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Cost-utility analysis of primary treatments for clinically localised prostate cancer

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Primary treatments for clinically localized prostate cancer: a comprehensive lifetime cost-utility analysis

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Abstract

- To characterize the costs and outcomes associated with radical prostatectomy (open, laparoscopic, or robot-assisted) and radiation therapy (dose-escalated 3-dimensional conformal radiation, intensity-modulated radiation, brachytherapy, or combination), using a comprehensive, lifetime decision analytic model.
- A Markov model was constructed to follow hypothetical men with low-, intermediate-, and high-risk prostate cancer over their lifetimes following primary treatment; probabilities of outcomes were based on an exhaustive literature search yielding 232 unique publications.
- Patients could experience remission, recurrence, salvage treatment, metastasis, death from prostate cancer, and death from other causes.
- Utilities for each health state were determined, and disutilities were applied for complications and toxicities of treatment.
- Costs were determined from the U.S. payer perspective, with incorporation of patient costs in a sensitivity analysis.
- Differences in quality-adjusted life years across modalities were modest, ranging from 10.3 to 11.3 for low-risk patients, 9.6 to 10.5 for intermediate-risk patients, and 7.8 to 9.3 for high-risk patients.
- There were no statistically significant differences among surgical modalities, which tended to be more effective than radiation modalities, with the exception of combination external beam + brachytherapy for high-risk disease.
- Radiation modalities were consistently more expensive than surgical modalities; costs ranged from $19,901 (robot-assisted prostatectomy for low-risk disease) to $50,276 (combination radiation for high-risk disease).

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- These findings were robust to an extensive set of sensitivity analyses.
- Our analysis found small differences in outcomes and substantial differences in payer and patient costs across treatment alternatives.
- These findings may inform future policy discussions regarding strategies to improve efficiency of treatment selection for localized prostate cancer.

Keywords

prostate neoplasms; decision analysis; comparative effectiveness; surgery; radiation

Introduction

Clinical practice guidelines for localized prostate cancer endorse active surveillance, radical prostatectomy, external-beam radiation therapy (EBRT), and brachytherapy (BT) as alternatives which should be offered to men with clinically-localized disease [1, 2]. However, few high-quality comparative effectiveness studies exist to guide decisions among these alternatives. Recently, studies from large observational cohorts have identified differences in long-term oncologic outcomes across treatment modalities [3, 4], but randomized trials comparing treatments have not been completed. Absent consensus regarding optimal treatment, prostate cancer treatment is both preference- and supply-sensitive, and tremendous variation exists in primary management strategies [5]. Differences across treatments in definitions of recurrence [6], HRQOL domains affected [7], and other considerations complicate efforts to compare surgical with radiation-based treatments. Substantial differences in cost also have been documented [8].

Decision and cost-effectiveness analyses have examined specific topics such as the utility of active surveillance [9] and proton-beam therapy [10], but no such analysis has yet addressed the larger question of relative cost-effectiveness, at various strata of disease risk, of the most commonly employed treatments—surgery vs. radiation therapy. We aimed to determine costs and quality-adjusted outcomes between surgery and radiation, including the various modalities within these two broad categories.

Methods

A four-phase literature search was conducted. In Phase 1, the published literature on local prostate cancer treatments was searched via Pubmed and yielded 7008 candidate articles. Limiting to English articles reporting on human subjects since 2002 reduced the pool to 3583, and further restricting to clinical trials (randomized or not), meta-analyses, and other explicit comparative studies yielded 988 articles. Titles and abstracts were then manually reviewed and studies were selected that reported a sample size of at least 20 men with clinically localized disease and did not combine results from different treatment modalities (e.g., BT and BT+EBRT). Meta-analyses were excluded at this stage, as were papers which were superseded by subsequent reports from the same cohort. A final set of 374 articles was thus identified at the end of Phase 1 (eTable 1).

Phases 2 and 3 of the literature search were performed concurrently. Systematic application of inclusion/ exclusion criteria specific to each clinical parameter was conducted for all articles from Phase 1 and 60 selected hand-picked manuscripts. For 3DCRT, in order to reflect contemporary practice only papers reporting results from dose-escalated series were included in the base-case analysis [11, 12]. Twenty-two cost and utility information sources were hand-selected. When duplicates were eliminated at the end of Phase 3, a total of 202 publications remained. In Phase 4, thirty additional articles were used in manuscript

preparation, yielding a final set of 232 unique publications provided sources for all study data (eTable 2). The final list of references is presented in eTable 3. Probabilities for all outcomes were derived from the literature review and validated by the expert panel for the following outcomes.

A decision-analytic Markov model was developed to evaluate the clinical outcomes, quality-adjusted life years (QALYs), and lifetime costs for a hypothetical cohort of men with clinically localized (clinical stage ≤T3aN0M0) prostate cancer. Following each treatment analyzed (open radical prostatectomy [ORP], laparoscopic-assisted radical prostatectomy [LRP], robot-assisted radical prostatectomy [RARP], 3D conformal radiation therapy [3DCRT], intensity-modulated radiation therapy [IMRT], BT, and EBRT+BT), possible post-treatment health states for each one-month Markov cycle were remission, biochemical recurrence, metastasis, death from prostate cancer, and death from other causes. With each cycle, patients incurred costs, and those experiencing complications or adverse effects of treatment accrued disutilities. eFigure 1 presents the full decision tree. The analysis was stratified by clinical risk at diagnosis according to the 3-level classification endorsed by the clinical practice guideline[1]; however, because this schema is frequently modified or adapted in various studies in the published literature, strict adherence to the risk criteria was not required for study inclusion.

