INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

FINAL APPRAISAL DOCUMENT

BRACHYTHERAPY & PROTON BEAM THERAPY FOR TREATMENT OF CLINICALLY-LOCALIZED, LOW-RISK PROSTATE CANCER

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EXECUTIVE SUMMARY

Introduction

Prostate cancer is the second leading cause of cancer deaths and the seventh overall cause of death in men in the United States (Centers for Disease Control and Prevention, 2008). Given that most new cases are diagnosed at an early, localized stage, significant attention has been focused on understanding the risks and benefits of alternative management strategies for patients with low-risk disease. The major options include active surveillance and various forms of radiation therapy and surgery. Data to compare the long-term survival benefits of these options are limited, and thus the choice for many patients is based largely on considerations of the potential short and long-term side effects of different treatment options.

ICER has previously appraised the comparative clinical effectiveness and value of two forms of external beam radiation therapy (EBRT): intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3D-CRT). IMRT has largely replaced 3D-CRT in the United States and is now viewed as the standard against which EBRT alternatives should be compared. The other major radiation modalities currently employed to treat localized prostate cancer are interstitial brachytherapy and proton beam therapy (PBT). These two treatment options are the primary focus of this appraisal. Data on active surveillance are included to give context to the findings on radiation therapy alternatives, but both active surveillance and surgical prostatectomy will be topics of formal ICER appraisals in 2009 that will, when completed, provide a full set of reviews on management options for localized prostate cancer.

For brachytherapy and PBT there are several key questions that have served to frame this review:

1) The impact of brachytherapy and PBT on survival and freedom from disease recurrence relative to IMRT and active surveillance
2) The relative rates of treatment-induced acute and late toxicities of brachytherapy and PBT and the impact of these toxicities on patients' quality of life
3) The potential negative impact of radiation exposure from treatment
4) The generalizability to community practice of published evidence on brachytherapy and PBT arising from studies at highly specialized, academic practices
5) The budget impact and cost-effectiveness of brachytherapy and PBT for low-risk prostate cancer relative to IMRT and active surveillance

Because these treatments may vary in terms of their net health benefit, and because reasonable alternatives exist for prostate cancer patients and clinicians, health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of alternative radiation therapy options for localized prostate cancer.

Alternative Treatment Options

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 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 EBRT while providing a higher radiation dose to the target (American Brachytherapy Society, 2008). The procedure is not indicated for patients with large prostate size or those with a history of urethral stricture, as the procedure results in short-term inflammation and swelling of the gland 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, 2008; 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.

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

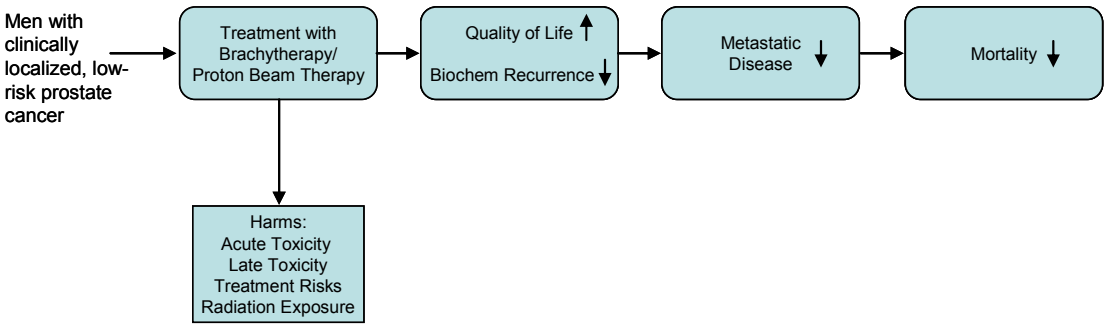
prostate cancer, as these tumors are more deep-seated relative to other cancers historically treated by protons, and current scanning techniques may not allow for conformation of the radiation to the target as accurately as with IMRT (Nguyen, 2008).

PBT 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 PBT 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 PBT 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.

Analytic Framework for Evaluation of Brachytherapy and Proton Beam Therapy
The analytic framework for this review is shown in the Figure below. There are little to no data directly demonstrating the impact of these therapies on overall patient survival, so judgments about the effectiveness of these interventions must rest almost exclusively upon consideration of the strength of surrogate endpoints as well as evaluation of treatment-associated risks.

Analytic Framework: Brachytherapy and Proton Beam Therapy in Prostate Cancer Treatment



Within this analytic framework, the link between biochemical evidence of disease recurrence and survival has been the subject of much debate. Because of the slow growth of most prostate cancers, and the consequent need for extremely long follow-up periods to measure survival accurately, biochemical recurrence, or "failure," as marked by changes in PSA levels following a low, or nadir value post-treatment, is widely used as a predictor of

survival; indeed, there is an active body of literature dedicated to finding the most appropriate method for measuring biochemical recurrence (Kuban, 2003; Roach, 2006). 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. Studies of patients receiving radiation therapy and androgen deprivation therapy (ADT) have found no association between biochemical failure rates and long-term mortality (Kupelian, 2002; Sandler, 2003). Nonetheless, biochemical failure has gained broad consensus among clinicians and researchers as a valid surrogate outcome. Clinicians use it as a trigger for treatment decisions, 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.

Summary of Comparative Clinical Effectiveness

Data Quality

A total of 166 studies met all entry criteria for review. Randomized controlled trials do not exist that compare measures of benefit and/or harm between brachytherapy, PBT, IMRT, and active surveillance. Only one study involved an internal comparison of these treatment alternatives: a single-center evaluation of toxicity rates in two distinct case series of patients treated with either brachytherapy or IMRT (Eade, 2008). Nearly all of the remaining studies were relatively small single-center case series of a single modality, a body of evidence further limited by considerable variability across studies in population demographics, number of patients with low-risk disease, and definitions of measures of treatment failure, making even indirect comparisons across treatments problematic.

Information on PBT is limited to case-series from a single institution, and is thus extremely limited in providing robust evidence on either biochemical failure or rates of acute and chronic toxicities of treatment.

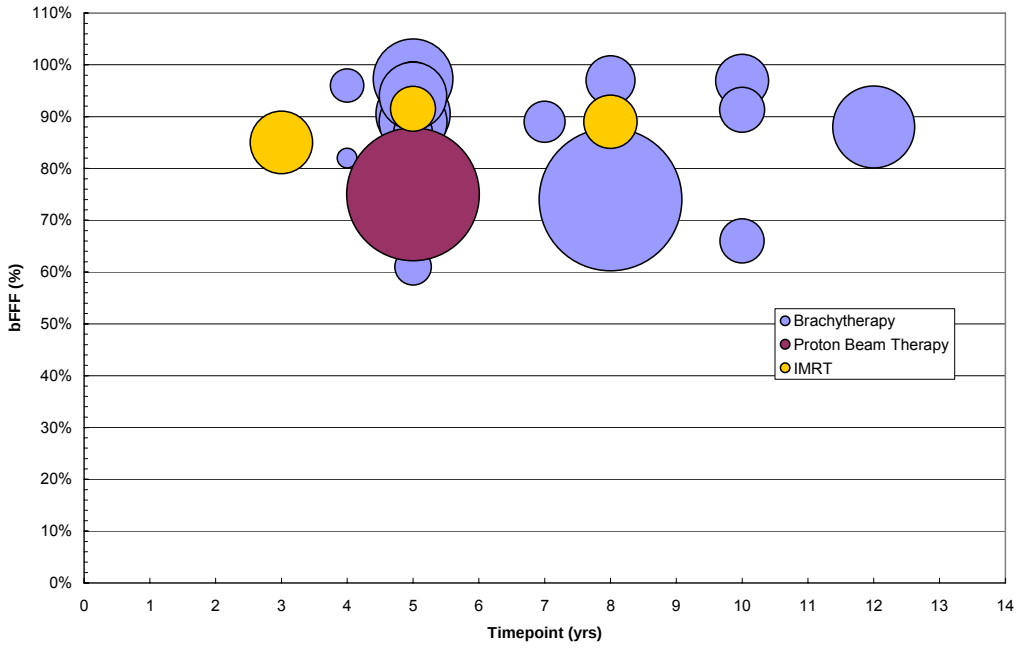
Survival and Freedom from Biochemical Failure

Data on overall and disease-specific survival from studies that met our eligibility criteria were only available on brachytherapy and active surveillance. Overall survival varied substantially across studies due to variation in study populations; at 5 years, estimates ranged from 69%-90% for active surveillance and 77%-97% for brachytherapy. Disease-specific survival was similar across brachytherapy and active surveillance studies, ranging between 93%-100% at median follow-up periods between 5 and 12 years.

Comparisons of biochemical failure across modalities is complicated by the use of several different definitions of biochemical failure; with guidance from the ICER Evidence Review Group, data on this outcome were only evaluated from studies with a median follow-up of at least 5 years, since by 5 years outcomes across studies with different definitions of biochemical failure should normalize. Of the 28 studies that met this 5-year criterion, 24 were of brachytherapy, 3 of IMRT, and 1 of PBT.

The results from these studies are shown in the Figure below; the size of the "bubbles" correlates with study sample size. Despite normalization of outcomes across different definitions of biochemical failure, other differences between studies in population demographics, proportion of low-risk disease, use of adjuvant or neoadjuvant ADT, and other factors complicate comparisons for this surrogate endpoint, and the substantial overlap in the estimates observed demonstrates no discernable difference in freedom from failure results among treatments.

Figure ES1. Biochemical freedom from failure, by treatment and timepoint.



NOTE: Bubble size used to illustrate study sample size

It should be noted that a larger body of literature is available for PBT and IMRT when the 5-year follow-up restriction is removed. Rates of freedom from biochemical failure for all PBT (n=6) and IMRT (n=7) studies that report such outcomes are in a similar range to those displayed in the Figure (79%-95% and 69%-99% for PBT and IMRT respectively) at timepoints between 1.5 and 6 years. We could not include active surveillance in this comparison because biochemical failure is defined as a change from a nadir value following treatment. A number of active surveillance studies do report surrogate outcomes for active surveillance in terms of "treatment-free" or "progression-free" survival; in the 7 studies identified, estimates ranged from 45%-73% at between 5 and 15 years of follow-up.

Harms

Risks Specific to Particular Treatments

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.

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 PBT. PBT 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).

Radiation-induced Malignancies

The risk of secondary malignancy from the radiation exposure of brachytherapy, IMRT, and PBT 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 PBT 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.

Acute and Late Radiation Toxicity

Side effects due to radiation toxicity affecting the bowel, bladder, and sexual organs are the most prominent harms posed by radiation treatment of localized prostate cancer. For this review, evidence on treatment-related gastrointestinal (GI) and genitourinary (GU) toxicity was limited to studies using standardized scoring criteria in an effort to identify the rate of toxicities serious enough to require some form of treatment. This level of severity is represented by a score of ≥ 2 on most scoring systems.

For toxicities common to all treatments, reported estimates ranged widely. As with measures of effectiveness, indirect comparisons of data on harms was made problematic by underlying differences in the study populations, percentage of low-risk patients, institution-specific modifications to the standardized toxicity scales, and other factors.

With full recognition of the heterogeneity of clinical populations in the published literature, the ICER review performed a random-effects meta-analysis to compare rates of toxicities across treatment modalities (see Table ES1 on following page). The results of the meta-analysis suggest some distinctions in rates of acute and late toxicities among the treatments. For example, the pooled rate of acute GI toxicity appears notably lower with brachytherapy (2.1%) compared to IMRT (18.4%); the rate of late GI toxicity appears to be higher for PBT (16.7%) than for either IMRT (6.6%) or brachytherapy (4.0%). Rates for most other toxicities, however, do not differ substantially between brachytherapy and IMRT, with the scarcity of evidence available on PBT making other comparisons of its outcomes impossible.

All results from the meta-analysis must be viewed with caution. Given the greatly differing rates of toxicity within the published results for each individual treatment, the meta-analysis produced pooled estimates with wide confidence intervals. The ICER review was unable to find evidence or clinical opinion that could provide principles by which to judge which published outcomes were most representative of "true" toxicity rates. Accordingly, while pooled estimates are presented in Table ES 1 and in the body of the review, the degree of clinical and statistical heterogeneity in published studies limits the usefulness of explicit comparisons of these pooled estimates across treatments. While the few studies that are available on PBT suggest, on balance, a comparable toxicity profile to other radiation modalities, the conceptual confidence interval around PBT's effects remains so broad that very low certainty can be assigned any judgment of its comparative clinical effectiveness. There is a good possibility that further evidence could demonstrate the toxicity profile and clinical effectiveness of PBT to be *superior or inferior* to that of IMRT and brachytherapy.

Table ES 1. Reported effects on acute and late radiation-induced toxicity, by treatment type.

Toxicity	Brachytherapy	PBT	IMRT
GI≥2*			
Acute	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%)
Late	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%)
GU≥2			
Acute	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%)
Late	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%)
Other			
Acute Urinary Retention	Studies: 9 High: 17.0% Low: 1.7% Pooled: 9.7% (1.7%,17.1%)	N/A	N/A
Erectile Dysfunction	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

*As measured on RTOG or NCI-CTC toxicity scales

†From random-effects meta-analysis (with 95% confidence intervals)

Comparative Value

We used findings from our systematic review on clinical effectiveness and treatment-related toxicity to perform a cost-utility analysis of immediate treatment or treatment deferred for 3 years with brachytherapy, IMRT, and PBT in 65-year-old men with localized prostate cancer. PBT was included in the model even though the results of the systematic review suggested very low certainty in estimates of clinical effectiveness and rates of toxicity. Deferred treatment was modeled on the basis of evidence showing that many patients initially opting for active surveillance switch to definitive treatment within 5 years, and in many cases do so without evidence of clinical progression of disease (Parker, 2004). For this reason we assumed patients would be on active surveillance for 3 years prior to

initiating the radiation treatment of their choice. Utilities (i.e., the value, between 0 and 1, placed on quality of life in a particular state of health) for patients with individual toxicities or toxicity combinations were obtained from published literature; risks of secondary malignancy were incorporated as an average decline in utility across all patients.

The ICER review of clinical effectiveness provided the base case assumption that the effectiveness of brachytherapy, IMRT, and PBT are equivalent; therefore, the economic model results show life expectancy for a 65-year old man to be approximately 17 years no matter which treatment is selected or whether such treatment is immediate or deferred. Toxicities for each treatment option reduce the final total of quality-adjusted life years to a narrow range shown below in Table ES 2. The systematic review provided base case estimates of relatively similar toxicity rates for these treatments, and therefore only small differences are found in overall quality-adjusted life expectancy. Large differences are observed in lifetime cost, however, with immediate or deferred brachytherapy having costs 30% and 60% lower than those of strategies involving IMRT and PBT, respectively.

Table ES 2. Lifetime costs and quality-adjusted life expectancy, by treatment type.

Treatment	Cost	QALYs
Brachytherapy	$29,575	13.90
Deferred BT	$31,305	13.95
IMRT	$41,591	13.81
Deferred IMRT	$42,118	13.84
Deferred PBT	$70,661	13.73
PBT	$72,789	13.70

BT=Brachytherapy; IMRT=Intensity-modulated radiation therapy; PBT=Proton beam therapy; QALYs=Quality-adjusted life years

Immediate treatment with brachytherapy or IMRT is slightly less costly than deferred treatment due to the additional costs of surveillance, which include biopsy, serial PSA testing, and treatment of disease-associated obstructive symptoms. This is not the case with PBT, as the discounted cost from deferred PBT outweighs the additional costs of surveillance. Quality-adjusted life expectancy is slightly higher with deferred strategies, as the model was structured so that men could not progress to metastatic disease while on active surveillance. In any event, effectiveness is within the narrow range estimated for immediate treatment.

The model was also run for a younger cohort of 58 year-old men; immediate and deferred brachytherapy remained the least costly and most effective strategies. Also, while not a large component of lifetime costs, it is worth noting that the estimated cost of patient time spent in treatment, a cost typically borne by the patient (and/or his employer), is >50% lower for brachytherapy than for either IMRT or PBT ($686 vs. $1,544 and $1,715 respectively); this is based on estimates of about 5 days out of work for brachytherapy treatment vs. 11-12 days for the treatment cycle of IMRT or PBT. Even when these costs

were removed from the analysis, immediate and deferred brachytherapy remained the least costly strategies.

Given the limitations of the evidence on clinical effectiveness and rates of toxicity for these treatments, multiple sensitivity analyses were conducted. Table ES 3 below illustrates the effects of varying toxicity rates and toxicity-related utility on the effectiveness of each strategy. These sensitivity analyses showed that effectiveness was highly sensitive to small changes in base case rates of toxicity. For example, under scenarios with small absolute increases in the rate of late GU or late GI toxicities for brachytherapy, IMRT becomes the more effective treatment, although the magnitude of incremental effectiveness remains extremely small. Larger changes in the base case estimates of toxicity rates or utilities are required in order for PBT to emerge as the most effective strategy. Under all of these scenarios, because the difference in QALYs is very small and the cost differential between brachytherapy, IMRT, and PBT are so large, the incremental cost-effectiveness ratios for IMRT and PBT are very high ($1.2 - $18 million per QALY).

Table ES 3. Threshold analyses for changes in rates of late toxicities and toxicity-related utilities.

Parameter varied	Baseline Value	Range analyzed	Effectiveness Threshold	Most Effective Strategy	Incremental Effectiveness
Probability of					
ED after BT	0.1970	0.1065- 0.3400	0.23	IMRT	0.009
GU toxicity after BT	0.0540	0.0250-0.0820	0.073	IMRT	0.004
ED after IMRT	0.1970	0.1065-0.3400	0.16	IMRT	0.008
GU after IMRT	0.0435	0.0250-0.0870	0.25	IMRT	0.001
ED after PBT	0.1970	0.1065-0.3400	0.13	PBT	0.002
GI toxicity after PBT	0.0542	0.0050-0.1000	0.026	PBT	0.011
Utility of					
GI toxicity	0.7100	0.3500-1.000	0.91	PBT	0.010
GU toxicity	0.8300	0.4200-1.0000	0.55	PBT	0.007

ED=Erectile Dysfunction; BT=Brachytherapy; PBT=Proton Beam Therapy; IMRT=Intensity-Modulated Radiation Therapy; Inc=Incontinence; GI=Gastrointestinal toxicity

Summary

In summary, the assumption of no difference in survival or biochemical recurrence among all treatment modalities produces model findings of very small differences in quality-adjusted life expectancy. The sparse and highly variable nature of data on toxicities must be stressed again, as the nominal differences arising from the meta-analysis are uncertain and suggest differences that amount to "tradeoffs" by type of toxicity. In short, even though brachytherapy appears to be marginally superior in lifetime quality-adjusted expectancy, neither the findings from the systematic review nor those from the economic model suggest a clear pattern of significant clinical superiority for any treatment modality. While the uncertainties described in this summary might merit prospective comparative study to further refine our understanding of each treatment approach's relative benefits and harms, such study could only be supported if there is reasonable likelihood of

demonstrating a substantial improvement in net health benefit for the newer technologies over brachytherapy, given the wide disparity in current reimbursement levels and the significant opportunity cost in conducting prospective research.

ICER Evidence Review Group Deliberation

The ICER Evidence Review Group deliberation (see section starting on page 24 for membership and details) focused on many important issues regarding the evidence provided by the ICER review. Major points of discussion are shown in the numbered points below.

1) *While active surveillance was not reviewed systematically, the tone of the report should clearly reflect the fact that active surveillance remains a viable option for many men with localized disease, and that this review did not formally set out to perform a full review of active surveillance. It should be emphasized that while the focus of the current review is on the evidence on radiation therapy, ICER is not advocating for intervention over surveillance.*
   In response to guidance from the ERG, "deferred treatment" was included in the economic model as a proxy for a short period of surveillance followed by treatment, but it has always been recognized that a fair evaluation of active surveillance must include a comprehensive and systematic review of the evidence on benefits and harms as well as a separate and distinct modeling effort. The discussion on active surveillance in the draft review has been expanded in the executive summary and body of this final report.

2) *The issue of seed migration receives relatively little attention in the report; if there is rationale for its exclusion as a potential harm, it should be clearly stated.*
   As discussed during the ERG meeting, seed migration was not systematically reviewed because, other than a few individual case studies, there is no published evidence of its short- or long-term detrimental effects. This discussion has been significantly expanded in both the executive summary and body of the review.

3) *Modifications to the RTOG toxicity scales are not uncommon and often institution-specific; in some cases (for example, coding of alpha-blocker use for urinary symptoms as "grade 1"), this can make comparisons across studies problematic.*
   Given the already scant literature on toxicity for IMRT and PBT, further exclusion of study reports based on use of modified toxicity scales will not likely be a useful endeavor; instead, the issues surrounding these modifications have been noted as a potential source of bias along with the other between-study differences already mentioned.

4) *Of the three radiation modalities of interest, brachytherapy is subject to the greatest amount of technical variability, due to the complex and invasive nature of the procedure as well as its widespread use.*
   The description of training and competency standards for brachytherapy has been expanded, and the potential sources of variability in treatment and outcomes with this procedure are now discussed in the executive summary and body of the review.

