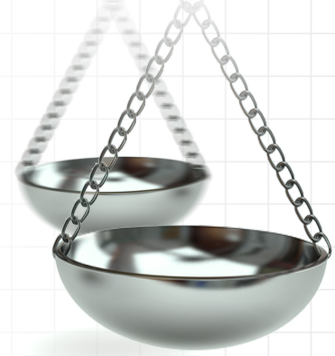
Research Article



Journal of Comparative Effectiveness Research

Reconsidering adjuvant versus salvage radiation therapy for prostate cancer in the genomics era

Aim: We developed a decision analysis framework to simulate the clinical choice of early adjuvant versus delayed salvage radiation therapy after radical prostatectomy. **Materials & methods:** We designed a Markov decision analysis model to represent two alternative treatment approaches for prostate cancer after prostatectomy over a 10-year time horizon. The model contained individualized inputs including genomic classifier score. Sensitivity analyses were performed to evaluate model results. **Results:** Observation with delayed salvage radiation is preferred according to the base case, with greater average length and quality of life. However, adjuvant therapy is preferred over observation with salvage when genomics-based estimates of recurrence are high. **Conclusion:** Model results were sensitive to genomics-based estimates of cancer recurrence and to nonprostate cancer mortality.

First draft submitted: 19 November 2015; Accepted for publication: 11 January 2016; Published online: 13 June 2016

Keywords: comparative effectiveness research • genomics • oncology

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In the USA, there were an estimated 233,000 new prostate cancer diagnoses during 2014 [1]. Nearly half of these men with localized prostate cancer chose radical prostatectomy (RP) as their initial treatment approach [2]. Among those who underwent RP, around 20% will subsequently recur [3]. Recurrence rates are much higher, around 40–60%, among prostate cancer patients with adverse pathological features such as extraprostatic extension, seminal vesicle invasion and/or an pathologically involved surgical margin [4]. Radiation therapy provides a potentially curative intervention for men who are at high risk of recurrence based upon the presence of adverse pathological features after RP, termed adjuvant radiation therapy (ART) [5]. Alternatively, radiation therapy also provides a potentially curative intervention in men which develop a biochemical recurrence after RP, termed salvage radiation therapy (SRT) [6]. This is typically identified by a rising prostate-specific antigen (PSA) blood test value after RP.

Although ART has been shown in randomized trials to improve outcomes compared with observation [5,7,8], those trials did not directly compare the contemporary alternatives of ART and SRT. Because of the lack of evidence comparing ART to SRT, current consensus guidelines recognize either ART or observation with selective SRT as reasonable options and recommend that clinicians present both alternatives to patients when appropriate [9]. Elliott and colleagues reported their results of a decision analysis model comparing clinical outcomes and quality-adjusted life years (QALYs) for these two alternatives: ART versus observation with SRT [10]. Inputs for transition probabilities and utilities in their study reflected the best available evidence for average values. Observation with SRT resulted in greater QALYs than ART over a 10-year time horizon, suggesting that observation is preferred over ART for the average patient [10].

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When considering the results of Elliott and colleagues [10], it is important to note that decision analyses that incorporate group level average may have limited relevance to clinical decisions for any given individual patient. Cowen and colleagues convincingly demonstrated the significance of this point in a decision analysis of treatment options for localized prostate cancer, showing that group level average values for utilities misrepresent the optimal treatment choice in 25–48% of cases compared with individual-level estimates of patient preferences for treatment outcomes [11]. Whereas the analysis provided by Cowen *et al.* highlights how critical and distinct the utility estimates of individual patients are [11], the recent advances of cancer genomics have demonstrated likewise the critical importance of individual level estimates of cancer recurrence [12,13].

