Economic evaluation of screening and treatment for prostate cancer in the Midland Cancer Network region in New Zealand

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Abstract

Background: Prostate cancer is the most frequently diagnosed cancer and the third most common cause of cancer death for men in New Zealand.

Aim: This thesis aims to use economic approaches to examine the screening and treatment pathway for prostate cancer in the Midland Cancer Network Region.

Methods: This thesis comprises two systematic reviews, and five original studies: 1) the costs of identifying a new case of prostate cancer by screening; 2) survival in a cohort of men with prostate cancer; 3) the cost-effectiveness of active surveillance compared to radical prostatectomy for low risk localised prostate cancer; 4) the cost-effectiveness of active surveillance for intermediate risk prostate cancer; 5) the management and costs of metastatic prostate cancer.

Results: The screening costs per cancer detected in New Zealand were NZ$10,777, and varied by subgroups. For men diagnosed with low risk localised prostate cancer at the age of 45-55 years, the life-time costs of active surveillance were higher than the costs of radical prostatectomy. For men diagnosed with low risk or intermediate risk prostate cancer at the age of 60-70 years, the life-time costs of active surveillance were lower than the costs of radical prostatectomy. The cost-effectiveness of active surveillance compared to radical prostatectomy depends on the quality of life under these treatments and the annual probability of having radical prostatectomy in the active surveillance arm. The daily prostate cancer related costs for men with metastatic prostate were highest during the terminal phase (NZ$57) and lowest during the treatment phase (NZ$18).

Conclusions: General practice screening costs for prostate cancer could be reduced by better targeting. In terms of the life-time treatment costs, active surveillance is a reasonable option for men diagnosed with low risk or intermediate risk localised prostate cancer at the age of 60-70 years. If active surveillance is to be recommended, better evidence is needed to support of improved quality of

life. On current evidence, radical prostatectomy in younger men seems more likely to be cost-effective. The management costs for patients with metastatic prostate cancer varied by phase, with terminal phase being the most expensive.

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Abbreviation definition

Abbreviation	Full name
3D-CRT	Three-dimensional conformal radiotherapy
ACC	The Accident Compensation Corporation
AJCC	American Joint Committee on Cancer
AS	Active surveillance
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
cPSA	Complexed PSA
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
DHB	District Health Board
DRE	Digital rectal examination
ERSPC	European Randomised Studies of Screening for Prostate Cancer
EVPI	Expected value of perfect information
fPSA	Free PSA
GnRH	Gonadotrophin releasing hormone blocker
GP	General practitioner
HRQoL	Health related quality of life
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IGF-1	Insulin-like growth factor 1
IMRT	Intensity-modulated radiotherapy
ISUP	International Society of Urological Pathology
LHRH	Luteinising hormone-releasing hormone analogs
MCRPC	Metastatic castration-resistant prostate cancer
MORT	National Mortality Collection
MRI	Magnetic resonance imaging
NICE	UK National Institute for Health and Clinical Excellence
NMDS	National Minimum Dataset

Abbreviation	Full name
NNPAC	National Non-Admitted Patient Collection
NZCR	New Zealand Cancer Registry
OR	Odds ratio
PCA3	Prostate cancer antigen 3
PCPT	Prostate Cancer Prevention Trial
PHARMS	Pharmaceutical Information Database
PLCO	Prostate, lung, colorectal, and ovarian cancer screening trial
PSA	Prostate specific antigen
PT	Proton beam therapy
QALY	Quality-adjusted life-year
RP	Radical prostatectomy
SBRT	Stereotactic body radiation therapy
SEER	US Surveillance, Epidemiology, and End Results Program
SES	Socioeconomic status
SF-6D	Short form-6D
SNPs	Single-nucleotide polymorphisms
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
TNM	Tumour-nodes-metastasis system
tPSA	Total PSA
TRUS	Transrectal ultrasonography
TURP	Transurethral resection of the prostate
WIES	Weighted Inlier Equivalent Separation
WW	Watchful waiting
WWAS	Watchful waiting with active surveillance

Glossary

Terms	Description
Active surveillance	Active surveillance aims to avoid or delay definitive treatment for localised prostate cancer, thereby reducing the potential treatment-related harms. Men under active surveillance are closely monitored with PSA tests, DREs, biopsies and MRIs, and will receive radical treatment when cancer progression is detected.
Cost-effectiveness acceptability curve	Cost-effectiveness acceptability curve indicates the probability of each treatment being cost-effective under a range of willingness-to-pay values.
Cost-effectiveness analysis	Cost-effectiveness analysis is one form of full economic evaluation where both the costs and consequences (e.g. life-years gained, disability-days gained, etc.) of health programmes or treatments are examined.
Direct costs	All resources that are directly associated with care: e.g. Inpatient, outpatient, tests, drugs
Discounting	A technique which allows the calculation of present values of inputs and benefits which accrue in the future. Discounting is based on a time preference which assumes that individuals prefer to forego a part of the benefits if they accrue it now, rather than fully in the uncertain future. By the same reasoning, individuals prefer to delay costs rather than incur them in the present.
Economic Evaluation	The comparative analysis of alternative courses of action in terms of both their costs and consequences
Expected value of perfect information	The expected value of perfect information is equal to the average of the maximum net benefits across all model iterations (i.e., the expected net benefit using perfect information), minus the maximum of the average expected net benefits across all treatment strategies (i.e., the expected net benefit using the currently available (imperfect) information).'
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio of a new pharmaceutical or a new technology compared to the existing one can be generated through the incremental analysis of costs and health gained.
Indirect cost	Indirect costs consist of (1) morbidity costs, the value of lost productivity by persons unable to perform their usual activities or to perform them at a level of full effectiveness due to the illness and (2) mortality costs, the value of lost productivity due to premature death resulting from the illness, calculated as the present discounted value of future market earnings plus

Terms	Description
	an imputed value for housekeeping services.
Influence diagram	Influence diagrams are graphical tools for formulating and solving decision problems under uncertainty.
Sensitivity analysis	Sensitivity analysis examines the impact on the model's results by varying parameter(s) across a range.
Opportunity cost	The cost of a unit of a resource is the benefit that would be derived from using it in its best alternative use.
Perspective in health economics	The point of view from which an analysis is carried out. The perspectives that are commonly used include the societal perspective, payer's perspective, patient's perspective and the perspective of the health care system.
Probabilistic sensitivity analysis	Probabilistic sensitivity analysis assesses the joint uncertainty of parameters.
Prostate specific antigen test	Prostate specific antigen (PSA) test is to measure the PSA level in the blood. A raised PSA level can be caused by prostate cancer, benign prostate hyperplasia or prostatitis.
Quality-adjusted life-year	Quality-adjusted life-year is a measure of health output that can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure
Scenario analysis	Scenario Analysis is a process to ascertain and analyse possible events that can take place in the future.
Watchful waiting	Men under watchful waiting are monitored with PSA tests, will not undergo radical treatment, but will receive palliative treatment when symptoms occur.
Willingness-to-pay	Individuals are asked the maximum, in monetary terms, they are willing to give up (from surplus income) to acquire the benefits of the intervention.

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Nature of contribution by PhD candidate	The development of methodologies, data cleaning and data analysis, interpretation of result, and preparation of the manuscript
Extent of contribution by PhD candidate (%)	80%

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Certification by Co-Authors

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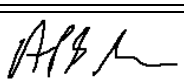
Prof Paul Rouse		06/11/2015
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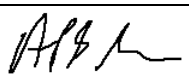
Prof Paul Rouse		06/11/2015
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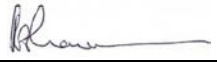
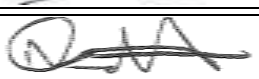
- that the candidate wrote all or the majority of the text.

Name	Signature	Date
Prof Ross Lawrenson		26/01/2016
Dr Zuzana Obertová		25/11/2015
Dr Charis Brown		23/11/2015
Dr Michael Holmes		15/11/2015
Dr Nina Scott		09/11/2015

Chapter 1. Introduction and background

1.1 Introduction

Health care resources are limited and there are opportunity costs involved in decision making. For example, if resources are spent on a health care programme for one group of patients, this may deprive another group's access to services which might produce greater benefits. Economic evaluation research plays a central role in decision making for health care resources distribution,[1] by comparing the "alternative courses of action in terms of both their costs and consequences".[2] This thesis used economic evaluation approaches in the management of prostate cancer.

Prostate cancer is the most frequently diagnosed cancer and the third most common cause of cancer death for men in New Zealand.[3] Around 3,000 new prostate cancer cases are identified and around 600 men die of prostate cancer every year.[3] The age-standardised incidence rate was 97.4 per 100,000 men and the age-standardised mortality rate was 16.5 per 100,000 men in 2011.[3] The prevalence of diagnosed prostate cancer in men aged 40 years and over has been estimated to be 2.7% in the New Zealand Midland Cancer Network region in 2010.[4]

Prostate cancer can be cured if it is detected and treated at an early stage, which makes it a good candidate for screening. The argument for prostate cancer screening can be supported by evidence from the European Randomised Studies of Screening for Prostate Cancer (ERSPC)[5] and the Göteborg study.[6] These studies indicated that screening could reduce the prostate cancer specific mortality rate for men aged less than 70 years. However, other research (including the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial[7] and a Cochrane review[8]) demonstrated no difference in the overall or cancer-specific mortality between the screened and unscreened groups.[8]

The introduction of prostate cancer screening in many countries has increased the proportion of cancer detected at a localised stage.[9] In the US, a high screening country, 81% of prostate cancer cases are localised at diagnosis, 12% are locally-advanced, 4% are metastatic and 3% are of an unknown stage.[10] The stage distribution of prostate cancer in the US is similar to that in Australia where 84% of new cases are localised, 13% are locally-advanced and 3% are metastatic.[11] Data from a New Zealand study[12] suggested that 76% of new cases are localised, whilst locally spread cancer is diagnosed in 11% cases and the rest 13% are metastatic.

Prostate cancer screening also results in overdiagnosis, overtreatment and increasing medical costs.[13] Men being screened may need to go through biopsies that can cause bleeding or infection.[14] Many screen-detected, low risk cancers will not cause death and will be indolent during a patient's life time.[7,15] These men will not benefit from early diagnosis and may suffer from unnecessary harms, including complications caused by investigations, treatments and the psychological impact of living with a cancer diagnosis.[13,16,17] After a prostate cancer diagnosis 28% of men suffered from high anxiety.[17] It was also reported that 80-91% of men treated with radical prostatectomy suffered from

erectile dysfunction and 39-49% had urinary problems, and 30-35% of men treated with radiotherapy had bowel problems within 12 months after treatment.[18]

Because of the potential harms, prostate cancer screening is not recommended by the Ministry of Health. However screening is widespread in New Zealand, with over 345,000 PSA tests ordered in 2010.[4] General practitioners (GPs) in New Zealand opportunistically screen men aged 40 years and older using the prostate-specific antigen (PSA) test. They believe that there are benefits to prostate cancer screening.[19] The majority of PSA tests (80%) ordered for the purpose of screening were GP initiated.[19,20] Only about 5% of PSA tests were requested by patients.[19] The annual screening rate in men aged 40+ in New Zealand was 18% in 2008 and 22% in 2003–2007.[20] The probability of being screened varied in different age groups and ethnic groups. Men aged 50-79 years were more likely to be screened than men aged 40-49 or 80 years and older.[4] Non-Māori men were twice as likely to be screened as Māori men.[21]

In addition to the effect on health outcomes, the financial impact of screening and treatment for prostate cancer may also need to be considered in the decision to screen. Existing studies are not consistent in terms of the cost-effectiveness of prostate cancer screening.[22-27] It was reported that by introducing screening, the costs for diagnosis and treatment would increase by 100%, with 89% of total costs related to the treatment and management for screen-detected cancers.[13]

The treatment options for localised prostate cancer, including radical prostatectomy, radiotherapy, watchful waiting and active surveillance, differ in terms of costs, complications and effects on cancer-specific mortality.[28] Since most prostate cancer cases are localised, treatment costs for these localised prostate cancers may account for a large proportion of the cost of illness of prostate cancer. The economic evaluation of treatments for localised prostate cancer might have a substantial impact on the cost of illness of prostate cancer, by influencing the decision making of treatment for localised prostate cancer.

In the ERSPC screening arm, 60% of the prostate cancer cases had a clinical stage T1–2 with a Gleason score ≤6, while 22% of the cancer cases had a clinical stage T1–2 with a Gleason score 7 or T3 with a Gleason score ≤7.[29] Given that most of the screening costs were associated with the treatment for the screen-detected cancer[13] and most of the screened-detected cancers are localised,[29] identifying the most cost-effective treatment option for localised prostate cancer would be critical for improving the cost-effectiveness of prostate cancer screening.

The 5-year relative cancer-specific survival rate for men diagnosed with localised prostate cancer is almost 100%, while the 5-year relative survival rate for men diagnosed with metastatic disease is only 28%.[10,30] Improvements in survival may be achieved not only by earlier diagnosis and early treatment but also by improving management of metastatic disease. The costs of management of metastatic prostate cancer, including treatments to prolong patients' life and palliative care for end-stage patients, can be significant. A substantial proportion of cancer costs occur in the last weeks and months of life.[31]

The Midland Cancer Network is one of four cancer networks in New Zealand, coordinating health services related to cancer for three health boards with a combined population of around 691,000 people. The Midland Cancer Network has a mix of urban and rural areas and a relatively high Māori population (approximately 25%). The annual PSA testing rate (22.1%) in this region was similar to the rate (22%) across the whole country.[4] Māori, the indigenous population in New Zealand, comprise 15.6% of the population.[32] There are great differences in the prostate cancer registration rate and mortality rate between Māori and non-Māori. Māori men diagnosed with prostate cancer were 1.94 (95% CI, 1.76, 2.14) times more likely to die of prostate cancer than non-Māori men.[33]

The research question of this thesis is how to use economic evaluation approaches to improve the decision making for management of prostate cancer. This thesis aims to examine and cost the entire screening and treatment pathway of prostate cancer in the Midland Cancer Network, to improve decision making on the diagnosis and management of prostate cancer. It provides updated data on the economic impact of prostate cancer screening, the cost-effectiveness of treatments (active surveillance and radical prostatectomy) for localised prostate cancer, the treatment patterns and the costs of management of metastatic prostate cancer. The thesis structure is shown in Figure 1.

The remainder of this chapter provides the background information on prostate cancer including etiology, epidemiology, diagnostic tools, risks of overdiagnosis and overtreatment, and treatments. The New Zealand healthcare system is described as well as approaches to economic evaluations in health care and associated models.

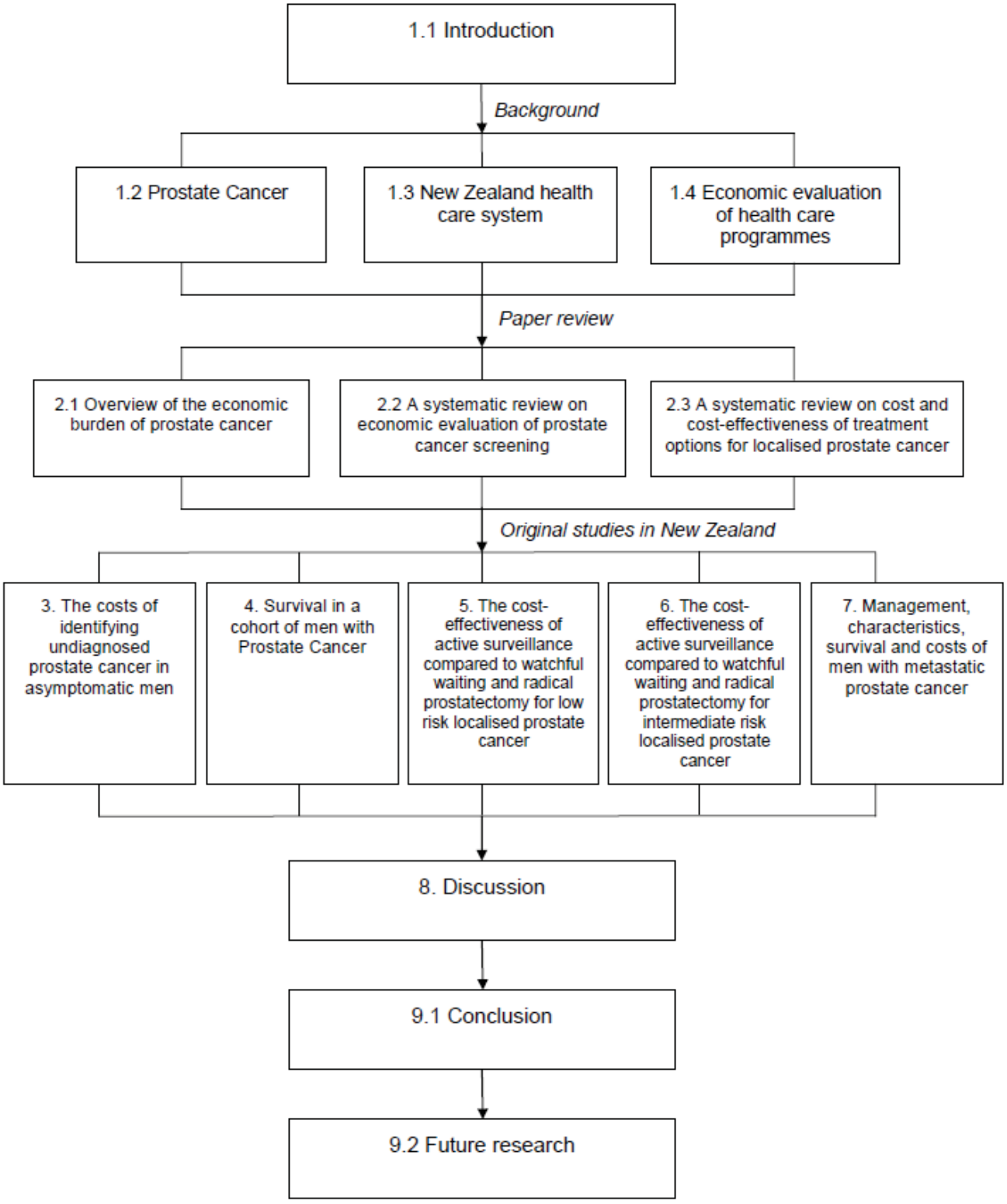


Figure 1. Thesis structure

1.2 Prostate Cancer

1.2.1 Etiology and natural history

The prostate gland is located at the base of the male bladder. It produces prostate secretions that mix with spermatozoa held in the seminal vesicles. Prostate cancer is common. The lifetime risk of a prostate cancer diagnosis for a man has been estimated as 15-20%,[34-36] although most prostate cancers are slow growing and not life-threatening with the lifetime risk of death from prostate cancer being 3%.[34-36] Most early stage prostate cancers have an indolent course in the first 10 to 15 years after diagnosis. However, significant cancer progression, or even aggressive metastatic disease is common in the 15 to 20 years after diagnosis.[37] Some prostate cancers are very aggressive and progress rapidly, involving local structures, such as the seminal vesicles, bladder and rectum. They may metastasize to lymph nodes, other organs and bones. The median life expectancy for patients who have developed bony metastatic cancers is approximately 24 to 36 months.[33,38]

Prostate cancer is curable, but some patients might experience a recurrence after radical treatments. In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), 26.1% of men who underwent radical prostatectomy had metastatic prostate cancer after 18 years follow-up.[39] Biochemical recurrence might be detected before clinical recurrence in some patients who had radical treatments. For example, approximately 20% of men treated with external beam radiotherapy had biochemical recurrence (defined as 'prostate specific antigen (PSA) >1.0 ng/mL and increasing >0.2 ng/mL on 2 consecutive visits' in this study) after 4.5 years follow-up.[40] The definition of biochemical recurrence used in studies for patients' follow-up after radical prostatectomy differs. A biochemical recurrence definition was proposed by Stephenson et al in 2006: a PSA value of at least 0.4 ng/mL followed by another increase.[41] In 2007, the American Urological Association Prostate Guideline Update Panel reviewed 53 different definitions of biochemical recurrence and recommended using a definition of a PSA serum level higher than 0.2 ng/ml, with a second confirmatory level above 0.2 ng/ml.[42] This recommendation is similar to the definition proposed by a European Consensus committee in 2004.[43]

Most of the newly diagnosed localised prostate cancer cases are early stage prostate cancers and are asymptomatic.[44] Some prostate cancers might cause urinary retention, reduced urinary flow, nocturia, urgency, frequency, haematuria, and erectile dysfunction.[19] Patients with metastatic prostate cancer may suffer from bone pain, or anemia.

The etiology of prostate cancer is still uncertain. There are two assumptions for the origin of prostate cancer. One hypothesis (hierarchical or stem cell model) posits that prostate cancer originates from the mutation of stem cells with secretory differentiation instead of from the secretory cells. The opposite stochastic model posits that all neoplastic cells may be tumour-initiating cells.[45]

A combination of endogenous and exogenous factors was believed to be associated with the origin of prostate cancer. Endogenous factors include age, ethnicity, family/genetic risk and hormonal

influences. Exogenous factors include diet, exercise and environmental agents. Some factors together might have synergistic effect.[46-48] For example, hormone levels can be affected by age, ethnicity, environmental agents (e.g. chemicals), and diet (varies in different ethnicities).[46-48] The effect of endogenous factors on the risk of prostate cancer was more commonly examined. [49-52]

Hormones

A reduction in androgen is known to slow down the progression of prostate cancer, therefore it is possible that androgens might influence the growth of prostate cancer.[49] A meta-analysis indicated that men with serum testosterone level or insulin-like growth factor 1 (IGF-1) in the highest quartile are 2.34 (95% CI, 1.30 to 4.20) times more likely to develop prostate cancer than those in the lowest quartile.[53] The Prostate Cancer Prevention Trial (PCPT) examined whether finasteride which can lower androgen levels could reduce the incidence of prostate cancer. Between January 1994 and May 1997, 18,882 men aged 55 years or older were randomly distributed to the finasteride group and the placebo group. After 7 years follow-up, a 24.8% reduction in the incidence of prostate cancer was identified in the finasteride group compared with the placebo group.[54]

Another review conducted by Hong[55] showed inconsistent results in terms of circulating levels of androgens with prostate cancer risk: a substantial increased risk of prostate cancer with high testosterone level (ORs by quartile:1.00 for the first quartile with the lowest testosterone level; 1.41 for the second quartile; 1.98 for the third quartile, 2.60 for the fourth quartile) in the Physician's Health study;[56] no association between serum testosterone and occurrence of prostate cancer in the Mobile Clinic Health Examination Survey[57] or in the Linkage of Norwegain National Cancer Registry.[58] Though the effect of testosterone on prostate cancer risk is uncertain, it was suggested that men having testosterone therapy should be regularly monitored for prostate cancer.[59]

Age

The risk of prostate cancer increases with age. An American study showed that the risk of being diagnosed with prostate cancer for men aged 60 years or older was more than three times the risk for men aged 59 years or younger (Table 1).[60]

Table 1. Age-specific incidence of prostate cancer per 100,000 men in the US in 2005

Age	America[60]
Younger than 50 years	9.4
50-59 years	212.7
60-69 years	666.9
70-79 years	896.8

Ethnicity

The risk of prostate cancer was shown to vary among different ethnic groups: African men are at a higher risk of having prostate cancer and at a younger age.[61] A UK study reported that the prostate cancer age-adjusted incidence rate were 647 per 100 000 for African Caribbeans, 213 for Europeans and 199 for South Asians in 1999 and 2000.[62] The relative risk for prostate cancer in African Caribbeans was 3 times the risk in Europeans. Similar results were found in studies conducted in America. During 2000 to 2004, African-American males (age-adjusted incidence rate: 255.5 per 100,000; age-adjusted mortality rate: 62.3 per 100,000) were 1.6 times more likely to be diagnosed and 2.4 times more likely to die of prostate cancer than European-American males (age-adjusted incidence rate: 161.4 per 100,000; age-adjusted mortality rate: 25.6 per 100,000).[63,64] The median age at prostate cancer diagnosis was 66 years for African-Americans and 69 years for European-Americans.[51]

Ethnicity also influences the prostate cancer stage at diagnosis. The B. A. Jones study[63] indicated that 60% (69/115) of the prostate cancer cases found in African-Americans were nonlocalised, while 42.7% (58/136) of the cases in Europeans were nonlocalised in Connecticut between January 1987 and October 1990. Hoffman et al[65] found a higher proportion of clinically advanced-stage prostate cancers in African-Americans (12.3%) and Hispanics (10.5%) than in non-Hispanic whites (6.3%) in a population-based cohort of 3173 men diagnosed with prostate cancer between October 1, 1994 and October 31, 1995. After adjusting for socioeconomic, clinical, and pathologic factors, the risk remained: odd ratio of 2.26 (95% CI: 1.43-3.58) for African-Americans and 1.23 (95% CI: 0.73-2.08) for Hispanics compared to non-Hispanic whites. A UK study also reported a slightly higher proportion of distant metastatic cases in African Caribbeans (26.4%) than in Europeans (23.0%).[62]

Family/genetic risk

The lifetime risk of prostate cancer for men who do not have a family history of prostate cancer is 8%, compared with 35%-45% for a man who has a hereditary prostate cancer history.[48] A US population-based cohort study showed that men whose brother or father was diagnosed with prostate cancer have a 3.7 (95% CI: 1.9-7.2) times risk of having prostate cancer than other men after adjustment for age, alcohol and diet.[66] A similar result was found in a study conducted in the US and Canada.[67] The relative risk of having fatal prostate cancer is 1.60 (95% CI: 1.31-1.97) for men whose brother or father had prostate cancer, compared to other men.[68] The risk of prostate cancer is related to the number of relatives with prostate cancer and the degree of relatedness, but is inversely related to the age at diagnosis of the relatives.[48] The risk of having prostate cancer is 15% if father or brother had prostate cancer, and the risk doubles if both father and brother had prostate cancer.[69] If the father or brother was diagnosed with prostate cancer at the age of less than 60 years, the risk of having prostate cancer increased to 20%.[69] Rodriguez[68] and colleagues found that the relative risk (2.03; 95% CI: 1.33-3.09) of prostate cancer for men whose father or brother was diagnosed with prostate cancer

before 65 years old is higher than relative risk (1.50; 95% CI: 1.17-1.91) for men whose relatives were diagnosed at the age ≥65 years.

Five single-nucleotide polymorphisms (SNPs) in the five chromosomal regions at 8q24 and 17q were found to be significantly associated with prostate cancer after adjustment for other SNPs and family history.[52] Men who had any five or more of these factors (the five SNPs and family history) are 9.46 time more likely to have prostate cancer than men without any of the factors.[52]

1.2.2 Prevalence, incidence and mortality

Prostate cancer is the most frequently diagnosed cancer for men in developed countries and the second most common cancer for men worldwide, following lung cancer.[70,71] In 2012, there were approximately 1,111,600 men worldwide diagnosed with prostate cancer, comprising 15.0% of total registered cancers in men.[70] The number of men with prostate cancer would be higher than the reported number, considering that many prostate cancer cases remain undiagnosed. Autopsy studies have provided some insights into the prevalence of prostate cancer (Table 2).[72] For men aged older than 70 years, half of them have undiagnosed prostate cancer.

Table 2. Autopsy prevalence of prostate cancer at different age groups

Country/Ethnicity	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years	71-80 years	81-90 years	Ref
European-American	8%	31%	37%	44%	65%	83%	-	[73]
European-African	8%	31%	43%	46%	70%	81%	-	[73]
Japan	0%	20%	13%	22%	35%	41%	48%	[74]
Spain	4%	9%	14%	24%	32%	33%	-	[75]
Greece	0%	0%	3%	5%	14%	31%	40%	[76]
Hungary	0%	27%	20%	28%	44%	58%	73%	[77]

Note: Men included in the autopsy studies all died of unrelated causes and did not know that they had prostate cancer.

As shown in Table 2, the prevalence of prostate cancer increased substantially with age. The incidence of prostate cancer also increases exponentially with age (Figure 2).[78] The decreased incidence of prostate cancer for men aged 75 years or older in some countries might be associated with the practice that a biopsy is less likely to be performed on men aged 75 years or older. The data in this figure also confirmed that African-Americans had the highest risk of developing prostate cancer and Asian men had the lowest risk.

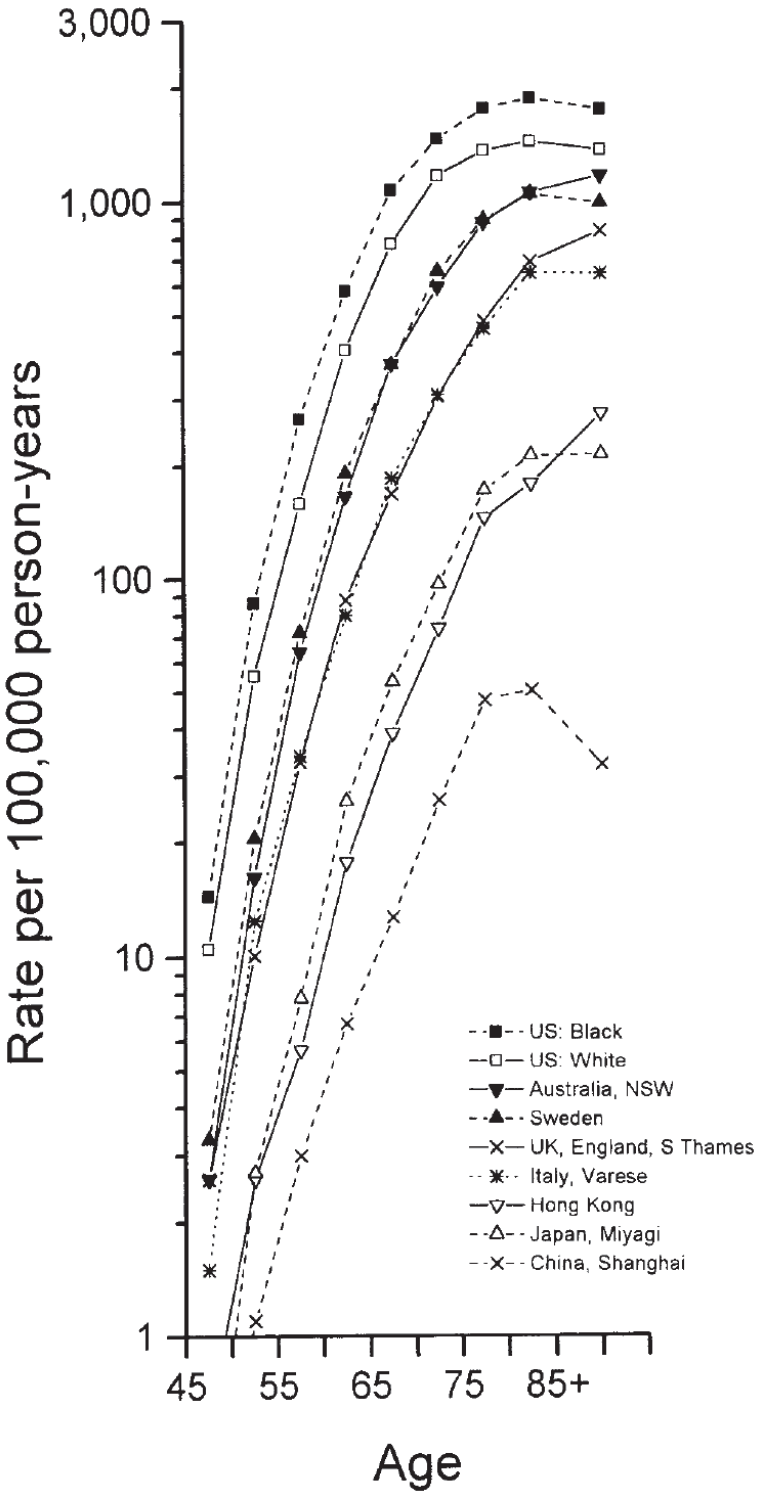


Figure 2. Age-specific incidence curves of prostate cancer detection in 8 countries, 1988–92

Source: International trends and patterns of prostate cancer incidence and mortality[78] (License for reusing the figure has been granted)

The GLOBOCAN project demonstrated that men in Australia/New Zealand had the highest prostate cancer incidence rate, and men in South-Central Asia had the lowest prostate cancer incidence rate.[50,71] Martinique had the highest prostate cancer incidence rate (227.2 per 100,000) in 2012, followed by Norway (129.7 per 100,000) and France (metropolitan) (127.3 per 100,000).

Prostate cancer is the third most common cancer death for men in developed countries and the sixth leading cancer death for men worldwide.[70,71] In 2012, approximately 307,400 men died of prostate cancer worldwide, comprising 6.6% of total cancer deaths in men. The Caribbean had the highest prostate cancer specific mortality rate in the world, while South-Central Asia had the lowest.[50,71] The prostate cancer mortality rate was the highest in Trinidad and Tobago (58.9 per 100,000) in 2012, followed by Guyana (48.2 per 100,000) and Barbados (45.6 per 100,000).[50,71]

New Zealand has the 18th highest prostate cancer incidence rate (92.2 per 100,000) and the 88th highest prostate cancer mortality rate (12.8 per 100,000) in the world in 2012.[50] Prostate cancer is the most frequently diagnosed cancer for New Zealand men, comprising 27.0% of all male cancer registrations in 2010. It is the third most common cause of cancer death for men, following lung cancer and colorectal cancer. The prostate cancer registration rate (World Health Organization (WHO) age standardised rate) decreased from 132.9 per 100,000 men in 2000 to 106.5 per 100,000 men in 2007, and then fluctuated afterward. The registration rate for men aged 55-69 years and men aged 70 years and older declined by 11.6% and 30.0%, from 559.1 and 1205.7 per 100,000 men in 2000 to 494.4 and 843.7 per 100,000 men in 2007 (Figure 3).The mortality rate experienced a similar pattern, decreasing from 24.9 per 100,000 men in 2000 to 19.0 per 100,000 men in 2007 and then fluctuated afterward.[79] The mortality rate for men aged 55-69 years and men aged 70 years and older declined by 24.3% and 18.5%, from 44.5 and 364.2 per 100,000 men in 2000 to 33.7 and 296.7 per 100,000 men in 2007 (Figure 4).

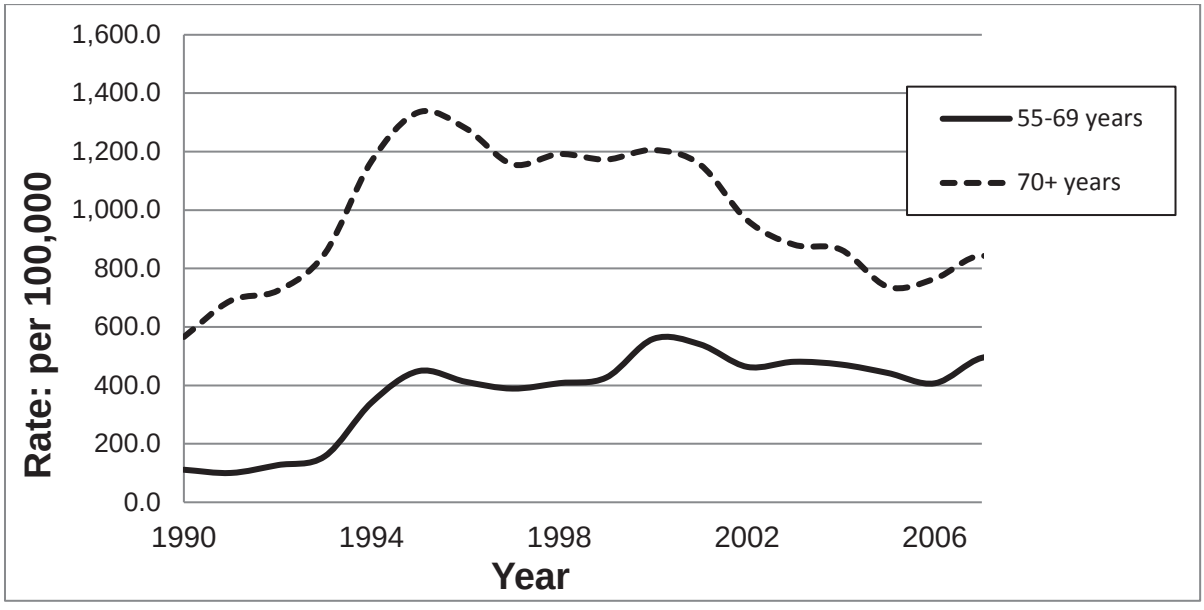


Figure 3. Prostate cancer registration rate by age and year in New Zealand in 1990-2008

Source: New Zealand Health Information Service

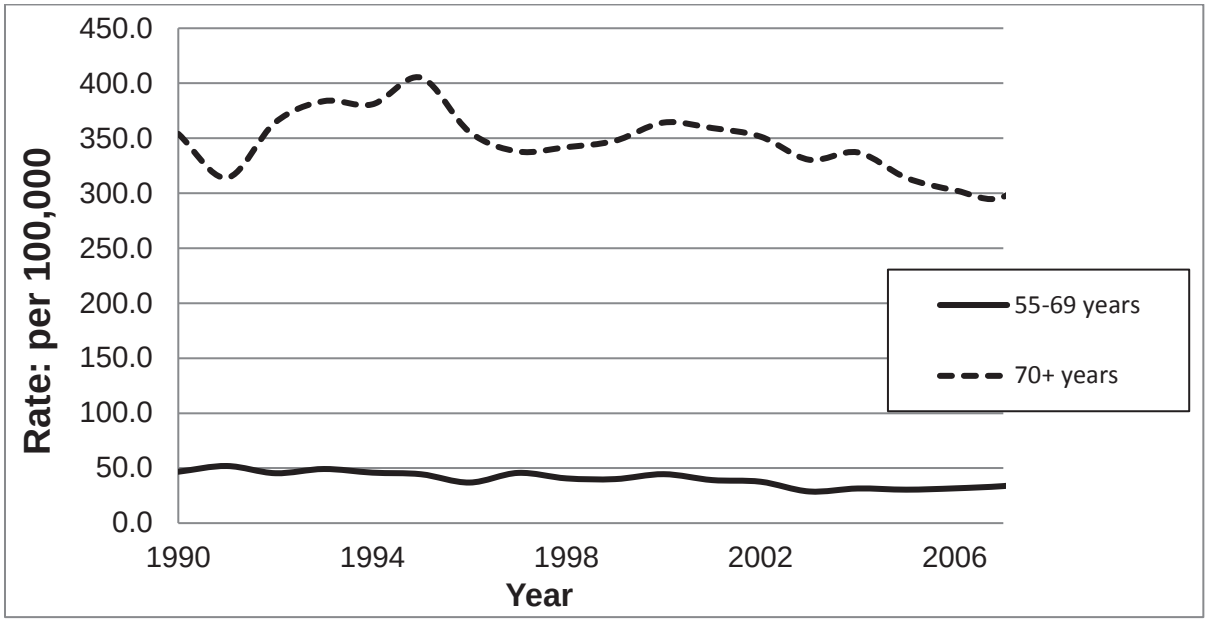


Figure 4. Death rate from prostate cancer by age and year in New Zealand in 1990-2008

Source: New Zealand Health Information Service

1.2.3 Diagnosis of prostate cancer

Prostate cancer used to be primarily detected by clinical symptoms or through a digital rectal examination (DRE) or following a transurethral resection of the prostate (TURP). TURP is a surgical procedure that removes portions of the prostate gland via the urethra. It is often recommended for urinary problems caused by benign prostatic hyperplasia. In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a clinical trial conducted before the screening era, 42% of the localised prostate cancer cases were identified by symptoms, 14% by TURP, 5% by screening, 26% were identified coincidentally, and 13% were identified through other methods.[80]

After the introduction of screening/testing asymptomatic men for prostate cancer, many more early stage cancer cases have been identified. Since the PSA test was introduced for prostate cancer screening (in the late 1980s and early 1990s[81]), the incidence of prostate cancer increased dramatically (Figure 5). Because of the imperfect sensitivity of PSA test as screening/testing tool, some prostate cancer cases might not be identified. Some cancer cases are still identified accidentally during a transurethral resection or open surgery for benign prostate hyperplasia.[44,82]

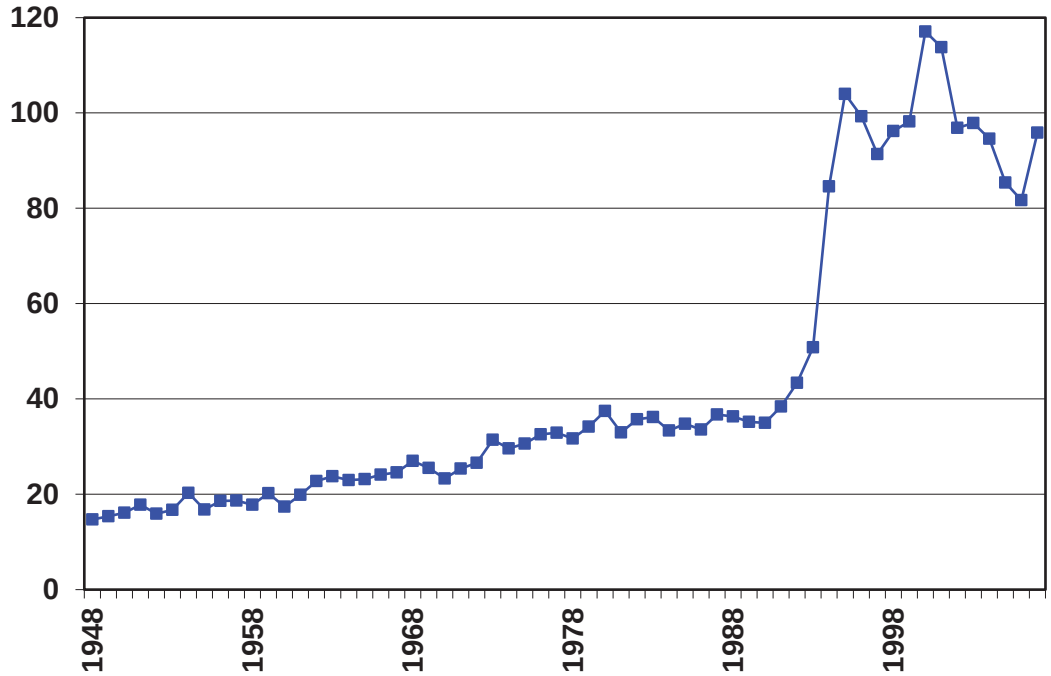


Figure 5. Age standardised incidence of prostate cancer per 100,000 men in New Zealand in 1948-2007

Source: New Zealand Health Information Service

Diagnostic tools

Today the diagnosis of prostate cancer includes several stages. The 'first line' diagnostic tools include digital rectal examination (DRE) and PSA test.[83] Patients with an abnormal DRE or an elevated PSA test will be followed-up with further PSA tests, and will be referred for a specialist appointment for a prostate biopsy. Additional investigations including transrectal ultrasonography, X-ray computed tomography (CT), magnetic resonance imaging (MRI), or a bone scan may also be performed.

Digital rectal examination (DRE)

DRE is a simple procedure where the clinician puts a gloved and lubricated finger into the patient's rectum and palpates the prostate. If the prostate is swollen, lumpy or hard, there might be some underlying problems with the prostate, including prostate cancer.[84] DRE was the principal 'first line' method for identifying prostate cancer before the introduction of PSA testing, and is still recommended for prostate cancer detection by physicians, as some cases of prostate cancer have normal levels of PSA.[83] However, due to the invasive procedure, DRE can be uncomfortable and embarrassing.[85]

Prostate specific antigen (PSA) test

PSA is a protein produced by the prostate gland. Problems with the prostate can cause an elevated PSA level in the blood. The higher the PSA level, the more likely the patient has prostate cancer. However, the PSA test is not a perfectly sensitive and specific test. A raised PSA level can be caused by prostate cancer, benign prostate hyperplasia or prostatitis.[86] On the other hand, some prostate cancers may not cause an elevated PSA level. A number of prostate cancers with low PSA values can be missed.[87] In the ERSPC study, 17,543 underwent biopsy after an elevated PSA value and 13,308 (75.9%) men had a false positive PSA result.[88] Of 9,211 men who had a PSA level of 0-3.9 ng/ml, 127 were diagnosed with prostate cancer by digital rectal examination and transrectal ultrasonography.[87] Approximately half of these cancer cases had a Gleason score 7 or greater.[87] Sensitivity and specificity were not calculated in this study because of the unknown underlying prevalence of prostate cancer.

In order to increase the specificity of PSA testing, several methods have been introduced, including age-specific reference ranges, PSA density, PSA velocity, and the measurement of free and complexed PSA.[83] Age-specific reference ranges for PSA testing were developed because it has been demonstrated that the PSA concentration increases with age.[89] A PSA value of 3.5 ng per milliliter for a 50-year-old man is more relevant to prostate cancer than 4.5 ng per milliliter for a 70-year-old man.[90] Age specific PSA has been shown to increase detection of prostate cancer in younger men (50-59 years old) by 15%.[91] A lot of studies and organisations used age-specific reference ranges for PSA testing.[19,92,93] Men with enlarged prostates often have elevated PSA levels due to benign disease.

PSA density is measured by dividing the serum PSA by the size of the prostate. It was shown that transition zone PSA density improves the efficiency of PSA in diagnosis of prostate cancer and decreases the unnecessary prostatic biopsy in men with a PSA of both 4.0-10.0 and 10.1-20.0 ng/ml in Chinese men.[94]

The PSA velocity measures the rate of change in serum PSA over time.[83] A large Swedish preventive medicine study including 5,772 men aged ≤ 50 years old reported that adding PSA velocity did not significantly improve the accuracy of PSA testing in predicting prostate cancer.[95]

The PSA can exist in serum in two molecular forms: ‘free’ and ‘complexed’. Approximately 70-90% complex to serum proteins and is called complexed PSA (cPSA). The other 10-30% is not bound to serum proteins and is called free PSA (fPSA).[96] The level of free PSA for men with prostate cancer is lower compared with men with benign prostate hyperplasia. The level of free and complexed PSA can be used to distinguish prostate cancer and benign prostate hyperplasia.[83] The median cPSA/ total PSA (tPSA), fPSA/tPSA, and fPSA/cPSA ratios were significantly different between patients with benign prostate hyperplasia and prostate cancer: 78.7% vs 90.7%, 25.5% vs 12.1%, and 36.8% vs 14.3%, respectively (P <0.001).[96] It was demonstrated that diagnostic percentage of free serum PSA (%fPSA) provides no additional prognostic value when compared to other predictors already in use in

active surveillance protocols. However, %fPSA velocity during surveillance may aid in predicting the probability for future treatment change.[97] The cost of a free PSA test in the Waikato region is about NZ$15 that is 50% higher than the cost of a PSA test: NZ$10 (unpublished data from a local laboratory).

Other biomarkers

Biomarkers can be proteins, metabolites, RNA transcripts, DNA, or epigenetic modifications of DNA. Next generation prostate cancer biomarkers are under research, including prostate cancer antigen 3 (PCA3), TMPRSS2-ERG, α-Methylacyl–coenzyme A racemase, Germline risk loci, Other "-omic" biomarkers, Circulating tumor cells and Exosomes.[98] PCA3, the most prominent one, is long noncoding RNA. It was found to be elevated in more than 90% of prostate cancer tissues, but not in normal or benign prostatic hyperplasia tissues.[99,100] Compared with the new biomarkers, PSA is less costly and is a sensitive test at low cut off levels. Therefore, other new biomarkers may have a complementary role but are not expected to replace PSA.[98,101]

Prostate biopsy

Prostate cancer is diagnosed by histological examination of some prostate tissues. The tissue samples can be obtained by a fine needle biopsy. Prostate biopsy is a procedure where a series of small tissue sample from the prostate are removed by an urologist and examined by a pathologist. The tissue samples need to be collected in different positions, and generally 12 or more samples are taken to ensure cancer cells are not missed. This procedure can be painful and may require local anaesthetic. As some tissues from the prostate gland are removed, it may cause bleeding or infection.[86]

There are two approaches for prostate biopsy. The most common one is transrectal prostate biopsy. An ultrasound probe is inserted into the rectum, and then a fine needle is put into the prostate gland along the probe to obtain the tissue samples. Usually at least 12 samples are taken from different regions of the prostate cancer gland. Transperineal prostate biopsy is less commonly used. In this technique, the needle passes through the skin of perineum, which is more sensitive so a general anaesthetist is needed. This means the cost of a transperineal biopsy is considerably more than a transrectal prostate biopsy which can be done without a anaesthetist. Though transrectal prostate biopsy is less time-consuming and less costly, it has a higher risk of septic complications than transperineal prostate biopsy. It is recommended that patients with severe comorbidities and who would tolerate sepsis poorly might be better to receive transperinel prostate biopsy instead of the transrectal one.[102]

Transrectal ultrasonography (TRUS)

TRUS is the most commonly used modality for guiding needle biopsies.[83] It can produce an image of the prostate on a video screen using sound waves. A lubricated ultrasound probe is inserted into the rectum and produces high frequency sound waves aimed at the prostate gland. The echoes produced by the sound waves are analysed by a computer. A black and white image of the prostate is displayed on a computer screen.[103]

X-ray computed tomography (CT)

CT can produce tomographic images of the prostate gland with the X-rays. It can display the shape and size of the gland. It can be used for staging for patients with suspected metastatic disease,[89] but it cannot stage the local involvement.[83]

Magnetic resonance imaging (MRI)

MRI can produce the images of the prostate in three planes (axial, coronal and sagittal), enabling better evaluation of the prostate (Figure 6).[104] MRI is believed to display more accurate images than CT.

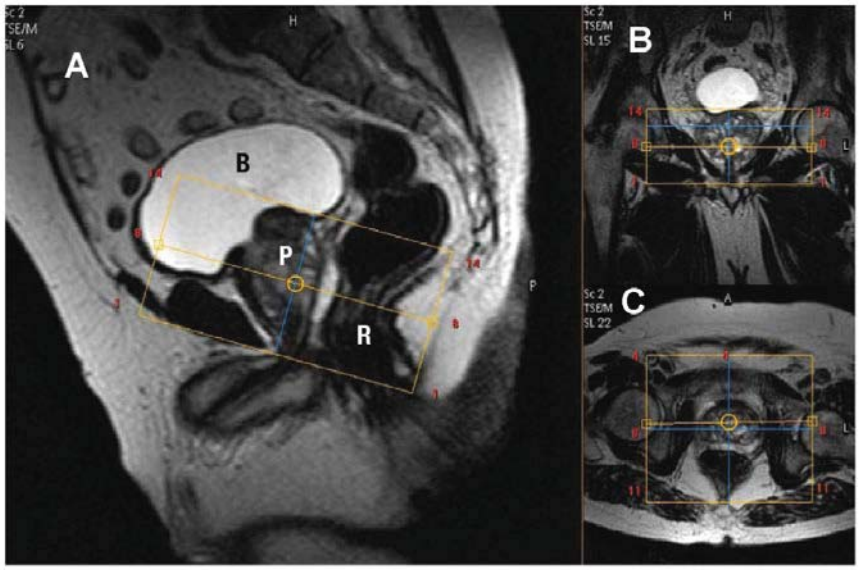


Figure 6. MR1 T2-weighted sections

(A) Sagittal section showing oblique reference plane perpendicular to the rectal surface of the prostate similar to the section plane used to obtain RP specimens by the Stanford technique; (B) coronal section; (C) axial section

Source: Dynamic Contrast-Enhanced MRI for Preoperative Identification of Localised Prostate Cancer[105] (License for reusing the figure has been granted)

1.2.4 Grading and staging systems

Prostate cancer cases can be stratified into different categories by grading and staging systems. These systems assess the histological and pathological information of individual cancers, and are vital in deciding the cancer management strategy. The most commonly used grading system is the Gleason system that describes how aggressive the cancer is. The Gleason system comprises five levels: 1 - 5, from the least to the most aggressive level. For each cancer, the Gleason score is generated by summing the grades of the two most representative specimens, and thus the Gleason score ranges from 2 to 10. Cancer cases with a Gleason score less than 6 are now considered to be benign. The risk of cancer progression increases with Gleason score.[106]

The Gleason grading system was modified by the International Society of Urological Pathology (ISUP) in 2005.[107] The ISUP modified Gleason system contains five patterns (Table 3). Pierorazio[108] and colleagues identified 7869 men who had radical prostatectomy and without a tertiary pattern in 2004-2011. They found great variations in the 5-year biochemical recurrence free survival for men with different Gleason score (Table 4).

Table 3. 2005 ISUP modified Gleason system

Pattern	Description
Pattern 1:	Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)
Pattern 2:	Like pattern 1, fairly circumscribed, yet at the edge of the tumour nodule there may be minimal infiltration Glands are more loosely arranged and not quite as uniform as Gleason pattern 1
Pattern 3:	Discrete glandular units Typically smaller glands than seen in Gleason pattern 1 or 2 Infiltrates in and amongst nonneoplastic prostate acini Marked variation in size and shape Smoothly circumscribed small cribriform nodules of tumour
Pattern 4:	Fused microacinar glands Ill-defined glands with poorly formed glandular lumina Large cribriform glands Cribriform glands with an irregular border Hypernephromatoid
Pattern 5:	Essentially no glandular differentiation, composed of solid sheets, cords, or single cells Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

Source: The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma[107] (License for reusing the figure has been granted)

Table 4. 5-year biochemical recurrence free survival after radical prostatectomy by Gleason score

Gleason score	5-year biochemical recurrence free survival after radical prostatectomy	
	Biopsy Gleason score	Radical prostatectomy Gleason score
≤6	94.6%	96.6%
3 + 4	82.7%	88.1%
4 + 3	65.1%	69.7%
8	63.1%	63.7%
9–10	34.5%	34.5%

The most commonly used staging systems are the tumour-nodes-metastasis (TNM) system and the ABCD system, indicating how large the cancer is and how the cancer spreads. The TNM classification was updated by the American Joint committee on Cancer (AJCC).[109] It reflects the clinical progression of the cancer. 'T' describes the extent of the primary tumour. 'N' describes the extent of regional lymph node metastasis. 'M' describes the occurrence of distant metastasis.