Treatments

Men undergoing ORP, LRP, or RARP were assigned probabilities of erectile dysfunction (ED) and incontinence at each Markov cycle (Table 1). 76% of surgery patients in biochemical recurrence were assumed to receive salvage treatment.[4] Low-, intermediate-, and high-risk patients were 75%, 50%, and 25% likely, respectively, to receive salvage radiation and the remainder of patients received androgen deprivation therapy (ADT) alone. Salvage radiation was assumed to IMRT given with 6 months of ADT [4, 13]. Salvage radiation yielded a possibility of returning to the remission state, whereas salvage ADT alone did not. Both salvage modalities entailed costs and potential adverse effects.

The decision tree for men undergoing 3DCRT, IMRT, BT, or EBRT+BT was similar, but incontinence was replaced with grade ≥2 gastrointestinal and/or genitourinary toxicity per RTOG criteria (Table 1) [14]. Patients receiving a treatment including EBRT were assumed not to receive concurrent ADT if they were low-risk, 50% likely to receive 6 months of treatment if they were intermediate-risk, and 75% likely to receive 18 months of treatment if they were high-risk [15]. 25% of brachytherapy patients were assumed to receive a short course of neoadjuvant ADT for prostate downsizing [15]. Radiation patients in recurrence likewise had the possibility of salvage and return to the remission state with surgery, or of secondary treatment with ADT alone. 44% of radiation patients were assumed to receive salvage therapy, 4% with prostatectomy and 96% with ADT only [4, 13].

Outcomes

Short-term outcomes (surgical complications and acute radiation toxicity) could only accrue once. ED, incontinence, and delayed radiation toxicity could persist for multiple cycles, with a probability of resolution. Perioperative mortality was assumed to be 0.2% for RRP and 0.1% for LRP and RARP [16]. Parameter estimates for other complications and adverse events are listed in Table 1.

Over 150 different definitions of biochemical recurrence have been proposed [6]. We included studies reporting the most common: for surgery patients, PSA ≥0.2 ng/ml with or without verification, PSA >0.3 ng/ml, or PSA ≥0.4 ng/ml, also allowing for secondary treatment to define failure. For radiation patients, we included studies reporting outcomes

using the ASTRO or Phoenix definitions, two PSA rises above the nadir to at least 1.0 ng/ml, or a PSA ≥0.4 ng/ml after nadir [6]. The parameter estimates used for biochemical recurrence derived from the literature are listed in Table 2. For both surgical and radiation, success rates for salvage local therapy in returning the patient to the remission state were 70%, 60%, and 50% for low-, intermediate-, and high-risk disease, respectively [17–21].

Biochemical recurrence is itself an important endpoint to the extent that it leads to additional testing and treatment, and causes anxiety. However, definitions of recurrence following surgery and radiation are not comparable—by the nature of their calculation, reflecting the different biological effects of radiation and surgery, the radiation definitions shift the survival curves substantially to the right, and thus may introduce bias in favour of radiation [22, 23]. Moreover, recurrence by no means uniformly predicts progression to metastasis and prostate cancer-specific mortality (CSM) [24].

Therefore, estimates for time to metastasis from recurrence for prostatectomy [24, 25] and radiation patients [26] were determined based on the literature to account for these variances. The median times used in the model for surgery and radiation patients were 10 and 6 years, respectively for low-risk patients, 8 and 4 years for intermediate-risk patients, and 6 and 2 years for high-risk patients. These times were further varied in sensitivity analyses. Time to CSM following first onset of metastasis was assumed to be 3.5 years for all patients [4]. Mortality from non-prostate cancer causes was based on National Center for Health Statistics actuarial data [27]. Use of ADT was assumed to increase risk of non-prostate cancer mortality by 1% annually. Radiation therapy was assumed to be associated with an annual probability of bladder or rectal cancer of 0.16% starting 5 years after treatment [28]; mortality from these secondary pelvic malignancies was assumed to be 12.9% annually [29].

Each of the health states was assigned a utility weight, determined from the literature and the Cost-Effectiveness Analysis Registry (www.cearegistry.org). These utilities, listed in Table 3, were validated by the expert panel and extensively tested in sensitivity analyses. Disutility values for short- and long-term complications of surgery or radiation were subtracted from the health state utilities. Use of ADT was also assigned a fixed disutility value. For each cycle, the final utility score was multiplied by one month and discounted by 3% annually. These quality-adjusted life-months were summed over the lifetime to determine the QALYs.

Costs

To determine costs, medical resource utilization (office visits, procedures, hospitalizations, medications, imaging and laboratory tests, etc.) was assigned to each treatment, and subsequently to each health state, reflecting complications of treatment where relevant. All services and products were described using coding taxonomies applicable to the Medicare fee-for-service payment system and validated by a certified coding expert. Costs associated with the resources were derived from the Fiscal Year 2009 National Medicare Fee Schedules and, in the case of medications, the 2009 Drug Topics Redbook. Costs were validated by clinical experts. In the case of BT+EBRT, two-thirds of the EBRT treatments was assumed to be IMRT and one-third was assumed to be 3DCRT. In either case, the cost of salvage EBRT was assumed to be two-thirds the cost of EBRT given as primary monotherapy. Costs were determined from the payer perspective; thus capital and maintenance costs for equipment were not separately included, as these are purported to be reflected in aggregate payment to providers.. However, time spent by patients in treatment and recovery was estimated by the expert panel, and indirect costs were assessed by associating these times with wage losses based on 2008 Bureau of Labor Statistics hourly rates weighted by employment status and age cohort size and inflated by 2%.

Statistical analyses

QALY outcomes and cost differences among treatments were assessed using ANOVA; adjustment for multiple comparisons across treatments was made using the Tukey test. The study employed a cost-utility analysis, in which the marginal cost for a treatment with improved outcomes is determined in terms of cost per QALY gained. In the event that one treatment was found to be dominant—that is, more efficacious and less costly—then cost-minimization analysis was utilized in lieu of cost-utility analysis.

