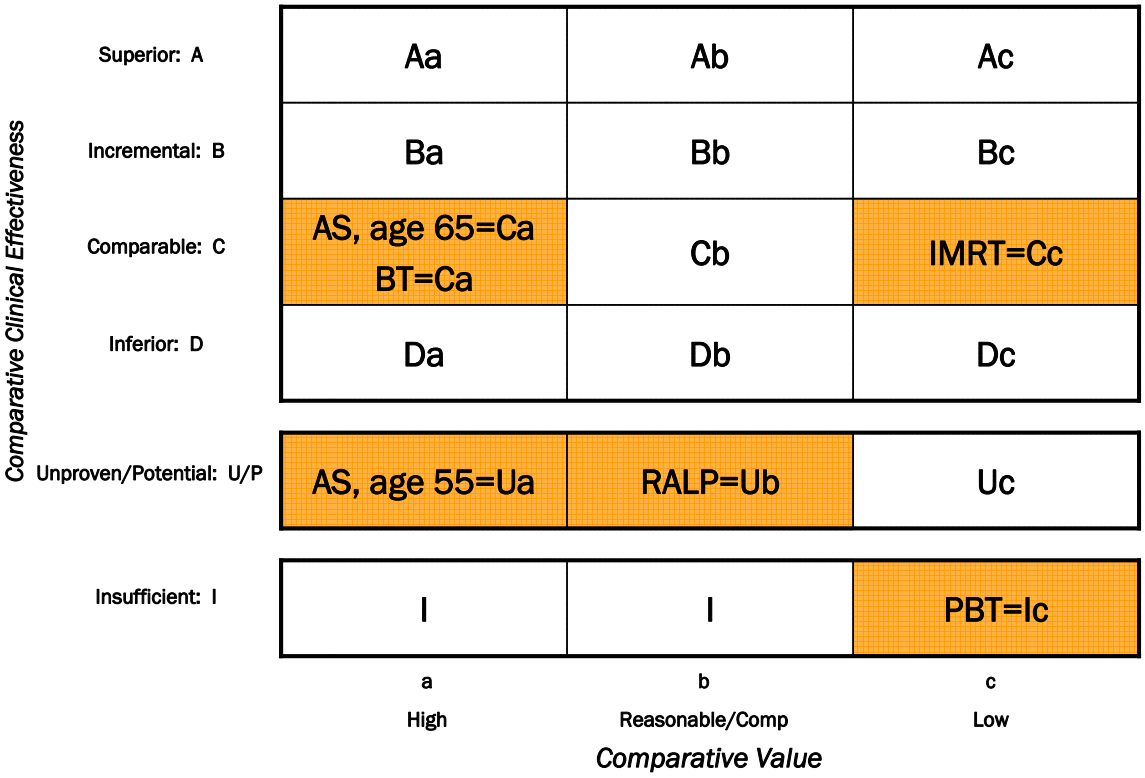
- The management options for localized prostate cancer differ substantially in terms of the cost to third party payers. Using Medicare reimbursements as a basis, annual costs for active surveillance range from $300-$1,000 depending on whether re-biopsy is performed. Costs for definitive treatment range from ~$10,000 for brachytherapy and radical prostatectomy to $20,000 for IMRT and $50,000 for proton beam therapy. Input to ICER from health plans and providers suggests that reimbursement rates are generally higher among private payers, and that the magnitude of differences between external beam therapies (IMRT and proton beam therapy) and other treatments is greater than that in Medicare.

- Findings from the ICER economic model suggest that, on a lifetime basis, quality-adjusted life expectancy for a 65 year-old man is highest for active surveillance and quite similar among the definitive treatment options. Model results indicate that, on average, the benefits of avoiding definitive treatment and its associated side effects from active surveillance translate into 1 year or more of increased quality-adjusted survival relative to immediate definitive treatment. Lifetime costs for active surveillance, brachytherapy, and surgery are similar ($25-$30K), while lifetime costs for IMRT and proton beam therapy are substantially higher ($40-$55K).

LOW-RISK PROSTATE CANCER MANAGEMENT DECISION GUIDE

	Active Surveillance	Radical Prostatectomy	Brachytherapy	IMRT
Potential Comparative Advantages	~40% never show clinical progression requiring active treatment	Single procedure Low risk of bowel side effects	Single procedure Minimally invasive Lower risks of short-term incontinence or impotence than surgery	Non-invasive Lower risks of short-term incontinence or impotence than surgery
Potential Comparative Disadvantages	Risk of "missed" aggressive tumors or tumor progression Monitoring and biopsies required	Surgical complications Higher rates of short-term incontinence and impotence	Risk of short-term urinary obstruction	Higher (~45) number of visits for treatment Higher risk of bowel side effects (proctitis)
May Not Be Best For	Extended life expectancy (>20 yrs) High anxiety High potential for failure to follow-up	Higher surgical risks Higher concern for sexual function and urinary continence	Large prostate History of urinary obstruction	Higher concern for normal bowel function
Relative Cost to Insurers				

ICER Integrated Evidence Rating™: Multiple Management Options vs. Radical Prostatectomy for Clinically-Localized, Low-Risk Prostate Cancer



NOTES: AS: Active surveillance; BT: Brachytherapy; IMRT: Intensity-modulated radiation therapy; RALP: Robot-assisted laparoscopic prostatectomy; PBT: Proton beam therapy

Background on the ICER rating methodology, including descriptions of the rating categories for comparative clinical effectiveness and comparative value, can be found in Appendix B of this document. Further description of the ratings for this report as well as the rationale for the ratings selected can be found on pages 56-58.

EVIDENCE REVIEW GROUP

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.

A list of all the participants in the Evidence Review Groups for the separate appraisals of radiation, surgery, and active surveillance is listed below; participant affiliations are listed as those in place at the time each appraisal was conducted.

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I. 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 Tumor, Node, Metastasis (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 one-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 used by the National Comprehensive Cancer Network (NCCN) has been well-validated and widely published (D'Amico, 1999). The definitions of risk levels used in current NCCN guidelines are shown on the following page (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 very 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.

II. The Alternative Management 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 most commonly used management options for prostate cancer are:

1) Active surveillance
2) Radical prostatectomy
3) Interstitial brachytherapy
4) Three-dimensional conformal radiation therapy (3D-CRT)
5) Intensity-modulated radiation therapy (IMRT)
6) Proton beam therapy

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. Most clinical experts believe that the existing data suggest that many of these interventions have comparable cure rates but that rates of certain harms may differ (Jani, 2003). In the United States, use of IMRT has grown exponentially; in 2006, for example, IMRT accounted for over 50% of all Medicare expenditures for radiation oncology (Simone II, 2007). Clinical experts advised ICER that IMRT has largely supplanted 3D-CRT as the external beam radiation modality of choice for prostate cancer; as such, 3D-CRT was not evaluated for this report.

Active Surveillance

Because of the limited aggressiveness of many localized prostate cancers, active surveillance is a reasonable strategy for many men (NCCN, 2009). The term 'watchful waiting' is also sometimes used interchangeably with active surveillance. However, the phrase "watchful waiting" was first coined during an era when most men were first diagnosed with prostate cancer through presentation with obstructive urinary symptoms or a palpable nodule. Today, the vast majority of prostate cancer is diagnosed through routine PSA screening of asymptomatic men. 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). Recently-published data suggest that 50-70% of men who elect to defer treatment remain untreated after 7-8 years of follow-up (Shappley III, 2009; Klotz, 2009); treatment deferral may be longer among those with low-risk disease.

Following the publication of randomized controlled trials that showed a survival advantage at 10-12 years 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 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 up to 50% 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 an indicator of disease progression. Still others contend that results of repeat biopsies provide the best predictor of more aggressive disease behavior. 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 has 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).

Brachytherapy

Prostate brachytherapy refers to placement of radioactive "seeds" into the prostate in the area affected by cancer. There are two major forms of prostate brachytherapy currently in use today: permanent, low-dose rate (LDR) brachytherapy, in which radioactive seeds are permanently implanted and emit a low dose of radiation over several months; and the newer, temporary, high-dose rate (HDR) procedure, in which seeds are inserted through micro-catheters and removed after less than an hour. The HDR procedure is typically reserved for intermediate- or higher-risk patients, and thus LDR brachytherapy is the focus of this appraisal. This procedure typically involves a dose planning physician visit, an overnight hospital stay or same-day discharge 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 therapy (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 (i.e., >60 cc) or those with a history of obstructive urinary symptoms, as the procedure results in short-term inflammation and swelling of the gland which could lead to acute urinary obstruction (Mayo, 2008). Other potential risks of brachytherapy include infection, injury, and anesthesia-related complications from the procedure; migration of radioactive seeds to parts of the body outside the prostate; acute and late-onset urinary incontinence or irritative symptoms; rectal morbidity (e.g., proctitis, hemorrhage); and sexual dysfunction. In addition, there are concerns regarding the long-term risk of treatment-induced secondary malignancy common to all forms of radiation therapy.

Clinical experts on the ICER Evidence Review Group agreed that brachytherapy training in postgraduate residency and fellowship is suitable to prepare all practicing clinicians to perform the procedure with competency. There exists a well-defined minimum hands-on experience mandated by the Accreditation Council for Graduate Medical Education (ACGME) Residency Review Committee for Radiation. However, due to the complex technical aspects of brachytherapy, there is acknowledged variation in clinician procedural skills and associated patient outcomes. The results of several studies suggest that a clinician's level of experience with brachytherapy is correlated with disease recurrence and death, although no clear link to complications has been documented (Chen, 2009; Chen, 2006). Concern regarding variability in technical competency and outcomes may apply somewhat more to brachytherapy, but the same issue is also relevant for IMRT and proton beam therapy; unfortunately, no evidence exists with which to compare the relationship between clinician skills and patient outcomes across the 3 modalities.

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 relies on inverse treatment planning using digitally reconstructed radiographs generated from 3-dimensional images (e.g. CT scans), and either modulates intensity of radiation beams to achieve non-uniform cross-sections, or spirally delivers a single narrow beam (tomotherapy), to target highly conformal radiation at tumors. Unlike conventional, three-dimensional conformal radiation therapy (3D-CRT), which delivers radiation at a constant dose to a defined field, IMRT delivers non-uniform beam intensities that are consecutively cross firing and converging at the treatment target to maximize dose at the target and reduce dose to the surrounding normal tissue.

Proponents of IMRT feel that the technology is able to deliver escalated doses of radiation while maintaining acceptable levels of toxicity (Esiashvili, 2004). IMRT is typically performed as an outpatient procedure; patients will typically have a dose planning visit, followed by 37-45 brief (15-20 minutes) daily treatments. 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. In addition, while not as well-documented as with brachytherapy, there is significant potential for variability in treatment planning and/or delivery of IMRT by clinician and center, particularly as the technology moves from highly specialized centers into the community.