5) *Despite the theoretical benefits of the dose distribution from protons vs. conventional radiation, there is still much uncertainty regarding the actual dose delivered to nontarget tissue, particularly with conventional proton scanning techniques and in a deep-seated target area like the prostate.*

6) *An important point of discussion was the source of data on toxicity, which is most commonly obtained via clinical outreach and/or review of medical records. The evidence base is notable for its dearth of patient-reported outcomes; many ERG members felt that this should be highlighted as an important priority for future research.*

7) *The viability of active surveillance in this population was underscored by anecdotal evidence from some on the ERG that this strategy is being employed with increasing frequency, even at academic centers that provide all of the available treatment modalities. Several ongoing clinical trials of active surveillance (e.g., PIVOT, ProtecT) may serve as models for evaluating competing technologies in prostate cancer moving forward.*

Discussion of ICER Integrated Evidence Ratings

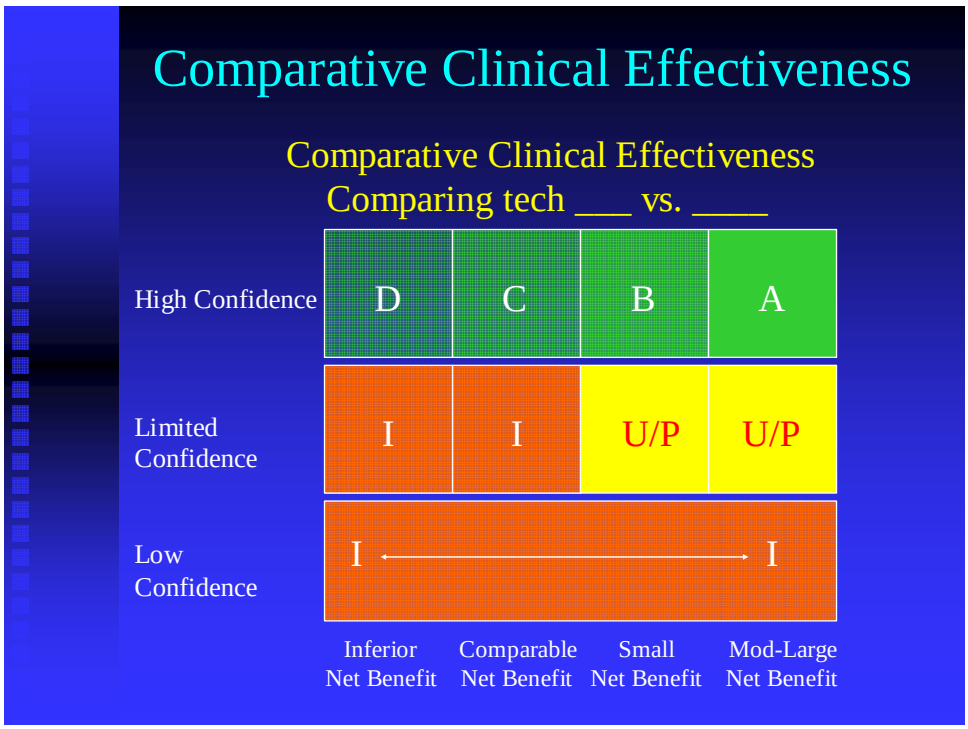
The specific discussion of the assignment of ICER ratings for comparative clinical effectiveness and for comparative value used two separate frameworks: 1) PBT vs. IMRT; and 2) brachytherapy vs. IMRT. There was unanimous consensus that, compared to IMRT, PBT should be rated "Insufficient" in comparative clinical effectiveness, due to the dearth of data on its benefits and harms in this patient population. According to ICER's rating methodology (see section on the following pages), technologies rated in this fashion do not require a rating of comparative value, as there is insufficient evidence to make a firm judgment of clinical benefit. However, many members of the ERG felt that, because PBT is an expensive technology, some judgment of comparative value should be made in the review. Again, the consensus was unanimous in rating PBT as "Low Value" relative to IMRT.

The discussion surrounding brachytherapy was more complex. Several ERG members felt that the comparison to IMRT should be reversed, as brachytherapy is the more established therapy. This in part reflected the relative uncertainty that remains regarding the evidence on IMRT. The group was unanimous, however, in concluding with high confidence that brachytherapy was at least "Comparable" to IMRT in terms of clinical effectiveness. While some ERG members (3/10) felt that increased patient convenience with brachytherapy translated into an "Incremental" clinical benefit, others felt that the effects of convenience would fade over time. Still, many in the group (6/10) felt that a rating of "Comparable" should be accompanied with note of a lower level of certainty that the evidence in fact suggests an incremental benefit with brachytherapy, due both to patient convenience and to the possibility of a better toxicity tradeoff. One member voted to rate brachytherapy as "Insufficient" to reflect the lack of comparative data. The group was unanimous in considering brachytherapy a "High Value" technology, whether compared to PBT or to IMRT. Background on the ICER rating methodology is shown on the following pages, with the final ICER ratings immediately afterward.

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 confidence provided by the body of evidence and the magnitude of the net health benefit -- the overall balance between benefits and harms. This method for rating the clinical effectiveness is modeled on the "Evidence- Based Medicine (EBM) matrix" developed by a multi-stakeholder group convened by America's Health Insurance Plans. This matrix is depicted below:



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

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

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

Confidence
The vertical axis of the matrix is labeled as a degree of confidence with which the magnitude of a technology's comparative net health benefit can be determined. This operational definition of confidence 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 confidence 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 Confidence:
An assessment of the evidence provides high confidence in the relative magnitude of the net health benefit of the technology compared to its comparator(s).

Limited Confidence:
There is limited confidence in the assessment the net health benefit of the technology. Limited confidence 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 limited confidence. First, there may be limited confidence in the magnitude of any net health benefit, but there is high confidence that the technology is *at least* as effective as its comparator(s). The second kind of limited confidence applies to those technologies whose evidence may suggest comparable or inferior net health benefit and for which there is not nigh confidence that the technology is at least comparable. These two different situations related to "limited confidence" 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. Among the most important types of limitations to evidence we follow the GRADE and AHRQ approaches in highlighting:

1. Type of limitation(s) to confidence
    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 Confidence:
There is low confidence 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.

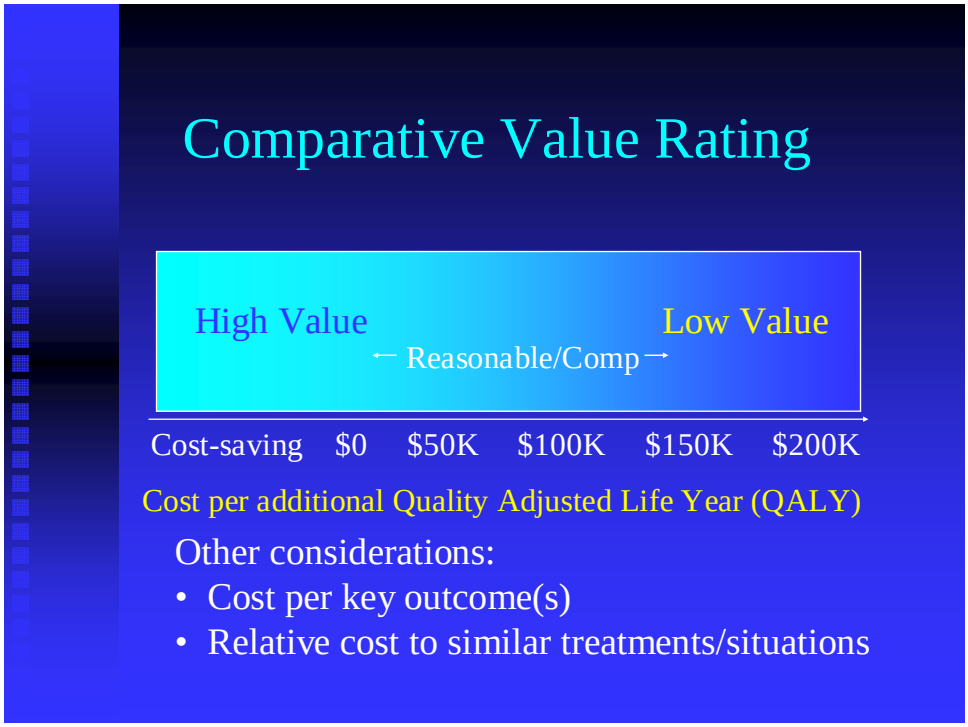
Whether judged quantitatively or qualitatively, there are two general situations that decision-making groups face in judging the balance of benefits and harms between two alternative interventions. The first situation arises when both interventions have the same types of benefits and harms. For example, 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. Among the most important is the incremental cost-effectiveness of the technology being appraised The most commonly used metric for an assessment of cost-effectiveness is the quality adjusted life year, or QALY. This measure adjusts any improvement in survival provided by a technology by its corresponding impact on the quality of life as measured by the "utilities" of patients or the public for various health states. While ICER does not operate within formal thresholds for considering the level at which a cost per QALY should be considered "cost-effective," the assignment of a rating for comparative value does build upon general conceptions of ranges in which the incremental cost-effectiveness ratio can be generally assumed to indicate relatively high, reasonable, and low value compared to a wide range of health care services provided in the US healthcare system. These broad ranges and shown in the figure below. 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.



Although the cost per QALY is the most common way to judge the cost-effectiveness of alternative medical interventions, ICER also considers the sub-component parts of the QALY, including the cost per key clinical benefits. Additional data and perspectives are also considered whenever possible, including potential budget impact, impact on systems of care and health care personnel, and comparable costs/CEA for interventions for similar clinical conditions.

ICER Integrated Evidence Rating™: Brachytherapy vs. IMRT

The Comparative Clinical Effectiveness of Brachytherapy vs. IMRT in the treatment of clinically-localized, low-risk prostate cancer is rated as:

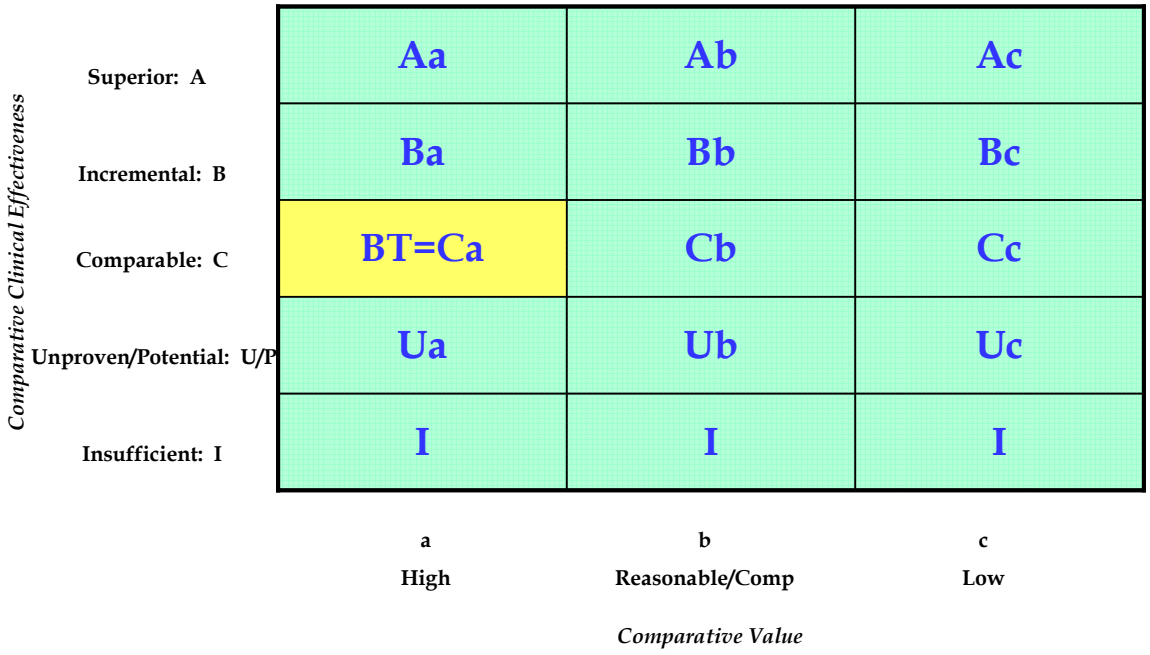
- **C --- Comparable**

The Comparative Value of Brachytherapy vs. IMRT in the treatment of clinically-localized, low-risk prostate cancer is rated as:

- **a --- High***

The Integrated Evidence Rating = Ca*

*** Within assumptions of the economic analysis**



Note: the yellow shade for the Integrated Evidence Rating indicates *high* confidence that brachytherapy is at least comparable to IMRT and *limited* confidence in an incremental net health benefit.

ICER Integrated Evidence Rating™: Proton Beam Therapy vs. IMRT

The Comparative Clinical Effectiveness of Proton Beam Therapy vs. IMRT in the treatment of clinically-localized, low-risk prostate cancer is rated as:

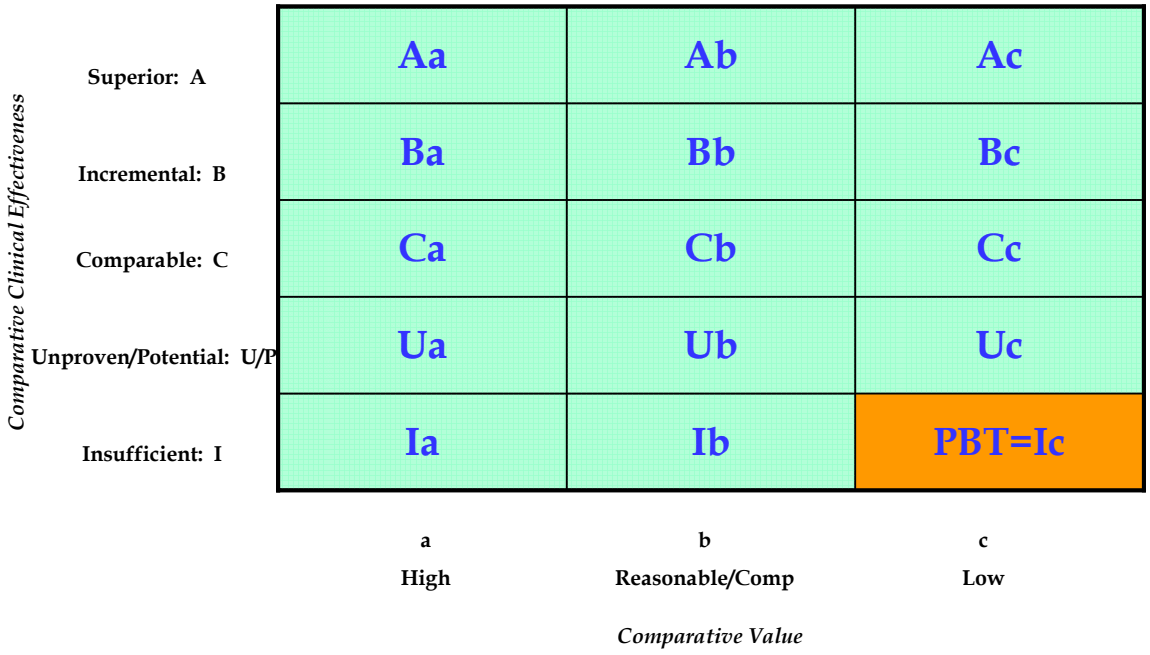
- **I --- Insufficient**

The Comparative Value of Proton Beam Therapy vs. IMRT in the treatment of clinically-localized, low-risk prostate cancer is rated as:

- **c --- Low***

The Integrated Evidence Rating = Ic*

*** Within assumptions of the economic analysis**



Note: the orange shade for the Integrated Evidence Rating indicates *low* confidence that there is sufficient evidence of a net health benefit for proton beam therapy relative to IMRT. Also, while technologies rated "insufficient" are not typically presented with a comparative value rating, ICER's base case assumptions suggest that proton beam therapy has low comparative value at current rates of reimbursement.

Sample Physician-Patient Script

Discussing the evidence on potential risks and benefits of treatment options is a central element of shared decision-making between clinicians, patients, and families. ICER offers the script below as an example of how clinicians could initiate a conversation with patients that would foster consideration of the findings of this evidence review. Conveying this amount of information in one conversation may not be practicable or appropriate for many patients; the intent is to suggest only one of many styles through which clinicians can empower their patients to share in the consideration of the evidence on reasonable clinical alternatives and to help them choose the option that will reflect their broader best interests.

"I know you've narrowed down your consideration to radiation treatment or what is called "active surveillance" for your prostate cancer. We've talked a little bit about these options already. Today let's go further. First, I'd like you to know that evidence reviews and national expert groups have concluded that – for men like you with low-risk prostate cancer – there is no evidence that any of these radiation treatments is better than active surveillance at curing your cancer, keeping it at bay longer, or extending your life. Active surveillance is, therefore, a reasonable option for you to consider. On the other, hand, many men opt for treatment right away, so let's talk about the radiation options. Here you should know that none of them has been proven superior to the others. We have had more years of experience with brachytherapy; IMRT has been in use for about 8 years; and PBT is fairly new so we have far less data on its longer-term outcomes. Each option has some potential advantages and disadvantages with regard to possible side effects of treatment, which I'll go over with you. In addition, each requires differing amounts of time and numbers of visits to the doctor. And, some are more expensive than others, both for your own out-of-pocket costs and for your health plan. Before we run through these pros and cons together, let me stop here to see if you have any questions or if you've heard anything about any of these options that you'd like to discuss…."

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

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

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

ERG Participant Name and Affiliation	Potential Influences on Expertise
John Z. Ayanian, MD, MPP Professor of Medicine & Health Care Policy Harvard Medical School & Brigham & Women's Hospital Professor of Health Policy & Management Harvard School of Public Health	None
Mike Barry, MD Professor of Medicine Harvard Medical School & Massachusetts General Hospital	Not present at meeting

Marc Berger, MD Vice President, Global Health Outcomes Eli Lilly and Company	Employed by pharmaceutical manufacturer developing and/or marketing compounds to treat prostate cancer and/or related symptoms
William Corwin, MD Medical Director, Medical Management & Policy Harvard Pilgrim Health Care	Not present at meeting
Michele DiPalo Director, Health Services Evaluation Blue Cross & Blue Shield of Massachusetts	Employed by payer; involved in evaluation of new/emerging technology
Wendy Everett, ScD President, New England Healthcare Institute	None
Ted Ganiats, MD Chair, Dept. of Family & Preventive Medicine University of California at San Diego (UCSD) School of Medicine Executive Director, UCSD Health Services Research Center	None
G. Scott Gazelle, MD, MPH, PhD Director, Institute for Technology Assessment, Massachusetts General Hospital Professor of Radiology, Harvard Medical School Professor of Health Policy & Management, Harvard School of Public Health	None
Marthe Gold, MD Professor & Chair, Community Health and Social Medicine City College of New York	None
Lou Hochheiser, MD Medical Director, Clinical Policy Development Humana, Inc.	Not present at meeting
Nora Janjan, MD, MPSA, MBA Professor Radiation Oncology and Symptom Research MD Anderson Cancer Center	None
Phil Kantoff, MD Professor of Medicine Harvard Medical School & Dana-Farber Cancer Institute	None

Andre Konski, MD, MBA, MA Chief Medical Officer Fox Chase Cancer Center	Co-chair, American Society of Therapeutic Radiology & Oncology Emerging Technology Committee; Chair, Radiation Therapy Oncology Group Economic Impact Committee
Armin Langenegger Varian, Inc.	Employed by manufacturer of proton beam systems
Marcel Marc Varian, Inc.	Employed by manufacturer of proton beam systems
Newell McElwee, PharmD, MSPH Vice President, Evidence-Based Strategies Pfizer, Inc.	Employed by pharmaceutical manufacturer developing and/or marketing compounds to treat prostate cancer and/or related symptoms
David Most, PhD Patient/Consumer Representative	None
Lisa Prosser, PhD Research Scientist Henry Ford Health System	None
Manny Subramanian, PhD Best Medical, Inc.	Employed by manufacturer of brachytherapy equipment
Steven M. Teutsch, MD, MPH Executive Director, US Outcomes Research Merck & Co., Inc.	Employed by pharmaceutical manufacturer developing and/or marketing compounds to treat prostate cancer and/or related symptoms
Sean Tunis, MD, MSc Director Center for Medical Technology Policy	No financial conflict
Bhadrasain Vikram, MD Chief, Clinical Radiation Oncology National Cancer Institute	None

Milt Weinstein, PhD Professor of Health Policy & Management Harvard School of Public Health	None
Fiona Wilmot, MD, MPH Medical Director of Policy, Pharmacy & Therapeutics Blue Shield of California	Employed by payer; involved in evaluating new/emerging technology
Anthony Zietman, MD Professor, Radiation Oncology Harvard Medical School & Massachusetts General Hospital	President-elect, American Society of Therapeutic Radiology & Oncology

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

APPRAISAL OVERVIEW

BRACHYTHERAPY & PROTON BEAM THERAPY FOR TREATMENT OF CLINICALLY-LOCALIZED, LOW-RISK PROSTATE CANCER

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

Final Scope

Rationale for the Appraisal
Given the prevalence of prostate cancer as well as the large and increasing numbers of incident cases of disease that are diagnosed at an early, low-risk stage, a significant amount of attention has been placed on alternative therapies for low-risk prostate cancer. ICER has previously appraised the comparative clinical effectiveness and value of two of these options—intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3D-CRT). Input from the ICER Evidence Review Group (ERG) indicated that, since the earlier appraisal, IMRT has become the standard radiation treatment for prostate cancer against which radiation alternatives should be compared. In addition to IMRT, the two major radiation modalities currently employed in this population are interstitial brachytherapy and proton beam therapy (PBT). Also, because active surveillance (i.e., treatment delay with careful monitoring for disease progression) may be a reasonable option for men with low-risk disease, the general opinion of the ERG was that available evidence on active surveillance should be included in the ICER appraisal. Radical prostatectomy was not included due to time constraints; the appraisal therefore focused on active surveillance and alternative radiation therapies for low-risk prostate cancer.