Probabilistic Monte Carlo simulation was employed to follow hypothetical prostate cancer patients undergoing the treatment alternatives. For critical variables, parameter distributions were used rather than fixed point estimates. A normal distribution centred at age 65 was assumed for age at first treatment, triangular distributions for treatment costs, and beta distributions for utilities and biochemical failure probabilities. These are illustrated in eFigure 2. The probability distributions were sampled 250 times and 250 first-order simulations were performed with each parameter set.

An extensive set of one-way and multi-way sensitivity analyses were performed to determine the effects of varying the parameter estimates for various cost and outcome variables. Where modality- and risk-specific comparisons allowed, validation of the model-based predictions of prostate cancer death with outcomes published from two large cancer centres [30] were conducted. The value ranges included for sensitivity analyses are included in Tables 1–4. The analyses were performed using TreeAge Pro 2009 (TreeAge Software, Williamstown, MA).

Results

The results from the base case analysis are presented in Table 5. The likelihood of disease recurrence, progression, and mortality increased with increasing baseline disease risk, as did associated lifetime costs. QALYs for each of the modalities studied were relatively similar within a given risk stratum, and fell with increasing levels of risk. The differences across modalities were modest but statistically significant; among low-risk patients, 3DCRT was the least effective radiation modality (10.3 QALYs), and for intermediate- and high-risk patients EBRT+BT was the most effective radiation modality (10.1 and 9.1 QALYs, respectively, $p<0.001$). There were no significant differences among the surgical modalities in terms of QALYs (11.3, 10.3–10.4, and 9.2–9.3 QALYs, respectively, for low-, intermediate-, and high-risk), and, in all comparisons except EBRT+BT vs. ORP for high-risk patients, the surgical alternatives were statistically significantly more effective than the radiation modalities in terms of QALYs.

As a validation test of the oncologic outcomes resulting from our model, we compared rates of CSM derived from the model for IMRT and ORP patients to those published in a large, multi-centre academic series reported by Zelefsky et al.[4] Assuming a starting age of 60 for ORP patients and 69 for IMRT patients, as was reported in the Zelefsky et al series, CSM rates at 8 years in our model were 0.9%, 3.2%, and 8.8% for low-, intermediate-, and high-risk IMRT patients, respectively, and 0.3%, 2.0%, and 5.0% for ORP patients. These results matched closely to the published rates of 0%, 4.5%, and 9.5% for IMRT and 0%, 1.9%, and 3.8% for ORP (Figure 1) ([4].

As summarized in Table 5, given similar biochemical outcomes and payer and patient costs across the surgical modalities, lifetime costs were statistically and clinically similar within risk strata across the surgical modalities (approximately $20,000, $28,500, and $35,500, respectively, for low-, intermediate, and high-risk patients). Lifetime costs for radiation, conversely, varied substantially across modalities within risk strata. For low- and

intermediate-risk patients, BT was less expensive than the other modalities ($25,067 and $32,553 for low- and intermediate-risk); for high-risk patients, BT ($43,952) and 3DCRT ($42,397) were both less expensive than BT+EBRT ($50,376) or IMRT ($53,539, p<0.001). Regardless of risk, the radiation modalities consistently entailed higher costs than the surgical modalities in each risk stratum (p=0.008).

We conducted an extensive set of sensitivity analyses, varying the key parameters in the model to determine which exert the most influence on the model outcomes (Table 6). Many of these analyses had no or minimal impact on the model. For example, varying the probabilities, duration, disutility penalties, and costs for functional outcomes—including incontinence, erectile dysfunction, and late radiation toxicity—had no substantial impact on the relative costs and benefits for any of the treatment modalities. Incorporating patient time costs into the model increased total costs for all modalities by roughly $4,000 to $7,000, but again had little effect on the relative costs among modalities; the same was true of varying probabilities of salvage therapy use, secondary malignancy rates and costs, other costs such as those assigned to salvage therapy, and the discount rate (including a non-discounted analysis).

In the base case, the median age for all patients was 65; if surgical patients were assumed to be younger and radiation patients older, reflecting actual practice [31], the differences in costs and CSM between surgical and radiation patients were reduced, but corresponding differences in QALYs and overall survival increased. Varying the costs of salvage therapy and management of biochemical failure and metastasis, as well as the probability of mortality attributable to ADT use, impacted the model for intermediate- and high-risk patients only. While varying the estimates for these parameters resulted in changes of approximately 5%–15% from the base case results, the changes were not sufficiently different by treatment modality to alter conclusions related to the relative costs and benefits of the modalities. Including reported literature on non-dose-escalated 3DCRT resulted in substantially worse survival and QALY outcomes for this modality.

Varying the time from biochemical recurrence to metastasis had the greatest impact on clinical and economic outcomes. Varying the assumption of a 4-year differential in terms of time between recurrence and metastasis had a strong effect on CSM estimates for men at intermediate- and high-risk. The CSM rates cross at 0 years differential for intermediate-risk tumours and at 1 year for high-risk tumours [4] (Figure 1). These changes resulted in differences in QALYs and costs as well.

Discussion

Absent consensus defining optimal management of localized prostate cancer, patterns of management vary tremendously [15, 32, 33]. To date, clinical trials of intervention vs. conservative management have been completed [34, 35]. but those comparing surgery to radiation have no [36]. One such trial has now accrued, but results will not be available for several years [37]. In the interim, cost-effectiveness analyses may shed important light on the question of which modality or modalities offer the best value relative to cost. These analyses are notably scarce in prostate cancer, however; a recent systematic review identified only 22 studies published through 2007, compared to 86, for example, in breast cancer [38].

