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Economic Evaluation

Lifetime Health and Economic Outcomes of Active Surveillance, Radical Prostatectomy, and Radiotherapy for Favorable-Risk Localized Prostate Cancer

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ABSTRACT

Objectives: To estimate the lifetime health and economic outcomes of selecting active surveillance (AS), radical prostatectomy (RP), or radiation therapy (RT) as initial management for low- or favorable-risk localized prostate cancer.

Methods: A discrete-event simulation model was developed using evidence from published randomized trials. Health outcomes were measured in life-years and quality-adjusted life-years (QALYs). Costs were included from a public payer perspective in Australian dollars. Outcomes were discounted at 5% over a lifetime horizon. Probabilistic and scenario analyses quantified parameter and structural uncertainty.

Results: A total of 60% of patients in the AS arm eventually received radical treatment (surgery or radiotherapy) compared with 90% for RP and 91% for RT. Although AS resulted in fewer treatment-related complications, it led to increased clinical progression (AS 40.7%, RP 17.6%, RT 19.9%) and metastatic disease (AS 13.4%, RP 6.1%, RT 7.0%). QALYs were 10.88 for AS, 11.10 for RP, and 11.13 for RT. Total costs were A$17 912 for AS, A$15 609 for RP, and A$15 118 for RT. At a willingness to pay of A$20 000/QALY, RT had a 61.4% chance of being cost-effective compared to 38.5% for RP and 0.1% for AS.

Conclusions: Although AS resulted in fewer and delayed treatment-related complications, it was not found to be a cost-effective strategy for favorable-risk localized prostate cancer over a lifetime horizon because of an increase in the number of patients developing metastatic disease. RT was the dominant strategy yielding higher QALYs at lower cost although differences compared with RP were small.

Keywords: active monitoring, active surveillance, cost-effectiveness, cost-utility, discrete-event simulation, health economics, localized prostate cancer, modeling, radiation therapy, radical prostatectomy, radiotherapy, simulation.

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Introduction

Active surveillance (AS) is a recommended management strategy to delay or avoid radical prostatectomy (RP) or radiation therapy (RT) for low-risk localized prostate cancer (PCa), which is defined by a prostate-specific antigen (PSA) level less than 10 ng/mL, clinical stage up to cT2a, and a Gleason score of 3 + 3 or lower (grade group 1).[1,2] For favorable to intermediate-risk PCa, defined as PSA between 10 and 20 ng/mL and grade group 1 or PSA less than 10 ng/mL and Gleason 3 + 4 (grade group 2) and cT less than or equal to 3, AS is associated with a higher risk of developing metastatic disease, but it is still considered as an initial management strategy.[1,2] Given that only a minority of low- and favorable- to intermediate-risk PCas represent life-threatening disease, AS may spare patients from common treatment-related sexual, urinary, and bowel complications, which may have a substantial impact on quality of life.[3]

The Prostate Testing for Cancer and Treatment (ProtecT) trial is the only clinical study to date that has randomized patients with PCa to AS, RP, or RT.[4] Of the 1643 patients with screen-detected PCa enrolled in the trial, approximately 80% were considered at low- or favorable- to intermediate-risk based on the distribution of Gleason score and clinical tumor stage. At a median follow up of 10 years, despite that 55% of the patients in the AS arm had received radical treatment, the rate of metastatic disease was significantly higher in the AS arm at 6.3 per 1000 person years than 2.4 and 3.0 for the RP and RT arms, respectively (P=.004). Nevertheless, no significant difference in PCa-specific and overall survival was observed.

Noble et al[5] performed a cost-utility analysis based on the ProtecT trial data, finding that all 3 strategies yielded similar quality-adjusted life-years (QALYs): 6.98 for AS, 6.91 for RP, and 7.09 for RT. Nevertheless, mean costs were lower for AS at £5913 than £7519 for RP and £7361 for RT. Given that this analysis was

based on a median of 10-year follow up, lifetime health and economic outcomes were not captured. Long-term differences between strategies may be different because of potentially increasing differences in clinical progression, development of metastatic disease, and cancer-specific mortality beyond the trial time horizon.