The Decipher® genomic classifier (GC) test (GenomeDx Biosciences, CA, USA) provides individual estimates of the risk of metastasis after RP using expression profile analysis of RP specimens [14,15] has been shown to influence clinical recommendations by physicians [16,17]. In the current study, we [11] evaluate the impact of individualized utilities and genomics-based estimates of cancer progression using the Decipher GC assay. After developing a decision analysis framework to simulate the clinical choice of early ART versus observation and selective use of SRT, we performed a simulation cohort experiment using individualized estimates of cancer progression based upon the GC assay to evaluate individual subject level model outcomes. We then performed sensitivity analyses to determine which personal attributes are likely to influence decisional analytic outcomes for individual patients in such a way that the individual's optimal treatment choice may differ from population level recommendations. This emphasis on broad-range values for sensitivity analyses was adopted to inform a planned program for personalized decision aids to guide patient decisions incorporating genomics information and other relevant factors.

Materials & methods

A Markov decision analysis model [18] was developed to compare the outcomes obtained for the two alternative treatment approaches of early ART versus observation with delayed use of SRT for PC patients at high risk of recurrence after RP. High risk was defined as presence of one or more adverse pathological feature (extraprostatic extension, seminal vesicle invasion and/or positive surgical margin) to reflect indications for ART [4]. The model includes the following key clinical health states associated with the patient population and PC disease course: no evidence of disease (NED), biochemical recurrence (BCR), BCR after treatment failure, distant metastasis (DM), death from prostate cancer and death from causes other than prostate cancer. The model also assumes that hormone therapy was given to patients that BCR after treatment failure or DM. Potential treatment-related complications in the model include bowel dysfunction (BD), urinary incontinence (UI) and erectile dysfunction (ED). These potential treatment-related complications were considered the most salient potential complications, and a more comprehensive list would have added more complexity without necessarily affecting model outcomes. The model was first established using inputs identified from published literature to represent group-average values (as shown in Table 1). Model calibration was confirmed by verifying that clinical model outcomes for the ART and for observation/SRT (Supplementary Figures 1 & 2) were comparable to observed rates of distant metastasis and recurrence from available published evidence [5,8,19].

Transitions between clinical health states are represented as probabilistic events that can occur within the context of the model, as illustrated in Figure 1. Monthly cycles of possible events in the model were considered over a 10-year time horizon. The 10-year time horizon is similar to that used in a prior decision analysis on this topic [10]. We used a cohort simulation approach, with 5000 subjects transitioning through ART and another 5000 subjects transitioning through observation for a total sample size of 10,000. The sample size was chosen to ensure estimation of expected QALYs to within 0.1 QALYs. We used paired sample runs to estimate the average differences between groups in QALYs for each comparison. A similar methodology has been reported previously by our group [20]. In this study, we deemed the 'preferred' treatment alternative to be the one with more average QALYs.

Model inputs

Sources for model inputs were based upon a recent published decision analysis of ART versus SRT [10], with additional updates and supplementation of model estimates obtained from a PubMed search of the available published literature (Table 1). Estimates for probabilistic events are shown in Table 1 as annual probabilities, but were converted to monthly probabilities for use in the model. Complication events were entered as incremental beyond the baseline risks associated with prostatectomy, as all subjects were assumed to be post prostatectomy. All subjects in both groups entered with an assumed utility of NED of 1.0, as has been performed in a previously published model [10], so model results reflect a direct comparison of the two treatment alternatives. This provides for a simpler model and does not change model conclusions, but would be expected to overestimate overall QALYs for this population. Util-