Our model found, in the context of the US reimbursement system, statistically significant but relatively modest differences among treatment modalities in terms of QALYs (Table 5). In general, surgery was preferred over radiation for lower-risk men, whereas combination EBRT+BT compared favourably for high-risk men. However, across the risk spectrum,

radiation was consistently more expensive. Some treatment strategies are thus considered dominated: IMRT for low- and intermediate-risk men, for example, is no more effective than surgery or brachytherapy, and is substantially more expensive. These findings generally were robust to a wide range of sensitivity analyses. The assumption which led to the greatest change in outcome in sensitivity analysis was the differential in time from recurrence to metastasis between surgical and radiation patients. These effects were most dramatic in intermediate and high risk patients and could lead to changes in conclusions related to the relative costs and benefits of radiation and surgery for prostate cancer. Future research related to correction for different recurrence definitions is warranted.

Our findings also are consistent with other recent studies based on carefully risk-adjusted retrospective studies of prospectively collected cohorts, which have found consistent evidence for improved distal clinical outcomes following surgery compared to EBRT. A study from the community-based CaPSURE registry found a roughly 2-fold increase in CSM among men treated with a variety of radiation therapy approaches compared to surgery [3]. The Zelefsky series likewise found a 3-fold difference in CSM comparing RRP patients to those receiving high-dose IMRT.[4] Of note, both studies found the greatest differences among men at relatively high levels of risk, and neither included men treated with BT. Another multicenter academic series, reached similar conclusions; this study did include BT patients, whose outcomes were better in some analyses than those of EBRT patients [39].

Our results are also generally consistent with other recently published studies on costs and outcomes of treatment. A recent Medicare study demonstrated statistically significant but relatively modest benefits for IMRT over conventional radiation therapy in some but not all quality of life domains [40]. Another Medicare study found that while the marginal costs of robotic compared open prostatectomy were relatively modest and declined over time through the middle part of the last decade, the costs of IMRT compared to conventional radiation were very high, and relatively stable [41]. Neither of these studies included brachytherapy patients. Our analysis found relatively minor differences between ORRP and RARP. Indeed, a recent meta-analysis found advantages for RARP in terms of short-term perioperative outcomes and margin rates, but no large study has yet demonstrated clear advantages for either approach in terms of longer-term oncologic or quality of life outcomes [42]. In the context of a lifetime decision analysis, any impact of short-term outcomes will generally be limited.

As described above, the absolute rates of risk-stratified CSM in our model corresponded fairly closely to those reported by Zelefsky et al [4]. However, the relative difference in mortality between radiation and surgery patients was lower in our model than in either the Zelefsky et al study or the CaPSURE study, suggesting that our analysis is relatively conservative in its estimation of the life-year and QALY differences between the surgical and radiation modalities. Our cost assumptions are generally consistent with those recently determined by another CaPSURE study [8].

Several limitations to this analysis should be considered. Primary ADT monotherapy for localized disease is commonly used in practice [15], but outcomes of this approach in the U.S. are sparsely reported, and it is not included as a standard option in the practice guideline [1]. Active surveillance, conversely, is rapidly gaining acceptance—including endorsement in practice guidelines [1]—as a viable option for men with low-risk disease [43, 44], and for carefully selected men with intermediate-risk disease [45]. A recent cost-effectiveness analysis in fact found slightly greater QALYs for surveillance compared to immediate treatment for low-risk disease [9]. This study did not include costs, but another did find cost savings for initial surveillance over treatment, depending in part on likelihood and timing of delayed treatment among patients initially surveilled [46]. We agree entirely

that for low-risk disease active surveillance may well be preferred to any of the modalities included in this analysis. However, neither long-term oncologic outcomes nor HRQOL outcomes have been reported to date. Therefore, to avoid adding additional layers of complexity, active surveillance was included in our model, but will certainly be the subject of future modelling efforts.

Multiple assumptions underlie the model. Utilities for various post-treatment health states, for example, are based on the best available in the literature, but these have not been extensively validated. Our literature review began in 2002; thus not all studies used to derive probabilities reflected the most recent improvements in treatment modalities. Other variables, such as increased mortality attributable to ADT or secondary malignancy, are the subject of significant ongoing controversy. Fortunately, none of these factors proved to be strong determinants of overall QALYs or costs, and were tested in sensitivity analyses with only minor impacts. It is important to stress that the economic analysis was performed from the U.S. payer perspective, with the additional incorporation in sensitivity analysis of indirect patient time costs. This approach does not account for hospital investments in capital equipment, disposables, and maintenance. These costs are theoretically reflected in insurance payments, but in fact in the U.S. government and private payers reimburse at substantially higher levels for IMRT, for example, compared with 3DCRT, but do not do so for RARP vs. ORP. Particularly germane to the question of the cost-effectiveness of RARP vs. ORP, then, is the fact that the costs associated with the robotic platform which are absorbed by hospitals are not reflected.