Sanghera et al[6] extrapolated data from the ProtecT trial to a lifetime horizon for different subgroups. Like Noble et al,[5] they found comparable health outcomes between strategies, but overall, the lifetime costs were found to be the highest for AS. Although this was an indication of less favorable long-term economic outcomes for AS, the use of a Markov cohort model had several implications. For example, fixed state costs and utilities suggest that the AS protocol was time and age independent and that treatment use and the risk of complications were stable over time, which is not supported by the published ProtecT data.[4] Furthermore, transitions from states other than the initial state were assumed to be stable over time, which is inconsistent with the corresponding time-to-event curves. Finally, given the low number of metastases and cancer deaths observed over the median 10 years of follow up, extrapolation was very uncertain. Consequently, substantial structural and parametric uncertainty exists in the cost-effectiveness estimates of management strategies for localized PCa.

We sought to negate the existing uncertainty regarding the cost-effectiveness of AS, RP, and RT for localized PCa by supplementing the evidence from the ProtecT study with evidence from randomized studies in the metastatic setting and by using an individual-level simulation technique to accurately model the clinical pathway and available evidence.

Methods

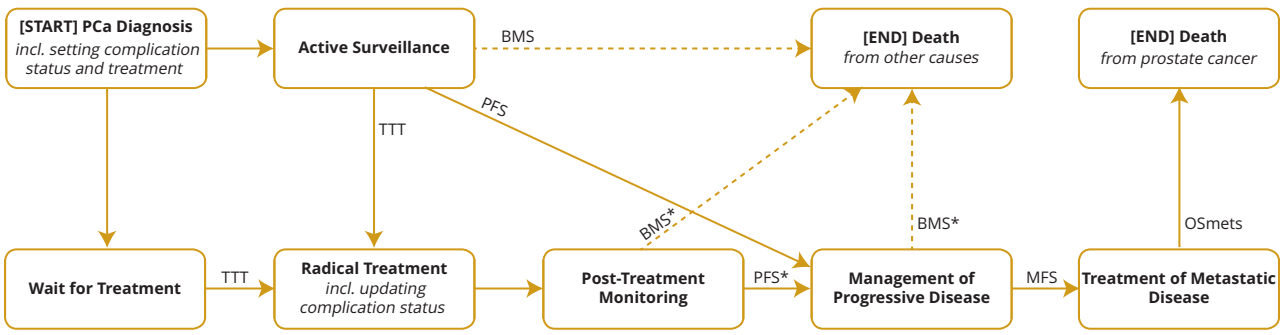
A model-based analysis was performed to estimate the long-term health economic outcomes of AS, RP, and RT for a population of 61-year-old men with newly diagnosed low- or favorable-risk localized PCa, based on the population of the ProtecT trial, the evidence of which served as foundation for this study. Although this section provides a comprehensive overview of the health economic model, a more detailed overview, including the model structure, validation, and analyses, is available from Appendix 1 in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.06.004. An overview of all model parameters and their values is provided in Appendix 2 in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.06.004.

Overview

A discrete-event simulation (DES) model was developed in R version 3.6.1 (R Core Team, Vienna, Austria). DES is an individual-level continuous-time simulation technique in which individuals can experience events at any point in time, with the simulation efficiently progressing from event to event. Because DES is an individual-level simulation technique, individuals' histories and attributes or characteristics can influence what and when events occur.[7] The increased flexibility of DES compared with state-transition models, such as Markov cohort models, allows complex clinical pathways to be modeled more naturally and efficiently.[8,9]

The model was constructed using different modules, each representing a group of clinical events (Fig. 1). In the AS module, individuals were monitored until they received radical treatment with RP or RT, turned 75 years old, or died of other causes. From age 75 years, individuals were transferred to a watchful waiting (WW) protocol, and it was assumed no radical treatment would be started after this age. In accordance with what is recommended and considered current best practice in Australia, the simulated AS protocol included a PSA test every 3 months, a digital rectal examination every 6 months, and a transrectal ultrasound-guided biopsy and multiparametric magnetic resonance imaging after 1 year and 3 years and subsequently every 3 years.[10] The WW protocol existed for a PSA test every 6 months. The Radical Treatment module simulated the impact of either RP or RT in terms of complications and resource use (see section Complications and Quality of Life and section Resource Utilization and Costs for details). The Post Treatment Monitoring module simulated a monitoring protocol until disease progression, age 75 years, or death due to other causes. This monitoring protocol consisted of 3 monthly PSA tests until 2 years after treatment, followed by 6 monthly PSA tests until 5 years, and annual PSA tests thereafter.