The ABCD system is less frequently used compared to TNM system. It includes four stages. In Stage A, the tumour is located in the prostate only and undetectable by a digital rectal examination (DRE). In Stage B, the tumour is still confined to the prostate but can be detected by a DRE. In Stage C, the tumour has spread to the nearby tissues, including the seminal vesicles. In Stage D, the tumour has spread to other distant parts of the body, including the lymph nodes, bones and other organs.[110]

Many cancer registries, including those supported by the US Surveillance, Epidemiology, and End Results (SEER) Program, use "summary staging" which consists of five main categories[111]: 1) In situ: abnormal cells are present only in the layer of cells in which they developed; 2) Localised: cancer is limited to the organ in which it began, without evidence of spread; 3) Regional: cancer has spread beyond the primary site to nearby lymph nodes or tissues and organs; 4) Distant: cancer has spread from the primary site to distant tissues or organs or to distant lymph nodes; 5) Unknown: there is not enough information to determine the stage. The NZCR classifies the cancer extent into: B (localised), C (invasion of adjacent tissues or organs), D (invasion of regional lymph nodes), E (distant metastases), and F (unknown).[112] C and D extent can be grouped as regional disease.[33] Most studies of cancer registry data were recorded as local, locally advanced and metastatic.[10,71]

The Gleason system or the TNM system alone might not be able to predict the progression and prognosis of localised prostate cancer comprehensively. Several methods have been developed to predict the possibility of recurrence or metastatic progression after treatment in patients with localised prostate cancer combining the prognostic factors. One of them was created by D'Amico et al in 1998[113], that combines the Gleason system, the TNM system and the preoperative PSA level. The D'Amico risk classification system comprises three risk levels: low risk (biopsy Gleason score ≤6, clinical stage T1c-T2a and PSA level ≤10 ng/mL), intermediate risk (biopsy Gleason score 7, clinical stage T2b and PSA level of higher than 10 ng/mL but no higher than 20 ng/mL) and high risk (biopsy Gleason score 8-10, clinical stage T2c and PSA level >20 ng/mL). This system is only used for men

diagnosed with localised (T1-T2) prostate cancer. Patients in these three groups have statistically significant differences in biochemical recurrence-free survival, progression-free survival and cancer-specific survival.[80,113] Compared to other risk classification systems, the D'Amico risk classification system is simpler, more generalizable and commonly used.[114]

Kattan MW[115] and colleagues in 1998 developed prognostic nomograms to predict the recurrence of prostate cancer after radical prostatectomy. Different from the D'Amico system[113], the nomograms link the PSA level, clinical stage and biopsy Gleason score with a point system. The 5-year PSA progression-free survival can be generated based on the cumulative points. This system is only applicable to patients whose treatment was radical prostatectomy.

Han M[116] and colleagues in 2004 created three preoperative and two postoperative look-up tables for the prognosis for patients who had clinically localised prostate cancer and were treated with radical prostatectomy. The biochemical recurrence-free survival at 3, 5, 7 and 10 years can be found in the preoperative/postoperative tables based on the PSA level, clinical stage and biopsy/surgery Gleason score.

1.2.5 Prostate cancer screening

In 2003, the National Advisory Committee on Health and Disability (National Health Committee) published the screening programme assessment criteria in New Zealand.[117] The criteria are shown in Table 5.

Table 5. Screening programme assessment criteria in New Zealand

Screening programme assessment criteria in New Zealand
• The condition is a suitable candidate for screening. • There is a suitable test. • There is an effective and accessible treatment or intervention for the condition identified through early detection. • There is high quality evidence, ideally from randomised controlled trials, that a screening programme is effective in reducing mortality or morbidity. • The potential benefit from the screening programme should outweigh the potential physical and psychological harm (caused by the test, diagnostic procedures and treatment). • The health care system will be capable of supporting all necessary elements of the screening pathway, including diagnosis, follow-up and programme evaluation. • There is consideration of social and ethical issues. • There is consideration of cost-benefit issues.

Screening for prostate cancer using a serum PSA test meets a number of the screening criteria. Prostate cancer can be cured if it is detected and treated at an early stage, which makes it a good candidate for screening. The PSA test is less costly and simpler than other diagnostic tools,[118] and has been widely used as the screening tool since the late 1980s. Many indolent and asymptomatic prostate cancers were identified through screening and the incidence of prostate cancer increased dramatically.[119] It resulted in more than 1 million additional prostate cancer cases identified in the US.[60] Since most of the screen-detected prostate cancers are localised, the proportion of advanced prostate cancers in all cancer cases was reduced.[8] A study conducted in Norway showed that the annual incidence of localised cancers for men aged 50-65 and 66-74 rose from 41.4 and 255.2 per 100,000 before the screening era to 137.9 and 418.7 per 100,000 in 2001-2010, corresponding to 3.3 and 1.6 times increase. The incidence of regional cancers increased by seven times for men less than 75 years old and by four times for men aged 75 years and older, while the incidence of distant metastatic cancers decreased by 26.5%, 37.6% and 29.1% in men aged 50-65, men aged 66-74 and men aged 75 years and older.[120]

Three large randomised clinical trials were carried out to examine the effect of prostate cancer screening, including the European Randomised Study of Screening for Prostate Cancer (ERSPC)[5], the Göteborg study[6] and the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial[7]. The ERSPC study[5] was conducted in eight European countries. Researchers randomly allocated 82,816 men aged 50-74 years (72,890 aged 55-69 years) to the screening group and 99,184 men at the same age (89,353 aged 55-69 years) to the control group. The median screening interval was 4.02 years. In the core age group (men aged 55-69 years), 6,963 (9.7%) men in the screening group and 5,396 (6.0%) men in the control group were diagnosed with prostate cancer after a median follow-up of 11 years. There were 299 men in the screening group died of prostate cancer compared with 462 men in the control group, resulting in a 29% reduction in the screening group. It also concluded that 1055 men need to be screened and 37 cancers need to be treated to prevent one death from prostate cancer.[5]

The Göteborg study[6] was carried out in Göteborg, Sweden. A computer randomly sampled cohort of 20,000 men aged 50-64 years were assigned to either a screening group or a control group. The first screening round was in 1995-96 and the last round was in 2007-08. The screening interval in the intervention arm was 2 years. After a median follow-up of 14 years, 1,138 (12.7%) men in the screening group and 718 (8.2%) men in the control group had been diagnosed with prostate cancer. The prostate cancer-specific mortality was reduced almost by half in the screening group: 44 deaths from prostate cancer in the screening group and 78 in the control group. Compared with the ERSPC study, the screening benefits in the Göteborg study were more favourable: 293 men need to be screened and 12 cancers need to be treated to prevent one death from prostate cancer.[6]

The PLCO[7] trial recruited 76,685 men (38,340 in the intervention arm and 38,345 in the control arm) aged 55-75 years in America 1993-2001. Men in the intervention arm received organized annual PSA testing for 6 years and annual DRE for 4 years. Men in the control arm had opportunistic screening. After 13 years of follow-up, 4,250 men in the intervention arm and 3,815 men in the control arm were

diagnosed with prostate cancer. The prostate cancer-specific mortality was similar in two groups: 158 in the intervention arm and 145 in the control arm. No significant difference was identified (RR = 1.09, 95% CI = 0.87 to 1.36).

A Cochrane review used meta-analysis to synthesize the results of five randomized controlled trials. The trials included the ERSPC study (the Göteborg study was considered to be part of the ERSPC study in this systematic review), the PLCO, the Norrkoping study,[121] the Quebec study[122] and the Stockholm study,[123] and demonstrated that the impact of screening on prostate cancer-specific mortality might not be manifested within 10 years after screening. Men aged 70 years and older or men with a life expectancy of 10-15 years due to comorbidities are not recommended for prostate cancer screening.[8]

The U.S. Preventive Services Task Force recommended against prostate cancer screening because they believed the harms caused by PSA screening outweight the benefits.[124] Though this recommendation was protested officially by the American Urology Association,[125] it has resulted in significant declines in PSA testing from 2008 to 2013 in American men (especially in men aged ≥75 years).[126] The decreased number of biopsies performed and fewer low risk prostate cancers being diagnosed in Canada may also reflect the impact of the U.S. Preventive Services Task Force recommendations.[127]

No guideline recommends population-based prostate cancer screening, but shared decision making on PSA testing was stressed in some guidelines. The American Cancer Society recommends that 'asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision with their health care provider about screening for prostate cancer after they receive information about the uncertainties, risks, and potential benefits associated with prostate cancer screening'.[128]

1.2.6 Overdiagnosis and overtreatment

Overdiagnosis and overtreatment are the two major problems associated with prostate cancer screening.[13,129,130] Prostate cancer screening has led to many low grade cancers being identified, including those with Gleason scores less than 6 that are now considered to be benign. Some screen-detected cancers might be not life-threatening or might even be indolent during a patient' life time. These men might not benefit from the early diagnosis but might suffer from the harms. After the diagnosis, 28% of men suffered from high anxiety, though it improved and remained stable after treatments.[17]

The Draisma study indicated that the overdetection (the detection of nonlethal cancer) rate was 27% if they screened men aged 55 years only and 56% if they screened men aged 75 years only. The overdetection rate was 48% if they screened men aged 55-67 at a 4-year screening interval. It increased to 50% if they screened these men annually.[131] The MISCAN (MIcrosimulation Screening

Analysis) model predicted that screening men aged 55–70 years at a 4-year interval would result in a 42% overdetection rate.[13] A later study[132] presented similar results for men aged 54-80 years: 42%, 28% and 23% using the MISCAN model, FHCRC model and UMich model. In New Zealand, the incidence of prostate cancer more than doubled since 1990 when the PSA testing era started[81] (Figure 5). By introducing screening, the medical costs related to prostate cancer would likely increase by 100%, and 78% of the increased costs would be attributed to overdection.[13]

If the identified prostate cancer cases are asymptomatic and are not fatal in one's life-time, treatment for these men is unnecessary.[133] In the Prostate Cancer Intervention versus Observation Trial (PIVOT),[15] most of the men detected with localised prostate cancer by PSA screening were still alive after a median follow-up of 10 years. These men will not benefit from definitive treatment but might suffer from the side effects caused by treatments including urinary incontinence, impotence, bowel dysfunction and depression.[16] In the USA, of 3001 men with low-risk prostate cancer and a life expectancy of less than 10 years, 2011 men (67%) were considered to be overtreated.[134] The cumulative annual cost attributed to overtreatment in the US was US$58.7 million.[134] The Heijnsdijk study[135] showed that screening resulted in more life-years gained but the same qualify-adjusted life years, which indicated that the survival benefit contributed by PSA screening was offset by the loss of qualify of life.

1.2.7 Management of localised prostate cancer

Approximately 80%-90% of the newly diagnosed prostate cancers in the US were localised.[34,136] The effects of prostate cancer screening are highly dependent on the management of the screen-detected localised prostate cancers. The available treatment options for localised prostate cancer include definitive treatments (prostatectomy, radiotherapy and hormone therapy) and conservative management/deferred treatments (active surveillance and watchful waiting).

1.2.7.1 Radical prostatectomy

The surgical approach to treating prostate cancer is radical prostatectomy. If the cancer has spread to the lymph node, a pelvic lymph node dissection will also be performed.[137] There are two types of radical prostatectomy classified by the position of the skin incision made for the open surgery: radical retropubic prostatectomy and radical perineal prostatectomy. The incision for radical retropubic prostatectomy is in the lower abdomen, from the umbilicus down to the pubic bone, whilst the incision for radical perineal prostatectomy is between the anus and scrotum (the perineum) in men with prostate cancers. Perineal prostatectomy is used more often, whilst retropubic prostatectomy is commonly used for men with benign prostate hyperplasia. Perineal prostatectomy causes less pain and requires shorter recovery time, whilst retropubic prostatectomy not only causes more pain, but also has difficulty in sparing nerves and removing lymph nodes.[138-142]

Laparoscopic radical prostatectomy is superior to open surgery in terms of the incision size, blood loss, pain and recovery time.[138,140,142] Laparoscopic radical prostatectomy requires six 1-inch incisions in the abdomen. It is minimally invasive and less traumatic. The most advanced prostatectomy is the robotic-assisted laparoscopic prostatectomy. The surgery is done through a robotic interface (da Vinci system).[143-145] Laparoscopic radical prostatectomy and robotic-assisted laparoscopic prostatectomy require the physician to be well-trained in the technique. Robotic-assisted laparoscopic prostatectomy is much more expensive than open surgery. In New Zealand, the cost of a robotic-assisted laparoscopic prostatectomy is twice the cost of an open radical prostatectomy (unpublished data: NZ$30,000 versus NZ$15,000 in private hospital; $11,000-12,000 for an open radical prostatectomy in public hospitals). Open surgery is still most commonly performed in public hospitals and robotic-assisted laparoscopic prostatectomy can only be accessed in private hospitals in New Zealand. In the United States, the robotic-assisted laparoscopic prostatectomy required more than US$1.4 million (capital cost in 2007) to purchase the da Vinci robot and then an annual cost of US$140,000 to maintain the robot.[146]

The most common side effects caused by prostatectomy include urinary incontinence and impotence. The muscles and nerves that control urinary continence may be swollen or damaged, which causes urinary problem, such as urinary incontinence. These problems generally improve over time. It was reported that 14% of men had big urinary problems at 6 months after radical prostatectomy, the number decreased to 8% at 12 months and 4% at 52 months.[147] During surgery, the nerves which control penile erection may be damaged or removed on purpose due to cancer spread, resulting in erectile dysfunction.[147]

1.2.7.2 Radiotherapy

Radiotherapy includes external beam radiotherapy or brachytherapy. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) are the most widely used external beam radiotherapy for prostate cancer. They all focus precisely on the tumour and reduce the radiation on the surrounding healthy tissue, thus decreasing the risk of side effects. 3D-CRT can measure the exact height and width of the tumours and generates beams of radiation to the tumours. IMRT is an advance form of 3D-CRT. It can modulate the shape and doses of radiation delivered to the tumours and adjacent healthy tissues more precisely and accurately.[148,149]

External beam radiotherapy is an external radiotherapy, whilst brachytherapy is an internal radiotherapy. The radiation is placed into the prostate gland by a specialist radiation oncologist and a specialist urologist. For permanent (low dose rate) brachytherapy, seeds containing radioactive Iodine 125 or radioactive Palladium 103 are implanted in the prostate permanently. The number of seeds implanted depends on the size of the tumour. For temporary (high dose rate) brachytherapy, radioactive iridium-192 or cesium-137 is put in the prostate for 5 to 15 minutes and then removed. This procedure is performed several times in two days. The guideline for prostate cancer in New

Zealand advised that low dose rate brachytherapy is most suitable for patients with good urinary function, a prostate size of less than 50–60 cm^3 and low risk cancer. In the intermediate risk group the most suitable patients for low dose brachytherapy are those with less than 30–50% positive biopsies, no perineural invasion and Gleason 3+4 =7 disease.[150] External beam radiotherapy can be used in conjunction with brachytherapy. It is most suitable for 'unfavourable' intermediate risk patients with more than 50% positive biopsies, Gleason 3+4=7, extensive perineural invasion and locally advanced bulky cancers.[150]

Radiotherapy may cause 1) bowel problems: diarrhea, rectal pain, bloody stool, rectal leakage and irritated intestine 2) bladder problems: bladder inflammation, hematuria, burning sensation on urination, 3) urinary problems: urinary incontinence and difficulty in passing urine 4) erection problems. In comparison with side effects caused by surgery that might be permanent, the problems caused by radiotherapy may improve over time.[151,152]

The cost of radiotherapy is substantial. The cost of stereotactic radiotherapy in New Zealand was NZ$12,925 in 2008/2009.[153] A study conducted in Sweden showed that the total cost of external radiotherapy comprised approximately 5% of the total cost of oncology care in Sweden in 2000. The capital cost (including the cost of equipment and buildings) was 26.2% of the total cost of external radiotherapy. The total cost of brachytherapy was about one-tenth of the cost of external radiotherapy.[154]

1.2.7.3 Hormonal therapy

The growth of prostate cancer relies on testosterone. Lowering the level of testosterone can stop the tumour from growing, shrink the size of the tumour or reduce the risk of relapse of the treated prostate cancer. There are two ways to lower the level of testosterone: 1) orchiectomy; 2) medication. Orchiectomy is a procedure that removes the testicle. Testosterone is produced by the testicles. Once the testicles are removed, the level of testosterone will fall immediately and the tumour might stop growing.[155] Over the last 40 years, medical castration has been developed to avoid the need for surgical castration.[156] Given the psychological impact of orchiectomy, medical castration is preferred by more patients.[49] The medicine used for hormone treatment includes four main types (Table 6).[157]

Table 6. Medicine used for hormone treatment

Pharmaceutical types of hormone therapy
1. Luteinising hormone (LH) blockers – they include goserelin (Trade name: Zoladex), buserelin, leuprorelin (Prostap), histrelin (Vantas) and triptorelin (Decapeptyl)
2. Anti androgens – they include flutamide (Drogenil) and bicalutamide (Casodex)
3. Gonadotrophin releasing hormone (GnRH) blocker – degarelix (Firmagon)
4. Abiraterone

Hormone treatments reduce the level of testosterone and estrogen, causing side effects related to the functions of these two types of hormone. The side effects include reduced or absent libido, impotence, hot flashes, breast tenderness and growth of breast tissue, osteoporosis, anemia, decreased mental sharpness, loss of muscle mass, weight gain, fatigue, increased cholesterol, depression, diarrhea, liver problems, high blood pressure, seizures, dizziness and upset stomach.[155,158] ADT was also found to be associated with higher risk of cardiac-specific mortality in men with congestive heart failure or prior myocardial infarction.[159] The length of treatment thus has to be balanced with the harms.

1.2.7.4 Active surveillance and watchful waiting

To prevent overtreatment, conservative management was introduced for prostate cancer. Conservative management is symptom guided. Patients will be followed-up and will not be treated until symptoms develop or the cancer progresses. The conservative management includes active surveillance and watchful waiting. Active surveillance is mainly for localised, low risk prostate cancer management in men with a long life expectancy. Watchful waiting has mainly been used in patients with a life expectancy less than 10 years.[150] The main difference between active surveillance and watchful waiting is that the candidates under active surveillance are eligible for definitive treatment and will be offered definitive treatment if the cancer progresses or the patient requests active treatments. Men under watchful waiting will be offered symptomatic treatment rather than curative treatments due to poor health conditions or a short life expectancy. Approximately 30% of men under active surveillance were reclassified as high risk (PSA doubling time of less than 3 years; histologic upgrade on repeat prostate biopsy; and clinical progression) and were offered active treatments.[160] As surgical treatment/radiotherapy can cause severe side effects, these treatments may do more harm than good for men with nonlethal prostate cancer.[148] Conservative management prevent patients suffering from side effects caused by aggressive treatments and optimises their quality of life.

There is no agreed protocol for watchful waiting in New Zealand. Men under watchful waiting are commonly monitored by PSA test or DRE biannually or annually.[161] Compared with watchful waiting, active surveillance is more structured and rigorous. Patients under active surveillance are closely monitored by PSA test, prostate ultrasound and repeat biopsy.[162] The New Zealand Ministry of Health published a guidance on using active surveillance to manage men with low risk prostate cancer in July 2015.[163] The basic protocol for active surveillance include three-monthly PSA +/-DRE and repeat assessment every 6-12 months using biopsy +/-MRI in the first year, and 3-12-monthly PSA +/-DRE and repeat assessment every 2-4 years using biopsy +/-MRI in the subsequent years.[163] MRI was advocated to be utilized in active surveillance for its non-invasive nature and accuracy in cancer risk assessment.[164,165]

It is demonstrated by P.C. Albertsen[166] that low grade, localised prostate cancer is not likely to progress within the first 15 years after diagnosis. This study was based on a competing risk analysis of men with localised prostate cancer and treated with observation or immediate or delayed androgen

therapy with a median follow-up time of 24 years.[166] Even without definitive treatments, only a small proportion of patients diagnosed with early stage prostate cancer will die of prostate cancer.[37,166] Considering the small likelihood of benefiting from the definitive treatments and high risk of suffering from the side effects, conservative management is regarded as a reasonable treatment option for early stage, low grade prostate cancer.[167-173]

Though active surveillance has been included in guidelines for the treatment of localised prostate cancer, including the American Urological Association, European Association of Urology and the National Comprehensive Care Network, uncertainties remain on the optimal patient selection, surveillance strategies and triggers for intervention.[174] One third of men under active surveillance received active treatment after a median follow-up of 2.5 years, with 7-13% treated without evidence of progression, 13-48% treated because the PSA value doubled in less than 3 years and 27-100% treated for histologic reclassification.[174]

1.2.8 Treatment effectiveness for localised prostate cancer

The comparative effectiveness of different treatments for localised prostate cancer has been presented in a systematic review published in 2008.[175] This systematic review synthesized 18 RCTs and 473 observational studies. Among the studies comparing primary treatment categories, three RCTs included radical prostatectomy. Of the three RCTs, two studies were considered to be low strength. The only medium strength study is the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a randomised trial of radical prostatectomy (347 men) versus watchful waiting (348 men) for localised prostate cancer.[39] The 695 men were enrolled from 14 centres in Sweden, Finland and Iceland from 1989 to 1999. Based on their updated publication, after 18 years of follow-up, 26.1% of men treated with radical prostatectomy had distant metastases compared with 38.3% of men under watchful waiting ($p=0.001$), and 17.7% of men in the radical prostatectomy group died of prostate cancer compared with 28.7% in the watchful waiting group ($p<0.001$). The difference in the possibility of distant metastases and mortality of prostate cancer between the watchful waiting group and the radical prostatectomy group in subgroups is shown in Table 7. There was a significant difference in distant metastases between the watchful waiting group and the radical prostatectomy group for men aged less than 65 years, for men aged 65 years or older, for men with low risk and for men with intermediate risk prostate cancer (Section 1.2.4), but not for men with high risk cancer. The mortality difference between the watchful waiting group and the radical prostatectomy group was significant for men aged less than 65 years and for men with intermediate risk prostate cancer, but not for men aged 65 years and older or for men with low risk or high risk cancer.[39]

Table 7. The cumulative incidence of distant metastases and death of prostate cancer in the SPCG-4 study

End Point	Radical Prostatectomy (N=347)		Watchful Waiting (N=347)		P Value
	No. of events	% (95% CI)	No. of events	% (95% CI)	
Death from prostate cancer					
All	63	17.7 (14.0 to 22.4)	99	28.7 (24.2 to 34.2)	0.001
Age					
<65 year	31	18.3 (13.1 to 25.7)	58	34.1 (27.3 to 42.5)	0.002
≥65 year	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	0.19
Tumor risk					
Low	11	10.2 (5.8 to 18.0)	20	14.0 (9.1 to 21.5)	0.17
Intermediate	24	15.1 (10.2 to 22.2)	50	39.3 (31.3 to 49.3)	<0.001
High	28	33.1 (24.0 to 45.7)	29	35.7 (26.3 to 48.5)	0.84
Distant metastases					
All	89	26.1 (21.7 to 31.4)	138	38.3 (33.4 to 44.0)	<0.001
Age					
<65 year	45	28.7 (22.2 to 37.1)	76	44.5 (37.3 to 53.0)	<0.001
≥65 year	44	23.8 (18.4 to 30.9)	62	32.7 (26.4 to 40.5)	0.04
Tumor risk					
Low	15	13.6 (8.4 to 21.9)	35	24.2 (17.8 to 33.0)	0.006
Intermediate	37	25.0 (18.8 to 33.3)	59	44.9 (36.9 to 54.7)	<0.001
High	37	45.9 (35.8 to 58.8)	44	50.8 (40.6 to 63.5)	0.39

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Most patients enrolled in the SPCG-4 study were not identified by PSA testing. In contrast to the SPCG-4 study, men enrolled in the Prostate Cancer Intervention versus Observation Trial (PIVOT) were detected with localised prostate cancer by PSA screening.[15] From 1994 to 2002, 364 men were assigned to the radical prostatectomy group and 367 men were assigned to the observation group. The results of this trial were first published in 2012 and thus this trial was not included in the systematic review.[175] After a median follow-up of 10 years, no significant difference in the prostate cancer-specific mortality was found between the two groups: 5.8% in the radical prostatectomy group and 8.4% in the observation group (p=0.09). However, there was significant difference in bone metastases between the two groups, with 17 (4.7%) men in the radical prostatectomy group and 39 (10.6%) men in the observation group detected with bone metastases (p<0.001). Though men in the PIVOT study[15] were identified by screening, the proportion of men in low (42%), intermediate (36%) and high (22%) risk were similar to that (36% low risk, 40% intermediate risk and 24% high risk) in the SPCG-4 study[39]. Almost half of the patients in the SPCG-4 study[39] had 15 years follow-up, while 5% of the men in the PIVOT study had 15 years follow-up.[15]

The systematic review[175] also identified four RCTs with medium or high strength that examined the effectiveness of ADT as an adjuvant therapy to radical prostatectomy for men with localised prostate

cancer. No benefit in biochemical progression was detected. Three RCTs with medium strength examining the effectiveness of ADT as an adjuvant therapy to external beam radiotherapy showed that ADT reduced the overall mortality, prostate cancer-specific mortality and biochemical/clinical progression for men with localised prostate cancer.[175] Men with low risk prostate cancer (PSA level <10μg/mL, tumour stage T1c to T2a, or Gleason score ≤6) under 8-months external beam radiotherapy were less likely to have biochemical failure compared with men under 3-months therapy.[175] An updated systematic review on radiation treatments also found that a higher external beam radiotherapy dose was associated with better biochemical control than a lower dose for men with localised prostate cancer.[176]

No randomised clinical trials have been carried out to compare the clinical outcome of active surveillance with radical prostatectomy for men with localised prostate cancer. Some observation studies reported that the cancer-specific mortality for patients under active surveillance was low (0-1%); however these observation studies only have a short follow-up, ranging from 1.8 to 6.8 years. Economic evaluation studies can compare the long term (including life-time) clinical and economic outcomes between active surveillance and radical prostatectomy for localised prostate cancer using modelling methods by synthesizing available data from different sources.

1.2.9 Management of advanced prostate cancer

For metastatic prostate cancer that cannot be cured by surgery or radiotherapy, hormone therapy can be used to slow down cancer progression. However, over a certain period of hormone treatment, the tumour(s) stops responding to the hormone treatment, the PSA level starts rising and the tumour(s) starts growing again. This circumstance is called castration-resistant prostate cancer (CRPC). Chemotherapy using docetaxel plus prednisone/prednisolone is the recommended first-line treatment for CRPC in many guidelines, including the National Comprehensive Cancer Network, European Society of Medical Oncology and European Association of Urology.[177] Other agents have been developed for treating CRPC, including abiraterone acetate, enzalutamide, sipuleucel-T, cabazitaxel and radium-223.[177]

Men with advanced prostate cancer might suffer from symptoms, such as bone pain. Treatments for symptoms included pain-relieving drugs, palliative radiotherapy and bisphosphonates.[178,179] The palliative radiotherapy includes external beam radiotherapy and radioisotopes (injectable radiotherapy). [178]

It was demonstrated that the increases in the costs of health care for cancer are driven by innovations.[180] Advanced prostate cancer that is no longer curable by surgical approaches is mainly treated with pharmaceuticals. In a study conducted in Canada, the mean cost of drug treatments for patients with metastatic castration-resistant prostate cancer (mCRPC) doubled (from CAN$48,428 per patient over an average period of 28.1 months to CAN$104,071) when patients included abiraterone

initiation prior to docetaxel therapy.[181] When patients received cabazitaxel in sequence after abiraterone and docetaxel, the mCRPC medications cost per patient per month increased by 60.2%.

The innovation of pharmaceuticals is the main contributor to the increased health care costs for advanced prostate cancer. It was reported that a new drug costs US$2.6 billion to develop, including the price of failure and the opportunity costs.[182] Considering the huge innovation cost, the price of patent drugs is set much higher than their cost of manufacture. The price of patent drugs often decline significantly once the patent expires.

1.3 New Zealand health care system

The practice of medicine differs from country to country. Prostate cancer screening is common in the US, while it is less commonly practiced in Europe.[183] The overall annual screening rate for men aged 40+ was 22.1% in New Zealand in 2010.[4] It varied among different age groups: 12.2% for men aged 40-49, 24.9% for men aged 50-59, 31.5% for men aged 60-69, 27.7% for men aged 70-79 and 16.6% for men aged 80+.[4] Only 10% of the patients with localised prostate cancer in the US are on active surveillance or watchful waiting.[166] However, 15% of men with low-intermediate risk localised prostate cancer are on active surveillance and 5% are on watchful waiting in Victoria, Australia, and the uptake of conservative management in the rest of Australia is increasing.[184] In New Zealand, 11% of men diagnosed with localised prostate cancer are on active surveillance and 11% are on watchful waiting in the Midland Cancer Network region.[12] The variation in management of prostate cancer might be associated with the differences in health care systems and population. This section aims to introduce the New Zealand health care system, the Midland Cancer Network and the indigenous population in New Zealand.

1.3.1 Overview of the health care system

New Zealand spent 10.3% of GDP on health in 2009 and 9.6% in 2008, compared to an average of 9.8% in 2009 and 8.9% in 2008 for the 33 OECD countries.[185] The percentage of health expenditure in GDP in New Zealand was the 9th highest among the OECD countries in 2008 and the 10th in 2009.[185] Health expenditure is continuously growing and in 2013/14, the health system's funding was over $14.655 billion.[186]

The New Zealand health care system is a mix of government funded and private health care. The public funded system is controlled and managed by the Ministry of Health. They fund District Health Boards (DHB) some crown entities and agencies, non-governmental organisations, public health units, health alliances, primary health organisations, regulatory bodies, ministerial health commitees and statutory bodies (Figure 7). The health care funding is mainly held by the Ministry of Health, 20 DHBs and the accident compensation corporation (ACC). The DHBs, created by the New Zealand Public Health and Disability Act 2000, hold 75% of health funding in New Zealand. DHBs fund most of the health care services in their respective districts, including primary care, hospital services, public health services, aged care services, home support and community care services. Other services, such as disability support services and public health services, are funded by the Ministry of Health. ACC covers accident services, including payment towards treatment, help around the home during recovery, and income assistance if the patient cannot work due to the injury.[185,187,188]

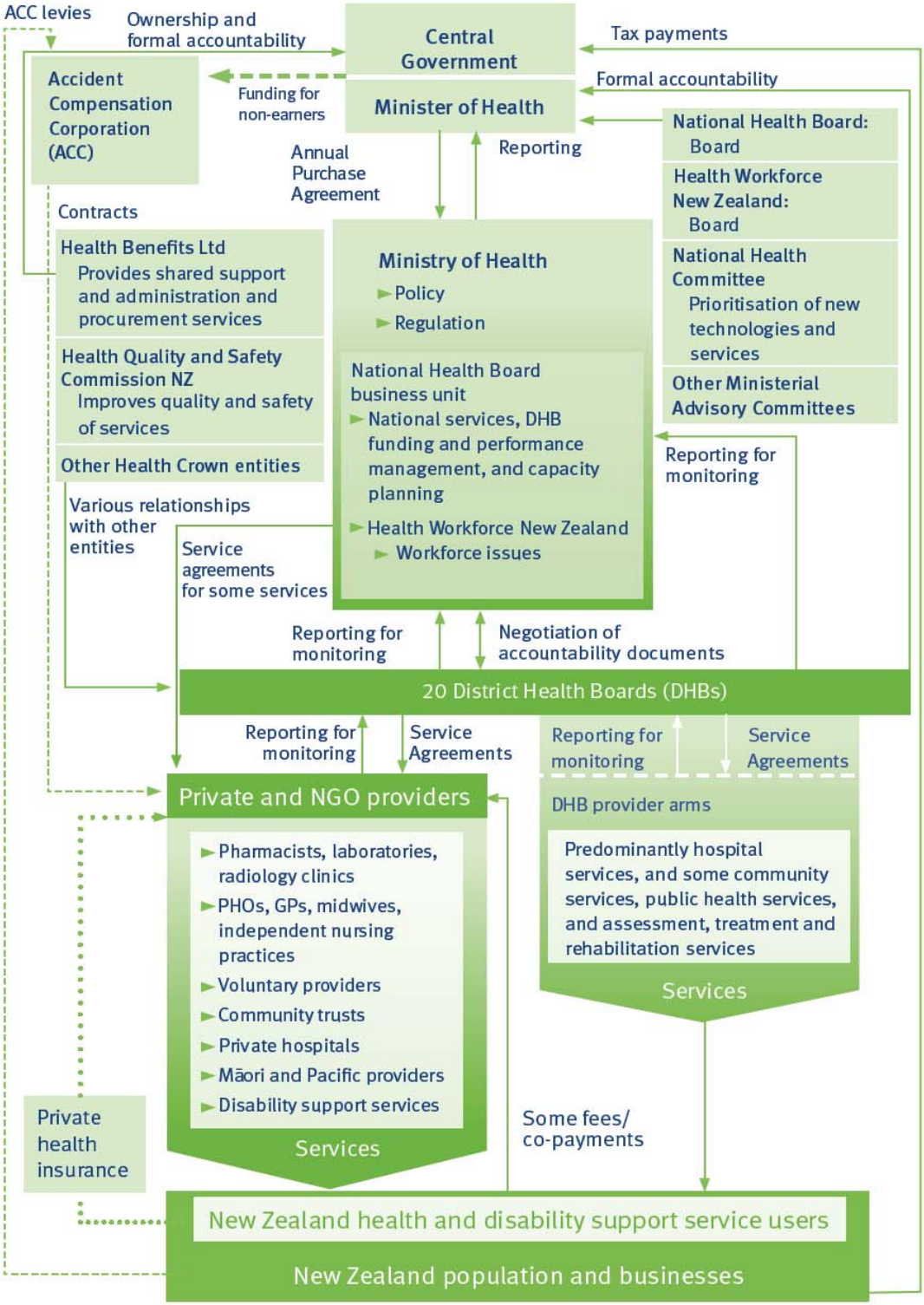

Figure 7. The structure of the New Zealand health and disability sector

Source: Overview of the health system in New Zealand[189]

The medical services provided by public hospitals funded by the DHBs are free for residents and other people who have a work visa for two years or longer. Once the patients are referred to a public hospital, they may be treated immediately, put onto a waiting list or referred back to their GPs. The waiting time for a specialist appointment or a surgery in a public hospital varies in response to the severity of the disease. Some patients might choose to seek health care in a private hospital, which is at the patients' own expense or is covered by insurance. Primary health care (general practice) and medications require co-payments. Whist they receive subsidy from the DHB and Ministry of Health, general practitioners are also entitled to charge patients a fee. The fees for medical treatments due to accident or injury are paid by the ACC without patient co-payment, if the patients are legally entitled to stay in New Zealand, including residents and visitors.[190,191]

1.3.2 Midland Cancer Network

There are four regional cancer networks in New Zealand, Northern Cancer Network, Midland Cancer Network, Central Cancer Network and Southern Cancer Network. They collaborate with DHBs, facilitating and coordinating the health care services related to cancer.[192] The Midland Cancer Network comprises Waikato, Lakes and Bay of Plenty DHBs (Figure **8**). Tairawhiti DHB joined in 2014 (after the completion of our patient recruitment and data collection). The Midland Cancer Network has a leadership, facilitation and coordination role in bringing together and working with stakeholders across organisational and service boundaries.' They aim to 'improve the journey of cancer patients and their family/whānau through the complex pathway of care, working towards equitable, high quality, patient centred, evidence based and multidisciplinary care.'[192]

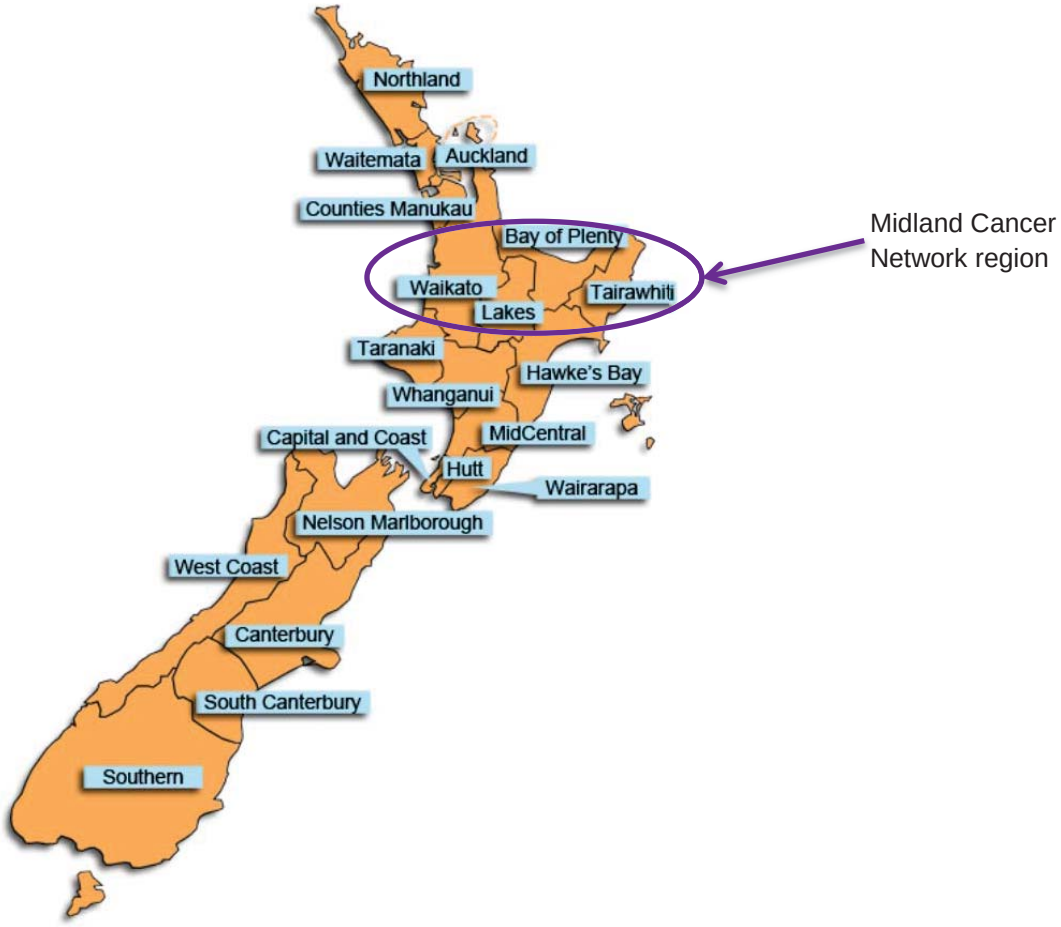

Figure 8. District Health Boards in New Zealand

Source: Overview of the health system in New Zealand[189]

1.3.3 Inequity in health status between Māori and non-Māori

Māori, the indigenous population in New Zealand, comprise 15.6% of the population.[32] Māori men have on average the poorest health status compared with other ethnic groups in New Zealand.[193] The life expectancy at birth is lower for Māori than for non-Māori: 76.5 years for Māori women and 72.8 years for Māori men compared with 83.7 years for non-Māori women and 80.2 years for non-Māori men in 2010-12.[194] Though the gap (7.3 years in 2010-12) is still great, it has been narrowed in recent years- 9.1 years in 1995-97, 8.5 years in 2000-02 and 8.2 years in 2005-07.[194] The disparity in life expectancy can be attributed to various reasons, including genetic factors, socioeconomic status (SES), diet, or access to and quality of health care. A nationally cross-sectional study showed that the quality of hospital care received by Māori was significantly worse than that for non-Māori.[195] A higher proportion of preventable adverse events was identified for Māori than non-Māori.[195]

The disparity in health status between Māori and non-Māori can be identified in many diseases, including cancer. In 2011, the age-standardised cancer registration rate for Māori was 409.8 per 100,000 men compared with 324.3 per 100,000 men for non-Māori. The age-standardised cancer mortality rate for Māori was almost twice the rate for non-Māori: 204.6 per 100,000 population for Māori and 118.9 for non-Māori.[3]

There are great differences in the prostate cancer registration rate and mortality rate between Māori and non-Māori. The age-standardised registration rate of prostate cancer was lower for male Māori (81.4 per 100,000 men) than the rate for non-Māori (99.0 per 100,000 men). In contrast, the age-standardised mortality rate of prostate cancer for male Māori (22.1 per 100,000 men) was much higher than that for non-Māori (16.2 per 100,000 men).[3] Māori men were 1.84 (95% CI, 1.72, 1.97) times more likely to die from any cause and 1.94 (95% CI, 1.76, 2.14) times more likely to die of prostate cancer than non-Māori men.[33] The survival disparity has not been reduced despite improvements in survival for men diagnosed after 2000.[33]

Māori men were half as likely to be screened compared to non-Māori men. When screened, the risk of having an elevated PSA result for Māori men was twice the risk for non-Māori men.[21] Māori were twice as likely to be diagnosed with distant metastases. When diagnosed with localised prostate cancer, Māori were more likely to be managed expectantly after adjustment for age, D'Amico risk strata, comorbidities, and socioeconomic deprivation.[12]

1.4 Economic evaluation of health care programmes

This section aims to provide some background to the economic evaluation of health care.

1.4.1 Importance and application of economic evaluation

Economic evaluation studies are critical for comparing the health care programmes in terms of the costs and effectiveness/benefits. The UK National Institute for Health and Clinical Excellence (NICE) adopted economic evaluation as a central part of their Technology Appraisal Programme in 1999 to decide whether a new pharmaceutical or a new health technology should be available through the public health care system.[1,196]

The different unit costs of medical resource, health care practice and population among countries result in variation of results of economic evaluation studies carried out in different countries.[197] A new pharmaceutical or a new technology might be cost-effective in one country, but might not be cost-effective in another country. Each country needs to perform its own analysis using local costing data and compare the result with its own cost-effectiveness thresholds relevant to the country.

The incremental cost-effectiveness ratio (ICER) threshold is a benchmark that is used to assess whether a healthcare programme is cost-effective or not. NICE 2004 guidelines stated that "Although the use of a threshold is inappropriate, comparisons of the most plausible ICER of a particular technology compared with other programmes that are currently funded are possible and are a legitimate reference for the Committee. Such comparisons are helpful when the technology has an ICER that is lower than programmes that are widely regarded as cost effective, substantially higher than other currently funded programmes or higher than programmes previously rejected as not cost effective by the Committee."[198]

1.4.2 Incremental cost-effectiveness ratio (ICER)

An incremental cost-effectiveness ratio (ICER) of two health care programmes is usually utilized in economic evaluation studies. The ICER of a new pharmaceutical or a new technology compared to the existing one can be generated through the incremental analysis of costs and health gained:

$$\text{ICER} = \frac{\text{Cost (new)} - \text{Cost (existing)}}{\text{Effectiveness (new)} - \text{Effectiveness (existing)}}.$$

This can be explained in the cost-effectiveness plane (Figure 9). The new treatment is less costly and more effective compared to the existing treatment in the southeast quadrant, and is more costly and less effective in the northwest quadrant. In the northeast quadrant, the new treatment is more effective but also more costly than the existing treatment. In the southwest quadrant, the new treatment is less effective but also less costly than the existing treatment. All points in the northeast

quadrant and in the southwest quadrant to the right of the dotted line (the maximum acceptable incremental cost-effectiveness ratio) involve a trade-off between costs and effectiveness that a decision maker might consider acceptable. [199]

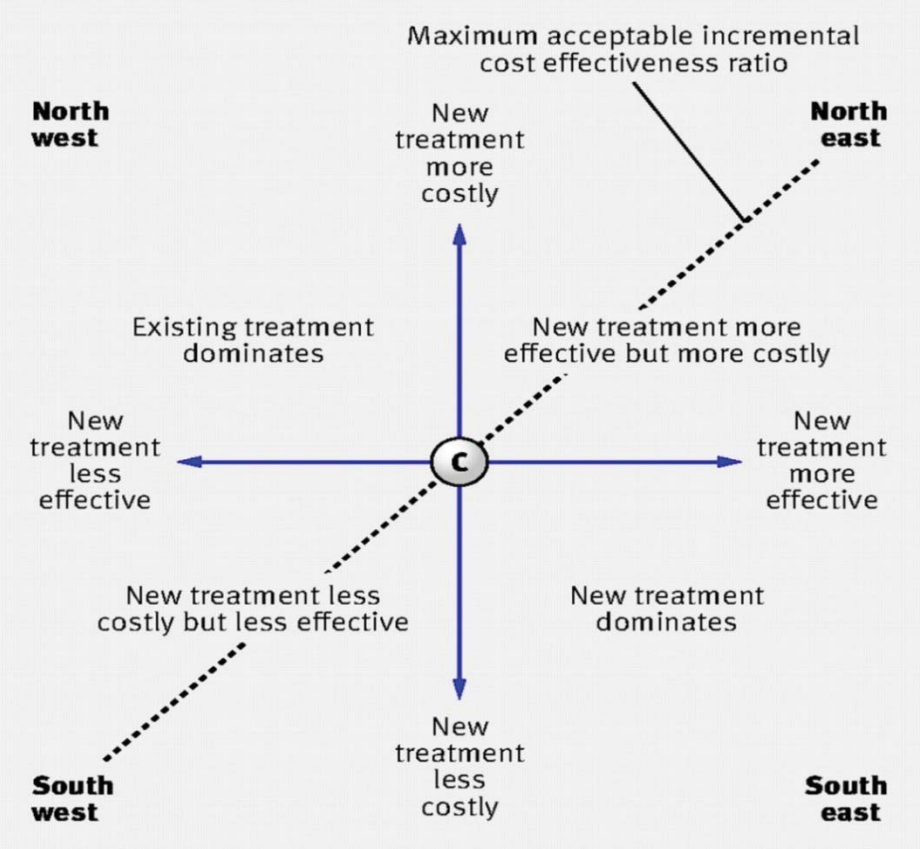

Figure 9. The cost-effectiveness plane

Source: Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting[199]

1.4.3 Quality of life

Quality-adjusted life-year (QALY) is a measure of health output that can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure.'[200] The number of QALYs can be calculated by multiplying the time in the state with the quality–adjustment weight for each health states.[200] A year of perfect health is scored 1 and death is scored 0. A year of imperfect health is less than 1 and a year of worse than death is a negative score.[201]

Quality of life can be measured by health related quality of life (HRQoL) instruments which can be classified into generic and disease-specific ones. The generic instruments include EQ-5D, Health

Utilities Index (HUI) and short form-6D (SF-6D), 15D.[202] The most commonly used one is EQ-5D.[202] EQ-5D, also called the EuroQol instrument, is a preference-based measure designed to summarise HRQoL in a single number.[203] The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The earliest EQ-5D has 3 levels for each dimension: no problems, some problems, severe problems. It only takes a few minutes to complete the EQ-5D. Based on the answers to the EQ-5D, the quality of life can be estimated.[204,205] To improve the instrument's sensitivity, a 5-level EQ-5D (EQ-5D-5L) was developed. The range of responses in each dimension has been expended from three to five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.[206] Based on the chosen level of each dimension, the quality of life can be calculated. EQ-5D was designed to be self-administered and short enough to be used in conjunction with other measures.[203] It is ideally suited for use in postal surveys, in clinics and face-to-face interviews.[207]

The HUI consists of two systems, HUI2 and HUI3. HUI3 was recommended to be used as the primary analysis HUI3 consists of eight attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/discomfort), with five or six levels per attribute. HUI3 can describe 972,000 different health states.[208] The HUI can also summarise the HRQoL with a single number using a scoring formula.[203,208] The SF-6D includes a multi-attribute health status classification system with six attributes (physical functioning, role limitations, social functioning, pain, mental health and vitality) and a scoring table.[200]

1.4.4 Perspective and costs

The first step in embarking on a cost estimation is to determine the research perspective (or viewpoint). The perspectives that are commonly used include the societal perspective, payer's perspective, patient's perspective and the perspective of the health care system. Some cost elements included from a certain perspective might not be considered if from another perspective. For example, all costs related to the disease or intervention should be identified from a societal perspective, including the costs from the health care system, patients' transportation and accommodation costs and productivity loss, while the costs borne by the patients should not be taken into account from the perspective of the Ministry of Health. Therefore, an intervention might be cost-effective from a certain perspective, but might be not cost-effective if analysed from another perspective.

After the cost elements to be included have been determined, the quantities of resources need to be measured and the unit costs or prices need to be assigned to calculate the aggregate costs. Theoretically, the unit cost (price) for a resource should be its opportunity cost, the value of benefits for its best alternative use. Pragmatically, the market prices (plus the subsidy if there is any) would be used as the unit costs.[200] Market price is the economic price for which a good or service is offered in the marketplace.

When estimating the long term costs or consequences, time preference needs to be considered. Earlier benefits and later costs are preferable to later benefits and earlier costs. Future costs and benefits need to be discounted to present values. The commonly used discounting rates are 3% and 5%.[200] A 3.5% discount rate was recommended in New Zealand by PHARMAC's guideline for cost-effectiveness analyses.[209]

1.4.5 Modelling tools

Mathematical modelling approaches are common in economic evaluation studies.[196] Buxton et al explored the role of modelling in economic evaluation: 1) extrapolating beyond the data observed in a trial; 2) linking intermediate clinical endpoints to final outcomes; 3) generalizing to other settings; 4) synthesizing head-to-head comparisons where relevant trials do not exist.[210] They also expressed their concerns on modelling about: 1) the inappropriate use of clinical data; 2) biases in observational data; 3) the difficulties of extrapolation; 4) the transparency or validity of models.[210]

Approaches to modelling used in economic evaluations in health care include Decision Trees and Markov models.[196,211] The Decision Tree is probably the simplest form of decision model.[211] It comprises a square decision node (□), circular chance nodes (O), triangle terminal nodes (Δ) and pathways (—) (Figure 10). The decision node shows a decision among alternative options. The chance nodes after the decision node indicate alternative options and the chance nodes after the last chance node show possible events. The terminal nodes indicate the tree ends. The pathways are the routes that link the nodes through the whole tree.[211] The expected costs and outcome of each option can be calculated based on the transition probabilities of all events following that option and the costs and outcomes at the terminal nodes. For example (Figure 10), the expected costs of Choice 1 = Transition probability 1 × Cost 1 + (1-Transition probability 1) × Cost 2.

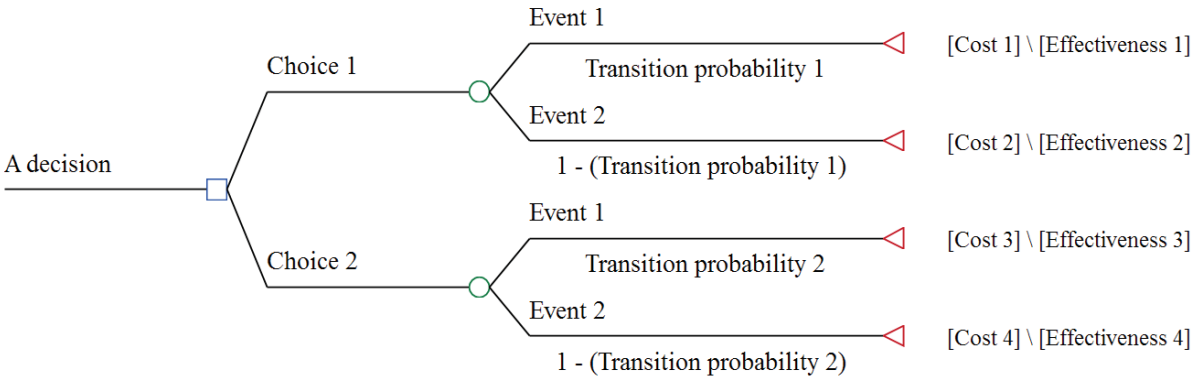

Figure 10. Decision tree structure

A Decision Tree is mainly used for short term modelling, while a Markov model is more commonly used for long term modelling. A Markov model comprises mutually exclusive states (the ellipse nodes) that a person can occupy at a given point in time (Figure 11). Each Markov state is associated with a

certain cost and utility. The arrows connecting the Markov states indicate possible transitions. Arrows that start and end at the same Markov states indicate staying in that Markov state. Markov states and transitions are repeatable. In each model cycle (a fixed time period depending on the disease or intervention), transition probabilities determine the speed of transition between Markov states. The transition probabilities from a certain Markov state or to a certain Markov state must sum up to 1.

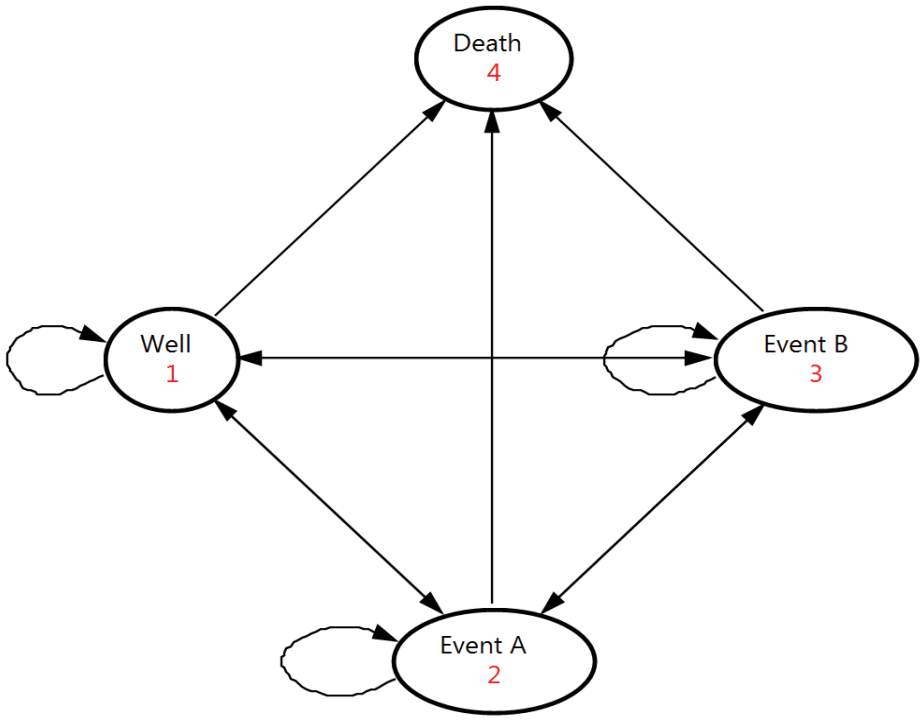

Figure 11. Influence diagram of a Markov model

The selection of the appropriate model type has been described by Barton P[196] and colleagues. The process is set out in Figure 12 as follows. If the interaction between individuals is an important issue for modelling, then either a systems dynamics model or discrete event / agent based simulation can be used depending on whether individual level modelling is needed. Otherwise, Decision Trees, Markov models or individual sampling models would be suitable options (Figure 12). A Decision Tree can be considered as an ideal choice on condition that patient pathways can be represented adequately by probability trees, otherwise Markov model would be preferable as long as the number of states is not excessive.

