COST-EFFECTIVENESS ANALYSIS OF RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIOTHERAPY AND EXTERNAL BEAM RADIOTHERAPY WITH BRACHYTHERAPY BOOST FOR VERY HIGH-RISK PROSTATE CANCER

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ABSTRACT

Objective: To evaluate the cost-effectiveness of radical prostatectomy (RP), external beam radiotherapy (EBRT) monotherapy, and EBRT+brachytherapy for men with very high-risk prostate cancer (VHRPC).

Methods: Using a decision tree with embedded Markov process models, a cost-utility analysis was performed comparing the three treatment strategies for hypothetical cohorts of men with VHRPC. The base case time horizon was ten years; consistent with the maximum follow-up reported in the literature. The model parameters for distant metastases and mortality were derived from a multi-institutional study utilizing patient-level data. Costs were from a societal standpoint and health state utilities were obtained via standard gamble techniques. Incremental cost-effectiveness ratios were calculated per quality-adjusted life year using a 3% discount rate. Sensitivity analyses (SA) addressed uncertainty in key variables.

Findings: EBRT+brachytherapy was both cost-saving and more effective than both EBRT monotherapy and RP, strongly dominating both alternative treatment strategies. These results remained robust to extensive SA.

INTRODUCTION

The American Cancer Society has estimated that nearly 192,000 new cases of adenocarcinoma of the prostate will be diagnosed in 2020, an increase of five percent from the prior year (American Cancer Society 2020). Prostate cancer is also expected to account for over 33,000 deaths and will top the 2020 list of male cancer diagnoses at 21 percent with its closest competitor being lung cancer at only 13 percent. Twenty-five percent of these men present with high-risk disease, defined as cancers with high-grade pathology by the Gleason scoring system, i.e. Gleason scores of 8-10 out of 10 or a serum prostate specific antigen level greater than 20 ng/mL (Parikh and Sher 2012). Further stratifying risk, seven to ten percent of all prostate cancer patients present with very high-risk disease with Gleason scores of 9 or 10, a particularly aggressive variant with a propensity for distant metastases and a high probability of prostate cancer-related death (Kishan *et al.* 2018).

The optimal management of very high-risk prostate cancer has remained unclear but typically has involved the following three state-of-the art treatment options, supported by national standards of care: 1) robotic-assisted laparoscopic prostatectomy (RALP), i.e. surgical removal of the prostate with a pelvic lymph node dissection; 2) external beam radiotherapy (EBRT) monotherapy via image-guided intensity modulated radiotherapy (IG-IMRT) involving 20 to 45 daily treatments, Monday through Friday; and 3) EBRT over 15 to 28 treatments followed by one or two transperineal brachytherapy (radioactive seed) interstitial implants, facilitating intense dose escalation to the prostate either via low dose rate radioisotopes such as Iodine-125 or high dose rate (HDR) radioisotopes such as Iridium-192 (National Comprehensive Cancer Network 2020). Both radiotherapy options are usually combined with 18 to 24 months of androgen deprivation therapy, which has been shown to improve survival in men with high-risk disease (National Comprehensive Cancer Network 2020). Which of these three contemporary treatments for very high-risk prostate cancer provides the best outcomes remains unclear and this question has not been studied in any randomized controlled clinical trial. In a multi-institutional collaborative effort to more definitively evaluate the optimal treatment strategy for this very high-risk prostate cancer cohort, Kishan *et al*. (2018) recently reported the results of a retrospective cohort study of 1,809 patients with Gleason score 9-10 prostate cancer utilizing the individual patient data from 11 tertiary referral centers in the United States and one in Norway. At a median follow up ranging from 4.2 to 6.3 years for the three treatment groups, the combination EBRT plus brachytherapy boost group was shown to have a statistically significant improvement in prostate cancer-specific survival and a lower risk of distant metastases than either the EBRT monotherapy or RALP groups.

In an environment of limited health care resources and with United States (US) national expenditures for prostate cancer care projected to reach over $20 billion in 2020, decision-making authorities will increasingly require information on the cost-effectiveness of alternative treatment paradigms such as RALP, EBRT monotherapy and EBRT plus brachytherapy in order to inform health policy (Marriotto *et al.* 2011). The nontrivial differences in costs, efficacy and quality-of-life effects associated with the various treatment strategies to manage very high-risk prostate cancer suggest that quantifying the cost-effectiveness of these different treatment protocols is important. The purpose of this study was to evaluate the cost-effectiveness of RALP, EBRT monotherapy, and EBRT plus brachytherapy for patients with very high-risk prostate cancer based on the results of Kishan *et al*. (2018).

METHODS

Overview

In health care economies with limited budgets, cost-effectiveness analysis provides an analytical framework to compare the net benefit of a particular intervention to those benefits that others must forfeit as a result of reallocating resources. Cost-utility analysis considers the difference in incremental costs and quality-of-life-adjusted survival among treatment programs being considered, reported as the incremental cost-effectiveness ratio (ICER), which is compared to a willingness-to-pay threshold, usually determined by society or payers, and measured in dollars per additional quality-adjusted life year (QALY) gained. This represents the health benefits that may be given up by others due to any additional costs associated with a particular program.

Decision Model

Using TreeAge Pro software (Williamstown, MA), a decision tree with three embedded Markov models was developed to estimate the QALYs and the direct medical and non-medical costs associated with the three very high-risk prostate cancer treatment strategies from a societal perspective (Figure 1). As recommended by Levine, Ganz, and Haller (2007), the base-case time horizon of the cost-utility analysis was ten years, consistent with the maximum follow-up reported by Kishan *et al*. (2018) and not on results projected into the future. The Markov cycle length was set at six months to be temporally in line with the clinical treatment paradigms being evaluated.

Markov Models

Markov simulations track patient transitions among mutually exclusive health states at fixed time cycles according to input probabilities. During each cycle, patients accumulate costs and QALYs (Sonnenberg and Beck 1993). The patient cohort entered the model in the Alive Without Distant Metastasis (AWODM) health state and transitioned among health states of Alive With Distant Metastases (AWDM), Dead from Prostate Cancer and Dead from Other Causes, based on probabilities derived from Kishan *et al.* (2018) (Table 1).