Figure 1. High-level overview of different modules (rectangles) in the simulation model. The abbreviations on the arrows relate to the time-to-event distributions used to inform whether and when the event occurs, with arrows without a distribution reflecting events that do not result in a delay. Wait for Treatment is not an explicitly modeled or discussed module, but it is included to visualize that patients who will undergo radical treatment may not do so immediately. Consequently, there is no BMS from Wait for Treatment because patients who will not end up receiving radical treatment are assumed to be on Active Surveillance until death because of other causes. See Appendix 1 in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2021.06.004 for further details. * indicates that the time-to-event is corrected for any time that has passed since the start of the simulation.



BMS indicates background mortality-free survival; MFS, metastases-free survival after progression; OSmet, overall survival after developing metastatic disease; PCa, localized prostate cancer; PFS, progression-free survival; TTT, time-to-treatment.

WW after treatment did not involve any routine testing. In the Management of Progressive Disease module, individuals had the option to receive further treatment with RT (for those who initially received RP) or androgen deprivation therapy (ADT) while being monitored until development of metastatic disease, age 75 years, or death due to other causes. The monitoring and WW protocols for this module were the same as in the Post Treatment Monitoring module. The Treatment of Metastatic Disease module simulated systemic treatments for metastatic disease until death.

Primary model outcomes included life-years (LYs), QALYs, and costs. Secondary outcomes included the proportions of patients eventually receiving radical treatment (ie, surgery or radiotherapy); experiencing clinical disease progression and developing metastatic disease; the probability of sexual, urinary, and bowel complications; and costs separated according to the following categories: PSA tests, digital rectal examination, transrectal ultrasound-guided biopsy, multiparametric magnetic resonance imaging, initial treatment, diagnosis of progression, treatment of progression, diagnosis of metastatic disease, and treatment of metastatic disease. All health and economic outcomes were discounted over a lifetime horizon at 5% per year according to the Australian reference case.[11]

Time to Events

The following time to events were modeled: time to radical treatment (TTT) with RP or RT, progression-free survival (PFS), metastases-free survival (MFS) after progression, background mortality-free survival (BMS), and overall survival after developing metastatic disease (OSmet). PFS was defined as the time from the start of the simulation to disease progression, with progression defined in accordance with the ProtecT study because the corresponding evidence was used to model PFS: metastases, T3/T4 disease, initiation of long-term ADT, ureteric obstruction, rectal fistulae, and the need for a urinary catheter owing to local tumor growth.[4]

TTT and PFS were modeled by replicating individual patient data from published Kaplan-Meier curves from the ProtecT trial using the method by Guyot et al,[12] allowing parametric survival distributions to be estimated by maximum likelihood and uncertainty in parametric estimates to be accounted for. Gamma, Gompertz, log-logistic, log-normal, and Weibull distributions were considered to model PFS for each management strategy independently. The log-normal distribution was selected based on clinical input from a urologist (NMC), radiation oncologist (SS), and medical oncologist (AAH) because this distribution reflected an expected "flattening of the curve" after 10 years. The impact of the selected distribution was assessed by using Weibull distributions in a scenario analysis.

TTT was modeled to account for the fact that in the ProtecT study and in clinical practice, a substantial proportion of patients who initially started on AS eventually received radical treatment, and that a minority of patients who initially were supposed to undergo surgery or radiotherapy did not receive treatment. TTT was modeled using flexible survival splines[13] because standard parametric survival distributions could not accurately reflect the data. In the simulation, a TTT was sampled for every individual, so that treatment would occur before or at the time of progression and compared with overall survival to determine whether treatment would occur.

No evidence from randomized studies on MFS after progression as defined in the ProtecT study could be identified. Therefore, Weibull distributions were calibrated to the rate of metastases observed in the ProtecT trial. Weibull distributions were selected because the shape of the hazard function (increasing, stable, or decreasing) can be controlled through the shape parameter. Based on clinical input (NMC, SS, AAH) and results from a study reporting MFS after RT specifically,[14] a decreasing hazard function was enforced during the calibration process through a shape parameter less than 1. Separate Weibull distributions for MFS were calibrated for AS, RP, and RT conditionally on whether PFS was modeled using log-normal or Weibull distributions.

BMS was modeled using a Gompertz distribution fitted to the Australian life tables for 61-year-old males.[15] Because distributions had to be modeled based on evidence from different sources, the competing risks of PFS, MFS, and BMS were modeled by simulating the first event to occur.[16] OSmet was modeled by pooling replicated individual patient data from the CHAARTED and GETUG15 trials and fitting separate distributions for patients with low- or high-volume disease and for ADT with or without docetaxel.[17] This approach acknowledged that patients with previous local treatment have different outcomes compared with those with de novo metastatic disease. Both standard-parametric and mixture-cure survival models based on Gamma, Gompertz, log-logistic, log-normal, and Weibull were considered. The standard Gamma distribution was selected based on slightly better likelihoods, and the standard Weibull distribution was used in a scenario analysis.

