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Estimating the healthcare costs of treating prostate cancer in Australia: A Markov modelling analysis

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Abstract

Purpose: To estimate the health system costs of prostate cancer by disease risk category and treatment type over 2016 to 2025 and to identify potential strategies to contain the cost increase.

Methods: A Markov cohort model was developed using clinical pathways from US prostate cancer guidelines and clinical expertise. Estimates of the probabilities of various treatments and outcomes and their unit costs were sourced from systematic reviews, meta-analyses, epidemiological publications and national cost reports. Estimated costs by stage of disease, by major treatments and by age at diagnosis were reported in 2016 US dollars. One-way and probabilistic sensitivity analyses assessed potential variation in the modeled costs.

Results: Australia-wide costs of prostate cancer were estimated at US$270.9 million in 2016 rising to US$384.3 million in 2025, an expected increase of 42%. Of this total increase, newly diagnosed low risk cases will contribute US$32.9 million, intermediate-risk US$56.8 million, high-risk US$53.3 million and advanced US$12.6 million. For men diagnosed at age 65 with low-risk disease, lifetime costs per patient were US$14,497 for surgery, US$19,665 for radiation therapies to the primary lesion, and US$9,234 for active surveillance. For intermediate- or high-risk disease, mean costs per patient were US$34,941 for surgery plus radiation and US$31,790 for androgen deprivation therapy plus radiation while advanced cancer therapies were at US$31,574 per patient. Additional costs for managing iatrogenic disease secondary to these treatments were excluded.

Conclusion: Strategies for identifying patients early before cancers have spread are critical to contain the estimated 42% increase in costs over the next decade. Increased uptake of active surveillance would also lead to substantial cost-savings in the management of low-risk prostate cancer.

Keywords: Prostate cancer; Cost analysis; Markov modeling; Active surveillance

1. Introduction

In 2012, an estimated 1.1 million men were diagnosed with prostate cancer throughout the world and a further 307,000 died of disease [1]. This condition is a significant public health issue for men and their families and will continue to be with a predicted 5-year global prevalence of 3.9 million [1]. Of all prostate cancers diagnosed in Australia, over 90% of men have clinically localized disease [2]. With an increase in the number of men living with this malignancy, it is important to plan for the resources and services needed to appropriately manage these patients. Healthcare costs are rapidly growing in many countries and one of the pressing issues for adopting promising new and expensive technologies is the health system's capacity to pay for them [3].

Using a mathematical model of the healthcare management of prostate cancer, we previously estimated the average cost to the Australian health system in 2016 for

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each case detected was US$18,825 (standard deviation [SD] = $3,118) [4]. Half of these costs were incurred in the first year following diagnosis (US$9,371). Mean patient costs were markedly higher with progressive disease; for very-low or low-risk cancer, were US$13,905, US$17,268 for intermediate-risk, US$26,387 for high-risk or locally advanced tumors, and US$32,130 (SD = $2,612) for advanced disease [4].

A significant proportion of men diagnosed with prostate cancer have clinically localized disease and it is important that these men are managed appropriately for this malignancy. The increased cost associated with additional interventions necessary for more advanced malignancy is apparent. However, less clear is the evidence for cost differences over time across alternative interventions for similar prostate cancer risk status. For example, for men with low-risk tumors, a regimen of regular biopsies and prostate specific antigen (PSA) testing while on active surveillance would incur costs over many years, which may exceed the costs of one-off prostatectomy [5]. Similarly, surgical vs. radiation therapies as first-line therapy may have different cost trajectories over time. The purpose of this study was to examine the health system costs by stage of disease at diagnosis and first-line treatment over the long term while accounting for secondary treatments if progression occurs and ongoing follow up and adverse sequelae.

2. Methods

2.1. Model structure

A Markov cohort health state transition model was constructed in *TreeAge Pro* (Version 2016) and we adhered to recent modeling guidelines [6,7]. The model was designed to describe initial management options, all subsequent adjuvant care related to prostate cancer, adverse events and associated costs over the long term. The treatments included surgery, radiation (external beam radiation therapy (EBRT) or brachytherapy), surgery plus radiation and, androgen deprivation therapy (ADT) and radiation. Watchful waiting and active surveillance were also included with the difference being that active surveillance leads to curative intent if disease progresses while symptom management is the aim if necessary with watchful waiting. Patients remain or move between 17 specified health states according to transition probabilities [4]. The health care costs for treatments, follow-up and sequelae associated with patient outcomes were assigned to the health states in the model.