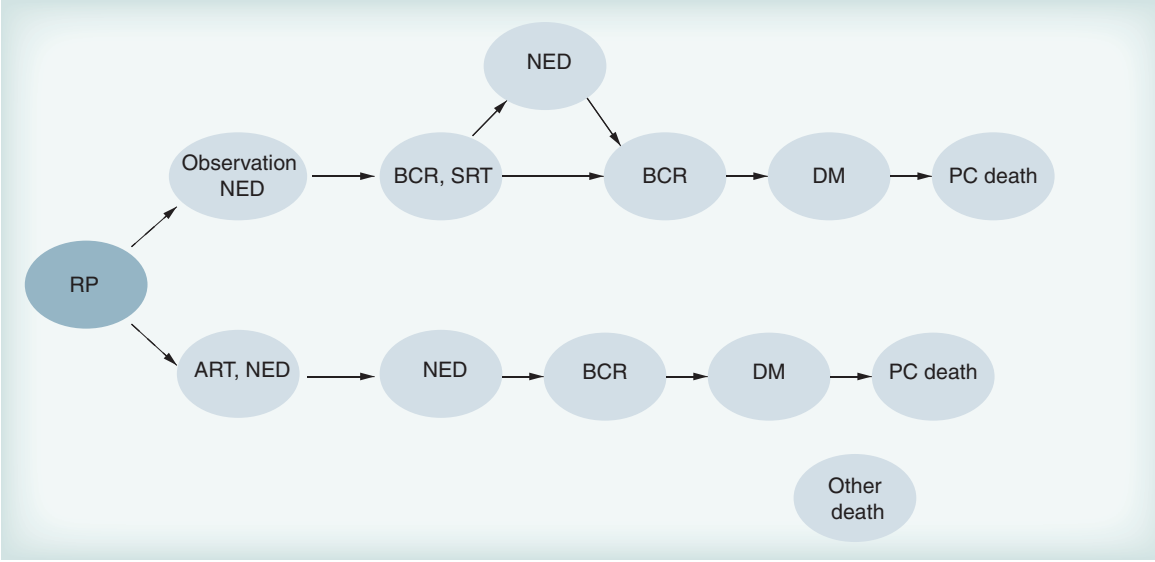

Figure 1. Markov process. The model is designed to represent prostate cancer events of recurrence, metastasis and death, as well as complications of treatment.
ART: Adjuvant radiation therapy; BCR: Biochemical recurrence; DM: Distant metastasis; NED: No evidence of disease; PC: Prostate cancer; RP: Radical prostatectomy; SRT: Salvage radiation therapy.

ity estimates are listed in Table 1. Utility estimates applied to time spent in the model health states, and their accrual for members of the cohort over time was used to calculate total QALYs obtained for both of the compared decision alternatives. A utility is a value that represents an individual patient's preference for a particular health state, with potential values ranging from 0 (death) to 1 (perfect health). Model inputs for utilities were obtained from the published literature, reflecting the average health state preferences of male patients who completed time trade-off experiments to evaluate how much time they would sacrifice to avoid a given health state [10]. Since model inputs were drawn from the best available published literature, it is possible that they may overestimate disutility if contemporary radiation techniques have resulted in improved utility values during therapy. Average values were used for the initial model, and then the upper and lower values were used for sensitivity analyses (described below) [10]. When patients are on treatment, the health state utility is multiplied by the treatment state utility. Probabilities for annual risk of death due to causes other than prostate cancer were based on recent life tables from the Centers for Disease Control and Prevention [21], with adjustment for aging of the cohort over the 10-year time horizon.

Importantly, the model design included GC-defined individualized estimates of prostate cancer BCR and DM. Data regarding these risks were obtained from the published literature [14,15]. GC-based estimates were assumed to be exact, although it should be noted that the area under the receiver operating characteristic curve (AUC) for the GC assay is actually reported to be 0.79 [14]. The assumption of perfect accuracy of the GC test was made for practical reasons related to the model, but this means that there is some inherent uncertainty in the model outcomes that mirrors the uncertainty of the GC assay. GC-based estimates of 5-year DM were used to proportionally adjust the baseline monthly probability inputs for BCR and DM during the 10-year time horizon, with an assumed association between BCR and DM.

Sensitivity analyses

Sensitivity analyses were performed to include a wide range of potential values in order to represent potential heterogeneity among individuals (Table 1). The following model estimates were included in the sensitivity analysis: yearly probability of death from other causes; GC-defined probability of BCR and DM; probability of complications, to represent the potential impact of a hypothetical predictive strategy or assay that would provide stratified estimate of RT-induced normal tissue toxicity; and utilities for health states and complications. Probability estimates for annual risk of death from causes other than PC were extracted from the National Vital Statistics Report [21], using the lower and upper values across a range of ages from 40 to 84 years. The range used for GC-defined risk of DM at 5 years reflects the highest and lowest estimates from the cohort reported by Karnes *et al.* [14]. The full range of utility values measured in a cohort of male participants in the Stewart *et al.* study [22] was applied in the sensitivity analyses, reflecting a wide range of preferences regarding PC treatments and outcomes. The use of the broad range of utili-

Table 1. Transition probability and utility inputs used as group level inputs for the model.

