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Costs of early adjuvant radiation therapy after radical prostatectomy: a decision analysis

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Background: This analysis was carried out to evaluate the cost-effectiveness of adjuvant radiation therapy (ART) versus observation, using a decision analysis model based primarily upon the published results of the Southwest Oncology Group prospective trial (SWOG 8794).

Patients and methods: A decision analysis model was designed to compare ART versus observation over a 10-year time horizon. Probabilities of treatment success, utilization of salvage treatments, and rates of adverse events were taken from published results of SWOG 8794. Cost inputs were based on 2010 Medicare reimbursement rates. Primary outcome measure was incremental cost per prostate-specific antigen (PSA) success (i.e. serum PSA level <0.4 ng/ml).

Results: ART results in a higher PSA success rate than observation with probability of 0.43 versus 0.22. The mean incremental cost per patient for ART versus observation was $6023. The mean incremental cost-effectiveness ratio was $26 983 over the 10-year period.

Conclusions: ART appears cost effective compared with observation based upon this decision analysis model. Future research should consider more costly radiation therapy (RT) approaches, such as intensity-modulated RT, and should evaluate the cost-effectiveness of ART versus early salvage RT.

Key words: adjuvant radiation therapy, cost-effectiveness, post, prostatectomy, prostate cancer

introduction

Prostate cancer (PC) is the most common nonskin cancer to affect males in the United States with an estimated 217 730 new cases in 2010 [1]. Ninety percent of these patients will choose to receive definitive treatment [2], resulting in a projected $12 billion in medical costs in the United States in 2010 [3]. The Institute for Clinical and Economic Review recently completed an analysis of the comparative effectiveness and value of the management options for low-risk PC, and the final report highlighted the substantial and variable lifetime of PC treatment, ranging from $25 000 to $30 000 for active surveillance, radical prostatectomy (RP), or brachytherapy, up to $40 000–$55 000 for high-technology radiation therapy (RT) [4]. Therefore, it is essential to critically consider the value of RT for PC; this report enriches our understanding of the treatment costs of PC by evaluating the cost-effectiveness of postoperative RT for selected PC patients.

An estimated one-third of newly diagnosed men with PC will undergo RP [5, 6]. Approximately one in five PC patients who undergo RP will recur [7] with higher rates of recurrence, 40%–60%, among patients with adverse pathological risk factors [8]. For patients with adverse pathologic features (APFs), adjuvant radiation therapy (ART), given before a rise in prostate-specific antigen (PSA) level, may be an appropriate course of treatment. Three key randomized trials have shown that ART improves biochemical progression-free survival [9–11] and overall survival [12]. In these trials, patients were eligible for study enrollment if one or more APFs were found in the RP surgical specimen: extracapsular extension (ECE) [9–11], seminal vesicle invasion (SVI) [9–11], or positive surgical margin (PSM) [10, 11].

Although prospective trials support the use of ART for select patients after RT, a recent treatment patterns analysis found that <20% of qualifying patients receive ART [13–15]. Instead of using ART, many physicians choose to observe these patients closely with serial PSA tests and offer RT selectively, only as a salvage treatment of a rise in PSA after RP. From the physician perspective, the predominant reasons for favoring close observation with selective salvage RT (SRT) over ART for patients with APF after RP include perceived toxicity of RT, the risk of overtreatment with ART (i.e. a proportion of patients who may not have developed biochemical failure after RP despite adverse pathologic factors), and the perceived equivalent effectiveness of SRT and ART [16], despite evidence suggesting otherwise [17, 18]. From the payers' perspective, the added financial costs

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associated with ART are a consideration. Therefore, we aimed to evaluate the cost-effectiveness of ART after RP for appropriately selected patients.