These assumptions clearly reflect the present situation in the U.S., and will vary substantially across other health care systems. Despite these caveats, we believe that through incorporation of both QALYs and costs, consistent risk-stratification, inclusion of multiple modalities within surgery and radiation, and use of a lifetime horizon, this analysis is the most comprehensive economic analysis yet undertaken for this disease. With the exception of the time to metastasis from recurrence, the findings are robust to sensitivity analyses, and may inform future policy discussions regarding strategies to improve efficiency and reduce variation in localized prostate cancer care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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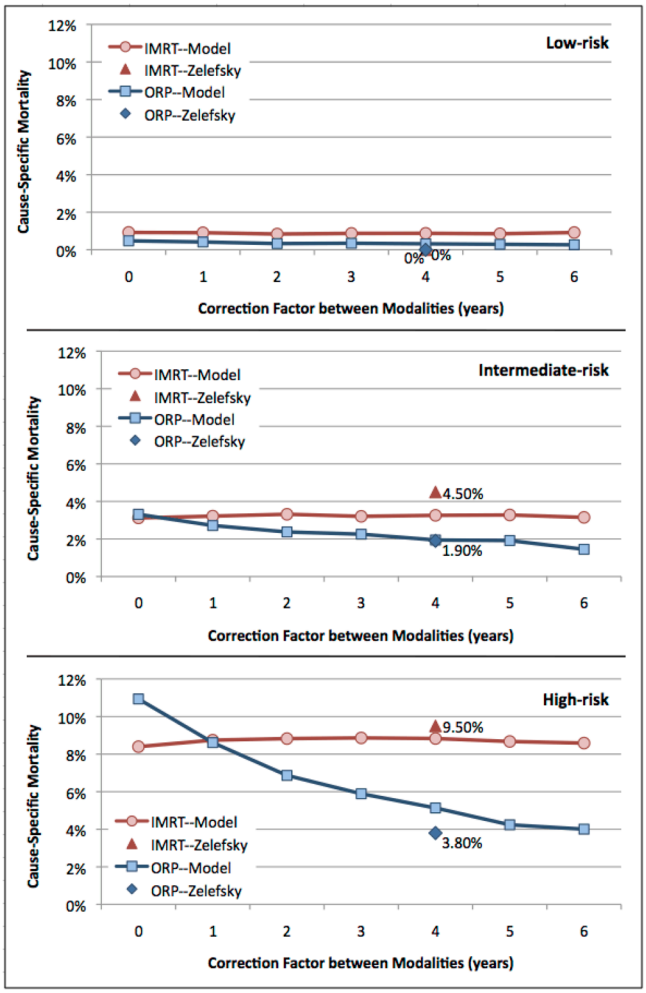

Figure 1.

Effects of varying assumptions of the interval between biochemical recurrence and metastasis. A correction factor of 4 years difference between surgical and radiation modalities was assumed in the base case, as detailed in the text, to reflect differences in definitions of biochemical recurrence across modalities. Model-derived cancer-specific mortality estimates are illustrated at this base case assumption, and with the difference varied from 0 to 6 years. The base case assumptions at 4 years are compared with the outcomes published for IMRT vs. ORP by Zelefsky et al.[4] IMRT = intensity-modulated radiation therapy; ORP = open radical prostatectomy.

Table 1

Surgical complications and radiation-related toxicities

Proportion of patients with surgical complications	**RARP**	**ORP**	**LRP**	
Hernia	0.6%	1.8%	2.1%	
Urinary retention	1.3%	1.5%	3.3%	
Rectal injury	0.5%	1.1%	1.4%	
Lymphocele	0.7%	1.8%	1.5%	
Sepsis	0.3%	0.3%	0.1%	
Ileus	0.6%	1.3%	1.3%	
Bleeding episode	1.2%	6.8%	0.8%	
Urinary tract infection	1.6%	1.8%	2.2%	
Deep vein thrombosis	0.5%	1.1%	0.5%	
Pulmonary embolism	0.5%	0.5%	0.5%	
Myocardial infarction	0.2%	0.2%	0.2%	
Anastomotic leakage	3.5%	5.2%	5.7%	
Urinary stricture/bladder neck contracture	1.0%	3.2%	1.2%	
Proportion of patients with acute radiation-related toxicity	**IMRT**	**BT**	**3DCRT**	**EBRT+BT**
GI Grade 2	15.6%	2.5%	33.9%	10.3%
GI Grade ≥ 3	0.1%	0.0%	2.2%	1.1%
GU Grade 2	29.8%	11.2%	35.2%	19.5%
GU Grade ≥ 3	2.3%	3.3%	3.7%	3.5%
Percentage of ED at baseline	**All Modalities**			
Age 50–59 years	26%			
Age 60–69 years	40%			
Age 70+	61%			
Proportion of patients with new-onset ED:	**RARP**	**ORP**	**LRP**	
3 months	66% (50%; 83%)	66% (50%; 83%)	75% (56%; 94%)	
6 months	50% (38%; 63%)	63% (47%; 79%)	58% (44%; 73%)	

Proportion of patients with surgical complications	**RARP**	**ORP**	**LRP**	
12 months	42% (32%; 53%)	58% (44%; 73%)	53% (40%; 66%)	
24 months	28% (21%; 35%)	49% (37%; 61%)	40% (30%; 50%)	
	IMRT	**BT**	**3DCRT**	**EBRT+BT**
12 months	27% (20%; 34%)	57% (43%; 71%)	27% (20%; 34%)	41% (31%; 51%)
24 months	42% (32%; 53%)	43% (32%; 54%)	42% (32%; 53%)	51% (38%; 64%)
Proportion of patients with UI at:	**RARP**	**ORP**	**LRP**	
3 months	19% (14%; 24%)	32% (24%; 40%)	41% (31%; 51%)	
6 months	9% (7%; 11%)	24% (18%; 30%)	28% (21%; 35%)	
12 months	9% (7%; 11%)	11% (8%; 14%)	10% (8%; 13%)	
Late radiation-related toxicity	**IMRT**	**BT**	**3DCRT**	**EBRT+BT**
GI Grade ≥2 (annual probability)	1.6% (0.8%; 2.4%)	1.3% (0.6%; 1.9%)	6.3% (3.1%; 9.4%)	2.3% (1.13%; 3.4%)
GU Grade 2 (annual probability)	2.3% (1.2%; 3.4%)	4.2% (2.1%; 6.4%)	4.1% (2.0%; 6.1%)	3.4% (1.7%; 5.10%)

For erectile dysfunction (ED), urinary incontinence (UI), and late radiation-related toxicity, the first number is the base-case estimate, and the numbers in parenthesis are the lower and upper bounds of the ranges tested in sensitivity analyses.