Model input	Input value	Range used in sensitivity analysis	Citations/notes
Disease progression probabilities (annual)			
BCR from NED state: – Under observation – After salvage Therapy – After adjuvant therapy Metastasis from BCR state: – After salvage therapy – After adjuvant therapy	 0.0945 0.1416 0.039 0.065 0.057	 (0.0118–0.5968) (0.0177–0.8943) (0.0049–0.2463) (0.008–0.411) (0.007–0.360)	 Stephenson *et al.* [19] Thompson *et al.* [5] Wiegel *et al.* [8] GC-based risk estimates extrapolated from 5-year DM range of 0.0095 to 0.48 in cohort with overall risk of 0.076; proportional adjustments were applied to BCR and metastasis estimates based on values from the Decipher genomic classifier [14,15]
Prostate cancer death from metastasis state: – After salvage therapy – After adjuvant therapy	 0.2412 0.2412	±10%	Boorjian *et al.* [24]
Complication probabilities after treatments			
Erectile dysfunction Urinary incontinence Bowel dysfunction	0.04 0.04 0.18	(0.02–0.08) (0.02–0.08) (0.09–0.36)	Elliott *et al.* [10], occurs in patients who have had radiation therapy. Sensitivity analysis ranges are for modeling the effect of comorbidities or hypothetical radiogenomics assay
Annual noncancer mortality risk	0.018443	(0.002484–0.072806)	From the National Vital Statistics Report [21] for age group 65–69 years; sensitivity range represents range for men 40–44 years versus 80–84 year of age
Utility values for health of treatment state			
NED	1	-10%	Assumption
Death	0	N/A	Assumption
BCR Metastasis	0.67 0.25	(0.56–0.84) (0.01–0.52)	Stewart *et al.* [22], interquartile ranges used to define lower and upper values
Radiation therapy	0.73	±10%	Stewart *et al.* [22], during a 3-month interval
Hormone therapy	0.73	±10%	Konski *et al.* [25]
Complication-related utility inputs			
ED	0.89	(0.86–1.00)	Stewart *et al.* [22]
UI BD UI, ED BD, ED BD, UI BD, UI, ED	0.83 0.71 0.79 0.57 0.70 0.45	(0.78–0.98) (0.61–0.90) (0.76–0.96) (0.41–0.76) (0.66–0.88) (0.17–0.78)	Interquartile ranges used to define lower and upper values

When patients are on treatment, the health state utility is multiplied by the treatment state utility. Citations are included, as well as notes to explain when the probabilities and utilities are applied within the model. The sensitivity analyses evaluated a broad range of probabilities and utilities, reflecting individual-level variability, to identify potential components to include in subsequent personalized decision aids. Unless otherwise states, the range used in the sensitivity analysis was 10% higher and lower than the input value.
BCR: Biochemical recurrence; BD: Bowel dysfunction; DM: Distant metastasis; ED: Erectile dysfunction; GC: Genomic classifier; N/A: Not applicable; NED: No evidence of disease; UI: Urinary incontinence.

ties values was designed to simulate the potential effects of a patient's individual responses to a questionnaire regarding prostate cancer treatment outcomes.

One-way deterministic sensitivity analyses were also performed for each model input. These results are summarized in a tornado diagram that lists the range of possible differences in QALYs compared with the baseline case estimates, in order to illustrate the relative impact of potential variation in model estimates on model results. Probabilistic sensitivity analyses was performed with inputs drawn from triangular distributions about the estimated mean values of estimates, with distribution end points set at plausible minimum and maximum values.