Proton Beam Therapy

Proton beams are known to deposit the bulk of their radiation energy at the end of their range of penetration, a radiation pattern referred to as the Bragg peak (Larsson, 1958). This feature allows for targeted dosing of proton radiation to a particular tumor site as opposed to the more disseminated distribution of photon radiation used for IMRT (Lundkvist, 2005). On the other hand, uncertainties remain regarding the true dose distribution of protons in prostate cancer, as these tumors are more deep-seated relative to other cancers historically treated by protons, and current scanning techniques may not allow for conformation of the radiation to the target as accurately as with IMRT (Nguyen, 2008).

Proton beam therapy is usually performed as an outpatient procedure; patients have an initial dose planning visit followed by approximately 40 daily treatment visits of 15-20 minutes' duration; patients must be completely immobilized during the procedure to limit radiation exposure to normal tissue. Potential treatment-induced toxicities from proton beam therapy are similar to those of brachytherapy (with the exception of acute urinary retention), and include early and late-onset urinary incontinence and/or obstructive symptoms, rectal toxicity, and sexual dysfunction.

While proton beam centers have expanded in recent years, they are relatively few in number; there are currently 5 centers operating in the US (California, Texas, Indiana, Florida, and Massachusetts), with two additional centers scheduled to come online in 2009. The relatively small number of proton centers may be due in part to the large investment ($125-$150 million) required to obtain the equipment and construct a suitable housing facility.

III. Clinical Guidelines and Competency Standards

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, transrectal ultrasound (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.

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

Brachytherapy

Clinical Guidelines

- National Comprehensive Cancer Network (2008): The NCCN Prostate Cancer Panel Members concluded that "permanent brachytherapy as monotherapy is indicated for patients with low-risk cancers. For intermediate-risk cancers consider combining brachytherapy with EBRT with or without neoadjuvant androgen deprivation therapy". http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

- European Organisation for Research and Treatment in Cancer (2000): The EORTC Radiotherapy Group, in conjunction with the European Society for Therapeutic Radiology and Oncology (ESTRO) and the European Urological Association (EAU), recommend permanent brachytherapy for patients with low risk disease. Brachytherapy with external radiation boost can be considered in intermediate-risk patients. http://www.estro.be/ESTRO/upload//seedimplanguidelines.pdf

- American College of Radiology (2008): The ACR concluded that high rates of biochemical control have been evident from brachytherapy as a monotherapeutic approach for patients with low-risk features. ACR appropriateness criteria suggest that, in patients with low-risk, clinically-localized disease, permanent, low-dose-rate interstitial brachytherapy monotherapy is considered one of the preferred approaches (rating of 9 on a scale of 1-9). http://acsearch.acr.org/ProceduresList.aspx?tid=68684&vid=3070787

- American Urological Association (2007): The AUA has concluded that interstitial brachytherapy is considered one of the viable monotherapy options for clinically-localized, low-risk prostate cancer and there is no clear-cut evidence for the superiority of any one treatment. http://www.auanet.org/guidelines/main_reports/proscan07/content.pdf

- American Brachytherapy Society (2006): The ABS considers permanent LDR brachytherapy appropriate in patients with a life expectancy >5 years, clinical stage T1b-T2c (and selected T3), Gleason scores ranging from 2-10, PSA ≤50 ng/mL, and no pathologic evidence of pelvic lymph node involvement or distant metastases. http://www.americanbrachytherapy.org/resources/prostate_low-doseratetaskgroup.pdf

Competency Standards

- American College of Radiology (2006): The ACR collaborated with the American Society for Therapeutic Radiology and Oncology (ASTRO) and the ABS to recommend training standards for the use of brachytherapy. If training is not obtained during a fellowship or residency program, radiation oncologists should obtain training in MRI, CT, or transrectal ultrasound methods, and must attend a hands-on workshop or conduct at least five proctored cases. Workshops must provide supervised

experience in seed implantation and evaluations; proctored cases must be supervised by a qualified physician.
http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/brachy_prostate_cancer.aspx

- Inter-society Standards (2003): The American Brachytherapy Society, The American College of Medical Physics (ACMP) and The American College of Radiation Oncology (ACRO) released a set of standards regarding the practice of brachytherapy. Radiation oncologists are required to have completed a residency in radiation oncology or radiation therapy and training at a brachytherapy center of excellence is strongly encouraged. In addition, clinicians must "meet applicable requirements imposed by federal, state, and/or local radiation control agencies." (full documentation not available online)
http://www.ncbi.nlm.nih.gov/pubmed/14585480?dopt=Abstract

IMRT

Clinical Guidelines

- National Comprehensive Cancer Network (NCCN, 2009): The NCCN Prostate Cancer Panel members consider IMRT or 3D-CRT techniques, with image guidance, appropriate for low-risk disease at doses of 70-79 Gy delivered in 35-41 daily fractions. IMRT is also considered appropriate for intermediate- or high-risk cancers, along with pelvic lymph node irradiation and/or androgen deprivation therapy.
http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

- American College of Radiology (2008): The ACR considers all forms of external beam radiation appropriate for treatment of clinically-localized, low-risk disease (rating of 9 on 1-9 scale); the appropriateness of treatment planning using IMRT or proton beam is rated 8, vs. 7 for 3D-CRT techniques.
http://acsearch.acr.org/ProceduresList.aspx?tid=68684&vid=3070787

- American Urological Association (2007): The AUA has concluded that external beam radiotherapy is considered one of the viable monotherapy options for clinically-localized, low-risk prostate cancer, along with active surveillance, interstitial brachytherapy, and radical prostatectomy, and that "study outcomes data do not provide clear-cut evidence for the superiority of any one treatment"; no distinction is made by type of external beam therapy.
http://www.auanet.org/guidelines/main_reports/proscan07/content.pdf

- American Society for Therapeutic Radiology and Oncology (2009): ASTRO has formally concluded that "IMRT makes possible conformal radiation dose distributions to the target while reducing exposure of adjacent nontarget structures, beyond the capabilities of traditional two-dimensional or three-dimensional conformal treatment techniques."
  http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/imrt.aspx

Competency Standards

- American Society for Therapeutic Radiology and Oncology (2009): ASTRO collaborated with the American College of Radiology to release a set of practice guidelines for IMRT. Requirements for radiation oncologists are the same as for general radiation oncology, and include: (a) certification by the American Board of Radiology in therapeutic radiology or radiation oncology, or completion of a certified residency program in radiation oncology; and (b) fulfillment of continuing medical education (CME) requirements, including 150 hours of CME every 3 years, 80% of which must be radiation oncology-specific.
  http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/radiation_oncology.aspx

Proton Beam Therapy

Clinical Guidelines

- National Comprehensive Cancer Network (2008): The NCCN Prostate Cancer Panel Members groups proton beam therapy with all other forms of external beam radiation; panel consensus was that "modern radiotherapy and surgical series show similar progression-free survival in low-risk patients", and that radiation therapy featuring use of conformal or intensity-modulated techniques should be considered a principal treatment option for clinically-localized disease.
  http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

- American Cancer Society (2006): The ACS concludes that early research results on proton beam therapy in prostate cancer are promising, but that long-term advantages over other forms of external beam radiation have not been proven.
  http://www.cancer.org/docroot/CRI/content/CRI_2_4_4X_Radiation_Therapy_36.asp?sitearea=CRI

- American College of Radiology (2008): The ACR considers all forms of external beam radiation appropriate for treatment of clinically-localized, low-risk disease (rating of 9 on 1-9 scale); the appropriateness of treatment planning using IMRT or proton beam is rated 8, vs. 7 for 3D-CRT techniques.
  http://acsearch.acr.org/ProceduresList.aspx?tid=68684&vid=3070787

- American Urological Association (2007): The AUA has concluded that external beam radiotherapy is considered one of the viable monotherapy options for clinically-localized, low-risk prostate cancer, along with active surveillance, interstitial

brachytherapy, and radical prostatectomy, and that "study outcomes data do not provide clear-cut evidence for the superiority of any one treatment"; no distinction is made by type of external beam.
http://www.auanet.org/guidelines/main_reports/proscan07/content.pdf

Competency Standards

There are no published competency standards or training guidelines for proton beam therapy. However, a training and development center for proton therapy was recently opened in Bloomington, Indiana by ProCure, Inc., a manufacturer of proton systems. The facility is working with several academic institutions to develop formal accreditation programs for medical professionals (Business Wire, 2008).

IV. Medicare and Representative Private Insurer Coverage Policies

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.

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 robot-assisted surgical techniques.

- United Healthcare: "Laparoscopic radical prostatectomy is proven for the treatment of localized prostate cancer. Robot-assisted radical prostatectomy is proven non-preferentially as a form of laparoscopic radical prostatectomy for the treatment of localized prostate cancer. Coverage for robot-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, "robot-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.

Brachytherapy

- Centers for Medicare and Medicaid Services (CMS): There are no National Coverage Decisions on brachytherapy. The majority of Local Coverage Decisions allow for coverage of both LDR and HDR brachytherapy, alone or in conjunction with surgery or external beam radiation, although at least one LCD recommends following ABS clinical criteria to determine medical necessity.

- United Healthcare: LDR brachytherapy is considered proven for the treatment of early stage, localized prostate cancer. HDR brachytherapy is only covered as an in-network benefit where LDR brachytherapy is unavailable.

- All other private health plans evaluated for this overview (including Humana, Aetna, and CIGNA) consider both LDR and HDR brachytherapy medically necessary for the

treatment of prostate cancer and do not distinguish between these techniques with regard to coverage levels.

IMRT

- Centers for Medicare and Medicaid Services (CMS): There is no Medicare National Coverage Decision on IMRT. A review of Local Coverage Decisions (LCDs) suggests that IMRT is universally covered as a form of conformal radiation therapy, stating that IMRT is "reasonable and necessary in instances where sparing the surrounding normal tissue is essential" and the patient meets at least one of several criteria regarding tumor shape, dose-limiting adjacent structures, etc., or "only IMRT techniques would decrease the probability of grade 2 or grade 3 radiation toxicity as compared to conventional radiation in greater than 15 percent of radiated similar cases."

- Aetna: IMRT is medically necessary for treatment of prostate carcinoma only when ultra high-dose radiation (dosage of 72 Gy) or more is planned.

- WellPoint (HealthLink): IMRT of the prostate is considered medically necessary in patients with non-metastatic prostate cancer for dose escalation >75Gy.

- United Healthcare: IMRT is indicated when the following criteria are met: irregularly shaped tumors in close proximity to vital structures or sensitive normal tissue AND one of the following criteria: non-metastatic prostate cancer for dose escalation > 75 Gy or equivalent hypofractionated regimen.

- CIGNA: IMRT is covered as medically necessary for patients when there is reasonable concern about damage to surrounding tissue with the use of conventional EBRT or 3D-CRT.