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Table 2

Estimates of biochemical recurrence

	RARP	ORP	LRP	IMRT	BT	3DCRT	EBRT+BT
Low-Risk Patients							
Weighted average annual probability of BCF	1.06% (Beta dist; SE=0.007)	1.06% (Beta dist; SE=0.007)	1.06% (Beta dist; SE=0.007)	1.11% (Beta dist; SE=0.003)	1.09% (Beta dist; SE=0.004)	2.17% (Beta dist; SE=0.003)	1.18% (Beta dist; SE=0.006)
10-year BCF-free survival	89.9%	89.9%	89.9%	89.4%	89.6%	80.3%	88.8%
Intermediate-Risk Patients							
Weighted average annual probability of BCF	3.74% (Beta dist; SE=0.020)	3.74% (Beta dist; SE=0.020)	3.74% (Beta dist; SE=0.020)	3.04% (Beta dist; SE=0.005)	3.67% (Beta dist; SE=0.010)	3.04% (Beta dist; SE=0.008)	2.11% (Beta dist; SE=0.009)
10-year BCF-free survival	68.3%	68.3%	68.3%	73.4%	68.8%	73.5%	80.8%
High-Risk Patients							
Weighted average annual probability of BCF	7.05% (Beta dist; SE=0.034)	7.05% (Beta dist; SE=0.034)	7.05% (Beta dist; SE=0.034)	5.63% (Beta dist; SE=0.012)	7.83% (Beta dist; SE=0.016)	6.50% (Beta dist; SE=0.005)	3.29% (Beta dist; SE=0.012)
10-year BCF-free survival	48.1%	48.1%	48.1%	56.0%	44.2%	51.1%	71.6%

Table 3

Utilities and disutilities for health states and side effects

Parameter	Utility Value (Duration)
Ongoing Health States	
Remission	0.92 [Beta dist; SE=0.020]
Biochemical failure without hormone therapy	0.84 [Beta dist; SE=0.031]
Biochemical failure with hormone therapy	0.78 [Beta dist; SE=0.031]
Metastasis	0.45 [Beta dist; SE=0.015]
Death (prostate cancer or all-cause)	0.00
Secondary malignancy	0.40
Late Toxicities (Disutilities; subtracted from current health state)	
Genitourinary (GU) grade 2+	0.15 (1 year) [0.075; 0.225]
Gastrointestinal (GI) grade 2+	0.20 (1 year) [0.1; 0.3]
Both GU and GI	0.25 (1 year) [0.175; 0.375]
Functional Outcomes (Disutilities; subtracted from current health state)	
Erectile dysfunction	0.10 [0.05; 0.15] (2 years) [5 years; lifetime]
Urinary incontinence	0.20 [0.1; 0.3] (2 years) [5 years; lifetime]
Both erectile dysfunction and urinary incontinence	0.25 [0.125; 0.375] (2 years) [5 years; lifetime]

For each health state, the base case utility or disutility value is presented along with the distribution or range tested in sensitivity analysis.

Table 4

Direct and indirect costs

Parameter	Direct Medical Cost	Patient Time Cost[1] (sensitivity analysis only)
Treatment Modalities and Expected Cost of First-Year Sequelae		
Treatment Modalities		
RARP	$8,547 ($6,410; $10,684)	$2,362
ORP	$8,056 ($6,042; $10,070)	$4,099
LRP	$8,547 ($6,410; $10,684)	$2,988
IMRT	$27,084 ($20,313; $33,855)	$1,529
BT	$14,106 ($10,580; $17,633)	$973
3DCRT	$13,013 ($9,827; $16,379)	$1,529
EBRT + BT	$29,142 ($21,857; $36,428)	$1,997
Short-term Surgical Complications		
RARP* v	$709	$152
ORP*	$1,518	$322
LRP*	$1,019	$229
Acute GI and GU Toxicities		
IMRT*	$340	$171
BT*	$230	$66
3DCRT*	$638	$375
EBRT + BT*	$383	$157
Late Toxicities		
Gastrointestinal (GI) Grade 2+*	$1,026 ($513; $2,052)	$897
Genitourinary (GU) Grade 2+*	$1,387 ($694; $2,774)	$188
Functional Outcomes		
Erectile Dysfunction		
Year 1 (accounts for patients who choose more invasive, one-time treatment)	$1,411 ($706; $2,822)	$167
Year 2+	$505 ($253; $1,010)	
Urinary Incontinence		
Year 1 (accounts for patients who choose more invasive, one-time treatment)	$946 ($473; $1,892)	$73
Year 2+	$565 ($283; $1,130)	
Ongoing Health States		
Remission (annual cost)		
Without androgen deprivation therapy (ADT)	$476 ($238; $952)	$139

Parameter	Direct Medical Cost	Patient Time Cost[1] (sensitivity analysis only)
With neoadjuvant ADT	$1,481	
With adjuvant ADT	$2,267	
Biochemical Recurrence (annual cost)		
Without salvage therapy	$1,775 ($888; $3,550)	
With salvage therapy		
ADT (one-time/annual)	$2,565 ($0/$5,130) / $1,791 ($896/$3,582)	$278
Radiation (one-time)	$27,586 ($20,690; $34,483)	
Surgery (one-time)	$8,547 ($6,410; $10,684)	
Metastasis		
Annual management	$2,212 ($1,106; $4,424)	
Work-up (one-time)	$960 ($480; $1,920)	$1,112
Treatment (one-time)	$15,773 ($7,887; $31,546)	
Secondary Malignancy	$11,465 ($5,733; $22,930)	$0
Prostate Cancer Death (last year of life)	$40,807 ($20,404; $81,614)	$0
All-cause Mortality	$0	$0

[*] Summation of the unit cost of treating each complication (from costing algorithm) multiplied by the probability that a patient will have the complication