Survival Data and Analytic Methods

A single study-based estimate of effectiveness was used because Kishan *et al.* (2018) is the largest published multi-institutional study to evaluate the comparative effectiveness of RALP, EBRT monotherapy and EBRT plus brachytherapy for patients with Gleason score 9-10 prostate cancer treated according current national guidelines (National Comprehensive Cancer Network 2020). The adjusted five- and ten-year cumulative incidences for distant metastases, prostate-cancer specific mortality and all-cause mortality were used. These incidences were derived using Kaplan-Meier estimates with inverse probability of treatment weights for the intervals of years one through five years and six through ten, determined by utilizing propensity scores calculated with multinomial logistic regression with each treatment group set as the outcome and prostate-specific antigen level, age, cancer stage, and Gleason score as pretreatment prognostic covariates (Table 1). It was assumed that mortality from causes other than prostate cancer was equal to all-cause mortality minus prostate-cancer-specific mortality for the years one through five and six through ten cumulative estimates. The probabilities for each 5-year time interval were converted to 6-month rates using the formula rate = -ln(1-p)/t, where p equals the probability and t equals time. The six-month rate was then converted back to a six-month probability to coincide with the selected Markov cycle length using the formula, probability = 1-

$e^{(-rt)}$, where r equals rate and t equals time. The model was then calibrated to accurately match the mortality and distant metastases risks reported in the study (Kishan *et al*. 2018).

Direct Medical and Non-Medical Costs

Consistent with a societal perspective, both direct medical and non-medical costs were considered. If necessary, costs were inflated to 2019 US dollars using the medical care component of the US Chained Consumer Price Index (United States Bureau of Labor Statistics 2020).

Direct medical costs for the AWODM health state of the EBRT monotherapy and EBRT plus brachytherapy treatment cohorts were obtained from the Centers for Medicare and Medicaid Services Physician Fee Schedule national payment amount and are shown in Tables 2 and 3 (Centers for Medicare & Medicaid Services 2020). For any radiotherapy treatment group, these costs included a comprehensive-level consultation with a radiation oncologist, treatment simulation and planning, dosimetry, ongoing physics support, treatment delivery, and weekly patient management. Patients in the EBRT monotherapy group were treated with a moderately hypofractionated EBRT program using IG-IMRT to a total dose of 60 Gy in 20 fractions of 3 Gy each, delivered on a five days per week schedule. Those in the EBRT plus brachytherapy group received EBRT in a similar fashion but to a final dose of 37.5 Gy in 15 fractions of 2.5 Gy each delivered five days per week followed by a single HDR Ir-192 brachytherapy treatment of 15 Gy. It was assumed that half of the brachytherapy cohort would undergo the implant at a hospital-based outpatient surgery department and half at an ambulatory surgery center in order to capture the cost differences associated with these diverse points of care (Hall, Schwartzman, Zhang, and Liu 2017). Based on National Comprehensive Cancer Network (NCCN) guidelines, all patients in the two radiotherapy treatment groups received a total of 24 months of androgen deprivation therapy by intramuscular leuprolide injections delivered on a once every three-month schedule (Table 4). The direct medical costs of RALP were obtained from a retrospective, cross-sectional study of hospital discharges based on national inpatient sample data of the Healthcare Cost and Utilization Project (HCUP), using Medicare reimbursement adjusted by the appropriate cost-to-charge ratios published by HCUP (Mukherjee 2019). As per Kishan *et al.* (2018), 33.3 percent of the RALP cohort received androgen deprivation therapy, which was assumed to consist of a total of six months of leuprolide, consistent with NCCN guidelines (National Comprehensive Cancer Network 2020). In addition, 42.8 percent of the RALP group received adjuvant or salvage EBRT (Kishan *et al*. 2018). Adjuvant/salvage EBRT was carried out using conventional fractionation and consisted of a total dose of 70 Gy delivered in 35 fractions of 2 Gy each on a Monday through Friday schedule with the associated direct medical costs shown in Table 5 (National Comprehensive Cancer Network 2020). The direct medical costs of RALP incurred during the first Markov cycle were $28,822; i.e., $18,974 for the procedure plus $9,400 and $447 for the proportions of the cohort receiving adjuvant/salvage EBRT and androgen deprivation therapy, respectively.

The direct medical costs for the AWDM health state are shown in Table 6 and were derived from a deterministic, decision analytic model that estimated the direct medical costs associated with the management of prostate cancer including metastatic disease from a US commercial-payer perspective (Gustavsen, Gullet, Cole, Lewine, and Bishoff 2019). In order to account for the differences in costs between patients with castrate-naïve disease, which is still responsive to androgen deprivation therapy, and castrate-resistant disease, which is resistant to androgen deprivation therapy and more expensive to manage, the total direct medical costs for the AWDM were weighted by the proportion of patients with either castrate-naïve or castrate-resistant metastatic prostate cancer (Sathianathan 2019). The costs associated with follow-up testing and office visits after definitive treatment are the same for all three treatment strategies and therefore, were not modelled (National Comprehensive Cancer Network 2020). Other potential downstream costs to manage potential late complications of each treatment modality were not considered since there is a paucity of data to accurately compare longer-term toxicities of these three treatment approaches in the modern era using state-of-the art treatment technologies (Yu and Hamstra 2017).

Direct non-medical costs were estimated for patient transportation and patient-related time lost from productive work or leisure associated with treatment and office visits (Table7). Direct non-medical costs of patient transportation for treatments included the average number of miles traveled to receive care and parking (Longacre, Neprash, Shippee, Tuttle, and Virnig 2019; Inrix 2017). Travel costs for any treatment-related visit were estimated using the AAA average cost-per-mile based on the average number of miles driven per year for men 55 to 64 years old which was found to be $0.58/mile (AAA Association 2018). The AAA cost/mile was multiplied by 22.6 miles, the median round-trip miles traveled for cancer care, totaling $18.11 per round-trip (Longacre *et al*. 2019). The total transportation cost for each treatment strategy was obtained by multiplying the number of visits associated with each strategy by the average cost per round-trip.