Proton Beam Therapy

- Medicare: There have been no National Coverage Decisions on proton beam therapy. Most Local Coverage Decisions allow for the use of proton beam therapy for prostate cancer only when there is documentation in the patient's record supporting its use over other treatment options and the following criteria are met:

    - For primary lesions, treatment intent must be curative; for metastatic lesions, there must be an expectation of long-term (>2y) benefit and complete eradication of metastases can only reasonably be expected through the dosimetric advantages of proton beam therapy;

AND at least one of the following conditions must be present:

    - Dose constraints to normal tissues limit the total dose of radiation safely deliverable to the tumor with other indicated methods; OR

- There is reason to believe that doses generally thought to be above the level otherwise attainable with other methods might improve control rates; OR

- Higher levels of precision associated with proton beam therapy as compared to other radiation methods are clinically relevant and necessary.

- Empire Blue Cross / Blue Shield (Wellpoint): Proton beam therapy is considered medically necessary for the treatment of prostate cancer, but current data do not support any claims of superiority over IMRT or conformal radiation therapy.

- United Healthcare: Proton beam therapy is considered equivalent, but not superior to, other forms of external radiation therapy for prostate cancer, and is covered as an in-network benefit only where other forms of external beam radiation are unavailable in the network.

- Humana: Proton beam therapy is considered a covered benefit for the treatment of prostate cancer.

- Aetna: Proton beam therapy is considered to be medically necessary for the treatment of prostate cancer; use of stereotactic techniques for administration of proton beam therapy is not covered, however.

- CIGNA: Proton beam therapy is considered equivalent, but not superior to, conventional external beam radiotherapy, and is not covered as an in-network benefit when conventional techniques are available in-network.

- PriorityHealth: Proton beam therapy for prostate cancer is not covered, because "alternate equally effective forms of therapy which are more cost-effective exist."

V. Previous Systematic Review/Technology Assessments

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 III).

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 Robot-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.

Brachytherapy

- Agency for Healthcare Research and Quality (AHRQ) (2008): AHRQ determined that the paucity of comparative evidence on different treatment options and the lack of randomized studies on brachytherapy limit the ability to make comparisons of effectiveness and adverse effects. http://effectivehealthcare.ahrq.gov/repFiles/2008_0204ProstateCancerFinal.pdf

- National Institute for Clinical Excellence (NICE, UK) (2005): Current evidence on the safety and efficacy of both LDR and HDR brachytherapy (the latter in combination with external beam radiation) appears adequate to support the use of these procedures. http://www.nice.org.uk/Guidance/IPG132/Guidance/pdf/English

- Medical Services Advisory Committee (MSAC, Australia) (2005): Subject to further evidence, public funding for brachytherapy (only LDR was considered) should continue for patients at clinical stages T1 or T2, Gleason scores ≤6, PSA ≤10 ng/ml, gland volume <40cc, and life expectancy >10 years. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/4753418A5C8F33DDCA25745E000A3933/$File/1089%20-%20Brachytherapy%20for%20the%20treatment%20of%20prostate%20cancer%20Report.pdf

- Institute for Quality and Efficiency in Health Care (IQWiG, Germany) (2007): IQWiG concludes that potential advantages of brachytherapy (only LDR was assessed) are insufficient to support its use and sound clinical studies must be conducted before comparisons can be made to other treatments. http://www.iqwig.de/download/N04-02_Executive_summary_Brachytherapy.pdf

IMRT

- Blue Cross Blue Shield Association Technology Evaluation Center (TEC) (2005): The BCBSA TEC reviewed IMRT for cancer of the breast and lung and concluded that available data were insufficient to determine whether IMRT is superior to 3D-CRT for improving health outcomes (summary not available online). TEC has not reviewed IMRT for prostate cancer.

- National Institute for Health and Clinical Excellence (NICE):
  NICE has not reviewed this topic.

- California Technology Assessment Forum (CTAF) (2005):
  CTAF evaluated IMRT for localized prostate cancer, producing a draft assessment in 2005. The assessment found that IMRT did not meet technology assessment criteria demonstrating that it improves net health outcomes. Negative response from the clinical community led CTAF to table its assessment. A roundtable symposium on IMRT for prostate cancer was held in January 2007 but CTAF decided not to issue a formal decision.
  http://www.ctaf.org/content/calendar/detail/654

- Canadian Agency for Drugs and Technologies in Health (CADTH)
  CADTH has not reviewed this topic.

- National Coordinating Center for Health Technology Assessment (NCCHTA) (2003):
  The NCCHTA in England produced a systematic review of the clinical and cost-effectiveness of new and emerging treatments for early localized prostate cancer. Their work considered IMRT an advanced form of 3D-CRT and concluded that "the quality and paucity of evidence and the reliance on the reporting of surrogate end-points do not allow conclusions to be drawn regarding the relative effectiveness of IMRT compared with 3D-CRT."
  http://www.ncchta.org/execsumm/summ733.htm

Proton Beam Therapy

Proton beam radiotherapy does not appear to have been extensively evaluated by HTA organizations for prostate cancer. Results of available systematic reviews are summarized below.

- Agency for Healthcare Research and Quality (AHRQ) (2008): As there have been no randomized trials conducted on proton beam therapy, large randomized control trials on this technology are recommended by AHRQ. At the time there is insufficient evidence to draw conclusions on the effectiveness of proton beam therapy.
  http://effectivehealthcare.ahrq.gov/repFiles/2008_0204ProstateCancerFinal.pdf

- California Technology Assessment Forum (CTAF, USA) (2007). While not an explicit topic for assessment, proton beam therapy was discussed at CTAF's roundtable on intensity-modulated radiation therapy (IMRT) for prostate cancer. The roundtable concluded that proton beam therapy was a distinct form of radiotherapy and should be a future focus for data collection, clinical trials, and technology assessment. (The meeting summary is no longer online).

- Brada et al. (2007): A recent systematic review of clinical evidence sponsored by the Royal Marsden National Health Service Foundation (UK) concludes that "there are currently no studies demonstrating improved tumour control or survival" with proton

beam therapy for localized prostate cancer compared to the best available photon therapy.

- Olsen et al. (2007): Another systematic review of clinical effectiveness, sponsored by the Norwegian Knowledge Centre for the Health Services, indicates that the effectiveness of proton therapy was not conclusively supported by available evidence in part because proton beam therapy patients in most of the comparative observational studies had less advanced disease than those receiving conventional radiotherapy.

VI. Key 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 ▪ PSA level of 10 ng/mL or less ▪ 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
Radiation Therapy Oncology Group (NCT00063882)	RCT	▪ Disease progression ▪ Biochemical failure ▪ Survival ▪ Distant metastases ▪ Quality of life	N=1520 with intermediate risk prostate cancer	Brachytherapy with and without EBRT	Estimated study completion date June 2008
M.D. Anderson Cancer Center (NCT00388804)	Randomized interventional	▪ PSA outcomes ▪ Survival ▪ Quality of life ▪ Prognostic indicators	N=340	Androgen suppression plus IMRT, 3D-CRT, or proton beam therapy vs. each radiation tx alone	Estimated primary completion date February 2012
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	Multicenter study, initiated in 2001

VII. Evidence on Comparative Clinical Effectiveness

Data Quality

A total of 361 studies were evaluated in three separate appraisals of the technologies of interest: IMRT and 3D-CRT (2007; n=84 studies); brachytherapy and proton beam therapy (2008; n=166 studies); and active surveillance and radical prostatectomy (2009; n=111 studies). Major exclusion criteria included studies with fewer than 50 participants as well as studies without a preponderance of patients with low-risk disease. Full details on the search strategies and entry criteria employed can be found in each appraisal report posted on the ICER web site (Pearson, 2007; Ollendorf, 2008; Ollendorf, 2009).

Randomized controlled trials do not exist that compare measures of benefit and/or harm between brachytherapy, radical prostatectomy, proton beam therapy, IMRT, and active surveillance. 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). Nearly all of the remaining treatment studies were relatively small single-center case series of a single modality as well as comparative series with historical or contemporaneous controls, a body of evidence further limited by considerable variability in population age and other demographics, treatment selection processes, follow-up duration, number of patients with low-risk disease, and definitions and measurement of treatment outcomes, making both direct and indirect comparisons across treatments highly problematic.

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 (Ollendorf, 2009).

The published data available on proton beam therapy is extremely limited in providing reliable, generalizable evidence on either biochemical failure or rates of acute and chronic side effects of treatment (Ollendorf, 2008). There are more studies from a greater number of institutions on the outcomes of robotic prostatectomy, but the body of evidence consists nearly entirely of case series from academic institutions, with widely varying documentation of patient outcomes, and with serious potential for selection bias (Ollendorf, 2009). Thus the evidence cannot support firm conclusions on the comparative clinical effectiveness of robotic prostatectomy vs. open prostatectomy.

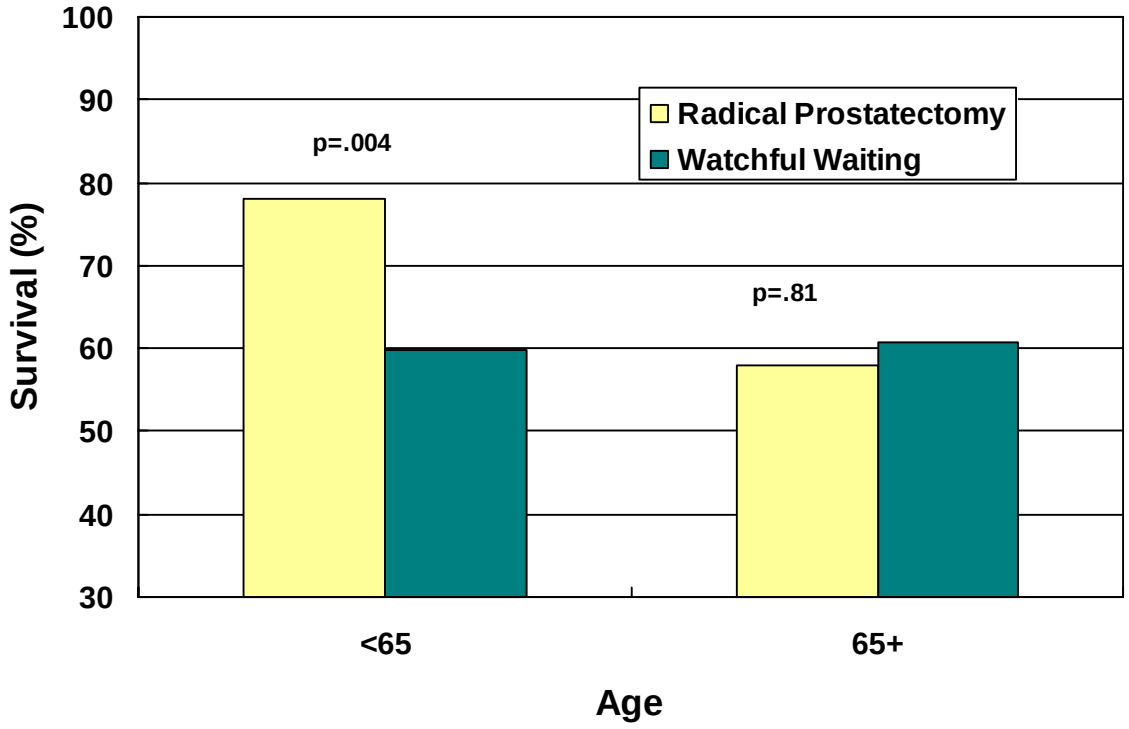
Comparative Clinical Effectiveness

Survival and Freedom from Biochemical Failure

There are no data available from randomized controlled trials to directly compare the impact of different management options on the overall and disease-specific survival of patients with