Although similar analyses have been conducted for other topics in PC [19–22], the cost-effectiveness of ART versus observation has not been previously described. We utilized the peer-reviewed, published data [11, 23, 24] from the Southwest Oncology Group (SWOG) prospective, randomized trial of ART versus observation (SWOG 8794) to estimate the effectiveness of ART. The SWOG 8794 study showed that ART, compared with observation, improves biochemical control, overall survival, and distant metastasis-free survival [12]. The objective of this study was to construct a decision analytic model to estimate the real world cost of ART versus observation from the payers' perspective. Cost per PSA success was used as the primary measure of effectiveness, which is a relevant consideration since PSA failure is associated with increased mortality and exposure to salvage PC treatments after RP [25–27].

methods

primary data source

This cost-effectiveness model is based primarily upon published data from the SWOG 8794 trial and estimated costs from calendar year 2010 Medicare reimbursement rates. The SWOG 8794 trial evaluated the effect of ART on outcomes, including the primary end point of metastasis-free survival, after RP for selected patients with APFs: ECE, SVI, or PSM [11, 12, 23].

The population that we included in the decision analysis model consisted of 242 patients, out of a total 431 patients enrolled in the SWOG study, with postoperative PSA data available and documented pre-RT PSA ≤0.2 ng/ml, as reported by Swanson et al. [23], representing a pure ART cohort. The analysis was restricted to those patients with PSA ≤0.2 ng/ml in order to evaluate only 'adjuvant' therapy, excluding those patients who, by definition [28], received 'salvage' therapy with persistently detectable PSA after RP.

model design

We designed a decision analysis model (Figure 1) from a payer's perspective, using the TreeAge Pro Suite 2009 program, to examine the cost-effectiveness of ART versus observation after RP for patients with APF (ECE, SVI, and/or PSM) over 10 years. The model is consistent with the best practices issued by the International Society for Pharmacoeconomics and Outcomes Research task force on good research practices in modeling studies [29]. Branches of the decision tree model (Figure 1) demonstrate the two arms of the SWOG 8794 trial (ART versus observation) with associated probabilities of PSA success, utilization of SRT and androgen deprivation therapy (ADT), and associated risk of adverse events: bone fracture, bladder neck contracture ('Stricture'), and rectal bleeding ('Bleed').

The primary objective of the decision analytic model was to determine the cost per PSA success for ART versus observation based upon the conditions and outcomes of the SWOG 8794 trial.