Complications and Quality of Life

The occurrence and impact of sexual, urinary, and bowel complications were implemented in the model based on discussions with consumer representatives and clinical input from a urologist (NMC), radiation oncologist (SS), and medical oncologist (AAH). Probabilities for experiencing complications were estimated based on the ProtecT study[18] using 4 mutually exclusive categories: ongoing complications from baseline regardless of treatment (baseline), treatment-related complications for the duration of 6 months after treatment (short term), ongoing treatment-related complications after treatment (long-term), or no complications.

Studies reporting health utility values (HUVs) were identified from a published systematic review.[3] A baseline HUV of 0.883 was estimated by pooling baseline values for AS, RP, and RT elicited using the EQ-5D-3L in the ProtecT study.[18] The disutility of complications was estimated based on a study that used the EQ-5D-3L to elicit HUVs and distinguished between patients with PCa with and without a complication,[19] with a disutility of 0.023 for sexual complications, 0.095 for urinary complications, and 0.209 for bowel complications. In case multiple complications were experienced simultaneously, the highest disutility was applied. For each complication type, 3 categories for the duration of complications and disutilities were simulated: from diagnosis to metastatic disease or death (baseline), for a duration of 6 months after treatment or until metastatic disease or death if that occurred within 6 months from the treatment (short term), or from treatment to metastatic disease or death (long-term). A HUV of 0.660 was applied for metastatic disease based on a study that elicited values using the EQ-5D-3L in a metastatic castration-resistant PCa population.[20] All these HUVs were believed to be based on utility weights for the United Kingdom given that they reported the use of UK utility weights[20] or were performed in a UK patient population.[18,19]

Resource Utilization and Costs

Resource use and costs in 2020 Australian dollars were considered from an Australian public payer perspective by mapping costs to events in the model. An overview of all cost parameters and assumptions is provided in Table 1. Costs of medical

Table 1. Overview of cost parameters and assumptions, with costs in 2020 Australian dollars.

Cost parameter	Type	Cost	Further information
Investigations and consults			
Urologist consultation	Per event	79.05	MBS 116
PSA test	Per event	37.30	MBS 66659/66660
DRE	Per event	79.05	As part of consultation
TRUS-Bx	Per event	458.35	Biopsy (MBS 37 219) and ultrasound (MBS 55600/55603), no consultation because performed concurrently with DRE
mpMRI	Per event	450.00	MBS 63541/63543
Bone scan	Per event	600.70	MBS 61 425
CT scan	Per event	520.98	MBS 56801/56807
Diagnosis of progression	Once	1688.03	Consultation, PSA test, mpMRI, bone scan, CT scan
Diagnosis of metastases	Once	1200.73	Consultation, bone scan, CT scan
Radical prostatectomy			
Planning of surgery	Once	1200.73	Consultation, CT scan, bone scan
Surgery	Once	1731.31	75% of procedures without (MBS 37 210) and 25% with pelvic lymphadenectomy (MBS 37 211)
Anesthesia	Once	204.00	MBS 20 845
Ward stay	Once	9653.62	90% stay of 1.4 days without complications (M01B) and 10% stay of 3 days with complications (M01A)
Radiation therapy			
Planning of treatment	Once	5461.58	Consultation, ultrasound, CT scan, bone scan, preparation of dosimetry plan (MBS 15 565), treatment simulation (MBS 15 555)
Fiducial markers	Once	142.60	MBS 37 217
Delivery of treatment	Once	5353.00	20 days of treatment verification (MBS 15 715) and use of linear accelerator (MBS 15 275)
2 cycles of 12 weeks ADT	Once	511.72	Intermediate-risk patients (25%) based on an average of different drugs goserelin (PBS 8093Y), leuprolide (PBS 8708H), triptorelin (PBS 9279P), degarelix (PBS 2785N and PBS 2784M), bicalutamide (PBS 8094B, once with goserelin, leuprolide, and triptorelin)
Treatment of progression			
Radiation therapy	Once	13 850.25	See costs for initial radiation therapy above but with 35 instead of 20 days of treatment and no ADT
ADT			
Continuing drug costs	Monthly	360.91	Average of different drugs goserelin (PBS 8093Y), leuprolide (PBS 8708H), triptorelin (PBS 9279P), degarelix (PBS 2785N and PBS 2784M)
Bicalutamide for first cycle	Once	47.98	PBS 8094B, based on 75% as only in combination with goserelin, leuprolide, and triptorelin
Treatment of metastases			
Advanced cancer treatments	Once	50 431.13	Based on Gordon et al[23]