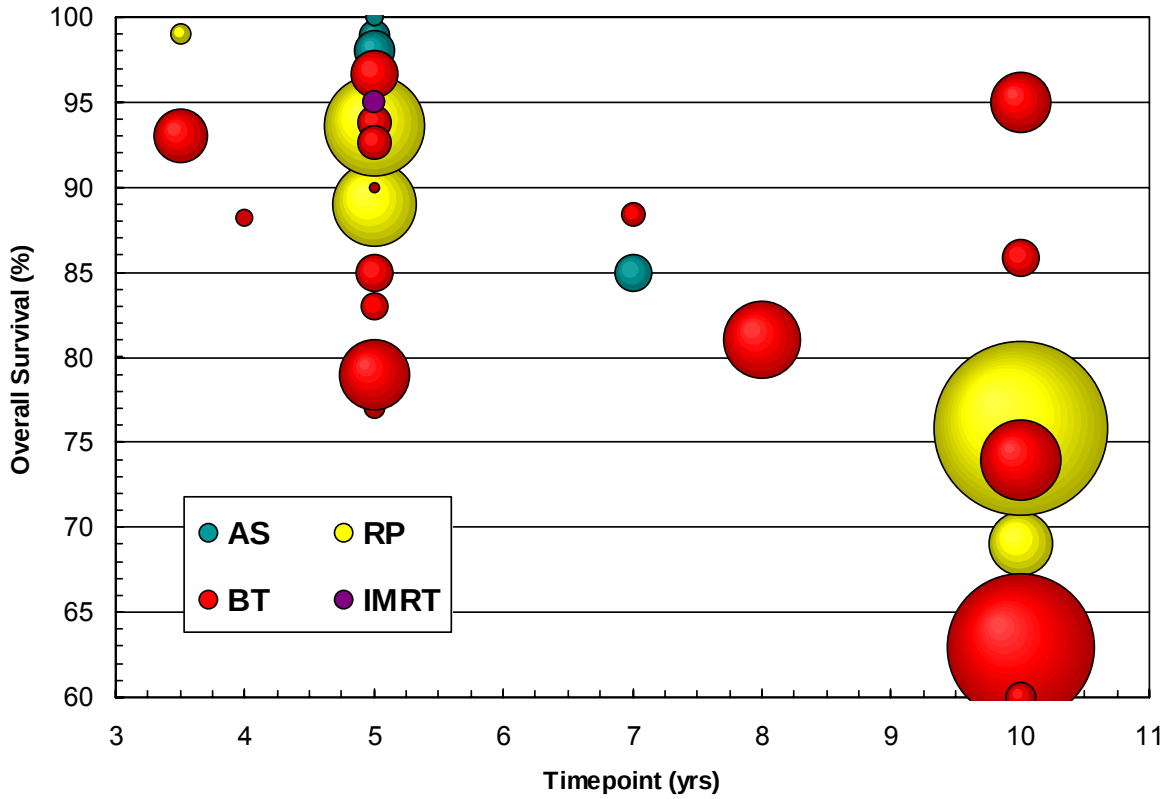
low-risk prostate cancer. For active surveillance, some articles draw inferences of a lower boundary of effectiveness from older randomized controlled data on watchful waiting vs. radical prostatectomy, in which the results indicated a survival benefit for surgery in men under age 65, but not in those 65 and older (see Figure 1 below). However, many clinical experts discount the relevance of these findings as a benchmark for the effectiveness of modern active surveillance (Parker, 2004; Dall'Era, 2009). They believe that active surveillance is very likely to have superior outcomes to watchful waiting given that patients today are largely diagnosed by routine PSA screening long before clinical symptoms would arise; and, as described earlier, active surveillance adopts an aggressive monitoring protocol in an effort to catch any signs of clinical progression early enough to allow definitive treatment to have effectiveness comparable to immediate definitive treatment at the time of initial diagnosis.

Figure 1. 12-year overall survival by age and treatment arm, SPCG-4 trial.
Source: Bill-Axelson, JNCI, 2008



While direct comparisons of rates of overall survival across active surveillance and all the immediate treatment options are unavailable, 5-year survival rates in published case series are comparable (range: 77-99%); as noted above, rates are influenced by differences in population demographics, proportion of subjects with low-risk disease, and other factors (see Figure 2 on the following page). Reports of newer technologies such as IMRT and proton beam have been based on relatively short follow-up durations, and have largely not documented the effects of these modalities on survival, relying instead on measures of biochemical control as a surrogate (see next page). ICER could identify only one report of the impact of IMRT on overall survival, and could not identify any report of survival with proton beam therapy.

Figure 2. Overall survival, by management approach and timepoint.



AS: Active surveillance; RP: Radical prostatectomy; BT: brachytherapy; IMRT: Intensity-modulated radiation therapy
NOTES: Bubble size illustrates study sample size; no data available for proton beam therapy

Similar evidence limitations characterize findings on disease-specific survival. Published case series estimates of 5-year disease-specific survival for all management options largely overlap in a tight range from 95-100%. As with overall survival, disease-specific survival is reported infrequently in studies of IMRT or proton beam therapy; this review identified 2 studies of IMRT (both reporting 100% disease-specific survival at 5 years), and no studies of proton beam reporting this outcome.

Given the long duration needed to assess impact on overall or cancer-specific survival, many studies of radiation therapy treatments and radical prostatectomy use biochemical failure as an intermediate outcome. The link between biochemical evidence of disease recurrence and survival has been the subject of much debate. 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.

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

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 (Klotz, 2006; Carter, 2007; Dall'Era, 2008; Roemeling, 2007; van den Bergh, 2009). 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, 2006). 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 (Klotz, 2009).

Potential Harms

Risks Common to All Treatments

Reported rates of side effects common to all forms of radiation and radical prostatectomy (i.e., urinary incontinence and erectile dysfunction) are displayed in Table 1 on the following page, as are rates of gastrointestinal side effects for radiation treatments. For radiation modalities, side effect rates are classified as moderate-to-severe based on an RTOG or CTC score of 2 or higher. For surgery, classification systems are rarely used, so the literature synthesis focused on strict definitions of incontinence (any pad use) and erectile dysfunction (no erections or erections insufficient for intercourse).

Urinary Incontinence

Incontinence remains a significant side effect of all radiation treatments for prostate cancer as well as radical prostatectomy. In all cases, the rates of "short-term" incontinence (i.e., within 90 days after treatment) are relatively high (30-50%), particularly for surgery, with some resolution over time; by 2 years following treatment, rates of "long-term" incontinence have declined to 5-15%. Evidence is not sufficiently robust to distinguish rates of incontinence by surgical approach or by radiation modality.

Table 1. Reported short- and long-term side effects, by treatment type.

Side Effect	Brachytherapy	Proton Beam Therapy	IMRT	Radical Prostatectomy
*Gastrointestinal**				
Short-term	Studies: 9 High: 9.6% Low: 0.0% Pooled†: 2.1% (0.0%,4.1%)	Studies: 1 High: 0.0% Low: 0.0% Pooled: NR	Studies: 4 High: 50.3% Low: 2.3% Pooled: 18.4% (8.3%,28.5%)	N/A
Long-term	Studies: 18 High: 12.8% Low: 0.0% Pooled: 4.0% (2.5%,5.4%)	Studies: 3 High: 26.0% Low: 3.5% Pooled: 16.7% (1.6%,31.8%)	Studies: 7 High: 24.1% Low: 1.6% Pooled: 6.6% (3.9%,9.4%)	N/A
*Urinary**				
Short-term	Studies: 11 High: 64.8% Low: 9.7% Pooled: 28.7% (17.1%,40.4%)	Studies: 1 High: 40.1% Low: 40.1% Pooled: NR	Studies: 4 High: 49.0% Low: 6.9% Pooled: 30.0% (13.2%,46.7%)	Studies: 25 High: 90.2% Low: 6.7% Pooled: 40.1% (28.5%, 51.6%)
Long-term	Studies: 12 High: 40.3% Low: 0.0% Pooled: 16.7% (7.7%,25.7%)	Studies: 3 High: 5.7% Low: 5.0% Pooled: 5.5% (4.6%,6.5%)	Studies: 5 High: 28.3% Low: 3.5% Pooled: 13.4% (7.5%,19.2%)	Studies: 43 High: 52.2% Low: 3.0% Pooled: 13.6% (11.5%, 15.7%)
Sexual				
Short-term	N/A	N/A	N/A	Studies: 18 High: 95.1% Low: 46.9% Pooled: 70.7% (63.0%, 78.4%)
Long-term	Studies: 7 High: 43.0% Low: 14.3% Pooled: 32.3% (25.7%,38.9%)	Studies: 0	Studies: 2 High: 49.0% Low: 48.0% Pooled: NR	Studies: 40 High: 91.2% Low: 18.8% Pooled: 40.3% (36.1%, 44.5%)

*As measured on RTOG or NCI-CTC toxicity scales for radiation modalities
†From random-effects meta-analysis (with 95% confidence intervals)

Erectile Dysfunction

Information on both short- and long-term erectile dysfunction is available from the literature on radical prostatectomy, although there is no evidence that rates differ among the various surgical approaches. Rates of short-term ED following surgery are quite high, even with the use of "nerve-sparing" surgical techniques; approximately 70% of previously potent men will have ED within 90 days after surgery. As with urinary incontinence, resolution does occur over time, but long-term ED following surgery remains a substantial concern, affecting about 40% of men at 12-24 months.

Available evidence on ED following radiation treatment is very limited; only long-term ED has been reported in these series, and has primarily been studied for brachytherapy only. These limited data suggest rates of long-term ED similar to that of surgery, affecting 30-45% of men at 24 months following radiation. Patient-reported quality-of-life data suggest a substantial decrement in sexual function following surgery, with steady improvement over the long-term; in contrast, smaller decrements are seen after external beam radiation or brachytherapy, but these remain relatively constant over time (Sanda, 2008). In any event, long-term sexual function appears to be similar across all of these treatment options.

Gastrointestinal Toxicity

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

Radiation-induced Malignancies

The risk of secondary malignancy from the radiation exposure of brachytherapy, IMRT, and proton beam therapy is very difficult to assess but is assumed by most experts to be approximately 0.5%-1% (Brenner, 2000; Abdel-Wahab, 2008; Kry, 2005; Schneider, 2006). The literature is limited to registry-based observational studies of cancer prevalence among patients receiving older-generation radiation technologies, and dose-extrapolation studies for newer-generation radiation modalities. Given that EBRT modalities such as IMRT and proton beam therapy involve greater radiation exposure outside the prostate than does brachytherapy, the ICER review and economic models assume a lifetime attributable risk of 1% for these approaches and 0.5% for brachytherapy. Since other treatment options for localized prostate cancer involve no radiation, these risks may be particularly relevant for some patients, particularly younger men.