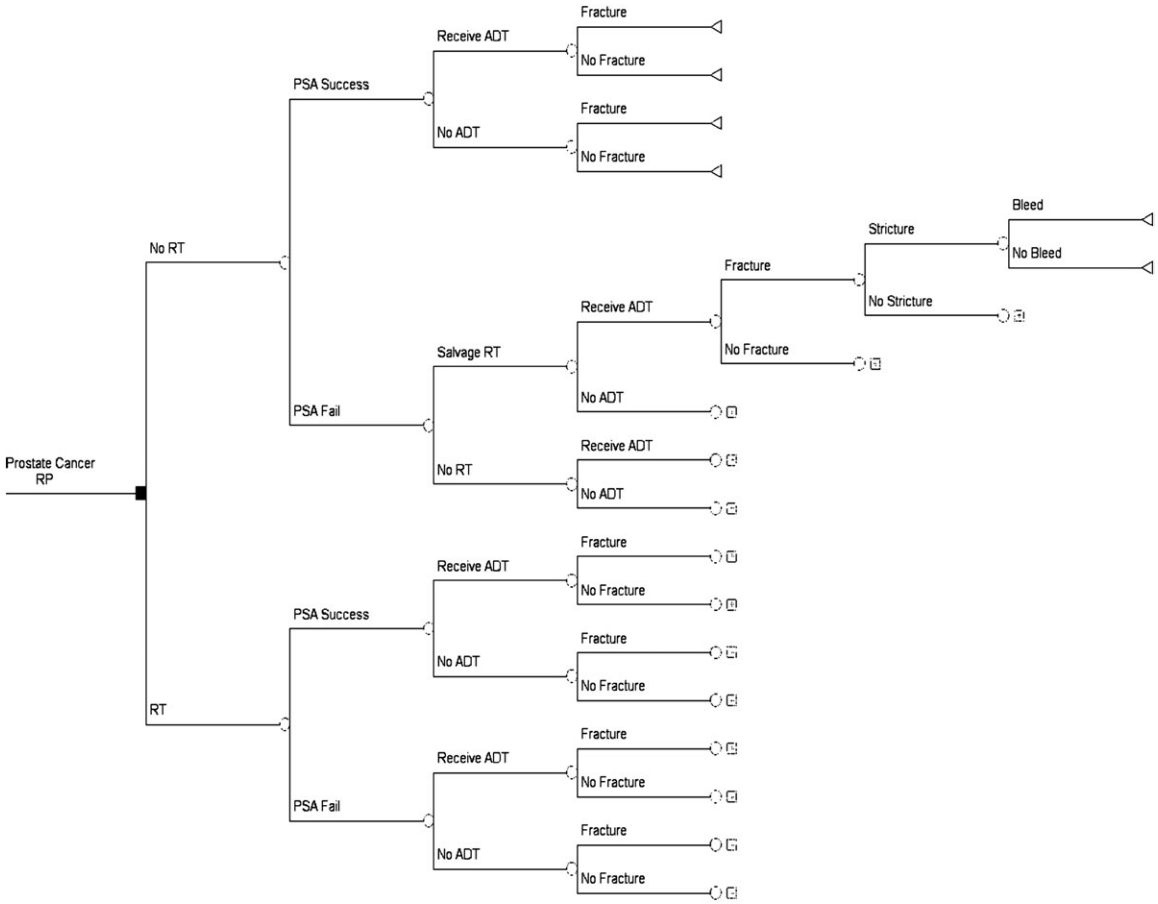

Figure 1. Decision analysis model of adjuvant radiation therapy versus observation. The initial decision point [radiation therapy (RT) versus observation] and subsequent probabilities of PSA success, salvage RT, and ADT are based upon the design and results of SWOG 8794. Subsequent decision points reflect the probabilities of adverse events: bone fracture, bladder neck contracture, and rectal bleeding. SWOG, Southwest Oncology Group.

outcome measure

The primary outcome measure used in the model was treatment success, defined as the absence of PSA failure (PSA ≥0.4 ng/ml), consistent with the methods described in SWOG 8794. [23] Probabilities of treatment success were taken from published results of SWOG 8794 [11, 23].

costs

All probability and costs assumptions used to inform the model are shown in Tables 1 and 2. In short, total cost is a function of cost inputs and the probability of occurrence for each input. Costs included the costs of receiving ART, SRT, management of rectal bleeding, and management of bladder neck contracture. All costs were based on the published national average for 2010 Medicare reimbursement rates [32], assuming that four-field conformal RT was delivered to 60–64 Gy (as used in SWOG 8794). Cost estimates for treatment of adverse events assumed two colonoscopies and one laser treatment of rectal bleeding and two cystoscopies and one cystoscopy with dilation for bladder neck contracture, which reflect worst-case scenario, high-utilization rates based upon discussions with physicians. Costs associated with ADT and treatment of bone fractures were taken from a report published by Krupski et al. [31].

Table 1. Probability values used in the base-case decision analytic model

Probability Variable	Value	Low	High	Reference
No adjuvant radiation therapy				
PSA success	0.28	0.22	0.33	Swanson et al. [23]
Receive ADT	0.21	0.15	0.30	Thompson et al. [11]
Receive salvage adjuvant radiation therapy	0.33	0.44	0.66	Thompson et al. [11]
Adjuvant radiation therapy				
PSA success	0.58	0.45	0.69	Swanson et al. [23]
Receive ADT	0.10	0.08	0.13	Thompson et al. [11]
Radiation therapy adverse events				
Bladder neck contracture	0.178	0.14	0.21	Thompson et al. [11]
Bleed	0.03	0.026	0.039	Feng et al. [30]
Fracture rates				
Fracture with ADT	0.187	0.69	1	Krupski et al. [31]
Fracture without ADT	0.146	0.33	0.49	Krupski et al. [31]

The low and high values shown were used as the range for one-way sensitivity analyses.

discounting

Because the model was over a time span of 10 years, we discounted our outcome measure at a rate of 3%. Costs that were incurred in the first year (ART) were not discounted. All other costs were discounted based on the estimated year they would be incurred in; bleeding and stricture were discounted at 2 years, and fracture and ADT were discounted at 5 years.