The median age of patients in the Kishan *et al.* study (2018) was 61 years and the value of patients' time lost from productive work or leisure was determined from the median hourly wage rate for men of 54 to 61 years old, assuming 40 hours/week (U.S. Bureau of Labor Statistics 2019). The median time spent in round-trip travel for any treatment-related visit was

40.6 minutes based on a study evaluating the travel distance to cancer-care facilities among rural and urban cancer patients (Longacre *et al*. 2019). The time that was allotted for the each of the various types of treatment-related visits were obtained from the literature or based on expert opinion and included the following: any initial physician consultation, 1 hour; post-operative visit, 0.5 hour; total brachytherapy procedure time, 6 hours; RALP hospital admission, 13.6 hours calculated from 1.7 days mean length of stay with 8 hours per day assumed to be lost from work or leisure (Yu *et al*. 2012; Weinstein, Siegel, Gold, Kamlet, and Russell 1996). The time lost from work or leisure associated with convalescence from brachytherapy and RALP procedures were 3 days and 42 days at 8 hours per day, respectively (Mechow *et al*. 2018; UCLA Health 2020).

Health State Utilities

Patient preferences for health states associated with organ-confined and metastatic prostate cancer were obtained from the literature and were elicited from members of the general public using standard gamble techniques (Stewart, Lenert, Bhatnagar, and Kaplan 2005). The disutility associated with potential late complications of each treatment modality was not evaluated since the probability of late complications remains unclear in the era of modern prostate cancer treatment modalities and was not modelled (Yu and Hamstra 2017). The utility values for the AWDM and AWODM health states are shown in Table 1.

Cost-Effectiveness Analysis

Expected costs and QALYs were calculated for each treatment strategy. The ICER was obtained by dividing the incremental cost of the more expensive strategy by its incremental benefit in QALYs. A three percent annual discount rate was used for costs and benefits to foster comparability of the results with those of many other economic evaluations (Muennig 2008). As recommended by Neumann, Cohen, and Weinstein (2014), willingness-to-pay values of $50,000, $100,000, and $200,000 per additional QALY gained were considered as thresholds for cost-effectiveness.

Sensitivity Analyses

Deterministic sensitivity analyses were carried out to evaluate the effect of plausible changes in key variables on the ICER, including costs, health state utility values, annual discount rate and the probabilities of distant metastasis, prostate cancer-specific mortality, and other-cause mortality. Probabilistic sensitivity analysis was conducted using Monte Carlo simulation on all parameters, which were randomly and simultaneously sampled from defined probability distributions over 1,000 iterations. Sampling from Beta distributions, mortality, and distant metastases probabilities were varied by their reported 95 percent confidence intervals while health state utility values were studied over their reported standard deviations. Direct costs of RALP and all radiotherapy treatment programs were varied by plus or minus 25 percent to approximate two standard deviations and a normal distribution was used because these were based on solid estimates obtained from Medicare reimbursement (Singer 2006). The costs of managing metastatic disease were Medicare estimates obtained using a decision analytic model with a higher degree of uncertainty. Therefore, these costs were doubled and halved to approximate a wider confidence interval and a Gamma distribution was used with standard deviation of (high value-low value)/4 (Singer 2006).

RESULTS

Model Validation

The results generated by the model were found to accurately mirror the five- and ten-year distant metastasis, prostate cancer-specific survival and other-cause mortality risks reported by Kishan *et al.* (2018).

Base Case Analysis

The results of the base case analysis are shown in Table 8. EBRT plus brachytherapy resulted in a net savings of $12,262 and $31,989 versus EBRT monotherapy and RALP, respectively. This reflects the higher upfront costs associated with RALP and the discounted savings due to lower cumulative costs to manage progressive metastatic disease for the EBRT plus brachytherapy group compared to the other strategies. EBRT + brachytherapy yielded an incremental 1.30 and 1.12 QALYs over EBRT monotherapy and RALP, respectively. EBRT + brachytherapy was both cost-saving and more effective than both EBRT monotherapy and RALP and therefore, strongly dominated both alternative treatment strategies.

Sensitivity Analysis

The results of the one-way deterministic sensitivity analysis are illustrated in the tornado diagrams shown in Figure 2. Tornado diagrams are graphical representations of all one-way sensitivity analyses results for all the variables studied, presented in one figure. The gray vertical line shows the base case ICER. The horizontal bars represent the ICER values over the range of the variable values studied. The ICER for EBRT plus brachytherapy was most sensitive to the total direct costs associated with the AWDM health state. However, regardless of society's willingness-to-pay for an additional QALY gained, EBRT plus brachytherapy strongly dominated both competing strategies on deterministic sensitivity analysis of all key variables over plausible ranges.

The result of the probabilistic sensitivity analysis is illustrated in the cost-effectiveness acceptability curve (Figure 3). An acceptability curve illustrates the percentage of Monte Carlo simulations that each treatment strategy is preferred over the others at a certain societal willingness-to-pay for an additional QALY. For the ten-year time horizon EBRT plus brachytherapy was expected to be the optimal and preferred strategy in 99% of the simulations at a willingness-to-pay of $50,000/QALY.

DISCUSSION

Cost-effectiveness analysis provides the framework for an evidence-based approach to the comparison of the costs and quality-of-life adjusted clinical outcomes of the three modern treatment programs for very high-risk prostate cancer. Through the use of sensitivity analysis, it also allows the investigator to evaluate the base case results over a wide range of assumptions, which may confirm or lead to modifying the base case conclusions. Using the actual follow up interval reported in the Kishan *et al.* (2018) multi-institutional study, it was found that EBRT plus brachytherapy saved costs, improved quality-of-life adjusted survival, and strongly dominated its comparator treatment paradigms of EBRT monotherapy and RALP. This conclusion was supported by the results of the probabilistic sensitivity analysis, which found EBRT plus brachytherapy to be the preferred treatment strategy in 99 percent of the simulations at a willingness-to-pay threshold of $50,000/QALY. This suggests that there is a high likelihood that EBRT plus brachytherapy either dominates its comparators or is cost-effective over a ten-year time horizon. Deterministic sensitivity analysis also demonstrated that the model was most sensitive to total direct costs associated with the management of distant metastatic disease highlighting the importance of the reduced risk of distant metastasis seen with the EBRT plus brachytherapy cohort despite similar overall (all-cause) survival of the three treatment cohorts at ten years.