The model accumulated costs over annual cycles. The starting age of the cohort was specified at 65 years [2] and a time horizon of 25 years was used for the base case. A man aged 65 could remain in the model for a maximum of 25 years; however, may die earlier, either of prostate cancer or other causes. Where relevant, as men age in the model over time, they face different outcomes for mortality and choices of treatment. Because the management decision is partly determined by the patient's life expectancy, age and existing comorbidities, we set the maximum age for receiving active surveillance at 74 years at which time we would expect that men would switch to watchful waiting. For example, a man diagnosed with low-risk prostate cancer at 76 years would be more likely to undertake watchful waiting while a man aged 62 with no comorbidities might be more likely to undergo active surveillance or radical prostatectomy. The model was tested over various age-at-diagnosis cohorts in 5-year groups from age 55 to 75 years.

The model structure is summarized in Fig. 1 and more details of the 17 mutually exclusive health states in the model are provided in our previous report [4]. Briefly, men are diagnosed with prostate cancer and categorized into National Comprehensive Cancer Network (NCCN) 2015 [8] staging of 1 of 4 health states defined by clinical staging (T score), Gleason and PSA markers:

(1) Very low and low risk (T1–T2a, Gleason ≤6, PSA < 10 ng/ml).
(2) Intermediate risk (T2b–T2c, Gleason 7, PSA10–20 ng/ml).
(3) High risk to locally advanced (T3–T4, Gleason 8–10, PSA > 20 ng/ml).
(4) Advanced disease (node positive and metastatic) [8].

"Very low" and "low risk" stages were combined because these men have the same treatment choices and

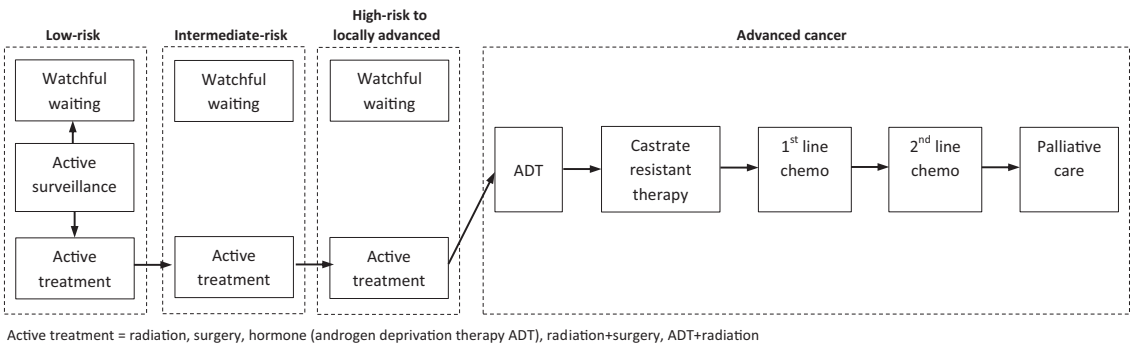

Fig. 1. Simplified model structure.

"locally advanced" was combined with "high risk" because only a small group of men have locally advanced cancers and they have not spread beyond the prostate gland clinically [9]. For very-low and low-risk individuals, a proportion of men will undergo active surveillance or, for men ≥ 75-years old, watchful waiting while the remainder are likely to receive surgery or radiation (either EBRT or brachytherapy). For individuals with intermediate and high-risk cancer, some men will undergo watchful waiting but most will receive active treatment. Major treatments in localized disease include surgery alone, radiation alone, surgery plus radiation, and radiation plus ADT. After the first year of diagnosis and treatment, men will receive adjuvant therapies as relevant. For example, a proportion of men after first-line prostatectomy will undergo second-line radiation or ADT plus radiation.

Treatment for advanced disease consists of ADT or if the patient experiences disease progression, therapies for castrate-resistant prostate cancer such as further hormone manipulation and first-line chemotherapy (docetaxel and second-line chemotherapy [cabazitaxel] or second line ADT such as enzalutamide or abiraterone and prednisone (Table 1). Supplements for bone health, zoledronic acid and bone scans were included as supportive care while men were on ADT and costs from the complications from chemotherapy affecting some men were also estimated (Table 1). In the first year, active surveillance typically includes a regimen of 2 urologist consultations, 4 PSA tests and 1 biopsy while after year 1, there would be 2 urologist consultations, 2 PSA tests and 1 biopsy every 2 years. While on active surveillance, some men will switch to active treatment for various reasons including worsening disease (e.g., short PSA doubling time, grade progression, stage progression, biopsy volume increase, and ureteral obstruction) and also patient choice.