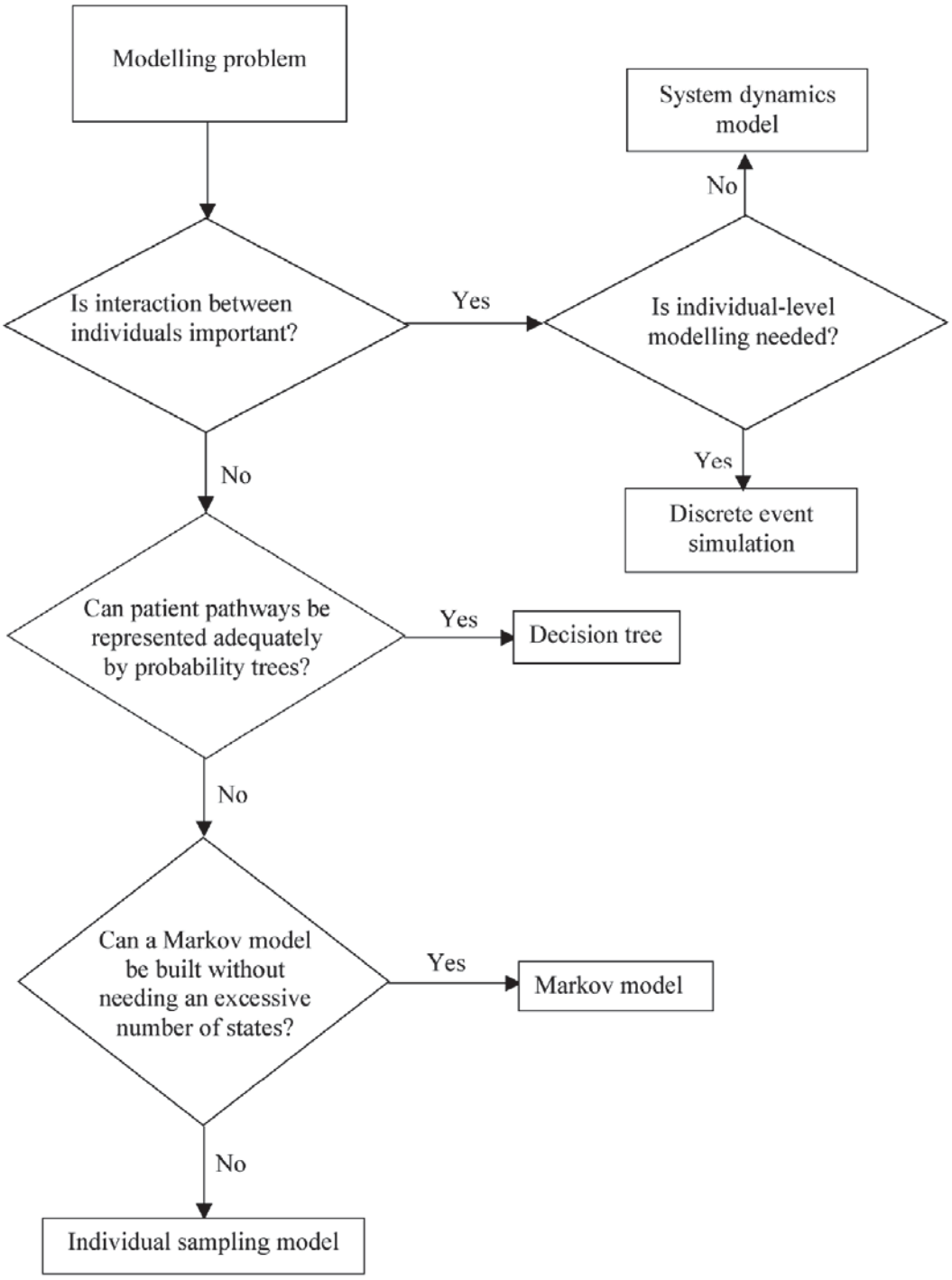

Figure 12. Selecting an appropriate model type

Source: Modelling in the economic evaluation of health care: selecting the appropriate approach[196] (License for reusing the figure has been granted)

1.5 Summary of Chapter 1

Prostate cancer is the most frequently diagnosed cancer and the third most common cause of death for men in New Zealand.[3] Most of the diagnosed prostate cancer cases are localised and slow growing, but some are very aggressive and may metastasize to lymph nodes, other organs and bones.[33-38] Prostate cancer can be cured if it is detected and treated at an early stage, which makes it a good candidate for screening. Though whether the benefits of prostate cancer screening outweigh the harms is uncertain,[13] prostate cancer screening is widely practiced in some countries, including in New Zealand.[4,127]

Most of the diagnosed prostate cancer cases are localised.[12] The treatment options for localised prostate cancer, including radical prostatectomy, radiotherapy, watchful waiting and active surveillance, differ in terms of the short-term costs, long-term costs, complications and effects on cancer-specific mortality.[175] The 5-year relative cancer-specific survival rate for men diagnosed with localised prostate cancer is almost 100%, while the 5-year relative survival rate for men diagnosed with metastatic disease is only 28%.[10,30] Improvements in survival may be achieved not only by earlier diagnosis and early treatment but also by improving management of metastatic disease.

Health care resources are scarce. Economic evaluation studies play a central role in decision making for health care resources distribution.[1] They can compare the short term or long term costs and health consequences of alternative health care programmes,[2] by synthesizing data from different sources. The costs and cost-effectiveness of prostate cancer screening and management of prostate cancer in New Zealand are imperative and can be estimated using local clinical and economic data. Before performing the economic studies of prostate cancer in New Zealand, it is necessary to review the papers in this field, in order to find out what is already know in this area and how economic evaluation approaches are used for screening and management of prostate cancer.

Chapter 2. Literature review: cost of prostate cancer

As described in the introduction, the main objectives of this thesis are to examine whether prostate cancer screening is cost-effective, the cost-effectiveness of active surveillance compared to radical prostatectomy for low risk and intermediate risk localised prostate cancer and the costs of treatment for metastatic prostate cancer. This chapter sets out the existing literature around the areas of the overall economic burden of prostate cancer, economic evaluation of prostate cancer screening and economic evaluation of treatment options for localised prostate cancer.

2.1 Overview of the economic burden of prostate cancer

With the high prevalence of prostate cancer, the economic burden of prostate cancer is considerable, including the screening costs, diagnostic costs, treatment costs and costs of palliative care. A US study[212] followed up 49,228 men aged 66-74 years who had never been diagnosed with prostate cancer at the end of 2006 for 3 years. Approximately 51.2% of them had PSA tests and 2.9% had a biopsy. The medicare expenditures of prostate cancer screening for these men were US$301 million (in 2009 US dollars). The biopsy related costs (biopsy, pathologic analysis, and hospitalization due to biopsy complications) comprised 72% of the overall medical costs of screening. Another study conducted by Heijnsdijk et al[13] demonstrated that the direct medical costs of diagnosis and treatment for prostate cancer for 25 years in the Netherlands would increase 100% from €30,284,000 without screening to €60,695,000 by screening men aged 55-70 with a 4-year interval. The costs included €3,045,000 for screening tests, €3,391,000 for biopsies and €54,259,000 for treatment. This study also showed that the costs of palliative therapy decreased by 25% by introducing screening.[13]

Roehrborn C.G. and Black L.K. summarised the prostate cancer cost data from different countries, and adjusted the costs to 2010 constant values (Table 8).[213] They found considerable variation in the costs across different countries, and explained that the difference might be related to variation in population characteristics, rate of screening, treatment patterns and health care systems.[213] Men in the US had the highest first-year costs after diagnosis per patient of US$17,725, twice to four times the costs for men in the UK, Germany, France, Italy and Spain. It was reported that patients with low-grade cancers in the US are often treated aggressively,[214] and the first two-year costs for men receiving treatment were five times the costs for men under observation.[215]

Table 8. Summary of prostate cancer costs adjusted to 2010 levels and converted to US dollars, euros and pound sterling

Author	Country	Cost at 2010 level	US$	€	£	Ref
Annual costs						
J. Chamberlain	England/Wales	£ 94 240 004	136 044 870	109 949 813	94 240 004	[216]
G.C. Marks	Australia	AU$204 136 795	178 514 585	144 273 321	123 659 314	[217]
M.A. Koopmanschap	Netherlands	€ 147 865 973	182 959 903	147 865 973	126 738 642	[218]
National Cancer Institute	USA	$11 524 053 605	11 524 053 605	9 313 600 264	7 982 857 859	[219]
First-year costs after diagnosis						
Per Patient						
C. Lazzaro	Italy	€ 10 165	12 578	10 165	8 713	[220]
R.O. Fourcade	UK	€ 3 705	4 585	3 705	3 176	[221]
	Germany	€ 4 741	5 866	4 741	4 063	
	France	€ 6 837	8 460	6 837	5 860	
	Italy	€ 6 107	7 556	6 107	5 234	
	Spain	€ 3 805	4 708	3 805	3 261	
C.G. Roehrborn	USA	$17 725	17 725	14 325	12 278	[222]
Total prostate cancer						
R.O. Fourcade	UK	€ 136 367 578	168 732 524	136 367 578	116 883 156	[221]
	Germany	€ 209 167 065	258 809 956	209 167 065	179 280 933	
	France	€ 195 728 958	242 182 500	195 728 958	167 762 885	
	Italy	€ 124 682 267	154 273 867	124 682 267	106 867 461	
	Spain	€ 133 913 663	165 696 206	133 913 663	114 779 860	
Diagnosis, treatment and 5 years plus follow-up costs						
Per patient						
M.E. Stokes	USA	$23 116	23 116	18 722	16 047	[170]
Total prostate cancer						
V.K. Sangar	UK	£ 136 278 237	196 731 262	158 995 819	136 278 237	[223]

Source: Roehrborn, C.G. & Black, L.K. The economic burden of prostate cancer. BJU International 108, 806-813 (2011)[213]

The 2010 Medical Consumer Price Index published by the US Bureau of Labour Statistics was used to project published direct costs up to recent rates. Figures were then converted to US dollars ($), pound sterling (£) and euros (€), using exchange rates (Australian $1.6508, US$1.4436, €1.1667) published by the Bank of England for 18 May 2010.

(License for reusing the figure has been granted)

Roehrborn et al[222] showed that the treatment costs differed by prostate cancer stage. The average first year costs in the US were $11,590 for men with Stage I prostate cancer (T1a or T2a, N0, M0), $12,191 for Stage II cancer (T1b or T2b, N0, M0), $13,920 for Stage III cancer (T3, N0, M0) and $18,371 for Stage IV (T4, N0, M0; any T, N1-3, M0; and any T, any N, M1).[222]

With the global aging population,[224,225] the burden of prostate cancer is expected to keep increasing. Mariotto et al[226] projected 2.3 and 3.3 million prostate cancer survivors and 11.85 and 16.34 billion 2010 US dollars in the US in 2010 and 2020, respectively. The largest increases were found in the continuing phase of care for prostate cancer (42%). A Japanese study conducted by Kitazawa et al[227] estimated the cost of illness of prostate cancer in 2002 (174.5 billion yen), 2005 (246.9 billion yen), 2008 (286.0 billion yen) and 2011 (307.3 billion yen), and then predicted the cost of illness in 2014 (354.7–378.3 billion yen), 2017 (370.8–421.0 billion yen) and 2020 (385.3–474.1 billion yen).

Overall, the costs of the management pathway of prostate cancer, from screening, management of the newly diagnosed cancer to end-of-life care, are substantial. The costs of screening and diagnosis of prostate cancer account for a small proportion of the overall costs, and the costs of treatment comprise the largest proportion.[13] By introducing screening, the economic burden of prostate cancer would increase substantially. Though the prostate cancer-specific mortality has been decreasing, the economic burden of prostate cancer is expected to climb due to the increased number of men diagnosed and improved survival, unless new strategies are introduced to ‘reduce the number diagnosed and/or focus treatment where it is clinically most appropriate’.[213]

2.2 A systematic review on economic evaluation of prostate cancer screening

2.2.1 Introduction

The screening programme assessment criteria in New Zealand[117] required cost-effectiveness/cost-utility issues to be considered in a screening programme. Notwithstanding, currently there is no comprehensive economic evaluation studies on prostate cancer screening conducted in New Zealand. Some insights can be sought by examining studies on this issue conducted in other countries, especially in countries with a health care system similar to New Zealand's. This review aims to 1) describe the reported cost of prostate cancer screening in published studies; and 2) find out whether prostate cancer screening is cost-effective, by synthesizing the existing evidence on economic evaluation of prostate cancer screening.

2.2.2 Methods

2.2.2.1 Search strategy and study selection

Medline, Scopus and Embase were searched for literature on economic evaluation of prostate cancer screening. The search terms included 'prostate', 'prostate cancer', 'screening', 'early detection' and 'cost'. The search was limited to literature which was: 1) an original study; 2) in English; and 3) published in or after 1990 (because the PSA test began to be used for identifying asymptomatic prostate cancer in the late 1980s and early 1990s[81]).The search was last conducted on 14 March 2014.

In total, 355 studies were identified from the three databases after duplicates were removed (Figure 13). After the titles and abstracts of these studies were examined, 306 articles were excluded either because they were not related to prostate cancer screening or because they were not economic evaluation studies. The full-texts of 49 papers were searched and independently reviewed by two researchers (C.Lao, R.Lawrenson). Another 29 articles were excluded due to the following reasons:

1) Full texts were not available;
2) The study was not an original article;
3) The study was irrelevant to screening;
4) The study was irrelevant to economic evaluation;
5) The data source and methods were not specifically mentioned.

Finally, 20 studies were included for this systematic review. The paper by the author is presented in chapter 4 and therefore is not included in this section.

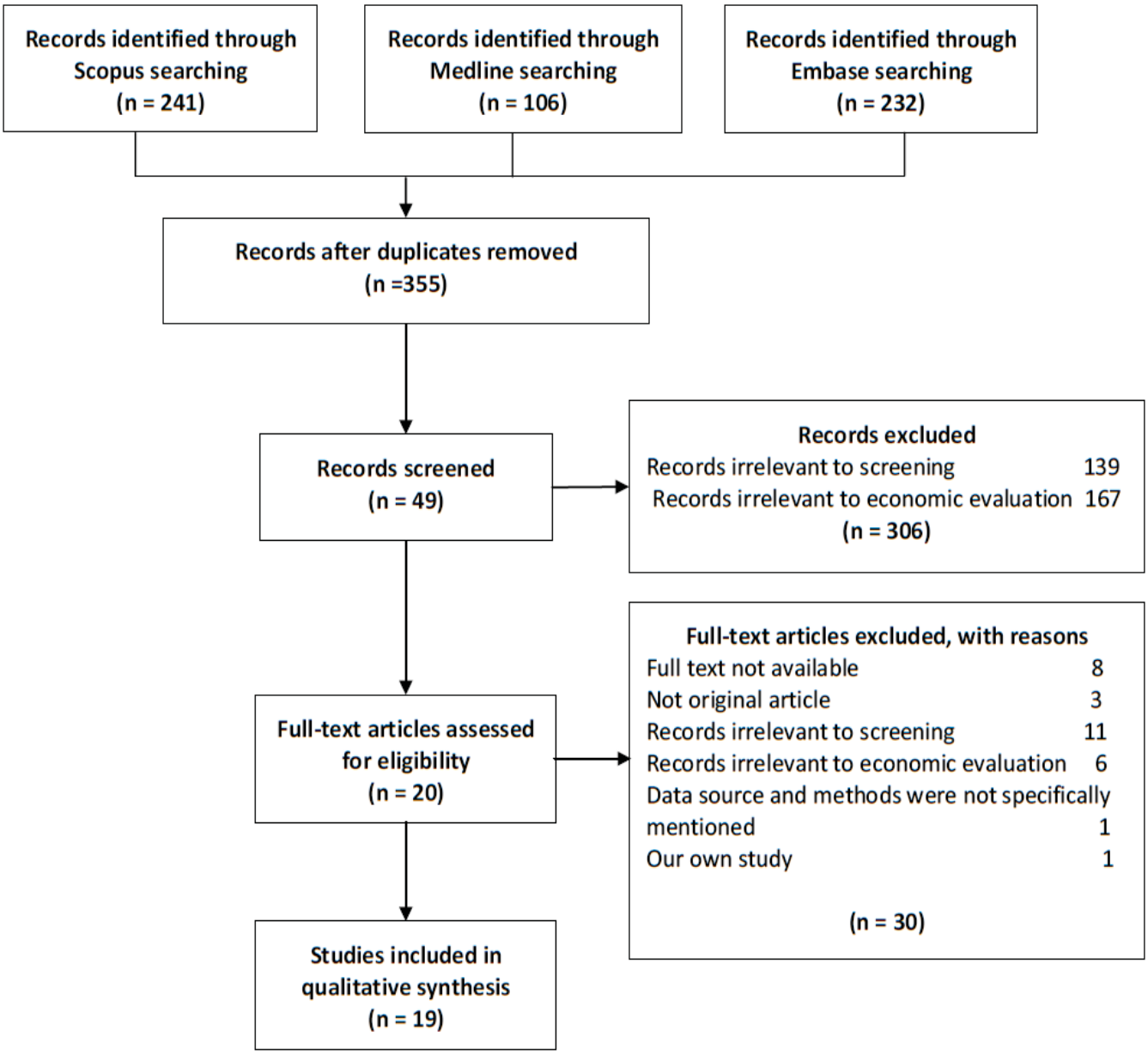

Figure 13. Flow Diagram of selecting studies of economic evaluation of prostate cancer screening

2.2.2.2 Quality assessment

The checklist for economic evaluations developed by Drummond MF[200] and colleagues identifies and assesses the key elements of an economic evaluation study. The checklist includes ten questions that are set out across the columns in Table 9. The quality of eligible studies was assessed using the checklist (Table 10).[200]

Table 9. Checklist for economic evaluations developed by Drummond MF and colleagues

Label	Checklist questions
Q1.	Was a well-defined question posed in answerable form?
Q2.	Was a comprehensive description of the competing alternatives given?
Q3.	Was the effectiveness of the programme or services established?
Q4.	Were all the important and relevant costs and consequences for each alternative identified?
Q5.	Were costs and consequences measured accurately in appropriate physical units?
Q6.	Were the cost and consequences valued credibly?
Q7.	Were costs and consequences adjusted for differential timing?
Q8.	Was an incremental analysis of costs and consequences of alternatives performed?
Q9.	Was allowance made for uncertainty in the estimates of costs and consequences?
Q10.	Did the presentation and discussion of study results include all issues of concern to users?

All these studies had well-defined questions (Q1), which were to estimate the clinical and economic effects of prostate cancer screening. Four studies[22,24,228,229] did not provide description of the competing alternatives (Q2). Other studies used either no screening or other screening strategies as competing alternatives. The effectiveness of programmes (Q3) was well-displayed in all studies. Three studies[228,230,231] did not identify all relevant costs (Q4). For example, the study conducted by Abramson et al[230] included the costs of laboratory tests, ultrasonic examinations and biopsies, but did not consider the costs of clinician appointments. Most studies (17/19) measured and valued the costs and consequences accurately (Q5, Q6). Three studies[13,23,232] did not adjust the costs for differential timing (Q7). For studies where the time frame was one year, timing did not need to be considered for costs. However, in studies where the follow-up time was more than one year, the future costs needed to be discounted. Only eight studies conducted an incremental cost-effectiveness analysis (Q8) and nine had a sensitivity analysis (Q9). Six studies compared their results with those of other studies, including all issues of concerns to users (Q10). Three studies[233-235] met all the criteria. Of these three studies, two[233,235] were conducted in Canada and one[234] was in Japan.

Table 10. Quality assessment of the eligible studies using Drummond's checklist

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Ref
K. V. Pedersen, 1990	Yes	No or not stated	Yes	No or not stated	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	228
M. D. Krahn, 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	233
N. Abramson, 1994	Yes	Yes	Yes	No or not stated	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	230
W. Kantrowitz, 1995	Yes	No or not stated	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	22
O.Gustafsson, 1995	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	236
C. Snyder, 1998	Yes	No or not stated	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	24
H. Holmberg, 1998	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	Yes	23
M. D. Krahn, 1999	Yes	No or not stated	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	229
K. Perez-Niddam, 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	237
C. Hamashima, 2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	234
H. Bonkhoff, 2000	Yes	Yes	Yes	No or not stated	No or not stated	Yes	Yes	No or not stated	No or not stated	No or not stated	231
R. M. Benoit, 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	No or not stated	25
L. Ellison, 2002	Yes	Yes	Yes	Yes	No or not stated	No or not stated	Yes	No or not stated	Yes	No or not stated	238
K. Sennfält, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	239
T. Kobayashi, 2007	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	Yes	No or not stated	232
EAM Heijnsdijk, 2009	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	Yes	13
A. Shteynshlyuger, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	No or not stated	27
A. J. Martin, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	26
R. Pataky, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	235

2.2.2.3 Grouping and data extraction

The outcome measures in economic evaluation studies of cancer screening include the cost per cancer identified, the cost per life-year gained, the cost per QALY gained and others. The health consequences (intermediate outcome: number of cancer cases identified; or final outcome: i.e. number of deaths prevented, number of life-years gained, number of QALYs gained), cost elements (included treatment costs or not) and length of time (short term or long term) differ among these outcome measures. Therefore, the cost comparison was based on the outcome measures with the eligible articles categorized into the following groups:

Group 1: the cost of intermediate outcomes (the cost per cancer identified)

Group 2: the cost of final outcomes (i.e. cost per life-year/ cost per QALY)

Twelve studies were classified in Group 1, and eight in Group 2. One study was included in both groups, because it estimated both a cost per cancer detected and a cost per life-year gained.[25] Key information was extracted, including the author, year of publication, country, research perspective, timeframe, comparison, research methods, men tested and economic evaluation results. The incremental cost-effectiveness ratio (ICER - see Section 1.3.2) threshold value varies from country to country and is based on the currency used in each country. The ICER threshold is £20,000-30,000 per QALY in the UK, AU$69,900 per QALY in Australia and US$50,000 per QALY in the USA.[240] The estimated ICERs in economic evaluation studies need to be compared with the ICER threshold in the country where the study was conducted, and the ICER threshold is based on the currency used in the country. Therefore, the reported costs in different currencies were not converted into the same currency.

2.2.3 Results

2.2.3.1 Description of the included studies

The extracted information of the eligible studies is listed in Table 11 and Table 12. Of the 19 articles, 14 were published more than 10 years ago (before 2005). The others were published in 2007 (1), 2009 (1), 2011 (1), 2013 (1) and 2014 (1). Seven studies were conducted in the USA. Other studies were conducted in Sweden (4), Canada (3), France (1), Australia (1), Japan (2), and Netherlands (1).

Only eight articles reported their research perspectives, including the third-party payer perspective (2), employer's perspective (1), societal perspective (2), perspective of Ministry of Health (1) and the perspective of health care system (2). The included cost elements were in accordance with the research perspective and the time frame of the study. Seven studies were descriptive costing studies. Markov model was used in 11 studies and Decision Tree was used in one study. Seven studies considered age in the models.

Table 11. Studies in Group 1: the cost of per cancer identified

Author, year	Country	Perspective	Horizon	Comparison	Method	Men tested	Results	Ref
K. V. Pedersen, 1990	Sweden	N/A	N/A	No comparison	Descriptive costing study	1163 Men aged 50-69	£2,093 per cancer detected; £2,477per potentially curable cancer	228
N. Abramson, 1994	USA	N/A	N/A	No screening	Descriptive costing study	564 asymptomatic men aged 40+	US$7,240 per cancer detected; US$16,300 to find and treat a patient	230
W. Kantrowitz, 1995	USA	N/A	1 year	No comparison	Descriptive costing study	1219 men aged 50-65	US$6,012 per cancer detected	22
O.Gustafsson, 1995	Sweden	N/A	1.5 year	Other screening strategies	Descriptive costing study	2,400 men aged 55-70	TRUS of individuals with PSAs≥4 ng/ml was the most cost-effective strategy: US$4,465 per cancer detected	236
C. Snyder, 1998	USA	Employer's perspective	1993-1995	No comparison	Descriptive costing study	385 aged 40+ men	US$44,355 per cancer detected	24
H. Holmberg, 1998	Sweden	N/A	1987–1996	No screening	Decision Tree	1492 men aged 50-69	18,600 SEK per cancer detected; 49,800 SEK per patient receiving a potentially curative treatment	23
M. D. Krahn, 1999	Canada	Perspective of Ministry of Health	1 year	No comparison	Descriptive costing study	N/A	Can$4,289-8,325 per cancer detected	229
K. Perez-Niddam, 1999	France	N/A	1 year	No screening	Decision Tree	Asymptomatic/symptomatic men aged 50-70	FF. 10,255 per potentially treatable cancer	237
H. Bonkhoff, 2000	Canada	N/A	N/A	No screening	Descriptive costing study	7,195 asymptomatic men aged 45–80	Can$2,420 and Can$ 7,105 per cancer detected (first and follow-up visits, respectively, when PSA is used as prescreening)	231
R. M. Benoit, 2001	USA	N/A	Life time	No screening	Markov model	100,000 simulated men aged 50 – 70, life expectancy ≥10 years	US$2,371 per cancer detected	25
K. Sennfält, 2004	Sweden	N/A	1987–1996	No screening	Markov model	1492 men aged 50-69	198,481 SEK per cancer detected; 168,000 SEK per extra detected localised cancer; 356,000 SEK per potentially curable cancer	239
EAM Heijnsdijk, 2009	Netherlands	N/A	Over 25 years (for the period 2008–2033)	No screening	Markov model	100,000 simulated men aged 55 to 70 or 75	€1,299 per cancer detected (only include costs of PSA tests and biopsies)	13

N/A: not available from the article

Table 12. Studies in Group 2: the cost of final outcome (ie cost per life-year/ cost per QALY)

Author, year	Country	Perspective	Horizon	Comparison	Method	Men tested	Results	Ref
M. D. Krahn, 1994	USA	Third-party payer perspective	Life time	No screening and other screening strategies	Markov model	Asymptomatic men	US$113,000–729,000 per incremental life-year gained	233
C. Hamashima, 2000	Japan	Third-party payer perspective	Life time	No screening and other screening strategies	Markov model	100,000 simulated men aged 40-69	Screening with PSA test was the most cost-effective strategy: US$3,000–32,900 per incremental year of life gained	234
R. M. Benoit, 2001	USA	N/A	Life time	No screening	Markov model	100,000 simulated men aged 50 – 70, life expectancy ≥10 years	US$3,574-4,627 per year of life gained	25
L. Ellison, 2002	USA	Societal perspective	N/A	Other screening strategies	Markov model	2138 men aged 40-75	Use of cPSA with a positive threshold of 3.8 ng/mL is the dominant strategy: US$139.9 per utility	238
T. Kobayashi, 2007	Japan	N/A	N/A	No screening and other screening strategies	Markov model	N/A	Biennial screening in participants with baseline PSA 3.0 ng/ml is the most cost-effective strategy: cost per QALY was unavailable	232
A. Shteynshlyuger, 2011	USA	Societal perspective	Life time	No screening	Markov model	N/A	US$5,227,306 to prevent 1 death from prostate cancer: US$262,758 per life-year gained	27
A. J. Martin, 2013	Australia	Perspective of health care system	Life time	No screening and other screening strategies	Markov model	Men aged 50+	AU$291,817 per QALY for men with average risk, AU$110,726 per QALY for men with two times the average risk, and AU$30,572 per QALY for men with five times the average risk	26
R. Pataky, 2014	Canada	Perspective of health care system	Life time	No screening and other screening strategies	Markov model	40-74	When patients' quality of life was not considered, the most cost-effective screening method was a single screen for men aged 60 ($27,000/ per year of life gained). When patients' quality of life was considered, the most cost-effective screening method was 'a single screen at age 60 years, followed by a screen at age 65 years for men with PSA above the median' ($340,300/ QALY)	235

N/A: not available from the article

The age of screened men ranged from 40 years to 80 years in these studies except in two studies where the oldest screening age was not defined. Four papers reported that only asymptomatic men were included in their studies. The screening tests included digital rectal examination (DRE), transrectal ultrasonography (TRUS), total PSA (tPSA), free PSA (fPSA) and complex PSA (cPSA). The outcome measures included the cost per cancer detected (12), the cost per potential curable cancer (5), the cost to prevent one death (1), the cost per life-year gained (5) and the cost per QALY (2).

2.2.3.2 Costing results in Group 1

The 13 studies in Group 1 are presented in Table 11. If only the screening cost was included (excluding the treatment cost for the detected cancers), the cost per cancer detected ranged from €1,299 in Netherlands[13] to US$44,355 in the US.[24] Four studies (Benoit,[25] Kantrowitz,[22] Abramson[230] and Snyder[24]) were conducted to estimate the cost per prostate cancer detected in the USA. The reported cost was US$2,371 in 2000 (converted to US$3,275 in 2015 using the inflation calculator provided by the US Bureau of Labor Statistics[241]),[25] US$6,012 in 1992 (US$10,192 in 2015),[22] US$7,240 in 1992 (US$12,273 in 2015)[230] and US$44,355 in 1996 (US$67,236 in 2015),[24] respectively.[242] The sample sizes and the number of cancers identified were critical for the cost results. Only one out of 385 men was diagnosed with prostate cancer in the study[24] where the cost per cancer detected was the highest, while 4,600 out of 100,000 men,[25] 12 out of 1219 men[22] and 10 out of 569 men[230] were identified with prostate cancer in the other studies. The countries where the studies were conducted and cost elements might be also important reasons for the diversity of costing results. A Canadian study[231] showed that the cost of identifying a new case of prostate cancer was Can$2,420 which was generally lower than the costs in the American studies. Compared to the Canadian study (where only the costs of diagnostic tests were included), the American studies included a broader range of cost items (labour, supply, administration, education, overhead and lost productivity).

Some studies compared the cost-effectiveness of different screening strategies. Gustafsson[236] found that TRUS of men with PSA level ≥4ng/ml was more cost-effective than the other five screening strategies: 1) DRE; 2)TRUS; 3) DRE, TRUS, and PSA tests for men with PSA ≥7 ng/ml; 4) DRE for men with PSA ≥4 ng/ml; 5) DRE and PSA test for men with PSA ≥4 ng/ml. Kobayashi[232] indicated biennial screening for men with PSA ≥3.0 ng/ml was the most cost-effective rescreening strategy, while customised rescreening strategy based on individual baseline PSA level was more cost-effective than the uniform rescreening.

2.2.3.3 Costing results in Group 2

The studies included in Group 2 are shown in Table 12. Two studies estimated the cost per QALY. One is an Australian study where the ICER was AU$291,817 for men with average risk, AU$110,726 for men with two times the average risk and AU$30,572 for men with five times the average risk.[26] Only the ICER for men with five times the average risk was lower than the Australian cost-effectiveness threshold (AU$69,900 per QALY).[240] The other is a Canadian study where the ICER was Can$340,300 per QALY for the most cost-effective screening strategy.[235] It was much higher than the Canadian cost-effectiveness threshold.[240]

The estimated cost per life-year gained was US$3,574-4,627 in 2000 (US$4,900-6,345 in 2015),[25] US$3,000–32,900 in 2000 (US$4,900-6,345 in 2015),[234] US$113,000–729,000 in 1992 (US$190,174-1,226,876 in 2015)[233] and US$262,758 in 2003 (US$337,186 in 2015),[27] respectively. The great variation among the results of these studies could be ascribed to the different cost elements, the year when the data were collected, and more importantly, the lives (life-years) gained by screening in the models. Only the study where a cost of US$262,758[27] per life-year gained was presented estimated the health outcomes from a randomised trial,[5] the others used prostate cancer specific mortality from the cancer registry or Life-Table analysis. However, the prostate cancer specific mortality did not represent and was higher than the prostate cancer death prevented by screening. If the harm caused by screening and treatment was considered within QALY estimates, the cost per QALY would be much higher.[235]

In a study conducted in the USA, the cost per life-year gained was US$3,574–4,627 for men aged 50–69 screened with PSA and DRE, compared with US$3,822–4,956 for men aged 50–70 screened with PSA alone.[25] This result was not consistent with a Japanese study[234] which showed that screening with PSA tests was the most cost-effective screening strategy, compared with either DRE or a combination of DRE and PSA. Amongst the available types of PSA tests, one study suggested the derivative cPSA with a threshold of 3.8 ng/mL was preferable.[238] The Australian study[26] also indicated that the ICER of PSA screening could be decreased by more than 50% for men with twice the average risk and by almost 90% for men with five times the average risk, in comparison with the ICER for men with average risk. It was shown that among different screening strategies (varied age range and screening frequency), the most cost-effective screening method was ‘a single screen at age 60 years, followed by a screen at age 65 years for men with PSA above the median’.[235] However, it was still not cost-effective.

2.2.4 Discussion

Despite the fact that no official guidelines recommend population-based screening, screening is commonly practiced in many countries.[27,232] High-quality economic evaluation studies are needed to inform decision making about the cost-effectiveness of prostate cancer screening, taking into account the harm caused by overdiagnosis and overtreatment, as well as any potential benefit from reducing prostate cancer mortality.

Four studies concluded that prostate cancer screening is cost-effective compared to no screening.[22-25] These studies estimated the cost per cancer detected, including the cost of screening but excluding the cost of treatment and the cost of side effects. The screening cost is only a small part (less than 39%) of the life-time cost for the screened cohort, while the treatment cost accounted for the largest proportion (over 61%).[13,243] The cost per cancer detected can be deemed as the cost of an intermediate health outcome. Whether prostate cancer screening is cost-effective depends in part on the value of an ultimate health outcome, such as the cost per QALY gained. The Göteborg study[6] demonstrated that 12 cancers needed to be detected and treated to prevent one death from prostate cancer after 14 years of follow-up. The figure shown by the latest ERSPC study[5] was even higher: 37 cancers to be diagnosed to prevent one death from prostate cancer after 11 years of follow-up. Thus the cost of screening to prevent one death from prostate cancer can be estimated: the screening cost ÷ the proportion of screening cost in the life-time cost (including screening and treatment costs) × number of cancers to prevent one death from prostate cancer. The cost to prevent one cancer death will be more than 12/39% – 37/39% (number of cancers to be detected and treated to prevent one death divided by the proportion of screening cost in the life-time cost) times the cost per cancer detected.

A cost-effectiveness analysis of PSA screening in the USA[27] was carried out by extrapolating the results from the ERSPC study.[5] The cost to prevent one death from prostate cancer and the cost per life-year gained was US$5,227,306 and US$262,758.[27] Prostate cancer screening can lead to overdetection,[131] and lower quality of life caused by anxiety and depression after the cancer diagnosis and the complications caused by treatments.[17] When the harm from screening on patients' quality of life is taken into account,[13] the cost per QALY in this study would be higher than US$262,758,[27] compared with the commonly used cost-effectiveness threshold in the US of US$50,000-100,000 per QALY.[244] An Australian study[26] found that the cost per QALY was AUS$291,817 for men with average risk, which was much higher than the cost-effectiveness threshold AUS$69,900/QALY in Australia.[240] An ICER of Can$340,300 was estimated in a Canadian study.[235] This number was more than three times the cost-effectiveness threshold in Canada (Can$80,000/QALY).[240]

A study[233] published in 1994 demonstrated that screening resulted in higher health care cost and lower quality of life for the screened patients. Perez-Niddam[237] and colleagues recommended against prostate cancer screening after comparing the cost-effectiveness ratio of the diagnosis strategy with that of the screening strategy. Studies using economic models based on RCTs also suggested population-based prostate cancer screening is not cost-effective.[26,27] The PLCO and Cochrane

studies demonstrated no benefit in survival by prostate cancer screening,[7,8] suggesting that the medical resources used for prostate cancer screening and management of the screen-detected cancers not only might produce no health benefits, but also might decrease the quality of life for the screened men.[13]

2.2.5 Conclusion

Most of the literature on economic evaluation of prostate cancer screening estimated the cost per cancer detected, while the decision making for prostate cancer screening should be based on the cost per QALY gained. The estimated costs per QALY gained by prostate cancer screening were higher than the cost-effectiveness threshold, suggesting that even when based on favourable RCTs in younger age groups prostate cancer screening is not cost-effective.

Prostate cancer screening has increased the proportion of cancer detected at a localised stage,[9] and would increase the costs for diagnosis and treatment by 100%.[13] Identifying the most cost-effective treatment for localised prostate cancer is vital for improving the cost-effectiveness of prostate cancer screening. The next section focused on the cost and cost-effectiveness of treatments for localised prostate cancer.

2.3 A systematic review on cost and cost-effectiveness of treatment options for localised prostate cancer

2.3.1 Introduction

The main treatments for localised prostate cancer include radical prostatectomy, brachytherapy, external beam radiotherapy, active surveillance and watchful waiting. An American study[245] including 12,732 men aged less than 60 years old diagnosed with localised prostate cancer between 2010 and 2011, showed that 12.5% of men received no active treatment, 61.6% had radical prostatectomy, 22.0% had radiotherapy and 3.3% had radical prostatectomy with adjuvant radiotherapy. In New Zealand, 44.6% of men diagnosed with localised prostate cancer in 2007-2010 had radical prostatectomy, 26.7% radiotherapy, 10.8% active surveillance, 11.0% watchful waiting, and 4.9% hormonal therapy/ orchidectomy.[12] These treatments differ in terms of clinical outcomes (biochemical free survival and prostate cancer specific survival), side effects and costs.[168,246] This review aims to 1) find out the reported costs and cost-effectiveness of different treatments for localised prostate cancer in published studies; and 2) examine how these studies were conducted, including economic and clinical outcome measurement and model construction, to provide guidance on carrying out an original study on comparing the cost-effectiveness of treatments for localised prostate cancer in New Zealand (Chapter 5 and Chapter 6). The included studies were also used as comparisons in the discussion in Chapter 5 and Chapter 6.

2.3.2 Methods

2.3.2.1 Search strategy and study selection

Medline, Scopus and Embase were searched for literature on cost and cost-effectiveness of treatment for localised prostate cancer. The search terms included ‘localised prostate cancer’, ‘treatment’, ‘cost’ and ‘economic evaluation’. The search was limited to literature which was: 1) an original study; 2) in English; and 3) published in or after 1990.The search was last conducted on 24 October 2014. In total, 236 studies were identified from the three databases after duplicates were removed (Figure 14).

After the titles and abstracts of these studies were examined, 183 articles were excluded either because they were not related to treatment for localised prostate cancer or because they were not cost or cost-effectiveness studies. The full-texts of 53 papers were searched and independently reviewed. Another 30 articles were excluded due to the following reasons:

1) Full texts were not available;
2) The study was not an original article;
3) The study was irrelevant to treatment for localised prostate cancer;
4) The study was irrelevant to cost or cost-effectiveness;

5) The data source and methods were not specifically mentioned.

Therefore, 23 studies were included for this systematic review, including 14 cost analysis studies and nine cost-effectiveness studies.

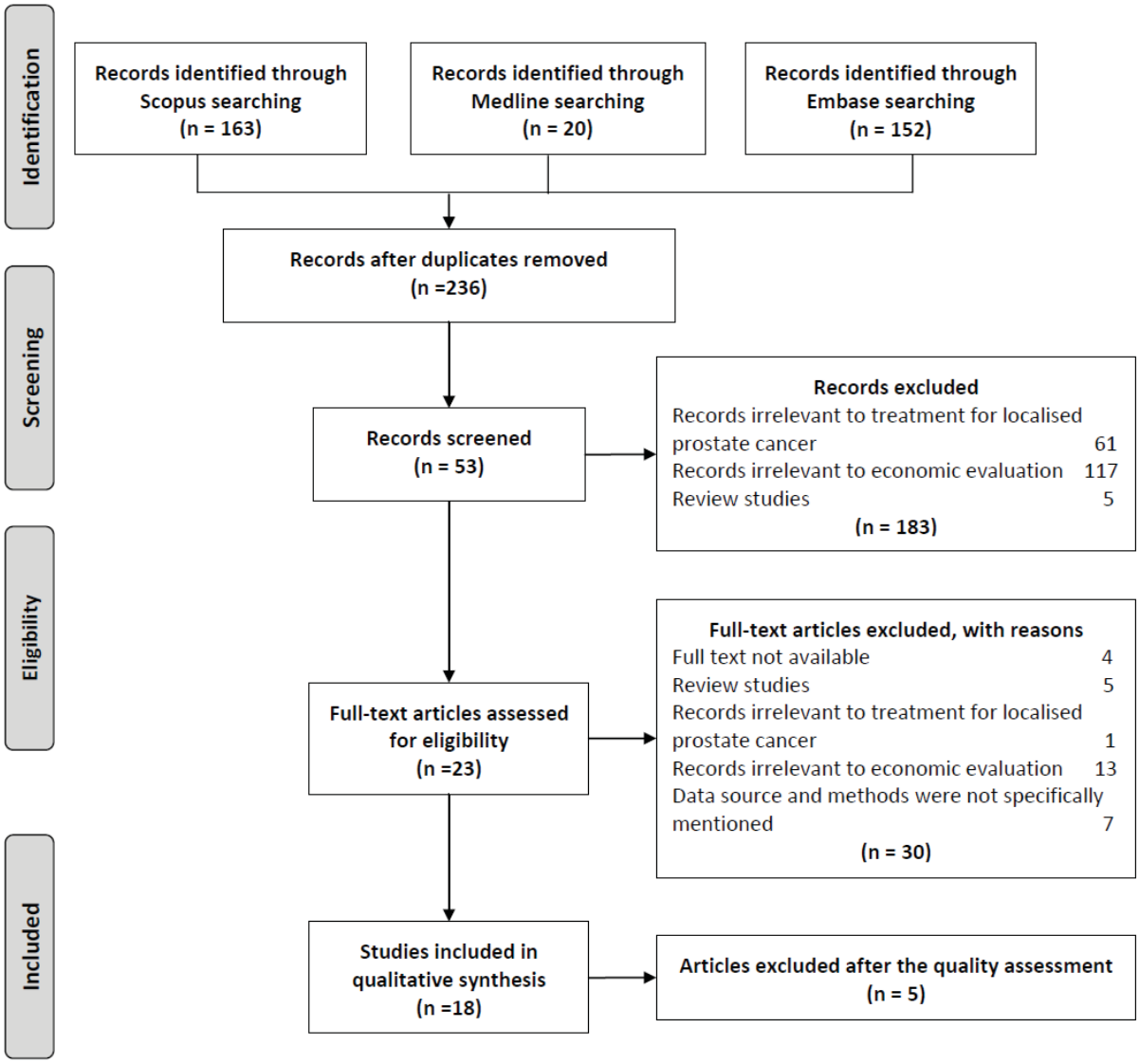

Figure 14. Flow Diagram of selecting studies related to costs and cost-effectiveness of treatments for localised prostate cancer

2.3.2.2 Quality assessment

Seven questions (Q3, Q4, Q5, Q6, Q7, Q8 and Q9) in the Drummond's checklist are related to the measurement of health outcomes of intervention. However health outcomes were not considered in costing studies. Competing alternatives are not necessary in costing studies (Q2). Therefore, the quality of the 14 costing studies was assessed with an adjusted checklist (Table 13). The quality of the nine cost-effectiveness studies (Table 14) was assessed with the full Drummond's checklist.

Table 13. Quality assessment of the costing studies using adjusted checklist

Author, year	Q1	Q4	Q5	Q6	Q7	Q9	Q10	Ref
RM Benoit, 1998	Yes	Yes	Yes	Yes	Yes	No or not stated	No or not stated	247
JP Ciezki, 2000	Yes	Yes	Yes	No or not stated	No or not stated	No or not stated	Yes	248
AA Makhlouf, 2002	Yes	No or not stated	Yes	Yes	Yes	No or not stated	No or not stated	249
JH Burkhardt, 2002	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	250
AD Silverstein, 2004	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	251
V Mouraviev, 2007	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	252
C Buron, 2007	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	253
SB Zeliadt, 2007	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	254
CF Snyder, 2010	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	255
AT Corcoran, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	168
SO Andersson, 2011	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	256
PL Nguyen, 2011	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	257
L Perrier, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	258
SY Wang, 2014	Yes	No or not stated	No or not stated	No or not stated	Yes	No or not stated	Yes	259

Adjusted checklist:

Q1. Was a well-defined question posed in answerable form?

Q4. Were all the important and relevant costs for each alternative identified?

Q5. Were costs measured accurately in appropriate physical units?

Q6. Was the cost valued credibly?

Q7. Were costs adjusted for differential timing?

Q9. Was allowance made for uncertainty in the estimates of costs?

Q10. Did the presentation and discussion of study results include all issues of concern to users?

Table 14. Quality assessment of the cost-effectiveness studies using Drummond's checklist

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Ref
J Lyth, 2012	Yes	Yes	Yes	Yes	No or not stated	No or not stated	Yes	Yes	Yes	No or not stated	[260]
Hummel SR, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[261]
Lena Hohwü, 2012	Yes	Yes	Yes	Yes	Yes	No or not stated	Yes	Yes	Yes	Yes	[262]
JHE Yong, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[263]
A Parthan, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[264]
A Close, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[265]
JH Hayes, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[266]
MR Cooperberg, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[267]
F Koerber, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No or not stated	[268]

Two costing studies[248,259] and three cost-effectiveness studies[260,264,265] were excluded after the quality assessment, because the costs (and consequences) in these studies were not valued credibly. In one costing study, only the ratios of costs in different subgroups were available, but the actual costs were not presented.[248] In the other costing study, the surgery cost was US$1,800 that was only 16% of the cost of radiotherapy (US$11,200).[259] In Lyth's study,[260] the unit costs used in the model were not shown in the paper, and the equations that used in the model were not displayed in the paper, therefore it was not possible to assess whether the estimated costs were reliable or not. In Hohwü's study[262] and Close's study[265], the costs of regular replacement of the robotic arm were not included in the costs of robot-assisted laparoscopic prostatectomy. Including these costs, the cost-effectiveness results of robot-assisted laparoscopic prostatectomy compared to laparoscopic prostatectomy would be altered substantially.

2.3.2.3 Grouping and data extraction

Key information from the costing studies and the cost-effectiveness studies was extracted, including the author, year of publication, country, research perspective, timeframe, management options, research methods, men treated and results.

2.3.3 Results

2.3.3.1 Costing studies

The extracted information from the 12 costing studies is listed in Table 14. Four were published before 2005. The others were published in 2007 (3), 2010 (2), 2011 (2) and 2012 (1). Nine studies were conducted in the US. Other studies were conducted in France (2) and Sweden (1). Five articles reported their research perspectives, including payer's perspective (2), societal perspective (1), hospitals' perspective (1) and the perspective of health care provider (1). Only one study[253] included the cost of productivity loss. The timeframe was less than 1 year in six studies, 1-2 years in three studies and ≥5 years in three studies (with the longest horizon of 15 years). Only one study[168] used a Markov model as the research tool. Others are descriptive costing studies. The management options included watchful waiting/ active surveillance (3), radical prostatectomy (11), cryosurgical ablation of the prostate (2), radiotherapy (7) and hormonal therapy (1) (Table 14).

Table 15. Extracted information from costing studies

Author, year	Country	Perspective	Horizon	Management options	Method	Men treated	Results	Ref
RM Benoit, 1998	US	Payer's perspective	From hospital admission to discharge	Radical prostatectomy versus cryosurgical ablation of the prostate	Descriptive statistical analysis	114 men underwent CSAP and 67 men underwent RP	Cryosurgical ablation of the Prostate: US$4,150; Radical prostatectomy: US$5,660; Significantly different	[247]
AA Makhlouf, 2002	US	N/A	A 2-month period beginning 1 month before RP or USBT	Transrectal ultrasound-guided brachytherapy versus radical prostatectomy	Descriptive statistical analysis	66 men	Transrectal ultrasound-guided brachytherapy: US$26,320; radical prostatectomy: US$22,660; Not significant different	[249]
JH Burkhardt, 2002	US	N/A	1 month before to 9 months after diagnosis	External beam radiation therapy versus Radical prostatectomy	Descriptive statistical analysis	10,255 men 65 years old and over	External beam radiation therapy: US$14,048 for 10 months; Radical prostatectomy: US$17,226; Significantly different	[250]
AD Silverstein, 2004	US	N/A	21 months	Radical perineal prostatectomy versus radical retropubic prostatectomy	Descriptive statistical analysis	402 men	Radical perineal prostatectomy: US$7,195, range US$5,052 to US$36,237; radical retropubic prostatectomy: US$9,757, range US$6,935 to US$27,771; Significantly different	[251]
V Mouraviev, 2007	US	N/A	From hospital admission to discharge	Minimally invasive technique versus open surgery	Descriptive statistical analysis	452 men	cryosurgical ablation of prostate: US$8,796; laparoscopic robotic prostatectomy: US$9,343; radical retropubic prostatectomy: US$9,724; radical perineal prostatectomy: US$9,251 significant differences between the minimally invasive technique and open surgery groups	[252]
C Buron, 2007	France	Societal perspective	2 years	Brachytherapy versus radical prostatectomy	Descriptive statistical analysis	435 men with localized low risk prostate cancer	Brachytherapy: €7,702 at 12 months, €8,019 at 24 months; Radical prostatectomy: €8,353 at 12 months, €8,715 at 24 months; Not significantly different	[253]
SB Zeliadt, 2007	US	N/A	First 6 months	Radical prostatectomy, external beam radiotherapy, brachytherapy	Descriptive statistical analysis	48,308 men	Radical prostatectomy: US$14,866 in 1991 to US$12,135 in 1999; External beam radiotherapy: US$11,172 in 1991 to 9,182 in 1999; Brachytherapy: US$15,137 in 1991 to US$11,088 in 1999 (not mentioned whether the difference was significant not)	[254]

N/A: not available from the article

Table 15. Continued

Author, year	Country	Perspective	Horizon	Management options	Method	Men treated	Results	Ref
CF Snyder, 2010	US	N/A	5 years	Watchful waiting (if they received no treatment in the first 9 months), radiotherapy, hormonal therapy, surgery	Descriptive statistical analysis	13,769 men	Watchful waiting: US$4,270 in the first year and US$9,130 in 5 years; Radiotherapy: US$12,120 and US$15,589 Hormonal therapy only: US$11,034 and US$26,896 hormonal + radiation: US$17,474 and US$25,097; Surgery (may have received other treatments): US$15,197 and US$19,214; Significantly different	[255]
AT Corcoran, 2010	US	Payer perspective	15 years	Radical prostatectomy versus watchful waiting with active surveillance (model 1: prostate biopsy Annually; model 2: biopsy at 18-month intervals after the initial biopsy 12 months after diagnosis)	Markov model	Simulated patients	Radical prostatectomy: US$15,235 for 15 years; watchful waiting with active surveillance: US$6,558 to US$11,992; Significantly different	[168]
SO Andersson, 2011	Sweden	Perspective of health care provider	12 years	Watchful waiting versus radical prostatectomy (SPCG-4)	Descriptive statistical analysis	105 randomized to WW and 107 to RP	Radical prostatectomy: €24,247; Watchful waiting: €18,124 in 12 years. Significantly different	[256]
PL Nguyen, 2011	US	N/A	1 year	Three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, brachytherapy, Open radical prostatectomy, minimally invasive radical prostatectomy	Descriptive statistical analysis	45,636 men age ≥ 65 years who received definitive surgery or radiation	Three-dimensional conformal radiation therapy: US$22,384 in 2002 to US$20,588 in 2005 intensity-modulated radiation therapy: 37,418 in 2002 to US$31,574 in 2005 brachytherapy: US$21,117 in 2002 to US$17,076 in 2005 Open radical prostatectomy: US$18,070 in 2002 to US$16,469 in 2005 minimally invasive radical prostatectomy: US$29,988 in 2002 to US$16,762 in 2005; (not mentioned whether the difference was significant not)	[257]
L Perrier, 2012	France	Hospitals' perspectives	From the first irradiation Fraction to the last fraction	Image-guided radiation therapy (Cone Beam Computed tomography (CBCT) versus orthogonal electronic portal imaging with fiducial markers (EPI-FM))	Descriptive statistical analysis	208 patients	CBCT: €2,311 for with daily imaging and €1,632 with weekly imaging; EPI-FM: €2,065 with daily imaging and €1,878 with weekly imaging; (not mentioned whether the difference was significant not)	[258]

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The 1-year costs of treatments for localised prostate cancer decreased in 2002-2005, including three-dimensional conformal radiation therapy (US$22,384 in 2002 to US$20,588 in 2005), intensity-modulated radiation therapy (US$37,418 in 2002 to US$31,574 in 2005), brachytherapy (US$21,117 in 2002 to US$17,076 in 2005), open radical prostatectomy (US$18,070 in 2002 to US$16,469 in 2005), minimally invasive radical prostatectomy (US$29,988 in 2002 to US$16,762 in 2005).[257] Zeliadt[254] and colleagues also showed that the first 6 months costs for radical prostatectomy declined from US$14,866 in 1991 to US$12,135 in 1999, External beam radiotherapy from US$11,172 in 1991 to US$9,182 in 1999, and brachytherapy from US$15,137 in 1991 to US$11,088 in 1999.

Cryosurgical ablation of the prostate from hospital admission to discharge (US$8,796 including physician cost[252]; US$4,150 not including physician charges[247]) was shown to be less expensive than radical prostatectomy (US$9,251-9,724 including physician cost;[252] US$5,660 not including physician charges[247]). The cost difference between minimally invasive radical prostatectomy and open radical prostatectomy was only about US$300.[252,257] The costs for a radical retropubic prostatectomy (US$9,757) were significantly higher than a radical perineal prostatectomy (US$7,195) after 21 months' follow-up.[251]

There was no significant difference between radical prostatectomy and brachytherapy in a study (US$26,320 vs US$22,660)[249] with a 2-months follow-up or in a study (€8,715 vs €8,019)[253] over a 2-year period. Radical prostatectomy was significantly more expensive than external beam radiation therapy (US$17,226 vs US$14,048 from 1 month before to 9 months after diagnosis).[250]

Watchful waiting was significantly less expensive than radical prostatectomy.[168,255,256] Using cost models with annual conversion rates of 5% and 7% from watchful waiting with active surveillance (WWAS) to radical prostatectomy, the costs in the WWAS arm were US$6,558 to US$11,992 compared with US$15,235 in the radical prostatectomy arm over a 15-year period.[168] Based on the SPCG-4 study[39] data, the costs for watchful waiting in 12 years were €18,124 compared to €24,247 for radical prostatectomy.[256] A similar finding was also demonstrated in a 5-year retrospective study which showed US$9,130 for watchful waiting and $19,214 for surgery.[255] In this study, the first year costs were only US$4,270 for watchful waiting and $12,120 for surgery.