Results

We first developed a Markov model with group level averages, which represents the base case example. On average, the ART cohort obtained lower QALYs (6.73; 95% CI: 6.67–6.79) in the base case scenario than the observation/SRT cohort, which received 8.1 QALYs (95% CI: 8.03–8.17). Paired sample runs demonstrated that observation/SRT was preferred over ART 83.04% of the time. Supplementary Figures 1 & 2 illustrate the percentage of the cohort in each model health state over the 10-year time horizon for the base case estimates for the ART and for the observation/SRT cohorts, respectively. Overall life years were not significantly different for the two alternatives of ART (9.03; 95% CI: 8.96–9.09) and observation/SRT (9.08; 95% CI: 9.01–9.14).

Sensitivity analyses

One-way sensitivity analyses were conducted using the broad ranges shown in Table 1. Observation/SRT was preferred over ART, meaning more QALYs, in most instances even when the model was subjected to a broad range of potential values for probabilities of BCR and DM (as estimated based on GC assay), risk of death from causes other than prostate cancer (estimated based upon age) and complications (BD, UI, and/or ED), as well as for utilities associated with health states and complications.

The model results were sensitive only to the higher genomics-based estimates of the probability of BCR for the ART and SRT cohorts (as shown in Table 1). When the risk of BCR from the observation state was high, ART was favored 78.22% of the time, with an average of 6.73 QALYs (95% CI: 6.67–6.79). In comparison, observation/SRT obtained an average of 6.22 QALYs (95% CI: 6.17–6.28). Similarly, when the risk of BCR from NED was high, ART was favored 63.88% of the time, with an average of 5.15 QALYs (95% CI: 5.10–5.20), more than the average of 4.55 QALYs obtained with observation/SRT (95% CI: 4.50–4.59).

On the other hand, observation/SRT was favored over ART over 98% of the time when the genomics-based estimate of BCR from the observation or NED states was low. Therefore, the model results were only sensitive in one-way analyses to a high risk of BCR, which reflected a high risk of recurrence as defined by the GC assay.

One-way sensitivity analyses demonstrated the following top five determinants of differences in QALYs from the base case scenario (in descending order of magnitude of effect): probability of BCR from NED, probability of death from causes other than prostate cancer, probability of BCR while under observation, probability of BCR after ART, and complication utilities (Figure 2). Probabilistic sensitivity analysis resulted in lower overall life years and QALYs compared with the base case results, for both ART and observation/SRT. On average, the ART cohort obtained higher overall life years (8.10; 95% CI: 8.02–8.18) and QALYs (5.63; 95% CI: 5.57–5.70) in the probabilistic sensitivity analysis scenario compared with observation/SRT (7.92 life years; 95% CI: 7.85–8.00; 5.88 QALYs; 95% CI: 5.81–5.96), although observation/SRT was still preferred 59.94% of the time.

Discussion

For the base case scenario, our simulation cohort experiment showed that observation/SRT was associated with better model outcomes (overall life years and QALYs) than ART. These findings were robust to potential variation in most factors included in the one-way sensitivity analyses. Probabilistic sensitivity analyses, performed with a range of assumed utility values, demonstrated that the model outcomes are relatively robust to variations in the combined effects of probability inputs: ART was associated with higher average QALYs, but SRT was favored in the majority of cases. In sum, these results demonstrate that observation/SRT was preferred over ART in the majority of sampling runs. Interestingly, the findings were sensitive to genomics-based estimated values for probability of developing BCR while under observation after RP as well as age-based estimates of risk of noncancer related mortality. Our sensitivity analyses were designed to reflect a particularly broad range of potential values for subjects in order to represent genomics-driven decisions based on personalized risk of cancer progression (using the GC score), incorporation of patient age when evaluating life expectancy (using life tables) and consideration of individual patient preferences for treatment outcomes (using utilities). Our findings would suggest that optimal patient decision-making regarding ART after RP should consider individualized, patient-level inputs for the genomics-based estimates of BCR DM, as well as for risk of nonprostate cancer related mortality, as these factors were shown to significantly influence model outcomes.