For these treatment options, there are several key issues regarding the body of evidence accumulated to date:

1) The impact of brachytherapy and PBT on survival and freedom from disease recurrence relative to IMRT and active surveillance
2) The relative rates of treatment-induced acute and late toxicities of brachytherapy and PBT and the impact of these toxicities on patients' quality of life
3) The potential negative impact of radiation exposure from treatment
4) The generalizability to community practice of published evidence on brachytherapy and PBT arising from studies at highly specialized, academic practices
5) The budget impact and cost-effectiveness of brachytherapy and PBT for low-risk prostate cancer relative to IMRT and active surveillance

Because these treatments may vary in terms of their toxicities and clinical effectiveness, and because many reasonable treatment alternatives exist for prostate cancer patients and clinicians, all health care decision makers will benefit from a formal appraisal of the comparative clinical effectiveness and comparative value of active surveillance as well as alternative radiation therapy options for clinically-localized, low-risk prostate cancer.

Objective:
To appraise the comparative clinical effectiveness and comparative value of brachytherapy, IMRT, and PBT for men with clinically-localized, low-risk prostate cancer.

Key questions:

1. What is known about the relative impact of active surveillance, brachytherapy, IMRT, and PBT on patient outcomes?

2. How do these alternative treatment strategies differ in terms of the rates of major treatment-related toxicities?

3. What is the potential for secondary malignancy from radiation therapy modalities?

4. How does the performance of these treatment options vary according to important patient subgroups, such as age?

Key considerations highlighted by the Evidence Review Group:

1. Comparators: While the previous ICER appraisal examined IMRT in comparison to 3D-CRT, IMRT is now recognized as the general standard for external beam radiation therapy, and should replace 3D-CRT as the standard against which brachytherapy and PBT are judged.

2. Treatment Variants: While other variants of these treatment options exist, the modalities of primary interest to payers and other decision-makers are permanent, low-dose-rate brachytherapy with radioactive palladium or iodine seeds, and proton beam monotherapy.

3. Harms: While other analyses (including ICER's previous appraisal of IMRT and 3D-CRT) have focused primarily on so-called "late" toxicities of treatment, a systematic review of the effects of brachytherapy and PBT on both acute and late toxicities was felt to be warranted. The potential for secondary malignancy from these treatments was also felt to be of interest.

4. Costs: The investment in proton beam facilities is many times greater than that for other treatment options. There was strong feeling that an alternative cost-effectiveness perspective that includes an estimate of capital costs be included in the economic evaluation. In addition, because these treatments differ in terms of patient time commitment, time in therapy should be a consideration in estimates of cost-effectiveness.

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

1. Background

1.1 The Condition

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

Formal diagnosis of prostate cancer is made via biopsy. The TNM 2002 classification scheme of the American Joint Committee on Cancer provides a framework for assigning clinical stage. Clinically localized disease is subdivided into the following stages:

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

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

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

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

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

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

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

The progression of prostate cancer is typically slow and localized. Low-risk disease is unlikely to metastasize prior to the development of signs or symptoms of local progression (Cornell Urology, 2008). This has led to the oft-cited conclusion that "men are much more likely to die with, rather than from, prostate cancer" (Wilt, 2008). Because of localized prostate cancer's slow progression serial PSA testing is often used to monitor the disease and provide prognostic information as part of a strategy of "active surveillance" or to monitor for recurrence after treatment. In 1996, the American Society for Therapeutic Radiology and Oncology (ASTRO) published a definition of biochemical (i.e., PSA) failure following external-beam radiation therapy (EBRT), which was based on 3 consecutive PSA rises after a nadir value occurred (ASTRO, 1997). Over time it was determined that this definition was inadequate, particularly for patients undergoing hormone therapy and in those studies with shorter follow-up, as many patients had clinical recurrence prior to biochemical failure. A subsequent ASTRO consensus panel revised the definition of biochemical failure to be based on a rise in PSA of at least 2 ng/mL following a nadir (Roach, 2006).

Despite the interest in biochemical definitions of disease recurrence, the link between biochemical evidence of disease recurrence and overall survival has been the subject of much debate. Studies of patients receiving radiation therapy and androgen deprivation therapy have found no association between biochemical failure rates and long-term mortality (Kupelian, 2002; Sandler, 2003). Other evidence suggests that biochemical failure may be an appropriate surrogate in certain subgroups, such as high-risk patients younger than 75 years (Kwan, 2003).

2. The Technologies and Their Comparator(s)

The primary goal of treatment of prostate cancer is to prevent death and disability from prostate cancer among those most in need of intervention and to minimize complications and discomfort from interventions (Wilt, 2008). Factors such as age, pre-existing medical conditions, potential toxicities, and aggressiveness of the cancer are taken into account in the determination of the appropriate treatment path.

Although this review will focus primarily on radiation therapy alternatives, it should be emphasized that active surveillance remains a reasonable strategy for many patients with localized prostate cancer (National Comprehensive Cancer Network, 2008). For example, one study demonstrated that the probability that a patient with a Gleason score of 2-4 will die of prostate cancer within 15 years is only 6 per 1000 person years. Even among men who have moderately differentiated disease (Gleason 7), this study found that a majority will die from competing medical conditions during a period of 15-20 years (Albertsen, 2005). On the other hand, another long-term study of early-stage prostate cancer found that the mortality rate from prostate cancer was approximately 6-fold higher after 15 years of follow-up when compared with the first 5 years (Johansson, 2004). In addition, a recent randomized controlled trial of radical prostatectomy versus watchful waiting for patients with early-stage prostate cancer demonstrated reductions in all-cause mortality of 2 and 5 percent after 5 and 10 years, respectively (Bill-Axelson, 2005). There are two ongoing randomized trials evaluating active surveillance as one of the primary treatment options in men with early-stage prostate cancer, but the results of these studies are not expected until after 2010. In the meantime, until better prognostic markers are developed, many patients and physicians will continue to prefer aggressive treatments for clinically localized disease at the time of diagnosis.

The list of common treatment options for prostate cancer includes:

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

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

2.1 Active Surveillance

Because of the limited aggressiveness of many localized prostate cancers, active surveillance is a reasonable strategy for many men (National Comprehensive Cancer Network, 2008). Active surveillance involves forgoing immediate treatment while monitoring closely for signs of progression of disease (i.e., through periodic PSA testing and biopsy). If the patient shows signs or symptoms of advancing disease, the decision can be made to initiate treatment with the intention to cure the patient (Adolfsson, 2008). Active surveillance is a viable option for patients who are at low risk of both progression of disease and death from the tumor. The term is often used interchangeably with 'watchful waiting'; however, these are clinically distinct treatment options, as the latter refers to initiation of treatment (typically in older patients) with palliative intent only. With either approach, there is a chance that disease progression may be missed and therefore the patient's tolerance for a certain amount of uncertainty must be taken into consideration with these options (National Comprehensive Cancer Network, 2008).

2.2 Brachytherapy

Prostate brachytherapy refers to interstitial placement of radioactive seeds for clinically localized prostate cancer. There are two major forms of prostate brachytherapy currently in use today: permanent, low-dose rate (LDR) brachytherapy, in which seeds (typically iodine^{125} or palladium^{103}) are permanently implanted and emit a low dose of radiation over several months; and the newer temporary, high-dose rate (HDR) procedure, in which iridium^{192} seeds are inserted through micro-catheters and removed after a short period (typically less than an hour). The HDR procedure is typically reserved for intermediate- or higher-risk patients, while the LDR procedure predominates in low-risk populations. The LDR procedure typically delivers a prescribed dose of between 120-160 Gray (Gy) units; while HDR brachytherapy delivers a lower total dose (72-105 Gy), it is often used concomitantly with a course of photon radiation, and the dose to the prostate itself is typically higher than with LDR brachytherapy. LDR brachytherapy (the focus of this appraisal) typically involves a dose planning visit, an overnight hospital stay for the procedure, 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 EBRT while providing a higher radiation dose to the target (American Brachytherapy Society, 2008). The procedure is not indicated for patients with large prostate size or those with a history of urethral stricture, as the procedure results in short-term inflammation and swelling of the gland (Mayo, 2008). Other potential risks of brachytherapy include infection, injury, and anesthesia-related complications from the procedure, migration of radioactive seeds to other parts of the anatomy, acute urinary retention, other acute and late-onset urinary incontinence or irritative symptoms, rectal morbidity (e.g., proctitis, hemorrhage), and sexual dysfunction. In addition, there are concerns regarding the long-term risk of treatment-induced secondary malignancy common to all forms of radiation therapy.

While brachytherapy technique has remained relatively standardized over the years, some recent technological advancements have been reported. The use of so-called "stranded" brachytherapy seeds, in which seeds are connected via a polymer strand prior to implantation, has gained interest in recent years. There is some early evidence that the use of stranded seeds increases radiation dose to the prostate and reduces the risk of migration of seeds outside of the gland (Heysek, 2007). In addition, cesium^{131} has been approved as an additional isotope for brachytherapy treatment. This isotope has a shorter half-life than conventional palladium or iodine seeds, delivering 90% of its therapeutic dose within one month; concerns have been voiced, however, regarding its relative efficacy with a short half-life (Heysek, 2007). Additional advancements in technology, such as the improvement of ultrasound technology to provide higher resolution images for treatment planning, have the potential to make treatment planning and dose delivery more precise.

Despite these advancements, there remains potential for variability in performance and associated outcomes with brachytherapy due to its complex nature and use in both specialized and community settings. Chen (2008) examined the correlation between provider case load and outcomes following brachytherapy and found that men treated by higher-volume physicians were at slightly lower risk for recurrence and death from prostate cancer, but did not observe a clear association between case volume and complications; in an earlier study, however, there was a significant decline in complication rates over time, suggesting an improvement in technique with additional experience (Chen, 2006). Variability in practice and results may occur at multiple points during the procedure, including target contouring, seed implantation, estimation of post-implantation dose and seed placement, and general intra-operative quality assurance (Cormack, 2008; Merrick, 2005; Dubois, 1998; Yu, 1999; Lee, 2002; Xue, 2006; Ishiyama, 2008; Thomadsen, 2000).

2.3 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.

2.4 Proton Beam Therapy (PBT)

Protons are positively charged subatomic particles that feature particular characteristics of interest for clinical use. Specifically, proton beams are known to deposit the bulk of their radiation energy at the end of their range of penetration, or what is 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 (i.e., gamma- or X-ray) radiation (Lundkvist, 2005). This has led to an increase in the use of protons to treat clinically localized prostate cancer, in which the tradeoff between tumor control and perineal toxicity is an important consideration.

Clinical use of proton radiation, either alone or as a boost to photon therapy, was first employed at 2 major US centers (Loma Linda, CA and Boston, MA) in the 1970s, and has grown steadily over time; there are now approximately 25 operating or planned major proton therapy centers worldwide (including 5 in the US), and over 50,000 patients have received clinical proton beam therapy (PBT). The expense of constructing proton treatment facilities may exceed $150 million for full-sized facilities (Greene, 2008).

Among patients with prostate cancer, PBT has been used both in combination with conventional photon radiation (i.e., "boost" therapy) and alone. In either case, total dose to the patient currently ranges from 75-82 Gray unit equivalents (GyE). PBT is performed in a similar setting and schedule to that of IMRT (see above). Potential treatment-induced toxicities from PBT are similar to those of brachytherapy (with the exception of acute urinary retention) and IMRT, and include early and late-onset urinary incontinence and/or obstructive symptoms, rectal toxicity, and sexual dysfunction. Also, as was noted with IMRT, given the few centers currently online in the U.S. and the lack of consensus competency and/or training standards for PBT, there is potential for significant variability in practice and results as the number of centers delivering PBT increases.

There are additional uncertainties regarding PBT's dose distribution. Findings from a recent dosimetric comparison using PBT delivered by 2 lateral parallel opposed beams and IMRT with 7 coplanar beams suggest that IMRT technology yields better radiation conformality to the target; for example, radiation dose to the bladder was 50% higher with protons (Trofimov, 2007). Also, while the total amount of normal tissue irradiated is higher with IMRT, it appears that most of this radiation is relatively low-dose in comparison to the radiation delivered to non-target tissue by protons (Nguyen, 2008). Finally, the dose distribution from the most commonly-used proton scanners deposits a significant amount of radiation in the femoral heads, raising concerns about a possible increased risk of hip fracture.

The technology of PBT continues to evolve. While many centers still use passive methods for beam delivery, active beam delivery techniques such as raster scanning, in which a pencil-like beam is swept across the tumor to effectively "paint" the radiation within the tumor's boundaries, are beginning to be employed. Intensity modulation, similar to that employed in IMRT, is therefore possible at centers with active beam technology, and may serve to mitigate some of the dose distribution concerns mentioned above. The first U.S center to deliver so-called intensity-modulated proton therapy (IMPT) has recently come on-line (MD Anderson Cancer Center, 2004), and most existing facilities in the US also have this capability or can retrofit their technology to accommodate it. Also, delivery of higher-dose fractions of PBT, a process known as hypofractionation, has been explored as a method of reducing both the frequency of fraction delivery and the length of the overall treatment course (Nguyen, 2007). Finally, a compact proton delivery system is under development that is expected to cost $25-$30 million to construct, or approximately one-fifth of the cost of a conventional accelerator and housing facility; the technology will also use substantially less physical space. Proponents of the compact system feel that, by making proton beam technology more affordable and manageable for medical centers, its accessibility to patients should increase (Lawrence Livermore National Laboratory Public Affairs, 2007).

3. Clinical Guidelines & Competency Standards

3.1 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 that monotherapy with permanent brachytherapy be considered for patients with low risk disease. Brachytherapy with external radiation boost can be considered in those with intermediate risk. http://www.estro.be/ESTRO/upload//seedimplanguidelines.pdf

- American College of Radiology (2006): 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 interstitial brachytherapy monotherapy is considered one of the preferred approaches (rating of 8 on a scale of 1-9). http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonRadiationOncologyProstateWorkGroup/PermanentSourceBrachytherapyforProstateCancerDoc5.aspx

- 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, and a PSA ≤50 ng/mL. Patients should also have 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 American Brachytherapy

Society (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

3.2 Proton Beam

Clinical Guidelines

- National Comprehensive Cancer Network (2008): The NCCN Prostate Cancer Panel Members groups PBT 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 PBT 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 (2006): Guidelines for external beam radiation therapy are currently being updated. The ACR appropriateness criteria for treatment planning consider PBT-, three-dimensional conformal radiation therapy (3D-CRT)-, and intensity-modulated radiation therapy (IMRT)-based plans appropriate for clinically-localized disease, although IMRT plans receive a slightly higher score on ACR's appropriateness rating system (8 vs. 7 on a 1-9 scale).
http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonRadiationOncologyProstateWorkGroup/ExternalBeamRadiationTherapyTreatmentPlanningforClinicallyLocalizedProstateCancerDoc2.aspx

- 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).

4. Medicare and Representative Private Insurer Coverage Policies

4.1 Brachytherapy

- Medicare: 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 (see above) 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.

4.2 Proton Beam

- Medicare: There have been no National Coverage Decisions on PBT. Most Local Coverage Decisions allow for the use of PBT 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 PBT;

  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): PBT 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: PBT 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: PBT is considered a covered benefit for the treatment of prostate cancer.

- Regence: Coverage of PBT is allowed as a primary therapy for clinically localized prostate cancer.

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

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

5. Previous Systematic Reviews/Tech Assessments

5.1 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

- Committee on Evaluation and Diffusion of Innovative Technologies (CEDIT, France) (2001): CEDIT recommended that the application of brachytherapy be reserved for use at one center with sufficient experience in the technique due to the many reservations surrounding its effectiveness in treating early prostate cancer. There has been no further update to this opinion.
  http://cedit.ap-hop-paris.fr/servlet/siteCeditGB?Destination=reco&numArticle=01.06/Re1/01

- Swedish Council on Technology Assessment in Health Care (SBU, Sweden) (2000): SBU concluded that brachytherapy should be used "only within the framework of controlled clinical studies until further evidence becomes available." The report has not been materially updated.
  http://www.sbu.se/en/Published/Alert/Brachytherapy-for-prostate-cancer/

5.2 Proton Beam

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, PBT was discussed at CTAF's roundtable on intensity-modulated radiation therapy (IMRT) for prostate cancer. The roundtable concluded that PBT 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).

- Center for Evaluation and Diffusion of Innovative Technologies (CEDIT, France) (2002): CEDIT's original guidance suggested that PBT has only shown proven effectiveness in melanomas of the eye and skull-based chordomas and chondrosarcomas. There has been no update to this guidance. http://cedit.aphp.fr/servlet/siteCeditGB?Destination=reco&numArticle=01.10

- 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 PBT 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 PBT patients in most of the comparative observational studies had less advanced disease than those receiving conventional radiotherapy.

6. Ongoing Clinical Studies

Brachytherapy Clinical Studies Summary Table

Trial Sponsor	Design	Primary Outcomes	Populations	Interventions	Comments
Radiation Therapy Oncology Group (NCT00063882)	Randomized Interventional Trial	▪ 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
British Columbia Cancer Agency (NCT00407875)	Randomized Controlled Trial	▪ Acute and late toxicities ▪ Quality of life ▪ Survival	N=50	IMRT vs. permanent brachytherapy	Estimated Study Completion date November 2016
National Cancer Institutes of Canada and US (NCT00499174)	Prospective, randomized, multicenter study	▪ Disease-specific survival	N=2,130	Active surveillance vs. radical intervention (permanent brachytherapy is one option)	Estimated Study Completion date April 2023
Massachusetts General Hospital (NCT00681694)	Observational	▪ Changes in quality of life over time ▪ Comparison between two brachytherapy techniques ▪ Factors associated with adverse events	N=414 who had elected to receive brachytherapy	Ultrasound-guided vs. MRI-guided brachytherapy	Estimated study completion date March 2010
MD Anderson Cancer Center (NCT00525720)	Non-randomized interventional	▪ Effectiveness in control of intermediate risk ▪ Safety	N=100 with intermediate risk prostate cancer	Brachytherapy	Estimated study completion date August 2010

Proton Beam Therapy Clinical Studies Summary Table

Trial Sponsor	Design	Primary Outcomes	Populations	Interventions	Comments
Massachusetts General Hospital (NCT00585962)	Non-randomized interventional	▪ Morbidity	N=85	PBT	Primary completion date was March 2007. The study is ongoing.
M.D. Anderson Cancer Center (NCT00388804)	Randomized interventional	▪ PSA outcomes ▪ Survival ▪ Quality of life ▪ Prognostic indicators	N=340	Androgen suppression plus: o IMRT o 3D-CRT o PBT Vs. each radiation tx alone	Estimated Primary Completion Date: February 2012

7. The Evidence

7.1 Systematic Literature Review

Objectives
The primary objectives of the systematic review were to:

- Identify and summarize the published evidence on the clinical effectiveness of active surveillance, brachytherapy, IMRT, and PBT in the treatment of clinically-localized, low-risk prostate cancer; and

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

    - Direct complications of the procedure, if any
    - Gastrointestinal toxicity (e.g., proctitis)
    - Genitourinary toxicity (e.g., incontinence, obstructive symptoms)
    - Sexual dysfunction

In our review of clinical effectiveness, we sought studies that examined the impact of these treatments on overall survival; however, in anticipation of limited data on these outcomes, we also examined data on disease-specific survival as well as rates of freedom from biochemical failure (i.e., as defined by serial PSA testing). Information on gastrointestinal and genitourinary harms was restricted to data graded as moderate-to-severe (grade 2 or higher) on the Radiation Therapy Oncology Group (RTOG) or National Cancer Institute Common Toxicity Criteria (NCI-CTC) morbidity scales (National Cancer Institute, 1999; Radiation Therapy Oncology Group, 2008); where reported, information on both acute (typically within 90 days following treatment) and late effects were recorded. Data on sexual harms were recorded as reported, and information on baseline levels of potency was also recorded where noted in the literature.

In addition, while not a component of our systematic review, we also examined the literature on future risks associated with radiation dose delivered by primary treatment, as well as studies of the economic impact and/or cost-effectiveness of the therapies of interest. Our review was supplemented with expert guidance as well as examination of review articles and other health technology assessments.

Methods
This review included studies of the benefits and harms of brachytherapy and PBT in the treatment of clinically-localized, low-risk prostate cancer. Low-risk disease was identified as follows:

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

Guidance from the ICER Evidence Review Group suggested that the forms of treatment of most interest to decision-makers were permanent, low-dose-rate (LDR) brachytherapy with I^{125} or Pd^{103} isotopes, and monotherapy with protons. Other variants of these treatments (see eligibility criteria below) were not considered. The literature was also scanned for studies of IMRT that were published since the completion of ICER's 2007 review of this topic, as well as studies of active surveillance (as this was felt to be an important comparator in economic modeling).