2.3.3.2 Cost-effectiveness studies

The extracted information from cost-effectiveness studies is listed in Table 16. All studies were published after 2005, including three in 2012, two in 2013 and one in 2014. The studies were conducted in the US (3), UK (1), Canada (1) and Germany (1). All articles reported their research perspectives, including the perspective of a health care system (2), societal perspective (2) and payer's perspective (2). They all estimated the lifetime costs and consequences for men diagnosed with localised prostate cancer. Modelling was the main research tool in the cost-effectiveness studies. Five studies used a Markov model and one used a discrete event simulation model. Treatment options that were investigated included watchful waiting/active surveillance in two studies, radical prostatectomy in three studies and radiotherapy in five studies.

Observational management (active surveillance or watchful waiting) was shown to be dominant (less costly and more effective) compared to definitive treatments (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) in an American study.[266] Similar results were found in a German study which showed that active surveillance was associated with an additional 0.04 QALYs and a cost reduction of €6,883 per patient compared with open prostatectomy.[268] Compared with active surveillance, watchful waiting provided 2 additional months of quality-adjusted life expectancy at a savings of US$15,374 in men aged 65 years and 2 additional months at a savings of US$11,746 in men aged 75 years.[266] The transition probabilities used in the model in these two study[266,268] were based on the PIVOT study[15] where no significant survival difference among the watchful waiting, active surveillance and radical prostatectomy group was identified. Given that men having radical prostatectomy were assumed to have worse quality of life than men without definitive treatments in these studies, the quality-adjusted life expectancy for men in the active surveillance arm was worse than men in the watchful waiting arm but was better than men in the radical prostatectomy arm.

Brachytherapy was the most effective and least expensive definitive treatment in the study conducted by JH Hayes[266] and colleagues. MR Cooperberg[267] found that radical prostatectomy was more effective and less costly than radiotherapy. Three studies compared the radiotherapy options for localised prostate cancer. [261,263,264] Stereotactic body radiation therapy (SBRT) was less costly but more effective than intensity-modulated radiation therapy (IMRT) and proton beam therapy (PT).[264] Compared to three-dimensional conformal radiotherapy (3D-CRT), the ICER of IMRT was CAN$26,768 per QALY gained in an Canadian study.[263] In the UK, IMRT was cost-effective at a threshold value of £20,000 per QALY gained when the estimated survival was greater for IMRT than 3D-CRT.[261]

Table 16. Extracted information from cost-effectiveness studies

Author, year	Country	Perspective	Horizon	Management options	Method	Men treated	Results	Ref
Hummel SR, 2012	UK	A UK National Health Service perspective	Life time	Intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy	Discrete event simulation model	Simulated patients	At a threshold value of £20,000 per QALY gained: IMRT was cost-effective in scenarios where estimated survival was greater for IMRT than 3D-CRT; A 20% probability that IMRT is cost-effective at a maximum threshold of £20,000 and a 48% probability at a threshold of £30,000, for the most likely scenario, a 15% difference in late gastrointestinal toxicity;	261
A Parthan, 2012	US	Payer's and societal perspectives	Life time	Intensity-modulated radiation therapy (IMRT), proton beam therapy (PT), stereotactic body radiation therapy (SBRT)	Markov model	Simulated men with localized prostate cancer aged 65 years	Compared to IMRT and PT, SBRT was less costly and resulted in more QALYs. At a threshold of US$50,000/QALY, SBRT was cost-effective in: 75% and 94% of probabilistic simulations compared to IMRT and PT, respectively, from a payer perspective; 75% and 96% of simulations compared to IMRT and PT, from a societal perspective	264
JHE Yong, 2012	Canada	Perspective of the health care system	Life time	Intensity-modulated radiotherapy versus three-dimensional conformal radiotherapy	Markov model	Simulated patients	IMRT produced 0.023 more QALY than 3D-CRT at an additional cost of CAN$621, yielding an ICER of CAN$26,768 per QALY gained.	263
JH Hayes, 2013	US	Societal perspective	Life time	Treatment (brachytherapy, intensity-modulated radiation therapy, or radical prostatectomy) or observation (active surveillance (AS) or watchful waiting (WW))	Markov model	Simulated men aged 65 and 75 years	Observation was more effective and less costly than initial treatment. Compared with AS, WW provided 2 additional months of quality-adjusted life expectancy at a savings of US$15,374 in men aged 65 years and 2 additional months at a savings of US$11,746 in men aged 75 years. Brachytherapy was the most effective and least expensive initial treatment.	266
MR Cooperberg, 2013	US	Payer's perspective	Life time	Radical prostatectomy (open, laparoscopic, or robot-assisted) and radiation therapy (dose-escalated three-dimensional conformal radiation therapy, intensity-modulated radiation therapy, brachytherapy, or combination)	Markov model	Simulated patients	The surgical methods were more effective and less costly than radiotherapy.	267
F Koerber, 2014	Germany	Societal perspective	Life time	Open prostatectomy versus active surveillance	Markov model	Simulated men aged 65 years	With quality adjustment, AS was the dominant strategy compared with initial treatment. In the base case, it was associated with an additional 0.04 QALYs (7.60 QALYs vs. 7.56 QALYs) and a cost reduction of €6,883 per patient. Considering only life-years gained, prostatectomy was more effective with an ICER of €96,420/life year gained.	268

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2.3.4 Discussion

Each treatment option for localised prostate cancer has its own benefits, risks and associated costs. Economic evaluation studies incorporating comprehensive information on health outcomes and costs are important for decision making on choosing the right treatment. Of the 18 included studies, 15 were conducted in the US. Since the results of economic evaluation studies carried out in the US might not be generalisible to other countries, other countries need to conduct their own economic evaluation studies to support their decision making. Only 6 studies were cost-effectiveness studies, and 12 were costing studies.

Though the economic burden of prostate cancer on the health care system is increasing,[269] the costs of some treatments for localised prostate cancer decreased over time, including external beam radiotherapy, brachytherapy, open radical prostatectomy and minimally invasive radical prostatectomy.[257,254] The reasons for the reduced costs of these treatments were not explored in these studies. However, it was demonstrated in Sullivan's study[180] that the costs of health care for cancer are generally driven by innovation, including new approaches to early detection, new pharmaceuticals, surgical or radiation devices. The price of these new pharmaceuticals or technologies can decline over time because patents expire and/or similar products become available.

With regards to the short term treatment costs, watchful waiting is the least costly option.[255] However, the costs of watchful waiting increased substantially over time. The costs of watchful waiting in 5 years were more than double the costs in the first year.[255] When considering the short term (within one year) costs, radical prostatectomy and brachytherapy are more expensive than cryosurgical ablation of the prostate and external beam radiotherapy.[247,249,250,252] However, the lifetime cost in the radical prostatectomy group is less than the cost in the radiotherapy group.[267] The cost difference between an open radical prostatectomy and a minimally invasive radical prostatectomy is not significant,[252,257] When considering the long term costs in different treatment arms, WWAS (expectant management) was still less costly than radical prostatectomy.[168,255,266,268] According to these cost-effectiveness studies, observational management was the dominant treatment option for patients with low risk prostate cancer.[266,268]

The ICER is generated through the incremental analysis of costs and health gained. If the incremental costs are small and the health gains are high, the estimated ICER will be very likely to be under the cost-effectiveness threshold in the country where the analysis is performed. In Hayes's study[266], the health gained by active surveillance for men aged 65 and diagnosed with low risk localised prostate cancer was high (0.9 QALYs) compared to radical prostatectomy and the incremental costs were low (US$1,714). Therefore, active surveillance was cost-effective in this subgroup compared to radical prostatectomy with a low ICER of US$1,904 per QALY gained. In this study, watchful waiting was the least costly and the most effective management option for men aged 65 and diagnosed with low risk localised prostate cancer, which indicated that watchful waiting was the optimal option for this group

of men. When the incremental costs and the health gains are both large, or they are both small, the ICER and the conclusion on cost-effectiveness is susceptible to changes.

The structure of models constructed in the cost-effectiveness studies differ. The influence diagrams indicating the model structure were not available in two studies.[266,267] Four studies included biochemical recurrence in their models,[261,263,266,267] but only one study[268] included local recurrence/progression. Though biochemical failure is a good indicator of cancer relapse, biochemical failure might not be treated. Therefore, it is hard to estimate the treatment costs for biochemical recurrence. On the other hand, local recurrence/progression can incur significant treatment costs and has a significant impact on patients' quality of life. It should be considered as an important part of the model. The data on transition probabilities relevant to local recurrence/progression are scarce, which might be also an important reason why biochemical recurrence was more frequently used. Parthan's model[264] did not include any cancer progression information (biochemical recurrence, local progression and metastasis). The health outcome differences of different external beam radiotherapies are mainly on the complications (urinary, sexual and gastrointestinal problems) caused by radiotherapies.[264] Young's model[263] and Hummel's model[261] focused on gastrointestinal toxicity, but did not include genitourinary toxicities or sexual dysfunction. It was advised that the difference in incidence of genitourinary toxicities between IMRT and 3D-CRT is not significant.[270,271] The exclusion of sexual dysfunction might bias the results, because IMRT as a more targeted treatment, may cause less sexual dysfunction.[263]

Buxton et al expressed their concerns on the data used in modelling, which were found in these cost-effectiveness studies.[210] The utility score for patients with metastatic prostate cancer in the cost-effectiveness studies was inconsistent, ranging from 0.12 to 0.69. The variation might be ascribed to the method used in measuring the utility score. A 0.12 score (the data source was not shown) was used in Hayes's study,[266] a 0.25 score measured with standard gamble in Koerber's study,[268] a 0.45 score (data source uncertain) in Cooperberg's study,[267] and a 0.69 score measured with HUI in Yong's study.[263] The utility score for patients under active surveillance was 0.99 in Koerber's study,[268] compared with 0.83 (measured with TTO) in Hayes's study.[266] Some men under active surveillance suffered from anxiety and depression after the prostate cancer diagnosis,[17] therefore a utility score of 0.99 for these men might not be very reliable.

The economic data varied considerably among the cost-effectiveness studies. For example, the cost of a PSA test in Parthan's study[264] was US$103, US$29 in Hayes's study[266], £10.19 in Hummel's study[261], and £4.8 in Koerber's study[268]. The different follow-up protocols after treatments contribute considerably to the variation of economic outcomes between studies. Two PSA tests and two office visits in the first year after external beam radiotherapy were assumed in Parthan's study[264], while only one PSA test and one GP visit in the first year after external beam radiotherapy were applied in Hummel's study[261]. Similarly, the clinical data also differed among the studies. The 5 years biochemical recurrence-free survival after IMRT and 3D-CRT in Yong's study[263] was both 70%, but the 5 years biochemical recurrence-free survival after IMRT and 3D-CRT in Hummel's model[261] was 85% and 74-85%. The different data inputs made comparison between studies difficult.

In the two cost-effectiveness studies comparing active surveillance and radical prostatectomy,[266,268] the transition probabilities in the observational management arms were based on the PIVOT study[15] where most patients were identified through PSA testing. No survival difference was found between the watchful waiting group and the radical prostatectomy group in this study. The review in this chapter of economic evaluation of prostate cancer screening concluded that population-based prostate cancer screening is not cost-effective. A new economic evaluation study comparing observational management and radical treatments using data based on men diagnosed with prostate cancer by symptoms is needed. Most men enrolled the SPCG-4 study[39] were identified by symptoms and a significant survival difference was found between the watchful waiting arm and the radical prostatectomy arm. A cost-effectiveness analysis study based on the SPCG-4 study will yield different results in the scenario that prostate cancer cases were mainly detected by symptoms.

2.3.5 Conclusion

Watchful waiting was the least costly (in both short term costs and long term costs) treatment option for men with localised prostate cancer. In terms of short term costs, active surveillance was less costly than radical prostatectomy. However, the costs of observational management increased substantially over time. Therefore, the gap in costs between active surveillance and radical prostatectomy reduce over time, and there is a possibility that the life-time costs of active surveillance exceed the costs of radical prostatectomy.

The published cost-effectiveness studies comparing active surveillance and radical prostatectomy were based on PIVOT study where most patients were identified through PSA testing. No survival difference was found between the watchful waiting group and the radical prostatectomy group in this study. A new economic evaluation study comparing observational management and radical treatments using data based on the SPCG-4 study where patients were identified by symptoms is needed.

There are great variations in the costs and cost-effectiveness of treatments for localised prostate cancer. The quality of economic evaluation studies needs to be improved, and the quality of life data and transition probabilities would be the keys to improvement.

2.4 Summary of Chapter 2

The costs of the management pathway of prostate cancer, from screening, management of the newly diagnosed cancer to end-of-life care, are substantial. The costs of screening and diagnosis of prostate cancer account for a small proportion of the overall costs, and the costs of treatment comprise the largest proportion.[13] By introducing screening, the economic burden of prostate cancer would increase substantially. Though the prostate cancer-specific mortality has been decreasing, the economic burden of prostate cancer is expected to climb due to the aging of the population leading to an increased diagnosis caused by screening and improved survival, unless new strategies are introduced to 'reduce the number of diagnosis and/or focus treatment where it is clinically most appropriate'.[213]

The systematic review in economic evaluation of prostate cancer screening included 19 papers. The estimated cost per cancer detected ranged from €1,299 in Netherlands to US$44,355 in the US. The estimated cost per life-year saved ranged from US$3,000–729,000, while the cost per QALY was AU$291,817 and Can$371,100. The most appropriate data for economic evaluation of prostate cancer screening should be the cost per QALY gained. The estimated costs per QALY gained by prostate cancer screening were significantly higher than the cost-effectiveness threshold, suggesting that even when based on favourable RCTs in younger age groups, prostate cancer screening is still not cost-effective.

The review in costs and cost-effectiveness of treatments for localised prostate cancer included 18 papers. Watchful waiting was the least costly (in both short term and long term costs) treatment option for men with localised prostate cancer. In terms of short term costs, active surveillance was less costly than radical prostatectomy. However, the costs of observational management increased substantially over time. Therefore, the gap in costs between active surveillance and radical prostatectomy shrink with increasing follow-up time, and there is a possibility that the life-time costs of active surveillance exceed the costs of radical prostatectomy. The published cost-effectiveness studies comparing active surveillance and radical prostatectomy were based on PIVOT study where most patients were identified through PSA testing. No survival difference was found between the watchful waiting group and the radical prostatectomy group in this study. A new economic evaluation study comparing observational management and radical treatments using data based on the SPCG-4 study where patients were identified by symptoms is needed. There are great variations in the costs and cost-effectiveness of treatments for localised prostate cancer. The quality of economic evaluation studies needs to be improved, and the quality of life data and transition probabilities would be the keys to improvement.

The country or region where the study was conducted is critical for cost-effectiveness analysis, given the different cost-effective thresholds, different health care practice, different unit costs of medical resources, and different population who might benefit from the new technology. A new pharmaceutical or a new technology might be cost-effective in one country, but might not be cost-effective in another

country. Each country needs to perform its own analyses using local costing and clinical data and compare the result with its own cost-effectiveness thresholds relevant to the country.

2.5 Research objectives and original studies in New Zealand

The cost-effectiveness of prostate cancer screening compared to no screening also depends on the population screened. Therefore, an economic evaluation of prostate cancer screening needs to be conducted in a New Zealand setting. Most of the prostate cancer cases identified through screening are localised and have good prognosis.[29] Active surveillance might be a reasonable treatment option for men with localised prostate cancer.[266,268] The prognosis of men with localised prostate cancer depends on the Gleason grade and stage.[77,111] Some men might develop metastatic prostate cancer and might die of prostate cancer.[39] The costs of management of metastatic prostate cancer, including treatments to prolong patients' life and palliative care for end-stage patients, can be substantial.[31] This thesis aims to use economic evaluation approaches to assist the decision making for management of prostate cancer in New Zealand. Five original studies were conducted: 1) The costs of identifying undiagnosed prostate cancer in asymptomatic men; 2) Survival in a cohort of men with Prostate Cancer; 3) The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer; 4) The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for intermediate risk localised prostate cancer; and 5) Management, characteristics, survival and costs of men with metastatic prostate cancer. This section outlines the objective, null hypothesis and methods of each study.

2.5.1 Study one: The costs of identifying undiagnosed prostate cancer in asymptomatic men

Objective: This study aims to estimate the costs of identifying a new case of prostate cancer by age group, ethnicity and previous PSA testing history, using data from general practice in the Midland Cancer Network region.

Null hypothesis: There are no differences in the costs of identifying a new case of prostate cancer by age group, ethnicity and previous PSA testing history.

Methods: Men aged 40 years or older who had PSA tests in 31 general practices in the Midland Cancer Network region during 2010 were identified. Asymptomatic men without a history of prostate cancer were eligible for this study. A Decision Tree mapping the screening pathway was constructed to estimate the screening costs.

2.5.2 Study two: Survival in a cohort of men with Prostate Cancer

Objective: This study aims to analyse the survival in a cohort of New Zealand men diagnosed with prostate cancer by cancer extent in the Midland Cancer Network region, to examine the effects of ethnicity, treatment, cancer grade and comorbidities on survival, and to inform study three, four and five.

Null hypothesis: There are no survival differences in patients with localised, regional and metastatic prostate cancer by ethnicity, treatment, cancer grade and comorbidities.

Methods: Men aged 40 years or older in the Midland Cancer Network region registered with prostate cancer in 2007-2010 were identified from the Cancer Registry. Data were extracted from the patient notes of all Māori men and a sample of New Zealand Europeans. The 5-year survival was estimated using the Kaplan-Meier method. A Cox proportional-hazards regression model was used to examine the effect of ethnicity, biopsy Gleason score, comorbidities and primary treatment on survival.

2.5.3 Study three: The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer

Objective: This study aims to compare the cost-effectiveness of active surveillance, watchful waiting and radical prostatectomy for men diagnosed with low risk localised prostate cancer.

Null hypothesis: There are no differences in the cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for men diagnosed with low risk localised prostate cancer.

Methods: A lifetime Markov model was constructed, synthesizing the international and local clinical and economic data. Simulated patients were diagnosed with low risk localised prostate cancer at the age of 45, 50, 55, 60, 65 or 70 years.

2.5.4 Study four: The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for intermediate risk localised prostate cancer

Objective: This study aims to compare the cost-effectiveness of active surveillance, watchful waiting and radical prostatectomy for men diagnosed with intermediate risk localised prostate cancer.

Null hypothesis: There are no differences in the cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for men diagnosed with intermediate risk localised prostate cancer.

Methods: A lifetime Markov model was constructed, synthesizing the international and local clinical and economic data. Simulated patients were diagnosed with intermediate risk localised prostate cancer at the age of 60, 65 or 70 years.

2.5.5 Study five: Management, characteristics, survival and costs of men with metastatic prostate cancer

Objective: This study aims 1) to characterise men diagnosed with metastatic prostate cancer in New Zealand; 2) to describe the management of these men; 3) to look at the outcomes of treatment and survival in men with metastatic prostate cancer; and 4) to estimate the treatment costs across the management pathway for metastatic prostate cancer.

Null hypothesis: There are no differences in the management and survival in men with metastatic prostate cancer. There are no differences in the treatment costs across the management pathway for metastatic prostate cancer by phase (diagnostic, treatment and terminal), age group and ethnicity.

Methods: Patients registered with prostate cancer in the Midland Cancer Network Region in 2009-2012 were identified from the New Zealand Cancer Registry. These patients' clinical records were examined to identify the metastatic cases. Patients' characteristics and the treatment pattern were examined. All-cause survival was estimated by Cox proportional hazards model. The treatment pathway was divided into: diagnostic phase (the first three months after the metastatic diagnosis), treatment phase (the follow-up time between the diagnostic and terminal phase) and terminal phase (last three months prior to patient's death). The overall health care costs and the costs associated with the management of prostate cancer were estimated.

Chapter 3. The costs of identifying undiagnosed prostate cancer in asymptomatic men

3.1 Introduction

Prostate cancer screening is commonly practiced in New Zealand, with half of New Zealand adult males having had a PSA test.[20] GLOBOCAN 2008 identifies New Zealand as having one of the highest age-standardised incidence rates worldwide, in excess of both the US and UK (99.7 vs. 83.8 and 64 per 100,000 respectively), which appears to be related to a high rate of PSA testing. The New Zealand incidence rate appears similar to Canada and Australia (101.5 and 105), which may provide the closest comparisons amongst the OECD.[272]

GPs in New Zealand believe in the benefits of PSA screening though studies on prostate cancer screening showed inconsistent results.[5-8] However, without a clear guideline on prostate cancer screening, GPs and practices varied considerably in the way that they screened men. In a study including 31 practices in the Midland Cancer Network region, eight practices tested more than 30% of their male patients aged 40+ years in 2010, whereas three practices tested less than 10% of their male patients.[30] There is also variation in the uptake of PSA testing in different cancer network regions. The number of PSA tests per 100 men aged 40 years and older was 42 in the Northern Cancer Network region and was less than 30 in the Southern Cancer Network region.[30] The annual prostate cancer screening rate in the Midland Cancer Network region (22.1%)[4] was similar to the rate across the whole country (22%).[20] The research results in this region might reflect the whole picture in New Zealand.

The possibility of having PSA screening differed by age group and ethnicity.[4,21] Men aged 50-79 (screening rate: 24.9%-31.5%) were more likely to be screened compared to men aged less than 50 years (12.2%) or men aged 80+ (16.6%).[4] Māori men (11.2%) were shown to be as half likely to be screened as non-Māori men (22.6%).[21] Though it has not been examined yet, there might be variations in interval between screening rounds by age group and ethnicity. A longer interval can reduce the harms and screening costs but might be associated with more interval cancers.[273]

Of the new prostate cancer cases diagnosed with an elevated PSA, less than 20% were screen-detected, while over 80% were identified in men with histories of prostate pathology or lower urinary tract symptoms.[19] Whether population-based prostate cancer screening can save lives is still uncertain, and screening can cause overdetection and overdiagnosis. To identify asymptomatic prostate cancers by screening and to manage the screen-detected cancers require great medical resource inputs. This raises the question whether it is worthwhile to spend scarce medical resources on prostate cancer screening when it is not certain whether the benefits outweigh the harms caused by prostate cancer screening.

The systematic review in this thesis showed great variations in the costs per new case of prostate cancer identified by screening.[28] The screening population and the number of cancer cases identified were critical for the costing results. Therefore, the uptake of PSA screening that is related to age, ethnicity and screening interval would be important as well. This study estimates the costs of identifying a new case of prostate cancer by age group, ethnicity and former PSA testing history, using data from general practice in the New Zealand Midland Cancer Network.

3.2 Methods

3.2.1 Data collection

All general practices in New Zealand use a computer system and all patients have a National Health Index (NHI) number linked to the data used for capitation payments. The NHI number is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand. Information collected on patients' characteristics from the general practices, including ethnicity, age and gender is almost complete. All patients need to provide these data before they are enrolled in the general practices. The electronic patient medical records from 31 general practices were linked to laboratory data using the NHI number, to identify male patients aged 40+ who had one or more PSA tests in 2010. The database in the New Zealand Cancer Registry, a population-based tumour register in New Zealand, was also linked to the practice data by the NHI numbers to exclude men with a previous prostate cancer history. For all men identified, their PSA records in 2007-2009 were identified. Men with a previous record of raised PSA values in 2007-2009 were excluded. All medical records for men with a raised PSA were examined and whether lower urinary tract symptoms or other prostate problems were present at the time of PSA testing were noted. Symptomatic men were excluded, and all other men were considered to be "screened" patients.

For eligible men, their age, ethnicity, PSA testing histories, PSA tests, referrals to specialists and biopsy results were recorded. These data were collected from general practices and relevant community laboratories. Patients who underwent biopsies were followed up to the date of biopsy. Men who had elevated PSA results but did not undergo biopsies were followed up for 12 months since the date of their first PSA test in that year. The raised PSA levels defined in this study were age-specific, used by a local laboratory: ≥2.5 ng/mL for men aged 40-49; ≥3.5 ng/mL for men aged 50-59; ≥4.5 ng/mL for men aged 60-69; ≥6.5 ng/mL for men aged 70-79; ≥7 ng/mL for men aged 80+. Where necessary, missing number of PSA tests in 2011 was imputed by a statistical package, R 2.14.1, using the nearest neighbour imputation approach.[274,275] The missing numbers of PSA tests in 2011 for specific men were imputed by choosing the values for men with similar age, ethnicity and PSA testing history.

3.2.2 Cost estimation

This study estimates direct medical costs in 2010 and 2011 from a health service perspective. This perspective includes charges levied by general practitioners for consultations (with the remainder subsidised by the New Zealand Ministry of Health) but excludes other indirect costs to patients, such as wages foregone and the cost of travel to attend appointments.

A Decision Tree was constructed to map the screening pathway and to document the costs associated with each node (Figure 15). Medical resources considered in this study comprised initial general practitioner consultations (the first consultation related to PSA testing), follow up general practitioner consultations, PSA tests, first specialist assessments (FSA), follow-up specialist consultations, prostate biopsies, pathology reports of prostate biopsy and hospitalization due to complications after prostate biopsy. The volumes of the PSA tests, FSAs, prostate biopsies and pathology reports were calculated from the data collected. The number of general practitioner consultations was estimated based on records of PSA tests ordered by general practitioners. The number of follow-up specialist consultations was estimated from the number of prostate biopsies and PSA tests ordered by specialists. A 2% complication rate[14] and a 4.87-days mean length of hospital stay for complications of prostate biopsy were assumed to quantify the hospitalization after prostate biopsy.

The quantity of health care resources was multiplied by the unit cost of each type of medical resource to generate an aggregate cost. The unit costs of medical resources are provided in Table 17, alongside the sources. The subsidy per general practitioner consultation was estimated by dividing the capitation rate by the average number of general practitioner consultations per patient (Table 17). The unit costs corresponding to different time periods were converted into 2010 values (as the base year of this analysis) by applying the New Zealand Inflation Calculator developed by the Reserve Bank (the central bank in New Zealand). All costs were valued in 2010 New Zealand dollars (NZ$).

The time spent on discussion about PSA testing in the initial general practitioner consultation differs from general practice to general practice. It is related to the level of informed consent, ranging from almost no time (ticking the box of a laboratory form) to the whole consultation spent on discussing the harms and benefits associated with prostate cancer screening. Three percentages (20%, 50% and 100%) of the cost of an initial general practitioner consultation were assumed to be attributed to prostate cancer screening. The 20% was inferred from a Ministry of Health report demonstrating approximately 80% of PSA tests were general practitioner initiated and only 20% were patient initiated. The 50% was based on an assumption that on average half of the general practitioner consultations were spent on discussion of prostate cancer screening. The 100% was based on a gold standard of PSA testing recommended by the Ministry of Health "All men who are concerned about prostate cancer or are requesting a PSA test must be presented with high-quality, culturally appropriate information", assuming that the delivery of "high-quality, culturally appropriate information" would take a full general practitioner consultation (15 minutes). All the follow up general practitioner consultations were assumed to be spent on discussion about the PSA testing.

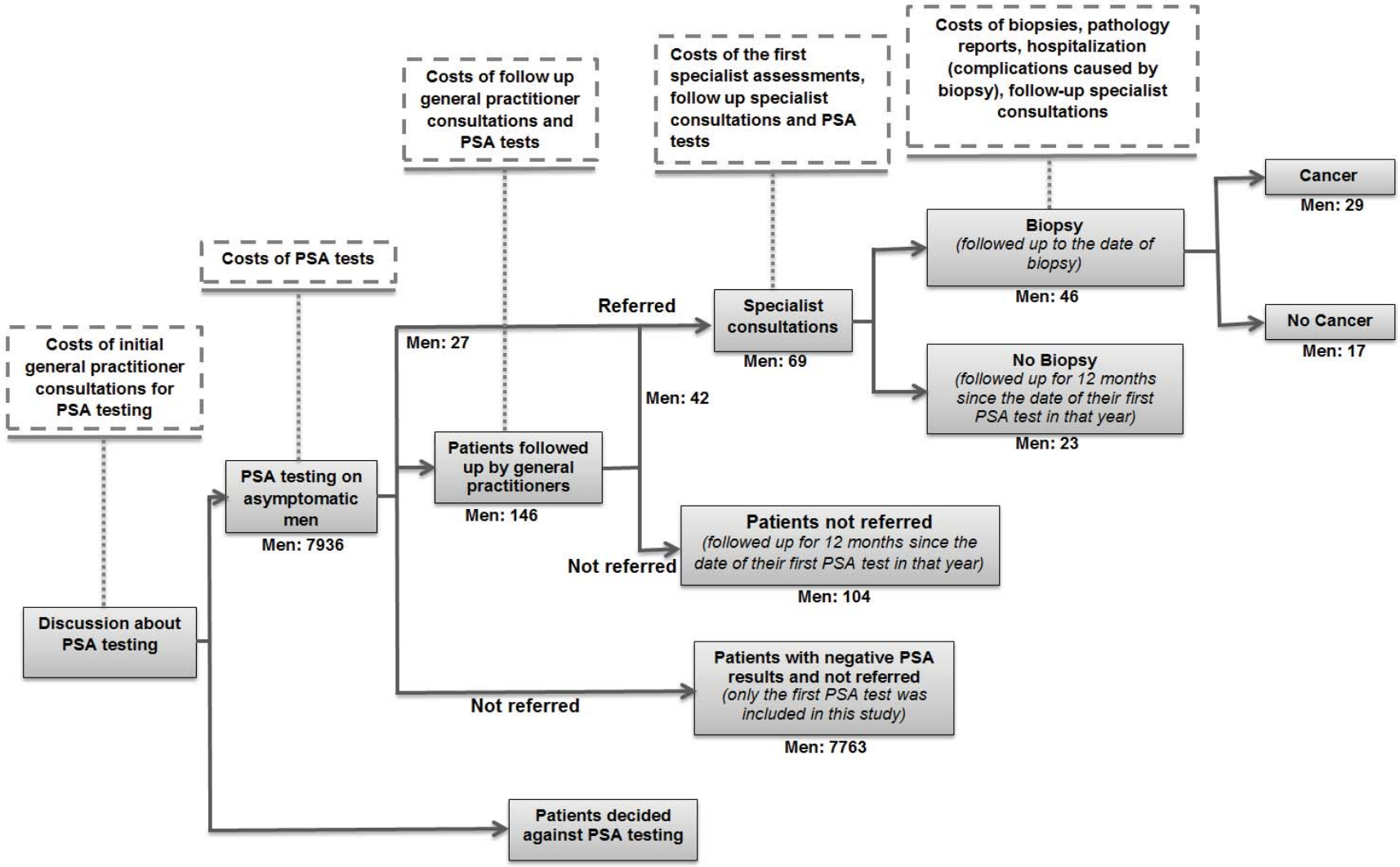

Figure 15. Pathway of screening for prostate cancer in New Zealand

Table 17. The unit costs of medical resources

Medical resources	Corrected cost in 2010 New Zealand Dollars	Unit cost collected		
		Reported cost	Year	Data source
PSA test	NZ$11.07	NZ$10.44	2008-2009	Report from the Ministry of Health[153]
general practitioner consultation	NZ$73.54			
charge	NZ$35.88	NZ$36.73	2012	Unpublished data from the Ministry of Health
subsidy	NZ$37.66	NZ$38.69	2012	Website of the Ministry of Health[276], Report from the Royal New Zealand College of General Practitioners[277]
First specialist assessment	NZ$268.79	NZ$276.36	2012	Unpublished data from Urology Services Ltd & Venturo Ltd
Follow-up specialist consultation	NZ$233.64	NZ$213.09	2006-2008	Report from the Ministry of Health[153]
Biopsy	NZ$427.96	NZ$440.00	2012	Unpublished data from Urology Services Ltd & Venturo Ltd
Pathology report of biopsy	NZ$710.02	NZ$730.00	2012	Unpublished data from Waikato Hospital in WDHB
Hospitalization after biopsy (per bed day)	NZ$405.82	NZ$349.50	2005	Website of World Health Organization[278]

Note: All the unit costs of medical resources in hospitals were based on data from public hospitals.

3.2.3 Sensitivity analysis

One way sensitivity analysis was conducted to assess the uncertainty in the results. Each parameter used in the cost estimation, including the number of cancers detected, the unit cost and the volume of each type of medical resource, was decreased or increased by 20% of the original value (the data collected) at one time to appraise its impact on the screening costs (Appendix 1).

3.3 Results

3.3.1 Number of men screened

After data cleaning, 1006 men with a previous prostate cancer history were excluded, and 35,958 men aged 40 years or over, without a prostate cancer history and registered with the 31 general practices were identified. Of the eligible men, 9,344 (26%) of them had one or more PSA tests in 2010, and 7,936 (85%) men were considered to be screened (asymptomatic). A very small number (30) of men had missing follow-up data on repeated PSA tests that required imputation. The missing PSA values were imputed by choosing the PSA values for men with similar age, ethnicity and PSA testing history.

After the first PSA test, 27 men were referred to the specialists and 146 men were followed up by general practitioners, of whom 42 men were referred to the specialists in 2010 or 2011. Of the 69 men referred to specialists, 46 men had biopsies, and 29 men were diagnosed with prostate cancer.

The number of asymptomatic men needed to be screened to identify a new case of prostate cancer was 274 for the whole screening group but differed according to patient characteristics (Table 18). The number of men who needed to be screened was below this average figure (of 274) for the following groups: those aged 60-69 (127), Māori men (139), and those who had not previously been tested in 2007-2009 (188).

Table 18. Number of cancers identified and Number of men screened per cancer identified

Categories	Number of cancers identified	Number of men screened per cancer identified
Age group		
40-49	2	717
50-59	3	868
60-69	19	127
≥70	5	298
Ethnicity		
Māori	4	139
Non-Māori	25	295
PSA testing history		
No PSA tests in 2007-2009	18	188
Had PSA tests in 2007-2009	11	413
Overall	29	274

3.3.2 Quantity of medical resources

The quantity of medical resources for prostate cancer screening is reported in Table 20, consisting of 7,936 initial general practitioner consultations, 197 follow up general practitioner consultations, 8,165 PSA tests (ordered by general practitioners and specialists), 69 FSAs, 78 follow up specialist consultations, 46 biopsies, 46 pathology reports, and 4.48 hospital bed days.

As shown in Table 19, the costs incurred in general practice, including the cost of initial general practitioner consultations (37.3%), the cost of follow up general practitioner consultations (4.6%) and the cost of PSA tests ordered by general practitioners (28.8%), accounted for 70.7% of the total costs, if 20% of the general practitioner time was spent on discussing the harms and benefits of prostate cancer screening. The proportion of each type of medical resource cost (incurred in hospitals) in total costs was 10.5% for pathology reports, 6.3% for biopsies, 5.9% for FSAs, 5.8% for follow-up specialist consultations, 0.6% for hospitalization after prostate biopsy and 0.1% for PSA tests ordered by specialists. If more general practitioner time was assumed to be involved in a PSA test, the proportion of the cost of general practitioner consultations in total costs increased substantially, while the percentages of the costs of the other health resources in total costs decreased.

Table 19. Proportion of the cost of each type of medical resources in total cost

Medical resources	Proportion of initial general practitioner consultation cost included		
	20%	50%	100%
First general Practitioner Consultation	37.30%	59.80%	74.90%
PSA tests ordered by general practitioners	28.80%	18.50%	11.60%
Pathology report	10.50%	6.70%	4.20%
Biopsy	6.30%	4.00%	2.50%
First specialist assessment	5.90%	3.80%	2.40%
Follow up specialist consultation	5.80%	3.70%	2.30%
Follow up general Practitioner Consultation	4.60%	3.00%	1.90%
Hospitalization after prostate biopsy	0.60%	0.40%	0.20%
PSA tests ordered by specialists	0.10%	0.10%	0.00%

Table 20. Quantity of medical resources for prostate cancer Screening

Categories	PSA test ordered by general practitioner	Initial general practitioner consultation	Follow up general practitioner consultation	First specialist assessment	Follow-up specialist consultation	PSA test ordered by specialist	Biopsy	Pathology report	Hospitalization after biopsy (bed days)
Age group									
40-49	1448	1434	14	8	10	5	5	5	0.49
50-59	2645	2604	41	17	18	9	9	9	0.88
60-69	2492	2407	85	31	41	14	27	27	2.63
≥70	1548	1491	57	13	9	4	5	5	0.49
Ethnicity									
Māori	570	557	13	11	17	10	7	7	0.68
Non-Māori	7563	7379	184	58	61	22	39	39	3.80
PSA testing history									
No PSA tests in 2007-2009	3490	3391	99	48	57	25	32	32	3.12
Had PSA tests in 2007-2009	4643	4545	98	21	21	7	14	14	1.36
Overall	8133	7936	197	69	78	32	46	46	4.48

3.3.3 Cost per prostate cancer identified

The total costs from initial consultation through to hospitalization after biopsy to identify a prostate cancer are shown in Table 21. When 20% of general practitioner consultation cost was considered to be attributable to prostate cancer screening, the costs per cancer detected were NZ$10,777, compared with NZ$16,814 and NZ$26,877 when 50% and 100% of general practitioner consultation cost was utilized in the cost estimation, respectively.

The costs per cancer identified for men aged 60-69 (NZ$6,268-13,721 if 20%-100% of the general practitioner consultation cost was included) were the lowest, followed by the costs for Māori men (NZ$7,685-15,877) and the costs for men without a PSA testing history in 2007-2009 (NZ$8,887-19,970). The costs for men aged 40-49 (NZ$24,290-66,472), 50-59 (NZ$30,022-81,089) and 70+ (NZ$10,957-28,501) were 3.9-4.8 times, 4.8-5.9 times and 1.7-2.1 times the costs for men aged 60-69. The costs for non-Māori men (NZ$11,272-28,637) were 1.5-1.8 times the costs for Māori men. The costs per cancer detected for men with a prior history of PSA testing in 2007-2009 (NZ$13,870-38,178) were 1.6-1.9 times the costs for men without previous PSA tests in that period.

Table 21. Costs per prostate cancer identified

Categories	20% of initial general practitioner consultation cost included	50% of initial general practitioner consultation cost included	100% of initial general practitioner consultation cost included
Age group			
40-49	NZ$24,290	NZ$40,108	NZ$66,472
50-59	NZ$30,022	NZ$49,172	NZ$81,089
60-69	NZ$6,268	NZ$9,063	NZ$13,721
≥70	NZ$10,957	NZ$17,536	NZ$28,501
Ethnicity			
Māori	NZ$7,685	NZ$10,757	NZ$15,877
Non-Māori	NZ$11,272	NZ$17,784	NZ$28,637
PSA testing history			
No PSA tests in 2007-2009	NZ$8,887	NZ$13,043	NZ$19,970
Had PSA tests in 2007-2009	NZ$13,870	NZ$22,985	NZ$38,178
Overall	NZ$10,777	NZ$16,814	NZ$26,877

3.3.4 Sensitivity analysis

The number of cancers detected in the screened men had the strongest impact on the costs per prostate cancer identified, followed by the unit cost/ volume of general practitioner consultations, and

then the unit cost/ volume of PSA tests. The variation of other parameters did not lead to significant impact on the costs per cancer case detected.

3.4 Discussion

3.4.1 Key findings

Of the men with positive PSA results, only 25.9% had biopsies and 63.0% of the biopsies were positive. These results from general practice are greatly different from the results from the ERSPC trial, in which 85.9% of men with positive PSA tests underwent biopsies but only 24.1% of the biopsies were positive. There is a clear difference in clinical practice, although it is important to note that the detection rates of cancer in men with raised PSA are broadly similar (16.3% in New Zealand, 20.7% in ERSPC). It is unclear how much of these differences result from protocol-based care in the ERSPC trial as against routine clinical practice reported in this study, and how much depends upon country-specific differences.

The costs of identifying a new case of prostate cancer by screening asymptomatic men were substantial. If on average 3 minutes of general practitioner time (20% of the consultation cost) was spent on discussing PSA testing for each man, the costs per cancer detected were NZ$10,777. The costs increased to NZ$26,877 if every screened man received a full 15 minutes consultation for prostate cancer screening. It is difficult to compare the costs of detecting a new case of prostate cancer in New Zealand with the costs in other countries, due to the various screening strategies, diverse time frames of the studies, and more importantly, the different cost components and unit costs. For example, the cost for a 15 minutes general practitioner consultation in the UK in 2010 was £46.5 (NZ$104.0), compared to NZ$73.54 in New Zealand.

Some studies have only involved the costs of diagnostic tools, while our study indicates that the costs of physician consultations (including general practitioner consultations and specialist consultations) accounted for 53.6%-81.5% of the total costs. A Canadian study showed that the costs of identifying a new case of prostate cancer was Can$2,420 in 1998 (NZ$ 4,128 in 2010) if only the costs of diagnostic tools were estimated, which is less than half the costs in our study. Most of the screening costs were incurred in general practice (70.7%). Additional input from general practitioners providing informed consent would add substantially to the total costs.

The lowest screening costs per cancer detected were for men aged 60-69, the group in whom most cancers were identified. It is noteworthy that the percentage of costs incurred in general practice in total costs for those aged 60-69 was smaller than the percentages in the other age groups. It might be ascribed to the higher referral rate in this age group, resulting in greater costs incurred in hospitals for men aged 60-69. Men aged 70+ were less likely to be referred or to undergo biopsies. These men are unlikely to benefit from prostate cancer screening. In the age groups 40-49 and 50-59, prostate

cancer was rarely found. More men in these age groups needed to be screened to identify a new case of prostate cancer.

For men with a PSA testing history in 2007-2009, the costs per cancer detected were much greater in comparison with the costs for men without such a history. Considering the long lead time for prostate cancer, although more cancers can be detected if men are screened more frequently, the possibility of detecting new cases of prostate cancer at each screening round will be smaller. The costs per cancer detected will increase. Similar results have also been shown by Nordström et al., demonstrating retesting men with negative PSA values too frequently would lead to unnecessary harm and costs. Compared with non-Māori, Māori were less likely to be screened and were less frequently screened. The possibility of detecting new cases of prostate cancer in Māori at each screening round was greater and the costs per cancer detected were lower.

3.4.2 Strengths and limitations

One of the strengths of this study is that it was based on data collected from general practice rather than data from clinical trials. The information reflected the activities in the health care system. The results of studies based on data from clinical trials might not mirror reality. Patients in the clinical trials comply strictly with the protocols set by the researchers. However, in our study 104 men with positive PSA records were not referred to specialists. Among the referred patients, 23 patients did not undergo biopsies. Another difference with our study is that the PSA records and patient medical records were examined to identify the reasons for the PSA tests. Only asymptomatic men were included in this study. The detection of symptomatic prostate cancer should not be ascribed to the effect of screening.

This study has several limitations. As the data relates to one area of New Zealand serviced by an existing network (Midland Cancer Network), the findings are not necessarily generalisable to those in other areas. There are some costs that this study could not cover, namely the indirect costs to patients or society, the costs of initial general practitioner consultation for those patients who decided against PSA testing, and the costs of time spent by the health professionals on informing patients the test results and arranging consultations. The total number of prostate cancer identified was relatively small (29), resulting in a lack of precision in the costs per cancer detected in the subgroup analyses. Despite this these analyses are believed to be of interest. Finally, as this analysis considers only the cost of screening without assessing either the cost of subsequent treatment or the benefits arising from that treatment, it can provide at best partial information when informing decision making.

3.5 Conclusions

Screening of asymptomatic men for prostate cancer is widely practiced in New Zealand. Most of the estimated costs of screening were incurred in general practice. Calls for men to receive increased

information on the harms and benefits of screening will substantially increase the costs per cancer identified. The costs could be reduced by better targeting of screening.

3.6 Summary of Chapter 3

This chapter used a Decision Tree to estimate the costs of identifying a new case of prostate cancer by screening asymptomatic men aged 40 years or older in 31 general practices in the Midland Cancer Network region in 2010. We assumed general practitioners spent three minutes of the initial consultation on informed consent of prostate cancer screening. 70.7% of the estimated costs were incurred in general practice. The screening costs per cancer detected were NZ$10,777 (€5,820; £4,817). The estimated costs for men aged 60-69 were NZ$6,268 compared to NZ$24,290 for men aged 40-49, NZ$30,022 for 50-59 and NZ$10,957 for those aged 70 years or older. The costs for Maori were NZ$7,685 compared to NZ$11,272 for non-Maori. The costs for men without PSA testing history in 2007-2009 were NZ$8,887 compared to NZ$13,870 if the men had PSA tests in 2007-2009. If we assumed a PSA test involved a full 15 minutes general practice consultation, the estimated costs increased to NZ$26,877 per prostate cancer case identified. Calls for men to receive increased information on the harms and benefits of screening will substantially increase the costs. The current costs could be reduced by better targeting of screening.

This chapter estimates the cost of an intermediate outcome (descripted in Section 2.2). To estimate the costs of final outcomes (i.e. cost per life-year/ cost per QALY) by prostate cancer screening, the cost-effectiveness of the management of screen-detected prostate cancer cases would need to be incorporated. Chapter 6 and Chapter 7 evaluate the cost-effectiveness of treatments for localised prostate cancer, and Chapter 8 examines the costs across the management pathway for men with metastatic prostate cancer. The evaluation of prostate cancer screening needs to take into account the results from Chapter 6, Chapter 7 and Chapter 8.

As shown in Chapter 2, the treatment costs differed by prostate cancer stage.[222] The survival of men with localised prostate cancer is excellent, but the survival of men with advanced prostate cancer is poor.[33] Therefore, the life-time treatment costs of a cohort of men with prostate cancer are associated with the proportion of men by cancer stage and the survival time of these men. Before conducting the original studies in economic evaluation of treatments for prostate cancer in New Zealand, the distribution of cancer stage and the survival information in New Zealand men with prostate cancer need to be examined. The next chapter demonstrates the cancer stage at diagnosis, management and survival in a cohort of men with prostate cancer in New Zealand.

Chapter 4. Survival in a cohort of men with Prostate Cancer

4.1 Introduction

Prostate cancer is the most frequently diagnosed cancer and the third most common cause of cancer death for men in New Zealand.[3] Compared to men with lung cancer or colorectal cancer that are the first and second most common cause of cancer death, men with prostate cancer have a better cancer-specific survival.[279] In a cancer register based cohort of 37,529 men aged 40+ years diagnosed with prostate cancer in New Zealand between 1996 and 2010, the 5-year and 10-year cancer-specific survival was 75.8% and 62.8% for Māori men and was 84.9% and 75.8% for non-Māori men.[33] The New Zealand national cancer registry has very incomplete data on prostate cancer staging.[33] Therefore, the prostate cancer-specific survival by cancer stage in New Zealand is rarely reported. However, this information is vital for the survival comparison among countries and for finding the right approach to improve the survival for men diagnosed with prostate cancer.

Comorbidities and age were reported to be important indicators of other-cause mortality for men diagnosed with localised prostate cancer.[280] The 14-year cumulative other-cause mortality rates were 24%, 33%, 46%, and 57% for men with 0, 1, 2, and 3 or more comorbid conditions. Among men with three or more comorbid conditions, the 10-year other-cause mortality rates for men aged 60 years or younger, 61-74 years, and 75 years and older were 26%, 40%, and 71%.[280]

As shown in the national data in New Zealand, prostate cancer-specific survival for Māori men is poor compared with non-Māori and this gap is not changing over time.[33,281,282] It has been hypothesised that differences in prostate cancer detection and management are the most likely contributors to survival disparities between Māori men and non-Māori men in New Zealand.[33] Māori men were twice more likely to be diagnosed with metastatic prostate cancer than NZ European. When diagnosed with localised prostate cancer, Māori men were less likely to have radical prostatectomy compared to NZ Europeans.[12] Māori men diagnosed with prostate cancer were more likely to have comorbidities than non-Māori men.[12] It was also shown that 41.1% of Māori men and 50.7% of non-Māori men diagnosed with prostate cancer at the age of less than 70 years old.[33]

Survival for men with prostate cancer can also be affected by treatments. For example, The SPCG-4 study demonstrated a significant survival difference between watchful waiting and radical prostatectomy in men diagnosed with localised prostate cancer.[80] In patients with locally advanced prostate cancer, early bicalutamide was found to result in a significant overall survival benefit over a median follow-up of 14.6 years.[283] The effects of other treatment regimens on patients' survival have also been demonstrated.[284,285]

Overall, the prognosis for men with prostate cancer seems to be related to the cancer extent, patient's age, comorbidities and treatment.[183,286,287] This study aims to analyse the survival in a cohort of New Zealand men diagnosed with prostate cancer by cancer extent in the Midland Cancer Network region, and to examine the effects of ethnicity, treatment, cancer grade and comorbidities on survival.

4.2 Methods

4.2.1 Data collection

After data cleaning, 2011 men aged 40 years and older were identified in the Midland Cancer Network region registered with prostate cancer from 1 January 2007 to 31 December 2010 in the New Zealand Cancer Registry (NZCR). All 31 men (2 Māori and 29 NZ Europeans) diagnosed at death were excluded. The studied cohort included all eligible Māori patients (150 men) to compare their treatment with NZ Europeans. Each Māori man was matched by age with three randomly sampled New Zealand European men. Consequently, the study cohort included 150 Māori and 450 of the eligible 1442 NZ European men.

The cancer extent at diagnosis is not available for most prostate cancer cases in the NZCR.[33] Therefore patients' clinical records in the three DHBs (in both private and public hospitals) were retrospectively examined. The cancer diagnosis was ascertained and then the cancer stage was determined. For patients whose clinical or pathological reports did not specify the cancer extent, their records were examined by an urologist to determine the cancer extent at diagnosis. Patients' investigations (PSA test, DRE, biopsy and imaging), management options (active surveillance (AS) / watchful waiting (WW), radical prostatectomy, external beam radiotherapy, low dose brachytherapy and high dose brachytherapy) and comorbidities were recorded. The recorded terms active surveillance and watchful waiting were not clearly defined. Therefore a group of men who did not receive active treatments were categorised to be under AS or WW. The Charlson Comorbidity Index[288] was calculated for each man. Since Gleason score less than 6 tumours are no longer considered as cancer, these cases were excluded. This final cohort of men with detailed data on characteristics of prostate cancer at diagnosis and subsequent treatment were used to examine outcomes. The date of death and cause of death for the cohort were extracted from the national Mortality Collection and the accompanying death certificates. The access to NZCR and the clinical records in hospitals was approved by Northern Y (Ref. No. NTY/11/02/019) and Multi-Region Ethics Committees (Ref. No. MEC/11/EXP/044).

4.2.2 Survival analysis

The endpoints in this study were all-cause and cancer-specific survival. If there was no record of death, the patient was considered to be censored on the date of the latest update of Mortality Collection which was the 31st December 2013. Survival was measured in months, from the date of diagnosis to the date of censoring or death.

The 5-year survival of patients with prostate cancer by cancer stage and by ethnicity was estimated using the Kaplan-Meier method. A Cox proportional-hazards regression model was used to examine the effect of ethnicity (Māori, NZ European), biopsy Gleason score (6, 7 or 8+), comorbidities

(Charlson score 0 or 1+) and primary treatment (active treatment or AS/WW) on all-cause and cancer-specific survival by cancer stage.

4.3 Results

4.3.1 Overview

Of the 600 men who had a detailed review, 65 (15 Māori and 50 NZ European) were excluded. Reasons for exclusion were a diagnosis before 2007 (20 men), misdiagnosis (including 3 bladder cancer cases, and 9 cases were histology recorded as benign or a Gleason score <6), or the cancer extent could not be confirmed due to missing information (32 men).[12]

Not every patient had a biopsy- e.g. those diagnosed with metastatic disease by imaging and clinical examination. Similarly those with positive biopsy and normal DRE usually did not have imaging and were classified as localised cancer. Of the 535 patients, 507 had histology or pathology records, 230 had imaging, 357 had DRE and 499 had PSA records. These records were examined by 3 researchers (C.Lao, R.Lawrenson and Z. Obertová) and the cancer extent was decided first based on the imaging results, then based on histology or pathology results and DRE results. In 515 cases stage seemed straightforward. In 20/535 (4%) cases stage was uncertain due to ambiguous results and so the urologist was invited to discussion.

Among the 535 eligible men, 407 were diagnosed with localised prostate cancer, 63 were locally-advanced and 65 had metastatic prostate cancer (Table 22). The median follow-up time was 4.7 years for patients diagnosed with localised prostate cancer, 4.5 years for patients diagnosed with locally-advanced prostate cancer and 1.6 years for patients diagnosed with metastatic prostate cancer.

Table 22. Patients' characteristics at baseline

	Localised	Locally-advanced	Metastatic
Age at diagnosis			
40-59 years	108 (83%)	16 (12%)	6 (5%)
60-69 years	200 (83%)	19 (8%)	21 (9%)
70-79 years	83 (65%)	22 (17%)	23 (18%)
80+ years	16 (43%)	6 (16%)	15 (41%)
Ethnicity			
Māori	96 (71%)	13 (10%)	26 (19%)
NZ European	311 (78%)	50 (13%)	39 (10%)
Biopsy Gleason score			
6	243 (93%)	16 (6%)	2 (1%)
7	119 (78%)	22 (14%)	11 (7%)
8-10	41 (46%)	21 (24%)	27 (30%)
Unknown	4 (12%)	4 (12%)	25 (76%)
Charlson Comorbidity Index			
0	195 (83%)	24 (10%)	15 (6%)
1+	212 (70%)	39 (13%)	50 (17%)
Treatment			
Active treatment	311 (72%)	59 (14%)	63 (15%)
Active surveillance/watchful waiting	88 (97%)	3 (3%)	0 (0%)
Unknown	8 (73%)	1 (9%)	2 (18%)
Overall	407 (76%)	63 (12%)	65 (12%)

During the follow-up period, 99 men died. Sixty two men (63%) died of prostate cancer (Four initially diagnosed with localised cancer, eight with locally advanced and 50 with metastatic disease) and 37 died from other causes (27 diagnosed with localised disease, five locally advanced and five metastatic disease). The survival of these patients by cancer stage estimated by the Kaplan-Meier method is shown in Table 23, Figure 16 and Figure 17. After 5 years from the initial diagnosis, 92.4% of patients diagnosed with localised prostate cancer were still alive, compared to 82.1% of men with locally-advanced prostate cancer and only 17.6% of men with metastatic disease. The mortality rate

for men with metastatic prostate cancer was highest in the first two years from diagnosis: 30.8% of patients died within 12 months and 63.1% within 24 months.