2.2. Model inputs

Table 1 summarizes the key model inputs with their values, ranges and sources with full details provided in our online report [4]. We assume that all patients receive the highest standard of care. The key probabilities for initial diagnosis by risk stratification and treatment modalities were based on a population-based Australian registry study ($n = 2{,}724$) [2]. Other values for treatment modalities by risk stage, treatment complications and recurrence or progression estimates, were obtained from a systematic search of literature including meta-analyses, randomised controlled trials, observational studies, as well as clinical trial registries. Where appropriate, systematic reviews and meta-analyses were preferred for studies reporting recurrence rates after different treatments [10–12], and high-quality studies reporting disease progression [13–16,4] (Table 1). All rates were converted into probabilities using the rate to probability formula ($1 - e^{-\text{rate} \times \text{time}}$) where relevant. Survival duration will affect follow-up, ongoing treatment sequelae and overall lifetime costs. The model included age-dependent mortality rates and the increased risk of death from prostate cancer (relative risks). Background mortality rates in the general Australian male population, by age, were based on Australian Bureau of Statistics life tables [17]. For localized disease, relative mortality rates were derived from US Surveillance, Epidemiology and End Results estimates. For advanced disease, mortality rates were based on a meta-analysis from the Prostate Cancer Trialists' Collaborative Group [18] whereas several chemotherapy trial outcomes (Table 1) provided the probabilities of death after these treatments.

The study used an Australian health sector perspective to determine the costs (Table 1 in US dollars). Most services for prostate cancer care in Australia are provided by the State and Federal governments. Hospital costing reports and national Medicare reports (via the Medicare Benefits Schedule and Pharmaceutical Benefits Schedule) were used to value these resources. We did not report quality adjusted life expectancy in the context of this cost study. This type of outcome is used for cost-effectiveness studies when investigating the comparative costs and outcomes of various treatment strategies.

2.3. Analyses

The analyses aggregated the probabilities and values assigned to the different health states using an expected value (mean per person) analysis. We assessed the mean costs by treatment type as appropriate for the 4 risk categories and averaged overall by risk stage, and the cumulative costs per year to understand the ongoing burden and to compare strategies within risk groups. Costs by risk category were used to extrapolate costs Australia-wide over the next decade. We performed one-way sensitivity analyses for starting age, the threshold age for active surveillance (baseline 75 years and tested 72 and 78 years), the duration of active surveillance (baseline 10 years and tested 7–15 years) before men would switch to watchful waiting and model duration (baseline 25 years and tested 5–35 years). Probabilistic sensitivity analysis was also undertaken with 5,000 Monte Carlo simulations to determine the extent of parameter uncertainty of the model inputs simultaneously (Table 1) [6]. These analyses produced simulated means and 95% credible intervals (CrI). Future costs were discounted at 5% per year to adjust to present values and a half-cycle correction was applied throughout the model. Costs are provided in 2016 US dollars using http://eppi.ioe.ac.uk/costconversion/default.aspx (1 AUD = 0.7056 USD).

3. Results

Australia-wide costs of prostate cancer were estimated at US$270.5 million in 2016 rising to US$383.8 million in

Table 1
Key model inputs, sensitivity values, and sources [1]