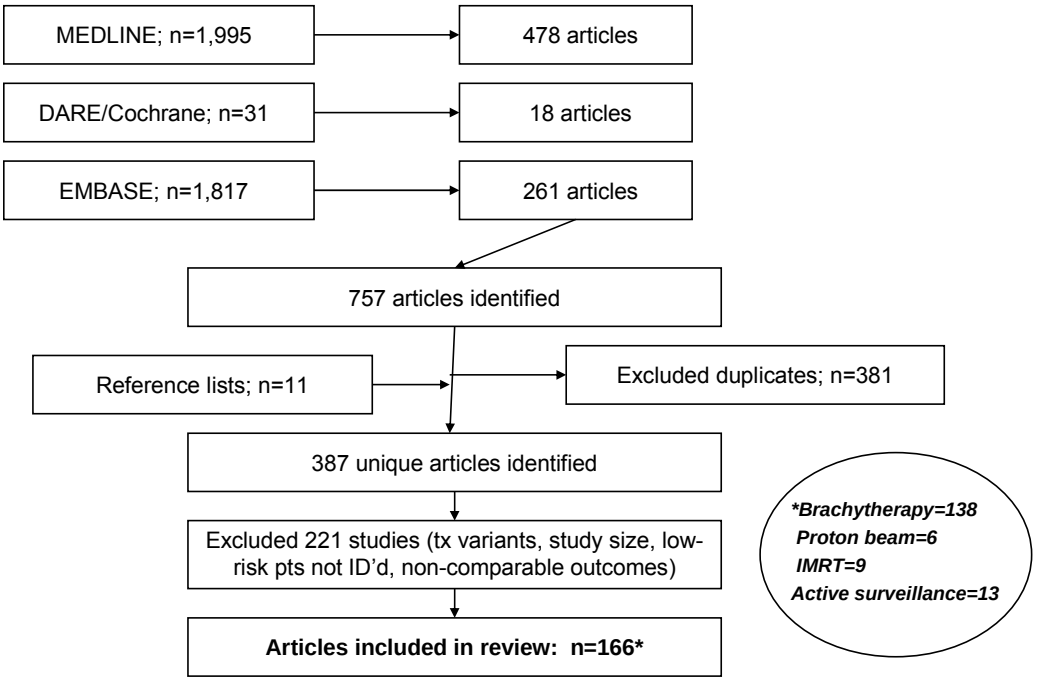
Electronic databases searched included MEDLINE, EMBASE, and *The Cochrane Library* (including the Database of Abstracts of Reviews of Effects [DARE]) for eligible studies, including health technology assessments (HTAs), systematic reviews, and primary studies. Reference lists of all eligible studies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

Included studies had a study population of adult males who underwent one of the treatments of interest. The search included studies published during the period January 1995 – August 2008; for IMRT, publications between January 2007 and August 2008 were added to studies from the previous ICER appraisal. Because adjuvant or neoadjuvant use of androgen deprivation therapy (ADT) has been found to affect rates of certain treatment-related toxicities such as sexual dysfunction (Lubeck, 2001), outcomes were preferentially reported separately in patients not treated with ADT; if such data were not available, the percentage of the sample that did receive ADT was reported along with other evidence presented. Other major eligibility criteria included:

- Exclusion of other variants of treatment (e.g., temporary, high-dose-rate [HDR] brachytherapy, proton "boost" therapy in combination with standard photon radiation)
- Preponderance of patients met criteria for low-risk disease, or data presented for subpopulation meeting low-risk criteria
- Sample size ≥50 patients
- English-language only

Studies were not restricted by instrumentation or manufacturer, treatment planning technique, or radiation dose delivered. Figure 1 on the following page shows a flow chart of the results of all searches for included primary studies (n=166).

Figure 1. QUORUM flow chart showing results of literature search



7.2 Data Analyses

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

Freedom from Biochemical Recurrence
Per guidance from the ICER ERG, examination of reported rates of freedom from biochemical failure (also described as disease-free survival, biochemical no evidence of disease (bNED), or freedom from biochemical recurrence) to those from studies with a median follow-up of 5 years or longer. This was done to account for biases introduced by the presence of multiple failure definitions in the literature (e.g., 3 consecutive PSA rises, change from nadir PSA), which are not easily comparable at shorter durations of follow-up (Roach, 2006).

Harms
Data on treatment-related morbidity was collected if reported using RTOG or NCI-CTC criteria for genitourinary (GU) and gastrointestinal (GI) toxicity, with a focus on toxicity graded 2 or higher (i.e., requiring treatment or intervention). In addition, data were recorded on the incidence of acute urinary retention with brachytherapy, as this is an important complication specific to this modality, and was reported separately in a significant number of studies. Finally, the rate of erectile dysfunction was recorded, whether on an overall basis or among those reporting potency at study baseline.

As mentioned above, information on radiation risks was not part of the systematic review; however, selected epidemiologic and dosimetry studies were examined in an attempt to create a contextual discussion of secondary cancer risk from radiation therapy.

In comparison to external beam radiation, 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 alarming to patients and clinicians (particularly if a seed is passed through the urethra), 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).

In similar fashion, the dose distribution of proton beams indicates a higher dose to the femoral heads relative to other forms of external beam radiation, raising concerns about an increased risk of hip fracture (Nguyen, 2008); there are no published data, however, that document an increased risk. Due to the lack of data on the physical harms associated with both seed migration and radiation to the hip that would require treatment or intervention, these were not evaluated as part of our systematic review or economic modeling.

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

Data Synthesis
Data were collected on a variety of study characteristics, including treatment paradigms, duration of follow-up, proportion of patients with low-risk disease, and individual harms. An example of the data abstraction form can be found in Appendix B.

Meta-analyses were conducted to generate pooled estimates of effect for the therapies of interest. Due to variability in study population demographics, prevalence of low-risk disease, definition of outcomes, and other factors, random-effects models were employed using the DerSimonian-Laird method (DerSimonian, 1986) with inverse variance weighting; effect estimates were generated along with 95% confidence intervals. Heterogeneity was assessed via the tau-squared statistic, a quantification of the variance in effect size between studies, as well as observations regarding overlap in the estimates by treatment type and the width of the analysis-generated confidence interval.

Estimates were generated for all toxicity types and radiation modalities that were the focus of our study, provided that at least 3 studies were available for each toxicity and treatment.

It is important to note that, due to the expected paucity of data on treatment-related toxicity, particularly for newer modalities, meta-analyzed estimates were generated for informational purposes rather than the formation of firm conclusions on clinical superiority. These estimates also served as base case parameters in the economic model (see Section 8).

Given the high potential for publication or other evidence dissemination bias from the type of evidence reviewed (i.e., mostly single-center case series), estimates were subjected to multiple tests of such bias. Specifically, rank correlation-tau and Egger's regression were performed and assessed for significance; if either result was significant, the trim-and-fill method was employed to adjust the pooled estimate.

Meta-analyses were conducted using MIX software version 1.7 (Bax, 2006).

7.3 Results

Evidence Quality

Of the 166 studies identified via systematic review, a total of 4 RCT reports were included: one randomized comparison of brachytherapy with I^{125} vs. Pd^{103} isotopes (Wallner, 2002), and 3 RCTs in active surveillance, all from the Scandinavian Prostate Cancer Group (SPCG) (Bill-Axelson, 2005; Holmberg, 2002; Iversen, 2006). Nearly all of the remaining articles represented single- or multi-center case series. While some of these studies retrospectively compared the 3 radiation treatments of primary interest to other treatment options (e.g., 3D-CRT), only one study involved a direct comparison of the modalities of interest in this appraisal. This study was a retrospective comparison of toxicity with IMRT vs. I^{125} brachytherapy at Fox Chase Cancer Center (Eade, 2008).

The absence of randomized designs and/or prospective comparisons in these studies makes interpretation of these studies problematic. The selection bias of patients receiving alternative radiation treatments is not adequately explored in the literature, and comparisons across case series are made difficult by temporal differences in their conduct; many of the brachytherapy series, for example, were conducted in an entirely different era relative to PBT or IMRT. Post hoc comparisons of stage, PSA, and other clinical factors are often made to try to demonstrate that patients were clinically comparable across the years, and that any difference in outcomes can therefore be ascribed to the treatment modality. There are two specific problems with this approach. First, patients from earlier time periods will have had, on average, longer follow-up periods within which to demonstrate late toxicities, biasing the results in favor of the new treatment (Peschel, 2003). Second, there is evidence that Gleason scoring has changed over time, and subtle changes in scoring may have caused an "upshift" in Gleason scores that will make the outcomes of patients in more recent years appear superior relative to those with comparable Gleason scores from earlier periods (Chism, 2003).

Information on PBT is extremely limited in general, and particularly sparse with respect to measures of survival and acute toxicities of treatment. The number of identified studies

with any available measures for proton monotherapy was only 6; none of these reported any impact on disease-specific or overall survival, and only one reported on acute toxicity rates. In addition, available data for prostate cancer come primarily from the Loma Linda site only.

Clinical Effectiveness

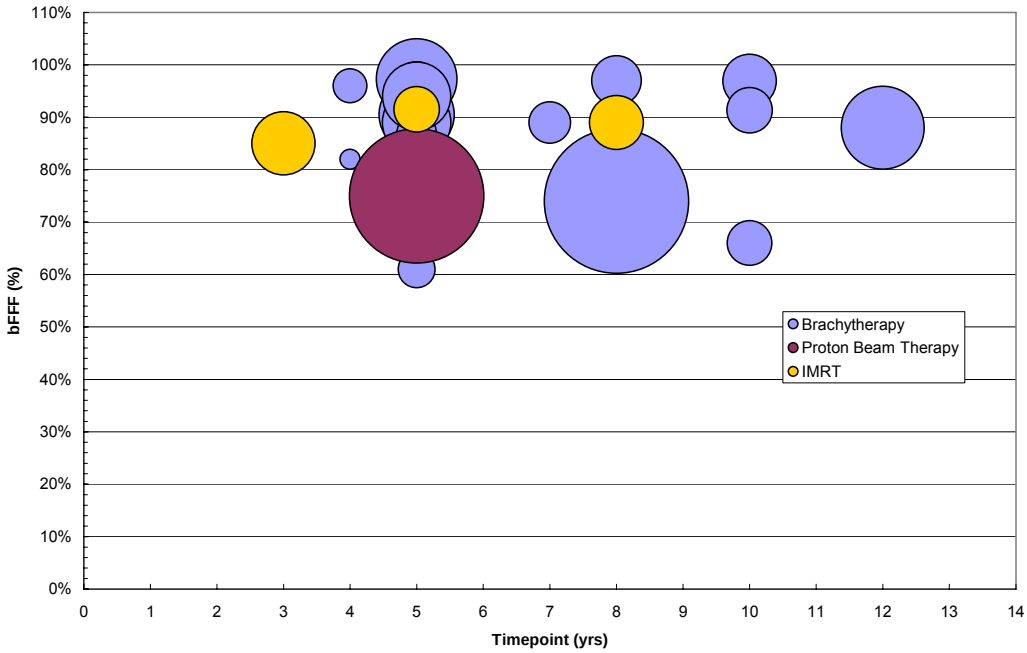
Overall Survival
A total of 31 studies were identified that evaluated the impact of treatment on overall survival – these were studies of either active surveillance (n=9) or brachytherapy (n=22). Overall survival was not measured in any included study of PBT or IMRT. Not surprisingly, survival rates varied substantially, as there was considerable variation in population demographics, proportion of patients with low-risk disease, duration of follow-up, and other factors (see Table 1, as well as all other tables for the systematic review, on page 93 following the References section of the report). At 5 years post-treatment initiation, the most commonly reported timepoint in these studies, survival ranged from 69-90% in the active surveillance studies, and from 77-97% in the brachytherapy reports.

As evidence of the effects of differences in study populations on this outcome, a retrospective analysis using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, found that 10-year survival differed significantly by age among men undergoing brachytherapy: 92.1% among men aged <60 years at time of treatment vs. 62.9% among those aged 60 years or more (Tward, 2006).

Disease-specific Survival
Similar to reported rates of overall survival, rates of disease-specific survival were only reported in studies of active surveillance (n=7) and brachytherapy (n=6). Rates were very similar across these studies, generally ranging between 93-100% at between 5 and 12 years of follow-up (Table 2). The only exception to this was reported in a study of the natural history of early prostate cancer in Sweden, in which a cohort of patients diagnosed during the period 1977-1984 underwent a watchful waiting strategy and were followed for an average of 21 years (Johannson, 2004). Disease-specific survival at 15 years was estimated to be 78.7% (95% CI: 70.8%, 86.7%); however, 60% of patients in this study were aged 70 years or older at time of diagnosis, the enrollment time period predated the advent of PSA testing for progression, and the definition of watchful waiting included a subset of very elderly patients who were not definitively treated as a matter of clinical policy.

Biochemical Freedom from Failure (FFF)
We found a total of 28 studies with median follow-up of 5 years or longer that reported freedom from biochemical failure (FFF). However, most of the accumulated evidence was for brachytherapy (24 of 28 studies); we identified only one PBT study and 3 IMRT studies (2 of which were from our earlier review) with sufficient follow-up. Studies of active surveillance were not included, as FFF was not measured as such in these studies. Results are presented by treatment, timepoint, and sample size (as approximated by bubble size) in Figure 2 on the following page.

Figure 2. Biochemical freedom from failure, by treatment and timepoint.



NOTE: Bubble size used to illustrate study sample size

As with the other measures of survival, significant overlap was observed in measures of FFF across treatments, and variability was observed in population demographics, definition of and prevalence of low-risk disease, and detail in reporting of adjuvant therapies received (Table 3).

Rates of FFF in the brachytherapy studies ranged from 61-99% at between 5 and 12 years of follow-up. These included a large, multi-institutional case series of approximately 2,700 patients who received I^{125} or Pd^{103} brachytherapy between 1988-1998 and were followed for a median of 63 months. Using the Phoenix definition, the 8-year rate of FFF among low-risk patients (n=1,444) was 74% (Zelefsky, 2007).

No discernible trends of FFF were observed when estimates were examined by year of study publication, biochemical failure definition, duration of follow-up, or proportion of patients with low-risk disease. For example, in one study featuring late follow-up (Ragde, 2000), 140 patients receiving permanent brachytherapy (64% of whom were low risk) were followed for a median of 10 years; the 10-year FFF rate (ASTRO consensus definition) was 66%. However, other studies with sufficient follow-up to report 10-12 year rates have estimates ranging from 88-91% (Potters, 2005; Stone, 2005). Rates of FFF in studies only of patients with low-risk disease or in an identified subset of low-risk patients ranged from 74-99%, while overall estimates from studies not separately reporting results among low-risk patients varied between 66-96%.

The 3 IMRT studies included estimated FFF at different timepoints (3, 5, and 8 years) and varied in duration of follow-up between a median of 5 and 7 years, but generated rates that were similar (85%, 91.5%, and 89% at 3, 5, and 8 years respectively) in subgroups that were identified as low or favorable risk (Vora, 2007; Zelefsky, 2001; Zelefsky, 2006).

The one PBT study with sufficient follow-up for analysis was a series of 1,255 patients treated between 1991-1997 at the Loma Linda proton center and followed for a median of 62 months (Slater, 2004). Approximately 60% of the sample was identified as low risk, although findings were not stratified by risk. The 5-year estimate for FFF was 75%. It is worth noting that treatment was a mix of proton boost therapy (in early years of the study) and proton monotherapy; unfortunately, the authors do not stratify their findings by the type of therapy received.

We did not explicitly include active surveillance in this comparison, as the notion of biochemical recurrence is based on change from a nadir value following definitive treatment. A number of active surveillance studies do report surrogate outcomes in terms of "treatment-free" or "clinical progression-free" survival; in the 7 studies identified, estimates ranged from 45%-73% at between 5 and 15 years of follow-up.

Harms

As noted earlier, there are no head-to-head trials prospectively comparing toxicity rates among patients receiving brachytherapy, PBT, and/or IMRT, and only one study that retrospectively compares toxicity rates for brachytherapy and IMRT (Eade, 2008). Much of the comparison of toxicity rates between these treatments must therefore be made indirectly across studies that differ in patient populations, study timeframe, dose received, and other characteristics as noted previously. In addition, institution-specific modifications to the RTOG toxicity scales are not uncommon; for example, the use of alpha blockers to treat obstructive urinary symptoms in the above-mentioned comparative case series of IMRT and brachytherapy (Eade, 2008) was coded as RTOG grade 1 rather than 2 on the standard scale; while this was done for both treatment groups, it makes comparisons of genitourinary toxicity rates to those in other studies problematic.

The evidence on acute and late gastrointestinal and genitourinary toxicity, as well as erectile dysfunction and radiation-induced cancer, is described below. Note that, while disease- and age-related side effects (e.g., obstructive urinary symptoms, erectile dysfunction) are known to occur during active surveillance, the discussion below is limited to radiation-induced toxicity. We do address these concerns in the design of the economic model, however (see Section 8).

As described earlier, pooled estimates of toxicity were generated using meta-analytic techniques. Not surprisingly, given the general paucity of data and variability in reported rates, these estimates were subject to a relatively high degree of heterogeneity, as evidenced by wide confidence intervals and nonzero tau-squared values (range: .007-.033).

Gastrointestinal Toxicity

Acute Toxicity

Rates of acute GI toxicity were reported in 9 brachytherapy studies, 4 IMRT studies, and one PBT study (Table 4). We note that, while the one published PBT study that examined acute GI morbidity did not technically meet our entry criteria (only 22% of patients were low risk), we nevertheless present the results for comparative purposes with the other treatments.

Among patients receiving brachytherapy, rates of RTOG ≥2 toxicity ranged from 0-10%; 3 of the 10 studies reported no observed cases of moderate-severe acute toxicity. Rates were more variable in the IMRT studies, ranging from 2-50%. It should be noted, however, that in the two studies with the highest reported rates, a "modified" RTOG scale was employed; however, the modification used was not clearly described (Jani, 2007; Vora, 2007). When all findings are considered together, rates of acute GI toxicity are nominally lower for brachytherapy in comparison to IMRT.

The one comparative study mentioned above compared patients receiving IMRT (n=216) in 2001-2004 and brachytherapy (n=158) during 1998-2004 at a single institution (Eade, 2008); IMRT recipients were treated to 74-78 Gy, and brachytherapy patients received I^{125} implants at a median dose to 90% of the prostate of 153.6 Gy. Treatment groups differed significantly by age, tumor stage, prostate size, baseline AUA score, and prior TURP. The rates of acute GI toxicity (within 3 months following treatment) did not significantly differ between IMRT and brachytherapy (2.3% vs. 1.9%, p=1.0). Note that, while FFF was calculated in this study, the median duration of follow-up (43 months) did not meet our minimum criteria; therefore, only comparisons of toxicity rates are reported.

The single PBT study was an examination of acute morbidity at the Hyogo Ion Beam center in Japan (Mayahara, 2007), in which 287 patients received PBT monotherapy to 74 GyE and were followed for acute GI and GU morbidity at 90 days. Acute GI morbidity was limited to NCI-CTC grade 0 or 1 proctitis; no patients were found to have experienced more severe GI toxicities at 90 days of follow-up. In addition, while not yet published, findings from a small series of 85 men at Massachusetts General Hospital and Loma Linda University with localized, T1-T2a disease and PSA <15 ng/mL who were treated with PBT monotherapy to an escalated dose of 82 GyE were recently presented (Zietman, 2008). Acute GI toxicity ≥2 was found in one patient (1.2%).

Late Toxicity

Radiation toxicities occurring more than 90 days after therapy (or whose effects last longer than 90 days) tend to generate more clinical concern than acute effects, which are frequently transient and self-limiting. Not surprisingly, we found a greater number of reports of late GI toxicity in our review: 18 brachytherapy, 7 IMRT, and 3 PBT studies (Table 5). Rates of late GI toxicity were similar in the brachytherapy and IMRT studies, ranging from 0-13% in the former and 2-24% in the latter; when all rates are considered, the overall rate was similar (4-6%) in both groups. It is important to note that, while most estimates of late

toxicity were calculated on an "actuarial" (i.e., Kaplan-Meier) basis, detail on the methods and/or timepoints employed was lacking in many articles.

While the sample of PBT studies was small, and findings were generated by multiple case series within the same institution (Loma Linda), reported rates of late GI toxicity were nominally higher with PBT (range: 3-26%). In particular, the results of two large case series (Slater, 1998; Slater, 1999) estimate the rate of late GI toxicity to range between 21-26%, although these studies employed a modified RTOG toxicity scale, in which the use of non-narcotic medications for GI pain is classified as grade 2 toxicity (Schultheiss, 1997). Results from the above-described Zietman presentation indicate that, at a median follow-up of 32 months, actuarial 2-year incidence of late GI toxicity ≥2 was 11.8%. A theoretical basis for higher GI toxicity rate with protons has been postulated, as most currently-available proton technology does not allow for as precise "sculpting" of the beam as with IMRT, and may therefore deliver a higher dose to the rectum (Nguyen, 2008).

The rate of late GI toxicity in the comparative IMRT-brachytherapy study described above (Eade, 2008) was significantly higher among patients receiving brachytherapy (7.9% vs. 2.4% for IMRT, p=.03), primarily due to proctitis. This difference did not remain significant, however, in multivariate analyses controlling for patient characteristics.

Genitourinary Toxicity

Acute Urinary Retention

A total of 9 brachytherapy studies separately report the rate of acute urinary retention, or the sudden and complete inability to urinate. Reported rates ranged along a fairly tight spectrum between 2% and 17% (with an overall rate of about 10%) (Table 7), and generally represented cases of urinary retention requiring urethral catheterization for between 4-10 weeks following onset.

Acute Toxicity

A total of 11 brachytherapy and 4 IMRT studies reported rates of RTOG-graded acute GU toxicity in our review (Table 6); as with GI toxicity, only the Mayahara study reported acute toxicities with PBT. Rates of acute RTOG ≥2 toxicity in the brachytherapy studies varied widely, ranging from 10-65%. It is important to note, however, that some of these studies separately report cases of acute urinary retention, a complication specific to brachytherapy (see summary below), while it is unclear in other studies whether urinary retention is being considered as part the overall GU analysis. A high degree of variability in estimates of acute GU toxicity also was observed in the IMRT studies (7-49%). Consideration of all presented findings (including acute urinary retention) yields an estimate that is moderately higher for brachytherapy as compared to IMRT (~40% vs. ~30% respectively). Finally, the rate of acute GU toxicity with PBT in the Mayahara study (Mayahara, 2007) was estimated to be 40.1%; in the Zietman presentation (Zietman, 2008), however, it was much lower (14.1%).