ADT indicates androgen deprivation therapy; CT, computed tomography; DRE, digital rectal examination; MBS, Medicare Benefits Schedule; mpMRI, multiparametric magnetic resonance imaging; PBS, Pharmaceutical Benefits Scheme; PSA, prostate-specific antigen; TRUS-Bx, transrectal ultrasound-guided biopsy.

services, tests, and treatments used in the context of localized PCa were obtained from the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme. The cost of ward stays after RP and treatment-related complications was based on the National Hospital Cost Data Collection Round 22 (financial year 2017-2018)[21] with the length of stay based on an Australian study.[22] Because treatment of metastatic disease was assumed to be independent of the type of previous treatment of localized disease, the cost of treating metastatic disease was included as a lump sum based on a recent study by Gordon et al.[23] This study modeled cost for the management of different stages of PCa for Australia. The costs of ward stays and treating advanced disease were inflated to 2020 Australian dollars using the consumer price index for health.[24]

Model Validation and Analyses

Common random numbers were used to decrease variation between simulations of different management strategies. The stability of model outcomes was assessed based on simulations of up to 200 000 individuals per strategy. Based on visual inspection, it was determined that a simulation of 100 000 individuals per strategy was sufficient to obtain stable outcomes.

The simulated outcomes were validated against the data from the ProtecT trial by running the simulation for 10 years to approximate the median 10-year follow up of the trial. Lifetime extrapolations were validated by a urologist (NMC), radiation oncologist (SS), and medical oncologist (AAH) for clinical feasibility.

The model was evaluated through probabilistic analyses of 1000 runs in which 100 000 individuals were simulated for each strategy. Uncertainty in the correlated parameters of survival distributions was quantified using multivariate normal distributions,[25] whereas uncertainty in other parameters was quantified using standard parametric distributions. Parameter uncertainty was not reflected in TTT, BMS, and fixed-cost parameters relating to Medicare Benefits Schedule and Pharmaceutical Benefits Scheme item numbers.

Structural uncertainty was explored in scenario analyses by changing the parametric distributions used to extrapolate PFS and

Table 2. Lifetime health outcomes and 95% confidence based on the probabilistic analysis.

Outcome	AS	RP	RT
Sexual complications (%)			
Short term	8.5 (7.3-9.8)	16.0 (13.3-19.1)	9.7 (7.6-12.1)
Long-term	15.8 (14.3-17.3)	27.1 (23.8-30.6)	20.2 (17.1-23.3)
Urinary complications (%)			
Short term	2.6 (1.9-3.4)	7.9 (5.8-10.2)	-
Long-term	1.9 (1.3-2.6)	5.9 (4.1-8.0)	-
Bowel complications (%)			
Short term	1.9 (1.3-2.6)	-	5.8 (4.1-7.7)
Long-term	0.7 (0.4-1.2)	-	2.3 (1.2-3.6)
Radical treatment (%)			
Radical prostatectomy	30.1 (26.7-33.6)	90.3 (90.3-90.3)	-
Radiotherapy	30.3 (26.7-33.6)	-	90.9 (90.8-91.0)
Clinical event (%)			
Clinical progression	40.7 (35.0-47.2)	17.6 (13.5-24.1)	19.9 (15.2-26.8)
Metastatic disease	13.4 (9.2-17.2)	6.1 (1.4-12.1)	7.0 (2.7-13.1)
Overall survival			
LYs	21.8 (21.4-22.1)	22.6 (22.0-23.0)	22.6 (22.0-22.9)
QALYS	18.8 (16.3-20.4)	19.4 (16.9-21.2)	19.4 (17.0-21.3)

Note. "-" (hyphen) not applicable.
AS indicates active surveillance; LY, life-year; QALY, quality-adjusted life-year; RP, radical prostatectomy; RT, radiation therapy.

OSmet to Weibull distributions. To allow for a comparison with results from previous studies, health economic outcomes were additionally simulated over 6- and 10-year time horizons.