Risks Specific to Particular Treatments

Brachytherapy

Brachytherapy has a unique risk of "seed migration" in which one or more radioactive seeds become dislodged and travel to nearby organs inside the body. Seed migration is a relatively common phenomenon, occurring in 6-55% of patients (Ankem, 2002; Older, 2001; Eshleman, 2004). Seeds migrate most commonly to the lung (Chauveinc, 2004), but have also been found in the urethra, bladder, and vertebral venous plexus (Nakano, 2006). While

the phenomenon may be somewhat alarming to patients, the potential for a single seed's radiation to cause significant damage is extremely small, and findings from the vast majority of follow-up studies have documented no short- or long-term detrimental effects (Davis, 2000; Davis, 2002; Ankem, 2002; Dafoe-Lambie, 2000; Chauveinc, 2004; Eshleman, 2004; Nag, 1997; Older, 2001; Stone, 2005). The few available reports of harm from seed migration are limited to individual case studies (Miura, 2008; Zhu, 2006).

Brachytherapy also has a unique risk of acute urinary retention due to swelling of the prostate gland in reaction to the local inflammation caused by the seeds. This adverse outcome occurs in approximately 10% of patients, requiring short-term catheterization and medication.

Proton Beam

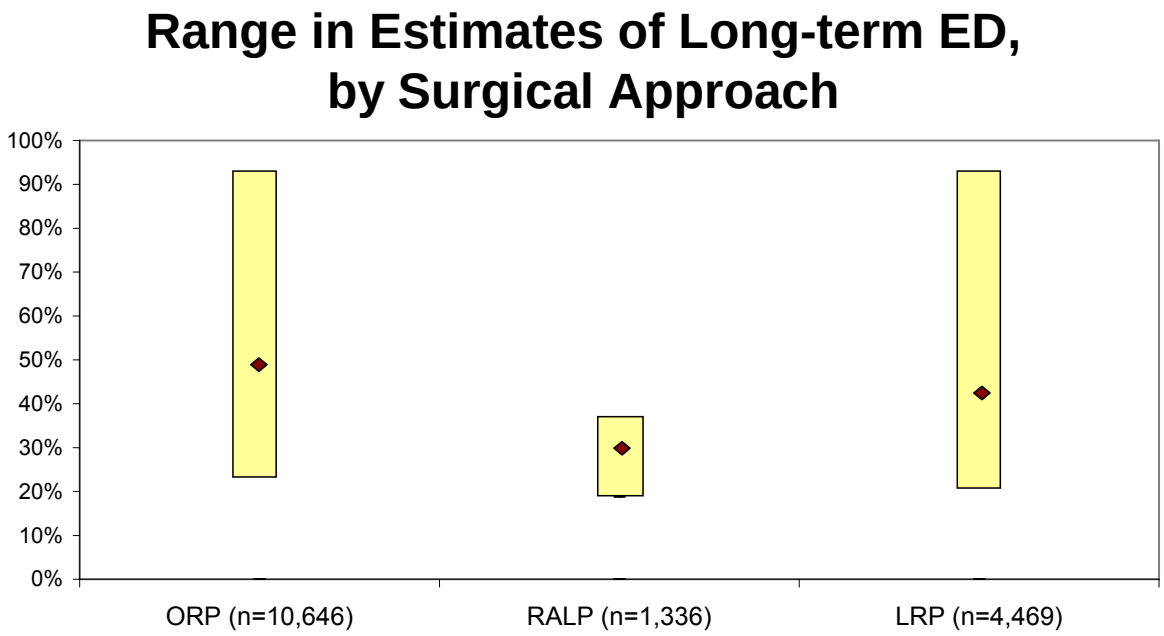
Another modality-specific risk raised by clinical experts on the ICER Evidence Review Group and discussed in the literature is a potential risk of increased hip fracture for patients treated with proton beam therapy, in excess of the risk posed by pelvic irradiation. Proton beam therapy delivers a higher dose of radiation through the femoral heads than does IMRT, but there are no published studies which have sought to evaluate whether this increase is associated with a greater incidence of hip fracture (Nguyen, 2008).

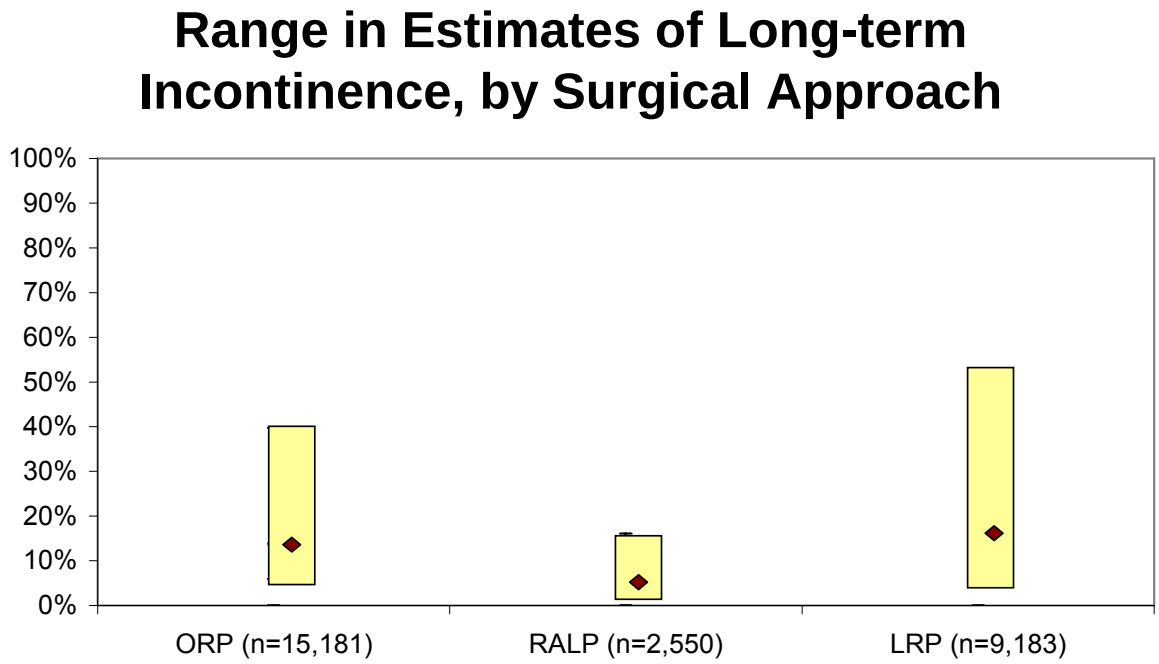
Radical Prostatectomy

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. A 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 for long-term erectile dysfunction and incontinence respectively in Figure 3 on the following page.

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.

Figure 3. Variability in estimates of long-term side effects, by surgical approach.





ORP: Open radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy; LRP: Laparoscopic radical prostatectomy
NOTE: Diamonds represent pooled mean rate; rectangles represent full range of estimates

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.

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).

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.

Other Concerns

Learning Curve

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.

While brachytherapy, proton beam therapy, and IMRT are also technically complex procedures, the evidence on the presence and impact of any learning curve for these modalities is extremely limited. A recent report on a series of 805 men undergoing prostate brachytherapy at Vancouver Cancer Centre indicated a substantial decline in acute urinary retention between the first 200 and last 200 patients in the series (17.0% vs. 6.3%, p=.002) (Keyes, 2006); much of this decline was attributed to programmatic changes (e.g., reductions in numbers of needles used and more efficient OR scheduling) rather than individual practitioner competence, however.

IMRT and proton beam therapy are complex and time-intensive therapeutic options; most experts agree that there is a substantial learning curve involved, but this has not been measured in any appreciable way for prostate cancer. There is evidence of a learning curve

in the accuracy of capturing gland and tumor volume during IMRT treatment planning for treatment of other cancers (Clark, 2009); in addition, comparisons of costs at 9 French medical centers suggest that "learning effects" account for nearly 50% of the variation in IMRT treatment costs between centers (Bonastre, 2007).

Institutional Costs and Efficiency

Active Surveillance

Institutional costs associated with an active surveillance protocol include those necessary to provide serial monitoring visits, regular PSA testing, periodic re-biopsy, and possible imaging to monitor for spread of disease beyond the prostatic capsule.

Radical 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.

Brachytherapy

Creation and outfitting of a single brachytherapy afterloading suite has been estimated to cost $110,000 in 2009 dollars (Glasgow, 1993). The most significant institutional cost is that of the seed implants; costs range from $2,000-$10,000 per case depending on prostate size and the isotope utilized (Maguire, 2000). Other costs include those of image-guidance systems used during seed placement, as well as radiation handling and disposal.

IMRT & Proton Beam Therapy

Capital costs associated with newer external beam radiation modalities are also substantial. Acquisition costs for IMRT systems have been estimated to range from $1.8 - $5.4 million, depending on whether modifications are made to existing linear accelerators or new accelerators are purchased, as well as whether image-guidance systems are employed (National Horizon Scanning Centre, 2006). Annual maintenance costs range from $65,000-$115,000. Proton beam therapy costs represent a different order of magnitude altogether, as installation of a proton-capable facility is estimated to cost between $25 million for a compact, single-treatment facility to $150 million for a full-size facility (Matthias, 2009).

VIII. Evidence on Comparative Value

We used findings from our systematic review on clinical effectiveness to inform a primary cost-utility analysis of active surveillance and immediate treatment with radical prostatectomy, brachytherapy, IMRT, or proton beam therapy in 65-year-old men with clinically-localized, low-risk prostate cancer. Although the review determined that the evidence on proton beam therapy was not sufficient to determine whether this intervention produces superior, comparable, or inferior outcomes relative to existing alternatives, proton beam was nevertheless included in the economic model to provide a complete picture of the most popular current and emerging treatment options for low-risk prostate cancer.

As noted previously, the evidence on comparative clinical effectiveness for robotic vs. open prostatectomy was judged to be too limited to provide high certainty of any differences in clinical outcomes between these surgical approaches, and open prostatectomy was therefore used in base case analyses. However, because the robotic approach is now the dominant form of prostatectomy in the U.S., the potential effects of nominal differences between these approaches in clinical outcomes and costs as recorded in our systematic review were explored in sensitivity analyses.

Open prostatectomy was used as the "reference" treatment against which all other management options were compared. It should be noted, however, that this status in no way implies that ICER considers surgery a more proven technology or the standard of care. Rather, the rating system is designed to make two-way comparisons, and ICER decided to make the most frequently-employed and longest-standing therapy the "reference" intervention in this case.

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, radiation, 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. Alternative analyses were performed using payment rates obtained from private health plans in the U.S.