	Value	95% CI/range	Distribution	Source
Structural inputs				
Model duration	25 years	5–35 years	–	Long-term and short-term assessed
Starting age	65	45–75	–	Most prostate cancers diagnosed in sixth decade of life (Evans, 2013)
Discounting	5%	0%	–	Future costs discounted at 5% as per Australian guidelines
Diagnosis probabilities				
Very low to low-risk disease	29%	27%, 31%	Dirichlet (785;1,201;647;91)	Evans (2013); Victorian Cancer Registry [2]
Intermediate-risk disease	44%	42%, 46%	Dirichlet (785;1,201;647;91)	Evans (2013); Victorian Cancer Registry [2]
High-risk to locally advanced disease	24%	26%, 22%	Dirichlet (785;1,201;647;91)	Evans (2013); Victorian Cancer Registry [2]
Advanced disease (N1 or M1)	3%	2.5%, 3.5%	Dirichlet (785;1,201;647;91)	Evans (2013); Victorian Cancer Registry [2]
Treatment probabilities				
No treatment (active surveillance or WW) in low risk	41%	37%, 45%	Beta (299;437)	Evans (2013); Victorian Cancer Registry [2]
Threshold age for active surveillance (AS)	75 years	72–78 years	–	Assumption; life expectancy and comorbidities would limit active surveillance participation
Men on AS switching to active therapy (annual)	Years 1–5: 4.86%, years 6–10: 2.44%, years 11–15: 1.70%, years 16–20: 0.00%		–	Klotz et al. [19] cumulative % pts leaving an AS program: Yrs 1–5: 24.3%,Yrs 6–10: 36.5%,Yrs 11–15: 45%,Yrs 16–20: 45%
Surgery in low-risk (of those treated)	68%	63%, 73%	Beta (291;134)	Evans (2013); Victorian Cancer Registry [2]
Radiation in low-risk (of those treated)	100%–68%	–	–	Complement of above
EBRT in low-risk (remainder are brachytherapy)	31%	23%, 39%	Beta (41;91)	Evans (2013); Victorian Cancer Registry [2]
No treatment (WW) in intermediate-risk	16%	13%, 19%	Beta (198;1,003)	Evans (2013); Victorian Cancer Registry [2]
Surgery in intermediate-risk (of those treated)	59%	56%, 62%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [2]
Surgery plus radiation in intermediate-risk (of those treated)	8%	6%, 10%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [2]
Radiation in intermediate-risk (of those treated)	26%	23%, 29%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [2]
EBRT in intermediate risk (remainder are brachytherapy)	62%	54%, 68%	Beta (139;84)	Evans (2013); Victorian Cancer Registry [2]
ADT plus radiation in intermediate risk (of those treated)	8%	6%, 10%	Dirichlet (579;76;253;76)	Evans (2013); Victorian Cancer Registry [2]
No treatment (WW) in high risk and locally advanced	14%	11%, 17%	Beta (80;495)	Evans (2013); Victorian Cancer Registry [2]
Surgery in high risk (of those treated)	38%	33%, 43%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [2]
Surgery plus radiation in high risk (of those treated)	11%	8%, 14%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [2]
Radiation in high risk (of those treated)	16%	13%, 19%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [2]
ADT plus radiation in high risk (of those treated)	35%	30%, 40%	Dirichlet (179;51;76;166)	Evans (2013); Victorian Cancer Registry [2]
Probability of recurrence and progression				
Recurrence after first-line surgery in low-risk	1%	0.5%, 2%	Beta (220;1,981)	Mullins (2012); cohort (1992–2011), 10% recurred in 15 years [15]
Recurrence after radiation treatment as first-line in low risk	2%	0.5%, 3.5%	Beta (3,555;14,221)	Grimm (2012) and Cooperberg (2013); 20% recurrence in 10 years [13,14]
Recurrence after surgery in intermediate to high risk	2.4%	0.5%, 4.5%	Beta (355;785)	Mullins (2012); cohort (1992–2011), 31% recurred in 15 years [15]
Recurrence after first-line rad in intermediate and high-risk	4%	2%, 6%	Beta (2211;4,107)	Grimm (2012) and Cooperberg (2013); 35% recurrence in 10 years [13,14]
Recurrence after ADT plus radiation	4%	2%, 6%	Beta (639;1,122)	A meta-analysis of six studies by Zhou (2013); around 36% had recurrence over 10 years [12]
Recurrence after surgery plus radiation	6%	4%, 8%	Beta (222;600)	A meta-analysis by Thompson (2013) of the three randomised trials SWOG 8794, EORTC22911, and ARO 96–02; around 27% had recurrence in 5 years [11]
Recurrence as advanced disease following surgery in intermediate to high-risk patients	1%	0.5%, 1.5%	Beta (131;993)	Mullins (2012); around 10% of intermediate-risk and 25% of high-risk patients developed metastatic disease over 15 years [15]
Recurrence as advanced disease following radiation in intermediate and high-risk patients	2%	1%, 3%	Beta (311;1,290)	Zelefsky (2008); around 30% high-risk and 10% of intermediate-risk patients developed metastases after radiation [16]