Results

Table 2 presents lifetime clinical and health outcomes and shows that 60% of patients in the AS arm eventually received radical treatment (ie, RP or RT) compared with 90% and 91% in the RP and RT arms, respectively. Due to the high rate of radical treatment in the AS arm, a considerable proportion of patients experienced treatment-related complications, which might not be expected per AS strategy. There were also significantly more clinical progression events and a higher risk of metastatic disease in the AS arm, which resulted in a decrease of 0.8 years in mean overall survival compared with RP and RT. Although slightly more patients in the RT arm had clinical progression and developed metastatic disease compared with the RP arm, this did not result in a noticeable difference in survival.

Lifetime costs are presented in Table 3. The higher total costs for the AS arm are explained by the number of patients in the AS arm who eventually received radical treatment. These treatments occur at a later point in time compared with those receiving treatment in the RP and RT arms, which explains the greater difference between the undiscounted and discounted costs. The higher proportion of patients progressing and developing metastatic disease in the AS arm resulted in higher costs for the diagnosis and treatment of their progressive and metastatic disease. Consequently, the discounted total costs for the AS arm (A$17 912) were higher than the RP arm (A$15 609) and RT arm (A$15 118).

The health economic outcomes are summarized in Table 4. The RT treatment arm yielded the highest QALYs at the lowest costs and, hence, dominated the AS and RP arms. Nevertheless, differences between RT and RP were small. Over a range of willingness-to-pay values, RT had an approximately 60% chance of being most cost-effective compared with 40% for RP (Fig. 2).

Over a 6-year time horizon, all arms yielded 4.4 discounted QALYs, but the AS arm had lower discounted total costs (A$10 273) than RP (A$12 668) and RT (A$11 839) because of lower treatment costs. When considering a 10-year time horizon, all arms yielded 6.5 discounted QALYs and the increase in progression in the AS arm resulted in similar discounted total costs for all strategies: A$13 877 for AS, A$13 774 for RP, and A$13 022 for RT.

RT still dominated AS and RP with regard to QALYs over a lifetime horizon in the scenario analyses in which Weibull distributions were used to model PFS and OSmet (Table 4). With regard to LYs, modeling PFS using Weibull distributions resulted in a small decrease for RT compared with RP.

Discussion

Short-term health and economic advantages of AS were found to be negated over the long-term because it resulted in delayed rather than reduced treatment and increased clinical progression and development of metastatic disease. Upfront radical treatment with RP or RT resulted in both improved health outcomes in terms of LYs and QALYs compared with AS and with lower lifetime costs. RT was the most cost-effective treatment strategy overall, although differences in incremental costs, LYs, and QALYs compared with RP were small. This was consistent in scenario analyses addressing structural uncertainty arising from selected extrapolation methods.

Even though AS was not found to be cost-effective from a health economic perspective, QALYs may insufficiently capture the impact of the different management strategies from a patient perspective. For example, if 1000 patients were to be managed through AS rather than RP, that would prevent 75 patients from experiencing short-term sexual complications and 113 from experiencing long-term sexual complications. This would come at a cost of an estimated 10-month decrease in overall survival, but from a patient perspective, that may be considered worthwhile based on a life expectancy of about 22 years. Each patient may value such tradeoffs differently, and it is unlikely that HUVs elicited using the EQ-5D-3L, which were used in this analysis, sufficiently represent this patient perspective.

Table 3. Lifetime economic outcomes in Australian dollars and 95% confidence based on the probabilistic analysis.