The policy implications of this study are not insignificant. There are approximately 200,000 new cases of prostate cancer diagnosed annually in the United States and nearly 1.3 million globally (American Cancer Society 2020; Rawla 2019). About 20,000 and 130,000 of these cases are expected to be very high risk in the US and worldwide, respectively (Kishan 2018). Based on the results of this cost-effectiveness analysis and considering the proportional usage of RALP versus EBRT reported by Kishan *et al.* (2018), the use of EBRT plus brachytherapy in this cohort could decrease US health care expenditures by about $431 million annually. Annual global health care expenditures could potentially be reduced over a range of about $16 billion to $42 billion, depending on the existing worldwide treatment mix of EBRT monotherapy and RALP for very high-risk prostate cancer, which is not well known.

There are no other studies that have evaluated the cost-effectiveness of EBRT plus brachytherapy versus EBRT monotherapy and RALP for organ-confined, very high-risk prostate cancer. However, Parikh and Sher (2012) developed a decision model to analyze the comparative effectiveness of primary radiotherapy versus radical prostatectomy for patients with high-risk prostate cancer. They evaluated the difference in QALYs associated with three treatment cohorts: EBRT with androgen deprivation therapy, prostatectomy plus adjuvant EBRT, and trimodality therapy consisting of radical prostatectomy, adjuvant EBRT and androgen deprivation therapy. Using a lifetime horizon, they found that EBRT with androgen deprivation therapy may be superior to radical prostatectomy plus adjuvant EBRT and that trimodality therapy may lower risks of progressive disease for a significant number of men. However, this study also included patients with Gleason score 8 disease, consistent with a high-risk group but not the very high-risk group. The investigators did not discount future health benefits to their present value and neither evaluated treatment-related costs nor the potential impact of brachytherapy on the results.

The current cost-effectiveness analysis being presented has some limitations. First, although others have compared the outcomes of the three treatments that were studied, a decision was made to use mortality and distant metastasis data from one large multi-institutional retrospective cohort study. In another retrospective cohort study, Ennis, Hu, Ryemon, Lin, and Mazumdar (2018) assessed the overall survival of high-risk patients treated by radical prostatectomy, EBRT with androgen deprivation therapy, and EBRT plus brachytherapy with or without androgen deprivation therapy using the National Cancer Database. After adjusting for prostate cancer prognostic factors, other competing medical comorbidities and socioeconomic characteristics, these investigators found EBRT monotherapy to be associated with inferior overall survival but there was no statistical difference in overall survival between the EBRT plus brachytherapy and radical prostatectomy cohorts. These results are comparable to those of Kishan *et al.* (2018), which showed an overall survival advantage for EBRT + brachytherapy before 7.5 years of follow up but similar overall survival for all three treatment cohorts at ten years, possibly reflecting an early prostate cancer-specific mortality advantage for EBRT plus brachytherapy that eventually was trumped by increasing other-cause mortality in later years. However, Ennis *et al.* (2018) did not limit their analysis to the Gleason score 9-10 very high-risk group and did not present data on prostate-cancer-specific mortality or the risk for development of distant metastases. These omissions provided additional support for the sole use of the Kishan *et al.* (2018) study, which also utilized patient-level data.

Second, the distant metastases, prostate cancer-specific mortality and other-cause mortality data reported by Kishan *et al.* (2018) was limited to ten years and this cost-effectiveness analysis was therefore, limited to this time horizon (Levine *et al.* 2007). Although a lifetime horizon was not evaluated in this cost-effectiveness analysis at this time, the fact that there are no anticipated dramatic differences in downstream costs or quality-of-life effects indicates that the base case results are unlikely to change over longer time horizons. Despite the fact that the overall survival of EBRT plus brachytherapy and RALP equalized by ten-years, the significant difference in the risk of distant metastases between the EBRT plus brachytherapy group compared to the other two treatment groups remained robust and review of the Kaplan-Meier curves shows this difference to continue to widen over time (Kishan *et al* 2018). Since the cost of managing distant metastatic disease appears to have one of the largest relative impacts on cost-effectiveness, it seems likely that the strategy of EBRT plus brachytherapy would only become increasingly preferred over the other treatment options over a lifetime horizon.

Third, there was some uncertainty surrounding the costs used in the model. The direct medical costs for EBRT plus brachytherapy, EBRT monotherapy, adjuvant/salvage EBRT after RALP and androgen deprivation therapy were calculated using a micro-costing approach using the Centers for Medicare and Medicaid Services Physician Fee Schedule, a well-established source with a high degree of certainty. Similarly, the direct medical costs associated with the AWODM health state for RALP were based on Medicare reimbursement. However, the costs associated with the AWDM for all treatment groups were obtained from a costing study using deterministic decision analytic techniques. Despite reporting Medicare estimates for the cost of managing distant metastatic disease, it is possible that this study could have a higher degree of uncertainty. To address this uncertainty, a wider confidence interval was used for sensitivity analysis of these costs and, despite this, the ICER for EBRT plus brachytherapy never became a positive number.

CONCLUSION

Using the actual follow-up interval reported by Kishan *et al.* (2018), EBRT plus brachytherapy strongly dominated the strategies of EBRT monotherapy and RALP for patients with very high-risk prostate cancer. Since the long-term incremental costs and distant metastases risks are unlikely to dramatically change after a decade of follow-up, it is likely that EBRT plus brachytherapy will either dominate the comparator strategies or remain cost-effective given contemporary willingness-to-pay thresholds of $50,000-$200,000 per QALY over a lifetime scenario.