Table 23. Survival by cancer extent by Kaplan-Meier method

Cancer extent	All-cause survival Estimate (Standard error)			Cancer-specific survival Estimate (Standard error)		
	1 years	2 years	5 years	1 year	2 years	5 years
All patients	95.0% (0.9%)	89.2% (1.3%)	82.1% (1.8%)	97.2% (0.7%)	92.7% (1.1%)	88.3% (1.5%)
Localised	98.3% (0.6%)	96.8% (0.9%)	92.4% (1.5%)	100.0% (-)	100.0% (-)	98.6% (0.7%)
Locally-advanced	100.0% (-)	93.7% (3.1%)	82.1% (5.3%)	100.0% (-)	96.8% (2.2%)	88.8% (4.5%)
Metastatic	69.2% (5.7%)	36.9% (6.0%)	17.6% (5.2%)	75.3% (5.5%)	40.1% (6.3%)	19.1% (5.6%)
Ethnicity						
Māori	90.4% (2.5%)	82.2% (3.3%)	72.5% (4.0%)	94.7% (1.9%)	88.4% (2.8%)	80.3% (3.7%)
NZ European	96.5% (0.9%)	91.5% (1.4%)	85.4% (1.9%)	98.0% (0.7%)	94.1% (1.2%)	90.9% (1.6%)

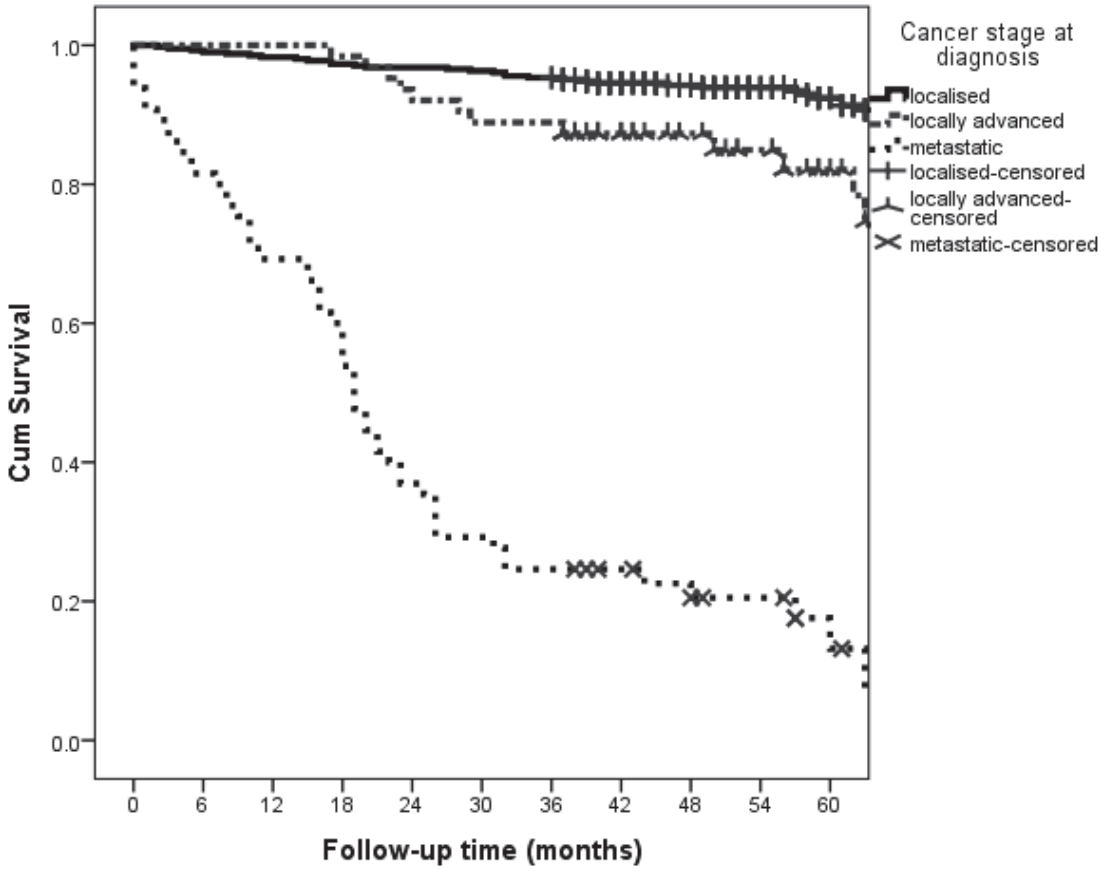

Figure 16. All-cause survival by cancer extent by the Kaplan-Meier method

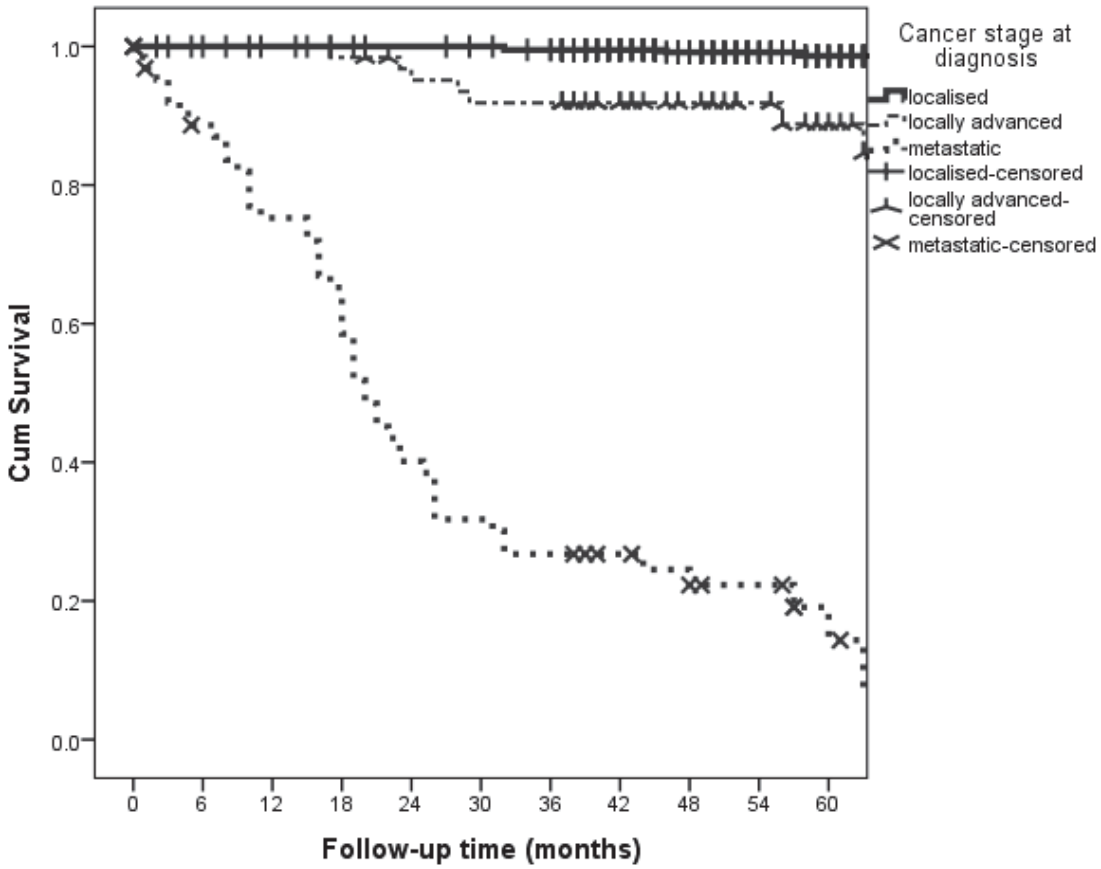

Figure 17. Cancer-specific survival by cancer extent by the Kaplan-Meier method

The 5-year cancer-specific survival for men diagnosed with localised prostate cancer was 98.6%, compared to 88.8% for men diagnosed with locally-advanced prostate cancer and 19.1% for men diagnosed with metastatic prostate cancer. The 1-year and 2-year cancer-specific survival for men diagnosed with metastatic prostate cancer was 75.3% and 40.1%, respectively.

4.3.2 Survival difference between Māori and NZ European men

Of the 62 men who died of prostate cancer, 24 were Māori and 38 were NZ European. Another 12 Māori and 25 NZ European died from other causes. Overall, the all-cause survival and the cancer-specific survival (Table 23, Figure 18 and Figure 19) were both significantly poorer for Māori men than for NZ European men (log rank test: p=0.004, 0.006, respectively). The hazard ratio (HR) of cancer-specific survival for Māori men was 2.01 (95% CI: 1.21-3.36) compared with NZ European.

For men with localised prostate cancer, there was no significant difference in either all-cause survival or cancer-specific survival between the two groups (Table 24) after adjustment for age, Charlson score, primary treatment and Gleason score. The HR of cancer-specific mortality in Māori men with locally-advanced prostate cancer compared to NZ European men with locally-advanced prostate cancer, after adjustment for age, Charlson score and Gleason score was 6.1 (95% CI: 1.0-35.9). The

difference in survival for men with metastatic prostate cancers was not statistically significant between Māori and NZ European men when controlling for age and Charlson score.

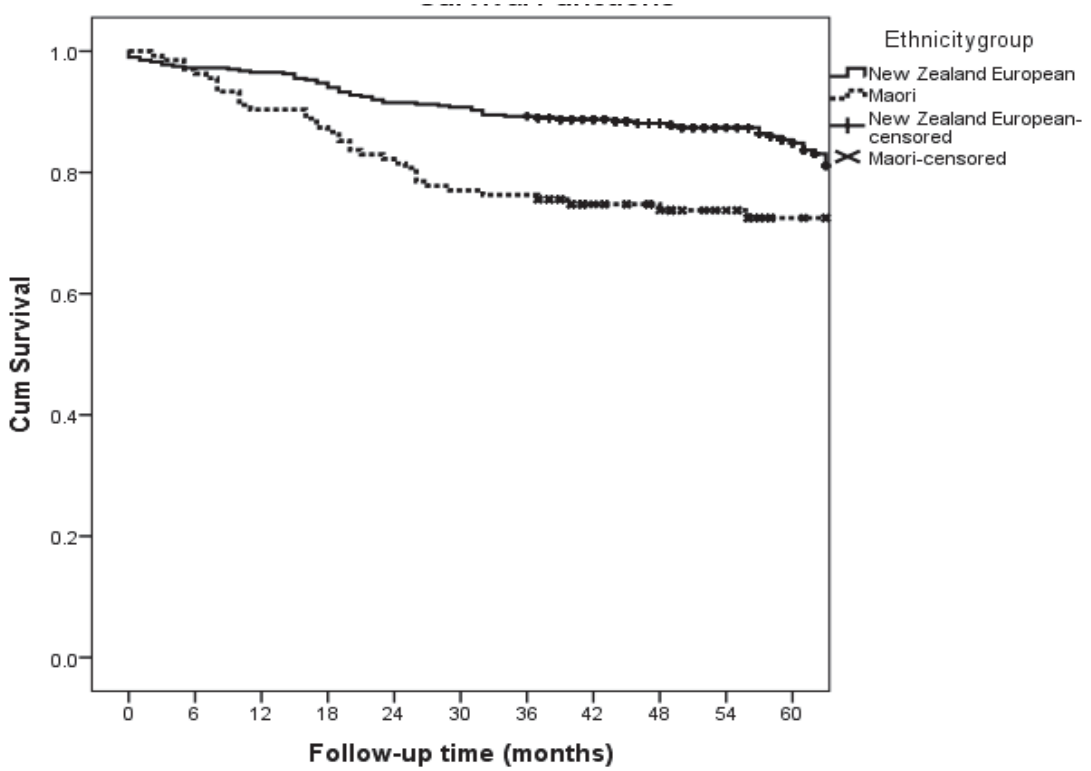

Figure 18. All-cause survival by ethnicity by the Kaplan-Meier method

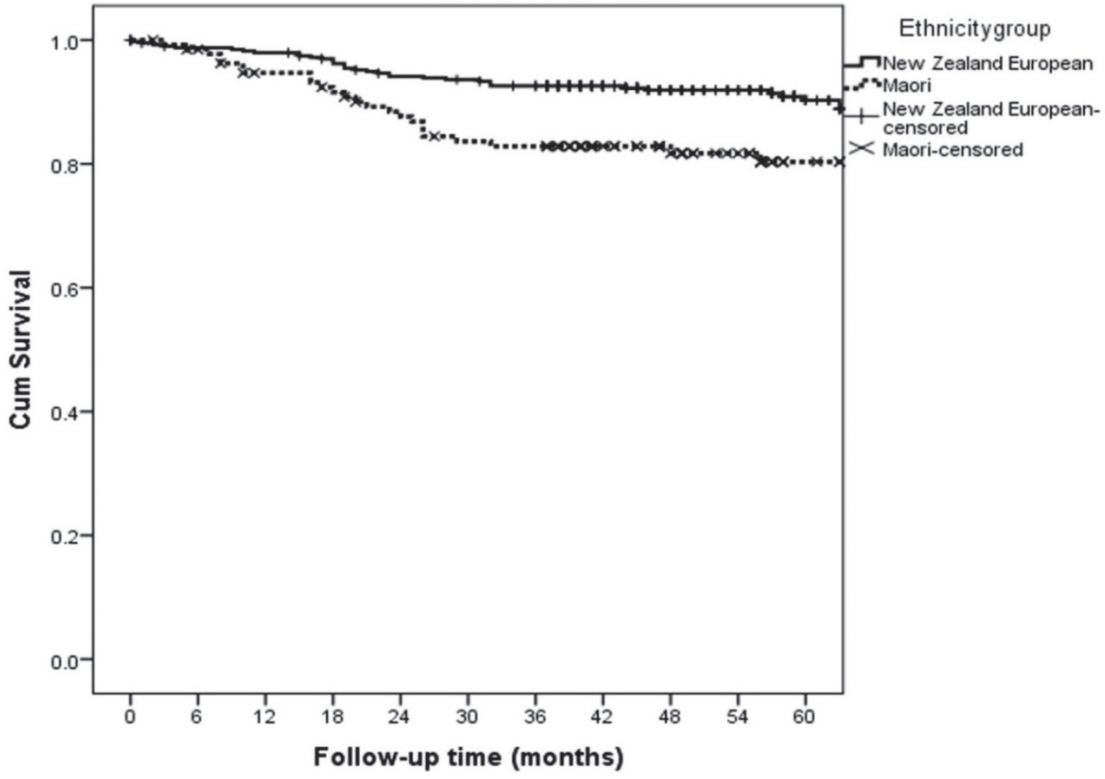

Figure 19. Cancer-specific survival by ethnicity by the Kaplan-Meier method

4.3.3 The effects of comorbidities, treatment and biopsy Gleason score

After adjustment for patients' age, ethnicity, biopsy Gleason score and treatment, the HR of all-cause death for men with localised prostate cancer and a Charlson score 1+ compared to those with Charlson score 0 was 4.1 (95% CI: 1.4-12.0) (Table 24). The effects of comorbidities were not substantial on the survival for men with locally-advanced or metastatic prostate cancer.

The effect of active treatment on all-cause survival was examined for men with localised prostate cancer compared with AS/WW. No significant differences were identified. There were not enough patients under AS/WW in the locally-advanced group and metastatic group to examine the effect of primary treatment.

Gleason score was only examined as a potential risk factor in men with locally-advanced disease. It was not considered in those with localised disease because so few men died of prostate cancer – a re-analysis after a follow-up of 10 years or more may be more productive. In men with metastatic disease, almost 40% had no biopsy data available and only 2/65 men had Gleason score of 6 suggesting further analysis would be unproductive. In those with locally-advanced disease, there were only 8/63 deaths from prostate cancer – of which 5/21 were in men with a Gleason score 8+. The HR for all cause and cancer-specific mortality for men with a Gleason score 8+ compared with those with a Gleason score 6 were both over 5, but with wide confidence intervals.

Table 24. Effects of variables on the survival: results from Cox proportional-hazards regression models

Examined factors	Adjusted factors	All-cause survival		Cancer-specific survival	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Localised *					
Māori vs NZ European	Age, Charlson score, treatment, Gleason score	1.76 (0.79-3.95)	0.169	-	-
Charlson score 1+ vs 0	Age, ethnicity, treatment, Gleason score	4.09 (1.39-11.99)	0.010	-	-
Treatment vs AS/WW	Age, ethnicity, Charlson score, Gleason score	1.18 (0.48-2.91)	0.716	-	-
Gleason score 7 vs 6	Age, ethnicity, Charlson score, treatment	0.97 (0.40-2.34)	0.939	-	-
Gleason score 8+ vs 6	Age, ethnicity, Charlson score, treatment	1.35 (0.48-3.83)	0.569	-	-
Locally-advanced †					
Māori vs NZ European	Age, Charlson score, Gleason score	2.49 (0.59-10.50)	0.213	6.09 (1.03-35.92)	0.046
Charlson score 1+ vs 0	Age, ethnicity, Gleason score	1.67 (0.35-7.91)	0.521	1.53 (0.17-13.91)	0.706
Gleason score 7 vs 6	Age, ethnicity, Charlson score	2.17 (0.33-14.38)	0.423	0.81 (0.07-10.08)	0.872
Gleason score 8+ vs 6	Age, ethnicity, Charlson score	5.65 (1.06-30.25)	0.043	5.13 (0.77-34.39)	0.092
Metastatic ‡					
Māori vs NZ European	Age, Charlson score	0.94 (0.54-1.65)	0.828	1.14 (0.63-2.06)	0.658
Charlson score 1+ vs 0	Age, ethnicity	1.12 (0.57-2.20)	0.747	0.94 (0.47-1.88)	0.861

* The effects of variables on cancer-specific survival for men diagnosed with localised prostate cancer was not estimated, because only 4 (<1%) patients diagnosed with localised cancer died of prostate cancer.

† Only 5% of men with locally-advanced prostate cancer were on AS/WW, therefore the effect of primary treatment was not considered in the model.

‡ Primary treatment and biopsy Gleason score was not used in the model, because no men with metastatic prostate cancer were on AS or WW, 25 (38%) men had no biopsy information and only 2 (3%) men had a Gleason score of 6.

4.4 Discussion

4.4.1 Survival comparison with other studies

Survival information is essential for decision making for the management of prostate cancer. The survival was poorer for men with metastatic prostate cancer. Of the 62 men who died of prostate cancer, 50 (80.6%) had metastatic prostate cancer at the initial diagnosis. The survival (especially the cancer-specific survival) in a cohort of men with prostate cancer depends on the proportion of metastatic prostate cancer cases. This assumption was confirmed in a study conducted among three Nordic countries.[183] The percentage of metastatic prostate cancer in all prostate cancer cases was 43% in Denmark, 20% in Iceland and 19% in Sweden, and the respective 5-year relative survival were 43% (38% - 49%), 75% (67% - 84%) and 72% (66% - 78%).[183] The proportion of metastatic disease in all new prostate cancer cases was 11% in our study which was lower than that in the three Nordic countries. The lower proportion of metastatic disease in new prostate cancer cases can be linked to the high screening rate in New Zealand despite routine prostate cancer screening not being recommended.[4,93] The 5-year cancer-specific survival (88.3%) in this cohort was better than the survival in the three Nordic countries[183] and the survival in the UK (81%),[289] but was worse than the survival in the US (99%).[10] In the US, prostate cancer screening is more common and more asymptomatic low risk prostate cancer cases are identified.[10]

In men with metastatic prostate cancer, the 2-year cancer-specific survival (40.1%) was poorer than the survival in the UK (60%). There was a smaller gap between the 5-year cancer-specific survival rates: 19.1% in this cohort; 32.6% (95% CI: 30.4% - 34.9%) in the UK.[289] The reason for the comparatively poor survival for men with metastatic prostate cancer in New Zealand is uncertain. It may reflect a group of men with more advanced disease than men diagnosed as metastatic in other countries. It may also reflect less aggressive treatment including less use of chemotherapy which can prolong a patient's lives in some cases.[112]

4.4.2 The effects of ethnicity, comorbidities, treatment and biopsy Gleason score

The survival for Māori men was poorer than the survival for NZ European men. The differences might be attributable to the later presentation and multiple comorbidities for Māori men.[33] Māori men are half as likely to be screened compared to non-Māori men,[21] which can explain the lower proportion of localised cancer cases and a higher proportion of metastatic disease in Māori men: 19.1% of prostate cancer cases in Māori men were metastatic at diagnosis compared to 9.8% in NZ European. It is uncertain whether prostate cancer screening can save lives,[8] but lead time bias[131] caused by screening will have a significant impact on the more favourable survival in NZ European men. When the data was partitioned by stage, the only significant difference in survival for Māori was seen in those with locally advanced disease. Although the numbers are small, this is consistent with our findings using cancer registry data where the greatest difference in survival between Māori and non-Māori was in those with locally advanced cancer.[33]

The proportion of Māori men (70%) having at least one comorbidity was higher than the proportion applying to NZ European (52%). This is important when considering all-cause mortality in men with localised disease. When the effect of ethnicity on survival was examined by cancer stage, the impact on cancer-specific survival for Māori men with locally-advanced prostate cancer was significant (hazard ratio: 6.1, 95%CI: 1.03-35.92). This may be partly an artefact in that Māori are less likely to be treated with prostatectomy which may influence the staging. Minimal invasion outside the prostate recorded after surgical excision of the gland does lead to increased diagnosis of locally-advanced disease compared to men who have only been assessed by a digital rectal examination and local imaging. However the disparity in this sub-group of patients does warrant further investigation. Ethnicity did not affect the survival for men with localised disease but this may be due to insufficient follow-up time. In the small number of men with metastatic disease, ethnicity was also not a significant factor to survival differences.

No survival difference for men with localised prostate cancer by primary treatment was identified. The median follow-up time in this study was only 4.7 years however. To show any survival difference (if there is any) for men with localised prostate cancer by treatment regime, a follow-up period of at least 10 years is likely to be required.[286,290] Studies with more than 10 years follow-up have shown that radical prostatectomy was associated with a more favourable survival for men with localised or locally-advanced prostate cancer compared with radiotherapy or AS/WW.[286,291] The all-cause survival for men with localised prostate cancer was mainly affected by the presence of comorbidities. Other-cause mortality rate or all-cause mortality rate for men with localised prostate cancer increases with the number of comorbidities.[280,292]

It has been demonstrated that the Gleason score is an important prognostic factor for non-metastatic prostate cancer.[293] Although this was not demonstrated in localised cancer, the data in locally-advanced cancer are consistent with the grade of cancer being an important prognostic indicator-although again this finding is based on a small number of deaths and maybe a chance finding.

4.4.3 Strengths and limitations

One of the strengths of this study is that patients' clinical files were each examined to identify the cancer extent at diagnosis. These data are rarely available in the NZCR. The cancer extent is vital for predicting the prognosis, advising patients and determining treatments. Data concerning five factors that might affect survival were collected, including age, ethnicity (our sample included 25% Māori), primary treatment, comorbidities and biopsy Gleason score. The cause of death was identified for each case. Men with localised prostate cancer were more likely to die from other causes rather than of prostate cancer, while most men with metastatic prostate cancer died of prostate cancer itself.

This study has several limitations. As the data were aged matched in order to compare the treatment of Māori men compared with NZ European and Māori tend to be younger, our cohort is slightly younger than a random sample. Some potential survival differences among subgroups might not have

been detected due to the relatively short follow-up time in this study (less than 10 years). The number of deaths was relatively small. However this is still one of the largest New Zealand studies of men with prostate cancer where accurate staging has been recorded. Since all the prostate cancer cases were identified in the Midland Cancer Network region, the results may not be generalisable to other regions in New Zealand or to other countries.

4.5 Conclusion

As expected survival in men with localised prostate cancer was excellent and those who did die were more likely to die of other diseases associated with the presence of co-morbidities rather than of prostate cancer. Five-year survival for men with metastatic disease was only 17.6% with 50/55 (91%) of the men dying of prostate cancer. The greatest disparities for Māori men were their increased risk of having more advanced disease at diagnosis. The residual difference in outcomes may be due to differences in treatment for Māori – and thus the disparities in survival might be improved by better management of men with higher risk disease.

4.6 Summary of Chapter 4

This Chapter included 535 men (135 Māori and 400 NZ European men) diagnosed with prostate cancer in the Midland Cancer Network region in 2007-2010. The 5-year cancer-specific survival was 98.6% for men diagnosed with localised prostate cancer, 88.8% for locally advanced disease and 19.1% for metastatic cancer. The cancer-specific survival for Māori men was worse with a hazard ratio of 2.01 compared with NZ Europeans. Most men with prostate cancer are diagnosed with localised disease and have an excellent prognosis. However, survival in men with metastatic prostate cancer is poor and seems worse than in other countries. Māori men were at risk of having more advanced disease at diagnosis, which explains some of their inequity in survival.

Chapter 6 and Chapter 7 used life-time Markov models to examine the cost-effectiveness of active surveillance compared to radical prostatectomy for men with low risk and intermediate risk localised prostate cancer. This chapter provides important local survival information for the model construction. Since survival in New Zealand men with metastatic prostate cancer is worse than in other countries. The transition probability from metastatic prostate cancer to death of prostate cancer needs to be based on local data. The survival of men with localised prostate cancer in New Zealand was consistent with international data. Therefore, the risk of cancer progression from localised prostate cancer can use the SPCG-4 study[80] results with a much longer follow-up and detailed information.

Chapter 5. The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for low risk localised prostate cancer

5.1 Introduction

In New Zealand, 3,000 new prostate cancer cases are diagnosed every year,[79] of which 76% are localised at diagnosis.[12] The 5-year cancer-specific survival for men diagnosed with localised prostate cancer is almost 100% (refer to chapter 4), and the 15-year cancer-specific survival is 80%.[80] According to the D'Amico risk classification system, localised prostate cancer can be stratified into low risk (biopsy Gleason score ≤6, clinical stage T1c-T2a and PSA level ≤10 ng/mL), intermediate risk (biopsy Gleason score 7, clinical stage T2b and PSA level (10, 20] ng/mL) and high risk (biopsy Gleason score 8-10, clinical stage T2c and PSA level >20 ng/mL).[113] Patients in these three groups have statistically significant differences in biochemical recurrence-free survival, progression-free survival and cancer-specific survival.[80,113] In the SPCG-4 study,[80] 10.2% of men with low risk, 15.1% of men with intermediate risk and 33.1% of men with high risk localised prostate cancer died of prostate cancer in 18 years after radical prostatectomy. For men under watchful waiting, 14.0% of men with low risk, 39.3% of men with intermediate risk and 35.7% of men with high risk localised prostate cancer died of prostate cancer in 18 years.[80]

Radical prostatectomy is the most common treatment for patients diagnosed with localised prostate cancer in New Zealand,[12] though it can cause urinary, sexual and gastrointestinal problems.[147] Active surveillance was introduced to prevent overtreatment and reduce costs while preserving the option of radical prostatectomy.[294] It was suggested to be a good alternative for patients with low risk localised prostate cancer,[266] since these cancer cases are unlikely to progress or to be fatal.[80] Though men under active surveillance do not experience radical prostatectomy and its complications, they need to have regular biopsies and might suffer from biopsy complications, anxiety and depression.[14,17] Watchful waiting has mainly been used in patients with a life expectancy less than 10 years, but it was included in two big randomised clinical trials to be compared with radical prostatectomy for men diagnosed with localised prostate cancer.[15,80] If there is no survival difference between men under watchful waiting and men undergoing radical prostatectomy, watchful waiting might be a reasonable option for men diagnosed with low risk localised prostate cancer or men with localised prostate cancer at all risk levels.

The SPCG-4 study showed that for men diagnosed with localised prostate cancer, being in the radical prostatectomy group was associated with better clinical outcomes (less local progression, metastatic disease and cancer-specific deaths) compared to men under watchful waiting after 18 years of follow-up.[80] However, the PIVOT study found no survival difference between the radical prostatectomy group and the observation group.[15] The inconsistent results might be associated with the different cohorts

and the different proportions of men with a long follow-up time. Only 5% of men in the SPCG-4 study were identified by screening,[295] while 76% of the prostate cancer cases in the PIVOT study were detected by PSA testing.[133] The mean age of enrolled men was 65 in the SPCG-4 study,[295] and was 67 in the PIVOT study.[133] Approximately 45% of men in the SPCG-4 study[80] compared to 5% in the PIVOT study[15] had 15 years follow-up.

Active surveillance was found to be cost-effective compared to radical prostatectomy for men diagnosed with low risk localised prostate cancer in other countries,[266,268] yet it has not been examined in a New Zealand context. The costs of active surveillance are minor in the first year compared to the costs of radical prostatectomy that are mostly incurred in the first year. However, the costs of active surveillance for men diagnosed at a younger age might be substantial and might exceed the costs of radical prostatectomy in a long term period.[266] This study aims to evaluate the cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for men diagnosed with low risk localised prostate cancer at different age groups in a New Zealand setting.

5.2 Methods

The methods in this study included an overview of the model construction, the transition probabilities attached to the model, the quality of life inputs, economic inputs, half-cycle correction, cost-effectiveness analysis, probabilistic sensitivity analysis, scenario analysis and expected value of perfect information.

5.2.1 Model construction

Based on the natural history of localised prostate cancer (please refer back to Chapter 1), an economic model (Figure 20) consisting of three Markov models (three treatment arms: watchful waiting, active surveillance and radical prostatectomy) was constructed. The cycle length was 1 year per cycle, considering the slow-growing nature of localised prostate cancer.[37] The model construction and data analysis were performed in TreeAge Pro 2015. Monte Carlo Simulation – Sampling + Trials was used, with 1000 2nd-order parameter samples (probabilistic sensitivity analysis) and 10,000 1st-order simulation trials (microsimulation). In the probabilistic sensitivity analysis, 1000 values were sampled from the distribution of each model parameter, and 10,000 men were simulated at each trial. Men diagnosed with low risk localised prostate cancer at the age of 45, 50, 55, 60, 65 and 70 years old were simulated. The simulation ended when the patient died or reached the age of 100 years old.

The health states in the model included ‘Localised’, ‘Post-surgery’, ‘Local progression’, ‘Metastatic’, ‘Death from prostate cancer’ and ‘Death from other causes’. Men in every health state could either stay in the same health state or transit to other health states (Figure 20). As shown in the influence diagram for radical prostatectomy (Figure 20 a), all men with low risk localised prostate cancer in the radical prostatectomy arm were assumed to have the surgery and move to ‘Post-surgery’ in the first

year. Therefore, men in all health states except those in the 'Localised' might die from other causes. After the surgery, men in 'Post-surgery' might have 'Local progression' or develop 'Metastatic' disease. Men with locally advanced or metastatic prostate cancer were assumed to be treated with hormone therapy and external beam radiotherapy. In the SPCG-4 study,[80] some men diagnosed with localised prostate cancer in both treatment arms developed metastatic disease in the first year. Therefore, some metastatic cases were assumed to develop directly from 'Localised' or 'Post-surgery' in this model. Men with metastatic disease might die of prostate cancer.

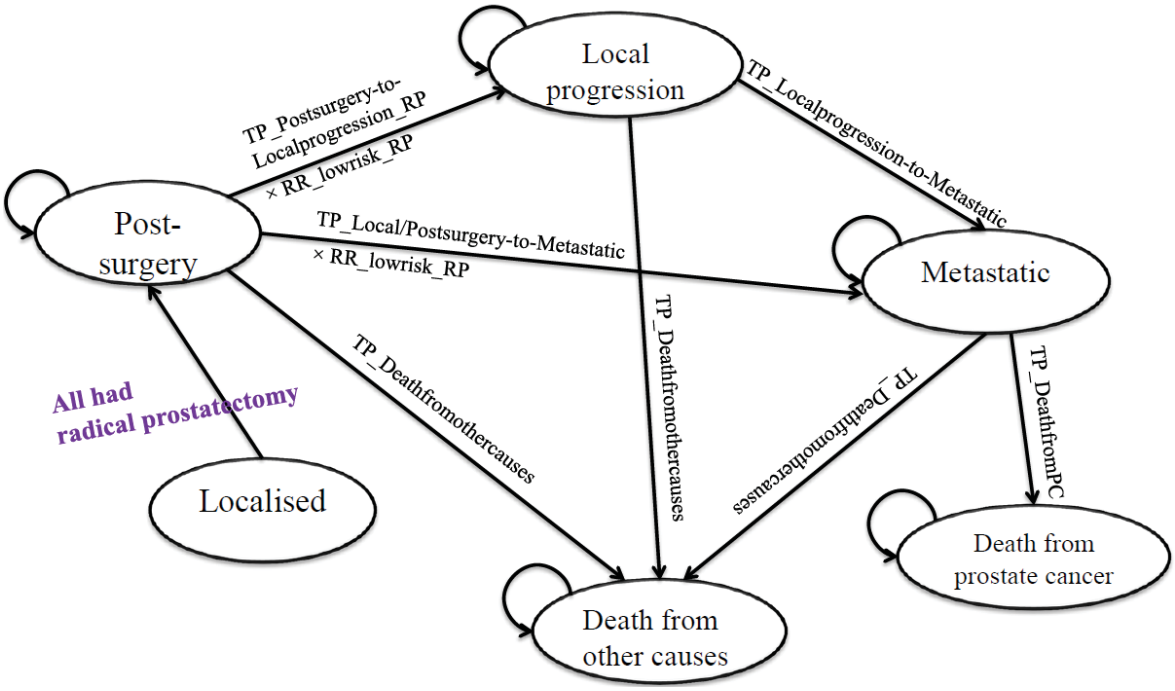

Figure 20 a. Influence diagram of the Markov model for radical prostatectomy

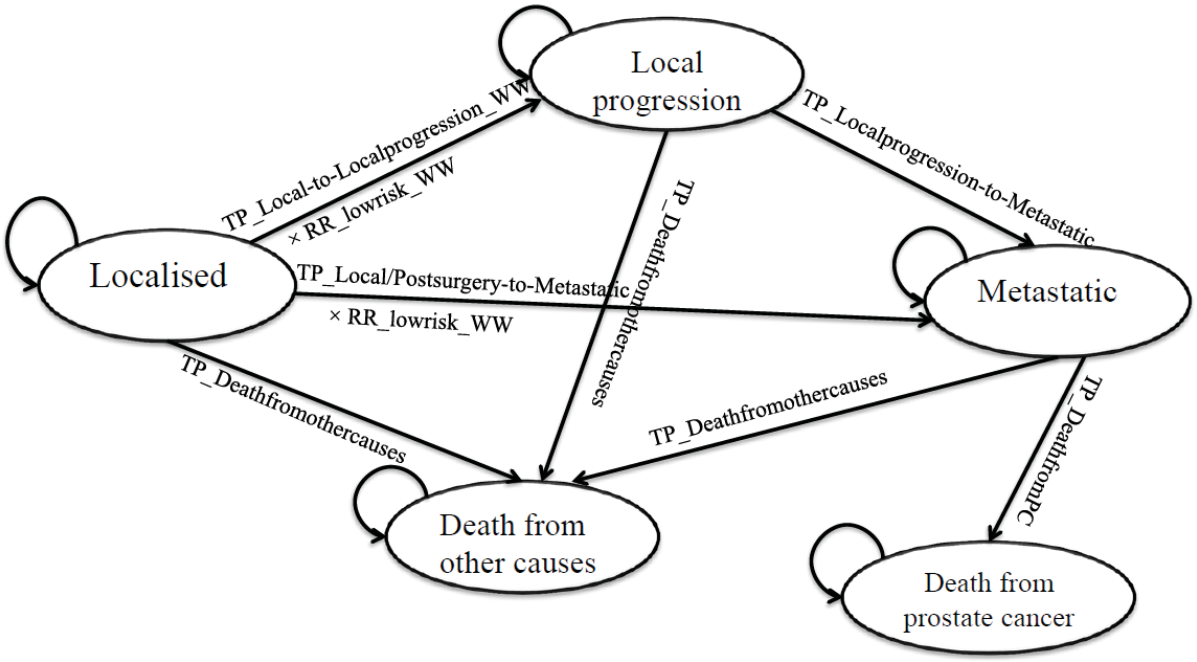

Figure 20 b. Influence diagram of the Markov model for watchful waiting

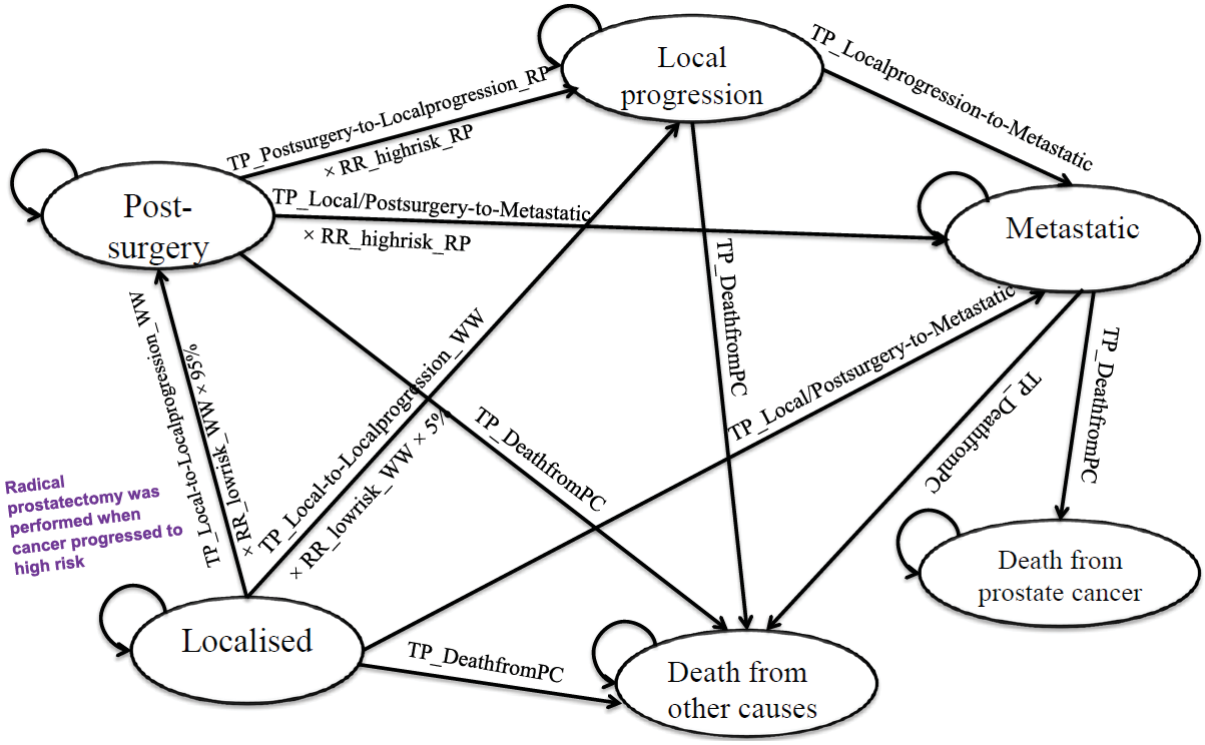

Figure 20 c. Influence diagram of the Markov model for active surveillance

Figure 20. Economic model of treatments for low risk localised prostate cancer

In the watchful waiting arm, Men with localised cancer would not receive radical treatment. They might develop from 'Localised' to 'Local progression' or 'Metastatic' disease (Figure 20 b). Men in all health states might die from other causes. Other parts of the model were the same as the model for radical prostatectomy.

Men under active surveillance were closely monitored and would have radical prostatectomy when high risk cancer was detected (Figure 20 c). In the active surveillance arm, patients were assumed to have radical prostatectomy when high risk localised prostate cancer was detected under the age of 75 years old, and were assumed to switch to watchful waiting (no more biopsy or radical prostatectomy) when they reached the age of 75 years old.

The arrows indicated all possible transitions among health states. The transition probabilities showed in the influence diagrams were demonstrated in 5.2.2. Between the biopsy/imaging intervals in the active surveillance arm, interval cancer progression might occur. Therefore, 95% of men who developed high risk cancer were assumed to be captured and receive radical prostatectomy, and 5% of men who developed high risk cancer were assumed to be not captured and develop local progression. The annual probability of progression to high risk localised prostate cancer was assumed to be equal to the annual probability of having local progression from low risk localised prostate cancer in the watchful waiting arm. After radical prostatectomy, the transition probabilities from 'Post-surgery' to 'Local progression' or to 'Metastatic' in the active surveillance arm were based on the transition probabilities for high risk patients.

This study was from the perspective of the Ministry of Health in New Zealand, therefore only direct medical costs were considered. It is difficult to identify from the hospital events which events were associated with prostate cancer (and related complications) and which events were not. However, events in urology and related pharmaceuticals are more relevant to men with low risk localised prostate cancer who chose active surveillance, watchful waiting or radical prostatectomy, and events in urology, oncology, palliative and terminal care and related pharmaceuticals are more relevant to men with locally advanced and metastatic prostate cancer. The estimated costs excluded goods and services tax (GST) and were valued in 2012/13 New Zealand dollars (NZ$). A 3.5% discount rate was applied for future costs and utilities.

5.2.2 Transition probabilities

The transition probabilities to 'Local progression' from 'Post-surgery' in the radical prostatectomy arm and from 'Localised' in the watchful waiting arm were based on the SPCG-4 study published in 2008.[296] Though more recent results of the SPCG-4 study were published in 2011 and in 2014,[80,297] the results of local progression were not presented in these two studies.

The transition probabilities to 'Local progression' from 'Localised' or from 'Post-surgery' were estimated using similar method as the one used in the study published by Guyot[298] and colleagues.

The cumulative hazard of local progression in the SPCG-4 study was digitalized (Table 25). The rates of local progression were estimated based on the cumulative hazard and were converted into transition probabilities (Table 26). The conversion of rates to probabilities was based on the following equation: tp= 1-EXP(-r*t); tp: transition probability; r: rate; t: time unit (note that the unit of time used in r and tp must be the same).[299]

Table 25. Digitalized cumulative incidence of local progression in the SPCG-4 study

Follow-up time	Radical prostatectomy (from post-surgery)	Watchful waiting (from localised cancer)
Beginning	0.0%	0.0%
2nd year	3.5%	8.6%
4th year	7.2%	22.7%
6th year	11.0%	34.2%
8th year	14.1%	38.5%
10th year	17.9%	41.7%
12nd year	21.6%	45.7%

Table 26. Average biennial transition probabilities to 'Local progression' in the SPCG-4 study

Follow-up time	Radical prostatectomy (from post-surgery)	Watchful waiting (from localised cancer)
first 2 years	0.0176	0.0433
Year 3 and 4	0.0201	0.0788
Year 5 and 6	0.0219	0.0779
Year 7 and 8	0.0208	0.0379
Year 9 and 10	0.0296	0.0347
Year 11 and 12	0.0427	0.0633

The correlation between follow-up time and transition probabilities was examined using linear regression. The correlation between follow-up time and transition probability to 'Local progression' was strong (Figure 21: R^2=0.7405) in the radical prostatectomy arm, but was much weaker (Appendix 2: R^2=0.1750) in the watchful waiting arm. Therefore, a time dependent annual transition probability from 'Post-surgery' to 'Local progression' was used in the radical prostatectomy arm (0.0152 (SE: 0.0026) + 0.0012 (SE: 0.0004) × T; T: time (years) from radical prostatectomy), and a constant (time independent) annual transition probability from 'Localised' to 'Local progression' was estimated in the watchful waiting arm (Mean: 0.0565; SE: 0.0098).

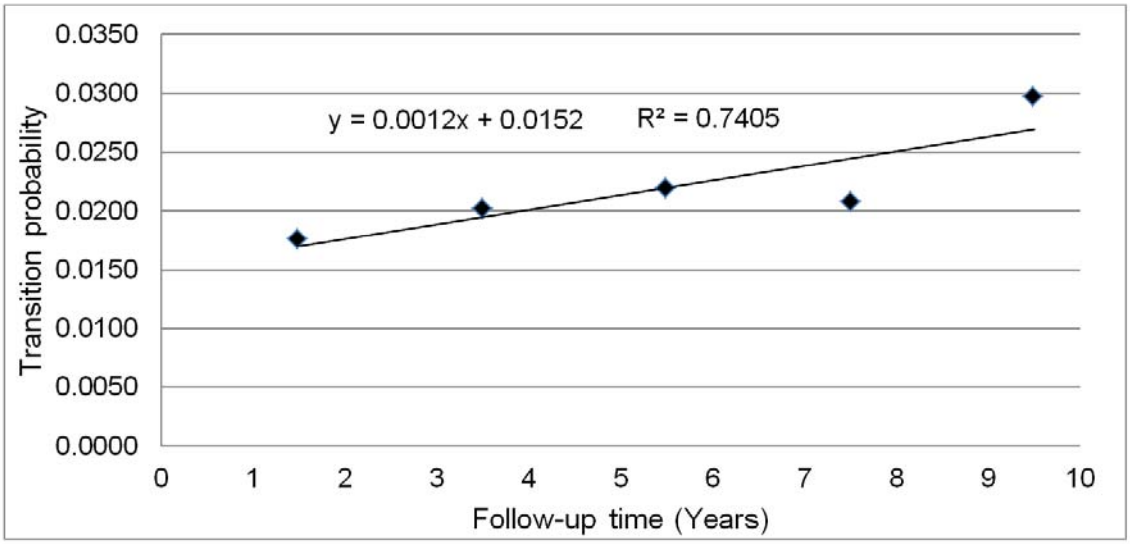

Figure 21. Correlation between follow-up time and transition probability to 'Local progression' from 'Post-surgery' in the radical prostatectomy arm in the SPCG-4 study

The constant (Mean: 0.0152; SE: 0.0026) and the slope (Mean: 0.0012; SE: 0.0004) in the transition probability from 'Post-surgery' to 'Local progression' in the radical prostatectomy arm were negatively correlated. To incorporate the correlation into the probabilistic sensitivity analysis, the cholesky decomposition was used.[211] The Cholesky decomposition provides correlated draws from a multivariate normal distribution, and starts from a variance-covariance matrix in the regression. The estimated variance-covariance matrix in the regression (0.0152 (SE: 0.0026) + 0.0012 (SE: 0.0004) × T) is shown in Table 27. The Cholesky decomposition was $\begin{vmatrix} \sigma 1 & 0 \\ a & b \end{vmatrix} = \begin{vmatrix} 0.0004 & 0 \\ -0.0023 & 0.0012 \end{vmatrix}$.

Table 27. Variance-covariance matrix for the constant and the slope in the transition probability from 'Post-surgery' to 'Local progression' in the radical prostatectomy arm

	Slope	Constant
Slope	1.80E-07	-9.89E-07
Constant	-9.89E-07	6.88E-06

The transition probabilities from 'Localised'/'Post-surgery' to 'Local progression'/'Metastatic' were estimated from a cohort of men with localised prostate cancer. The relative risks of these transition probabilities for low risk, intermediate risk and high risk cancer (Table 28, Table 29) were estimated based on the proportions of different risk level patients in the SPCG-4 cohorts[80,296] and the annual probabilities of biochemical recurrence after treatment for low risk (beta distribution: Mean 1.06%; SE 0.007%), intermediate risk (beta distribution: Mean 3.74%; SE 0.020%) and high risk localised prostate cancer (beta distribution: Mean 7.05%; SE 0.034%).[267] The relative risks were calculated by Dr Richard Edlin. The calculation was performed in Excel. The overall possibility of biochemical recurrence in the two groups (the whole radical prostatectomy and watchful waiting cohort in the

SPCG-4 study) was estimated. The relative risks of cancer progression for low, intermediate and high risk cancer in the two groups were estimated by dividing the possibility by cancer risk level with the overall group possibility. The calculation was repeated 100,000 times and Gamma distribution fit the result distribution. The use of these relative risks was presented in the influence diagrams (Figure 20).

Table 28. Relative risks of for low, intermediate and high risk cancer in the radical prostatectomy arm in the SPCG-4 study

Relative risk	Risk group	Mean	SE	Distribution
RR_lowrisk_WW	Low risk	0.2947	0.0100	Gamma
RR_intermrisk_WW	Intermediate risk	1.0397	0.0347	Gamma
RR_highrisk_WW	High risk	1.9600	0.0655	Gamma

Table 29. Relative risks of for low, intermediate and high risk cancer in the watchful waiting arm in the SPCG-4 study

Relative risk	Risk group	Mean	SE	Distribution
RR_lowrisk_RP	Low risk	0.3006	0.0107	Gamma
RR_intermrisk_RP	Intermediate risk	1.0606	0.0374	Gamma
RR_highrisk_RP	High risk	1.9993	0.0703	Gamma

It was shown in the SPCG-4 study[296] that approximately 0.75% patients developed metastatic disease after 1 year follow-up, therefore the annual transition probability to metastatic disease from localised cancer or from post-surgery was assumed to be 0.0075 (SE: 0.0010). A transition probability of 0.0800 (SE: 0.0050) from local progression to metastatic disease was estimated based on the incidence of local progression[296] and the cumulative incidence of metastatic cancer[80].

The probability of death from metastatic prostate cancer was estimated based on 276 patients: 234 men diagnosed with metastatic prostate cancer in 2009-2012 in the Metastatic Prostate Cancer Project[33,300], and another 42 men diagnosed with metastatic prostate cancer in 2007-2010 in the Midland Prostate Cancer Project.[30] The 1-year, 2-year and 3-year all-cause survival was 59.9%, 37.7% and 24.1%. It was demonstrated in the Midland Prostate Cancer Project that 92% of all-cause mortality was cancer-specific. Therefore, the 1-year, 2-year and 3-year cancer-specific survival were estimated to be 65.1%, 41.0% and 26.2%. The annual probability of dying of metastatic prostate cancer was 0.3221 (SE: 0.0115).

Since prostate cancer is not amongst the top five causes of death for men, the probability of death in the life table[194] from Statistics New Zealand was used as the annual probability of dying from other causes (Appendix 3).

5.2.3 Quality of life

Considering the variation of quality of life results estimated from different instruments,[147,301] EQ-5D based quality of life results for patients in different health states was used in this model (Table 30). No utility score for patients with locally advanced prostate cancer was identified from published literature. A utility score of 0.820 for patients who received external beam radiotherapy was used as the utility of patients with local progression, because patients diagnosed with locally advanced prostate cancer are mainly treated with radiotherapy and hormone therapy. The value of quality of life ranges (-∞, 1] and gamma distribution ranges [0, ∞). Therefore gamma distribution was used for the disutility values and used 1 to minus the disutility values to estimate the utility.

Table 30. EQ-5D based quality of life results for patients at different health states

Health states	Treatment	Utility	Disutility	SE	Distribution	Sources
Post-surgery	Radical prostatectomy	0.900	0.100	0.015	Gamma	[147]
Localised prostate cancer	Watchful waiting	0.890	0.110	0.013	Gamma	[147]
	Active surveillance	0.890	0.110	0.013	Gamma	[147]
Local progression	-	0.820	0.180	0.015	Gamma	[147]
Metastatic prostate cancer: Not last year in life	-	0.688	0.312	0.019	Gamma	[302,303]
Metastatic prostate cancer: final year of life	-	0.551	0.449	0.060	Gamma	[304]

The summarised annual transition probabilities are shown in Table 31.

Table 31. Annual transition probabilities in the economic model

Transition probability	Description	Transition probabilities (Mean)	SE	Distribution	Source
TP_Local-to-Localprogression_WW	From Localised to Local progression in the watchful waiting arm	0.0565	0.0098	Beta	Bill-Axelson[296] Own calculation
TP_ Postsurgery-to-Localprogression_RP	From Post-surgery to Local progression in the radical prostatectomy arm	0.0152+0.0012T (T: time (years) from radical prostatectomy)	Constant: 0.0026; Slope: 0.0004 (Cholesky decomposition applied: Table 27)	Multivariate normal	Bill-Axelson[296] Own calculation
TP_Local/Postsurgery-to-Metastatic	From Localised or from Post-surgery to metastases	0.0075	0.0010	Beta	Bill-Axelson[80] Own calculation
TP_Localprogression-to-Metastatic	From Local progression to metastases	0.0800	0.0050	Beta	Bill-Axelson[80] Own calculation
TP_DeathfromPC	From Metastases to death from prostate cancer	0.3221	0.0115	Beta	Lawrenson[30,33]
TP_Deathfromothercauses	Death from other causes	New Zealand Period Life Tables: 2010–12	-	-	Statistics New Zealand[194]

5.2.4 Costs

To identify hospital events and pharmaceutical information for eligible patients, the National Non-Admitted Patient Collection (NNPAC), National Minimum Dataset (NMDS) and the Pharmaceutical Information Database (PHARMS) were linked through patients' NHI numbers. The censor date for these datasets was 31 December 2010. NNPAC collects national records for outpatient and emergency department events (regarded as outpatient events in this study), NMDS contains clinical data for inpatients and day patients (inpatient events), and PHARMS includes all dispensing records for subsidised pharmaceuticals. The pharmaceuticals used for prostate cancer are shown in Table 32.

Table 32. Pharmaceuticals used for prostate cancer

Type of agents	Chemical name
Anti-androgen therapies	Flutamide, bicalutamide and cyproterone
LHRH analogs	Goserelin, leuprorelin
Bisphosphonate†	Alendronate sodium, etidronate disodium, zoledronic acid and pamidronate disodium
Chemotherapeutic agents	Doxorubicin, epirubicin, paclitaxel, mitozantrone, docetaxel
Antidepressants	Amitriptyline, citalopram hydrobromide, dothiepin hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, moclobemide, paroxetine hydrochloride and venlafaxine
Urinary agents‡	Finasteride, oxybutynin, solifenacin succinate and tamsulosin hydrochloride
Alpha adrenoceptor blockers‡	Doxazosin mesylate and terazosin hydrochloride

Bisphosphonate is used for patients who are at risk of having fractures after ADT.
Urinary agents and alpha adrenoceptor blockers are used to treat urinary problems.