In the Eade comparative study (Eade, 2008), the rate of acute GU toxicity was significantly ($p<.01$) greater among patients in the brachytherapy group (26.6% vs. 6.9% for IMRT); no multivariate analysis was performed on acute toxicity measures, however.

Late Toxicity

Rates of late GU toxicity were reported in 12 brachytherapy studies, 5 IMRT studies, and 3 PBT studies (Table 8). As with other toxicities reported above, use of modified RTOG scales as well as variability in actuarial estimation and timepoints complicated our review across studies. The reported range of late RTOG ≥2 GU toxicity varied widely in the brachytherapy (0-40%) and IMRT (3-29%) studies, with similar estimates when considered on an overall basis (13-16%). The comparative data from Eade suggested a fivefold higher rate of late GU toxicity with brachytherapy (19.2% vs. 3.5% for IMRT, $p<.01$), a difference that remained significant after multivariate adjustment. Late GU toxicity ranged only between 5-6% in the PBT studies, however; again, this is likely a reflection of the uniformity of the data source (multiple case series, all from Loma Linda). In contrast to the presented rates for other treatments (in which rates of late GU toxicity were generally lower than rates of acute toxicity), results from the recently-presented Zietman study suggest a 29% rate of late GU toxicity at a dose of 82 GyE (Zietman, 2008).

Erectile Dysfunction

In addition to the issues raised above regarding important differences across studies, the few studies that evaluate the impact of these treatments on erectile dysfunction (ED) are further complicated by lack of data on baseline potency, use of different survey instruments to measure potency, and adjuvant receipt of androgen deprivation therapy (which may result in at least short-term ED in many patients) (Lubeck, 2001). In addition, unlike the other toxicities described above, the incidence of ED from any cause increases exponentially as a function of age (Bacon, 2003).

A total of 7 brachytherapy and 2 IMRT studies measured the rate of ED in patients deemed to be potent at baseline; ED was not measured in any included PBT study. In the brachytherapy studies, the rate of ED ranged from 14-43% (Table 9). Rates in the 2 IMRT studies were very consistent (48-49%); as with the PBT data described previously, this is likely a result of both studies representing patient series from the same institution (Zelefsky, 2002; Zelefsky, 2006).

Radiation-Induced Cancer

Because all of the treatments described above involve delivery of a substantial radiation dose, there is concern that such exposure could lead to development of secondary malignancy in the treated field (or even outside of it), particularly in patients with low-risk prostate cancer who have a life expectancy of 15 years or more (Bostrom, 2007). Unfortunately, none of the series described above involve sufficiently late follow-up or large enough sample size to detect secondary cancer incidence in patients receiving specific treatments.

The literature summarizing this issue is restricted to general epidemiologic study from large cancer registries and dose-extrapolation studies. For example, in a recent examination of SEER data in men undergoing radiation therapy only, brachytherapy only, a combination of radiation and brachytherapy, or no radiation or surgery, the overall estimated radiation-induced cancer rate (defined as new malignancies in the pelvic area) was 0.16% (Abdel-Wahab, 2008); a significant and persistent difference in absolute risk was observed only between the radiation-only and no treatment groups; in other comparisons, small differences in risk converged over time, suggesting the presence of selection bias in the earlier estimates. Findings from an earlier analysis of radiotherapy vs. surgery using the same data suggest a similarly low absolute rate (0.34%), and a relatively modest relative risk (1.34), even in patients surviving for ≥10 years (Brenner, 2000). Both articles also highlight the inclusion of many patients treated before the advent of precise, localized radiation techniques such as IMRT and PBT in the sample, suggesting that some portion of the excess risk may be attributable to the larger irradiation field from older techniques.

In response to this concern, a number of studies have estimated the potential cancer risk attributable to newer radiation techniques. Kry and colleagues obtained maximum dose equivalents to 7 sensitive organs from one conventional and 6 step-and-shoot IMRT techniques that varied by treatment plan (6, 10, 15, and 18 mV) and accelerator type (Siemens and Varian); these were combined with risk coefficients from the National Council of Radiation Protection and Measurements (NRCP) (Kry, 2005). Findings suggested that IMRT was associated with a 70-140% increased risk of fatal second malignancy vs. conventional radiation. Another study focused on combined organ-equivalent dose data with information on dose distributions from a small sample of patients receiving conformal radiation therapy, IMRT using 6- and 15-MV plans, and spot-scanned protons to estimate secondary cancer risk (Schneider, 2008); multiple risk functions (i.e., linear-exponential, plateau, and linear dose-response) were tested. Risk was estimated to increase by 15-25% for the IMRT plans relative to conformal therapy; cancer risk was estimated to *decrease* by 40-41% with protons. The difference in risk between studies is likely due in part to the Schneider study's assumption that secondary cancer incidence would be confined to organs located within the irradiation field (Schneider, 2006).

Finally, recently-presented findings appear to support Schneider's notion that PBT may reduce secondary cancer risk relative to conventional photon radiation. While not restricted to prostate cancer, results from a matched retrospective cohort study comparing patients treated with PBT at the Harvard Cyclotron between 1974-2001 and those receiving conventional radiation in the SEER database during the same time period (Chung, 2008) suggest a 50% reduction in the risk of any secondary cancer with PBT (6.4% vs. 12.8% for conventional radiation).

Based on the estimates described above as well as the considerable uncertainty that remains in estimating radiation-attributable cancer risk, the ICER ERG felt that 0.5% was an appropriately conservative estimate for lifetime risk for older-generation technology such as brachytherapy. Because the balance of escalated dose vs. more precise dose delivery and

its relation to cancer risk is also unknown, the group felt comfortable assuming that newer modalities such as PBT and IMRT would be associated with a risk of about 1%.

Economic Impact
Evidence is limited on the economic impact of these radiation modalities in prostate cancer. Several studies have compared the costs of multiple treatment alternatives. Findings from an analysis of multiple treated cohorts during the period 1995-2004 in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) indicated that external beam radiation was associated with the highest average costs within 6 months after treatment ($24,204), while watchful waiting was associated with the lowest ($2,586) (Wilson, 2006). Cumulative (i.e., across all available follow-up) costs were highest for ADT, followed by external beam radiation; the study does not appear to distinguish between conventional photon radiation, PBT, and IMRT, suggesting that this category may represent a mix of these treatments. Interestingly, while brachytherapy had initial costs that were threefold higher than watchful waiting, cumulative costs were similar ($32,000-$35,000).

A cost-effectiveness analysis of PBT, at hypothetical escalated dose of 91.8 GyE, vs. IMRT at 81 Gy concluded that PBT appeared to only slightly exceed common thresholds for reasonable value in both 70- and 60-year old men (Konski, 2007); it is important to note, however, that this study assumed the escalated PBT dose would result in a 10 percentage-point improvement in freedom from biochemical failure at 5 years with no increase in toxicity. This study builds on earlier work by the same group suggesting that IMRT at 81 Gy was cost-effective relative to 3D-CRT at 78 Gy based on lower rates of biochemical recurrence and salvage therapy as well as improved quality of life (Konski, 2006).

7.4 Summary

Overall Survival & Freedom from Biochemical Failure
The gold standard for evaluating the clinical effectiveness of any intervention for early-stage cancer is examination of its impact on patient survival. Unfortunately, the available published evidence did not allow us to draw firm conclusions on this outcome, for two principal reasons. First, no evidence has been presented to date on the effects of either PBT or IMRT on overall or disease-specific survival, limiting the direct or indirect comparisons that could be made. Second, the estimates available from the brachytherapy and active surveillance literature come from studies that differ substantially in design, duration of follow-up, population demographics, and other key factors, and there is significant overlap in the estimates that are available.

Given the lack of data on survival, examination of the duration of time that patients are free from biochemical evidence of recurrence (freedom from failure) has been widely, but not universally, accepted as a valid surrogate for clinical effectiveness. Because this measure can be calculated with relatively short follow-up periods, it is not surprisingly the most frequently-published effectiveness outcome for the radiation treatment modalities under study. However, given the use of different definitions of FFF over time, a certain minimum duration of follow-up (median of 5 years or more) was deemed by the ERG to be an

appropriate filter to employ to mitigate the effects of different definitions. When this filter is applied, the available literature on PBT and IMRT is again unfortunately scant.

It should be noted that a larger body of literature is available for PBT and IMRT when the follow-up restriction is removed. Rates of freedom from biochemical failure for all PBT (n=6) and IMRT (n=7) studies that report such outcomes are in a similar range to those displayed in Figure 2 (79%-95% and 69%-99% for PBT and IMRT respectively) at timepoints between 1.5-6 years. As time passes, follow-up lengthens, and evidence grows, comparison of FFF rates between radiation modalities for prostate cancer may be feasible; at the present time, however, the lack comparative data and variability of the estimates available now do not allow for the formation of any conclusions regarding this surrogate endpoint.

Harms

Without any demonstrable advantage in survival or FFF among any of the treatment alternatives under study,, the discussion must then turn to the effects of these treatments on moderate-to-severe toxicities. Of course, certain effects are comparable across all alternatives, as patients undergoing active surveillance may experience age- and/or disease-related incontinence and sexual effects, but others (i.e., gastrointestinal and other genitourinary toxicities) are specific to radiation treatment only.

As mentioned above, attempts to pool the observed rates of toxicity from the currently-available evidence are subject to a high degree of heterogeneity and, in many cases, an extremely broad range of observed results (see Table A on the following page). Overt comparisons and judgments across treatments are therefore extremely difficult to make. Nevertheless, when examining findings as presented in the table below, brachytherapy appears to have a nominally lower risk of acute GI symptoms relative to IMRT, and a similar rate of late GI as well as acute and late GU symptoms. Brachytherapy is subject to an acute urinary retention rate of about 10%. PBT, on the other hand, may be associated with a higher rate of late GI toxicities relative to IMRT, but a lower rate of late GU symptoms.

Similarly, the long-term risks of secondary malignancy cannot be adequately assessed with current data. Clearly, most clinicians in the field do not believe that these treatments pose significant additional risks of malignancy, but the theoretical concerns will remain important, particularly for patients with life expectancy > 15 years, until long-term clinical follow-up data are available.

Table A. Reported effects on acute and late radiation-induced toxicity, by treatment type.

Toxicity	Brachytherapy	PBT	IMRT
GI≥2*			
Acute	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%)
Late	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%)
GU≥2			
Acute	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%)
Late	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%)
Other			
Acute Urinary Retention	Studies: 9 High: 17.0% Low: 1.7% Pooled: 9.7% (1.7%,17.1%)	N/A	N/A
Erectile Dysfunction	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

NOTES: PBT: proton beam therapy; IMRT: intensity-modulated radiation therapy
*As measured on RTOG or NCI-CTC toxicity scales
†From random-effects meta-analysis (with 95% confidence intervals); for informational purposes only

8. Economic Model

8.1 Objective

The primary objective of the economic model was to assess the incremental cost-effectiveness of using brachytherapy or proton beam therapy (PBT) vs. IMRT to treat patients with low risk, clinically localized prostate cancer. A strategy of deferred treatment was also considered for patients with this form of prostate cancer. The review of evidence on clinical effectiveness found no persuasive evidence of a difference in survival or biochemical recurrence between treatment strategies, so the economic model focuses on the differential toxicity rates of the therapies. The focus on toxicity was in accordance with the priority questions identified by the ERG.

8.2 Methods

Overview of Model

Men diagnosed with low-risk, clinically localized prostate cancer face a choice among brachytherapy, IMRT, proton beam therapy, or active surveillance. Radical prostatectomy was not considered in this model due to its sharply different range of toxicities and costs that would have required a modeling effort beyond the time and resources available. Our primary model assigned men to brachytherapy, IMRT, or PBT immediately upon model entry.

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

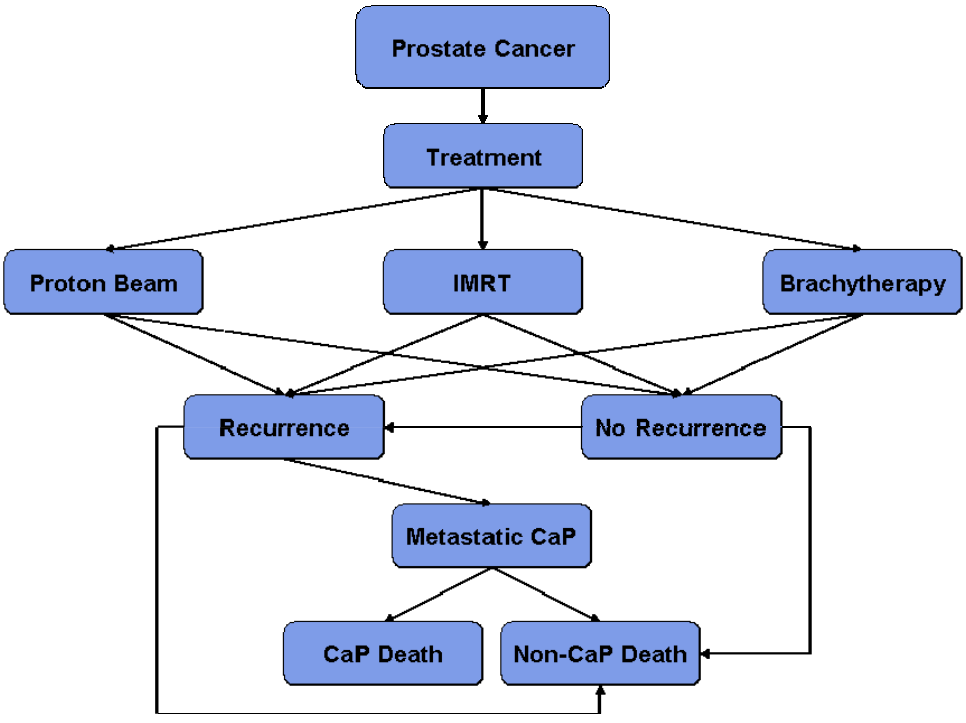


Figure 1 on the previous page traces the progression of men through the immediate treatment scenarios. Men enter the model and are immediately assigned to treatment with IMRT, proton beam therapy, or brachytherapy. Once treated, men may recur or not; those who recur may progress to metastatic disease and death due to prostate cancer or other causes. Men may die of non-prostate cancer causes from any health state.

We also created a second set of scenarios in which men were assigned either to immediate treatment or to deferred treatment. In this version of the model, men whose treatment is deferred are treated after 3 years and subsequently follow the same path as those undergoing treatment initially. Men on deferred treatment who progress to intermediate risk disease are treated with IMRT and 6 months of androgen deprivation therapy. Men may die of non-prostate cancer causes from any health state; patients who defer treatment are not at risk of recurrence (and therefore, metastatic disease), there is no risk of death due to prostate cancer during the 3-year period.

We refer to "deferred treatment" as opposed to active surveillance because we have not attempted to model the natural history of men on active surveillance. The natural history of men with low risk, clinically localized prostate cancer on active surveillance is not well understood. Few prospective studies have been completed to date, and the follow up of these studies has been relatively short (Klotz, 2008; Dall'Era, 2008; Patel, 2004; Zietman, 2001; Carter, 2007; McLaren, 1998; Koppie, 2000; Carter, 2003). Retrospective and non-randomized studies in carefully selected patients suggest that few men will develop metastatic disease while on active surveillance (Klotz, 2008; Dall'Era, 2008; Patel, 2004; Zeitman, 2001; Carter HB, 2007; McLaren 1998; Koppie, 2000; Carter CA, 2003). In practice, between 30% and 40% of men will progress to treatment within 5 years of diagnosis, either because of patient preference or due to progressive disease (Dall'Era, 2008). In addition, the data regarding progression of symptoms while on this therapy are sparse (Arredondo, 2004). A natural history model of low-risk clinically localized prostate cancer that could predict the underlying biology of this disease is not feasible within the structure of the model we created and would not inform our primary comparison of radiation modalities for active treatment of this disease. We therefore allowed men to defer treatment for 3 years; we modeled the underlying progression of obstructive urinary symptoms and erectile dysfunction over time based on data from studies in the general population, as discussed below. This approach allowed us to explore the effect of deferring treatment on quality of life and costs, but our conclusions on deferred vs. immediate active treatment must be considered tentative.

We modeled both the acute and late toxicities of each therapy and the symptoms associated with deferred treatment. For each treatment, the acute toxicities included urinary and gastrointestinal effects. Men who underwent brachytherapy were also at risk for acute urinary retention. Late toxicities modeled included urinary, gastrointestinal, and sexual effects (i.e., impotence). Men assigned to deferred treatment could develop obstructive urinary symptoms and progressive erectile dysfunction during the surveillance period.

Patients could experience all possible combinations of the presence or absence of late toxicities.

For each health state, utilities were assigned based upon a review of the literature. Our primary source was the work of Stewart et. al, who elicited preferences from men over 60 years of age using the standard gamble method, half of whom had been diagnosed with prostate cancer (Stewart, 2005). Utilities for urinary, gastrointestinal, and sexual toxicities of treatment either alone or in all possible combinations were included. In addition, utilities for health states in men with untreated disease, recurrent disease, and metastatic disease without symptoms were incorporated.

Major categories of costs included treatment costs, costs for management of toxicities, and patient time costs while in treatment. Base case treatment costs were estimated by using 2007 Medicare payments and patient time costs were based on 2007 US wages of age-matched men. The primary outcomes are costs and quality-adjusted life expectancy, both discounted at a 3% annual rate. Undiscounted life-expectancy is also reported.

Type of Analysis
This study is a cost-utility analysis (CUA). Incremental cost-effectiveness ratios (ICERS) are presented with costs in 2007 U.S. dollars, and effectiveness in quality-adjusted life-years (QALYs).

Perspective
We followed most recommendations of the Panel on Cost-Effectiveness in Health and Medicine (Gold, 1996) but, since we were not addressing societal questions of the full return on investment in various treatment strategies, we adopted a public payer perspective for the base case which includes capital expenditures in its reimbursement framework and took patient time in therapy into account. Note that 1st-copy costs for installation of a proton beam facility were excluded. Sensitivity analyses were performed in which we examined alternative perspectives. Specifically, we performed analyses that (a) excluded patient time costs from consideration; and (b) used a private payer perspective (i.e., no adjustment for capital expenditures, reimbursement estimates from private insurers).

Strategies
For the immediate-treatment scenarios, we evaluated 3 treatment strategies for patients with localized prostate carcinoma:

- IMRT (referent treatment)
- Proton beam therapy (PBT)
- Brachytherapy

Both PBT and IMRT were assumed to be administered in 39 fractions at a dose of 74 to 78 Gy/GyE. Brachytherapy was assumed to be administered as 100 sources of iodine^{125} (prescription dose of 145 Gy).

In our second set of analyses, we evaluated the strategies above as well as the following strategies:

- Deferred treatment followed by IMRT
- Deferred treatment followed by PBT
- Deferred treatment followed by brachytherapy
- Deferred treatment followed by IMRT and 6 months of androgen deprivation therapy (ADT) (for patients with intermediate risk of recurrence)

Target Population

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

Time Horizon

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

Prevalence of Toxicities and Symptoms

Patients were at risk of developing symptoms related to toxicities of treatment or to progressive disease. To estimate the likelihoods for combinations of toxicities, we assumed that the development of one side effect did not predict the development of a second side effect and allowed for varying degrees of overlap. It was assumed that all toxicities were treated.

Toxicities of Treatment

Only toxicities that met or exceeded grade 2 on the RTOG or CTC toxicity scales were considered, as these are the effects that typically require treatment (National Cancer Institute, 1999; Radiation Therapy Oncology Group, 2008). Estimated risks of toxicities from each treatment were based on the results of the systematic review. Acute toxicities were defined as toxicities occurring within 90 days of treatment; late toxicities occurred after 90 days and within two years of treatment and persisted for the duration of the patient's life.

Table A at the end of this section shows the base case probabilities of developing toxicities for each treatment modality. Because of the dearth of evidence examining acute toxicities in men undergoing proton beam therapy, acute toxicities of IMRT and proton beam therapy were assumed to be identical. In addition, based upon recommendations from our panel of experts, the rate of developing erectile dysfunction associated with treatment was estimated to be 20% greater than the probability of baseline erectile dysfunction associated with active surveillance. Men treated with IMRT in combination with androgen deprivation therapy were assumed to have erectile dysfunction for one year following treatment.

Secondary malignancy rates were estimated based on review of the literature and on the expert opinion of the ICER ERG (Abdel Wahab, 2008; Brenner, 2000; Kry, 2005; Schneider,

2008; Schneider, 2006; Chung, 2008; Bostrom, 2007). The risk of secondary malignancy was not modeled explicitly, but rather was included as a disutility men experienced beginning 3 years after treatment (see below).

Symptoms Associated with Deferred Treatment
Patients who defer treatment experience urinary and sexual symptoms associated with their age and their prostate cancer. Estimates of urinary symptoms were derived from the literature and were assumed to rise with time (Steineck, 2002). Due to the lack of literature describing the progression of these symptoms over time, the rate of progression was derived from studies of men without prostate cancer (Andersson, 2004). Similarly, the rate of erectile dysfunction associated with deferred treatment was derived from the literature, with a rate of progression of this symptom derived from studies of men without prostate cancer (Bacon, 2003).

Disease Outcomes

Men Immediately Treated with Brachytherapy, Proton Beam Therapy, or IMRT
Consistent with findings from our systematic review, it was assumed that brachytherapy, PBT, and IMRT are associated with similar disease-related outcomes. Therefore, rates of biochemical recurrence, subsequent development of metastatic disease, and death of prostate cancer in men with metastatic disease were the same after any immediate treatment of low-risk disease. Given the indolent natural history of low-risk prostate cancer, it was assumed that no man would die of prostate cancer within 3 years of diagnosis.