Progression to CRPC in advanced disease	23%	20%, 26%	Beta (663;741)	From Ross (2008); 300/553 (54%) patients progressed in 36 months [20]
Symptomatic metastases with CRPC	95%	92%, 98%	Beta (247;13)	Small (2004); around 95% of patients had metastatic disease confirmed by imaging [21]
Develop symptoms on observation	3%	2%, 4%	Beta (99;162)	Bill-Axelson (2014); around 38% of the patients on observation developed metastatic disease over 18 years [22]
Progression after first-line chemotherapy	24%	20%, 30%	Beta (127;208)	TAX 327 Study by Tannock (2004); 38% progressed over 21 months [23]
Progression after second-line chemotherapy	75%	70%, 80%	Beta (598;199)	de Bono (2011); 75% of the patient on abiraterone progressed in 12 [24]
Costs (US$ 2016)				
Prostate-specific antigen test	$30/test	Fixed	–	MBS items 66660 and 73928
Urology consultation and digital rectal examination	$61/visit	Fixed	–	MBS Item 104
Ultrasound guided biopsy	$495/procedure	Fixed	–	MBS items 37219; 55600; 72825, antibiotic prophylaxis and complications
Active surveillance in year 1	$738/year	Fixed	–	2 urology visits, four PSA tests, one biopsy
Active surveillance after year 1	$430/year	Fixed	–	Two urology visits, two PSA tests, biopsy every two years
Watchful waiting	$136.7/year	Fixed	–	1–2 urology visits and PSA tests
Radical prostatectomy	$10,484	$9,043, $11,869	Gamma (55;0.004)	MSAC Application 1089.1 [25]
External beam radiation therapy	$9,665	$8,252, $11,078	Gamma (40;0.003)	MSAC Application 1158. Assuming the same number of fractions for adjuvant treatment [26]
Low-dose rate brachytherapy	$9,286	$7,873, $10,699	Gamma (43;0.003)	MSAC Application 1089.1 [25]
Testosterone level	$21.5/test	Fixed	–	MBS item 66695
Antiandrogen	$36.70/2 weeks	Fixed	–	Bicalutamide 50 mg tab. PBS monthly price for 28 tablets
Medical androgen deprivation therapy	$3,134/year	Fixed	–	Leuprorelin acetate 22.5 mg injection every 3 months or goserelin 10.8 mg every 3 months. PBS monthly price for both is $1109/3 months
Follow-up after treatment for localized disease	$110/year	Fixed	–	Urology visit and PSA test 4 times in year 1, then 2 times in years 2–3, then once a year. Averaged over the model years = $150/year
Follow-up with androgen deprivation therapy	$329/year	Fixed	–	Urology visit, PSA test and testosterone every 3–6 months. Assumed every 4 months in the model
Supportive care for androgen deprivation therapy	$4,946/year	$4,239, $5,652	Gamma (49;0.007)	Includes zoledronic acid at 4 mg every 3 to 4 weeks ($318; PBS DPMQ) + calcium and vitamin D ($21/month) +dual-energy x-ray absorptiometry scan at $72 (MBS item 12,306). Total per year = $4,946
Recurrence workup	$831/workup	Fixed	–	Urology visit, biopsy, and bone scans
Bone scans	$495/image	$353, $710	Gamma (12;0.02)	MBS item 61421
First-line chemotherapy	$247/cycle	$210, $283	Gamma (49;0.1)	Cost of docetaxel 75 mg/m^2 + prednisone 5 mg, for BSA of 1.8 m^2 every 3 weeks; the cycle cost = $141 (PBS) + $46 administration cost (MBS item 13915) + $4 premedication cost (dexamethasone tablets) + $14 blood test + $35 complication cost (febrile neutropenia in 3% of patients at $1,201per episode)
Second-line chemotherapy	$3,179/month	$2,473, $3,886	Gamma (20;0.004)	Abiraterone 1 g daily (4 tablets of 250 mg), cost per month = $2,543 Cabazitaxel 25 mg/m^2 (for BSA 1.8 m^2), cost per month = $4,180 Enzalutamide capsules, cost per month $2,614 Average monthly cost = $3,179
Treating incontinence	$386/year	Fixed		Continence aids payment scheme in Australia
Palliative care	$23,315/year	$19,782, $26,847	Gamma (44;0.001)	Yabroff (2008); the cost for the last 12 months of prostate cancer treatment in USA was $23,315; (approximate) [27]

AS = active surveillance; BSA = body square area; DRE = digital rectal examination; DPMQ = dispensed price of monthly quantity; MSAC = medical services advisory committee; mpMRI = multiparametric magnetic resonance imaging; MR = magnetic resonance; MBS = medical benefits schedule www.mbsonline.gov.au; NZ = New Zealand; PBS = Pharmaceutical Benefits Schedule; PCa = prostate cancer; TRUS = transrectal ultrasound; WW = watchful waiting. The full list of model inputs and sources are provided in the full report at [4]. The key variables are listed here for brevity.

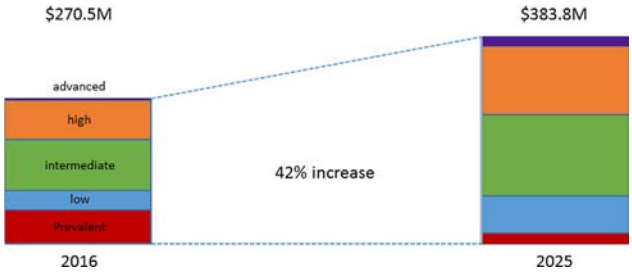

Fig. 2. Projected increase in costs of prostate cancer by stage ($US). (Color version of the figure available online.)