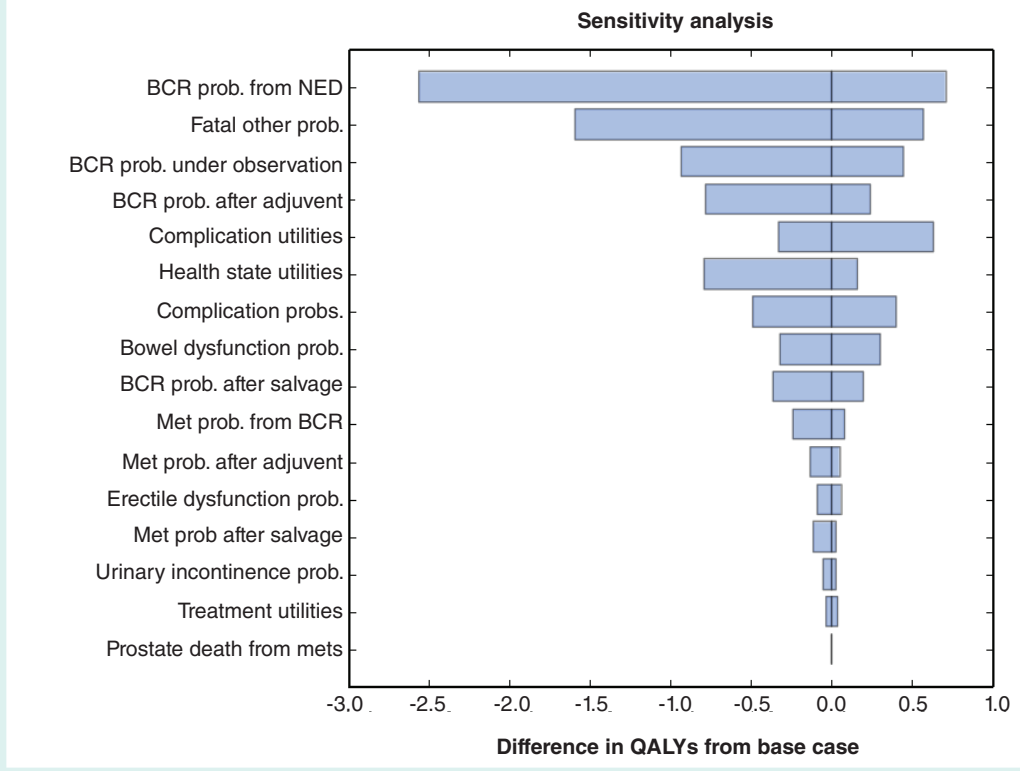

Figure 2. Tornado diagram from probabilistic sensitivity analysis of adjuvant radiation therapy versus observation and selective use of salvage radiation therapy. Each factor is ordered from largest to smallest variation in quality-adjusted life years from the base case scenario.
BCR: Biochemical recurrence; Prob.: Probability; Met: Distant metastasis; NED: No evidence of disease; QALY: Quality-adjusted life year.

For the base case scenario, our findings are similar to the decision analysis of ART versus observation with selective SRT that was previously reported by Elliott and colleagues [10]. They developed a Markov model and observed more QALYs after observation and SRT than after ART (6.80 vs 6.13 QALYs). Their results were sensitive to changes in the utility associated with receiving RT, with ART preferred over observation when the utility of receiving RT was above a threshold value of 0.85 [10]. Careful comparison of the Markov decision analytic models between studies also reveals differences in the model transitions to PC-related death between our study and that of Elliott *et al.* [10]. In the current model, the occurrence of PC-related death required development of metastatic disease during a previous monthly cycle. This design feature was chosen to represent the natural history of PC. The model developed by Elliott and colleagues permits the occurrence of PC-related death within the same cycle as PSA recurrence while under observation or within the cycle of NED after RT [10]. Such a design does not accurately represent the clinical behavior of PC, and our model constructs a more appropriate and accurate comparison between ART to observation and SRT.