Men Receiving Deferred Treatment
In our deferred treatment scenarios, men on deferred treatment progress to treatment with radiation therapy after 3 years. We modeled both election of treatment as a result of patient preference and because of disease progression, as discussed below.

Men who elect treatment in this model received definitive therapy with brachytherapy, PBT, or IMRT. However, men who defer treatment are at risk of developing disease characteristics associated with higher risk prostate cancer (Gleason score $\geq$7, PSA $\geq$10 ng/mL, clinical stage >T2a, rapid PSA doubling time). As discussed above, for the purposes of this model, it was assumed that no man will develop metastatic disease while on deferred treatment.

As a result, we included a strategy in which men are treated for intermediate risk disease after deferred treatment, consisting of IMRT plus 6 months of ADT. Their subsequent risk of biochemical recurrence (and accordingly, metastatic disease and prostate cancer death) is higher than in men with low-risk disease (D'Amico, 1999).

Table A at the end of this section lists the probabilities associated with disease outcomes for men treated with radiation therapy and men on active surveillance. Age-specific risks of

death from causes other than prostate cancer were based on US life tables (US Centers for Disease Control, 2008).

Health-related Quality of Life
Health state utilities were based primarily on the work of Stewart et al (Stewart, 2005), who elicited preferences from men over 60 years of age, half of whom had been diagnosed with prostate cancer. These utilities were obtained using the standard gamble method and included utilities for urinary, gastrointestinal, and sexual toxicities of treatment alone or in any possible combination. Utilities for men without symptoms but with untreated, recurrent, and metastatic disease were also reported. In some cases, the utilities presented by Stewart et al were lower than those presented elsewhere in the literature (Sommers, 2007; Alibhai, 2003). Sensitivity analysis was therefore performed on all utilities over a broad range.

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

The risk of secondary malignancy due to radiation therapy was estimated by review of the literature and expert opinion and was assumed to be 1% for PBT or IMRT, and 0.5% for brachytherapy. These risks were not modeled explicitly, but rather an annual disutility was exacted on patients treated with radiation beginning 3 years after treatment.

Table A lists the base case utilities for each health state. Sensitivity analysis was conducted over all parameters over a broad range.

Treatment Costs
Annual costs for treatments are provided in Table B. In addition to the radiation modalities, treatment costs included those of drugs, supplies, tests, and follow-up visits. Base case direct medical costs were assumed to equal the national average Medicare payment rates in a hospital setting, and drug costs were derived from the 2007 Red Book (Thomson Reuters, 2007). Medicare payments were estimated using current procedural terminology (CPT) codes, 2007 ambulatory payment codes (APCs) and relative value units (RVUs) from the 2007 Hospital Outpatient Prospective Payment System (OPPS), with the professional component in the hospital outpatient setting from the Physician Fee Schedule. Costs of additional treatment components were estimated from the 2007 Lab Fees and Durable Medical Equipment Schedules from the Centers for Medicare & Medicaid Services (CMS) (CMS, 2007). Total RVUs included work-related and facility-related components, with both technical and professional components where applicable.

PBT was estimated to cost $48,493 based on delivery of 39 fractions, with CPT codes for ultrasound localization and APC codes for level I proton beam delivery and weekly

management. Brachytherapy was estimated to cost $10,024 based on CPT codes for isodose planning and simulation, needle placement and ultrasound guidance, radiation treatment aids, physics consultation, insertion of radioelements, 100 sources of I^{125}, 6-week follow-up exams, and 1 month of Flomax to treat typical swelling and irritation that can lead to acute urinary retention.

IMRT was estimated to cost $19,760 based on delivery of 39 fractions and CPT codes for office consultation, IMRT treatment planning and delivery, immobilization and beam modifying devices, dosimetry calculations, port films, ultrasound localization and X-ray guidance, and a special physics consultation and treatment procedure. CPT codes from a recent economic evaluation of IMRT (Konski, 2006) were updated to reflect APC coding rules in 2007. Androgen deprivation therapy (as a 6-month adjunct to IMRT for intermediate risk patients) was estimated to cost $7,801 based on 2 injections of Leuprolide, daily Casodex, and associated office visits and monitoring of liver function tests.

Active surveillance costs were estimated at $820 based on codes for quarterly PSA tests and an annual biopsy. Post-treatment surveillance costs were estimated at $474 based on quarterly PSA tests.

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

Costs of Management of Toxicities

Costs of managing treatment-related toxicities were derived from CPT codes, published studies, and structured interviews with clinicians. Costs in Table B are weighted averages representing typical case mixes (severity, treatment modality) described in more detail below. All related office visits are included.

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

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

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

Patient Time Costs
Patient time required to undergo treatment and seek care for management of toxicities was valued at $137 per day, assuming an 8-hour work day at the 2007 U.S. median wage for men aged 65 and older (US Bureau of Labor Statistics, 2007). Estimates of the number of hours required for each intervention were derived from literature sources (Yabroff, 2007), online patient guides, and interviews with clinicians.

Briefly, office visits were estimated to require 4 hours (including travel) and daily visits for radiation therapy were assumed to require 2 hours. Brachytherapy was estimated to require a day visit for assessment, an overnight stay for implantation of the seeds, 2 days of at-home recuperation, and a 6-week follow-up visit. Colonoscopies and cystoscopies were assumed to require 1 day. Estimates of total patient time per condition were weighted by case mix as above.

Sensitivity and Threshold Analyses
We conducted 3 analyses using alternative scenarios, perspectives and cohorts. The first included our deferred treatment scenarios as described above. The second evaluated the standard payer perspective, setting patient time costs to zero. Estimates of non-Medicare reimbursements for treatment costs were derived from private-pay sources or the literature, adjusted by the medical care component of the CPI to 2007 US dollars. The third sensitivity analysis populated both sets of scenarios with a cohort of 58-year-old men (i.e., 10 years younger than the median age at diagnosis) (SEER, 2008), with corresponding changes in all-cause mortality, baseline (pre-treatment) rates of toxicities, and wage rate.

One- and Multi-Way Sensitivity and Threshold Analyses
Table A shows the ranges of parameters examined in one-/multi-way sensitivity analyses. Treatment costs, utility weights, rates of biochemical recurrence and probabilities of toxicities were varied widely. Other analyses examined the relative survival benefits of treatments (assumed to be equivalent in the base case). Threshold values of key parameters were identified at which the choice of optimal therapy changed or at which a specific therapy would have an incremental cost-effectiveness ratio (ICER) at or below common levels known to many decision-makers ($50,000, $100,000, or $150,000/QALY). We also simulated selected combinations of parameters (e.g., values least or most favorable to a

specific treatment); selection of these multi-way sensitivity analyses was guided by results of the base case analysis.

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

standard deviation = [(2*base case value – 0.5*base case value) / 4]

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

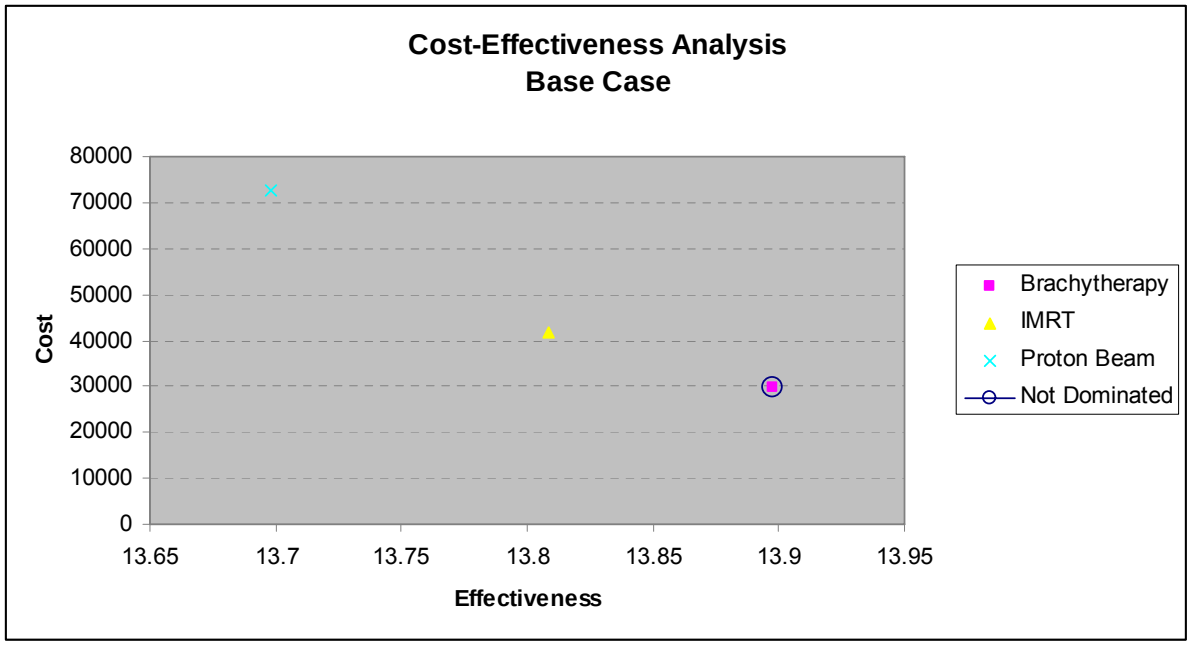
8.3 Results

Base Case Results
In our model, brachytherapy is cost-saving and more effective than IMRT, while PBT is more expensive and less effective than IMRT. Table 1 provides estimated costs and QALYs from each strategy, and Figure 2 on the following page provides this information in graphic form.

Table 1. Base Case Results for Immediate Treatment Strategies

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs
Brachytherapy	$29,575	-$12,016	13.898	0.0895
IMRT	$41,591	reference	13.808	reference
PBT	$72,789	$31,198	13.698	-0.1104

Figure 2. Base Case Results for Immediate Treatment Strategies



Brachytherapy is the least costly strategy and is more effective than IMRT, providing 13.90 QALYs at a cost of $29,575, for a savings relative to IMRT of approximately $12,000 and an additional 4.7 weeks of quality-adjusted life-expectancy. Proton beam therapy is both less effective and more costly than either brachytherapy or IMRT.

Alternative Perspectives and Cohort

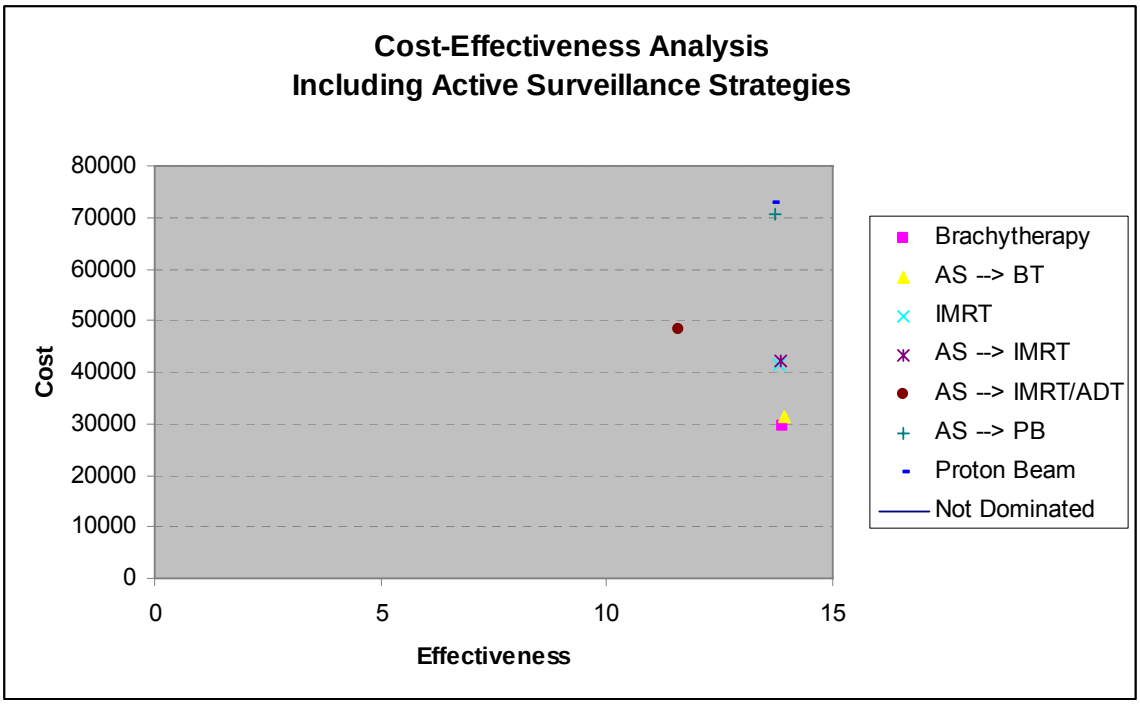
Model Including Deferred Treatment Strategies

This model included IMRT, brachytherapy, and PBT as well as active surveillance strategies. In these strategies, men progressed to treatment with IMRT, brachytherapy, proton beam therapy, or IMRT with 6 months of androgen deprivation therapy after 3 years on a deferred treatment strategy. The results are summarized in Table 2 and in graphic form in Figure 3 on the following page.

Table 2. Base Case Results for All Treatment Strategies

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Brachytherapy	$29,575	reference	13.89798	reference	reference
DT --> BT	$31,305	$1,730	13.95022	0.05224	$33,111
IMRT	$41,591	$12,016	13.80846	-0.08952	(Dominated)
DT --> IMRT	$42,118	$12,543	13.84151	-0.05647	(Dominated)
DT --> IMRT/ADT	$48,110	$18,535	11.57650	-2.32148	(Dominated)
DT --> PBT	$70,661	$41,086	13.72684	-0.17114	(Dominated)
PBT	$72,789	$43,214	13.69809	-0.19889	(Dominated)

Figure 3. Base Case Results for All Treatment Strategies



Brachytherapy again is less costly than all other strategies and is more effective than all strategies except for deferred treatment followed by brachytherapy. Deferred treatment followed by brachytherapy is more effective than initial brachytherapy, adding 2.8 weeks of quality-adjusted life-expectancy at an additional cost of $1,730, and an ICER of $33,111 relative to brachytherapy.

Cost-Utility Analysis of Men Aged 58 Years and Over

We also simulated a cohort of men aged 58 years. Younger men have lower baseline rates of erectile dysfunction and urinary symptoms; therefore the probability of these events was modified accordingly. In addition, the patient time costs of men below age 65 years are higher than those of men of retirement age; these costs were also modified accordingly. Results are displayed in Table 3.

Table 3. Model Results for 58-Year Old Men (Immediate Treatment)

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Brachytherapy	$34,885	Referent	17.7272	referent	referent
IMRT	$47,194	$12,309	17.6130	-0.11419	(Dominated)
PBT	$79,056	$44,171	17.4755	-0.25169	(Dominated)

In this younger cohort, brachytherapy remained the least costly and most effective strategy, at a cost of $34,885 and QALE of 17.73. Brachytherapy was associated with a savings of over $12,300 and a benefit in QALY of 5.9 weeks relative to IMRT. PBT was again substantially more costly and marginally less effective than brachytherapy or IMRT.

We also investigated the effect of younger age on cost and QALE in men who were treated either with radiation or followed on active surveillance. Results are displayed in Table 4.

Table 4. Model Results for 58-Year Old Men (All Treatment Strategies)

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Brachytherapy	$34,884		17.7272		
DT --> BT	$37,090	$2,205	17.9526	0.2254	$ 9,785
IMRT	$47,194	$12,309	17.6130	-0.1142	(Dominated)
DT --> IMRT	$48,421	$13,536	17.8026	0.0754	(Dominated)
DT --> IMRT/ADT	$53,369	$18,484	14.0671	-3.6601	(Dominated)
DT --> PBT	$78,396	$43,511	17.6516	-0.0756	(Dominated)
PBT	$79,056	$44,171	17.4755	-0.2517	(Dominated)

In this younger cohort, brachytherapy remained the least costly strategy. However, as in the base case, deferred treatment followed by BT was more effective than brachytherapy alone, yielding 11.8 weeks of QALE at an additional cost of approximately $2,200 for an ICER of $9,785 relative to brachytherapy. Deferred treatment followed by IMRT was also more effective than brachytherapy alone, though at an additional cost of $13,500 for an additional 3.8 weeks of quality-adjusted life expectancy. In this analysis, the benefit of deferring treatment for 3 years is greater than that in men aged 65 and older as a result of the higher incidence of baseline erectile dysfunction and obstructive urinary symptoms in older men.

Cost-Effectiveness Analysis Omitting Patient Time Costs

We conducted cost-effectiveness analysis comparing the three radiation strategies, omitting patient time costs in order to simulate a pure payer perspective. This analysis did not differ significantly from our base case analysis, in which such costs were included: brachytherapy remained the least expensive and most effective strategy, providing 4.7 additional weeks of QALE at a cost savings of over $10,000 compared to IMRT.

Table 5. Model results, excluding patient time costs (immediate treatment)

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Brachytherapy	$22,521	referent	13.8980	Referent	referent
IMRT	$32,698	$10,177	13.8085	-0.0895	(Dominated)
Proton Beam	$62,050	$39,529	13.6981	-0.1999	(Dominated)

Life Expectancy

For the purposes of this model, we assumed that IMRT, brachytherapy, and proton beam therapy were equally effective in the treatment of low-risk, clinically-localized prostate cancer. We estimated undiscounted life expectancy (LE) using our model and found no difference in life expectancy between the 3 treatment strategies in which men were treated immediately (undiscounted LE 16.5 years). Deferred treatment followed by IMRT, brachytherapy, or proton beam therapy was associated with a slightly longer life expectancy of 16.7 years. Deferred treatment followed by IMRT with ADT was associated

with a life expectancy of 15.9 years, as expected given the higher rate of recurrence with this health state, comprised of men with intermediate risk prostate cancer features.

Sensitivity Analysis
Given the dominance of brachytherapy over all strategies other than brachytherapy following deferred treatment in the base case, we sought to identify parameter values that would alter the ranking of strategies.

One-way Sensitivity Analysis
In this approach, a single parameter is varied while keeping all other parameters constant. The parameters subjected to one-way sensitivity analysis without affecting the ranking of strategies included:

1) Probability of acute and late toxicities associated with each treatment
2) Utilities associated with each toxicity
3) Disutility associated with risk of secondary malignancy
4) Cost of each treatment and of active surveillance
5) Cost of treatment of toxicities using private pay rankings

Brachytherapy remained the least costly strategy over all sensitivity analyses conducted. However, the effectiveness of brachytherapy relative to the other strategies was affected by assumptions related to utilities associated with late toxicities and the probability of those toxicities occurring at the extremes of the ranges analyzed. Threshold analysis was then performed, as in Table 6 below, to identify the probability or utility at which a strategy other than brachytherapy proved more effective.

Table 6. Sensitivity analysis of selected parameters that affected the relative effectiveness of treatment strategies for prostate cancer.

Parameter varied	Baseline Value	Range analyzed	Effectiveness Threshold	Most Effective Strategy	Incremental Effectiveness
Probability of					
ED after BT	0.1970	0.1065- 0.3400	0.23	IMRT	0.009
GU toxicity after BT	0.0540	0.0250-0.0820	0.073	IMRT	0.004
ED after IMRT	0.1970	0.1065-0.3400	0.16	IMRT	0.008
GU after IMRT	0.0435	0.0250-0.0870	0.25	IMRT	0.001
ED after PBT	0.1970	0.1065-0.3400	0.13	PBT	0.002
GI toxicity after PBT	0.0542	0.0050-0.1000	0.026	PBT	0.011
Utility of					
GI toxicity	0.7100	0.3500-1.000	0.91	PBT	0.010
GU toxicity	0.8300	0.4200-1.0000	0.55	PBT	0.007

(ED=Erectile Dysfunction; BT=Brachytherapy; PBT=Proton Beam Therapy; IMRT=Intensity-Modulated Radiation Therapy; Inc=Incontinence; GI=Gastrointestinal toxicity)

Varying the probability of toxicities associated with each strategy affected which strategy was most effective. These sensitivity analyses showed that effectiveness was highly sensitive to small changes in base case rates of toxicity. For example, under scenarios with small absolute increases in the rate of late GU or GI toxicities for brachytherapy, IMRT becomes the more effective treatment, although the magnitude of incremental effectiveness remains extremely small. Larger changes in the base case estimates of toxicity rates or utilities are required in order for PBT to emerge as the most effective strategy, and even under these circumstances the incremental effectiveness was very small. In addition, while not presented in the table, the effectiveness gained came at a high cost for all scenarios, generating incremental cost-effectiveness ratios that ranged from $1.2 - $18 million per QALY gained.

We also conducted sensitivity analyses on the model including deferred treatment strategies. Sensitivity analysis was performed on all parameters above as well as the probability of symptoms associated with deferred treatment. Brachytherapy remained the least costly strategy, and deferred treatment followed by brachytherapy the most effective. The ranking of the strategies did not change regardless of sensitivity analysis of costs over a wide range. The same parameters described above were associated with a shift in incremental effectiveness.

For example, the probability of erectile dysfunction associated with brachytherapy was varied over a range from 0.1065 to 0.34. At the lowest probability, brachytherapy was both most effective and least expensive. However, above a probability of 0.255, IMRT and deferred treatment followed by IMRT were more effective than brachytherapy.