Outcome	AS	RP	RT
Monitoring—PSA tests			
Undiscounted	1702 (1687-1718)	905 (896-913)	917 (909-925)
Discounted	1186 (1176-1196)	678 (671-683)	694 (689-699)
Monitoring—DRE			
Undiscounted	1193 (1192-1194)	190 (190-191)	182 (180-184)
Discounted	907 (907-908)	138 (138-138)	132 (130-133)
Monitoring—TRUS-Bx			
Undiscounted	1340 (1340-1341)	200 (200-201)	192 (189-193)
Discounted	1068 (1067-1068)	153 (152-153)	146 (144-147)
Monitoring—mpMRI			
Undiscounted	1316 (1315-1316)	197 (196-197)	188 (186-190)
Discounted	1048 (1048-1049)	150 (150-150)	143 (141-144)
Radical treatment			
Undiscounted	7326 (6241-8503)	11 586 (8375-15 045)	10 421 (10 414-10 436)
Discounted	5969 (5085-6927)	11 147 (8058-14 474)	10 198 (10 193-10 207)
Diagnosis of progression			
Undiscounted	687 (591-797)	297 (227-406)	336 (256-452)
Discounted	409 (348-472)	179 (137-239)	186 (143-247)
Treatment of progression			
Undiscounted	8428 (6233-10 896)	3196 (2579-3883)	4370 (3381-5344)
Discounted	3919 (2868-5057)	1539 (1215-1916)	1871 (1410-2360)
Diagnosis of metastases			
Undiscounted	173 (121-218)	76 (18-147)	85 (33-159)
Discounted	86 (56-112)	39 (7-81)	41 (15-79)
Treatment of metastases			
Undiscounted	6798 (3682-10 257)	3088 (714-6547)	3544 (1244-7157)
Discounted	3319 (1700-5149)	1587 (280-3529)	1706 (530-3551)
Total costs			
Undiscounted	28 963 (25 638-32 410)	19 735 (15 491-24 872)	20 236 (17 706-24 162)
Discounted	17 912 (16 164-19 743)	15 609 (12 040-19 445)	15 118 (13 864-17 116)

AS indicates active surveillance; DRE, digital rectal examination; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; TRUS-Bx, transrectal ultrasound-guided biopsy.

Sharma et al[26] were the first to report a model-based health economic analysis based on the published ProtecT results. Using a Markov model, they found AS to be the most cost-effective strategy over a 6-year time horizon and RP and RT to be more cost-effective over a 10-year horizon. Noble et al[5] performed a trial-based cost-utility analysis for the ProtecT study after a median follow up of 10 years. They found limited differences in QALYs but substantially lower costs for AS than RP and RT. Nevertheless, the authors concluded that longer follow up and extrapolation were required to determine the most cost-effective strategy over a man's lifetime. Subsequently, Sanghera et al[6] extrapolated the ProtecT study data over a lifetime horizon for specific patient subgroups. In line with our findings, their results suggested that AS was not cost-effective over a lifetime horizon and that differences between RP and RT were relatively small, which resulted in RP and RT each being the most cost-effective strategy for 3 out of 6 subgroups.

The analysis by Sanghera et al,[6] however, was subject to structural and parametric uncertainty. For example, fixed cycle costs and utility values may not have appropriately represented changes in the intensity of surveillance and uptake of radical treatments for AS over the years, or the impact of different durations of complications. Furthermore, there was a substantial uncertainty in the parameters of the distribution used for extrapolation because of a limited number of developed metastases and observed cancer-specific deaths over the trial follow. Additionally, the Markov model only allowed time-dependent transition probabilities for the initial model state, therefore, fixed transition probabilities (ie, exponential distributions) were used for transitions from all other states, whereas exponential distributions rarely provide an appropriate representation of time-to-event data. Furthermore, for the time-dependent transition probabilities from the initial state, only the strongly related Weibull and exponential distributions were considered. By employing an individual-level modeling method, synthesizing evidence on overall survival for metastatic disease from other randomized trials, and considering a broad range of commonly used survival distributions, we reduced both structural and parameter uncertainty in the cost-effectiveness estimates.

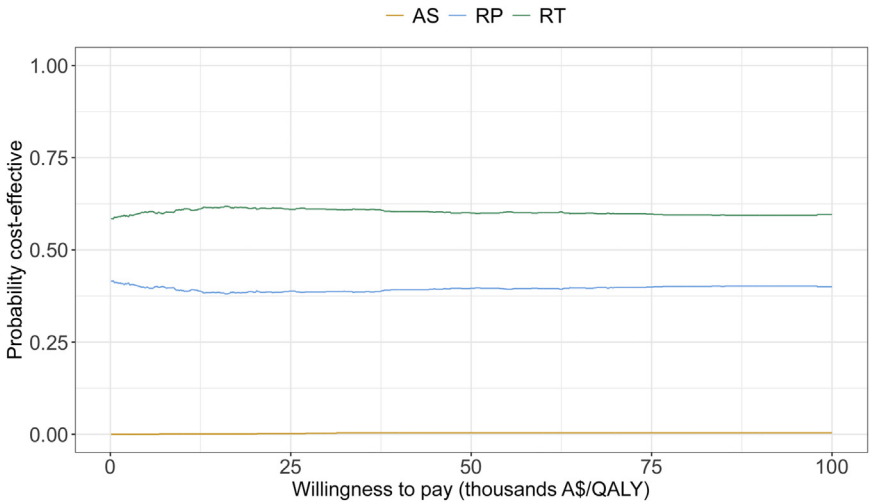
Nevertheless, despite replicating individual patient data from published time-to-event curves, our study was limited by a lack of access to individual patient data from the ProtecT trial. First, we could not consider heterogeneity in subgroups like Sanghera et al.[6] Second, because time-to-event curves for MFS after progression were not published, distributions had to be calibrated to published aggregated event rates. Finally, we assumed 20 fractions of radiotherapy (hypofractionated) as the standard of care in this favorable-risk cohort based on evidence from 3 randomized clinical trials and international consensus,[27] whereas fully fractionated longer courses of radiotherapy would have been more costly. Therefore, further