The estimated costs of active surveillance, watchful waiting and radical prostatectomy for localised prostate cancer included the costs of related pharmaceuticals and the costs of events in urology. Men diagnosed with localised prostate cancer undergoing active surveillance, watchful waiting and radical prostatectomy do not generally need to receive services in oncology or palliative and terminal care. Therefore the costs in oncology and palliative and terminal care department were not taken into account.

The costs of treatment for localised prostate cancer were based on the 270 men diagnosed with localised prostate cancer (44 under watchful waiting, 44 under active surveillance, and 182 undergoing radical prostatectomy) in the Midland Prostate Cancer project. For watchful waiting and active surveillance, the cost estimation started from 2 months after diagnosis (date of analysis) to exclude the diagnostic costs. For radical prostatectomy, the cost estimation started from the date when the patient was admitted for radical prostatectomy (date of analysis). One hundred and sixty six

men were excluded for the cost estimation. The exclusion reasons are shown in Table 33. Since patients under watchful waiting and patients who had radical prostatectomy would be referred back to general practice in the second year, the hospital costs were assumed to be $0 in subsequent years as long as the cancer stayed localised. This applied to patients aged 75 years and older in the active surveillance arm.

Table 33. Exclusion reasons for the cost estimation and number of men excluded

Exclusion reasons	Watchful waiting	Active surveillance	Radical prostatectomy
Date of radical prostatectomy was unknown	0	0	1
Had radical prostatectomy after 31 December 2010	0	0	19
Had external radiotherapy within 12 months from the date of analysis	0	3	18
Follow-up time was less than 12 months	17	16	44
Records of radical prostatectomy were not identified in the NNPAC or the NMDS for those who were recorded to have radical prostatectomy	0	0	48

The annual costs were estimated from those whose follow-up time in the first year and (or) subsequent years was complete, and no other treatments were received during that period. The annual costs of treatment for localised prostate cancer are shown in Table 34. The proportion of the estimated costs (costs of related pharmaceuticals and events in urology) in total costs was 8.1% ($323/$3980), 33.8% ($980/$2,898) and 78.2% ($13,527/$17,300), respectively, for watchful waiting, active surveillance and radical prostatectomy in the first year.

Table 34. Costs of treatment for localised prostate cancer

Treatment	Treatment year	Age	Patients	Mean	SE	Distribution
Watchful waiting	First year		27	$323	$193	Gamma
	Subsequent years[†]			$0	$0	
Active surveillance	First year		25	$980	$676	Gamma
	Subsequent years	<75 years	18[‡]	$812	$651	Gamma
		≥75 years		$0	$0	
Radical prostatectomy	First year		52	$13,527	$422	Gamma
	Subsequent years[§]			$0	$0	

[†] Men under watchful waiting would be referred back to their GP. Therefore no hospital costs were assumed to incur in the subsequent years for men under watchful waiting.

[‡] Only 18 men's follow-up time in the 2nd year was completed.

[§] Men undergoing radical prostatectomy were followed-up by specialists for 12 months after the surgery, and were referred back to GPs in the second year.

Among the 27 men who were under watchful waiting and were included for the cost estimation, 19 men had a Charlson score 1+, and 17 (10 of them had a Charlson score 1+) did not have any costs of urology or related pharmaceuticals. That explained why only 8.1% of the medical costs for these men under watchful waiting were used for prostate cancer.

Of the 25 men under active surveillance, two men had two biopsies, 11 had one biopsy, 12 did not have any biopsy and one (who had two biopsies) had two MRIs in the first year after the cancer diagnosis. Of the 18 men included for the cost estimation of active surveillance in the second year, only 4 men had biopsy and no men had MRI or other imaging.

In the model, patients with local progression would be treated with radiotherapy and hormone therapy which is similar to the treatment pattern for metastatic prostate cancer. The estimated costs for metastatic prostate cancer included the costs of related pharmaceuticals and the costs of events in urology, oncology and palliative and terminal care. The annual treatment costs for patients with local progression or metastatic disease (Table 35) were based on the 276 patients with metastatic prostate cancer mentioned above.[33] Forty four men were excluded because they were censored in the first year after diagnosis. There were significant differences between the costs in the first year and the costs in the subsequent years for men aged less than 80 years (Mann-Whitney U test: p=0.0010), and significant differences between the costs in the last year in life and the costs in other years for men aged 80 years (Mann-Whitney U test: p=0.0005).

Table 35. Costs of treatment for local progression and metastatic prostate cancer

Age	Treatment year	Sample size	Mean	SE	Distribution	Mann-Whitney U test
<80 years	In the 1st year	145	$8,899	$711	Gamma	p=0.010
	In the subsequent years		$6,573	$789	Gamma	
80+ years	Not last year in life	87	$3,887	$426	Gamma	p=0.005
	Last year in life		$3,438	$502	Gamma	

5.2.5 Half-cycle correction

In Markov models, all state transitions are assumed to occur simultaneously at the end of each cycle. However, in reality, they happen on average half way through a time interval. This can be adjusted by half-cycle correction where half of the initial and final rewards (cost and effectiveness rewards) of each health state were included in cost estimation.[305] The initial reward is the reward in the first cycle in each health state and the final reward is the reward in the last cycle. Half-cycle correction was applied in rewards of all health states except the costs of 'Post-surgery' in the first year after radical prostatectomy. Men in the radical prostatectomy arm were assumed to have the surgery when they enter the simulation, and most of the costs for patients who received radical prostatectomy were

incurred in the first month (cost of surgery), therefore all (instead of half) of the initial costs should be included.

5.2.6 Cost-effectiveness analysis

The life-time costs and utilities (including number of life-years and number of QALYs) were calculated for each treatment arm. Incremental analysis was performed in terms of incremental cost-effectiveness ratio (ICER). If the willingness-to-pay value (the maximum, in monetary terms, an individual is willing to give up (from surplus income) to acquire the benefits of the intervention) was higher the ICER, the more costly and more effective treatment was considered to be cost-effective.

5.2.7 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was performed, and cost-effectiveness acceptability curves (CEAC) were constructed to indicate the likelihood of each treatment being cost-effective under a range of willingness-to-pay values.[306] The optimal option should not be based on the probability of being cost-effective but the expected net benefits, regardless of the uncertainty associated with the decision.[306,307] Compared to the CEAC, the frontier plots only the probability that the optimal option is cost-effective.[306,307] In a cost-effectiveness model, the optimal option is the one with the highest expected net benefits. The net monetary benefit can be calculated though: (incremental number of QALYs × willingness-to-pay) – incremental costs.[308,309]

5.2.8 Scenario analysis

Four scenario analyses were conducted. The first scenario analysis used an annual conversion rate of 5% from active surveillance to radical prostatectomy. The 5% conversion rate was used in the cost model built by Corcoran[168] and colleagues. With this conversion rate, 30% of men in the active surveillance arm would receive radical prostatectomy in 7 years, which was consistent with the results in a long term follow-up study for a large active surveillance cohort.[160] The second scenario analysis was carried out using an average quality of life value of 0.83 (SE: 0.020) for men under active surveillance and 0.80 (SE: 0.022) for men after treatment. These values were used in the economic model built by Hayes JH and colleagues.[169,266] The third scenario analysis used new economic inputs for men with localised prostate cancer undergoing watchful waiting, active surveillance and radical prostatectomy. The annual costs for men under active surveillance were estimated based on the New Zealand guidance on using active surveillance to manage men with low risk prostate cancer.[163] Men under watchful waiting and men undergoing radical prostatectomy were assumed to be followed-up by specialists for 12 months and then referred back to GPs. The included medical resources and estimated costs for each treatment arm are shown in Table 36. The fourth scenario analysis used the

5% annual conversion rate from active surveillance to radical prostatectomy, new quality of life inputs and economic inputs.

Table 36. Scenario analysis: annual medical resources consumption for men in different treatment arms

Treatment	Year		Costs	Medical resources
Watchful waiting	First year		NZ$241	Annual PSA test and one follow-up specialist consultation
	Subsequent years		NZ$0	Referred back to GPs
Active surveillance	First year		NZ$1,715	One biopsy, following pathology report, hospitalization due to biopsy complications, 3-monthly PSA tests and two follow-up specialist consultations
	Subsequent years	<75 years	NZ$857	0.5× (A biopsy, following pathology report, hospitalization due to biopsy complications), 6-monthly PSA tests and one follow-up specialist consultation
		≥75 years	NZ$0	
Radical prostatectomy	First year		NZ$12,372	Radical prostatectomy, hospitalization due to complications and two follow-up specialist consultations
	Subsequent years		NZ$0	Referred back to GP

5.2.9 Expected value of perfect information (EVPI)

There are uncertainties associated with the modelling results. More accurate clinical and economic information can reduce the uncertainties and provide more robust results regarding the decision of the most cost-effective treatment option. To attain the information, more research needs to be conducted and more resources need to be allocated to research. Value of information analysis demonstrates the expected value of conducting more research to support a decision.

The expected value of perfect information (EVPI) can be estimated by simultaneously eliminating uncertainty on all parameters involved in model-based decision-making.[310] 'EVPI is equal to the average of the maximum net benefits across all model iterations (i.e., the expected net benefit using perfect information), minus the maximum of the average expected net benefits across all treatment strategies (i.e., the expected net benefit using the currently available (imperfect) information).'[310,311] To inform decision maker whether more research regarding the decision is desirable, the population

EVPI needs to be estimated and be compared with the costs of research (data collection). The population EVPI can be estimated by multiplying the EVPI per person with the population at risk.[310]

5.3 Results

5.3.1 Cost-effectiveness analysis

Men in the watchful waiting arm had the lowest life-time costs but also the poorest health outcomes (both in terms of QALYs and life-years) in the five age groups (Appendix 4, Table 37). Therefore, watchful waiting was considered to be the baseline treatment. The ICERs of active surveillance and radical prostatectomy compared to watchful waiting were estimated.

Table 37. Cost per QALY gained for men with low risk localised prostate cancer

Age	Life-time outcome	Watchful waiting	Active surveillance	Radical prostatectomy	Incremental cost-effectiveness ratio (ICER)
45 years	Cost (NZ$)	$15,884	$23,396	$22,316	AS compared to WW: $8,255 per QALY; RP compared to WW: $6,432 per QALY; AS was dominated by RP
	Effectiveness (QALYs)	15.43	16.34	16.43	
50 years	Cost (NZ$)	$14,192	$21,115	$20,991	AS compared to WW: $9,231 per QALY; RP compared to WW: $7,906 per QALY; AS was dominated by RP
	Effectiveness (QALYs)	14.49	15.24	15.35	
55 years	Cost (NZ$)	$12,258	$18,484	$19,612	AS compared to WW: $10,377 per QALY; RP compared to WW: $10,358 per QALY; RP compared to AS: $10,255 per QALY; AS was extended dominated by WW and RP
	Effectiveness (QALYs)	13.37	13.97	14.08	
60 years	Cost (NZ$)	$10,113	$15,461	$18,254	AS compared to WW: $12,155 per QALY; RP compared to WW: $14,282 per QALY; RP compared to AS: $21,485 per QALY
	Effectiveness (QALYs)	12.08	12.52	12.65	
65 years	Cost (NZ$)	$7,843	$11,998	$16,972	AS compared to WW: $14,839 per QALY; RP compared to WW: $21,230 per QALY; RP compared to AS: $33,160 per QALY
	Effectiveness (QALYs)	10.62	10.90	11.05	
70 years	Cost (NZ$)	$5,560	$7,976	$15,821	AS compared to WW: $17,257 per QALY; RP compared to WW: $32,066 per QALY; RP compared to AS: $43,583 per QALY
	Effectiveness (QALYs)	9.03	9.17	9.35	

RP: radical prostatectomy; AS: active surveillance; WW: watchful waiting

The life-time costs, the number of life-years and the number of QALYs decreased with increasing age at diagnosis at all treatment arms (Appendix 4, Table 37).The number of life-years for men in the active surveillance arm was close to that in the radical prostatectomy arm at all age groups (Appendix 4), while the number of QALYs in the active surveillance arm was slightly lower than that in the radical prostatectomy arm. The life-time costs in the active surveillance arm were higher than the costs in the radical prostatectomy arm for men diagnosed at the age of 45-50 years, but were lower than the costs

in the radical prostatectomy arm for men diagnosed at the age of 55-70. Therefore, the ICERs of radical prostatectomy compared to active surveillance were estimated in the age groups 55-70 years.

For men aged 45 and 50 years, radical prostatectomy was cost-effective compared to watchful waiting with a willingness-to-pay value of over $6,432 per QALY gained and over $7,906 per QALY gained, respectively, and was dominant (more effective and less costly) compared to active surveillance. For men aged 55 years, radical prostatectomy was more cost-effective than watchful waiting when the willingness-to-pay was over $10,358 per QALY gained. Active surveillance was extended dominated by watchful waiting and radical prostatectomy: active surveillance was less cost-effective than watchful waiting when the willingness-to-pay was less than $10,377 per QALY gained, and less cost-effective than radical prostatectomy when the willingness-to-pay was more than $10,255 per QALY gained. For men aged 60, 65 and 70 years, active surveillance was cost-effective compared to watchful waiting with a willingness-to-pay value of over $12,155, $14,839 and $17,257 per QALY gained, respectively. The respective ICER of radical prostatectomy compared to active surveillance was $21,485, $33,160 and $43,583 per QALY gained for men aged 60, 65 and 70 years. With a willingness-to-pay value of over these ICERs, radical prostatectomy was cost-effective compared to active surveillance.

5.3.2 Cost-effectiveness acceptability curve (CEAC)

The CEACs for all age groups are shown in Figure 22 to Figure 27. The frontier showed the optimal treatment option over a range of willingness-to-pay values. With the increasing willingness-to-pay values, the possibility of radical prostatectomy being cost-effective increased and the possibility of watchful waiting being cost-effective decreased in all age groups. When the willingness-to-pay value increased from $0 to $30,000 per QALY, the possibilities of being cost-effective increased or decreased rapidly. The possibilities of being cost-effective were stable when the willingness-to-pay value was at the range of $30,000 to $100,000 per QALY. At the willingness-to-pay value of $35,000 per QALY gained, radical prostatectomy was the optimal option for men aged 45-65 years, with a possibility of being cost-effective ranging from 59.4% for men aged 45 to 49.3% for men aged 65 (decreased with age). At this willingness-to-pay value, active surveillance was the most cost-effective management option for men aged 70 years, with a possibility of 53.9% being cost-effective.

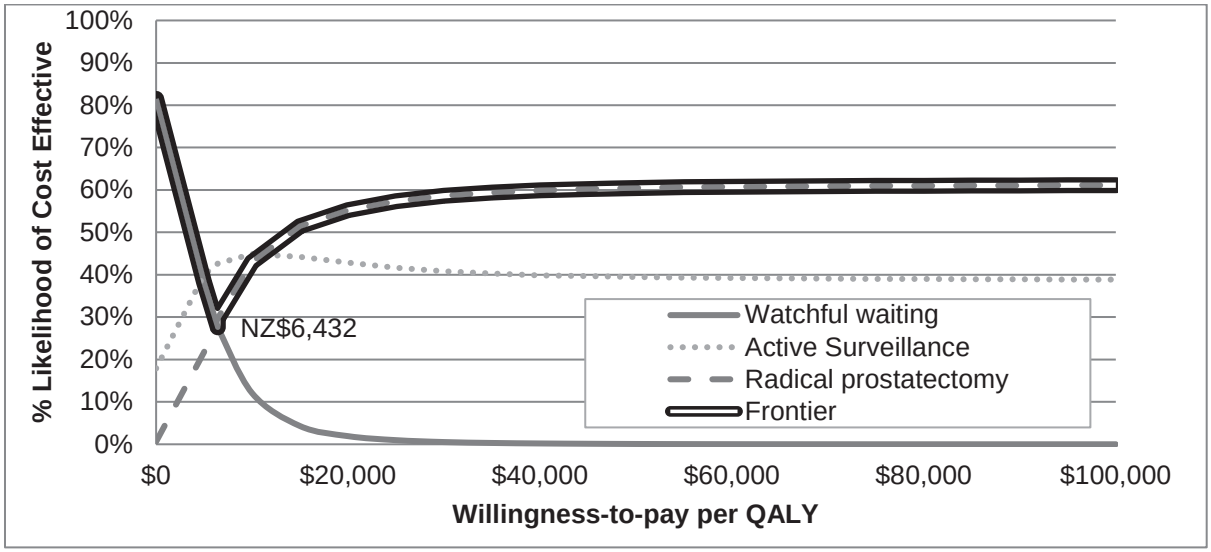

Figure 22. CEAC: men with low risk localised prostate cancer aged 45 years

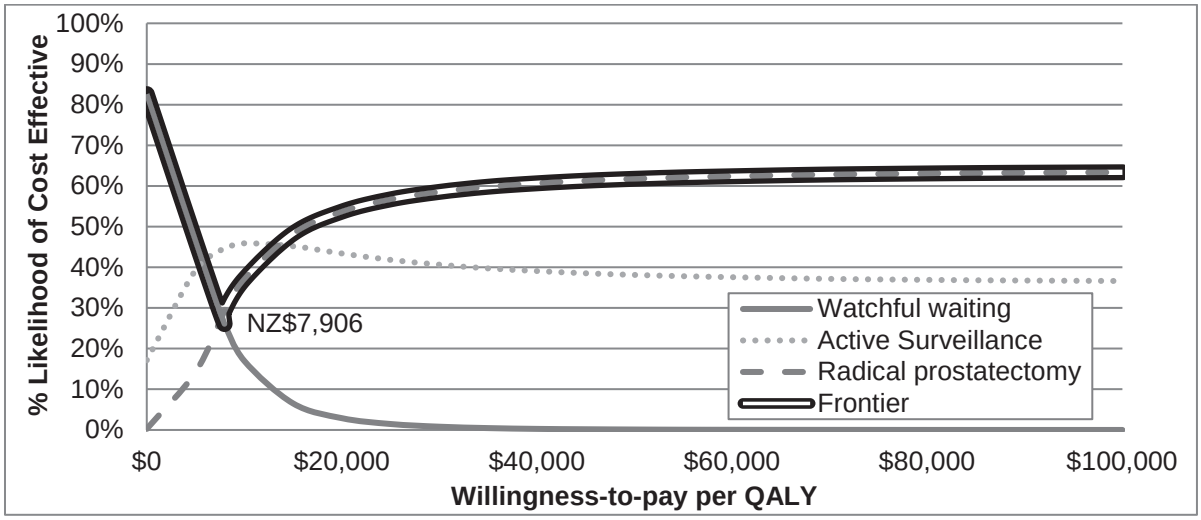

Figure 23. CEAC: men with low risk localised prostate cancer aged 50 years

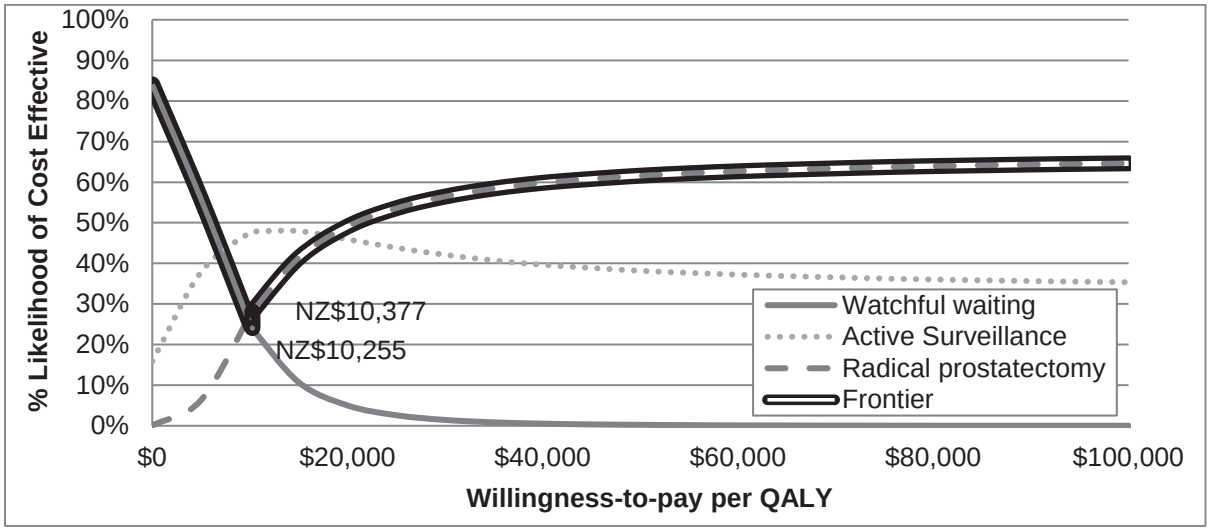

Figure 24. CEAC: men with low risk localised prostate cancer aged 55 years

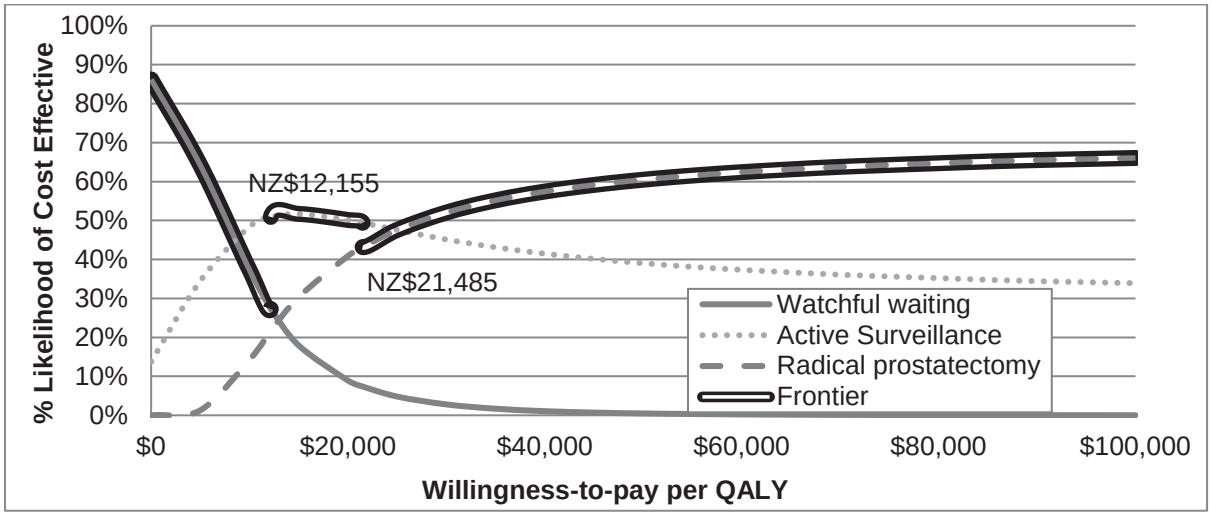

Figure 25. CEAC: men with low risk localised prostate cancer aged 60 years

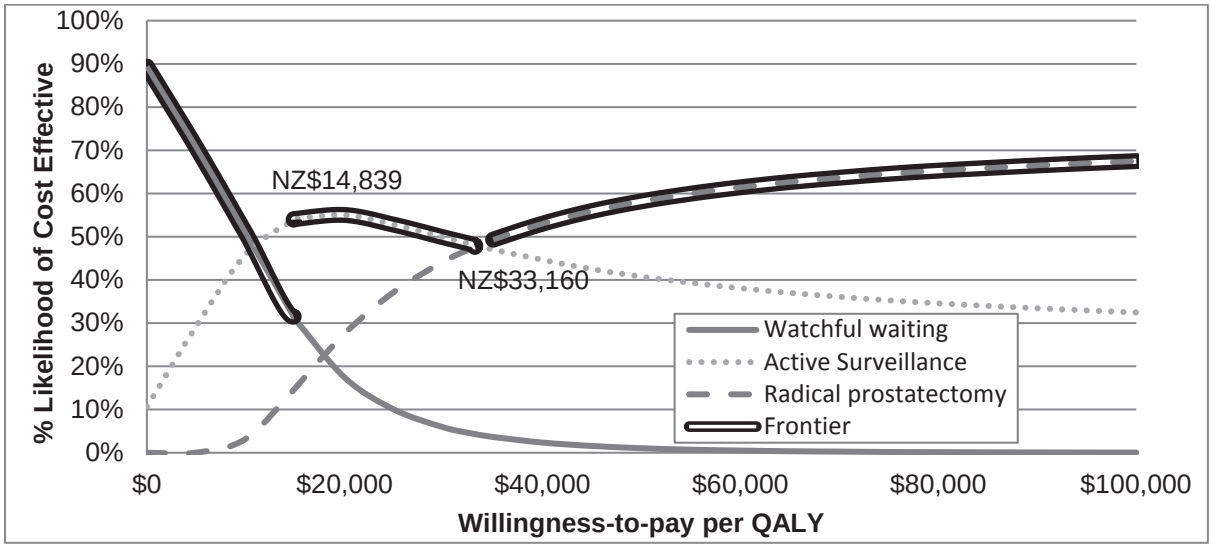

Figure 26. CEAC: men with low risk localised prostate cancer aged 65 years

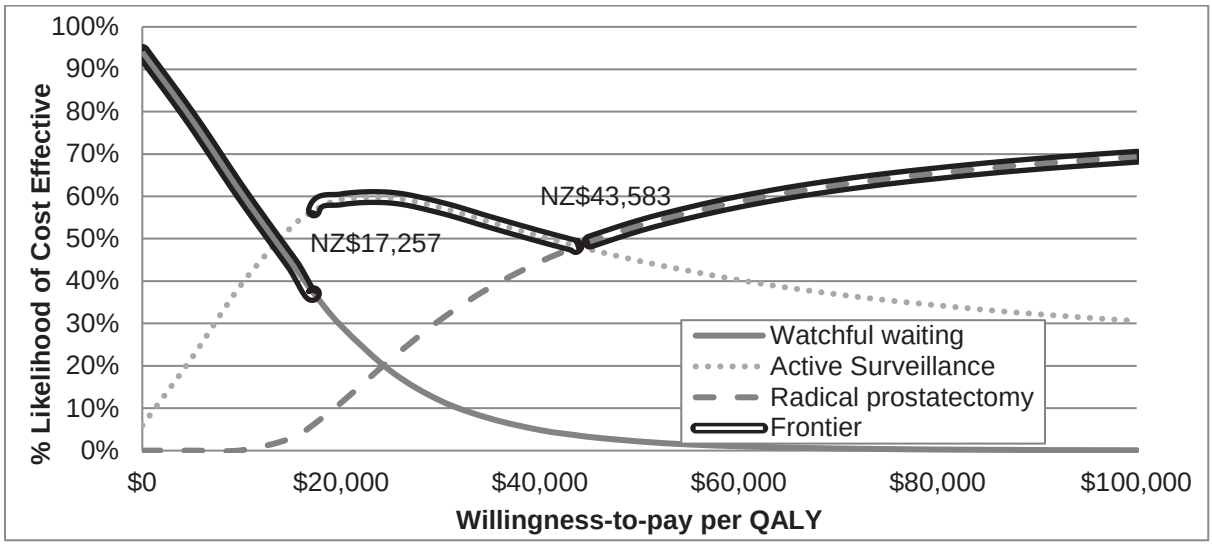

Figure 27. CEAC: men with low risk localised prostate cancer aged 70 years

5.3.3 Scenario analysis

At the first scenario analysis (using the 5% annual conversion rate from active surveillance to radical prostatectomy in the active surveillance arm), the model yielded similar numbers of life-years in the active surveillance arm and in the radical prostatectomy arm (Appendix 5). The number of QALYs in the active surveillance arm was smaller than that in the radical prostatectomy arm at all age groups (Appendix 6). The life-time costs in the active surveillance arm were higher than the costs estimated by the original model (Appendix 7). With a higher annual conversion rate from active surveillance to radical prostatectomy, more men in the active surveillance arm had radical prostatectomy in this model than in the original model. The life-time costs of active surveillance were higher than the costs of radical prostatectomy for men aged 45-60, but were lower than the costs of radical prostatectomy for men aged 65-70.

Active surveillance was dominated by radical prostatectomy (less costly and more effective) for men aged 45-60 (Table 38). For men aged 65 years, active surveillance was extended dominated by watchful waiting and radical prostatectomy. Active surveillance was only cost-effective for men aged 70 years old at a willingness-to-pay value of between $31,135 and 33,140 per QALY gained.

Table 38. Scenario analysis for men with low risk localised prostate cancer: cost per QALY gained by using the 5% conversion rate

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Radical prostatectomy compared to active surveillance	
45 years	-	$6,441	-	AS was dominated by RP
50 years	-	$7,908	-	AS was dominated by RP
55 years	-	$10,361	-	AS was dominated by RP
60 years	-	$14,021	-	AS was dominated by RP
65 years	-	$21,226	-	AS was extended dominated by WW and RP
70 years	$31,135	-	$33,140	-

RP: radical prostatectomy; AS: active surveillance; WW: watchful waiting

In the second scenario analysis (using the new quality of life values), the number of QALYs in the active surveillance arm was higher than that in the radical prostatectomy arm in all age groups (Appendix 8). Radical prostatectomy was dominated by active surveillance for men aged 55-70 years old (Table 39). For men aged 45 and 50 years, radical prostatectomy was extended dominated by active surveillance and watchful waiting.

Table 39. Scenario analysis for men with low risk localised prostate cancer: cost per QALY gained by using new quality of life inputs

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Active surveillance compared to radical prostatectomy	
45 years	$11,060	-	-	RP was extended dominated by WW and AS
50 years	$12,602	-	-	RP was extended dominated by WW and AS
55 years	$14,814	-	-	RP was dominated by AS
60 years	$17,807	-	-	RP was dominated by AS and by WW
65 years	$21,916	-	-	RP was dominated by AS and by WW
70 years	$26,833	-	-	RP was dominated by AS and by WW

RP: radical prostatectomy; AS: active surveillance; WW: watchful waiting

With the new costing inputs, the life-time costs in the active surveillance arm were higher than in the radical prostatectomy arm for men aged 45-55, but was lower for men aged 60-70 (Appendix 9). Since the life-time costs in the three arms in this scenario analysis were similar to the life-time costs in the original model, the estimated ICERs in this scenario analysis (Table 40) were similar to those in the original model.

Table 40. Scenario analysis for men with low risk localised prostate cancer: cost per QALY gained by using new costing inputs

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Radical prostatectomy compared to active surveillance	
45 years	-	$5,324	-	AS was dominated by RP
50 years	-	$6,613	-	AS was dominated by RP
55 years	-	$8,793	-	AS was dominated by RP
60 years	-	$12,332	-	AS was extended dominated by WW and RP
65 years	$15,732	-	$24,000	-
70 years	$19,364	-	$35,761	-

RP: radical prostatectomy; AS: active surveillance

When using the new quality of life inputs and the new economic inputs in the model, radical prostatectomy was dominated by active surveillance for men aged 60-70 and was extended dominated by active surveillance and watchful waiting for men aged 45-55 years (Table 41).

Table 41. Scenario analysis for men with low risk localised prostate cancer: cost per QALY by using new quality of life inputs and costing inputs

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Active surveillance compared to radical prostatectomy	
45 years	$11,254	-	-	RP was extended dominated by WW and AS
50 years	$12,882	-	-	RP was extended dominated by WW and AS
55 years	$15,248	-	-	RP was extended dominated by WW and AS
60 years	$18,520	-	-	RP was dominated by AS and by WW
65 years	$23,184	-	-	RP was dominated by AS and by WW
70 years	$30,122	-	-	RP was dominated by AS and by WW

RP: radical prostatectomy; AS: active surveillance

The number of QALYs in the active surveillance arm was higher than that in the radical prostatectomy arm at all age groups after changing the conversion rate and quality of life inputs in the model (Appendix 10). The life-time costs of active surveillance were still lower than the costs of radical prostatectomy for men aged 65-70, but were higher than the costs of radical prostatectomy for men aged 45-60 after changing the conversion rate and costing inputs in the model (Appendix 11). By using the new quality of life values, new costing values and the 5% conversion rate, radical prostatectomy was extended dominated by watchful waiting and active surveillance for men aged 45-55 years, and was dominated by both active surveillance and watchful waiting for men aged 60-70 years (Table 42). The ICER of active surveillance compared to watchful waiting was $44,090 per QALY for men aged 60, $59,769 per QALY for men aged 65 and $101,360 per QALY for men aged 70. In other words, for men aged 60-70, active surveillance was only cost-effective compared to watchful waiting at high willingness-to-pay values.

Table 42. Scenario analysis for men with low risk localised prostate cancer: cost per QALY by using new quality of life values, costing values and the 5% conversion rate

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Active surveillance compared to radical prostatectomy	
45 years	$22,904	-	-	RP was extended dominated by WW and AS
50 years	$27,385	-	-	RP was extended dominated by WW and AS
55 years	$33,790	-	-	RP was extended dominated by WW and AS
60 years	$44,090	-	-	RP was dominated by WW
65 years	$59,769	-	-	RP was dominated by WW and by AS
70 years	$101,360	-	-	RP was dominated by WW and by AS

RP: radical prostatectomy; AS: active surveillance

5.3.4 Expected value of perfect information (EVPI)

As shown in Figure 28, the EVPI increased with decreasing age and with increasing willingness-to-pay values. At the willingness-to-pay value of $35,000 per QALY gained, the EVPI was $4,065, $3,658, $3,462, $3,398, $3,479 and $2,143 per men aged 45, 50, 55, 60, 65 and 70 years old, respectively. In New Zealand, low risk localised prostate cancer cases comprised 25.6% of the newly diagnosed prostate cancer cases.[12,30] Given the 3,000 annual incidence of prostate cancer,[3] the number of new low risk cases would be 767. The number (proportion) of patients with low risk cancer at different age groups was not available. The estimated population EVPI was $3,117,855, $2,805,686, $2,655,354, $2,606,266, $2,668,393 and $1,643,681 if the 767 men with low risk localised prostate cancer are diagnosed at the age of 45, 50, 55, 60, 65 and 70 years old, respectively.

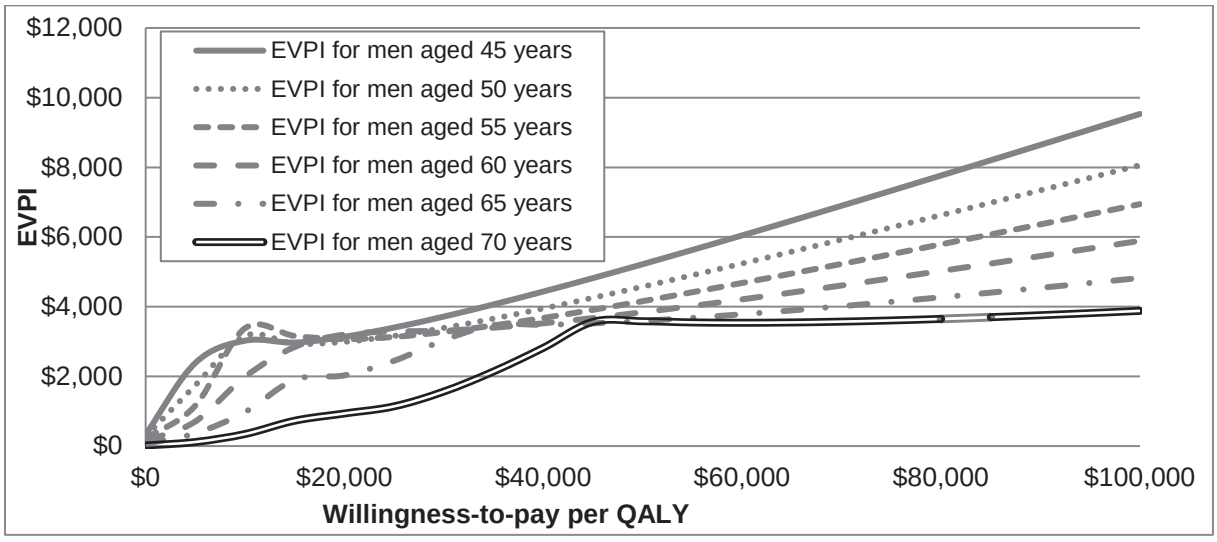

Figure 28. EVPI for men with low risk localised prostate cancer

5.4 Discussion

5.4.1 Overview

No RCTs or observational studies with a long follow-up have been conducted to examine whether there is a difference in prostate cancer-specific survival between men under active surveillance and men undergoing radical prostatectomy. However, active surveillance is considered to be a reasonable alternative to selected candidates with early stage prostate cancer.[312,313] The New Zealand Ministry of Health published a guidance on using active surveillance to manage men with low risk prostate cancer in July 2015.[163] The entry criteria for active surveillance included a life expectancy of greater than 10 years, but patient's age was not mentioned. This study showed that the life-time costs of active surveillance were lower than the costs of radical prostatectomy in the older age groups, but were higher than the costs of radical prostatectomy in the younger age groups. The cost-effectiveness of active surveillance was dependent on the quality of life inputs for men with localised prostate cancer under different treatment options, and the annual probability of having radical prostatectomy in the active surveillance arm.

The model in this study yielded similar numbers of life-years between the active surveillance arm and the radical prostatectomy arm for men in all age groups, which was consistent with the evidence that active surveillance and radical prostatectomy have similar effects on the survival of men with low risk localised prostate cancer.[163,174] The difference in the numbers of QALYs in both arms depends on the quality of life values assigned to men under observational management and men who received radical prostatectomy.

5.4.2 Impacts of parameter variations on results

In our previous systematic review (section 2.2), population-based prostate cancer screening was found to be not cost-effective.[28] Therefore, the simulated patients in this economic model were assumed to be identified by symptoms but by prostate cancer screening. The transition probabilities used in this model were estimated from the SPCG-4 cohort[80] where most patients were identified by symptoms (only 5% were identified by PSA screening). The SPCG-4 study[80] had more patients with a longer follow-up than the PIVOT study.[15,80] The estimated transition probabilities to local progression and metastatic disease in this study were higher than the probabilities used in other models where the transition probabilities were based on the PIVOT study.[168,266,268] Some researchers suggested that the cancer risk level of the SPCG-4 cohort was much worse than the screened patients today.[314] However, the difference in the proportion of cancer cases in different risk levels between the SPCG-4 cohort and the PIVOT cohort [15] (where patients were identified by screening) was not substantial: 36% low risk, 40% intermediate risk and 24% high risk in the SPCG-4 cohort; 42% low risk, 36% intermediate risk and 22% high risk in the PIVOT cohort.

The transition probability in Year 11 and 12 was not included in the regression because a smaller number of patients had a 12-year follow-up in the SPCG-4 study in 2008[296] (20% (71/348) in the watchful waiting arm and 32% (112/347) in the radical prostatectomy arm). Only the transition probabilities in the first 10 years were used in the estimation. If the transition probabilities in year 11 and 12 were used in the regression, the transition probability from 'Post-surgery' to 'Local progression' in the radical prostatectomy arm would become 0.0112 + 0.0022 × T; T: time (years) from radical prostatectomy, and the average annual transition probability from 'Localised' to 'Local progression' in the watchful waiting arm would be 0.0567 (SE: 0.0082).The change after adding the transition probability in year 11 and 12 in the watchful waiting arm was minor, while the change in the radical prostatectomy arm was more substantial. After 20 years, the transition probability in the radical prostatectomy arm would increase by 40% after adding the transition probability in year 11 and 12.

The triggers of intervention (having definitive treatment) in the active surveillance arm remain uncertain and different institutions have their own protocols. A systematic review reported that one third of men under active surveillance received definitive treatment after a median follow-up of 2.5 years, with 7-13% treated without evidence of progression, 13-48% treated because the PSA doubling time less than 3 years and 27-100% treated for histologic reclassification.[174] An early or unnecessary trigger of active treatment is not beneficial for cost reduction in the active surveillance arm. The model in this study assumed that active treatment is triggered only when high risk localised prostate cancer is detected. High risk localised prostate cancer can be cured by definitive treatment. Using this trigger in the model, approximately 1.6% of men in the active surveillance arm would have radical prostatectomy every year, 15% in 10 years (compared to 30% using annual conversion rate of 5%) and 28% in 20 years.

No uniform conversion rate from active surveillance to active treatment has been established before. Corcoran AT and colleague[168] used an annual conversion rate of between 5% and 7%. Half of the patients in the active surveillance arm would receive radical prostatectomy in 14 years with the conversion rate of 5%, and in 10 years using the 7% conversion rate. Because men under active surveillance have a life expectancy of at least 10 years, more than half of men would need a radical prostatectomy. The intention of reducing the treatment costs by active surveillance is to reduce the number of men receiving radical prostatectomy and to postpone the treatment costs (because later costs are preferred to earlier costs). For men with a long life-expectancy, the long term costs of active surveillance might exceed the reduced costs of surgeries, which was the case for younger men in our study. With the annual conversion rate of approximately 1.6% from active surveillance to radical prostatectomy used in this study, the life-time costs in the active surveillance arm were lower than the costs in the radical prostatectomy arm for men aged 55-70 (or for men aged 60-70 in the scenario analysis). However, with the annual conversion rate of 5%, the life-time costs in the active surveillance arm were higher than the costs in the radical prostatectomy arm for men aged 55-60. The likelihood of active surveillance being cost-effective compared to radical prostatectomy declined with a higher annual conversion rate. The last scenario analysis (Table 42) showed that with the annual conversion rate of 5% and the new costing values, active surveillance would only be cost-effective

compared to watchful waiting at a very high willingness-to-pay value, even if the quality of life for men under active surveillance was better than that for men having radical prostatectomy.

In our economic model, the quality of life data for men at different health states were all EQ-5D based. No EQ-5D based data on quality of life for active surveillance was available. The only available quality of life data for active surveillance was estimated by standard gamble (mean value: 0.83).[315] Half of men included in that study did not have prostate cancer when the study was conducted. Men who had not experienced active surveillance were asked to imagine that they had the condition(s) described in the health state and the quality of life for active surveillance was estimated based on the imagination. The uncertainties associated with the quality of life results could be substantial. The quality of life data for active surveillance used in our model was based on a study conducted by Korfage IJ.[147] A quality of life value of 0.89 for men before radical prostatectomy was used as the quality of life for men under active surveillance and a quality of life value of 0.90 after radical prostatectomy was used as the quality of life for men after radical prostatectomy in this model. Hayes JH [266] used 0.83 (mean value) as the quality of life after active surveillance and 0.80 (mean value) as the quality of life after treatment without complications in their economic model. However, the quality of life for men after treatment without complications should be better than that for men under active surveillance who need to suffer from the regular biopsies and might also suffer from continuous anxiety and depression from the cancer diagnosis. These quality of life values were used in the model for scenario analysis to predict the cost-effectiveness of active surveillance if the quality of life for men under active surveillance or watchful waiting was considerably better than that for men after radical prostatectomy.

Quality of life data for men under active surveillance and that for men who received radical prostatectomy are critical for the cost-effectiveness of active surveillance compared to radical prostatectomy. If the quality of life for men under active surveillance is better than that in the radical prostatectomy arm and men in the active surveillance arm would have radical prostatectomy only when high risk cancer was detected, active surveillance might be cost-effective for men at all age groups. Otherwise it might be only cost-effective for men diagnosed at an older age.

Informed decisions would be needed for men diagnosed with low risk localised prostate cancer, especially for those who are prone to depression and anxiety. Quality of life for men under active surveillance can be improved by providing patients more relevant information and psychological support. Decision making on the treatment option should still be based on patients' preference after understanding the possible benefits and harms. Preference is critical to patients' quality of life.[2]

MRI can assess the whole prostate from an anatomical and functional perspective. It can detect higher-risk disease and assess the volume of tumour. MRI has been increasingly proposed to be used in the follow-up of active surveillance.[316-318] The quality of life in the active surveillance arm might be improved by replacing biopsy with MRI because MRI is not invasive and does not cause severe complications.

5.4.3 Strengths and limitations

One of the strengths of this study is that it synthesized data from internationally recognised studies and local costing and outcome data to provide relevant economic information for decision making. The cumulative incidence of local progression and metastatic diseases in the watchful waiting arm and in the radical prostatectomy arm were consistent with the cumulative incidence in the SPCG-4 study, and the mortality from metastatic disease and the life-time costs reflected the health care practice in New Zealand. Variations in different age groups were taken into account, which was an advantage compared to other published studies.[168,266,268]

This study also has some limitations, including the uncertainties on quality of life for men under active surveillance and for men undergoing radical prostatectomy. The cost-effectiveness of active surveillance was closely related to the quality of life inputs. The quality of life for men at different ages was assumed to be the same if they had identical treatment. However, in reality, the quality of life may vary by age even under the same treatment. For example, sexual problems caused by radical prostatectomy might affect the quality of life more for men at their 50s than for men aged 70 years, because over 70% of men at the age of 50s are still sexually active while 60% of men aged 70+ year suffer from erectile dysfunction.[319] GP costs were not considered in this study. The number of GP consultations related to prostate cancer after the diagnosis was not available, but the number of GP consultations might be close to the number of PSA tests ordered by GPs. However, on average only one PSA test per prostate cancer patient per year was ordered by GPs (Appendix 12) and the subsidy per GP consultation was NZ$38.69, which implied that GPs do not play an important role in the management of prostate cancer patients. Therefore excluding GP costs would not bias the results substantially. The impacts of short-term side effects on patients' quality of life were not considered. Due to the long life expectancy for these patients, the impact of short-term side effects would be less important than the long-term side effects.

5.5 Conclusion

If men in the active surveillance arm are switched to radical prostatectomy only when significant cancer progression (e.g. high risk localised prostate cancer) is detected, active surveillance is less costly than radical prostatectomy for men diagnosed at the age of 60-70 years old. However the life-time costs of active surveillance might be higher than the costs of radical prostatectomy for men diagnosed at the age of younger than 55 years. The cost-effectiveness of active surveillance was dependent on the quality of life inputs for men with localised prostate cancer under different treatment options, and the annual probability of having radical prostatectomy in the active surveillance arm. Early or unnecessary trigger of active treatment is not beneficial for cost reduction in the active surveillance arm.

5.6 Summary of Chapter 5

This chapter examines the cost-effectiveness of active surveillance compared to radical prostatectomy for men diagnosed with low risk localised prostate cancer at the age of 45, 50, 55, 60, 65 and 70 years, using life-time Markov models and synthesizing clinical data from the SPCG-4 study, published quality of life data, and local clinical and economic data. This study showed that the life-time costs of active surveillance were lower than the costs of radical prostatectomy in the older age groups, but were higher than the costs of radical prostatectomy in the younger age groups. The cost-effectiveness of active surveillance was dependent on the quality of life inputs for men with localised prostate cancer under different treatment options, and the annual probability of having radical prostatectomy in the active surveillance arm. The likelihood of active surveillance being cost-effective compared to radical prostatectomy declined with an increasing annual probability of having radical prostatectomy in the active surveillance arm. If the quality of life for men under active surveillance is better than that in the radical prostatectomy arm and men in the active surveillance arm would have radical prostatectomy only when high risk cancer was detected, active surveillance might be cost-effective for men at all age groups. Otherwise it might be only cost-effective for men diagnosed at an older age.

Early or unnecessary trigger of active treatment is not beneficial for cost reduction in the active surveillance arm. The ICER of active surveillance compared to watchful waiting increased with rising annual probability of having radical prostatectomy in the active surveillance arm. If the quality of life for men under observational management was better than that for men having radical prostatectomy, active surveillance was cost-effective compared to radical prostatectomy, but was not cost-effective to watchful waiting for older men, with a high annual probability of having radical prostatectomy in the active surveillance arm.

Active surveillance should not be offered to men with high risk localised prostate cancer, but may be considered for selected men with favourable, intermediate risk localised prostate cancer.[163] The next chapter used similar methods as in this chapter to assess the cost-effectiveness of active surveillance compared to radical prostatectomy for men with intermediate risk localised prostate cancer.

Chapter 6. The cost-effectiveness of active surveillance compared to watchful waiting and radical prostatectomy for intermediate risk localised prostate cancer

6.1 Introduction

Compared to men with low risk localised prostate cancer, men with intermediate risk localised prostate cancer had worse overall and cancer-specific survival.[80] Treatments for intermediate risk localised prostate cancer included radical prostatectomy, brachytherapy and external beam radiotherapy.[246] A systematic review conducted by Klein[246] and colleagues showed similar short-term survival but domain-specific effects on quality of life among radical prostatectomy, brachytherapy, or external beam radiotherapy for intermediate risk localised prostate cancer. Ahmed suggested men with intermediate risk localised prostate cancer can choose active surveillance if they wish to avoid the side effects caused by deferred treatments.[320]

A US study demonstrated that some men with intermediate risk prostate cancer might choose active surveillance despite the risk of progression.[321] In the Midland Prostate Cancer Study,[30] 27% (12/44) men under active surveillance had intermediate risk localised prostate cancer. In 2010, 376 men with low risk localised prostate cancer and 90 men with intermediate risk localised prostate cancer consented to be managed with active surveillance in the prospectively accrued Urologic Oncology Database under supervision of the University of California, San Francisco. No difference was found in the proportions of men experiencing progression free survival between the low risk group and the intermediate risk group (low 54% vs intermediate 61%; p=0.22) or in the proportions of men who had active treatment (low 30% vs intermediate 35%; p=0.88).[321] Another study examined the outcome of active surveillance was carried out among 381 men with low risk localised prostate cancer and 128 men with intermediate risk localised prostate cancer who were identified through screening between 1993 and 2007 in the Rotterdam or the Helsinki arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC).[322] After a median follow-up of 7.4 years, 43.4% of men (low 39.9% and intermediate 53.9%; p=0.006) have switched to deferred treatment, 0.8% developed distant metastases (low 0.3% vs intermediate 2.3%; p=0.44), and 1% of men died of prostate cancer (low 0.8% vs intermediate 1.6%; p=0.44).[322]

Some researchers advised including men with Gleason score 3+4=7 intermediate risk localised prostate cancer in the candidates for active surveillance.[323-325] Pierorazio et al[108] found that men with a Gleason score 3+4 were associated with a better biochemical recurrence free survival than men with a Gleason score 4+3. The 5-year biochemical recurrence free survival was 82.7% (88.1%) for men with a biopsy (radical prostatectomy) Gleason score 3+4, and was 65.1% (69.7%) for men with a biopsy (radical prostatectomy) Gleason score 4+3.

Intermediate risk cancer cases comprised 45% of all localised prostate cancer cases.[12] Identifying the most cost-effective treatment option for men with intermediate risk localised prostate cancer would have a great impact on the landscape of management of prostate cancer. This study aims to compare the cost-effectiveness of active surveillance and radical prostatectomy for men with intermediate risk localised prostate cancer.