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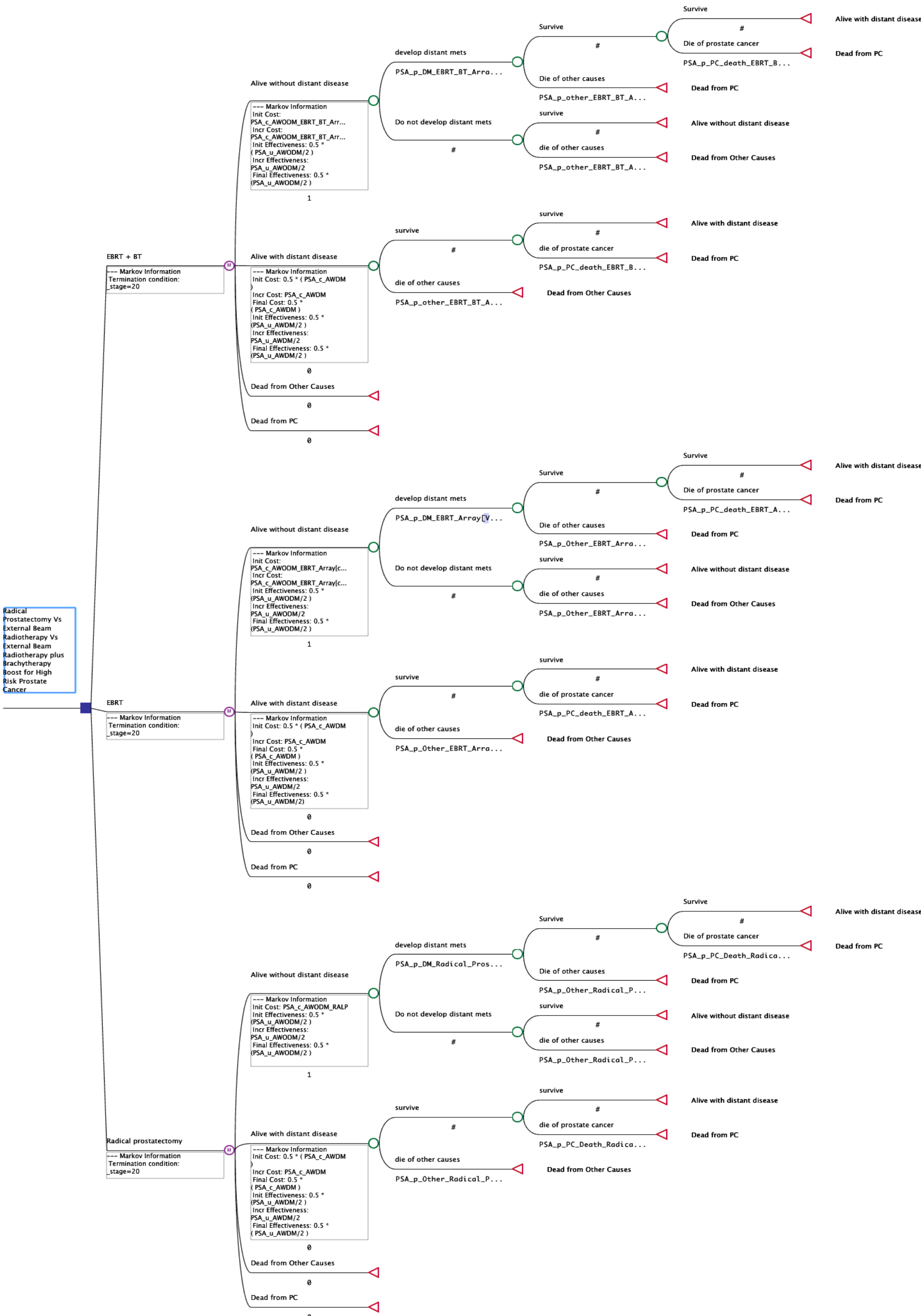

Figure 1. Decision Tree with three embedded Markov models for EBRT + brachytherapy, EBRT monotherapy, and RALP. Abbreviations: EBRT: external beam radiotherapy monotherapy; EBRT+BT: external beam radiotherapy with brachytherapy boost; RALP: robotic assisted laparoscopic prostatectomy.

Table 1. Model Parameters, Ranges Studied and Distributional Assumptions						
Probability						
Treatment Cohort	**Interval (years)**	**Base Case Value (mean)**	**Range Studied***	**Standard Deviation**	**Distribution for PSA**	**Reference Number**
Distant Metastasis						
RALP	0-5	0.24	0.19-0.30	0.028	Beta	8
	>5-10	0.46	0.38-0.54	0.04		
EBRT	0-5	0.24	0.20-0.28	0.02		
	>5-10	0.44	0.38-0.50	0.03		
EBRT+BT	0-5	0.08	0.05-0.11	0.015		
	>5-10	0.13	0.09-0.17	0.02		
Prostate Cancer Specific Mortality						
RALP	0-5	0.12	0.08-0.17	0.023	Beta	8
	>5-10	0.23	0.18-0.30	0.03		
EBRT	0-5	0.13	0.08-0.19	0.028		
	>5-10	0.26	0.20-0.32	0.03		
EBRT+BT	0-5	0.03	0.01-0.05	0.01		
	>5-10	0.13	0.08-0.19	0.028		
Death from Other Causes						
RALP	0-5	0.05	0.04-0.06	0.05	Beta	8
	>5-10	0.09	0.07-0.11	0.01		
EBRT	0-5	0.05	0.04-0.06	0.05		
	>5-10	0.13	0.10-0.16	0.04		
EBRT+BT	0-5	0.07	0.05-0.09	0.01		
	>5-10	0.18	0.14-0.24	0.025		
Health State Utility Values						
Alive with Distant Disease		0.25	0.14-0.36	0.11	Beta	22
Alive without distant disease		0.81	0.63-0.99	0.18		
Annual Discount Rate						
Rate		0.03	0.005-0.05		Uniform	13
Abbreviations: RALP, Robotic-assisted laparoscopic prostatectomy; EBRT, external beam radiotherapy; EBRT + BT, external beam radiotherapy with brachytherapy boost; PSA, Probabilistic Sensitivity Analysis. *95% confidence interval when provided.						