Notably, the model results in the current study were not sensitive to changes in utilities for health states associated with PC disease progression and/or treatment-related complications. This differed from our original expectations, which were based upon the results of Elliott and colleagues, who found that their model outcomes were sensitive to the utility associated with receiving RT [10]. In addition, the relatively low impact of utility input values in the current model differs from the seminal example in localized prostate cancer published by Cowen *et al.* [11].

Several limitations attend this analysis. The model outcomes are dependent upon conceptualization of the problem represented in the decision analysis design and the estimates included for probabilistic events. Importantly, we assumed 100% accuracy of the GC test, for the sake of feasibility in model design, so our model results therefore contain the inherent uncertainty of the GC test. This remains a challenge for decision analysis

modeling of genomic testing, but it should be noted that sensitivity analyses do represent inherent uncertainty in model estimates. We also assumed that all patients who experienced BCR would receive early SRT, meaning that SRT would be initiated when the PSA is low and the prostate cancer more likely to be cured with treatment [19]. In clinical practice, this is often not the case as many patients are lost to follow-up or not referred for SRT, but the model was designed to represent the scenario of ideal medical care in order to simulate decision-making under optimal conditions. Our model also assumes a uniform response rate after SRT, but this may vary among patients. Den and colleagues found that PC patients with high GC scores, but not those with low GC scores, had worse prostate outcomes after SRT than after ART [23]. Such variable effects of SRT were not captured in our model, so our model may overestimate QALYs obtained with observation/SRT. Our model and analyses focus upon QALY differences between ART and observation with SRT, and the use of sensitivity analyses to identify model inputs to which the results are sensitive. Our analysis focuses on QALYs to the exclusion of other considerations such as direct and indirect financial costs of healthcare or other decisional outcomes such as decisional regret or satisfaction, which may be important but are beyond the scope of our current study. Finally, our model is not able to provide results regarding which particular patients will derive clinical benefit from genomic classifier testing. Additional clinical validation studies may in the future provide insight on this question.

Conclusion

In conclusion, we developed a Markov model to compare estimated outcomes after ART versus observation with selective SRT for PC patients with adverse pathological features after RP. ART was preferred over observation in most instances across a broad range of utility estimates, but model results were sensitive to the genomics-based estimates of probabilities of BCR and age-based estimates of probability of death from causes other than PC. Our findings suggest that patients with high genomic classifier scores may benefit from including this information in their decision-making process. Future efforts to develop decisions aids for ART should emphasize the incorporation of genomic assay results as a basis for individualized inputs in the decision analytic model.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2015-0015

Financial & competing interests disclosure

This work is supported by an American Society of Radiation Oncology (ASTRO) Comparative Effectiveness Research Award. TN Showalter and JM Lobo have received research funding from GenomeDx, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- For prostate cancer patients with adverse pathological features after radical prostatectomy, the two treatment alternatives are adjuvant radiation therapy (ART) versus observation with delayed use of salvage radiation therapy (SRT) for a rising prostate-specific antigen blood test.
- A recent decision analysis model suggested that observation with SRT was preferred over ART.
- The development of genomic classifier testing, which provides individualized estimates of cancer recurrence, offers the possibility of considering a patient's personal risk of recurrence when making a decision regarding ART.
- We designed a Markov decision analysis model to represent the clinical alternatives of ART versus observation with selective SRT over a 10-year time horizon.
- Sensitivity analyses were performed using a broad range of potential values to represent heterogeneity in genomic classifier-based estimates of cancer recurrence and other model input estimates.
- On average, observation with SRT resulted in more quality-adjusted life years than observation.
- In sensitivity analyses, the higher estimate for genomic classifier score resulted in ART being preferred over observation.
- Model estimates of quality-adjusted life years were most sensitive to genomic classifier-based estimates of cancer recurrence and to age-based estimates of noncancer mortality.
- These results suggest that genomic classifier score influences model outcomes in the comparison of ART versus observation with selective SRT after prostatectomy for prostate cancer.

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