incremental cost-effectiveness ratio

The incremental cost-effectiveness ratio (ICER) represents the cost per additional PSA success for ART versus observation. The ICER was calculated as the mean difference in costs between ART and observation divided by the mean difference in effectiveness (probability of PSA success) of ART versus observation.

sensitivity analysis

A series of one-way sensitivity analyses were conducted to evaluate the relative importance of each cost and probability assumption in the model. The standard deviation, when not available, was assumed to be 10% of the mean. A range of two standard deviations (80%–120% of the mean) for each variable was used in the one-way sensitivity analyses (Tables 1 and 2). One-way sensitivity analyses only vary one input at a time. To account for overall variability in the model where each variable changes at the same time, we conducted a probabilistic sensitivity analysis using Monte Carlo simulation in TreeAge Pro Suite 2009 [33]. In a Monte Carlo simulation, each model input is assigned a distribution of values primarily based on the standard deviations (Tables 1 and 2). In cases where the calculated distribution was unavailable, information provided by experts (TNS, LGG, CL, EJT) was utilized. Monte Carlo simulation was then applied to the mean incremental cost and effect and the standard error of the means based on the 1000 microsimulations designed to represent 1000 iterations in which the values for all the variables were randomly selected within the designated distribution.

results

ART results in a higher PSA success rate than observation with a probability of 0.44 versus 0.21 over a 10-year period [23]. Therefore, the mean incremental effect was 0.23. Total cost of ART was $15 900 compared with costs in the observation group of $9876. The mean incremental cost for ART versus observation was $6023 (Table 3). Using the mean incremental cost and effectiveness, the ICER was $26 983 over the 10-year period (Table 3). On a per-year basis, over 10 years, the cost per additional PSA success achieved with ART was $2698.

Table 2. Cost values used in the base-case decision analytic model

Cost Variable	Value	Low	High	Source
Adjuvant radiation therapy	$11 295	$9036	$13 554	CY 2010 Medicare reimbursement rates
Management of Adverse Events				
Rectal bleeding treatment (2 colonoscopies + 1 YAG laser coagulation)	$2660	$2128	$3192	CY 2010 Medicare reimbursement rates
Bladder neck contracture treatment (2 cystoscopies + cytoscopy with dilation)	$4648	$3718	$5577	CY 2010 Medicare reimbursement rates
ADT (lupron)	$8991	$7192	$10 788	Krupski et al. [31]
Fracture	$14 000	$11 200	$16 800	Krupski et al. [31]

The low and high values shown were used as the range for one-way sensitivity analyses.

sensitivity analysis

One-way sensitivity analysis revealed that the model is most sensitive to the likelihood of treatment failure, ADT cost and costs of ART. For example, for the ART to cost as much as observation, then the cost of ART has to decrease to $2000 (from the baseline value of $11 295 in current model) (Figure 2).

The results from the Monte Carlo simulation (Figure 3) showed that ART continues to have higher incremental cost ($6061) and higher incremental effectiveness (0.22) than observation in all calculated conditions.

discussion

Based upon our decision analytic model, ART was both more costly and more effective than observation with each additional PSA success achieved at a cost of $26 983 over a 10-year time horizon. Sensitivity analyses confirmed that ART remained a more costly and more effective treatment than observation.