Table 2. Direct Medical Costs of External Beam Radiotherapy Monotherapy[3]					
Service	**CPT code**	**No. Units**	**2019 CMS physician fee schedule Medicare National Payment Amount, US $**	**Reimbursement per unit, US $**	**Reimbursement Total, US $**
Initial New Patient office visit-comprehensive	99204	1	167.09* 132.09**	147.14	147.14
Physician Prescription Treatment Plan; Complex	77263	1	174.31	174.31	174.31
Special Treatment	77470	1	136.78	136.78	136.78
IMRT Plan-Including DVH for Target & Critical Structures	77301	1	1,949.20	1,949.20	432.71
IMRT Multi-Leaf Collimator	77338	1	497.31	497.31	497.31
Basic Dosimetry calculation	77300	2	67.85	67.85	135.70
IMRT Treatment delivery- single or multiple fields	G6015	20	369.92	369.92	7,398.40
Daily CT image-guidance	77014	20	124.51	124.51	2,490.20
Radiation Treatment Management (weekly physician on-treatment visit)	77427	4	196.33	196.33	785.32
Continuing physics consultation	77336	4	81.20*	81.20	139.66
Total Direct Medical Cost for EBRT Monotherapy					**13,854**

Abbreviations: EBRT, external beam radiotherapy; IMRT, image-guided intensity modulated radiotherapy; DVH: dose volume histogram.
*fee for freestanding facilities (43% of radiotherapy centers)[26]
**fee for hospital-based facilities (57% of radiotherapy centers)[26]

Table 3. Direct Medical Costs of External Beam Radiotherapy + Brachytherapy Boost[3]					
Service	**CPT code**	**No. Units**	**2019 CMS Physician Fee Schedule Medicare National Payment Amount, US $**	**Reimbursement per unit, US $**	**Reimbursement Total, US $**
Initial New Patient Office Visit-comprehensive	99204	1	167.09* 132.09**	147.14	147.14
Physician Prescription Treatment Plan; Complex	77263	1	174.31	174.31	174.31
Special Treatment	77470	1	136.78	136.78	136.78
IMRT Plan-Including DVH for Target & Critical Structures	77301	1	1,949.20	432.71	432.71
IMRT Multi-Leaf collimator	77338	1	497.31	497.31	497.31
Basic Dosimetry calculation	77300	1	67.85	67.85	67.85
IMRT treatment delivery-single or multiple fields	G6015	15	369.92	369.92	5,548.80
Daily CT image-guidance	77014	15	124.51	124.51	1,867.65
Radiation Treatment Management (weekly physician on-treatment visit)	77427	3	196.33	196.33	588.99
Continuing physics consultation	77336	3	81.20*	81.20	104.75
Total for EBRT Component					**11,082.78**
Simulation; 3-Dimensional HDR	77295	1		498.04	498.04
Remote afterload HDR	77772	1		922.45	922.45
Simulation; simple	77280	1		283.30	283.30
Transperineal placement, needle/catheters into Prostate	55875	1		801.19	801.19
Treatment device; simple	77332	1		48.36	48.36
Hospital Outpatient and Ambulatory Surgery Center Facility Fee§		1		2,967	2,967
Total for Single brachytherapy HDR Implant					**5,520**
Total Direct Medical Cost of EBRT plus brachytherapy boost					**16,603**
Abbreviations: EBRT, external beam radiotherapy; IMRT, image-guided intensity modulated radiotherapy; DVH: dose volume histogram; HDR, High Dose Rate brachytherapy. *Fee for freestanding facilities (43% of radiotherapy centers).[26] **Fee for hospital-based facilities (57% of radiotherapy centers).[26] §50% Hospital Outpatient/50% Ambulatory Surgery Centers rates[6]					

Table 4. Direct Medical Cost of Androgen Deprivation Therapy per 6-Month Markov Cycle[3]				
Service	**CPT code**	**No. Units/ 6-month Cycle**	**2019 CMS Physician Fee Schedule Medicare National Payment Amount/unit, US $**	**Reimbursement Total, US $**
Drug cost of leuprolide	HCPCS code J9217	6	235.37	1,412.22
Hormone antineoplastic subcutaneous or intramuscular injections (administration of drug)	96402	2	32.12	64.24
Total Cost of Androgen Deprivation Therapy per 6-Month Markov Cycle				**1,476**

Table 5. Direct Medical Costs of Adjuvant/Salvage EBRT (42.8% of RALP Group)[3]					
Service	**CPT code**	**No. Units**	**2019 CMS physician fee schedule National Payment amount, US $**	**Reimbursement per unit, US $**	**Reimbursement Total, US $**
Initial New Patient Office Visit-comprehensive	99204	1	167.09* 132.09**	147.14	147.14
Physicians Prescription Treatment Plan; Complex	77263	1	174.31	174.31	174.31
Special Treatment	77470	1	136.78	136.78	136.78
IMRT Plan-including DVH for Target and Critical Structures	77301	1	1,949.20	1949.20	1,949.20
IMRT Multi-Leaf Collimator	77338	1	497.31	497.31	497.31
Basic Dosimetry Calculation	77300	2	67.85	67.85	135.70
IMRT Treatment delivery- single or multiple fields	G6015	35	369.92	369.92	12,947.20
Daily CT Image-Guidance	77014	35	124.51	124.51	4,257.85
Radiation Treatment Management (weekly physician on-treatment visit)	77427	7	196.33	196.33	1,374.31
Continuing Physics Consultation	77336	7	81.20*	81.20	244.41
Total Direct Medical Costs for Adjuvant/Salvage EBRT					**21,964**

Abbreviations: EBRT, external beam radiotherapy; IMRT: image-guided intensity modulated radiotherapy; DVH: dose volume histogram RALP, robotic-assisted laparoscopic prostatectomy. *Fee for freestanding facilities (43% of radiotherapy centers).[26] **Fee for hospital-based facilities (57% of radiotherapy centers).[26]