The "base case" economic model developed for this analysis was framed with the assumption that all management options 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 compared to immediate treatment. However, because the existing data cannot exclude some chance of a survival benefit for immediate treatment, an alternative scenario was created in which the prostate cancer-specific mortality of active surveillance patients is set at 2.5% higher than surgery or radiation at 10 years following initiation of treatment or surveillance. This 2.5% survival advantage for immediate treatment reflects another assumption: that any possible survival advantage over active

surveillance will be, at most, approximately half of the absolute survival difference seen in earlier trials of radical prostatectomy vs. 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 65 and over 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 under age 65 at the time definitive treatment is begun.

Other key assumptions within the economic model are shown below in Table 2 and are discussed more fully in the body of this review.

Table 2. 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 equal 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

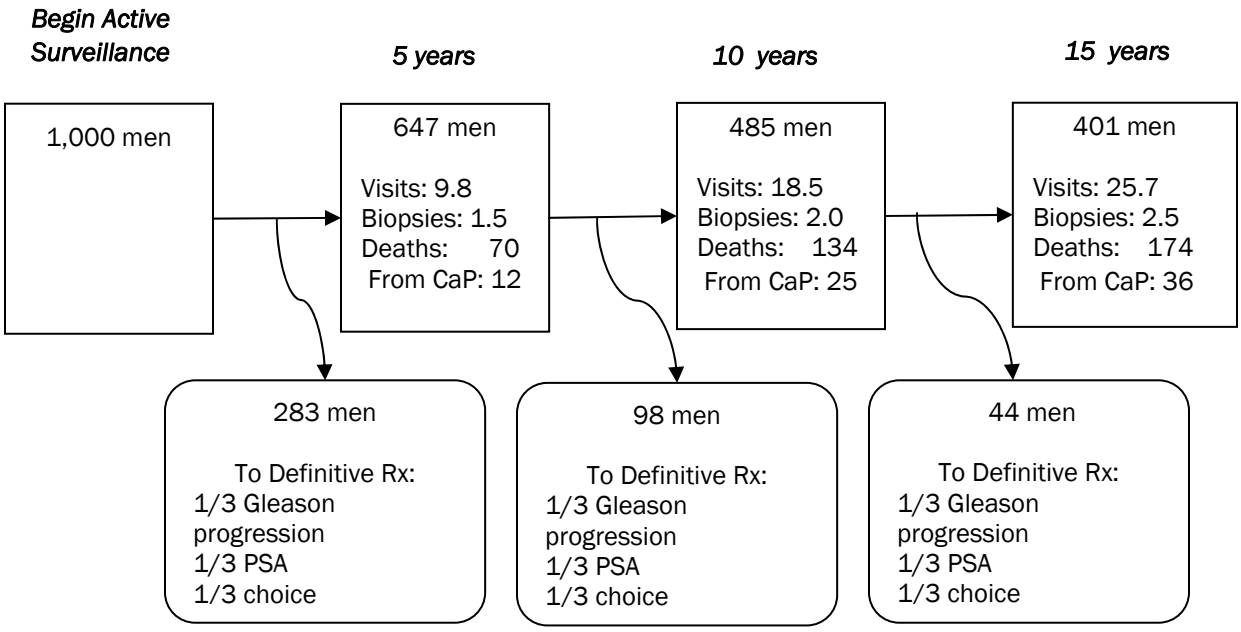
Base Case Model Results

Clinical Outcomes

Under the assumption that all management options confer equal survival, men at age 65 with low-risk prostate cancer have an additional life expectancy of approximately 16 years regardless of form of management. Complications, symptoms, 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 4 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 4. 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, long-term ED following radical prostatectomy is 31%, which is substantially higher than the 8% estimated for all forms of radiation therapy. The risk of urinary incontinence is 9% with surgery, 7% with brachytherapy, 6% with IMRT, and 2% with proton beam therapy. Among the radiation modalities, the risk of proctitis ranges from 2% for brachytherapy to 10% for proton beam therapy.

It should be noted that urinary and sexual side effect estimates used as the base case for the model 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 benefits observed with active surveillance (see Table 3 below). Among the men on active surveillance who ultimately receive IMRT, there are small increased risks of ED, incontinence, and proctitis compared to men on active surveillance who do not ever receive definitive treatment. A table summarizing the key rates for both short-term and long-term side effects for all management options in men aged 65 and 55 is shown in Table 3.

Table 3. 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	Radical Prostatectomy	Brachytherapy	IMRT	Proton Beam
Age 65 Years					
Prog. to treatment	61.1%	100.0%	100.0%	100.0%	100.0%
Peri-operative death	N/A	0.4%	N/A	N/A	N/A
Minor complications	0.2%	9.5%	N/A	N/A	N/A
Major complications	0.0%	4.8%	N/A	N/A	N/A
Treatment-related SE					
Urinary	3.6%	8.6%	6.9%	5.7%	2.4%
ED	5.3%	30.7%	8.4%	8.4%	8.4%
GI (from radiation)	2.7%	N/A	2.5%	4.1%	10.2%
Prostate cancer death	9.0%	9.0%	9.0%	9.0%	9.0%
Life years (mean)	16.0	16.0	16.0	16.0	16.0
QALYs (mean)	8.97	7.82	8.12	8.09	7.97
Age 55 Years					
Prog. to treatment*	72.1%	100.0%	100.0%	100.0%	100.0%
Peri-operative death	0.1%	0.4%	N/A	N/A	N/A
Minor complications	2.8%	9.5%	N/A	N/A	N/A
Major complications	1.1%	4.8%	N/A	N/A	N/A
Treatment-related SE					
Urinary	6.5%	10.4%	8.5%	7.0%	3.0%
ED	13.7%	35.7%	9.7%	9.7%	9.7%
GI (from radiation)	2.0%	N/A	2.6%	4.2%	10.4%
Prostate cancer death	16.0%	16.0%	16.0%	16.0%	16.0%
Life years (mean)	22.0	22.0	22.0	22.0	22.0
QALYs (mean)	11.54	10.33	10.72	10.67	10.54

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 model results indicated that the initial cost of treatment with radical prostatectomy is $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. Among the radiation modalities, first-year costs range from a low of $12,052 for brachytherapy to $38,007 for proton beam therapy. Active surveillance is less expensive than immediate treatment 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 somewhat higher than the least expensive forms of immediate treatment (surgery and brachytherapy), while remaining substantially lower than IMRT or proton beam therapy. A breakdown of costs for each pathway is shown in Table 4 below. As can be seen, total lifetime costs are largely driven by the costs of definitive treatment; most of active surveillance's costs are therefore manifested in the costs of definitive treatment received by approximately 60-70% of men. Findings from alternative analyses indicate that, active surveillance becomes less costly overall compared to *all* forms of immediate treatment if less-expensive brachytherapy or radical prostatectomy is used for definitive treatment in lieu of IMRT.

Table 4. 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	Radical Prostatectomy	Brachytherapy	IMRT	Proton Beam
Age 65 Years					
Year 1 treatment	4,228	13,553	12,052	23,853	38,007
Services	4,809	4,624	4,624	4,624	4,624
Visits	3,382	4,624	4,624	4,624	4,624
Biopsies	1,427	N/A	N/A	N/A	N/A
Definitive Rx (IMRT)	14,327	N/A	N/A	N/A	N/A
Patient time	8,156	6,150	6,292	7,806	9,744
Short-term SE	270	1,477	300	204	203
Long-term SE	589	786	720	730	789
TOTAL					
Undiscounted	38,542	33,589	30,684	43,122	59,979
Discounted	30,422	28,348	25,484	37,861	53,828
Age 55 Years					
Year 1 treatment	3,796	14,496	12,164	24,240	38,489
Services	5,530	5,213	5,213	5,213	5,213
Visits	3,848	5,213	5,213	5,213	5,213
Biopsies	1,682	N/A	N/A	N/A	N/A
Definitive Rx (IMRT/RP)	13,986	N/A	N/A	N/A	N/A
Patient time	12,226	9,132	10,273	12,258	15,673
Short-term SE	647	1,468	299	205	202
Long-term SE	545	718	651	662	713
TOTAL					
Undiscounted	46,690	40,699	38,109	51,202	69,417
Discounted	33,642	31,440	29,137	41,897	58,867

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

Model findings are shown in Table 5 below; strategies are listed in alphabetical order. The avoidance or delay of treatment-related harms afforded by active surveillance translates into a substantial net benefit in quality of life compared to any strategy of immediate definitive treatment. Active surveillance produces an additional 1.15 quality-adjusted years of life compared to immediate radical prostatectomy. Active surveillance produces 0.85 additional quality-adjusted years of life compared to brachytherapy, the most effective form of definitive treatment according to the model results. Findings were similar for 55-year-old men; for purposes of simplicity, only the results for 65-year-old men are shown in Table 5.

Under the assumption of equal cancer-specific and overall mortality across all management options, active surveillance was thus found to have higher clinical effectiveness due to the number of patients who never require definitive treatment, and the delay of treatment and its consequent complications and side effects for others. In comparison to radical prostatectomy, the lifetime costs of active surveillance were $2,074 higher, generating an incremental cost-effectiveness ratio of $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).

Across all the forms of definitive treatment, despite different rates of particular complications and side effects, the impact on quality of life balanced out, producing very similar total lifetime QALYs (range: 7.82 - 8.12). The lifetime costs of definitive treatment pathways differed substantially, however. Brachytherapy was found to save nearly $3,000 vs. radical prostatectomy, while IMRT and proton beam therapy were associated with incremental costs of $9,500 and $25,500 respectively. Although we judged the clinical outcomes comparable across the definitive treatments, we present formal incremental cost-effectiveness ratios in Table 5 as generated by the model for the purpose of complete transparency. Results were similar when examined in 55 year-old men.

Table 5. 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
AS	8.97	1.15	$30,422	$2,074	$1,803
Brachytherapy	8.12	0.30	$25,484	($2,864)	N/A†
IMRT	8.09	0.27	$37,861	$9,513	$35,233*
Proton Beam	7.97	0.15	$53,828	$25,480	$169,867*
RP	7.82	Reference	$28,348	Reference	

All incremental values calculated relative to radical prostatectomy; strategies appear in alphabetical order
NOTES: RP: radical prostatectomy; AS: active surveillance; IMRT: intensity-modulated radiation therapy QALY: quality-adjusted life years.
*Incremental cost-effectiveness ratios presented for purposes of transparency; findings of the ICER systematic review do NOT support substantial differences in overall effectiveness.
†Strategy is less costly and more effective than reference strategy

Alternative Scenarios and Sensitivity Analyses

Under the alternative model framework in which there is an assumed absolute prostate cancer-specific mortality difference starting at 10 years of 2.5% in favor of immediate treatment, the model results indicated that active surveillance still produced substantially more QALYs on a population basis than immediate treatment, providing an additional 0.69 - 0.99 QALYs.