2025, an expected increase of 42% (holding current screening and technological advances constant) (Fig. 2). Of this total increase, newly diagnosed low risk cases are expected to contribute US$32.9 million, intermediate risk US$56.8 million, high-risk US$53.3 million and advanced US$12.6 million. The costs of following up men who had already been diagnosed by 2016 are estimated to decrease by US $42.3 million (Fig. 2).

For men diagnosed at the median age for prostate cancer in Australia (65 years), the mean long-term cost of prostate cancer per patient and first-line treatment were US$14,479 for surgery and $19,640 for radiation therapies. These costs were both substantially higher than those for active surveillance (US$9,222, Table 2) that included all subsequent follow-up and management in the case of progression or switching to active treatment.

Overall, active surveillance was the least costly management option followed by watchful waiting at US$9,939 mean per patient whereas surgery plus radiation (US $34,941) and ADT plus radiation (US$31,790), offered to men with intermediate or high-risk cancer, were the most costly. Advanced cancer therapies were also high at US$ 31,765 per patient. The mean cost of watchful waiting was higher than for active surveillance because, unlike active surveillance for low risk disease only, men with intermediate and high-risk disease receive watchful waiting but face a higher rate of progression to advanced disease and ADT treatment. The cumulative costs for first-line treatments for low risk prostate cancer show low absolute costs for active surveillance increasing steadily over time, as expected with adherence to a regimen of testing and biopsies (Fig. 3).

Despite the rate of increase in costs over time for active surveillance being higher than for surgery, the overall costs remained at least US$3,533 lower per patient each year (Fig. 3). The difference in costs for radiation therapies and surgery was small in the first few years of treatment but radiation costs increased markedly up to US$19,665 vs. US $14,497 for surgery (Fig. 3). The reason for this increase is the higher rates of progression to high cost advanced disease following radiation (2%–4% annually [14]) compared with surgery (1%–2% annually [15]) (Table 1), based on meta-analysis evidence (Table 1). For surgery plus radiation and ADT plus radiation cost trajectories, given to men with intermediate or high-risk disease, costs doubled by 10 years after diagnosis and increased slowly thereafter both due to combining two treatments and annual recurrence rates being 4%–6% [11,12] (Fig. 3).

At different cohort starting ages, costs were higher the younger the cohort age (Fig. 4 for low-risk disease). This reflects the additional resources accumulating steadily over time. The difference in costs among younger and older cohorts was most notable for radiation therapies from US $28,022 at age 45 compared with US$12,107 at age 75 (Fig. 4). When the cohort starting age was 55 years, the mean cost of active surveillance (US$10,078) changed little when the threshold age in the base case (75 years) was set at 72 years (US$10,477) or 78 years (US$9,762). Different durations of active surveillance follow-up also did not change greatly from the baseline duration of 10 years; 7 years (US$9,509) to 15 years (US$10,764). Similarly, varying the model duration had a minor impact on mean costs for all treatments overall (5 years US$18,002, 15 years US$17,522, and 30 years US$17,402). In probabilistic sensitivity analyses, the greatest variation in costs was associated with more uncertainty in the estimates for surgery plus radiation (95% CrI: $31,242–$39,033), ADT plus radiation (95% CrI: $28,113–$35,784), and advanced therapies (95% CrI: $27,176–$36,474).

4. Discussion

The model predicted that there will be a substantial increase in the health system costs of prostate cancer in

Table 2
Health care costs for prostate cancer by first year management option

First year management	Applies to stage of prostate cancer				Mean	Low CrI	High CrI
	Very low/low	Inter	High/loc adv	Adv		US$ (2016)	
Watchful waiting	Yes	Yes	Yes	No	9,939	8,372	11,774
Active surveillance	Yes	No	No	No	9,234	8,506	10,039
Surgery	Yes	Yes	Yes	No	14,497	12,046	17,410
Radiation (EBRT or brachytherapy)	Yes	Yes	Yes	No	19,665	17,232	22,313
Surgery and radiation	No	Yes	Yes	No	34,941	31,242	39,033
ADT and radiation	No	Yes	Yes	No	31,790	28,113	35,784
Advanced cancer therapies	No	No	No	Yes	31,574	27,176	36,474
Mean across all treatments, all men	–	–	–	–	17,426	15,585	19,418