Table 5

Mean discounted costs and QALYs and undiscounted survival

Treatment Modality	Costs (SD)	QALYs (SD)	Life years (SD)	% PC Death (SD)
Low Risk				
EBRT+BT	$40,588 ($3,573)	10.7[§] (0.5)	16.2 (0.7)	7.4 (3.9)
BT	$25,067[‡] ($2,213)	10.8[§] (0.5)	16.2 (0.7)	6.9 (2.8)
3DCRT	$27,626 ($1,830)	10.3 (0.4)	15.5 (0.6)	12.1 (2.4)
IMRT	$37,718 ($3,033)	10.8[§] (0.4)	16.2 (0.7)	6.9 (2.7)
ORP	$20,245[*] ($2,701)	11.3[†] (0.4)	16.7 (0.6)	2.6 (2.1)
RARP	$19,901[*] ($2,684)	11.3[†] (0.4)	16.7 (0.6)	2.7 (1.9)
LRP	$20,497[*] ($2,877)	11.3[†] (0.4)	16.7 (0.6)	2.7 (2.1)
Intermediate Risk				
EBRT+BT	$43,566 ($4,218)	10.1[#] (0.5)	15.3 (0.7)	13.3 (5.0)
BT	$32,553[‡] ($3,311)	9.6 (0.5)	14.6 (0.7)	21.2 (5.1)
3DCRT	$30,838 ($2,699)	9.7 (0.5)	14.8 (0.7)	18.5 (4.4)
IMRT	$44,639 ($3,096)	9.6 (0.4)	14.7 (0.6)	19.0 (3.7)
ORP	$28,589[*] ($5,457)	10.4[†] (0.6)	15.6 (0.9)	13.0 (6.0)
RARP	$28,017[*] ($5,453)	10.5[†] (0.6)	15.6 (0.8)	12.8 (5.9)
LRP	$29,041[*] ($5,581)	10.4[†] (0.6)	15.6 (0.8)	13.4 (6.3)
High Risk				
EBRT+BT	$50,276 ($4,667)	9.1[#] (0.6)	14.1 (0.9)	23.6 (7.1)
BT	$43,952[∫] ($3,477)	7.8 (0.5)	12.1 (0.8)	43.0 (5.9)
3DCRT	$42,397[∫] ($2,348)	7.9 (0.4)	12.5 (0.6)	38.2 (3.6)
IMRT	$53,539 ($4,013)	8.2 (0.6)	12.9 (0.8)	34.2 (6.0)
ORP	$36,279[*] ($5,902)	9.2 (0.8)	13.9 (1.1)	27.9 (8.1)
RARP	$35,014[*] ($5,895)	9.3[†] (0.8)	14.1 (1.1)	26.8 (8.2)
LRP	$35,118[*] ($6,085)	9.3[†] (0.7)	14.2 (1.0)	26.4 (8.2)

No differences were found between surgical modalities for cost or QALYs.

[*] Significantly less expensive than each radiation modality ($p < 0.001$).

[†] Significantly more effective than each radiation modality ($p = 0.008$).

[‡] Significantly less expensive than other radiation modalities ($p < 0.001$).

[§] Significantly more effective than 3D-CRT ($p < 0.001$).

[#] Significantly more effective than other radiation modalities ($p < 0.001$).

[∫] Significantly less expensive than EBRT+BT and IMRT ($p < 0.001$).

Table 6

Sensitivity Analyses with Base Case Default Estimates and Analysis Range

Analysis Description	Radiation			Surgery			Comments
	Base Case	Upper	Lower	Base Case	Upper	Lower	
COSTS							
With patient time costs	Without	With	NA	Without	With	NA	
Annual ongoing management costs for remission	$476	$952	$238	$476	$952	$238	50%, 200% of base case estimate
Prostate cancer death costs	$40,807	$81,614	$20,404	$40,807	$81,614	$20,404	50%, 200% of base case estimate
Metastasis treatment costs	$960 / $15,773	$1,920 / $31,546	$480 / $7,887	$960 / $15,773	$1,920 / $31,546	$480 / $7,887	Work-up cost / treatment cost; 50%, 200% of base case estimate
Annual ongoing management costs for biochemical failure	$1,775	$3,550	$888	$1,775	$3,550	$888	50%, 200% of base case estimate
Annual ongoing management costs for metastasis	$2,212	$4,424	$1,106	$2,212	$4,424	$1,106	50%, 200% of base case estimate
Salvage therapy costs	Comment 1	Comment 2	Comment 3	Comment 1	Comment 2	Comment 3	**1** 1-time and annual ADT costs ($2,565/$1,791), radiation ($27,586), or surgery ($8,547) **2** 1-time and annual ADT costs ($5,130/$3,582), radiation ($34,483), or surgery ($10,684) **3** 1-time and annual ADT costs ($0/$896), radiation ($20,690), or surgery ($6,410)
Functional outcomes costs	Comment 1	Comment 2	Comment 3	Comment 1	Comment 2	Comment 3	**1** Annual Year 1 / Year 2+ ED costs ($1,411/$505); annual Year 1 / Year 2+ UI costs ($946/$565) **2** Annual Year 1 / Year 2+ ED costs ($2,822/$1,010); annual Year 1 / Year 2+ UI costs ($1,892/$1,130) **3** Annual Year 1 / Year 2+ ED costs ($706/$253); annual Year