Capital Costs and Treatment in Settings other than Hospitals

Medicare's Hospital Outpatient Prospective Payment System based on the Resource-Based Relative Value Scale was designed to represent all costs incurred in the provision of medical services (Latimer, 1992). Long-range capital costs of equipment and associated overhead required for provision of low-dose brachytherapy, IMRT, and proton beam therapy are included in the Practice Cost component of the Medicare payments used in the base case cost estimates. Installation of a proton beam facility at an estimated $150 million in capital costs (Anthony Zietman, MD, American Society for Therapeutic Radiology and Oncology meeting, Sept., 2008) is a special case of 1st-copy costs that should be amortized separately. However, estimation of amortized costs would require data on utilization and capacity rates and maintenance costs. Estimating nationally-representative costs would be difficult and somewhat arbitrary as there are only 5 currently-operating proton-beam facilities in the US, two of which are hospital-based and also used for research purposes. The results of our analysis suggest that including these (likely substantial) costs would further decrease the cost-effectiveness of proton beam therapy relative to brachytherapy or IMRT.

Note that although the overall conclusions of the analysis would be unchanged, outpatient treatment costs would be higher in free-standing treatment facilities (due to increased RVUs per procedure compared to the base case hospital setting). The cost of IMRT delivery in particular is substantially higher ($46,860 vs. $19,760 in the base case), while brachytherapy

($11,922 vs. $10,024 in the base case) and PBT ($50,780 vs. $48,493 in the base case) were not substantially higher.

Multi-Way Sensitivity Analysis

Favorable Assumptions for Proton Beam Therapy
We also conducted analyses to identify if conditions existed that would favor PBT in terms of cost-effectiveness. We used the lowest estimates of the incidence of side effects in our literature-derived range and the lowest cost found in our review ($21,615). The results of our analysis are shown below:

Table 7. Sensitivity analysis including most favorable assumptions for proton beam therapy.

Strategy	Cost	Incremental Cost	QALYs	Incremental QALYs	ICER ($/QALY)
Brachytherapy	29574.9	referent	13.898	referent	referent
PBT	37932.6	8357.63	14.3606	0.4626	18066.8
IMRT	41590.8	12015.9	13.8085	-0.5521	(Dominated)

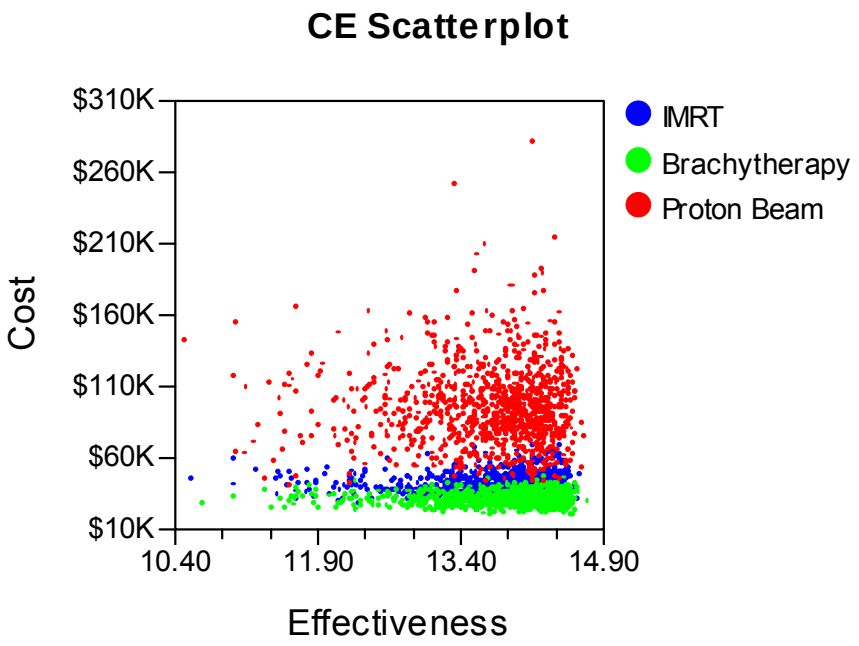
The magnitude of the effectiveness under these most favorable conditions is 0.46 QALYs, or 5.5 months of QALE, at an additional cost of $8358, for an ICER of $18,000/QALY.

Multi-way sensitivity analysis was also conducted to identify scenarios in which proton beam therapy would be associated with additional benefit over brachytherapy at an ICER of $75,000/QALY, a common decision-maker threshold for cost-effectiveness. The probabilities of side effects and costs of proton beam therapy were varied over the range of side effects identified by the systematic review. If, for example, the probability of toxicities is 50% of our basecase assumption, proton beam therapy provides additional benefit at an ICER of $75,000/QALY as compared to brachytherapy if the cost of treatment with PBT is also less than 95% of our basecase assumption (or $46,068). If the cost of PBT is lowered to the lowest estimate identified in our review ($21,615), the probability of toxicities after PBT must be below 62.5% of our basecase assumption in order for PBT to provide additional benefit as compared to brachytherapy at an ICER of $75,000 per QALY.

Second Order Multi-Way Sensitivity Analysis
A second-order analysis was performed to generate costs and effectiveness for brachytherapy, IMRT, and proton beam therapy while accounting for uncertainty around multiple inputs simultaneously. The model was re-analyzed 1,000 times after drawing from distributions around the following parameters (48 in total):

1) Probability of acute and late toxicities
2) Utilities associated with toxicities and health states
3) Costs of therapy and treatment of toxicities of each treatment strategy, including patient time costs

Figure 4. Cost-effectiveness Analysis: Second Order Multi-Way Sensitivity Analysis



As is evident in Figure 4, brachytherapy was the least expensive in most (89%) of the 1,000 samples and provided the most QALYs in 62% of the samples. Although not evident in the figure, brachytherapy provided the most QALYs *at the lowest cost* in 57% of the samples. IMRT provided the most QALYs at the lowest cost in 2% of the samples. In the remaining samples (41% of total), at least one incremental cost-effectiveness ratio could be calculated. In the 218 samples where IMRT provided more QALYs at a higher cost vs. brachytherapy, the ICER was $1.08million/QALY (range, $572 to $70 million/QALY). In the subset of these samples (n=113) where PBT provided an additional incremental benefit over IMRT, the ICER was $1.3million/QALY (range, $12,320 to >$15million/QALY). In a small number of samples (n=71), brachytherapy was more expensive than IMRT and provided more QALYs, with an ICER of $67,140/QALY (range, $785 to $698,070/QALY).

8.4 Summary and Discussion

In summary, the results from this decision analytic model suggest that brachytherapy is likely to be less expensive and result in slightly improved quality of life for a general population of patients compared to IMRT or proton beam therapy. This overall conclusion was robust to changes in individual input parameters and remained more than 56% likely when simultaneously considering uncertainty around inputs for probabilities, utilities, and costs.

In our analysis of IMRT, brachytherapy, and proton beam therapy in younger men, brachytherapy remained the least costly and most effective treatment strategy. Relative to

IMRT, brachytherapy offered a similar cost-savings (~$12,000) in men aged 58 years as in men aged 65 and a similar gain in QALE (0.090 in our base case and 0.11 in men aged 58 and older). The higher incremental effectiveness reflects the longevity of men aged 58 as compared to men aged 65. Omitting patient time costs to examine a payer perspective did not significantly affect the results of our model; the incremental cost of IMRT over brachytherapy was approximately $10,000, as opposed to $12,000 in our base case analysis.

In one-way sensitivity analysis, brachytherapy's position as the most effective strategy was affected by varying the utilities associated with side effects and the probability of experiencing side effects after treatment. Conditions that increased the probability of ED or GU toxicity after brachytherapy or that decreased the probability of ED or GU toxicity after IMRT led to an improvement in effectiveness of IMRT over brachytherapy. However, this improvement came at an ICER of between $58,332/QALY and $2.6 million/QALY. Likewise, analyses that decreased the probability of ED or gastrointestinal side effects of proton beam therapy caused proton beam to be more effective than brachytherapy, but at an ICER of >$400,000 in each case.

Threshold analysis of costs also confirmed the robust nature of brachytherapy's dominance. Only when the cost of brachytherapy was raised to $27,200 (nearly 300% of our base case estimate), did IMRT become the least expensive. We also sought to evaluate whether the dominance of brachytherapy could be affected by our assumption that the 3 treatment modalities were equally effective in treating prostate cancer. We found that only in the scenario in which brachytherapy was 33% less effective in preventing disease recurrence was IMRT more effective than brachytherapy.

We also conducted analyses to identify if conditions existed under which PBT would be favored: in the situation in which the lowest plausible incidence of side effects and the lowest recorded cost identified in our literature review were used, PBT was more expensive than brachytherapy but was also more effective, providing 5.5 months of QALE at an additional cost of $8,000, for an ICER of $18,000/QALY. Multiway sensitivity analysis was also conducted to identify scenarios at which proton beam therapy would be associated with additional effectiveness at an ICER of $75,000/QALY: side effects of proton beam therapy would have to be lowered to 50% of our baseline assumption at a cost that was less than 95% of our baseline cost assumption. If our lowest cost estimate for PBT was used, side effects would have to be 37% less frequent in order for the ICER to reach this threshold.

Second order multi-way sensitivity analysis of the three treatment strategies confirmed brachytherapy's position as the least costly and most effective strategy. Brachytherapy was the least expensive strategy in over 90% of the analyses conducted. Additionally, brachytherapy was the most effective therapy in over 60% of the analyses. Hence, this analysis that varied the probability of incurring side effects after treatment, the utility associated with side effects and with health states, and costs of initial therapy and treatment of side effects supported brachytherapy's dominance over other strategies in this model.

When deferred treatment strategies were included in the model, deferred treatment followed by brachytherapy proved more effective, yielding an incremental effectiveness of 2.8 weeks of quality-adjusted life-expectancy at an additional cost of $1,730 and an ICER of $33,111 relative to brachytherapy. Similarly, deferred treatment followed by IMRT or PBT was more effective than initial IMRT or PBT. Men on deferred treatment are at a risk of obstructive urinary symptoms that is higher than the risk of moderate-to-severe incontinence associated with treatment. However, despite this fact, the utility of deferring treatment for 3 years prior to therapy is higher than that of proceeding immediately to treatment, though at an increased cost. This model is not intended to evaluate the advisability of an active surveillance strategy; rather, it merely demonstrates that assuming that a strategy of active surveillance has no detrimental effect on disease outcomes, the practice of deferring treatment for 3 years is associated with a modest benefit in effectiveness at a modest cost as compared to immediate treatment.

Comparison of our findings to other economic evaluations in prostate cancer are problematic, as to the best of our knowledge, only one study has compared PBT and IMRT (Konski, 2007), and no study has compared these newer modalities to brachytherapy. The study conducted by Konski and colleagues assumed an effectiveness advantage at higher doses of PBT and no difference in toxicity; in contrast, the results of our systematic review correlated with no difference in effectiveness between PBT and IMRT, and nominal differences in toxicity that led to slightly better effectiveness for IMRT.

As noted in the systematic review section of this report, there is great uncertainty surrounding nominal observed difference in toxicity between the radiation modalities of interest. Because no firm conclusions could be drawn regarding differences in effectiveness, attention is naturally focused on the costs of these strategies. Cost estimates from the model, which estimate the cost of brachytherapy to be 30% and 60% lower than IMRT and PBT respectively, are directionally in line with other retrospective economic comparisons of brachytherapy to multiple forms of external beam radiation (Wilson, 2006).

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

Annual probabilities	Base Case Estimate	Ranges for Sensitivity Analysis	Source(s)
Disease-related Probabilities			
Disease-related probabilities: low-risk prostate cancer			
Biochemical recurrence after treatment	0.01 (year 1; lifetime risk 0.45)	50%-200%	ICER Review
Progression from biochemical recurrence			
to metastatic disease	0.05	NA	Horwitz, 2007
Death of prostate cancer after development			
of metastatic disease	0.22	NA	Alibhai, 2003
Disease-related probabilities: intermediate-risk prostate cancer			
Biochemical recurrence after treatment	0.01 (year 1; lifetime risk 0.60)	50%-200%	D'Amico, 2004
Progression from biochemical recurrence			
to metastatic disease	0.05	NA	
Toxicities			
Acute toxicities of treatment			
IMRT and proton beam therapy			ICER review
Urinary toxicities	0.3	0.15-0.6	
Gastrointestinal toxicities	0.18	0.09-0.36	
Brachytherapy			
Urinary toxicities	0.29	0.14-0.58	ICER review
Acute urinary retention	0.1	0.05-0.2	
Gastrointestinal toxicities	0.02	0.01-0.04	
Late toxicities of treatment			
IMRT			ICER review
Urinary toxicities	0.04	0.02-0.06	
Gastrointestinal toxicities	0.02	0.01-0.03	
Sexual toxicities	0.2	0.1-0.34	ICER review, expert opinion
Brachytherapy			ICER review
Urinary toxicities	0.05	0.025-0.082	
Gastrointestinal toxicities	0.01	0.008-0.02	
Sexual toxicities	0.2	0.1-0.34	ICER review, expert opinion

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

Proton beam therapy			ICER review
Urinary toxicities	0.02	0.15-0.2	
Gastrointestinal toxicities	0.05	0.025-0.082	
Sexual toxicities	0.2	0.1-0.34	ICER review, expert opinion
Deferred Treatment: Symptoms			
Erectile dysfunction	0.14	0-0.28	Steineck, 2002; Bacon, 2003
Urinary obstruction	0.13	0-0.26	Steineck, 2002 Andersson, 2004
Utilities			Stewart, 2005 Sommers, 2007 Alibhai, 2003
Asymptomatic men			
On deferred treatment: low risk disease	0.84	0.65-1	
Deferred treatment: intermediate risk disease	0.81	0.4-1	
Biochemical recurrence	0.67	0.34-1	
Metastatic disease	0.25	0.13-0.5	
Men with single side effect			
Urinary toxicities	0.83	0.42- 1	
Gastrointestinal toxicities	0.71	0.35-1	
Sexual toxicities	0.89	0.45-1	
Men with more than one side effect			
Urinary and gastrointestinal toxicities	0.7	SD 0.24	
Sexual and gastrointestinal toxicities	0.57	SD 0.26	
Urinary and sexual toxicities	0.79	SD 0.23	
Urinary, gastrointestinal, and sexual toxicities	0.45	SD 0.31	
Men on deferred treatment			
Utility of obstructive urinary symptoms	0.88	SD .13	
Disutility of secondary malignancy risk			
After brachytherapy	0.0025	0.0013 -0.005	ICER review, expert opinion
After IMRT or proton beam therapy	0.005	0.01-0.0025	

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

Category	Intervention	Annual Cost (2007$)	Details	Values in Sensitivity Analyses* (in 2007$)
Outpatient Surveillance	AS: quarterly PSA, annual biopsy	$820	4*{CPT 84152 + 99244} + {CPT 55700}	50%, 200%
	Post-treat: quarterly PSA	$474	4*{CPT 84152 + 99244}	50%, 200%
Outpatient Treatments	ADT	$7,801	CPT and Red Book	50%, 200%
	IMRT	$19,760	39 fractions, microcosted based on Konski, 2006	50%, 200% $43,019 (Konski, 2007)
	Brachy	$10,024	100 sources per patient	50%, 200% $11,573 (Wilson, 2006)
	PB	$48,493	39 fractions, APC 0667 (Level I), APC 0604, CPT 76950	50%, 200% $21,615 (PharMetrics/IMS, 2007)
	management ST GU SE except AUR	$204	see text	50%, 200%
	management AUR	$195	see text	50%, 200%
	management of ED	$469	see text	50%, 200%
	management of incontinence	$911	see text	50%, 200%
	management of ST GI SE	$1,108	see text	50%, 200%
	management of GI SE	$1,374	see text	50%, 200%
	management of urinary obstruction while on AS	$1,527	see text	50%, 200%
Patient Time Costs	*daily patient wage (men age 65+)*	*$137*	*BLS.gov, series ID LEU0252891700 if 5 work days/week*	$186.60/day for ages 55-64
	PSA test/provider visits	$274	2 days per year	50%, 200% $0
	TRUS-guided biopsy	$137	1 day per year	50%, 200% $0
	brachytherapy	$686	5 days	50%, 200% $412 for 3 recovery days $0
	IMRT	$1,544	11.25 days per year	50%, 200% $0
	IMRT + ADT	$1,681	12.25 days per year	50%, 200% $0
	PB	$1,715	12.50 days per year	50%, 200% $0

Table B. Costs for decision-analytic model of prostate cancer treatment (cont.).				
	management ST GU SE except AUR	$96	0.7 days	50%, 200% $0
	management AUR	$126	0.92 days	50%, 200% $0
	management of ED	$69	0.5 days	50%, 200% $0
	management of incontinence	$177	1.29 days	50%, 200% $0
	management of ST GI SE	$1,646	12 days	50%, 200% $0
	management of GI SE	$2,024	14.75 days	50%, 200% $0
	management of GU on AS	$480	3.5 days	50%, 200% $0

* See Methods text for description of gamma distributions used for multi-way sensitivity analyses of costs.

9. Recommendations for Future Research

As documented in this appraisal, there are notable areas of uncertainty regarding both the comparative effectiveness and comparative value of radiation treatment modalities in patients with clinically-localized, low-risk prostate cancer. Indeed, this appraisal found no evidence to suggest any differences in 2 of the 3 key measures of effectiveness (survival and biochemical recurrence), and the evidence base on which to make comparisons of the major harms of treatment is dubious at best.

Based on this level of uncertainty, and an assessment of which future research findings would have the greatest impact on judgments of the comparative clinical effectiveness and value of brachytherapy, IMRT, and proton beam therapy, ICER recommends that studies be pursued to address the following questions:

1) What is the relative impact of brachytherapy, IMRT, and proton beam therapy on key efficacy and safety outcomes?
In addition to the general paucity of available data on these radiation modalities, particularly the newer therapies, there is no published evidence involving direct comparisons of these three treatments. While it is unlikely that a large clinical trial could be implemented with sufficient follow-up duration to examine overall survival, a randomized trial at sites providing all three treatment options would be feasible to examine shorter-term outcomes, such as biochemical recurrence, acute and late treatment-related toxicity, quality of life, and other outcomes. Such a study could be conducted with a 3-5 year follow-up duration; a parallel long-term multi-site prospective cohort study could be combined with this randomized component to examine survival and other long-term outcomes, such as development of secondary malignancies.

A proposed study protocol developed by investigators associated with ASTRO, the Center for Medical Technology Policy, and several academic sites across the US, would accomplish these goals for IMRT and proton beam therapy. Plans do not currently call for incorporation of brachytherapy as one of the treatment modalities; were it to be included, however, it is likely that additional analysis would be required to examine the likelihood of a net health benefit with IMRT or PBT vs. brachytherapy that would be substantial enough to change policy, given the wide disparity in current reimbursement levels between these modalities.

2) What is the impact of individual acute and late treatment-related toxicity, as well as combinations thereof, on patient quality of life and utility?
While utility values for the toxicities of interest were obtained from the literature, there are currently no data available to ascertain the utility of health states characterized by acute vs. late toxicity, the duration of symptoms for each toxicity type, or even the incidence of individual toxicities vs. toxicity combinations. While some of these data might be obtained in the clinical trial described above, it is likely that a separate cohort study would need to be developed on these questions alone, particularly if quality of life would need to be examined at multiple time points.

3) What is the natural history of prostate cancer under active surveillance?
As noted in multiple sections of this appraisal, active surveillance is the one treatment option with currently-available as well as ongoing randomized trial data. However, much is still unknown about active surveillance, including the rate of progression of prostate cancer-related symptoms as well as the timing and rate of treatment initiation for clinical progression vs. patient preference. Examination of these questions could be accomplished using inception cohorts from existing registries (e.g., CaPSURE, SEER) along with the use of one or more survey instruments to collect data at multiple timepoints.