Table 4. Discounted health economic outcomes and 95% confidence intervals based on the probabilistic analysis for the base-case scenario and the scenario analyses, with costs in Australian dollars.

Scenario and Strategy	Discounted LYs	Discounted QALYs	Discounted Costs	Incremental LYs	Incremental QALYs	Incremental Costs	ICER (cost/LY)	ICER (cost/QALY)
Base-case scenario								
AS	12.61 (12.47-12.77)	10.88 (9.48-11.85)	17 912 (16 164-19 743)	-	-	-	-	-
RP	12.92 (12.70-13.11)	11.10 (9.64-12.14)	15 609 (12 040-19 445)	0.32 (0.04-0.56)	0.22 (−0.05 to 0.46)	−2303 (−5267 to 805)	Dominant	Dominant
RT	12.94 (12.75-13.09)	11.13 (9.75-12.18)	15 118 (13 864-17 116)	0.02 (−0.25 to 0.29)	0.03 (−0.23 to 0.30)	−492 (−4480 to 3349)	Dominant	Dominant
Scenario: PFS modeled using Weibull distributions								
AS	12.61 (12.32-12.88)	10.89 (9.49-11.90)	18 212 (16 046-20 757)	-	-	-	-	-
RP	12.95 (12.76-13.08)	11.13 (9.69-12.16)	15 651 (12 304-19 623)	0.33 (0.13-0.67)	0.23 (−0.08-0.58)	−2562 (−6288 to 1008)	Dominant	Dominant
RT	12.94 (12.68-13.09)	11.13 9.65-12.15)	15 429 (13 940-18 228)	−0.01 (−0.29 to 0.24)	0.00 (−0.28 to 0.26)	−222 (−4575 to 4019)	18 135	Dominant
Scenario: OSmet modeled using Weibull distributions								
AS	12.61 (12.48-12.77)	10.88 (9.48-11.85)	17 912 (16 166-19 740)	-	-	-	-	-
RP	12.92 (12.69-13.11)	11.10 (9.64-12.15)	15 609 (12 040-19 446)	0.32 (0.04-0.56)	0.22 (−0.05-0.45)	−2303 (−5272 to 807)	Dominant	Dominant
RT	12.94 (12.74-13.09)	11.14 (9.75-12.18)	15 118 (13 864-17 117)	0.02 (−0.25 to 0.29)	0.03 (−0.23 to 0.31)	−492 (−4481 to 3349)	Dominant	Dominant

Note. "-" (hyphen) indicates the reference for incremental outcomes.
AS indicates active surveillance; ICER, incremental cost-effectiveness ratio; LY, life-year; OSmet, overall survival after developing metastatic disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RP, radical prostatectomy; RT, radiation therapy.

Figure 2. Cost-effectiveness acceptability curve showing the probability that strategies are cost-effective for a range of willingness-to-pay thresholds.



AS indicates active surveillance; QALYs, undiscounted quality-adjusted life-year; RP, radical prostatectomy; RT, radiation therapy.

research may use individual patient data from the ProtecT study and randomized trials in the metastatic setting using patient-level modeling methods to address these limitations.

Conclusions

By synthesizing evidence from multiple sources in an individual-level simulation model, we reduced uncertainty regarding the cost-effectiveness of AS, RP, and RT for favorable-risk localized PCa. Over the lifetime of patients with PCa, AS was dominated by RP and RT from a health economic perspective because it was more costly and resulted in slightly lower LYs and QALYs. On an AS strategy, patients were more likely to experience disease progression and develop metastatic disease. Even though patients in the AS arm were also exposed to complications because 60% eventually received radical treatment, complications were most common in the RP and RT arms. RT was the most likely cost-effective treatment strategy overall but differences compared with RP were small.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2021.06.004.

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