Analysis Description	Radiation			Surgery			Comments
	Base Case	Upper	Lower	Base Case	Upper	Lower	
							1 / Year 2+ UI costs ($473/$283)
Late toxicity costs	Comment 1	Comment 2	Comment 3	NA	NA	NA	**1** Annual Grade 2+ GI cost ($1,026); annual Grade 2+ GU costs ($1,387) **2** Annual Grade 2+ GI cost ($2,052); annual Grade 2+ GU costs ($2,774) **3** Annual Grade 2+ GI cost ($513); annual Grade 2+ GU costs ($694)
Secondary malignancy costs	$11,465	$22,930	$5,733	$11,465	$22,930	$5,733	50%, 200% of base case estimate
PROBABILITIES							
Discount rate	3%	5%	0%	3%	5%	0%	
Escalated and non-dose-escalated 3D-CRT annual biochemical failure rate data							Data modified for 3D-CRT only, not other radiation modalities
--Low Risk	0.0217	0.0341	NA	NA	NA	NA	
--Intermediate Risk	0.0304	0.0608	NA	NA	NA	NA	
--High Risk	0.0650	0.0744	NA	NA	NA	NA	
Mets-free survival after biochem. failure							
--Low Risk	6 years	9 years	3 years	10 years	13 years	7 years	
--Intermediate Risk	4 years	6 years	2 years	8 years	10 years	6 years	
--High Risk	2 years	3 years	1 year	6 years	7 years	5 years	
Incremental mets-free survival period between modalities after biochemical failure	Comment 1	Comment 1	Comment 1	4 years	7 years	1 year	**1:** In order to conduct analyses, it was necessary to hold estimates for radiation modalities constant and vary estimates for surgical modalities
Time to prostate cancer death after	3.5 years	5 years	2 years	3.5 years	5 years	2 years	

Analysis Description	Radiation			Surgery			Comments
	Base Case	Upper	Lower	Base Case	Upper	Lower	
metastases							
Probability of salvage therapy success							
--Low Risk	70%	90%	50%	70%	90%	50%	
--Intermediate Risk	60%	80%	40%	60%	80%	40%	
--High Risk	50%	70%	30%	50%	70%	30%	
Probability of mortality related to ADT	1%	2%	0%	1%	2%	0%	
Probability of ED	Comment 1	Comment 2	Comment 3	Comment 1	Comment 2	Comment 3	**1** 12/24 month probabilities of ED for EBRT+BT, BT, 3D-CRT, and IMRT are 41%/51%, 57%/43%, 27%/42%, and 27%/42%, respectively; 3/6/12/24 month probabilities of ED for ORP, RALP, and LRP are 66%/63%/58%/49%, 66%/50%/42%/28%, and 75%/58%/53%/40%, respectively **2** 12/24 month probabilities of ED for EBRT+BT, BT, 3D-CRT, and IMRT are 51%/64%, 71%/54%, 34%/53%, and 34%/53%, respectively; 3/6/12/24 month probabilities of ED for ORP, RALP, and LRP are 83%/79%/73%/61%, 83%/63%/53%/35%, and 94%/73%/66%/50%, respectively [125% of base case estimates] **3** 12/24 month probabilities of ED for EBRT+BT, BT, 3D-CRT, and IMRT are 31%/38%, 43%/32%, 20%/32%, and 20%/32%, respectively; 3/6/12/24 month probabilities of ED for ORP, RALP, and LRP are 50%/47%/44%/37%, 50%/38%/32%/21%, and 56%/44%/40%/30%, respectively [75% of base case estimates]

Analysis Description	Radiation			Surgery			Comments
	Base Case	Upper	Lower	Base Case	Upper	Lower	
Probability of UI	NA	NA	NA	Comment 1	Comment 2	Comment 3	**1** 3/6/12 month probabilities of UI for ORP, RALP, and LRP are 32%/24%/11%, 19%/9%/9%, and 41%/28%/10%, respectively **2** 3/6/12 month probabilities of UI for ORP, RALP, and LRP are 40%/30%/14%, 24%/11%/11%, and 51%/35%/13%, respectively [125% of base case estimates] **3** 3/6/12 month probabilities of UI for ORP, RALP, and LRP are 24%/18%/8%, 14%/7%/7%, and 31%/21%/8%, respectively [75% of base case estimates]
Annual probability of late GI/GU toxicity	Comment 1	Comment 2	Comment 3	NA	NA	NA	**1** Annual probabilities of GI/GU toxicity for EBRT+BT, BT, 3D-CRT, and IMRT are 0.0225/0.0340, 0.0127/0.0424, 0.0626/0.0408, and 0.0157/0.0229, respectively **2** Annual probabilities of GI/GU toxicity for EBRT+BT, BT, 3D-CRT, and IMRT are 0.03375/0.051, 0.01905/0.0636, 0.0939/0.0612, and 0.02355/0.03435, respectively [150% of base case estimates] **3** Annual probabilities of GI/GU toxicity for EBRT+BT, BT, 3D-CRT, and IMRT are 0.01125/0.017, 0.00635/0.0212, 0.0313/0.0204, and 0.00785/0.01145, respectively [50% of base case estimates]
Probability of salvage therapy use	44%	60%	30%	76%	100%	50%	

Analysis Description	Radiation			Surgery			Comments
	Base Case	Upper	Lower	Base Case	Upper	Lower	
Annual radiation-related secondary malignancy rate	0.0016	NA	0	NA	NA	NA	
UTILITIES							
Functional outcomes disutilities	0.1 / 0.2 / 0.25	0.15 / 0.3 / 0.375	0.05 / 0.1 / 0.125	0.1 / 0.2 / 0.25	0.15 / 0.3 / 0.375	0.05 / 0.1 / 0.125	Disutility of ED, UI, and both ED+UI, respectively; range represents 50%, 150% of base case estimate
Late toxicity disutilities	0.15 / 0.2 / 0.25	0.225 / 0.3 / 0.375	0.075 / 0.1 / 0.125	0.15 / 0.2 / 0.25	0.225 / 0.3 / 0.375	0.075 / 0.1 / 0.125	Disutility of GU Grade 2+, GI Grade 2+, and both GU Grade 2+ and GI Grade 2+, respectively; range represents 50%, 150% of base case estimate
OTHER							
Starting age distribution	65 ± 6	69 ± 6	NA	65 ± 6	NA	60 ± 6	Based on approximate age distributions in Zelefsky, 2010
Time horizon	Lifetime	10 years	5 years	Lifetime	10 years	5 years	Both alternative estimates represent reductions from the base case estimate
Duration of functional outcomes	2 years	Lifetime	5 years	2 years	Lifetime	5 years	Both alternative estimates represent increases from the base case estimate