Several other alternative scenarios were examined, 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 immediate treatment. For example, when the rate of progression to intermediate-risk disease was doubled, the cost-effectiveness of active surveillance remained below $10,000 per QALY. Similarly, when the risk of developing urinary and/or sexual symptoms while on surveillance was doubled, costs were only slightly higher than for definitive treatments and quality-adjusted survival gains remained substantial.

In scenarios in which costs were increased for active surveillance, such as when representative private payer costs were examined, the absolute lifetime cost differences between active surveillance, brachytherapy, and prostatectomy remained small, leading to cost savings or incremental cost-effectiveness ratios for active surveillance and brachytherapy well below $10,000 per QALY. In contrast, private-pay estimates for IMRT and proton beam therapy were several orders of magnitude higher than those for radical prostatectomy, which effectively tripled the incremental cost-effectiveness ratios.

A subgroup analysis was performed examining outcomes for patients for whom erectile dysfunction is not a chief concern. This analysis produced even more narrow differences in QALYs between immediate treatments; removing the disutility associated with ED resulted in quality-adjusted life expectancy differences of 8 weeks or less across all forms of definitive treatment.

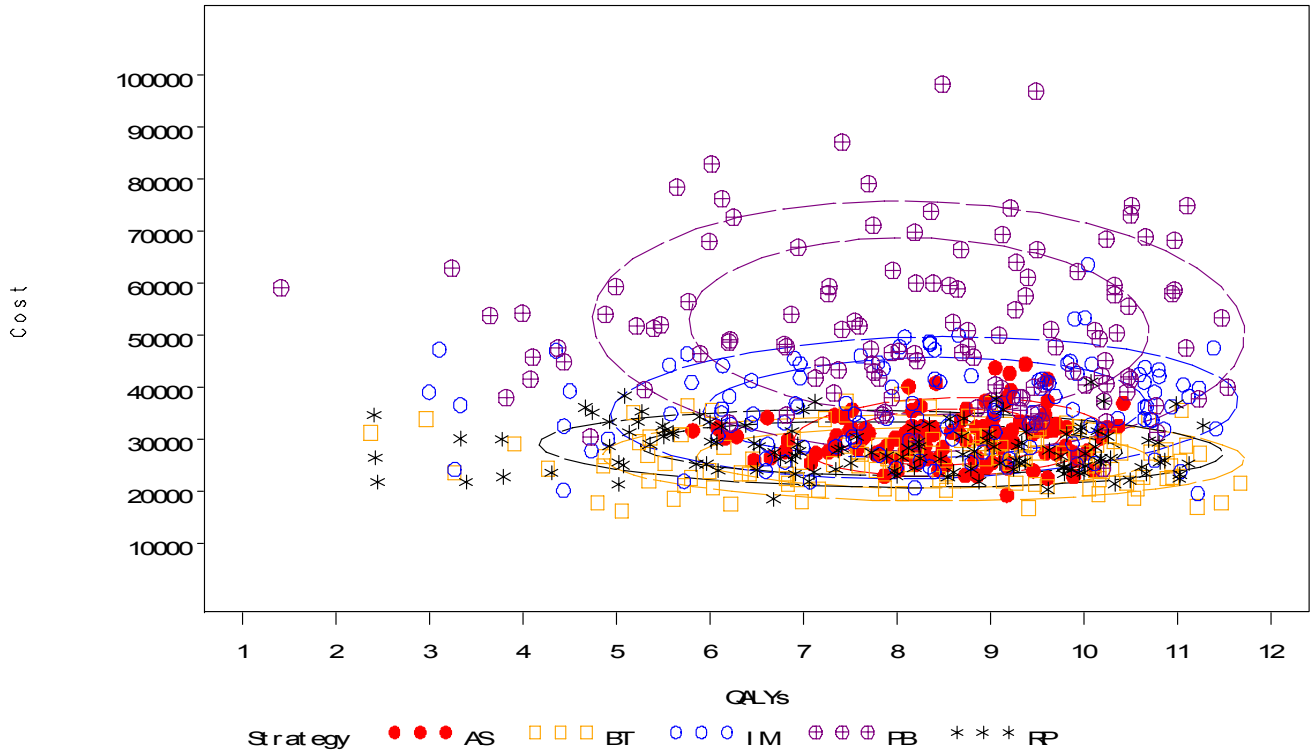
<u>Open Radical Prostatectomy vs. Robot-assisted Laparoscopic Prostatectomy</u>

The findings of our 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.

Model Uncertainty

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; results are summarized in Figure 5 below. Not surprisingly, the risks of treatment side effects and complications resulted in a greater degree of variability in QALY estimates for immediate treatment relative to active surveillance. Few differences in cost were observed for active surveillance, radical prostatectomy, and brachytherapy, while IMRT and proton beam therapy were associated with a greater degree of variability.

Figure 5. Probabilistic sensitivity analysis of costs and effectiveness for all management options for clinically-localized, low-risk prostate cancer.



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

Findings on Economic Impact

A summary of the economic impact of the management options of interest can be found in Table 6 on the following page; for the purposes of simplicity, results are presented only for 65 year-old men, and all cost-effectiveness comparisons are made to radical prostatectomy as the reference category. Note that all immediate treatment scenarios produce the same average number of visits, as survival is assumed to be equivalent and the post-treatment monitoring schedule is identical. Active surveillance results in slightly fewer monitoring visits over time, but patients also have nearly 3 biopsies on average.

Along with the incremental cost-effectiveness ratio, Table 6 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 between $6 and $30 million dollars relative to immediate treatment under current Medicare reimbursement rates, depending on the technology being compared; savings of $13-$50 million dollars would be expected under one of the private payer actual cost scenarios evaluated.

Table 6 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 6. Comparative Value Evidence Table (CVET): Additional findings on value for 65-year-old men with clinically-localized, low-risk prostate cancer.

Measure	Radical Prostatectomy	Active Surveillance	Brachytherapy	IMRT*	Proton Beam*
1. Service Impact					
Visits	37.2	35.9	37.2	37.2	37.2
Biopsies	0.0	2.8	0.0	0.0	0.0
Pathway Total	37.2	38.8	37.2	37.2	37.2
2. Cost per Life-Year Saved	†	†	†	†	†
3. Cost per QALY Gained (vs. RP)	N/A	$1,803	Cost-saving	$35,233	$169,867
SA 1: 55 yo men	N/A	$1,820	Cost-saving	$30,756	$130,605
SA 2: Private-pay estimate A	N/A	$3,434	Cost-saving	$81,011	$457,427
SA 3: Disutility from side effects only	N/A	$3,142	Cost-saving	$30,687	$149,882
4. Budget Impact (per 1,000, 2 years)	$13,591,000	$5,809,000	$11,704,000	$22,520,000	$36,491,000
Using Private-Pay Estimate A	$22,028,000	$8,721,000	$13,086,000	$43,371,000	$87,996,000
5. Fixed Budget Tradeoffs (Annual, vs. AS)					
Nurse FTEs @ $100K each	38.9	N/A	29.5	83.6	153.4
MD FTEs @ $200K each	19.5	N/A	14.7	41.8	76.7

NOTES: QALY: Quality-adjusted life year; FTE: Full-time equivalent; IMRT: Intensity-modulated radiation therapy

Cost-effectiveness comparisons made to radical prostatectomy as reference category;

*Incremental cost-effectiveness ratios presented for purposes of transparency; findings of review do NOT indicate substantial differences in effectiveness

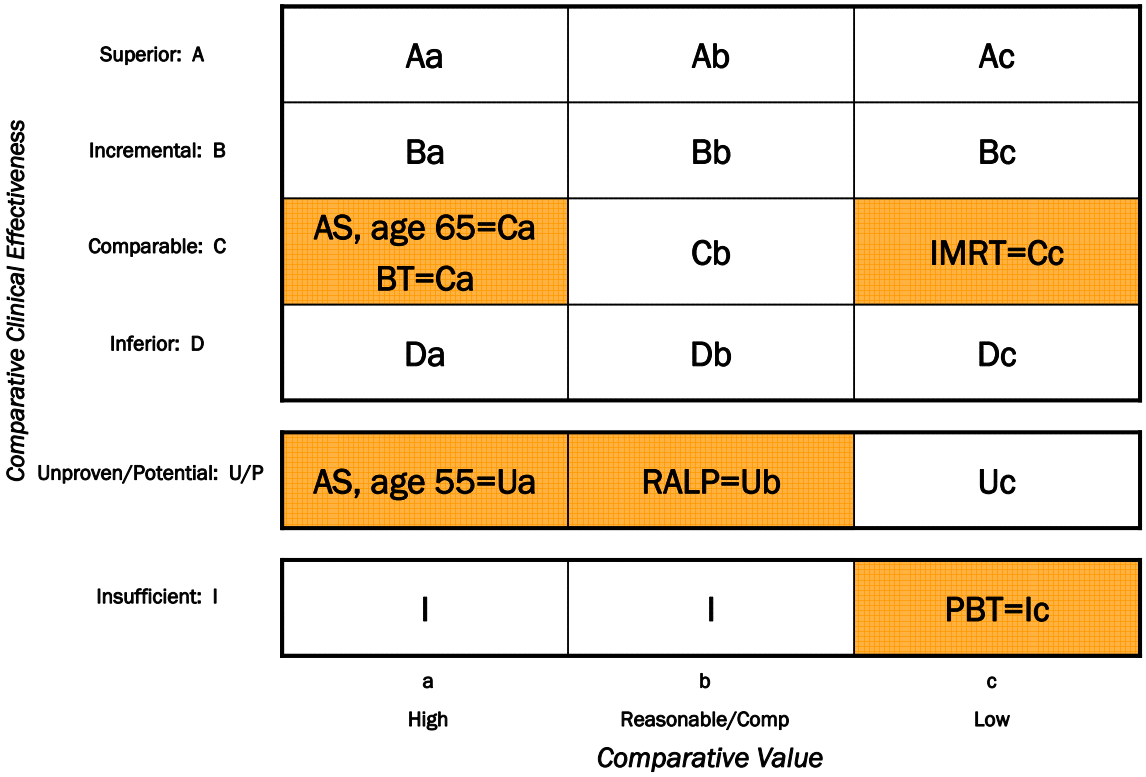
†Cost per life-year saved not generated based on assumed equivalent survival

Model Limitations

As with any decision-analytic model, the findings described above are subject to important limitations. First and foremost, estimates of side effects and complications of treatment were generated by the ICER systematic reviews, which were in turn based on largely low-quality evidence from individual case series. In addition, the model assumes no radiation therapy following radical prostatectomy, when in fact men may receive this therapy as adjuvant or salvage treatment. The lifetime cost estimates for surgery can therefore be viewed as conservative, as they do not include the costs of adjuvant or salvage therapy. Also, only limited data exist on the "failure rates" associated with active surveillance (e.g.,

missed clinical progression, increased patient choice of treatment due to anxiety, increased rates of clinical symptoms). However, when observed rates were subjected to rigorous sensitivity analyses, lifetime costs for active surveillance remained similar to those of definitive treatment, and quality-adjusted survival remained substantially longer. Finally, we are aware that the side-effect estimates produced by the model may appear to be lower than rates from patient-reported instruments or even from clinical reports. This is because our population-based model takes into account the baseline risk of age- and/or comorbidity-related symptoms; therefore, what is reported in Table 3 represents the risk of side effects that are fully attributable to treatment alone.