Table 6. Total Direct Medical Costs of the Alive With Distant Metastases Health State per 6-Month Markov Cycle			
	% of Total Cost	**Cost per 6-month Markov Cycle, Adjusted to 2019 US $***	**References**
Castrate Naïve Disease	94.25	1,535	5, 19
Castrate Resistant Disease	5.75	61,053	
Weighted 6-month Markov Cycle Cost		**5,053**	

*Adjusted from 2018 to 2019 US dollars using the medical care component of the US Chained Consumer Price Index.[24]

Table 7. Direct Non-Medical Costs: Value of Patients' Time Lost From Work or Leisure and Transportation Expenses															
	EBRT Monotherapy			**EBRT + Brachytherapy**			**RALP**			**Adjuvant or Salvage EBRT**			**Androgen Deprivation Therapy per 6 Month Markov Cycle^**		
Value of Patient Time Lost															
	Hours/ Unit	No.	Cost US$§	Hours/ Unit	No. Units	Cost US$§	Hours/ Unit	No. Units	Cost US$§	Hours/ Unit	No. Units	Cost US$§	Hours/ Unit	No. Units	Cost US$§
Initial Physician Consultation	1	1	28.43	1	1	28.43	1	1	28.43	1	1	28.43			
Daily EBRT Treatments or Office Visit	0.5	20	284.25	0.5	15	213.19				0.5	35	497.53	0.5	2	28.43
Pre-operative Visit				1	1	28.43	1	1	28.43						
Brachytherapy Procedure				6	1	170.58									
Post-Operative Visit				0.5	1	14.21	0.5	1	14.21						
Mean Hospital Length of Stay*							8	1.7	386.58						
Mean Time Out of Work**				8	3	682.20	8	42	9,550.80						
Travel Time[10]	0.667	21	398.15	0.667	19	360.23	0.667	4**	75.84	0.667	36	682.66	0.667	2	37.93
Total			**710.83**			**1,497.27**			**10,084.29**			**1,208.62**			**66.36**
Transportation Expenses															
Office or hospital visits		21	380.31		19	344.09		4	72.44		36	651.96		2	36.22
Total Direct Non-Medical Costs			**1,091**			**1,841**			**10,157**			**1,861**			**103**

Abbreviations: EBRT, external beam radiotherapy; RALP, robotic-assisted laparoscopic prostatectomy. §Median gender-specific wage rate is $28.43/hour.[25]; ^ EBRT monotherapy and EBRT + brachytherapy patients received a total of 24 months of androgen deprivation therapy.[15] Adjuvant or salvage EBRT patients received 6 months of ADT.[15] * Mean hospital length of Stay for RALP was 1.7 days and assumed 8 hours/day lost from work or leisure.[29] **Assumed to be 8 hours/day of convalescence (3 days for brachytherapy and 42 days for RALP)[12,23] **Includes roundtrip to hospital for RALP.

Table 8. Base Case Results			
	Strategies		
	EBRT + Brachytherapy	**EBRT Monotherapy**	**RALP**
Cost, US $	29,414	41,676	61,403
Incremental Cost, US $	0	12,262	31,989
Effectiveness	5.85	4.54	4.73
Incremental Effectiveness	0	-1.30	-1.12
Incremental Cost-Effectiveness Ratio (ICER)	0	-9,399	-28,575
Interpretation		Strongly dominated by EBRT + BT	Strongly dominated by EBRT + BT

Abbreviations: EBRT, external beam radiotherapy; RALP, robotic-assisted laparoscopic prostatectomy.