6.2 Methods

This study used similar methods as the previous study for low risk localised prostate cancer. An economic model consisting of three Markov models (three treatment arms: watchful waiting, active surveillance and radical prostatectomy) was constructed (Figure 29). The main difference between the influence diagrams for low risk patients and the influence diagrams for intermediate risk patients was the relative risks of cancer progression: relative risk for low risk patients used in the last study and relative risk for intermediate risk patients used in this model. The mean value of the relative risk of cancer progression for intermediate risk patients compared to the watchful waiting group in the SPCG-4 study was 1.0606 (Gamma distribution applied, SE: 0.0374, calculated by Dr Richard Edlin).[267,296] The mean value of the relative risk of cancer progression for intermediate risk patients compared to the radical prostatectomy group in the SPCG-4 study was 1.0397 (Gamma distribution applied, SE: 0.0347, calculated by Dr Richard Edlin).[267,296]

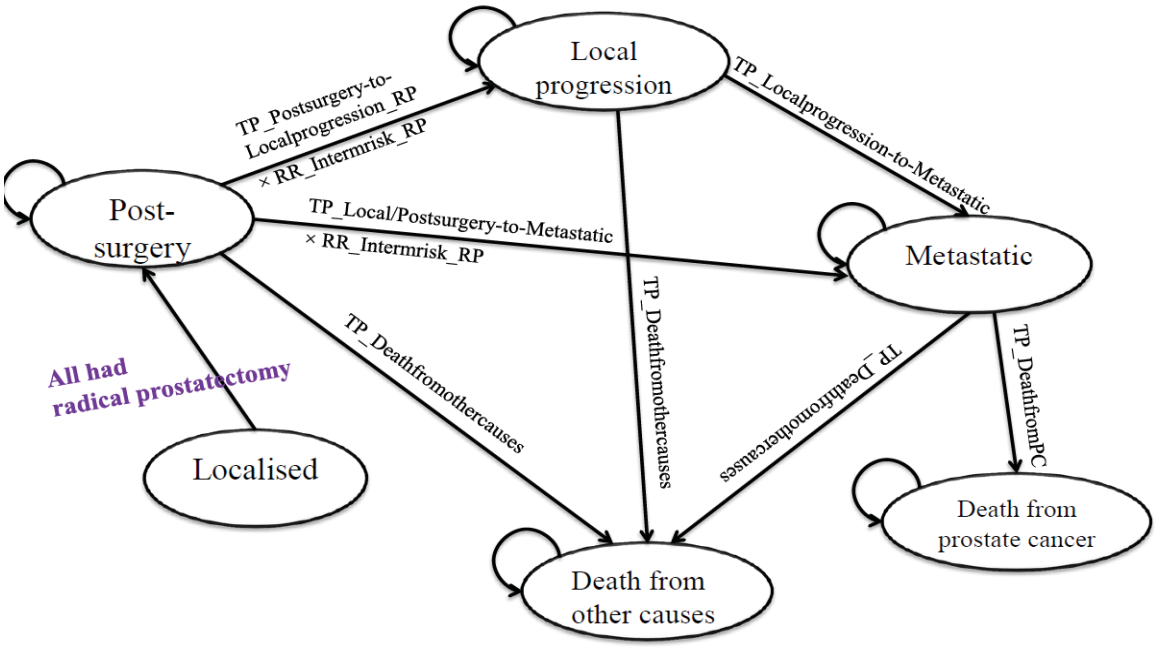

Figure 29 a. Influence diagram of the Markov model for radical prostatectomy

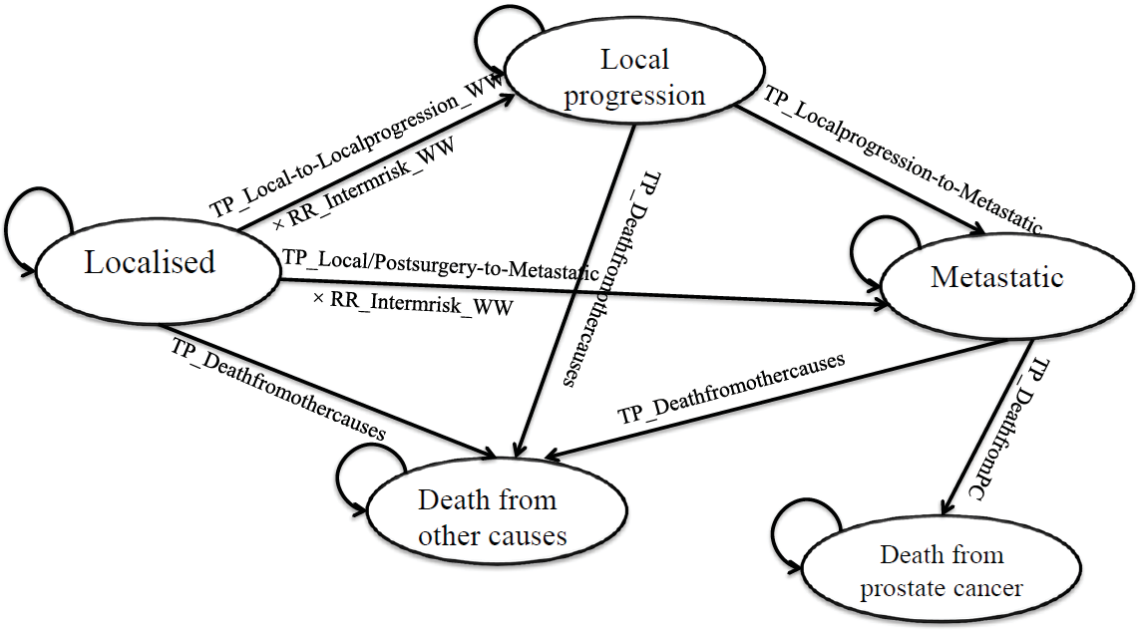

Figure 29 b. Influence diagram of the Markov model for watchful waiting

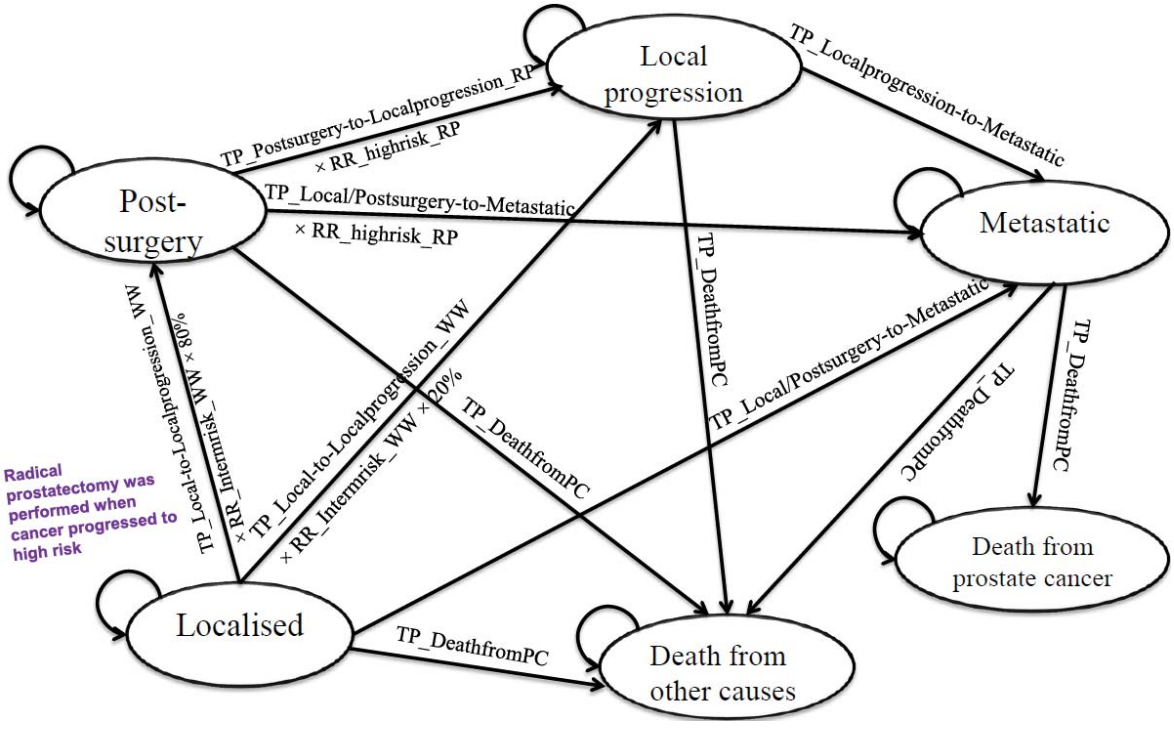

Figure 29 c. Influence diagram of the Markov model for active surveillance

Figure 29. Economic model of treatments for intermediate risk localised prostate cancer

Men in the active surveillance arm were also assumed to have radical prostatectomy when high risk localised prostate cancer was detected under the age of 75 years old, and were assumed to be

switched to watchful waiting (no more biopsy or radical prostatectomy) when they reached the age of 75 years old. Compared to low risk localised prostate cancer, more cancer progression were assumed to occur between the intervals of cancer monitoring (PSA testing, DRE, biopsy and imaging) in the active surveillance arm. In the active surveillance arm, 80% of men who developed high risk cancer were assumed to be captured and receive radical prostatectomy, and 20% of men who developed high risk cancer were assumed to be not captured and develop local progression.

The life-time risk of cancer progression for men with intermediate risk localised prostate cancer was higher than that for men with low risk localised prostate cancer.[80] The life-time risk increased with life expectancy, therefore the life-time risk of cancer progression might be high for men diagnosed at a younger age. There would be more uncertainties using the model to predict the life-time outcomes for men diagnosed with intermediate risk localised prostate cancer at a younger age. Therefore, younger men were not included in this study. Only three age groups (60, 65 and 70 years) were considered.

Cost-effectiveness analysis, probabilistic sensitivity analysis, scenario analysis and expected value of perfect information were also conducted in this study. Two scenario analyses were carried out: 1) using the quality of life values of 0.83 (SE: 0.020) for men under active surveillance and 0.80 (SE: 0.022) for men after treatment; 2) using the costing values in Table 36.

6.3 Results

6.3.1 Cost-effectiveness analysis

Men in the watchful waiting arm had the lowest life-time costs and the poorest health outcomes (both in terms of QALYs and life-years) for the three age groups (Appendix 13, Table 43). Therefore, watchful waiting was considered to be the baseline treatment. The number of life-years for men in the active surveillance arm was close to that in the radical prostatectomy arm in the three age groups (Appendix 13), while the number of QALYs in the active surveillance arm was slightly lower than that in the radical prostatectomy arm (Table 43). The life-time costs, the number of life-years and the number of QALYs decreased with increasing age at diagnosis at all treatment arms. The costs in the active surveillance arm were lower than the costs in the radical prostatectomy arm for men diagnosed at the age of 60-70.

For men aged 60, 65 and 70 years, active surveillance was cost-effective compared to watchful waiting with a willingness-to-pay value of over $530, $1,427 and $2,805 per QALY gained, respectively. The respective ICER of radical prostatectomy compared to active surveillance was $17,040, $16,567 and $18,378 per QALY gained. With a willingness-to-pay value of over these ICERs, radical prostatectomy was more cost-effective than active surveillance.

Table 43. Cost per QALY gained for men with intermediate risk localised prostate cancer aged 60 years

Age	Life-time outcome	Watchful waiting	Active surveillance	Radical prostatectomy	Incremental cost-effectiveness ratio (ICER)
60 years	Cost (NZ$)	$25,843	$26,384	$27,236	AS compared to WW: $530 per QALY; RP compared to WW: $1,302 per QALY; RP compared to AS: $17,040 per QALY
	Effectiveness (QALYs)	10.40	11.42	11.47	
65 years	Cost (NZ$)	$20,865	$21,878	$23,866	AS compared to WW: $1,427 per QALY; RP compared to WW: $3,616 per QALY; RP compared to AS: $16,567 per QALY
	Effectiveness (QALYs)	9.37	10.08	10.20	
70 years	Cost (NZ$)	$15,344	$16,410	$20,637	AS compared to WW: $2,805per QALY; RP compared to WW: $8,677per QALY; RP compared to AS: $18,378 per QALY
	Effectiveness (QALYs)	8.16	8.54	8.77	

RP: radical prostatectomy; AS: active surveillance; WW: watchful waiting

6.3.2 Cost-effectiveness acceptability curve (CEAC)

The CEACs for the three age groups were shown in Figure 30 to Figure 32. With the increasing willingness-to-pay values, the possibility of radical prostatectomy being cost-effective increased and the possibility of watchful waiting being cost-effective decreased in all age groups. At the willingness-to-pay value of $35,000 per QALY gained, radical prostatectomy was the optimal treatment option for men aged 60-70 years, with a possibility of being cost-effective ranging from 54% for men aged 60 years to 71.4% for men aged 70 years (increased with age).

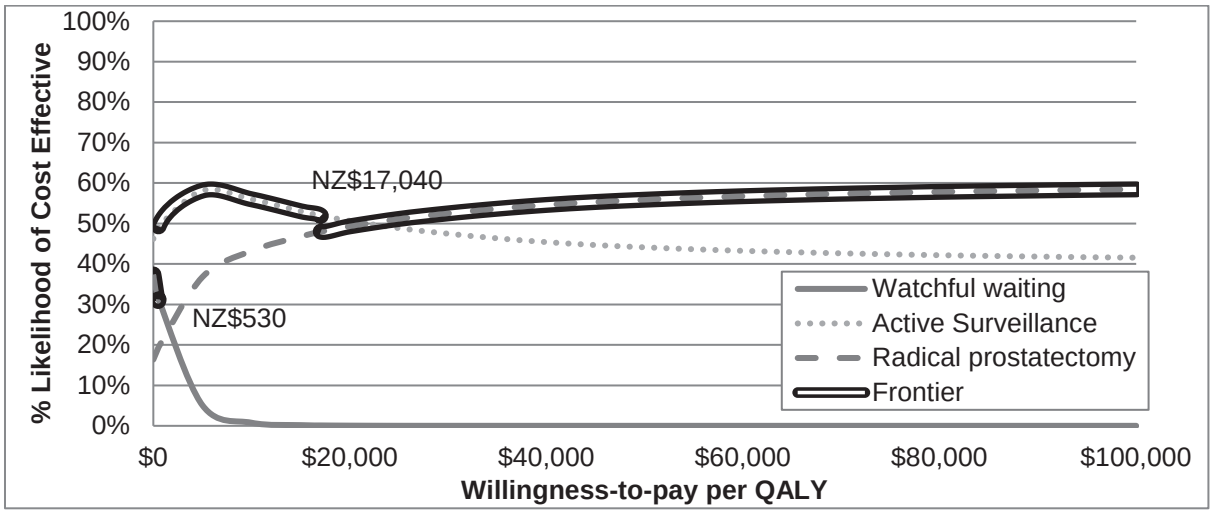

Figure 30. CEAC: men with intermediate risk localised prostate cancer aged 60 years

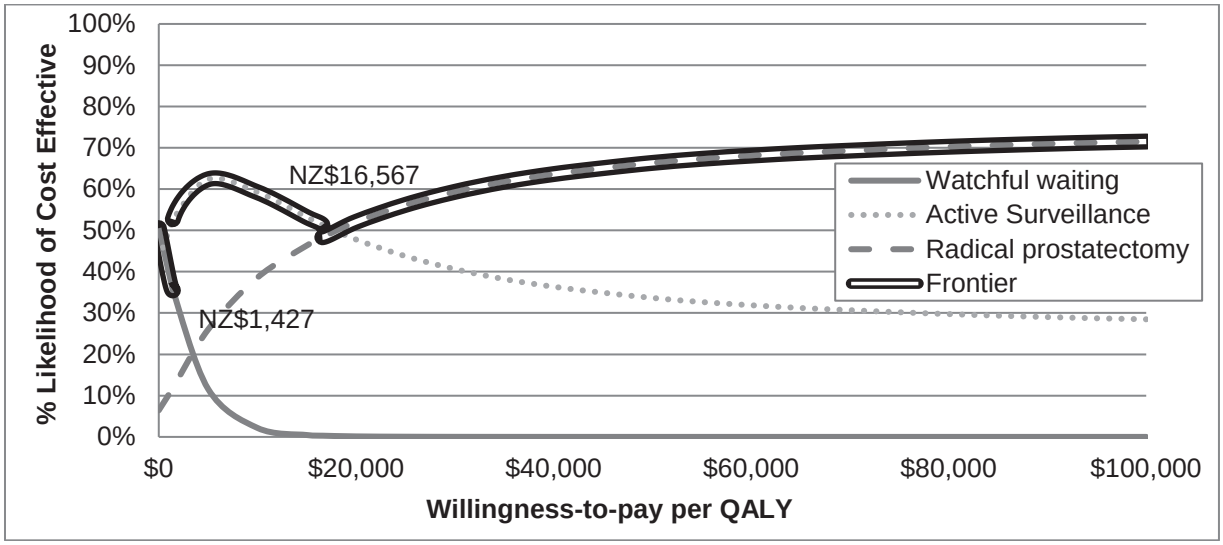

Figure 31. CEAC: men with intermediate risk localised prostate cancer aged 65 years

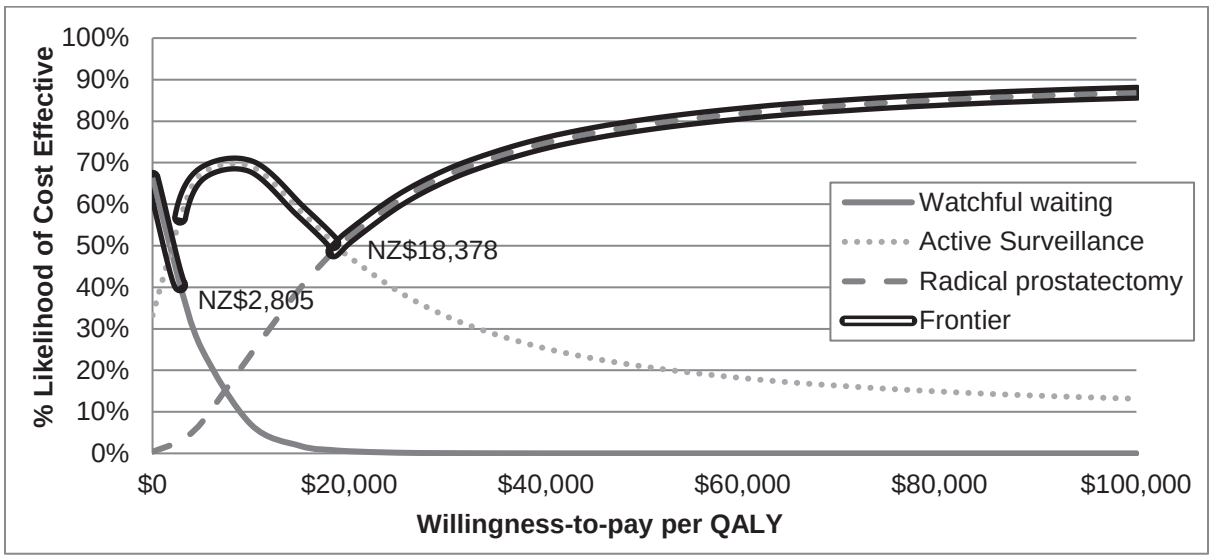

Figure 32. CEAC: men with intermediate risk localised prostate cancer aged 70 years

6.3.3 Scenario analysis

At the scenario analysis using the new quality of life inputs, the number of QALYs in the active surveillance arm was higher than that in the radical prostatectomy arm in the three age groups (Appendix 14). Under this circumstance, radical prostatectomy was dominated by active surveillance (less costly and more effective) in the three age groups (Table 44). The ICER of active surveillance compared to watchful waiting ranged from $762 to $4,442 per QALY gained.

Table 44. Scenario analysis for men with intermediate risk localised prostate cancer: cost per QALY gained by using new quality of life values

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Radical prostatectomy compared to active surveillance	
60 years	$762	-	-	RP was dominated by AS
65 years	$2,110	-	-	RP was dominated by AS
70 years	$4,442	-	-	RP was dominated by AS

RP: radical prostatectomy; AS: active surveillance

When using the new costing inputs, the life-time costs in the active surveillance arm were lower than that in the radical prostatectomy arm in the three age groups (Appendix 15). Watchful waiting was dominated by active surveillance for men aged 60 years old. The ICER of active surveillance compared to watchful waiting was $756 and $2,353 per QALY gained for men aged 65 and 70 years (Table 45). The ICER of radical prostatectomy compared to active surveillance ranged from $7,600 to $14,278 per QALY gained.

Table 45. Scenario analysis for men with intermediate risk localised prostate cancer: cost per QALY gained by using new costing values

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Radical prostatectomy compared to active surveillance	
60 years	-	-	$7,600	WW was dominated by AS
65 years	$756	-	$11,058	-
70 years	$2,353	-	$14,278	-

AS: active surveillance; WW: watchful waiting

When using the new quality of life values and the new costing values, radical prostatectomy was dominated by active surveillance in the three age groups (Table 46). Watchful waiting was dominated by active surveillance for men aged 60 years. The ICER of active surveillance compared to watchful waiting was $1,119 and $3,725 per QALY gained for men aged 65 and 70 years.

Table 46. Scenario analysis for men with intermediate risk localised prostate cancer: Cost per QALY by using new quality of life values and costing values

Age at diagnosis	ICER (Cost per QALY gained)			Dominance
	Active surveillance compared to watchful waiting	Radical prostatectomy compared to watchful waiting	Radical prostatectomy compared to active surveillance	
60 years	-	-	-	WW and RP was dominated by AS
65 years	$1,119	-	-	RP was dominated by AS
70 years	$3,725	-	-	RP was dominated by AS

RP: radical prostatectomy; AS: active surveillance; WW: watchful waiting

6.3.4 Expected value of perfect information (EVPI)

As shown in Figure 33, the EVPI generally increased with decreasing age and with increasing willingness-to-pay values. At the willingness-to-pay value of $35,000 per QALY gained, the EVPI was $3,190, $2,067 and $1,189 for men aged 60, 65 and 70 years old, respectively. In New Zealand, intermediate risk localised prostate cancer cases comprised 34.3% of the newly diagnosed prostate cancer cases.[12,30] Given the 3,000 annual incidence of prostate cancer,[3] the number of new intermediate risk cases would be 1029. The number of patients with intermediate risk cancer at different age groups was not available. Therefore the population EVPI was estimated under the assumption that all the 1029 men were at the same age group. The estimated population EVPI was $3,282,510, $2,126,943 and $1,223,481 if diagnosed at the age of 60, 65 and 70 years old, respectively.

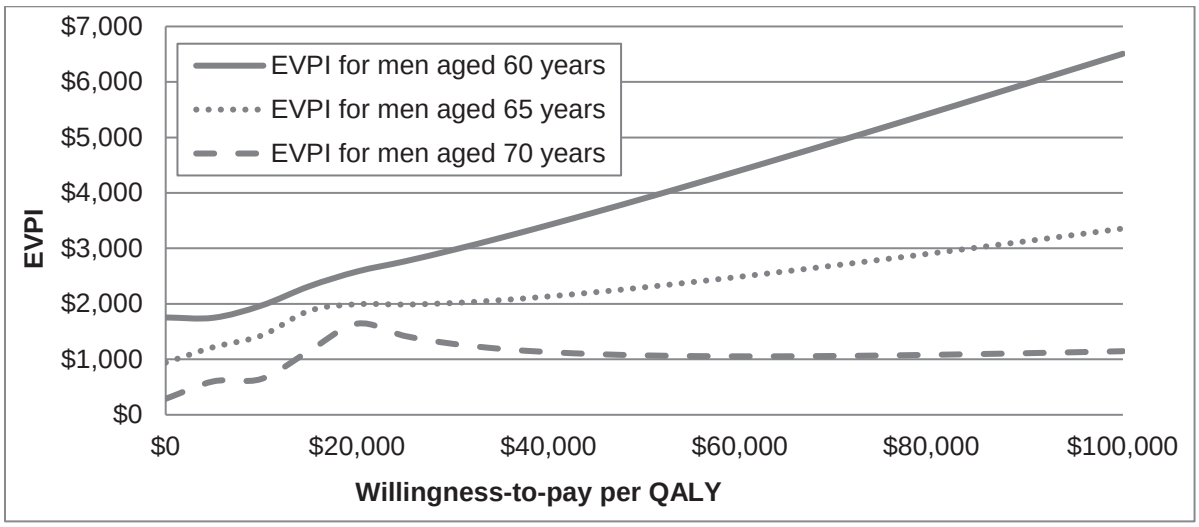

Figure 33. EVPI for men with intermediate risk localised prostate cancer

6.4 Discussion

This is the first study examining the cost-effectiveness of active surveillance compared to radical prostatectomy for intermediate risk localised prostate cancer. This study showed that active surveillance was associated with lower life-time health care costs compared to radical prostatectomy for men diagnosed with intermediate risk localised prostate cancer at the age of 60-70 years. The cost-effectiveness of active surveillance was associated with the quality of life values for men under observational management and for men having radical prostatectomy. The new costing inputs for men with localised prostate cancer did not have a substantial impact on the results. If the quality of life for men under active surveillance is worse than that for men undergoing radical prostatectomy, radical prostatectomy would be cost-effective compared to active surveillance in the three age groups with a willingness-to-pay value of $20,000 per QALY gained or over. If the quality of life for men under active surveillance is better than that for men undergoing radical prostatectomy, active surveillance would be a reasonable option for selected men with intermediate risk localised prostate cancer aged 60-70 years.

An average annual conversion rate of 4.8% from active surveillance to radical prostatectomy in this model was based on the assumption that 80% of men detected with high risk cancer in the active surveillance arm would receive radical prostatectomy. A scenario analysis using a bigger conversion rate from active surveillance to radical prostatectomy was not conducted in this study. However, with a higher proportion of men in the active surveillance arm receiving radical prostatectomy, the life-time costs in the active surveillance arm are expected to be higher, and the possibility of active surveillance being cost-effective would be lower. As shown in section 5.3.3, if the annual probability of having radical prostatectomy in the active surveillance arm is high, active surveillance might only be cost-effective compared to watchful waiting at a very high willingness-to-pay value, even if the quality of life for men under active surveillance was better than that for men having radical prostatectomy.

A systematic review conducted by Morash et al[325] recommended that radical prostatectomy and radiotherapy are appropriate for patients with intermediate-risk localised prostate cancer. For selected patients with low-volume Gleason 3+4=7 localised prostate cancer, active surveillance can be considered. This recommendation was based on three studies.[15,326,327] The first one was a single-arm cohort study of 50 intermediate risk patients under active surveillance with a 100% prostate cancer survival rate after a median follow-up time of 2.6 years.[326] Among these men, 44 (88%) men had a Gleason score 3+4=7 and had a better treatment-free survival than those with a Gleason score of 4+3=7. The other two studies were the PIVOT study[15] with a median follow-up time of 10.0 years (including low, intermediate and high risk patients) and a Sweden study[327] with a median follow-up time of 8.2 years (including low and intermediate risk patients). These two studies demonstrated no significant difference in prostate cancer-specific survival between men under observation and men receiving active treatment.

When considering the EVPI of this economic model in New Zealand, the population EVPI for low risk cancer and the population EVPI for intermediate risk cancer should be combined. The total EVPI

(N=1796) would range from $2,867,162 ($1,643,681+1,223,481) to $6,400,365 ($3,117,855+3,282,510).

6.5 Conclusion

For men diagnosed with intermediate risk localised prostate cancer at the age of 60-70, the life-time costs of active surveillance were lower than the costs of radical prostatectomy. The cost-effectiveness of active surveillance was associated with the quality of life values for men under observational management and for men having radical prostatectomy. If the quality of life for men under active surveillance is better than that for men in the radical prostatectomy, active surveillance is a reasonable option for men diagnosed with intermediate risk prostate cancer at the age of 60-70. The new costing inputs for men with localised prostate cancer did not have a substantial impact on the results.

6.6 Summary of Chapter 6

This chapter examines the cost-effectiveness of active surveillance compared to radical prostatectomy for men diagnosed with low risk localised prostate cancer at the age of 60, 65 and 70 years using life-time Markov models. For men diagnosed with intermediate risk localised prostate cancer at the age of 60, 65 and 70 years, the life-time costs of active surveillance were lower than the costs of radical prostatectomy. When the quality of life for men under observational management was better than that for men having radical prostatectomy, active surveillance was dominant (less costly and more effective) compared to radical prostatectomy in the three subgroups. When the quality of life for men under observational management was worse than that for men having radical prostatectomy, radical prostatectomy was cost-effective compared to active surveillance.

As described in the summary of Chapter 4, the costs of treatment and survival of men with metastatic prostate cancer are associated with the life-time cost-effectiveness of prostate cancer screening compared to no screening. The Markov models in Chapter 6 and Chapter 7 used the management, survival and costing information of men with metastatic prostate cancer that played an important role in the models. This information is elaborated in the next chapter.

Chapter 7. Management, characteristics, survival and costs of men with metastatic prostate cancer

7.1 Introduction

Approximately 11%-13% of the prostate cancer cases in New Zealand are metastatic at diagnosis,[30] and 65% of patients with metastatic prostate cancer died within two years.[33] The treatment of metastatic disease includes use of ADT, radiotherapy and chemotherapy. Access to treatment depends on appropriate access to specialist care from urologists, radiation oncologists and medical oncologists.[328] In addition, it is recognised that in some cases, general practitioners are involved in the management of men with metastatic disease.[150]

As there are no standardised New Zealand guidelines for the management of metastatic disease or the use of ADT, treatment regimens vary considerably depending on multiple factors that may include: patient characteristics, such as age, comorbidities, domicile, tolerance to specific drug type and patient acceptance of treatment. Clinician preference, access to a medical oncologist, and access to subsided medication may also be factors in the treatment pathway for men with metastatic disease.

ADT is commonly used for men with metastatic prostate cancer in New Zealand[112] and is fully subsidised[329]. The subsidised ADT agents used to treat metastatic prostate cancer include anti-androgens (flutamide, bicalutamide and cyproterone) and luteinising hormone-releasing hormone (LHRH) analogs (goserelin, leuprorelin).

Most prostate cancers are hormone sensitive and regress with ADT for a variable period of time.[330] A proportion of men will go on to develop CRPC. The definition of CRPC varies between studies and centres but is usually based on factors such as a rising PSA level whilst on ADT, symptomatic progression or changes to metastatic lesions on imaging. Generally, CRPC will develop in 10-20% of patients[331]. It has been shown that improvements in survival can be achieved by appropriately using different medications to treat castration-resistant tumours[331].

Chemotherapy can be used to treat patients with CRPC to prolong their life.[284] However, chemotherapy such as docetaxel is rarely used in New Zealand [112], with only 2% of men with metastatic prostate cancer receiving chemotherapy [33]. Docetaxel was approved and subsidised by PHARMAC since July 2011. Other emerging agents have been developed for treating CRPC and may alter future treatment patterns for metastatic prostate cancer.[177] Use of new therapies for treating metastatic prostate cancer may improve survival and quality of life, but many of these therapies are expensive.[177]

Patients with advanced prostate cancer might suffer from severe symptoms or complications especially in their final stage of life, including anaemia, pain, fatigue, nausea, anxiety and depression.[332,333] Palliative care is essential to improve the quality of life and provide early relief of

physical and psychosocial distress to patients with incurable disease.[332,334] The costs of management for metastatic prostate cancer, including treatments to prolong patients' life and palliative care for end-stage patients, can be substantial. However, this information is rarely available.

This study aims 1) to characterise men diagnosed with metastatic prostate cancer in New Zealand; 2) to describe the management of these men; 3) to look at the outcomes of treatment and survival in men with metastatic prostate cancer; and 4) to estimate the treatment costs across the management pathway for metastatic prostate cancer, using data from a cohort of men in the Midland Cancer Network region of New Zealand (Waikato, Lakes and Bay of Plenty DHBs).

7.2 Methods

7.2.1 Included patients

Patients diagnosed with prostate cancer were identified in the Midland Cancer Network Region between 1 January 2009 and 31 December 2012 from the NZCR. From this database, the NHI number, ethnicity, place of residence and date of birth of each man registered with prostate cancer during the requested period were received.

Prostate cancer on the NZCR is poorly staged with approximately 75%-80% of prostate cancers being un-staged. To correctly identify men who were metastatic within our cohort, access to public and private hospital and specialist medical files for each identified patient was sought. Every man was staged through a clinical file review where necessary staging information from both the diagnosis and treatment phases was recorded. Recorded data included PSA tests, DRE scores, primary and secondary Gleason scores, imaging results and clinical staging. For patients whose clinical or pathological reports did not specify the cancer extent, their records were examined by an urologist to identify the cancer extent at diagnosis. Patients whose cancer extent at diagnosis could not be identified were excluded. Patients who had metastatic disease in 2009-2012 were included in this study.

7.2.2 Characteristics, management and survival

Dates of all tests and treatments were recorded to ensure accuracy of diagnosis date. The date of death was extracted from the Mortality Collection which classifies the underlying cause of death for all deaths registered in New Zealand. The medication type and dispensing date were extracted from PHARMS. The PHARMS records claim and payment information from pharmacists for all subsidised dispensed medications. PSA values and dates were provided by Pathlab; a pathology service that provides medical testing within the Midland region. PSA at diagnosis included the PSA test nearest to the diagnosis date, i.e., within 3 months. The role of the physician who prescribed ADT and/or chemotherapeutic agents was identified from the clinical files, and was added to the PHARMS dataset.

The censored date in the PHARMS dataset was 31 December 2012. Overall this was the censor date for the study.

The characteristics of the eligible patients, including age, ethnicity (Māori/Pacific, non-Māori/non-Pacific (excluding Māori men and Pacific men)) and PSA level were examined. The approaches to ADT in New Zealand included orchiectomy, anti-androgens (flutamide, bicalutamide, and cyproterone) and luteinizing hormone-releasing hormone (LHRH) agonists (goserelin, leuprorelin). The pattern of ADT for metastatic cancer was examined, including the characteristics of men treated with ADT, the time from the metastatic diagnosis to the first ADT prescription, and the identification of clinicians who initiated prescribing ADT. Patients who had an orchiectomy or radiotherapy to treat metastatic complications and those who subsequently had chemotherapy (doxorubicin, epirubicin, paclitaxel, mitozantrone, docetaxel) were characterised.

The outcomes for men treated with ADT were believed to be of interest in understanding the use of ADT. Survival was measured in months, from the date of metastatic diagnosis to the date of death. Men were censored if they were alive by the date of 31 December 2012. The all-cause survival of patients with metastatic cancer was estimated by the Cox proportional hazards model with adjustment for patients' age and ADT use.

7.2.3 Included medical resources in cost estimation

To identify hospital events and pharmaceutical information, eligible patients were linked by their NHI to the following databases: NNPAC, NMDS and the PHARMS. NNPAC collects national records for outpatient and emergency department events (identified as outpatient events in this study), NMDS contains clinical data for inpatients and day patients (inpatient events), and PHARMS includes all dispensing records for subsidised pharmaceuticals. Pharmaceuticals used for metastatic prostate cancer are listed in Table 32.

Deaths amongst eligible patients were identified from the Ministry of Health's Mortality Collection. Events (resource utilisation) occurring after 31 December 2012 are not included in the study, as data from NNPAC, NMDS or PHARMS after this date was not available.

7.2.4 Treatment pathway: three phases

Follow-up time was measured from the date of metastatic diagnosis to the date of death or the end of 2012. Treatment pathway was divided into three phases: diagnostic, treatment and terminal [335]. The diagnostic phase was the first three months after the metastatic diagnosis. Where a death was identified, the terminal phase includes the last three months prior to a patient's death. The treatment

phase consisted of the time from the end of the diagnostic phase to the beginning of the terminal phase (if death occurred) or the end of 2012 (if death did not occur before then). The detailed principles of how patients' follow-up time was distributed are shown in Table 47. Though there are other ways of breaking down patients' follow-up time [336], the three-phases method was the most suitable one for our study because the follow-up time for these patients varied greatly.[33]

Table 47. Rules of distributing phase time to different phases

Patient died during the follow-up period	Length of phase time	Diagnostic phase	Treatment phase	Terminal phase
Yes	≤ 3 months	/	/	All the follow-up time
	(3,6] months	The follow-up time excluding the last three months	/	The last three months prior to patient's death
	> 6 months	The first three months after the metastatic diagnosis	The time between the diagnostic and terminal phase	The last three months prior to patient's death
No	≤ 3 months	All the follow-up time	/	/
	> 3 months	The first three months after the metastatic diagnosis	The follow-up time excluding the first three months	/

Note: Eight patients died during the period from 1 January 2013 to 31 March 2013 (within 3 months from the censor date for this study). For these eight patients, the last 3 months prior to patients' death (excluding the time in 2013) were distributed to the terminal phase. Since survival data was available until 6 months following the censor date in the three datasets, there was no follow-up time that should be recorded at the terminal phase was distributed to the treatment phase.

7.2.5 Cost estimation

The estimated costs excluded goods and services tax (GST) and were valued in 2012/13 New Zealand dollars (NZ$). The reported figures are not discounted, as 50% of the patients in our cohort died within 12 months.

Although events in oncology, urology and palliative and terminal care were considered to be more relevant to metastatic prostate cancer, it is difficult to identify in all cases which hospital events were associated with metastatic prostate cancer (and its complications) and which events are unrelated. Therefore, two cost estimations are presented: 1) total public hospital and pharmaceutical costs; 2) those costs from (1) which are directly associated with the management of prostate cancer. In this case, pharmaceuticals and hospital events are included if they occurred in oncology, urology or palliative and terminal care.

Inpatient costs were estimated by multiplying the accumulated cost weights for all events with the purchase unit price (NZ$ 4,614.36 in 2012/13). The cost weights which provide resource utilisation

information are calculated by the Ministry of Health for each DRG code using the Weighted Inlier Equivalent Separation (WIES) method, and a purchase unit price is set each year.[337] Outpatient events were costed using the purchase unit codes and the unit costs (per purchase unit) provided by the Waikato District Health Board. The pharmaceuticals identified were all fully subsidised in 2012/13 and the listed price that appears in the Pharmaceutical Schedule[329], plus a mark-up (4% of the drug costs below NZ$150, or 5% of the drug costs exceeding NZ$150)[338] were used. A NZ$5.30 dispensing fee was added for all pharmaceuticals, as recommended by PHARMAC [339].

7.2.6 Statistical analysis

The overall medical costs and the prostate cancer related costs were estimated by phase (diagnostic, treatment and terminal), age group (<60, 60-69, 70-79, 80+) and ethnicity (Māori/Pacific, non-Māori/non-Pacific). The differences in the overall medical costs and the prostate cancer related costs among different subgroups were examined using a Kruskal-Wallis test and Mann-Whitney U test. The Jonckheere-Terpstra test was used to identify whether there was any trend in the costs among the four age groups.

The medical costs and the prostate cancer related costs during the treatment phase were log-transformed (natural logarithm) to examine their correlation with phase time and age group (<80, 80+) by ordinary least-squares regression. The reason why the two age groups (<80, 80+) instead of the four age groups (<60, 60-69, 70-79, 80+) was used was that the pearson correlation showed that the difference in the costs during the treatment phase between the two age groups (<80, 80) was more significant ($p<0.001$).

7.3 Results

7.3.1 Characteristics of the eligible men

Two thousand, one hundred and twenty seven men had a diagnosis of prostate cancer in the Midland Cancer Network region during the period between 2009 and 2012. Māori and Pacific men accounted for 9.1% (193/2127) of these registrations. Among these men, 234/2127 (11%) were found to have metastatic prostate cancer in 2009-2012 - 26/193 (13.5%) of Māori/Pacific men and 208/1934 (10.8%) of non-Māori/non-Pacific men. The characteristics of the eligible patients are shown in Table 48. The mean age of the patients was 75 years at metastatic diagnosis. The mean age of the Māori/Pacific (72 years) men was lower compared to non-Māori/non-Pacific (76 years). The proportion of Māori/Pacific men diagnosed with metastatic cancer at the age of less than 70 years old was 38.5% compared with 28.8% for non-Māori/non-Pacific.

The PSA level at metastatic diagnosis is shown in Table 48. Of the PSA values at metastatic diagnosis, 79.1% were ≥20 ng/ml, 54.4% were ≥100 ng/ml, and 15.0% were ≥1000 ng/ml.

Māori/Pacific men with metastatic cancer were more likely to have a PSA level of ≥1000 ng/ml (22.7%) and less likely to have a PSA result of less than 20 ng/ml (13.6%) compared with non-Māori/non-Pacific (13.8% and 22.1%, respectively).

Table 48. Characteristics of eligible men

	Māori/Pacific (26)	non-Māori/non-Pacific (208)	Total (234)
Age			
<60	2 (7.7%)	15 (7.2%)	17 (7.3%)
60-69	8 (30.8%)	45 (21.6%)	53 (22.6%)
70-79	7 (26.9%)	66 (31.7%)	73 (31.2%)
80+	9 (34.6%)	82 (39.4%)	91 (38.9%)
PSA level within 3 months before or after the metastatic diagnosis			
<10	2 (9.1%)	22 (15.2%)	24 (14.4%)
10~20	1 (4.5%)	10 (6.9%)	11 (6.6%)
20~100	6 (27.3%)	36 (24.8%)	42 (25.1%)
100~1000	8 (36.3%)	57 (39.3%)	65 (39.0%)
≥1000	5 (22.7%)	20 (13.8%)	25 (15.0%)
No PSA test	4	63	67

7.3.2 Treatment for patients with metastatic prostate cancer

After the metastatic diagnosis, 194/234 (82.9%) of patients received anti-androgens or LHRH agonists. Two patients subsequently underwent orchiectomy after pharmacological ADT. Five men had chemotherapy (all were treated with docetaxel). To treat the complications caused by the metastatic cancer, 104/234 (44.4%) had radiotherapy. Among the 21 patients whose follow-up time was less than one month (either because of death or being censored), only seven (33.3%) received ADT. The characteristics of patients on different treatments are displayed in Table 49. Māori/Pacific men were no less likely to have radiotherapy (RR: 1.27 (95%CI: 0.83-1.93)) or to receive ADT (RR: 1.14 (95%CI: 0.49-2.66)), compared to non-Māori/non-Pacific men. The possibility of having radiotherapy decreased with age, from 70.6% for men aged less than 60 years to 33.0% for men aged 80+. A similar pattern was found for men on ADT, from 94.1% for men aged less than 60 years to 74.7% for men aged 80+. The two men who received an orchiectomy were both over 70 years at the time of treatment. The five patients who had chemotherapy were all non-Māori/non-Pacific men aged less than 80 years.

Table 49. Characteristics of patients treated

	Number of patients	Radiotherapy	ADT	Chemotherapy
Ethnicity				
Māori/Pacific	26	13 (50.0%)	21 (80.8%)	0
non-Māori/non-Pacific	208	82 (39.4%)	173 (83.2%)	5 (2.4%)
Age				
<60	17	12 (70.6%)	16 (94.1%)	1 (5.9%)
60-69	53	27 (50.9%)	48 (90.6%)	2 (3.8%)
70-79	73	26 (35.6%)	62 (84.9%)	2 (2.7%)
80+	91	30 (33.0%)	68 (74.7%)	0
Total	234	95 (40.6%)	194 (82.9%)	5 (2.1%)

The pharmacological ADT type first prescribed after metastatic diagnosis and what type of clinician prescribed the first pharmacological ADT is presented in Table 50. Of the 194 patients on ADT, the most common first prescription was cyproterone acetate (27.8%). The proportions of other drugs prescribed first for metastatic prostate cancer patients included: flutamide (24.2%), leuprorelin (15.5%), goserelin (11.9%), combined androgen blockade (CAB) (14.4%) and bicalutamide (6.2%). The first pharmacological ADT course was predominantly prescribed by urologists (74.7%). Urologists were more likely to prescribe anti-androgens as the first pharmacological ADT (62.6%), whilst oncologists were more likely to prescribe LHRH agonists and CAB (71.0%).

The timeframe from diagnosis to first pharmacological ADT was relatively short with most patients (72.2%) starting their first course of pharmacological ADT within 4 weeks. Of the 194 men with pharmacological ADT, 73.7% (143/194) switched to a different medication at some stage while only five (2.4%) were treated with docetaxel.

Table 50. The first ADT after the metastatic diagnosis, by department prescribed

Department	Bicalutamide	Cyproterone acetate	Flutamide	Goserelin acetate	Leuprorelin	Combined androgen blockade	Total
Oncology	2 (6.5%)	5 (16.1%)	2 (6.5%)	11 (35.5%)	0	11 (35.5%)	31
Urology	8 (5.8%)	40 (28.8%)	39 (28.1%)	11 (7.9%)	26 (18.7%)	15 (10.8%)	139
Others	1 (6.3%)	7 (43.8%)	3 (18.8%)	0	3 (18.8%)	2 (12.5%)	16
Unknown	1 (12.5%)	2 (25.0%)	3 (37.5%)	1 (12.5%)	1 (12.5%)	0	8
Total	12 (6.2%)	54 (27.8%)	47 (24.2%)	23 (11.9%)	30 (15.5%)	28 (14.4%)	194

The number of PSA tests for men treated with pharmacological ADT in 12 months after the metastatic diagnosis is shown in Table 51. No PSA test was recorded for 46 (24%) patients, whilst 80 (41%) had three or more tests. Thirty men were recorded as having a serum testosterone measured.

Table 51. Number of PSA tests for patients on ADT in 12 months after the metastatic diagnosis

Follow-up time	0	1	2	3	4+	Total
1-90 days	16	7	3	0	0	26
91-180 days	7	8	5	3	2	25
181-270 days	7	3	2	4	6	22
271-360 days	0	2	5	5	7	19
>360 days	16	14	19	11	42	102
Total	46	34	34	23	57	194

7.3.3 Survival in men with metastatic prostate cancer

By 31 December 2012, 134/234 men had deceased by 31 December 2012. The all-cause survival curve by ethnicity from the Cox proportional hazards model is displayed in Figure 34 and shows that survival for non-Māori/non-Pacific was superior. Māori/Pacific patients had 1.49-fold (95% CI: 0.89-2.49) risk of death in comparison with non-Māori/non-Pacific patients after adjustment for patient's

age and ADT use. Patients who did not receive ADT were 4.29-times (95% CI: 2.73-6.75) more likely to die than patients who were on ADT after adjustment for patient's age and ethnicity. Older patients were more likely to die than younger patients were (hazard ratio: 1.04, 95% CI: 1.02-1.06) after adjustment for ethnicity and ADT use.

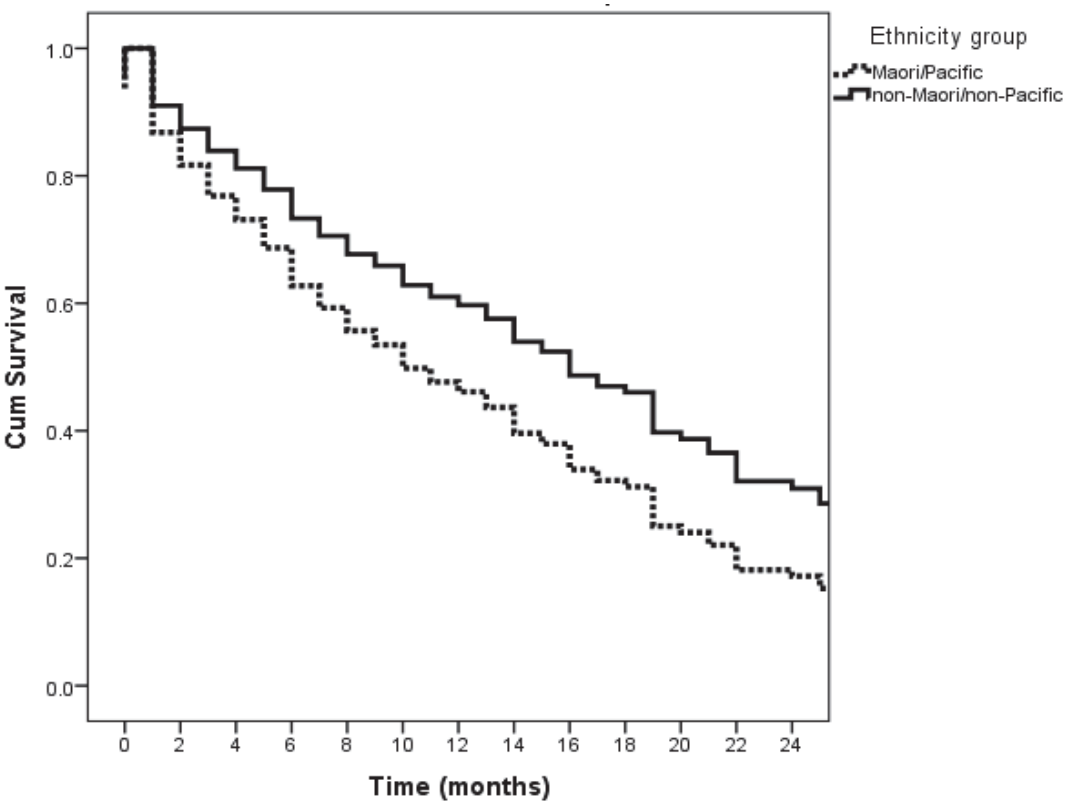

Figure 34. All-cause survival by ethnicity by Cox proportional hazards model

7.3.4 Phase time and average medical costs during the three phases

After each patient's pathway was divided into the three phases, 197 patients had phase time during the diagnostic phase, 162 patients during the treatment phase and 141 patients during the terminal phase (Table 52). The average phase time was 82 days during the diagnostic phase, 406 days during the treatment phase and 75 days during the terminal phase. Note that where the terminal phase is below 90 days, this means that death occurred within 90 days of diagnosis. The shortest follow-up time in the study was one day.

The average medical costs for these men were $5,576 (average prostate cancer related costs: $2,427) during the diagnostic phase, $13,428 (average prostate cancer related costs: $7,130) during the treatment phase and $10,558 (average prostate cancer related costs: $4,305) during the terminal phase (Table 52). The daily medical costs were $68 (daily prostate cancer related costs: $30) during the diagnostic phase, $33 (daily prostate cancer related costs: $18) during treatment phase, and $141 (daily prostate cancer related costs: $57) during the terminal phase. The daily prostate cancer related costs decreased with increasing age: from $31 for men aged less than 60 years to $17 for men aged

80+ (p<0.001). The daily prostate cancer related costs for Māori/Pacific and Non-Māori/Non-Pacific were both $24 (p=0.526).

Table 52. Average costs by age group, ethnicity and phase

	Number of patients	Average follow-up time (days)	Average overall medical costs	Daily overall medical costs	Average prostate cancer related costs	Daily prostate cancer related costs
By age group						
<60	17	654	$25,229	$39	$20,022	$31
60-69	53	454	$22,998	$51	$13,601	$30
70-79	73	445	$22,009	$49	$10,396	$23
80+	91	273	$16,558	$61	$4,601	$17
p value§				0.292		0.001
p value†				0.177		<0.001
By ethnicity						
Māori/Pacific	26	378	$18,403	$49	$8,998	$24
Non-Māori/Non-Pacific	208	398	$20,590	$52	$9,639	$24
p value‡				0.593		0.526
By phase						
Diagnostic phase	197	82	$5,576	$68	$2,427	$30
Treatment phase	162	406	$13,428	$33	$7,130	$18
Terminal phase	141	75	$10,558	$141	$4,305	$57
Overall	234	395	$20,347	$51	$9,568	$24

§ Kruskal-Wallis test †Jonckheere-Terpstra test ‡ Mann-Whitney U test

The results from the ordinary least-squares regression model were transformed into formulas to predict the medical costs and the prostate cancer related costs during the treatment phase (Table 53). The medical costs and the prostate cancer related costs during the treatment phase for men aged less than 80 years would be twice and three times, respectively, the costs for men aged 80+, when the phase time is the same. The medical costs would double every 231 days and the prostate cancer related costs would double every 173 days.

Table 53. Formulas to predict the costs during the treatment phase

Costs	Age group	Formula
Overall medical costs	<80	$C=1312\times e^{0.003T}$
	80+	$C=619\times e^{0.003T}$
Prostate cancer related costs	<80	$C=431\times e^{0.004T}$
	80+	$C=146\times e^{0.004T}$

C: costs

T: phase time during the treatment phase

7.3.5 Proportion of each cost element in total costs

Figure 35 displays the proportion of cost in different health specialties in total hospital costs (including inpatient and outpatient costs). Approximately 28% of the hospital costs incurred in oncology (highest during the treatment phase: 33%), 5% was associated with the services in urology (highest during the diagnostic phase: 4%), and 8% was for palliative and terminal care services (highest during the terminal phase: 13%). The proportion of oncology cost in total hospital costs decreased with age (Figure 36), from 65% for men aged less than 60 years to 12% for men aged 80+. In contrast, the percentage of hospital costs in other specialities (other than oncology, urology and palliative and terminal care) in total hospital costs increased with age, from 24% for men aged less than 60 years to 79% for men aged 80+. The proportion of cost of palliative and terminal care in total hospital costs decreased with age (expect for men aged <60 years): 11% for men aged 60-69 to 5% for men aged 80+.

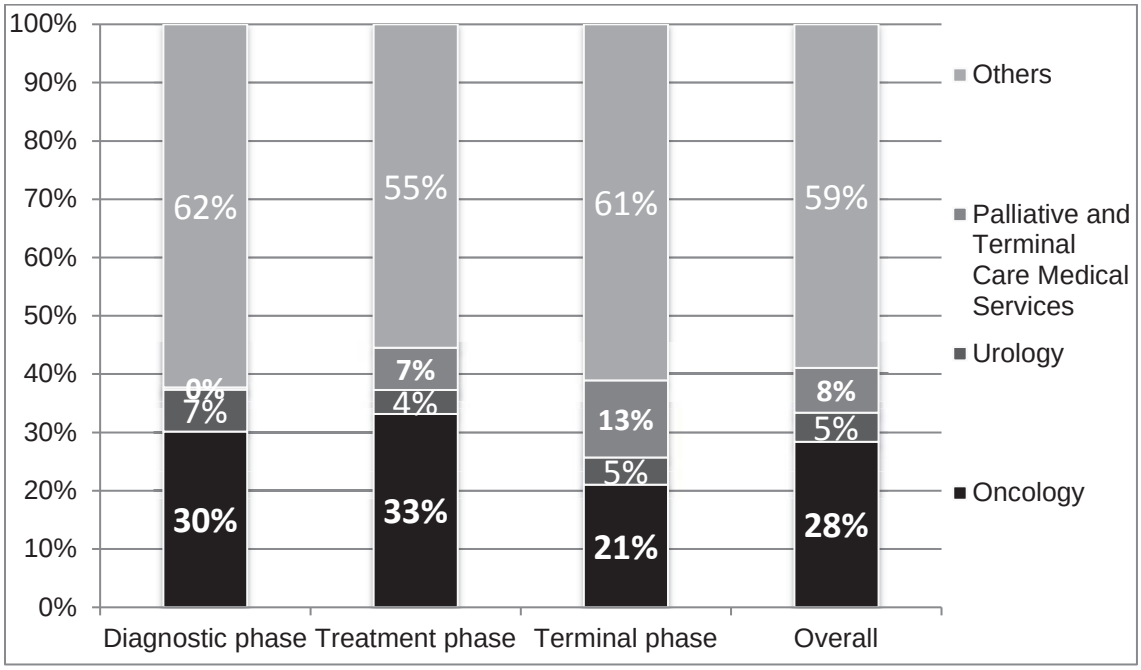

Figure 35. The proportion of hospital costs incurred in each health specialty in total hospital costs by phase

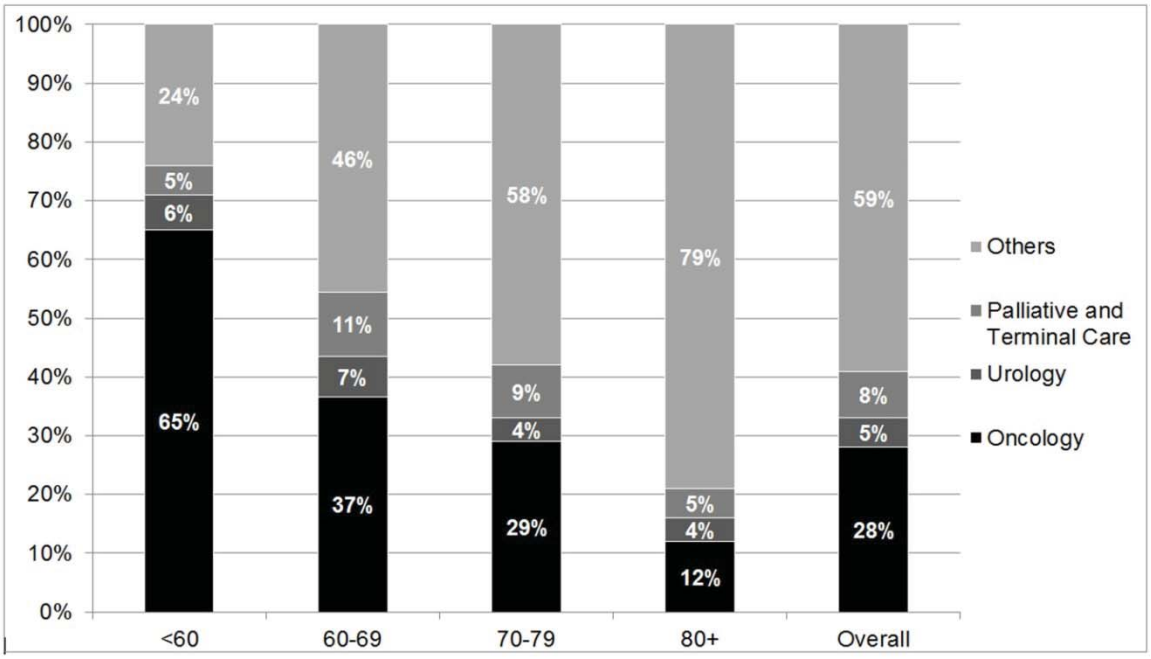

Figure 36. The proportion of hospital costs incurred in each health specialty in total hospital costs by age group

The proportion of each cost element in the prostate cancer related costs is shown in Figure 37. Overall, the inpatient costs accounted for the largest proportion (46%) in the prostate cancer related costs, followed by the outpatient costs (32%) and pharmaceutical costs (22%). The proportion of each cost element in the prostate cancer related costs differed in the three phases. The proportion of inpatient costs in the prostate cancer related costs was highest during the terminal phase (78%), and lowest during the diagnostic phase (31%). The percentage of pharmaceutical costs in the prostate cancer related costs was lowest during the terminal phase (7%), and highest during the treatment phase (29%). ADT cost comprised 95% (anti-androgens: 7%; LHRH analogs: 89%) of total pharmaceutical costs. Docetaxel was the only chemotherapeutic agent identified in the PHARMS for these patients (used in five patients). It only accounted for 3% of the total pharmaceutical costs.