ICER Integrated Evidence Rating™: Multiple Management Options vs. Radical Prostatectomy for Clinically-Localized, Low-Risk Prostate Cancer



NOTES: AS: Active surveillance; BT: Brachytherapy; IMRT: Intensity-modulated radiation therapy; RALP: Robot-assisted laparoscopic prostatectomy; PBT: Proton beam therapy

Background on the ICER rating methodology, including descriptions of the rating categories for comparative clinical effectiveness and comparative value, can be found in Appendix B of this document.

It is important to note that the input of the Evidence Review Group 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. Further description of ICER's rationale for the ratings is provided on the following page.

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 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 patient utilities for 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. This rating reflects our judgment that, even though the data are limited, there is reasonable certainty that modern active surveillance protocols 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."

With regard to radiation modalities, despite acknowledged limitations in the quality of the body of evidence, ICER felt that the evidence from multiple case series was consistent enough and robust enough to convey high certainty that the comparative clinical effectiveness of brachytherapy and IMRT was "comparable" when compared to open radical prostatectomy. This is in contrast to ICER's original rating of "unproven with potential" for IMRT in comparison to 3D-CRT, in which a documented lower rate of GI side effects for IMRT provided limited evidence of an incremental benefit. In the current comparison, there has been no demonstrated overall or prostate cancer-specific survival advantage for any of the immediate treatment options, and reported rates of side effects and procedural complications represent a set of tradeoffs for patients and clinicians to consider, rather than a documented advantage for any single treatment. For example, patients wishing to avoid proctitis may opt for surgery, while those wishing to avoid obstructive urinary side effects such as stricture and retention may choose IMRT.

ICER chose to assign different rating for comparative value to brachytherapy and IMRT. Data from public and private payers suggest that brachytherapy is reimbursed at the lowest rate of all of the immediate treatment options for low-risk prostate cancer; in multiple alternative scenarios in the economic model, brachytherapy emerged as a cost-saving alternative to radical prostatectomy when all costs were included. Brachytherapy was therefore deemed to be a "high value" treatment alternative.

IMRT's comparative value was rated as "low" because its clinical effectiveness was judged to be comparable to radical prostatectomy while its initial and lifetime costs are significantly higher. When private payer estimates were considered, differences were even more pronounced. Finally, public reimbursement for IMRT is substantially higher in non-facility than in facility settings; in areas of the country where non-facility use of IMRT predominates, the cost differential between IMRT and radical prostatectomy may be even greater.

Proton beam therapy's comparative clinical effectiveness rating of "insufficient" indicates that, at present there is not enough evidence to allow a reasonable judgment of the likely balance of harms and benefits of proton beam therapy in comparison to radical prostatectomy or other management options. While ICER does not always provide a comparative value rating for technologies with insufficient evidence on comparative clinical effectiveness, the decision was made to rate the comparative value of proton beam therapy as "low" relative to radical prostatectomy, based on current levels of reimbursement that are more than threefold higher for proton beam therapy.

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APPENDIX A:

COMPARATIVE VALUE EVIDENCE TABLE

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

Outcome (%, except where noted)	Active Surveillance	Radical Prostatectomy	Brachytherapy	IMRT	Proton Beam
Age 65 Years					
Prog. to treatment	61.1%	100.0%	100.0%	100.0%	100.0%
Peri-operative death	N/A	0.4%	N/A	N/A	N/A
Minor complications	0.2%	9.5%	N/A	N/A	N/A
Major complications	0.0%	4.8%	N/A	N/A	N/A
Treatment-related SE					
Urinary	3.6%	8.6%	6.9%	5.7%	2.4%
ED	5.3%	30.7%	8.4%	8.4%	8.4%
GI (from radiation)	2.7%	N/A	2.5%	4.1%	10.2%
Prostate cancer death	9.0%	9.0%	9.0%	9.0%	9.0%
Life years (mean)	16.0	16.0	16.0	16.0	16.0
QALYs (mean)	8.97	7.82	8.12	8.09	7.97
Age 55 Years					
Prog. to treatment*	72.1%	100.0%	100.0%	100.0%	100.0%
Peri-operative death	0.1%	0.4%	N/A	N/A	N/A
Minor complications	2.8%	9.5%	N/A	N/A	N/A
Major complications	1.1%	4.8%	N/A	N/A	N/A
Treatment-related SE					
Urinary	6.5%	10.4%	8.5%	7.0%	3.0%
ED	13.7%	35.7%	9.7%	9.7%	9.7%
GI (from radiation)	2.0%	N/A	2.6%	4.2%	10.4%
Prostate cancer death	16.0%	16.0%	16.0%	16.0%	16.0%
Life years (mean)	22.0	22.0	22.0	22.0	22.0
QALYs (mean)	11.54	10.33	10.72	10.67	10.54

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	Radical Prostatectomy	Brachytherapy	IMRT	Proton Beam
Age 65 Years					
Year 1 treatment	4,228	13,553	12,052	23,853	38,007
Services	4,809	4,624	4,624	4,624	4,624
Visits	3,382	4,624	4,624	4,624	4,624
Biopsies	1,427	N/A	N/A	N/A	N/A
Definitive Rx (IMRT)	14,327	N/A	N/A	N/A	N/A
Patient time	8,156	6,150	6,292	7,806	9,744
Short-term SE	270	1,477	300	204	203
Long-term SE	589	786	720	730	789
TOTAL					
Undiscounted	38,542	33,589	30,684	43,122	59,979
Discounted	30,422	28,348	25,484	37,861	53,828
Age 55 Years					
Year 1 treatment	3,796	14,496	12,164	24,240	38,489
Services	5,530	5,213	5,213	5,213	5,213
Visits	3,848	5,213	5,213	5,213	5,213
Biopsies	1,682	N/A	N/A	N/A	N/A
Definitive Rx (IMRT/RP)	13,986	N/A	N/A	N/A	N/A
Patient time	12,226	9,132	10,273	12,258	15,673
Short-term SE	647	1,468	299	205	202
Long-term SE	545	718	651	662	713
TOTAL					
Undiscounted	46,690	40,699	38,109	51,202	69,417
Discounted	33,642	31,440	29,137	41,897	58,867

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	Radical Prostatectomy	Active Surveillance	Brachytherapy	IMRT*	Proton Beam*
1. Service Impact					
Visits	37.2	35.9	37.2	37.2	37.2
Biopsies	0.0	2.8	0.0	0.0	0.0
Pathway Total	37.2	38.8	37.2	37.2	37.2
2. Cost per Life-Year Saved	†	†	†	†	†
3. Cost per QALY Gained (vs. RP)	N/A	$1,803	Cost-saving	$35,233	$169,867
SA 1: 55 yo men	N/A	$1,820	Cost-saving	$30,756	$130,605
SA 2: Private-pay estimate A	N/A	$3,434	Cost-saving	$81,011	$457,427
SA 3: Disutility from side effects only	N/A	$3,142	Cost-saving	$30,687	$149,882
4. Budget Impact (per 1,000, 2 years)	$13,591,000	$5,809,000	$11,704,000	$22,520,000	$36,491,000
Using Private-Pay Estimate A	$22,028,000	$8,721,000	$13,086,000	$43,371,000	$87,996,000
5. Fixed Budget Tradeoffs (Annual, vs. AS)					
Nurse FTEs @ $100K each	38.9	N/A	29.5	83.6	153.4
MD FTEs @ $200K each	19.5	N/A	14.7	41.8	76.7

NOTES: QALY: Quality-adjusted life year; FTE: Full-time equivalent; IMRT: Intensity-modulated radiation therapy

Cost-effectiveness comparisons made to radical prostatectomy as reference category;

*Incremental cost-effectiveness ratios presented for purposes of transparency; findings of review do NOT indicate substantial differences in effectiveness

†Cost per life-year saved not generated based on assumed equivalent survival

Major Factors Influencing Model Results

- Costs of definitive treatment:
  - Total costs of active surveillance are heavily influenced by the cost of the definitive treatment used. For example, when the treatment was changed from IMRT to brachytherapy, AS was $4,000 less expensive than radical prostatectomy (vs. $2,000 more expensive with IMRT as the treatment)
  - When payment estimates from private payers were used, the overall ranking of costs did not change; however, the differences in cost were greater, particularly for IMRT and proton beam therapy
- The benefit of avoiding side effects on active surveillance continued to outweigh the risks, even when higher rates of death due to prostate cancer were assumed for AS or the risk of "missed" cases of disease progression was doubled
- If the most favorable estimates of effectiveness and harms are used for robot-assisted prostatectomy, this approach saves approximately $1,500 and is slightly more effective than the open procedure

APPENDIX B:

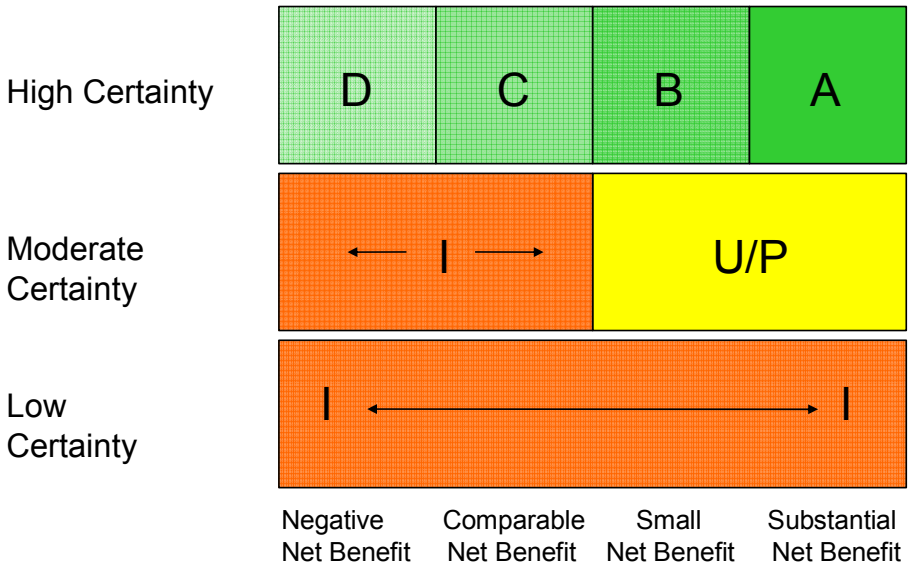
ICER RATING METHODOLOGY

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:

Comparative Clinical Effectiveness
Comparing tech_____ vs. _____



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.

ICER Integrated Evidence Rating™: Comparator X vs. Reference Technology Y