Standard cost-effectiveness analyses employ a quality-adjusted life year (QALY) as the primary outcome measure. However, since utilities are not available in the medical literature for the specific scenario of ART after RP, it was not possible to calculate QALYs for patients receiving ART (or SRT) after RP. A prior cost-effectiveness analysis of risk-prediction tools in selecting patients for early ART after RP used utilities from a group of 17 patients with intermediate-risk PC who received nonsurgical management with intensity-modulated RT (IMRT) as definitive therapy [22]. Due to significant anatomic changes after RP [34], with different rates of toxicity observed for definitive versus postoperative RT for PC [35, 36], it is not clear that utilities from definitive prostate RT should be applied to ART. Therefore, an alternate end point, cost per PSA success, was chosen for the current analysis. In addition to the data being available in the literature, we believe that PSA is an important outcome measure to payers, clinicians, and patients given that treatment decisions are often based on PSA values in this setting [16, 37]. PSA failure after prostatectomy is associated with higher rates of metastasis and mortality, as well as exposure to salvage treatments [25, 38]. Salvage PC treatments for PSA failure after RP are associated with significant adverse effects [30, 31], so the measure used in the current decision analysis model (cost per PSA success) is a relevant consideration. Although the recently published update of the SWOG 8794 trial showed improved overall survival with ART versus observation, overall survival was not reported by treatment arm for the subset of patients with confirmed undetectable PSA [12]. The other two randomized trials of ART showed improved biochemical progression-free survival but not overall survival [9, 10]. Therefore, the end point cost per PSA success permits the current analysis to reflect the shared conclusions of all three trials.

In our analysis, we used PSA success as our outcome measure rather then QALYS. Consequently, there is no published threshold value to determine cost-effectiveness using PSA success as an outcome measure. However, previous decision analytic modeling reports of IMRT [21], proton beam therapy [20], and a risk-prediction tool for ART decision-making [22] for PC while not using QALYS have compared results to the reference $50 000/QALY willingness-to-pay threshold. We believe that our ICER of $26 983 seems reasonable in consideration of the health gains achieved, though cost per PSA success may not be compared with cost per QALY. Furthermore, we believe that our findings lend further support to ART, which has also been shown to result in higher biochemical failure-free survival [9–11, 23], distant metastasis-free survival [12], and overall survival [12] in randomized trials of ART versus observation for patients with APFs.

The current decision analysis model adheres primarily to the design and outcomes of the SWOG 8794 trial and

Table 3. Mean Incremental cost, Incremental effect, and incremental cost-effectiveness ratio (ICER) of adjuvant radiation therapy (ART) versus observation in the decision analysis model

Strategy	Cost	Incremental cost	Effect	Incremental effect	ICER
Observation	$9876	—	0.21	—	—
ART	$15 900	$6023	0.43	0.22	$26 983

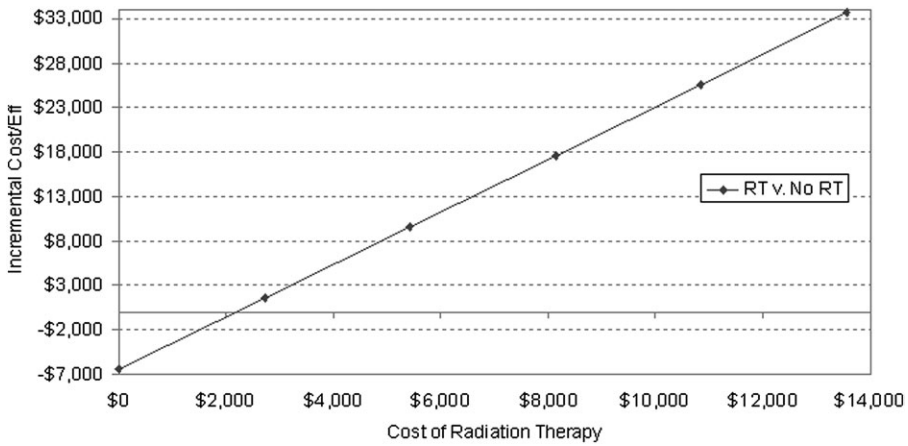

Figure 2. Graph of the linear relationship of incremental cost of adjuvant radiation therapy (versus observation) with incremental cost-effectiveness ratio. The solid horizontal line demonstrates the cost at which the ICER is zero, meaning that adjuvant radiation therapy (RT) costs no more than observation.