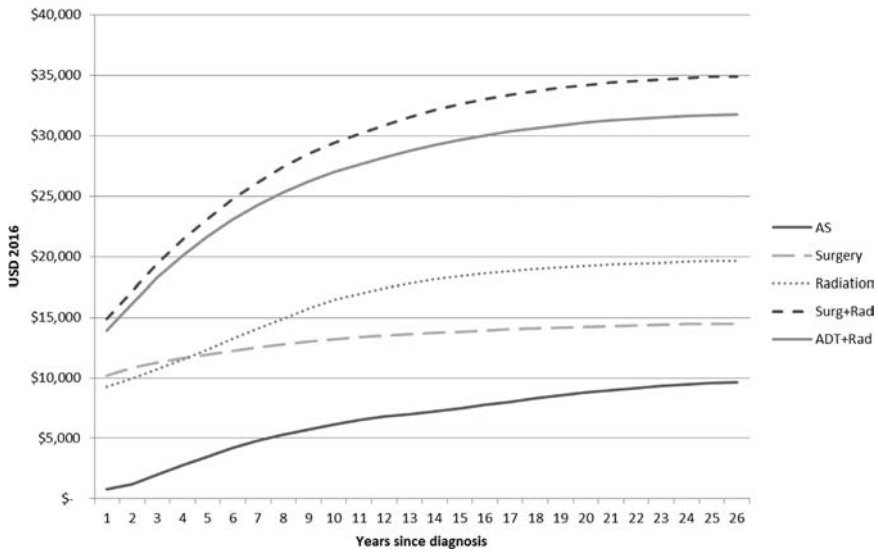

Fig. 3. Cumulative costs for treatment trajectories for localized prostate cancer. *Note*: Low-risk options include—active surveillance (AS), surgery and radiation. Intermediate-risk an high-risk options include surgery, radiation, surgery plus radiation, and androgen deprivation treatment (ADT) plus radiation.

Australia over the next decade. The growth in health care costs for prostate cancer is due to the combination of an aging population and higher absolute numbers of men facing intermediate- and high-risk cancers subject to holding constant the current levels of screening, surveillance and new technologies. Some 60% of the total increase arises from newly diagnosed cases of high risk and advanced cancer (US$ 65.8 million) with per patient treatment costs for high-risk and advanced cancers over US$28,260. This is attributed to combination therapies and higher progression rates, leading to additional health care services. The variation in treatment is also notable for men facing very-low or low-risk disease with active surveillance clearly incurring fewer costs to the health system over time than both surgery and radiation therapies. Radiation therapy had similar costs to surgery in the first few years from diagnosis but over time had notably higher costs than surgery.

Detecting prostate cancer before progression to high-risk, locally advanced and advanced cancer, comprising ~27% in total of all men diagnosed with prostate cancer, is important if cost-savings are possible. Early detection (and therefore treatment) of cancers that will progress appears to be a critical area of further research. Simultaneously, from a health economics perspective, those with low-risk disease should be managed conservatively with active treatment and every effort made at encouraging sustained participation in active surveillance. Our modeling predicted for all men with low-risk disease receiving active surveillance, the mean cost per patient was US$9,234 (or US$50.2 million Australia wide); however, at current levels of uptake (41%), these mean costs would be US$12,302 (or US$66.9 million). Therefore, significant annual cost-savings of US$16.7 million are possible for low-risk men if uptake of active surveillance increases. Active surveillance is clinically