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

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SYSTEMATIC REVIEW TABLES

Table 1. Overall survival among patients treated for prostate cancer, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Years)	Overall Survival (%)
Brachytherapy	Tward*	2006	1233	56	100.0%	unk	unk	43 mo	10	92.1%
	Tward*	2006	5404	69	100.0%	unk	unk	46 mo	10	62.9%
	Lawton	2007	95	67	100.0%	145.0	unk	5.3 yr	5	96.7%
	Crook	2007	292	64	95.0%	155.0	0.0%	64 mo	5	93.8%
	Kao	2008	549	unk	92.0%	197.5	31.0%	6.7 yr	5	96.7%
	Stock	2006	1561	67	66.4%	187.0	55.3%	3.8 yr	10	74.0%
	Merrick	2006	329	65	100.0%	125-145	39.9%	5.5 yr	10	85.8%
	Potters	2005	1449	68	92.9%	136-144	27.6%	82 mo	12	81.0%
	Beyer	2005	2378	73	47.8%	125-145	19.5%	4.1 yr	10	43.0%
	Ragde	2000	229	70	64.5%	115-144	unk	122 mo	10	60.0%
	Blank	2000	102	69	75.5%	134.0	4.9%	60 mo	5	77.0%
	Zelefsky	2007	1444	unk	100.0%	120-160	0.0%	63 mo	8	81.0%
	Potters	2003	883	70	94.2%	136-144	32.0%	55 mo	10	95.0%
	Battermann	2004	351	69	58.0%	144.0	5.7%	48 mo	5	85.0%
	Vicini†	2002	207	73	100.0%	unk	unk	62 mo	5	83.0%
	Ellis	2003	80	68	75.0%	115-144	16.3%	36 mo	4	88.2%
	Battermann	2000	249	69	54.6%	unk	unk	32.8 mo	3	87.5%
	Potters	2004	733	69	100.0%	136-144	0.0%	51.4 mo	4	93.0%
	Crook	2008	484	63	96.0%	160.6	14.1%	41.3 mo	3	98.6%
	Stone	2007	325	67	73.0%	167.0	23.1%	7 yr	5	92.6%
	Kwok	2002	41	71	100.0%	145.0	0.0%	7 yr	5	90.0%
	Beyer	2003	1266	73	43.5%	120-145	9.9%	4.1 yr	5	79.0%
	Ellis	2007	150	67	73.3%	125-144	20.9%	47.2 mo	7	88.4%
Active Surveillance	Adolfsson	2007	119	68	100.0%	N/A	unk	24 yr	5	85.0%
	Bill-Axelson	2005	348	65	70.4%	N/A	unk	8.2 yr	5	90.2%
	Fall	2007	267	unk	62.0%	N/A	54.6%	8.5 yr	8.5	73.0%
	Johannson	2004	223	unk	100.0%	N/A	unk	21 yr	15	21.5%
	Hardie	2005	80	71	91.3%	N/A	0.0%	42 mo	4	92.5%
	Klotz	2006	299	unk	80.9%	N/A	unk	64 mo	8	85.0%
	Roemeling	2007	278	70	94.2%	N/A	unk	3.4 yr	5	89.0%
	Zietman	2001	198	71	90.0%	N/A	1.0%	3.4 yr	5	77.0%
	Iversen‡	2006	505	69	60.7%	N/A	0.0%	7.1 yr	5	68.6%
PBT	*None reported*									
IMRT	*None reported*									

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

*Results in Tward study stratified by age <60 and 60+ years at time of treatment

†Findings on overall survival reported at one of 6 study sites

‡Results from placebo arm of randomized control of bicalutamide

Table 2. Disease-specific survival among patients treated for prostate cancer, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Years)	Disease-specific Survival (%)
Brachytherapy	Tward*	2006	1233	56	100.0%	unk	unk	43 mo	10	99.5%
	Tward*	2006	5404	69	100.0%	unk	unk	46 mo	10	94.7%
	Potters	2005	1449	68	92.9%	136-144	27.6%	82 mo	12	93.0%
	Beyer	2005	2378	73	47.8%	125-145	19.5%	4.1 yr	10	97.0%
	Ragde	2000	229	70	64.5%	115-144	unk	122 mo	10	98.0%
	Potters	2003	883	70	94.3%	136-144	32.0%	55.5	4.5	99.0%
	Beyer	2003	1266	73	43.5%	120-145	9.9%	4.1 yr	5	98.0%
Active Surveillance	Adolfsson	2007	119	68	100.0%	N/A	unk	24 yr	5	98.0%
	Bill-Axelson	2005	348	65	70.4%	N/A	unk	8.2 yr	5	95.7%
	Fall	2007	267	unk	62.0%	N/A	54.6%	8.5 yr	8.5	87.3%
	Johannson	2004	223	unk	100.0%	N/A	unk	21 yr	15	78.7%
	Klotz	2006	299	unk	80.9%	N/A	unk	64 mo	8	99.3%
	Roemeling	2007	278	70	94.2%	N/A	unk	3.4 yr	5	100.0%
	Zietman	2001	198	71	90.0%	N/A	1.0%	3.4 yr	5	98.6%
PBT	*None reported*									
IMRT	*None reported*									

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

*Results in Tward study stratified by age <60 and 60+ years at time of treatment

Table 3. Biochemical freedom from failure among patients treated for prostate cancer, by type of treatment, among studies with ≥5 years of median follow-up.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Failure Definition	Median Follow-Up	Timepoint (Years)	Biochemical FFF (%)
Brachytherapy	Martin	2007	396	65	68.9%	145.0	65.4%	Houston	60.4 mo	5	90.5%
	Zelefsky	2007	319	unk	100.0%	173.0	34.9%	ASTRO	63 mo	5	96.0%
	Lawton	2007	95	67	100.0%	145.0	unk	Phoenix	5.3 yr	5	93.6%
	Papagikos	2007	84	67	63.6%	138.0	3.8%	Phoenix	65 mo	5	95.0%
	Shah (a)*	2006	28	unk	66.7%	120-145	33.3%	Houston	63 mo	4	82.0%
	Shah (b)*	2006	81	unk	87.1%	120-145	33.3%	Houston	63 mo	4	96.0%
	Zelefsky	2007	1444	unk	100.0%	120-160	0.0%	Phoenix	63 mo	8	74.0%
	Kao	2008	452	unk	100.0%	197.5	30.9%	Phoenix	6.7 yr	5	97.3%
	Ciezki	2006	162	68	88.9%	127.7	38.3%	Phoenix	73 mo	5	96.0%
	Merrick	2006	201	68	100.0%	111.0	42.5%	unk	5.4 yr	5	95.9%
	Moyad	2005	447	66	77.4%	116.0	0.0%	PSA>0.4 after nadir	5.3 yr	8	94.3%
	Potters	2005	481	68	100.0%	102.0	22.7%	Houston	82 mo	12	88.0%
	Stone	2005	146	67	100.0%	164.0	22.9%	ASTRO	6 yr	10	91.3%
	Ragde	2000	140	71	100.0%	160.0	0.0%	ASTRO	122 mo	10	66.0%
	Blank	2000	97	69	75.5%	144.0	4.9%	ASTRO	60 mo	5	61.0%
	Vicini†	2002	207	73	100.0%	unk	unk	ASTRO	62 mo	5	82.0%
	Vicini†	2002	330	69	100.0%	unk	unk	ASTRO	78 mo	5	89.0%
	Rossi	2006	108	68	79.6%	129.0	17.6%	ASTRO	61 mo	5	87.0%
	Stokes	2000	72	74	100.0%	160.0	0.0%	Modified ASTRO	68 mo	5	80.0%
	Kollmeier	2003	73	68	100.0%	115-160	60.0%	ASTRO	75 mo	8	88.0%
	Zelefsky	1997	325	61	100.0%	unk	unk	2 inc. after nadir	11 yr	5	94.0%
	McMullen	2004	63	67	81.0%	144.0	unk	ASTRO	62 mo	5	85.0%
	Ragde	1997	122	70	78.7%	160.0	0.0%	2 inc. or nadir≠0.5, 1.0	69.3 mo	7	89.0%
	Kwok	2002	41	71	100.0%	145-160	0.0%	ASTRO	7 yr	5	85.0%
	Ragde	2001	542	69	100.0%	160.0	0.0%	Modified ASTRO	71 mo	5	79.0%
	Stock	2002	116	unk	75.0%	<140	32.7%	ASTRO	66 mo	5	68.0%
PBT	Slater	2004	1255	69	53.0%	74	0.0%	ASTRO	62 mo	5	75.0%
IMRT	Vora	2007	106	unk	100.0%	75.6	30.3%	Phoenix	5 yr	5	91.5%
	Zelefsky	2001	279	69	100.0%	81-86.4	39.0%	ASTRO	5 yr	5	85.0%
	Zelefsky	2006	203	68	100.0%	81	53.0%	Houston	7 yr	8	89.0%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; FFF=freedom from failure; IMRT=intensity-modulated radiation therapy; ASTRO=American Society for Therapeutic Radiology and Oncology (consensus definition)
*Results in Shah study stratified by (a) pre-operative; and (b) intra-operative planning
†Results stratified by study site: a=Arizona; b=Seattle

Table 4. Acute gastrointestinal toxicity, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Months)	Estimate (%)
Brachytherapy	Martin	2007	396	65	68.9%	145.0	65.4%	60.4 mo	<6	0.9%
	Zelefsky	2007	319	unk	100.0%	173.0	34.9%	63 mo	<12	3.8%
	Lawton	2007	95	67	100.0%	145.0	unk	5.3 yr	≤6	9.6%
	Zelefsky	1999	145	64	100.0%	150.0	11.0%	24 mo	≤3	0.0%
	Zelefsky	2000	248	65	75.0%	150.0	12.5%	48 mo	≤12	5.7%
	Wallner (a)*	2002	55	unk	100.0%	144.0	unk	24 mo	≤3	0.0%
	Wallner (b)*	2002	55	unk	100.0%	125.0	unk	24 mo	≤3	0.0%
	Eade	2008	158	65	100.0%	153.6	0.0%	48 mo	<3	1.9%
	Ishiyama	2006	100	68	66.0%	166.1	31.0%	36 mo	<12	2.0%
	Lesperance	2008	50	63	80.0%	unk	16.0%	37.4 mo	≤3	6.0%
PBT	Mayahara	2007	287	unk	22.0%	74	71.1%	unk	≤3	0.0%
IMRT	Vora	2007	145	unk	73.1%	75.6	30.3%	48.1 mo	≤6	50.3%
	Eade	2008	216	68	93.5%	74-78	0.0%	43 mo	<3	2.3%
	Jani	2007	108	unk	50.0%	unk	53.0%	unk	<3	21.3%
	Zelefsky	2002	772	69	35.6%	81-86	55.2%	24 mo	<3	4.5%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

*Wallner study was RCT of (a) i-125; and (b) Pd-103 implants

Table 5. Late gastrointestinal toxicity, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Months)	Estimate (%)
Brachytherapy	Martin	2007	396	65	68.9%	145.0	65.4%	60.4 mo	≥6	0.0%
	Zelefsky	2007	319	unk	100.0%	173.0	34.9%	63 mo	≥12	8.7%
	Lawton	2007	95	67	100.0%	145.0	unk	5.3 yr	>6	5.3%
	Momma	2006	86	73	65.0%	70.0	unk	28.9 mo	36	12.8%
	Zelefsky	1999	145	64	100.0%	150.0	11.0%	24 mo	>3	11.0%
	Zelefsky	2000	248	65	75.0%	150.0	12.5%	48 mo	>12	9.0%
	Blasko	2000	403	unk	64.7%	115-145	unk	58 mo	unk	2.0%
	Blank	2000	102	69	75.4%	144-160	4.9%	60 mo	>6	3.9%
	Wallner (a)*	2002	55	unk	100.0%	144.0	unk	24 mo	>3	1.0%
	Wallner (b)*	2002	55	unk	100.0%	125.0	unk	24 mo	>3	1.0%
	Peschel (a)†	2004	87	67	52.0%	145.0	33.3%	55.1 mo	≥6	4.0%
	Peschel (b)†	2004	155	67	80.0%	125.0	32.9%	44 mo	≥6	2.0%
	Vargas	2005	161	67	96.0%	120.0	31.1%	3.3 yr	36	0.6%
	Ohashi	2007	227	68	69.2%	145.0	62.6%	22 mo	≥12	4.9%
	Gelblum	2000	685	67	47.6%	120-144	21.0%	48 mo	unk	6.9%
	Eade	2008	158	65	100.0%	153.6	0.0%	48 mo	≥3	7.9%
	Stone	1995	71	68	70.7%	unk	unk	2 yr	unk	4.2%
	Koutrovelis	2000	301	69	66.8%	120-160	unk	26 mo	≥12	1.0%
	Ishiyama	2006	100	68	66.0%	166.1	31.0%	36 mo	≥12	1.0%
	Lesperance	2008	50	63	80.0%	unk	16.0%	37.4 mo	>3	2.0%
PBT	Slater	1999	315	unk	69.0%	75	0.0%	43 mo	36	26.0%
	Slater	1998	643	unk	59.6%	74-75	unk	43 mo	36	21.0%
	Schulte	2000	870	unk	59.4%	74-75	unk	39 mo	>12	3.5%
IMRT	Vora	2007	145	unk	73.1%	75.6	30.3%	48.1 mo	>6	24.1%
	Eade	2008	216	68	93.5%	74-78	0.0%	43 mo	≥3	2.4%
	Fonteyne	2007	241	65	61.0%	74-80	68.0%	42 mo	>3	12.0%
	Kirichenko	2006	489	unk	unk	74-78	25.0%	29.9 mo	36	6.2%
	Jani	2007	108	unk	50.0%	unk	53.0%	unk	≥3	6.0%
	Zelefsky	2006	561	68	54.0%	81	53.0%	7 yr	96	1.6%
	Zelefsky	2002	772	69	35.6%	81-86	55.2%	24 mo	36	4.0%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

*Wallner study was RCT of (a) i-125; and (b) Pd-103 implants

†Peschel study was cohort analysis of (a) i-125; and (b) Pd-103 implants

Table 6. Acute genitourinary toxicity, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Months)	Estimate (%)
Brachytherapy	Martin	2007	396	65	68.9%	145.0	65.4%	60.4 mo	<6	42.5%
	Lawton	2007	95	67	100.0%	145.0	unk	5.3 yr	≤6	50.0%
	Block	2006	114	65	100.0%	145.0	58.5%	48.9 mo	≤12	9.7%
	Morita	2004	95	71	46.3%	114.5	unk	26.7 mo	unk	16.8%
	Zelefsky	2000	248	65	75.0%	150.0	12.5%	48 mo	≤12	57.3%
	Wallner (a)*	2002	55	unk	100.0%	144.0	unk	24 mo	≤3	27.0%
	Wallner (b)*	2002	55	unk	100.0%	125.0	unk	24 mo	≤3	26.0%
	Wallner	1996	92	67	55.0%	160.0	unk	3 yr	≤3	46.0%
	Kang	2001	139	65	65.0%	115-160	40.0%	11 mo	≤6	64.8%
	Gelblum	1999	600	69	70.3%	120-160	0.0%	37 mo	≤2	43.2%
	Eade	2008	158	65	100.0%	153.6	0.0%	48 mo	<3	26.6%
	Ishiyama	2006	100	68	66.0%	166.1	31.0%	36 mo	<12	14.0%
PBT	Mayahara	2007	287	unk	22.0%	74	71.1%	unk	≤3	40.1%
IMRT	Vora	2007	145	unk	73.1%	75.6	30.3%	48.1 mo	≤6	49.0%
	Eade	2008	216	68	93.5%	74-78	0.0%	43 mo	<3	6.9%
	Jani	2007	108	unk	50.0%	unk	53.0%	unk	<3	37.0%
	Zelefsky	2002	772	69	35.6%	81-86	55.2%	24 mo	<3	28.2%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

*Wallner study was RCT of (a) i-125; and (b) Pd-103 implants

Table 7. Acute urinary retention (brachytherapy studies only).

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy)	% ADT	Median Follow-Up	Estimate (%)
Brachytherapy	Kao	2008	549	unk	92.0%	197.5	31.0%	6.7 yr	12.4%
	Crook	2002	100	65	89.0%	145.0	26.0%	6 mo	17.0%
	Mabjeesh	2007	590	67	90.0%	160.0	42.0%	45.4 mo	3.4%
	Lee	2000	91	unk	75.8%	unk	11.0%	unk	12.1%
	Bottomley	2007	667	63	70.2%	145.0	51.9%	26 mo	14.5%
	Matzkin	2003	300	unk	93.0%	145-160	18.3%	30 mo	1.7%
	Eade	2008	158	65	100.0%	153.6	0.0%	48 mo	7.0%
	Stone	1995	71	68	70.7%	unk	unk	2 yr	5.6%
	Crook	2002	150	66	96.0%	151.0	31.0%	13 mo	13.3%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

Table 8. Late genitourinary toxicity, by type of treatment.

Therapy	Author	Year	Sample Size	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Timepoint (Months)	Estimate (%)
Brachytherapy	Martin	2007	396	65	68.9%	145.0	65.4%	60.4 mo	≥6	23.0%
	Lawton	2007	95	67	100.0%	145.0	unk	5.3 yr	>6	22.6%
	Momma	2006	86	73	65.0%	70.0	unk	28.9 mo	36	30.2%
	Block	2006	114	65	100.0%	145.0	58.5%	48.9 mo	>12	0.0%
	Zelefsky	1999	145	64	100.0%	150.0	11.0%	24 mo	>3	37.9%
	Zelefsky	2000	248	65	75.0%	150.0	12.5%	48 mo	>12	40.3%
	Blank	2000	102	69	75.4%	144-160	4.9%	60 mo	>6	5.9%
	Wallner	1996	92	67	55.0%	160.0	unk	3 yr	>12	14.0%
	Peschel (a)†	2004	87	67	52.0%	145.0	33.3%	55.1 mo	≥6	11.0%
	Peschel (b)†	2004	155	67	80.0%	125.0	32.9%	44 mo	≥6	2.0%
	Gelblum	2000	685	67	47.6%	120-144	21.0%	48 mo	unk	0.0%
	Eade	2008	158	65	100.0%	153.6	0.0%	48 mo	≥3	19.2%
	Ishiyama	2006	100	68	66.0%	166.1	31.0%	36 mo	≥12	4.0%
PBT	Slater	1999	315	unk	69.0%	75	0.0%	43 mo	36	5.0%
	Slater	1998	643	unk	59.6%	74-75	unk	43 mo	36	5.7%
	Schulte	2000	870	unk	59.4%	74-75	unk	39 mo	>12	5.4%
IMRT	Vora	2007	145	unk	73.1%	75.6	30.3%	48.1 mo	>6	27.7%
	Eade	2008	216	68	93.5%	74-78	0.0%	43 mo	≥3	3.3%
	Kirichenko	2006	489	unk	unk	74-78	25.0%	29.9 mo	36	8.3%
	Zelefsky	2006	561	68	54.0%	81	53.0%	7 yr	96	14.9%
	Zelefsky	2002	772	69	35.6%	81-86	55.2%	24 mo	36	14.9%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

†Peschel study was cohort analysis of (a) i-125; and (b) Pd-103 implants

Table 9. Erectile dysfunction, by type of treatment.

Therapy	Author	Year	Sample Size	Potent at Baseline	Median Age (yrs)	% Low Risk	Dose (Gy or GyE)	% ADT	Median Follow-Up	Estimate (%)
Brachytherapy	Martin	2007	396	291	65	68.9%	145.0	65.4%	60.4 mo	43.0%
	Block	2006	114	74	65	100.0%	145.0	58.5%	48.9 mo	29.7%
	Zelefsky	2000	248	221	65	75.0%	150.0	14.0%	48 mo	29.0%
	Wallner	1996	92	56	67	55.0%	160.0	unk	3 yr	14.3%
	Bottomley	2007	667	402	63	70.2%	145.0	51.9%	26 mo	28.4%
	Stone	2007	325	236	67	72.0%	167.0	23.1%	7 yr	38.6%
	Vargas	2005	161	109	67	96.2%	120.0	31.1%	3.3 yr	41.3%
PBT	*None reported*									
IMRT	Zelefsky	2006	561	403	68	54.0%	81	53.0%	7 yr	49.0%
	Zelefsky	2002	772	540	69	50.9%	81-86	55.2%	24 mo	48.0%

NOTES: Gy=Gray units; GyE=Gray equivalents; ADT=androgen deprivation therapy; PBT=proton beam therapy; IMRT=intensity-modulated radiation therapy

APPENDIX A:
LITERATURE SEARCH STRATEGY

The search strategy for MEDLINE was:

1. brachytherapy [MeSH Terms]
2. protons [MeSH Terms]
3. radiosurgery [MeSH Terms]
4. radiotherapy, high-energy [MeSH Terms]
5. 3 OR 4
6. 2 AND 5
7. radiotherapy, intensity-modulated [MeSH Terms]
8. limit [7] to [2007-2008]
9. prostatic neoplasms [MeSH Terms]
10. prostate cancer [keyword]
11. 9 OR 10
12. [1 AND 11] OR [6 AND 11] OR [8 AND 11]

The search strategy for EMBASE was:

1. brachytherapy
2. proton beam therapy
3. intensity-modulated radiation therapy
4. limit [3] to [2007-2008]
5. high energy radiation therapy
6. 1 OR 2 OR 4 OR 5
7. prostate cancer
8. prostatic neoplasms
9. prostatic carcinoma
10. 7 OR 8 OR 9
11. 6 AND 10

The Cochrane Library was searched using the terms "proton", "brachytherapy", "intensity-modulated radiation therapy", cross-indexed with the term "prostate"

APPENDIX B

DATA ABSTRACTION FORM

Reviewer Initials: Study ID#: First Author Last Name, First Initial:

Year of Publication: Journal:

☐ Key Article (Reason):

STUDY DESIGN

Type: N/A Data Collection Timing (M/D/YYYY), From: To:

Institution(s): ☐ Single ☐ Multiple

Geographic Location: ☐ US ☐ Canada ☐ Multinational ☐ Other (please specify):

Primary Outcome Measures:

Reason for Study Rejection: N/A If Other, please specify reason:

PATIENT CHARACTERISTICS (by Intervention Group)

	Group 1	**Group 2**	**Group 3**	**Overall**
Group Name (If Other, please specify):	N/A	N/A	N/A	N/A
Sample Size (N):				
Age: ☐ Mean ☐ Median				
Age Range (yrs)				
Low-Risk Population (n,%)				

Non-Standard Low-Risk
Definition? ☐ Specify:

Survival Calculation Method:
☐ K-M ☐ Actuarial ☐ Observed ☐ Unknown

TREATMENT CHARACTERISTICS

	Group 1	Group 2	Group 3
Treatment Delivery (PBT/Brachy only):	N/A	N/A	N/A
Actual Follow-Up Duration: ☐Mean ☐Median ☐Mos. ☐Yrs.			
Total Dosage (Gy or CGE, as applicable): ☐Mean ☐Median			
Dose per Fraction			
Number of Fractions			

CLINICAL BENEFITS

Disease-Free Survival (n,%) ☐Clin ☐Biochem			
Disease-Specific Survival (n,%)			
Overall Survival (n,%)			

HARMS

Classification System
☐RTOG ☐WHO
☐Not Graded

	Acute ≥2	Chronic ≥2	Acute ≥2	Chronic ≥2	Acute ≥2	Chronic ≥2
Events (n,%)						
GI						
☐Incont. ☐All GU						
Sexual						
Other☐						
Acute Threshold (if not 90 days):						
2° Malignancy (n,%)						