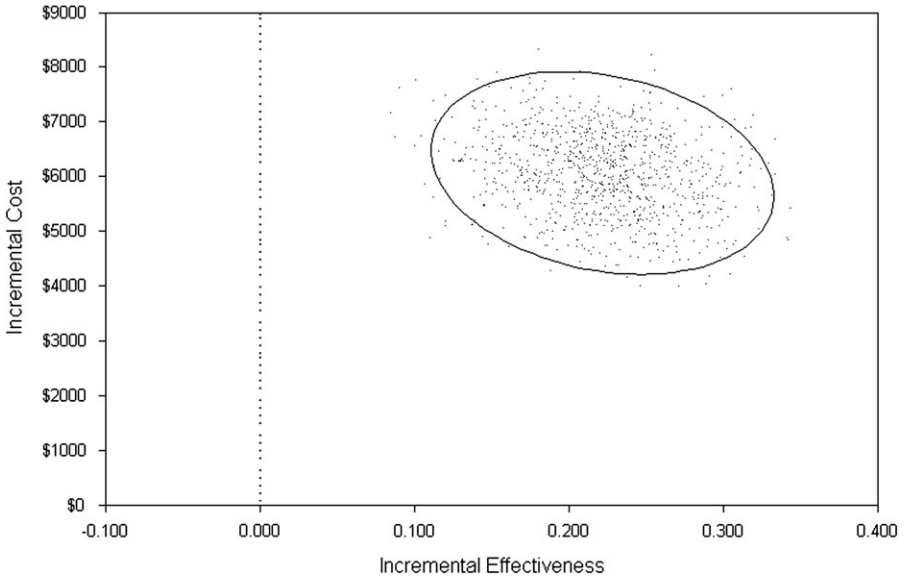

Figure 3. Monte Carlo simulation to evaluate probabilistic sensitivity of the incremental cost-effectiveness ratio. The solid oval denotes the 95% confidence interval around the point estimates.

contains limitations regarding the magnitude and scope of cost inputs, as well as the relationship of the model to contemporary practice, which favors decisions of ART versus early salvage therapy rather than observation [37, 39]. Cost inputs for ART were based upon 2010 Medicare reimbursements rates for 3D-conformal radiation therapy (CRT) to a total dose of 64 Gy, similar to the planning and dose-fractionation schedule permitted on SWOG 8794. It is worth noting that reimbursement rates from private payers may exceed the rates used in the model. Furthermore, a national survey of radiation oncologists conducted by our group suggests that IMRT is used as the standard approach for post-RP RT by ~80% of respondents with total doses commonly ~68 Gy (manuscript in preparation). Therefore, the current model may significantly underestimate the costs of ART since IMRT is significantly more costly than 3D-CRT. For instance, based on Medicare calendar year 2010 reimbursement, a 38-fraction course of post-RP IMRT (68.4 Gy in 1.8 Gy per fraction) would cost $22 313, nearly two times higher than the estimated cost of $11 295 for 3D-CRT used in our model. Another limitation of the current analysis relates to the scope of cost inputs since the costs of symptom-management medications, outpatient visits, and hospital charges were not included in the model.

Finally, the current model was designed to test ART versus observation rather than ART versus SRT. When SWOG 8794 was designed, the study question reflected the state of PC at that time, and the investigators evaluated ART versus observation. However, much controversy regarding optimal management for PC after RP now centers instead upon ART versus early SRT [16]. Current practice patterns support the trend toward SRT: Ghia et al. recently reported that <20% of patients, who qualify, based on APFs, receive ART [13]. Although the decision analysis model of ART versus observation does not directly inform decisions regarding ART versus early SRT, this cost-effectiveness analysis nevertheless provides a foundation for considering the value of postprostatectomy RT for PC.

In conclusion, ART is an effective and cost-effective strategy for appropriately selected PC patients, based upon this decision analysis model of ART versus observation using published results of SWOG 8794. This model provides a baseline for considering similar management dilemmas in PC and for evaluating changes in the details of ART planning and delivery that might increase (IMRT and image guidance) or decrease (shorter fractionation schedules) the financial costs of RT. Future research should focus on the comparative effectiveness and cost-effectiveness of ART versus early SRT and should incorporate comprehensive, prospectively collected costs incurred by medication charges and outpatient health care utilization, as well as on quality of life gains.

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disclosure

The authors declare no conflict of interest.

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