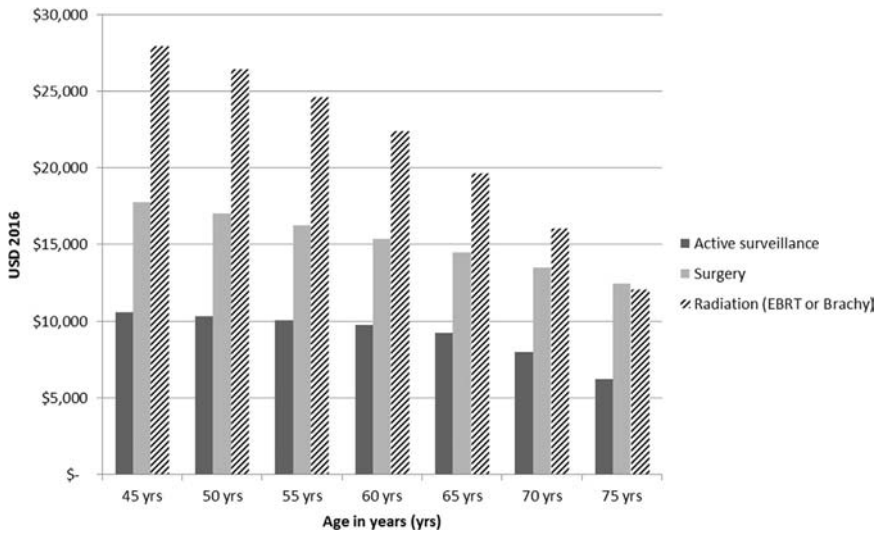

Fig. 4. Lifetime costs of prostate cancer by first line treatment with very low or low risk prostate cancer and different cohort ages (US$ 2016).

driven solution at stemming over-treatment, poorer patient outcomes and unnecessary use of resources. Although the proportion of men receiving active surveillance is rising globally, and investigators of the 10-year Prostate Cancer Research International Active Surveillance study have confirmed safety [28], recent changes to NCCN guidelines now recommend including men with favorable Gleason 3 + 4 and life-expectancy <10 years for active surveillance. However, active surveillance for men with Gleason 4 appears to be contentious with some asserting men with intermediate-risk disease will be at risk of developing incurable disease in future when opting for active surveillance [29].

Although the model estimates are based on the best available data inputs, the model remains a simplification of clinical practice patterns of care. For example, cost differences between surgery and radiation therapies within the same risk band are not perfect substitutes and patient characteristics may lead to radiation rather than surgery (and vice versa). For practical reasons, it was also not feasible to include every treatment combination or the potential of ADT-associated higher risk of cardiovascular diseases. For example, higher costs will occur for an artificial sphincter after prostatectomy, radiation proctitis management or costs related to ADT-associated Alzheimer's disease. There is uncertainty in the model relating to the assumptions around adherence to treatment follow-ups. A particular limitation of the model is the unknown development of new approaches and technologies [30], which are likely to have a key role in future costs [31]. For example, initial ADT with docetaxel may now be commonplace based on results of the STAMPEDE [32] and CHAARTED [33] trials but, due to timing of our analyses, are included at different lines of therapy in our model. In future, the routine use of magnetic resonance imaging as part of active surveillance, men with both low and intermediate-risk prostate cancer receiving active surveillance or newer therapies in advanced care are potential threats to the estimates reported here.

Currently, the model excludes personal healthcare costs made by men or indirect costs such as wages lost from treatment and recovery. This is a growing issue among patients with prostate cancer and their caregivers, and out-of-pocket expenses [34] may be considerable due to iatrogenic effects that affect patients variably in disrupting homeostasis. The main strength of this model is that it was designed and informed by high-quality evidence together with practising clinicians. This should ensure its relevance and currency in clinical practice. It includes practical health states such as palliative care, active surveillance and watchful waiting. It ensures that treatment of relapse or progression is dependent on patients' characteristics and previous treatments. It further includes some but not all adverse events from treatments.

Several previous studies in the United States [27,35], Canada [36,37], and Australia [38] have also looked at the costs of prostate cancer but are outdated now so comparisons are not practical. However, our findings agree with these earlier reports that consistently report the concentration of costs in the early years across stages but also higher cost associated treatments for more advanced disease [27,35]. Presently, the model is Australian based and its generalizability and transferability to other settings will be determined by variations in clinical practices, patient profiles and preferences by clinicians and patients, in addition to cross-country differences in health system structures, financing arrangements, currency purchasing power parities. For example, surveillance biopsies in the United States are performed annually rather than bi-annually in Australia, which will increase active surveillance costs. However, many of the estimates reflect treatment options from international guidelines that are uniformly accepted. Furthermore, our validation analyses show that the survival results are comparable with those observed in the UK, United States, and Canada [4]. Future use of the model in other jurisdictions can be overcome with systematic approaches to assess and change the data inputs where needed [39]. For example, in the United States the 5-year costs have been reported for robotic-assisted laparoscopic prostatectomy at US$16,946, US$23,565 for intensity-modulated radiation therapy, and US$11,448 for high-dose rate brachytherapy [40], whereas in Australia, surgery and radiation therapy have similar unit costs (Table 1).

5. Conclusion

Research into earlier detection of significant prostate cancers is warranted to avoid the very high expenses incurred by intermediate- and high-risk cancers. At current predictions, the long-term costs of active surveillance are substantially less costly than either radiation or surgical therapies in the Australian setting for men with low-risk prostate cancer. Investment in strategies to encourage active surveillance in eligible men is also likely to produce solid cost-savings to health providers.

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