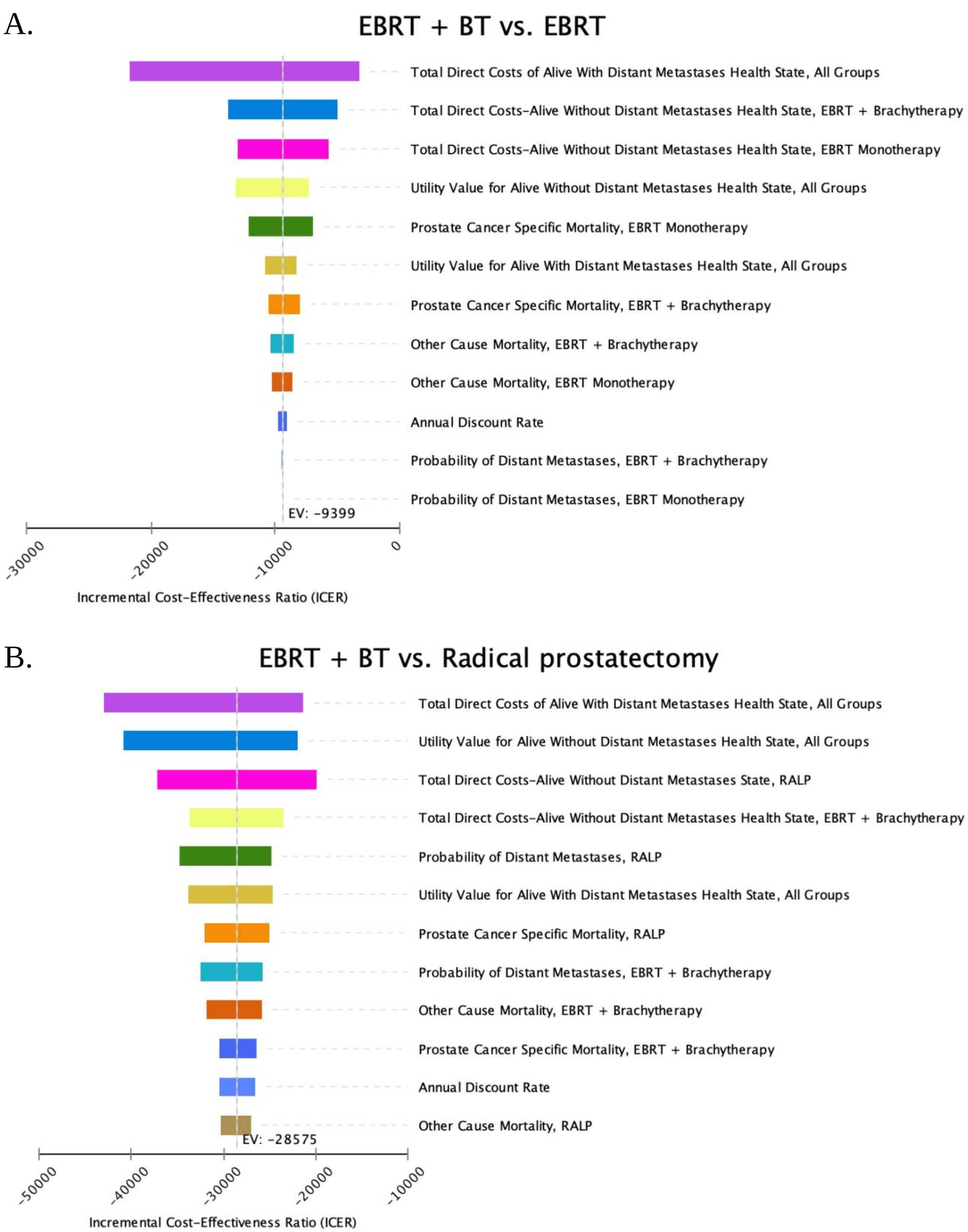

Figure 2. Tornado diagrams of one-way deterministic sensitivity analysis of key variables for A.) EBRT + Brachytherapy versus EBRT monotherapy and, B.) EBRT + Brachytherapy versus RALP. Abbreviations: EBRT: external beam radiotherapy monotherapy; EBRT+BT: external beam radiotherapy with brachytherapy boost; RALP: robotic assisted laparoscopic prostatectomy; EV: expected value

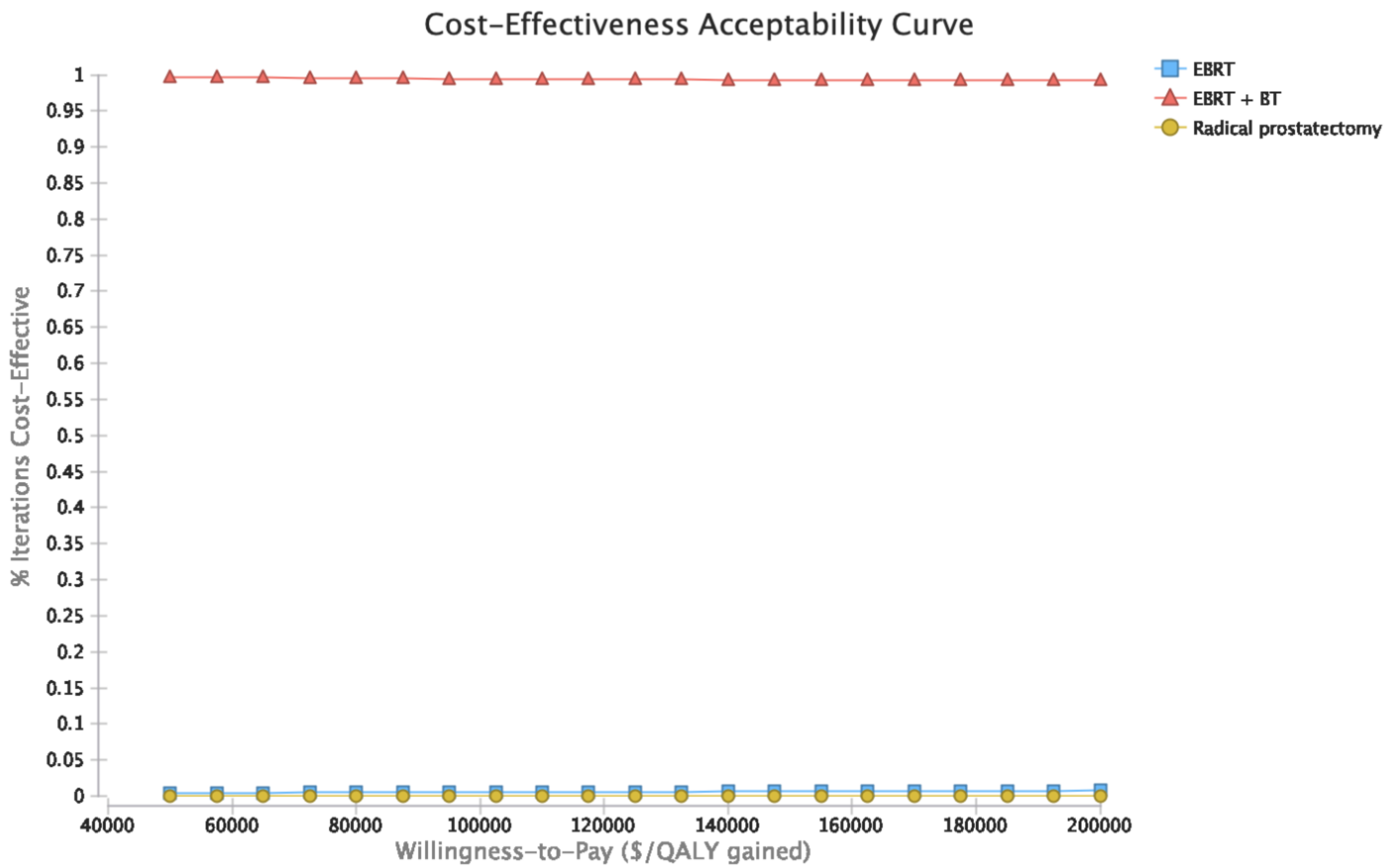

Figure 3. Cost-effectiveness acceptability curve for EBRT, EBRT+ BT, and robotic assisted laparoscopic radical prostatectomy at a willingness-to-pay of $50,000 to $200,000/QALY. Abbreviations: EBRT: external beam radiotherapy monotherapy; EBRT+BT: external beam radiotherapy with brachytherapy boost