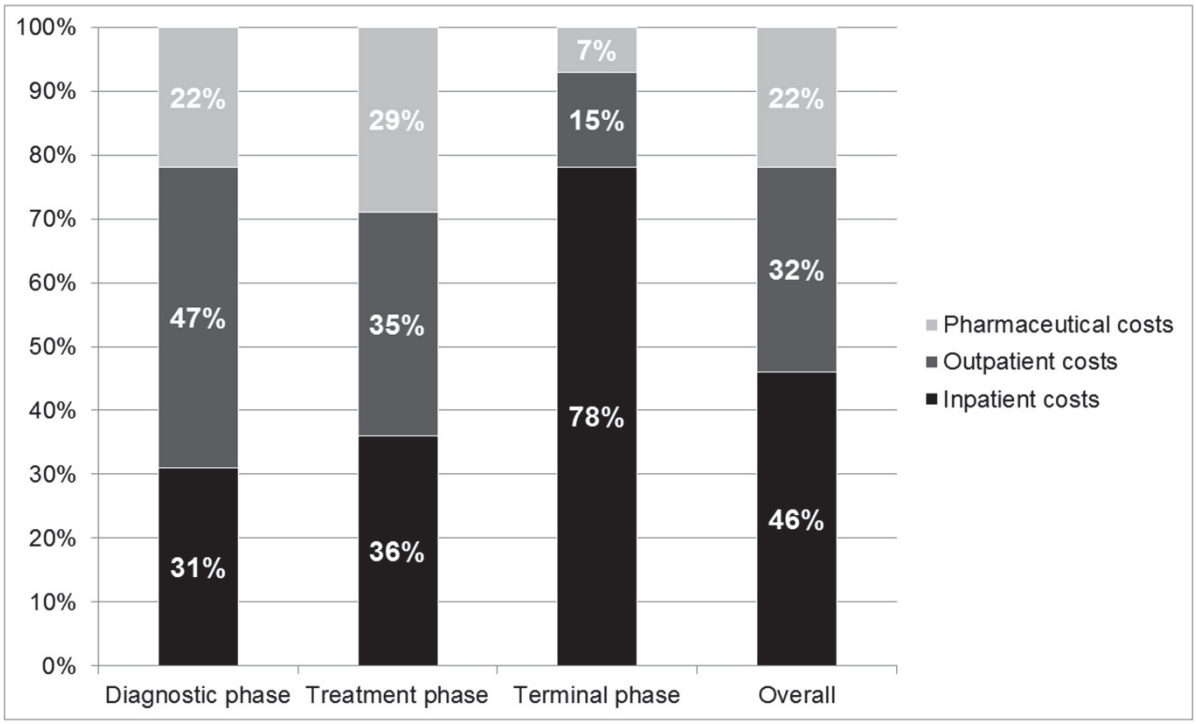

Figure 37. The proportion of each cost element in the prostate cancer related costs

7.3.6 Palliative and terminal care services

Palliative and terminal care services were received by 54/234 (23%) men during the whole follow-up period, and 37/141 (26%) men during the terminal phase. In the last 3 months in life, 27 men had outpatient consultations (average number of specialist consultations: 2.4; average costs: $898), and 18 men were admitted for hospitalization (average length of hospitalization: 6.8 days; average costs: $9,251.) in the palliative and terminal care department.

7.4 Discussion

7.4.1 Characteristics of men with metastatic prostate cancer

Eleven percent of men were presented with metastatic prostate cancer. This is a greater proportion than has been found to have Stage IV disease in a US study using the SEER data (6.4%)[340] or a similar study from Spain (4%)[341]. Both these countries have a high utilisation of PSA testing and therefore an increasing proportion of men with low risk prostate cancer at diagnosis. The prevalence of 11% is significantly lower than the proportion found in Scandanavia where PSA testing is less widespread.[183]

While the mean age of men diagnosed with prostate cancer in New Zealand is 68 years (during 2010), the mean age of men presenting with metastatic cancer is 75. Out of 2127, 17 men aged less than 60 years (0.8%) presented with metastatic disease. This is a small but important group of men who

would have a substantial life expectancy if not for their cancer. Māori/Pacific men were more likely to be present with metastatic disease and generally had higher PSA levels at diagnosis.[30]

7.4.2 Treatment and Management

Most of the men diagnosed with metastatic disease (83%) are treated with ADT. The reasons for why 17% of men were not treated with ADT were not identified. Some of these men might have developed CRPC before the metastatic diagnosis. We have shown that increasing age reduces the likelihood of pharmacological ADT being initiated. Only one-third of men who died within the first month post-metastatic diagnosis had begun treatment. A study from the US has suggested that only 11% of stage 4 prostate cancer patients were not treated compared with a quarter of stage 4 lung or kidney cancer patients who are not treated.[342] Our results show fewer men receive treatment than in the US but age and prognosis seem to be important indicators of reduced likelihood of active treatment. It is also noteworthy that the use of radiotherapy presumably for the treatment of bony metastases and pain seems to reduce with increasing age in our cohort.

While pharmacological ADT is commonly used to treat New Zealand men with metastatic prostate cancer a number of treatments seem to be used as first line. Orchiectomy which was a common first line treatment is now rarely used in the Midland Cancer Network Region of New Zealand although it is still used in the Southern Cancer Network Region[112] and is a recommended option by UK NICE 2014.[343] Androgen antagonists such as cyproterone or flutamide are commonly used as first line treatment especially by urologists. In contrast, radiation oncologists use LHRH more frequently, while a small proportion of patients are started on combined androgen blockade. The evidence for the use of these different agents is now dated and could be considered as unreliable.[344,345] There seems to be little demonstrable difference between cyproterone and flutamide with regards to survival and side effects although toxicity is said to be more pronounced with flutamide.[346] Bicalutamide is preferred by some as it is longer acting[347] and for those who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function it may be used as monotherapy.[343] LHRH antagonists are longer acting and equally effective as anti-androgens[348] – indeed they are considered marginally superior by NICE. In certain conditions such as in the presence of bony metastases, anti-androgens may be given for a short period to reduce the risk of flare that can be caused by LHRH antagonists. One of the issues in the use of various LHRH antagonists is cost and there is a suggestion that leuprorelin as a Depo treatment is the most cost effective LHRH formulation.[349] Combined androgen blockade has been suggested as more effective than monotherapy but is not recommended as first line therapy by NICE 2014. Overall, there is little to choose between the different treatments with regard to improved life expectancy, so costs and patient tolerability become very relevant. It also seems that physician preference is a factor with notable differences between the treatments used by urologists compared with radiation oncologists. However, it may be due to the differences in the patient mix (different characteristics) seen by different specialists.

Chemotherapy was rarely used with only 2.4% of patients being offered docetaxel.[112] Chemotherapeutic agents are usually used as second or third line treatments in the presence of CRPC. The definition of CRPC is not specific but is usually characterised by rising PSA levels, the development of further metastasis or increasing symptoms. In a review of studies looking at the prevalence of CRPC, it was shown between 9.5% to 53% of men who had undergone medical or surgical castration had CRPC.[331] It should be noted that many of these studies were on men treated for localised or locally advanced disease. However, it is well recognised that many men treated with ADT will progress to CRCP. It would seem to be reasonable that these men are monitored with PSA and when indicated imaging such as CT or bone scans. When men with prostate cancer develop evidence of hormone-refractory disease it is suggested that their treatment options should be discussed by the urological cancer multidisciplinary team. Those with CRCP could be considered for review by a medical oncologist and either more intensive ADT therapy[350] or chemotherapy[351]. Approximately 24% of men treated with ADT did not appear to be monitored with PSA. A significant proportion of men were found to switch ADT therapies although the reason for switching was not available but it is likely to be linked to tolerability and effectiveness. Evidence of other biomarkers (other than PSA test) being used to monitor treatment was not found, although 30 men did have testosterone levels measured. There does seem to be scope for guidelines in the monitoring of men on ADT with both bio markers and imaging in order to identify early evidence of CRPC and to ensure the most effective treatments are offered. It appeared that medical oncologists are rarely involved in the management of men with advanced prostate cancer. Our data showed that only 1% of the pharmacological ADT agents were prescribed by medical oncologists.

7.4.3 Survival

Our study of survival of men presenting with metastases has shown poor survival of this group of men. Only 59% of these men will survive 12 months and 35% 2 years. These findings are considerably worse than data from overseas – in the UK 80% of patients with metastatic prostate cancer survive one year and 60% survive 2 years[289]. Survival is poorer for older men and those with high PSA levels at diagnosis. The poorer prognosis in older men is likely due to not only the presence of age related comorbidities but also the decreasing use of ADT and radiotherapy for treatment in older men. Those men treated with ADT have better survival. This is probably a reflection of prescribing bias where patients who have a very poor prognosis are less likely to be offered active treatment. Survival is worse for Māori/Pacific men compared with non-Māori/non-Pacific despite their younger age. Māori/Pacific men tend to present with higher PSA levels and higher grade of disease.

7.4.4 Costs

This study showed that the daily medical costs during the terminal phase were twice the costs during the diagnostic phase and more than three times the costs during the treatment phase. The high costs

during the terminal phase might be ascribed to the expensive medical services for end-stage patients, e.g., palliative radiotherapy and inpatient hospitalisation. Changes in the treatment pattern for metastatic prostate cancer may alter the estimated results, especially the introduction of new and expensive therapies. Studies have been performed to assess the cost-effectiveness of different ADT agents.[349,352,353] Those results might not apply in the New Zealand setting where the management and overall costs of treating metastatic prostate cancer are different. This study provides important information on the economic burden of metastatic prostate cancer in New Zealand, and can contribute to the economic evaluation of new treatments for metastatic prostate cancer in New Zealand.

Costs in oncology, urology and palliative and terminal care were more directly related to the treatments for metastatic prostate cancer and its complications. The prostate cancer related costs decreased with increasing age, which means that younger patients received more treatments for metastatic prostate cancer than older patients. This might be related to the multiple comorbidities that older patients have. Though comorbidity data was not available to confirm this hypothesis, the finding that the higher costs incurred in other departments for older men was consistent with the hypothesis.

Though the probability of patients receiving palliative and terminal care services in the last 3 months of life was low (26%), it was consistent with a previous study which demonstrating that 46% of men dying from advanced prostate cancer had a cancer-related complication and 25% required related intervention(s) in their final year of life.[333]

The inpatient costs in our study accounted for the largest proportion (46%) in the prostate cancer related costs, followed by the outpatient costs (32%) and pharmaceutical costs (22%). The composition of costs was different from that in a Netherlands study where only 3% of the costs were for outpatient services and 84% of the costs were for treatment and hospital stay [354]. The Dutch study was based on data in the 1990s and may reflect different practices between New Zealand and the Netherlands. The different unit costs of resources in the two countries or methodological differences may also account for some of the variation.

The effect of chemotherapy on improved survival for patients with CRPC has been proven [284].Chemotherapy was only received by 5/234 (2%) of men with metastatic prostate cancer and none was used in men aged over 80 years old. If chemotherapy is more frequently used for metastatic prostate cancer, the treatment phase (where the cost per patient day was the lowest) may be prolonged. Though chemotherapy is expensive, the additional pharmaceutical cost is still less than the inpatient and outpatient costs. Wider use of chemotherapy is likely to be beneficial, especially amongst younger men in treating CRPC. Notwithstanding, the impact of such a change on total costs and health has not been formally assessed and no judgement of cost-effectiveness is made.

There was no significant difference between Māori/Pacific men and non-Māori/non-Pacific men in terms of both daily overall medical costs and daily prostate cancer related costs. This can be explained by the similar utilization of radiotherapy and ADT between Māori/Pacific men and non-Māori/non-Pacific men.

7.4.5 Strengths and limitations

As mentioned the staging of prostate cancer is rarely available in the NZCR. Only 5% of registrations were identified as metastatic on the NZCR. There would have been fewer patients eligible for this study if only patients whose cancer stage was recorded as metastatic in the NZCR were included. One of the strengths of our study was that the clinical records of men were examined to identify the cancer stage and date of diagnosis. More patients diagnosed with metastatic prostate cancer in 2009-2012 were identified and the medical costs for these patients from the date of metastatic diagnosis could be estimated. It is a population-based sample of men with prostate cancer – with complete data on metastatic disease recorded directly from clinical records. These data have been linked to prescribing and mortality data.

This study has some limitations. There are some costs that this study could not cover. These include the cost in private hospitals and general practices and patients' contributions for the pharmaceuticals. Because radiotherapy in our region during this period was only available in the public sector, costs for metastatic cancer in private hospitals in our region are minimal. The costs of different treatment sequences were not measured as there was significant variation in the initiation of ADT, also in the use of second line and subsequent therapies. Monitoring of ADT treatment with PSA is also variable. Better guidelines on the use of ADT and use of chemotherapy are needed. Among the health care services in the NNPAC and the NMDS, which services were associated with metastatic prostate cancer and which were used for patients' comorbidities were not identified. Considering this weakness, the urology and oncology costs which were more relevant to the management of metastatic prostate cancer were estimated. A weakness is that the study has been carried out in a region of New Zealand that may not be representative of other regions. However, the differences between regions are not large.

7.5 Conclusion

Overall metastatic disease is still commonly diagnosed at presentation in New Zealand and that the survival in these patients is substantially worse that would be expected from overseas comparisons. The incidence of metastatic disease is greater in Māori as its mortality compared to non-Māori. The use of different formulations of ADT is noteworthy as is the lack of consistency of monitoring for CRPC. There seems to be a strong case for the development of New Zealand guidelines on the management of metastatic disease including the use of first line treatments and the need for ongoing monitoring for the development of CRPC. There is a need for consistent action in the assessment of men who develop CRPC with assessment by a multidisciplinary team and improved access to chemotherapeutic agents. It would seem probable that better management of this group of patients could offer substantial improvements in outcomes.

The management costs for patients with metastatic prostate cancer varied by phase, with the terminal phase being the most expensive. The costs of treating metastatic prostate cancer decreased with increasing age. Wider use of chemotherapy in New Zealand may be warranted, as the current costs account for a small proportion of total treatment costs.

7.6 Summary of Chapter 7

Of the 2127 men registered with prostate cancer on the New Zealand Cancer Registry in the Midland Cancer Network Region in 2009-2012, 234 (26 Māori/Pacific and 208 non-Māori/non-Pacific) were diagnosed with metastatic prostate cancer. After the diagnosis, 194 (82.9%) patients received ADT, five had chemotherapy and 104 (44.4%) had radiotherapy. Of the patients treated with ADT, 46 (23.7%) had no monitoring PSA tests. Fifty nine percent of patients were alive in 12 months and 35% in 24 months. The hazard ratio for Māori/Pacific men was 1.49. The average daily medical costs were NZ$68 (daily prostate cancer relevant costs: NZ$30) during the diagnostic phase, NZ$33 (daily prostate cancer relevant costs: NZ$18) during the treatment phase and NZ$141 (daily prostate cancer relevant costs: NZ$57) during the terminal phase. The inpatient costs accounted for the largest proportion (46.4%) in the prostate cancer relevant costs. Chemotherapy comprised 2.5% of total pharmaceutical costs. The prostate cancer relevant costs during the three phases decreased with age.

Chapter 8. Discussion

This chapter aims to synthesize all the studies into context as a whole. It comprises a discussion on the cost-effectiveness of prostate cancer screening, the cost-effectiveness of treatments (particularly active surveillance versus radical prostatectomy) for localised prostate cancer, management and costs of metastatic prostate cancer, and difference in screening and management of prostate cancer between Māori/Pacific men and non-Māori/non-Pacific men.

8.1 Prostate cancer screening

8.1.1 Effectiveness of prostate cancer screening

The aim of cancer screening is to identify cancer cases early through testing asymptomatic men and to treat them at an early stage to reduce mortality. However, evidence of effectiveness of prostate cancer screening has been equivocal in reducing mortality.[5,6,8] Therefore, no country recommends population-based prostate cancer screening. Despite this, screening using PSA test is widespread in New Zealand and has been becoming common.[30]

The possibility of identifying a new case of prostate cancer by screening and the average screening costs varied by age, ethnicity and PSA testing history in this thesis. These might be related to the different prevalence and screening interval by subgroups. The prevalence of prostate cancer by age and ethnicity has been shown in section 1.2.1.

The optimal screening interval is unknown.[355] To identify more cancer cases, the screening interval could be shorter. Otherwise, more interval cancers would be missed. However, a longer interval would minimise the harms caused by screening and reduce the costs. As shown in Chapter 3, men who had no PSA tests in the past three years were 3.6 times more likely to be diagnosed with prostate cancer by screening than men who had PSA tests in the past three years. Subsequently, the costs of identifying a new case of prostate cancer by screening in men without PSA testing history in the past three years were 56%-91% higher than the costs in men with PSA testing history in the past three years.

With a long screening interval, the incidence of interval cancers is a concern that may contribute to prostate cancer mortality. The Antwerp centre, the Rotterdam centre and the Gothenburg centre were all part of the ERSPC study.[273,356] The 10 year cumulative incidence of aggressive interval cancers (stage M1 or N1, Gleason score higher than 7 or World Health Organisation (WHO) score of 3) was 0.5% (8/1660) in the Antwerp centre with an average 6-years screening interval, compared to 0.11% (15/13301) in the Rotterdam centre with an average 4-years screening interval and 0.12% (5/4202) in the Gothenburg centre with an average 2-years screening interval. [273,356] There was significant difference in the cumulative incidence of aggressive interval cancers between the Antwerp centre and

the Rotterdam centre, but there was no significant difference between the Rotterdam centre and the Gothenburg centre. Based on these studies, a 4-years screening interval seems reasonable.

The effectiveness of a prostate cancer screening programme depends on the identification of cancer cases and more importantly the management of the screen-detected cancers. The PIVOT study[15] that was based on a cohort of men with screen-detected localised prostate cancer demonstrated no significant difference in the prostate cancer-specific mortality between men who underwent radical prostatectomy and those under watchful waiting, particularly in those with low risk localised prostate cancer. If the results of this trial were robust, the screen-detected localised prostate cancer cases would make no contribution to the reduction of prostate cancer mortality by screening. Only the ERSPC[5] and the Göteborg study[6] have demonstrated a benefit from screening. On the other hand there are well recognised harms from treatments.

8.1.2 Impact on quality of life

During the whole screening pathway including screening, diagnosis and treatment, the quality of life for men involved in the pathway is compromised. The impact of screening on the quality of life for men being screened affects the whole screening population but is often not considered in the economic evaluation studies[26,235]. The harms for men participating in screening include the worry as to whether they had clinically significant prostate cancer, and the physical and psychological discomfort when undergoing DRE and biopsy. In a study conducted by Essink-Bot et al[357], physical discomfort was reported in 37% of men during DRE, 29% of men during transrectal ultrasound, and 55% of men during prostate biopsy. Men with a high predisposition to anxiety may experience high levels of anxiety during the screening process.[357] Cormier L[358] and colleagues recruited brothers or sons of men with prostate cancer to participant a screening programme. Of these men, anxiety moderately deteriorated in 20% of men and minimally deteriorated in another 20% of men during the screening process. The deterioration occurred not only when a positive result was found, but also sometime after normal test results. The patients may denied the negative result or fear of a positive result at the next test.

Compared to the impacts of the screening process on the quality of life for men screened, the utility loss associated with overdetection and overtreatment might be more substantial. After the diagnosis of prostate cancer, especially within the first 6 months, 28-37% of men suffered from high anxiety.[17,359] A population-based study in the US showed that men diagnosed with prostate cancer was associated with significantly worse outcomes in physical, mental and social aspects compared to the controls, though the HRQOL for men in both arms was similar before diagnosis.[360] All the treatments, including active surveillance (because of the repeated biopsies), can cause severe complications.[14,15,151,152] More details about the harms caused by treatments are demonstrated in section 1.2.7 and section 8.2.2. Without screening, these asymptomatic men might not need to experience the harms or the harms can be postponed till symptoms appear.

8.1.3 Costs and cost-effectiveness

The National Screening Unit oversees the population-based screening programmes in New Zealand, including National Cervical Screening Programme, BreastScreen Aotearoa, Universal Newborn Hearing Screening and Early Intervention Programme, the Newborn Metabolic Screening Programme, the Antenatal HIV Screening Programme and Antenatal Screening for Down Syndrome and Other Conditions.[361] The BreastScreen Aotearoa is the most costly screening programme (costs $60.0 million in 2013/14), followed by the National Cervical Screening Programme (Table 54).

Table 54. The costs of screening programmes in New Zealand

Screening programme	Overall budget 2013/14	Details
National Cervical Screening Programme	$40.4 million	Laboratory costs ($16.2 million), colposcopy costs ($9.3 million), regional services including promotion and coordination, some smear taking and supporting women through screening ($7.0 million), and other associated funding including monitoring, audits, the Register including invitation and recall, social marketing and programme resources ($7.9 million)
BreastScreen Aotearoa	$60.0 million	Screening and assessment ($48.3 million), regional recruitment, coordination and support, and supporting women through screening ($5.6 million), and other associated funding including monitoring, the rollout and support of a national digital picture archive and communication system, social marketing and programme resources ($6.1 million)
Universal Newborn Hearing Screening and Early Intervention Programme	$5.3 million	Screening costs ($4.4 million) and other associated funding including audits, monitoring and quality improvements ($0.9 million)
Newborn Metabolic Screening Programme	$2.3 million	Mainly laboratory screening costs
Antenatal HIV Screening Programme	$1.4 million	-
Antenatal screening for Down syndrome and other conditions	$4.6 million	-

Source: National Health Committee. An overview of screening in New Zealand. (Wellington: National Health Committee, 2015)[361]

The New Zealand Prostate Cancer Taskforce recommended that 'Primary health care should provide high-quality, culturally appropriate information on prostate cancer and PSA testing to men aged 50 to 70 years'.[150] The average costs per man aged 60-69 years being screened for prostate cancer in New Zealand was $24 ($6,268 × 29 ÷ 7936: average costs per prostate cancer identified for men aged 60-

69 years × number of cancer cases ÷ number of men screened). The male population aged 50-69 years (the number of men aged 50-70 is not available) in 2015 is approximately 404,670 in the Statistics New Zealand.[362] If 3% of men aged 50-70 years were assumed to have a prostate cancer diagnosis,[4] approximately 392,530 (97%) men aged 50-70 years are eligible for prostate cancer every year. If the screening interval is 4 years, the medical costs of prostate cancer screening every year would be $2.4 million ($24 × 392,530 ÷ 4: screening costs per man × number of men screened ÷ 4 years). The non-medical costs of prostate cancer screening would be similar to the counterparts in the cervical screening and in the breast cancer screening that are about $10 million (Table 54) including supporting services, monitoring, register, social marketing and programme resources. Therefore, the overall budget for a national prostate cancer screening programme would be approximately $12.4 million. The costs are expected to increase, given that more systematic screening tests would be performed and there would be more inputs from general practice providing information on the benefits and harms of prostate cancer screening after the screening programme launches. Currently, 350,000 PSA tests are carried out in New Zealand every year.[363] Approximately 80% are screening tests with many are performed in men over 70 years.[4,20]

When considering the economic impact of a screening programme, the costs of screening and the costs of treatments for the screen-detected cancers should both be considered. Though the costs of prostate cancer screening are relatively low compared to breast cancer screening, the costs of treating the screen-detected prostate cancer cases are substantial. The average costs per prostate cancer identified for men aged 60-69 years was $6,268 in New Zealand, while the costs of treating a prostate cancer case with radical prostatectomy were approximately $13,527. It was reported that by introducing screening, the costs for diagnosis and treatment would increase by 100%, and 89% of total costs are related to treatments for screen-detected cancers.[13]

Since the uncertainty about whether the benefits of prostate cancer screening outweigh the harms, prostate cancer screening is not recommended in New Zealand. A prostate cancer awareness and quality improvement programme was proposed and the Ministry of Health funded this programme in 2013 with $4.3 million over four years, to ‘develop information resources for men and their families, create GP support material to help men and their doctors make informed decisions about prostate cancer tests and treatment, and develop clinical standards to make sure all men have fair and equal access to quality cancer care’.[364]

A cost-effectiveness analysis of prostate cancer screening employing cost per QALY figures was not performed in this thesis. However, the costs per prostate cancer case identified through PSA testing were estimated. The least costly screening was for men aged 60-69 and the costs to identify a new case of prostate cancer in this age group were $6,472 in 2012/13 ($6,268 in 2010). The best reported outcome of prostate cancer screening was in the Göteborg study that demonstrating 293 men need to be screened and 12 cancers need to be treated to prevent one death from prostate cancer.[6] The screening costs of identifying 12 prostate cancers would be $77,664 ($6,472 × 12) in New Zealand. The average age of men diagnosed with localised prostate cancer was 65 years in the Midland Cancer Network region. The life-time treatment costs for men diagnosed with low risk localised

prostate cancer at the age of 65 were $11,998 if under active surveillance and $16,972 if treated with radical prostatectomy. The life-time treatment costs for 12 patients with low risk localised prostate cancer would be $143,976 to $203,664. The life-time costs for 12 men aged 65 years in the watchful waiting arm were $94,116 ($7,843×12). If the costs in the watchful waiting arm were considered to be the costs in the control arm, the costs of saving one life by prostate cancer screening would be $127,524 - 187,212. This is the most optimistic scenario.

While the costs of identifying a new case of prostate cancer and the potential costs per life year gained seemed reasonable in our systematic review, cost-effectiveness analysis studies based on the favourable study (screening can reduce prostate cancer mortality) leads to the conclusion that population-based prostate cancer screening is not cost-effective. A cost-effectiveness study on prostate cancer screening conducted by Heijnsdijk et al[365] was not included in our systematic review, because it was published after the systematic review was carried out. Harm of screening on the screened population was taken into account in this study and a disutility of 0.01 was used in the screening model. Based on data of the ERSPC trial, this study found that the optimal screening strategy was screening at ages 55 to 59 years with two-year intervals and the ICER was $73,000 per QALY gained.[365] A single screen at age 55 years resulted in the smallest ICER of US$31,467 / QALY gained.[365] The authors of this study have requested the Dutch Ministry of Health to consider implementing a prostate cancer screening programme. However, Noordzij and Blanker[366] questioned about the inputs of the screening model in this study.[365] Therefore, this screening study did not alter our conclusion that population-based prostate cancer screening is not cost-effective.[28]

8.1.4 Informed decision making

PSA-based screening for prostate cancer is not recommended. However, the common use of PSA testing is recognized on the premise that it is an informed decision made by patients. The American Cancer Society suggested an informed decision should be made based on patient's preferences and values after the individual has comprehended the uncertainties, potential harms and benefits of screening. The Prostate Cancer Taskforce in New Zealand advocated that systems providing "high-quality, culturally appropriate information on prostate cancer and PSA testing to all me aged 50 to 70 years" must be developed to facilitate the informed consent process. Increasing the emphasis and time spent on informed consent will substantially increase the screening costs. However, informed consent may contribute to better targeted screening and therefore increase the detection rate and decrease the costs per cancer detected.

Screening for men over 70 years old should be reduced or stopped. Men over 70 years old without any symptoms will not benefit from prostate cancer screening and will suffer from overdiagnosis and overtreatment. Similarly, the Cochrane review[8] demonstrated that 'men who have a life expectancy of <10-15 years should be informed that screening for prostate cancer is not beneficial and has harms', because any benefits from prostate cancer screening may take >10 years to accrue.

8.2 Treatments for localised prostate cancer

8.2.1 Prognosis and treatment effects

Men with localised prostate cancer have a good prognosis.[291,292,367] These men are more likely to die of their comorbidities than prostate cancer.[292] In our studied cohort, the 5-years all-cause and cancer specific survival for men with localised prostate cancer was almost 100% (refer to Chapter 4). In a cohort of 404,604 patients with clinically localised prostate cancer within 17 Surveillance, Epidemiology and End Results registries in the USA, the 10-year cancer specific mortality and other cause mortality rates were 6.1% and 29.2%, respectively.[291] The prognosis of men diagnosed with localised prostate cancer also depends on the cancer grade. A US population-based study[368] demonstrated substantial disparity in the 10-year prostate cancer specific survival for localised prostate cancer patients with a biopsy Gleason score 5-7 (76-91%) and those with a biopsy Gleason score 8-10 (43-76% in Table 55). Though this study showed better survival outcome for those treated with radical prostatectomy, it might be not because of the effect of radical prostatectomy but the selection bias of an observational study. Healthier and younger patients are more likely to be selected for radical prostatectomy and might lead to a better survival outcome.[18,368,369]

Table 55. 10-year prostate cancer specific survival for localised prostate cancer patients

Treatment	Biopsy Gleason score 5-7	Biopsy Gleason score 8-10
radical prostatectomy	91% (95% CI: 89-93%)	76% (95% CI: 71-80%)
radiotherapy	74% (95% CI: 71-77%)	52% (95% CI: 46-57%)
Observation	76% (95% CI: 73-78%)	43% (95% CI: 38-48%)

Source: Population-based study of long-term survival in patients with clinically localised prostate cancer[368] (License for reusing the figure has been granted)

In Chapter 4, no significant survival difference was demonstrated between men receiving definitive treatment and men under observational management. In the SPCG-4 study, when stratified by risk level, the difference in prostate cancer specific mortality between men in the radical prostatectomy arm and men in the watchful waiting arm was only found in the intermediate risk group.[39] The cumulative incidence of death from prostate cancer at 18 years for men diagnosed with low risk localised prostate cancer was 10.2% in the radical prostatectomy arm and 14.0% in the watchful waiting arm (p=0.17), for men with intermediate risk cancer was 15.1% in the radical prostatectomy arm and 39.3% in the watchful waiting arm (p<0.001), and for men with high risk cancer was 33.1% in the radical prostatectomy arm and 35.7% in the watchful waiting arm (p=0.84).[39]

8.2.2 Impact on quality of life

The treatments for localised prostate cancer all have adverse impacts on men's quality of life, though the severity and domains of side effects might differ. In a longitudinal cohort study, the quality of life

was assessed among 278 men diagnosed with localised prostate cancer during the period of June 1996 and May 1998 and treated with either radical prostatectomy or radiotherapy.[18] Men treated with radical prostatectomy were more likely to have urinary problems (39-49%) and sexual problems (80-91%), but were less likely to have bowel problems (6-7%) compared to those treated with radiotherapy (respectively, 6-7%, 41-55% and 30-35%) within 12 months after treatment.[18] Other studies showed similar results.[369-371] One study included 1,655 men diagnosed with localised prostate cancer in 1994 or 1995.[369] Of these men, 1,664 men had radical prostatectomy and 491 men had radiotherapy. Patients undergoing radical prostatectomy were 5-6 times more likely to have urinary incontinence and 2-4 times more likely to have erectile dysfunction, but were less likely to have bowel urgency (odds ratio, 0.39-0.47) than those treated with radiotherapy at 2 years and 5 years. The group difference was not significant at 15 years.[369] However, in the study conducted by Carlsson[371] and colleagues, radical prostatectomy was found to be associated with an increased risk of urinary incontinence (odds ratio 1.89, 95% CI: 1.36–2.62) and radiotherapy was associated with an increased risk of bowel dysfunction (odds ratio 2.46, 95% CI:1.73–3.49) compared with men in the control group after 12 years follow-up.

In the PIVOT study,[15] patients in the radical prostatectomy arm were more likely to have urinary incontinence and erectile dysfunction compared with men in the observation arm, but no significant difference was found in bowel dysfunction (Table 56). In the SPCG-4 study, bowel function, anxiety and depression were similar in the radical prostatectomy arm and in the watchful waiting arm after 5 years, while anxiety and depression deteriorated significantly in the watchful waiting arm.[372] In a study conducted by Reeve[360] and colleagues, an increased risk for major depressive disorder was observed among men who received either conservative management (ADT alone or no treatment) or external beam radiation compared to men who received radical prostatectomy or brachytherapy.

Table 56. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, according to Study Group in the PIVOT study

Dysfunction	Radical prostatectomy	Observation	P Value
Urinary incontinence †	49/287 (17.1%)	18/284 (6.3%)	<0.001
Erectile dysfunction ‡	231/285 (81.1%)	124/281 (44.1%)	<0.001
Bowel dysfunction §	35/286 (12.2%)	32/282 (11.3%)	0.74

† Urinary incontinence was defined by patient reports (“have a lot of problems with urinary dribbling,” “lose larger amounts of urine than dribbling but not all day,” “have no control over urine,” or “have an indwelling catheter”).

‡ Erectile dysfunction was defined as the inability to have an erection or an erection sufficient for vaginal penetration.

§ Bowel dysfunction was defined by patient reports that it was a “moderate” or “big” problem.

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Because the severity and domains of side effects differ among the treatment options for localised prostate cancer, a quality of life measure synthesizing the health impacts in different domains is needed. It is believed that the quality of life for men under active surveillance is better than that for men receiving radical prostatectomy, [266,268,315] but no good quality of life data is available to prove this. Therefore, scenario analysis using different quality of life data was conducted in Chapter 5 and Chapter 6.

The quality of life inputs in the economic models in Chapter 5 and Chapter 6 were measured by the EQ-5D that is a generic instrument comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[206] The EQ-5D data can be converted into a figure that can be used in the cost-effectiveness analysis. However, the EQ-5D lacks disease-specific dimensions. For example, some men with localised prostate cancer might have good scores measured by the EQ-5D, but they might be suffering from moderate urinary or sexual problems that might not have impacts on the responses of the five dimensions in the EQ-5D.[373]

8.2.3 Costs and cost-effectiveness

8.2.3.1 Low risk and intermediate risk localised prostate cancer

Published studies showed that the short term and long term costs of watchful waiting and active surveillance were lower than the costs of radical prostatectomy for (± low risk) localised prostate cancer.[168,256,268] These results were consistent with the costing results in this thesis (refer to Chapter 5 and Chapter 6) for low risk localised cancer patients aged 55-70 years (60-70 years in the scenario analysis when using the new costing inputs) and for intermediate risk patients aged 60-70 years, if radical prostatectomy was only offered to men in the active surveillance arm when high risk cancer was detected. For men diagnosed at a younger age (45-50 years or 45-55 years in the scenario analysis), the life-time costs of active surveillance were higher than the costs of radical prostatectomy. The cost reduction increased with increasing age and decreased with increasing annual conversion rate from active surveillance to radical prostatectomy.

The result that the life-time costs of active surveillance were higher than the costs of radical prostatectomy for younger men (aged <50 years) with low risk localised prostate cancer should be robust. However, there were uncertainties in the older age groups (aged ≥55 years). The scenario analysis showed that the life-time costs of active surveillance exceeded the costs of radical prostatectomy for low risk patients aged 45-60 years, if 5% of men in the active surveillance arm had radical prostatectomy every year. With a higher annual conversion rate, the life-time costs of active surveillance might even higher than the costs of radical prostatectomy for men with low or intermediate risk cancer at all age groups.

A 34% cost reduction was demonstrated in the watchful waiting group compared to the radical prostatectomy group in the SPCG-4 trial in 12 years.[256] This study included the costs of regular x-rays

and bone scans in both treatment arms. In reality, patients undergoing radical prostatectomy do not need regular imaging after the surgery and therefore the costs in the radical prostatectomy arm would be lower. In our model, men in the radical prostatectomy arm were assumed to be followed-up by specialists for 12 months after the surgery and will be referred back to the specialists if cancer replases. A study conducted by Hayes et al[266] showed a higher life-time costs in men aged 65 years and managed with active surveillance compared to men undergoing radical prostatectomy. Though this study did not highline this finding and used a 9% annual rate of conversion to treatment in the active surveillance arm, it implied a possibility that active surveillance might be more costly than radical prostatectomy if more men in the active surveillance arm receive radical prostatectomy every year. Men diagnosed with low or intermediate risk localised prostate cancer at a younger age in the active surveillance arm have a high possibility of undergoing radical prostatectomy and might be associated with higher life-time costs. This hypothesis was confirmed in our study where men diagnosed at the age of 50 or younger in the active surveillance arm had higher life-time costs than those in the radical prostatectomy arm.

A German study showed that active surveillance was associated with additional 0.04 QALYs per patient compared with open prostatectomy.[268] With this small quality of life difference, the uncertainty on whether active surveillance was cost-effective would be substantial. The models in Chapter 5 and Chapter 6 generated similar numbers of life-years in the active surveillance arm and in the radical prostatectomy arm, and therefore the number of QALYs would depend on the quality of life values for men undergoing active surveillance and radical prostatectomy. The cost-effectiveness of active surveillance compared to radical prostatectomy for the age groups where similar life-time costs were yielded would be sensitive to the quality of life values.

8.2.3.2 High risk localised prostate cancer

This thesis does not include an original study on the economic evaluation of treatments for high risk localised prostate cancer. However, we can have some insights into this field from literature review. Radical prostatectomy alone and external beam radiotherapy plus ADT provided similar long-term cancer control for patients with high-risk prostate cancer.[374] In terms of short term costs, radical prostatectomy was significantly more expensive than external beam radiation therapy (US$17,226 vs US$14,048 from 1 month before to 9 months after diagnosis).[250] However, in terms of the long term costs, MR Cooperberg[267] found that radical prostatectomy was more effective and less costly than radiotherapy for high risk patients. Yves Fradet demonstrated that patients with biochemical recurrence after radical prostatectomy can benefit from salvage external beam radiotherapy.[375] Even when the costs of salvage external beam radiotherapy were included, radical prostatectomy would be still less expensive than external beam radiotherapy. More than one third of high risk patients will not have biochemical recurrence and will not receive ADT, while all patients undergoing external beam radiotherapy will receive at least 6 months ADT (or longer upon biochemical recurrence).

8.3 Treatment of metastatic prostate cancer

8.3.1 Prognosis and treatment effects

The median life expectancy for patients who have developed bony metastatic cancers is approximately 24 to 36 months.[33,38] This was higher than the median life expectancy (approximately 10 months) in the 234 men with metastatic prostate cancer in this study. The survival for men with metastatic prostate cancer might be able to be improved by better management. Chapter 7 found very limited use of chemotherapy and poor monitoring using PSA test. PSA testing plays a critical role in management of metastatic prostate cancer with ADT. The EAU guidelines[285] recommended that a strict follow-up must be applied to men treated with ADT, including clinical examination every 3-6 months, with PSA measurements. The guidelines also advised the PSA threshold at which ADT must be stopped or resumed: 1) 'The treatment is stopped only if patients have a clear PSA response, empirically defined as a PSA level less than 4 ng/ml in metastatic patients or 0.5 ng/ml in relapsing patients'; 2) 'The treatment is resumed when there is either clinical progression or the PSA value rises above an empirically fixed threshold (10–15 ng/ml in metastatic situations). Treatment is continued as in the induction cycle, for between 6 and 9 months, depending on the time required to reach a PSA nadir.'

The EAU guidelines[285] recommended that men with metastatic CRPC should consider using docetaxel 75 mg/m^2 every 3 weeks, and CRPC patients who received prior docetaxel treatment should consider abiraterone/prednisone as an effective second-line treatment option. Both docetaxel and abiraterone have shown a significant survival benefits[285] and are now subsidised by the PHARMAC in New Zealand (since July 2011 and May 2015, respectively). Wider use of these two pharmaceuticals might improve the poor survival for men with metastatic prostate cancer in New Zealand.

8.3.2 Cost and cost-effectiveness

Metastatic prostate cancer is considered not curable and treatments are provided to prolong patients' life, manage symptoms and improve quality of life. The cost of ongoing treatments for patients with metastatic prostate cancer can be substantial. A Canadian study[181] reported that the mean cost of drug treatments for patients with mCRPC over an average period of 28.1 months was CAN$48,428 per patient. Of the metastatic prostate cancer cases, 80-90% is bone metastasis and skeletal-related events occur in half of patients with bone metastasis.[376,377] In the United States, the cost of skeletal-related event ranged from US$7,553 per radiation episode to US$88,838 per bone surgery episode.[377]

The costs for metastatic prostate cancer were estimated by diagnostic phase, treatment phase and terminal phase. The monthly costs in the terminal phase (NZ$1,710 ($57×30)) was three times the costs in the treatment phase (NZ$540) and twice the costs in the diagnostic phase (NZ$900). It has

been demonstrated that costs were the greatest in the resource-intensive 6 months before death, because of home-care services, hospitalization and palliative care costs.[378] The follow-up time division to the three phases were similar to the study conducted by Stokes et al: the initial phase included the first 6 months after prostate cancer diagnosis, the terminal phase included the last 12 months before death, and the continuing care phase included the time between initial and terminal phases.[170,379] The monthly cancer related costs for metastatic prostate cancer patients in this study were US$2,212 in the initial phase, US$344 in the continuing care phase, and US$1,185 in the terminal phase.[170,379] This study included prostate cancer cases in all stages. However, for metastatic prostate cancer patients whose median life expectancy was less than one year, the individual 3 months follow-up time to the diagnostic phase and the terminal phase would be more reasonable. The different allocation of follow-up time to the three phases in these two studies might contribute to the different costing results.

8.4 Screening and management of prostate cancer for Māori men

Māori men diagnosed with prostate cancer were 1.94 (95% CI, 1.76, 2.14) times more likely to die of prostate cancer than non-Māori men.[33] The survival disparity has not been reduced despite improvements in survival for men diagnosed after 2000.[33] Improving access to care is believed to be critical to addressing health disparities between Māori and non-Māori.[380]

Māori men were half as likely to be screened compared to non-Māori men. The possibility of detecting new cases of prostate cancer in Māori at each screening round was greater and the costs per cancer detected were lower than non-Māori men.[93] When diagnosed with localised prostate cancer, Māori men were more likely to be managed expectantly after adjustment for age, D'Amico risk strata, comorbidities, and socioeconomic deprivation.[12] On the contrary, when diagnosed with metastatic prostate cancer, there was no significant difference in the utilization of radiotherapy and ADT between Māori men and non-Māori men. Therefore, the daily prostate cancer related costs between Māori men and non-Māori men were similar.

When stratified into different cancer stage groups, there was no significant difference in prostate cancer specific survival between Māori men and non-Māori men. The overall survival disparity might be attributable to the later presentation and multiple comorbidities for Māori men.[33] Māori were twice as likely to be diagnosed with distant metastases: 19.1% of prostate cancer cases in Māori men were metastatic at diagnosis compared to 9.8% in non-Māori men. It is uncertain whether prostate cancer screening can save lives,[8] but lead time bias[131] caused by screening will have a significant impact on the more favourable survival in Māori men. The proportion of Māori men (70%) having at least one comorbidity was higher than the proportion applying to non-Māori men (52%). Comorbidity is an important factor affecting the choice of treatment option.[18,368,369] Healthier patients are more likely to be selected for radical prostatectomy. Therefore, improvement on access to cancer care for Māori men with prostate cancer would also depend on the improvement of their general health statues.

8.5 Strengths and limitations

One of the strengths of this thesis is that it was mainly based on local data collected from general practices and hospitals reflecting the activities in the New Zealand health care system. Patients' clinical files were examined to identify the cancer extent at diagnosis. These data are rarely available in the NZCR. Data on patients' age, ethnicity, treatments, comorbidities and biopsy Gleason score were collected. A life-time Markov model was built to compare the cost-effective of active surveillance and radical prostatectomy for low and intermediate risk localised prostate cancer. The model synthesized data from internationally recognised studies and local costing and outcome data to provide relevant economic information for decision making. The transition probabilities to local progression and to metastatic disease were generated from the SPCG-4 study, one of the largest randomised clinical trial of observation and radical prostatectomy for localised prostate cancer. This thesis comprised the economic impacts of prostate cancer screening, treatments for localised prostate cancer and management of metastatic prostate cancer. It provides a big picture of the economic impact of the pathway of prostate cancer screening and treatments.

This thesis has several limitations. Since the data was collected in the Midland Cancer Network region, the results may not be generalisable to other regions in New Zealand or to other countries. The Midland Cancer Network has a relatively high Māori population (approximately 25%) compared to the whole country (15.6%). However, the annual PSA testing rate (22.1%) in this region was similar to the rate (22%) across the whole country.[4] There are some costs that this study could not cover, namely the indirect costs to patients or society. However, these costs would only account for a small proportion of the total costs. This thesis did not examine the cost-effectiveness of radiotherapy and brachytherapy for localised prostate cancer or the cost-effectiveness of treatments for locally advanced prostate cancer due to lack of clinical data. The quality of life data played a crucial role in the cost-effectiveness of active surveillance compared to radical prostatectomy for low risk and intermediate risk localised prostate cancer. However, there are great uncertainties associated with the available quality of life data. Therefore, scenario analysis using different quality of life data was conducted. The quality of life for men at different ages was assumed to be the same if they had identical treatment. However, in reality, the quality of life may vary by age even under the same treatment.

Chapter 9. Conclusion and future research

9.1 Conclusions

Screening of asymptomatic men for prostate cancer is widely practiced in New Zealand. Most of the estimated costs of screening were incurred in general practice. Calls for men to receive increased information on the harms and benefits of screening substantially increased the costs per cancer identified. If GPs are going to persist in screening, the costs per cancer detected can be reduced by better targeting of screening (by age and ethnicity). The systematic review on economic evaluation of prostate cancer screening demonstrated that the estimated costs per QALY gained by prostate cancer screening were higher than the cost-effectiveness thresholds in the countries where the studies were conducted, suggesting that even when based on favourable RCTs in younger age groups population-based prostate cancer screening is not cost-effective. This suggests the Ministry of Health should not recommend population based screening for prostate cancer. The money spent on prostate cancer screening could perhaps be better spent on improving the management of diagnosed cancer cases.

Survival in New Zealand men with localised prostate cancer was excellent and those who did die were more likely to die of other diseases associated with the presence of co-morbidities rather than of prostate cancer. Five-year survival for men with metastatic disease was only 17.6% with 50/55 (91%) of the men dying of prostate cancer. The greatest disparities for Māori men were their increased risk of having more advanced disease at diagnosis. The residual difference in outcomes may be due to differences in treatment for Māori – and thus the disparities in survival might be improved by better management of men with higher risk disease.

If men in the active surveillance arm are switched to radical prostatectomy only when significant cancer progression (e.g. high risk localised prostate cancer) is detected, active surveillance is less costly than radical prostatectomy for men diagnosed at the age of 60-70 years old. However the life-time costs of active surveillance might be higher than the costs of radical prostatectomy for men diagnosed at the age of younger than 55 years. The cost-effectiveness of active surveillance was dependent on the quality of life inputs for men with localised prostate cancer under different treatment options, and the annual probability of having radical prostatectomy in the active surveillance arm.

For men diagnosed with intermediate risk localised prostate cancer at the age of 60-70, the life-time costs of active surveillance were lower than the costs of radical prostatectomy. The cost-effectiveness of active surveillance was associated with the quality of life values for men under observational management and for men having radical prostatectomy. The new costing inputs for men with localised prostate cancer did not have a substantial impact on the results.

If the quality of life for men under active surveillance is better than that for men in the radical prostatectomy, active surveillance is a reasonable option for men diagnosed with low risk and

intermediate risk localised prostate cancer at the age of 60-70. If active surveillance is to be recommended for these men, better evidence is needed to support of improved quality of life. On current evidence, radical prostatectomy in younger men seems more likely to be cost-effective.

The early or unnecessary trigger of active treatment reduces the cost-effectiveness in the active surveillance arm. The ICER of active surveillance compared to watchful waiting increased with rising annual probability of having radical prostatectomy in the active surveillance arm. If the quality of life for men under observational management was better than that for men having radical prostatectomy, active surveillance was cost-effective compared to radical prostatectomy, but was not cost-effective to watchful waiting for older men, with a high annual probability of having radical prostatectomy in the active surveillance arm.

Metastatic disease is still commonly diagnosed at presentation in New Zealand and the survival in these patients is substantially worse than that would be expected from overseas comparisons. The incidence of metastatic disease is greater in Māori as its mortality compared to non-Māori. It is shown that intensive therapy is more likely to be used for younger men with metastatic disease. The use of different formulations of ADT is noteworthy as is the lack of consistency of monitoring for CRPC. There seems to be a strong case for the development of New Zealand guidelines on the management of metastatic disease including the use of first line treatments and the need for ongoing monitoring for the development of CRPC. It would seem probable that better management of this group of patients could offer substantial improvements in outcomes.

The management costs for patients with metastatic prostate cancer varied by phase, with the terminal phase being the most expensive. The costs of treating metastatic prostate cancer decreased with increasing age. Wider use of chemotherapy in New Zealand may be warranted, as the current costs account for a small proportion of total treatment costs. The management of metastatic prostate cancer is expensive and currently the effectiveness seems variable. Evidence of the cost-effectiveness of different treatments for metastatic prostate cancer is needed for developing the guidelines.

9.2 Future research

9.2.1 Prostate cancer screening

If screening for prostate cancer is to be used in the future, we either need to prevent overdiagnosis and overtreatment or need new treatments that reduce the risks of cancer progression without causing induced harm. The key to prevent overdiagnosis is to distinguish the overdiagnosed cases from the true early detections, which is difficult.[381] A Gleason score 5 tumour in the prostate is no longer considered as malignant, and most Gleason score 6 disease does not progress even without definitive treatment. The development of a more specific test would reduce the added costs due to overdiagnosis and overtreatment.

Another aspect that needs to be considered is whether screening is cost-effective for high-risk patients: for example patients with a family history of prostate cancer. It was shown that the ICER of PSA screening for men with five times the average risk was only 10% of the ICER for men with average risk, which was lower than the cost-effectiveness threshold.[382] Screening for patients with family history in prostate cancer might be cost-effective. Some risk assessment tools have been developed, including the prostate cancer prevention trial prostate cancer risk calculator (PCPT-RC) and the European randomised study for prevention of prostate cancer risk calculator (ERSPC-RC).[383] The former calculator predicts the risk of prostate cancer based on age, race, PSA, DRE and family history, and the later utilises transrectal ultrasound (TRUS) findings, DRE, prostate volume and PSA to predict biopsy outcome. However, it is found that the PCPT-RC and the ERSPC-RC both overpredicted the risk of prostate cancer. These risk assessment tools might be more widely used in the future when they are better developed.

9.2.2 Treatments for localised prostate cancer

As shown in the scenario analysis, the quality of life value for men under active surveillance and that for men having radical prostatectomy were critical for the cost-effectiveness of these treatments for localised prostate cancer. Men undergoing different treatment regimens might suffer from side effects in different domains. Men under active surveillance experienced higher rates of anxiety and depression,[384] men having radiotherapy were more likely to have bowel dysfunction, and men undergoing radical prostatectomy suffered more urinary problems and sexual problems.[18] The comprehensive measurement of quality of life for men under different treatments would be imperative. The generic HRQoL instruments lack disease-specific dimensions, while disease-specific instruments can measure the impact of dysfunction in a single organ or disease on overall quality of life.[373] Disease-specific instruments can also examine the impact of diseases and treatments on quality of life in subtle ways, including the bowel irritability caused by radiotherapy on men with localised prostate cancer.[373] The cancer-specific HRQoL instruments included Functional Assessment of Cancer Therapy–General (FACT-G), Cancer Rehabilitation Evaluation System Short Form (CARES-SF), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30

(EORTC QLQ-C30), EORTC QLQ PR-25, Rotterdam Symptom Checklist, and Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q).[373]

If the results of the cancer-specific HRQoL instruments can be converted to a number that is no more than 1, the quality of life for men under active surveillance and that for men undergoing radical prostatectomy can be compared and can be used in decision models. Three studies[302,303,385] were conducted by mapping FACT-P and EORTC QLQ-C30 to EQ-5D in mCRPC patients, and two studies[386,387] mapped EORTC QLQ-C30 and FACT-P onto EQ-5D and SF-6D for the assessment of cancer patients. In these five studies, regression models were built to predict the EQ-5D or SF-6D scores when only data of the cancer-specific instruments were collected. However, with this approach, the quality of life results would still lack of disease-specific dimensions. Similar to the EQ-5D tariff,[204,205,388] tariffs to value the cancer-specific HRQoL instruments might be developed in the future.

9.2.3 Treatments for metastatic prostate cancer

The decision making of using which new pharmaceutical to treat metastatic prostate cancer would partly depend on the cost-effectiveness of these pharmaceuticals. In clinical trials, new pharmaceuticals are often compared with placebo instead of other similar pharmaceuticals. Head-to-head cost-effectiveness comparison among new pharmaceuticals for metastatic prostate cancer should be carried out. Wilson L et al[389] evaluated the cost-effectiveness of abiraterone, cabazitaxel, and enzalutamide compared to placebo for mCRPC and found that abiraterone was the most cost-effective one, with an ICER of US$123,400 per QALY gained. Enzalutamide would be cost-effective compared to abiraterone with a willingness-to-pay value of over US$437,600 per QALY, and cabazitaxel would be cost-effective compared to enzalutamide with a willingness-to-pay value of over US$351,900 per QALY. Gong CL et al[390] demonstrated that neither abiraterone nor sipuleucel-T was cost-effective compared with prednisone for asymptomatic, pre-docetaxel mCRPC, with an ICER of US$389,000 per QALY gained for abiraterone and an ICER of US$547,000 per QALY gained for sipuleucel-T. However, if the prices of medication drop, these pharmaceuticals might become cost-effective.[389]

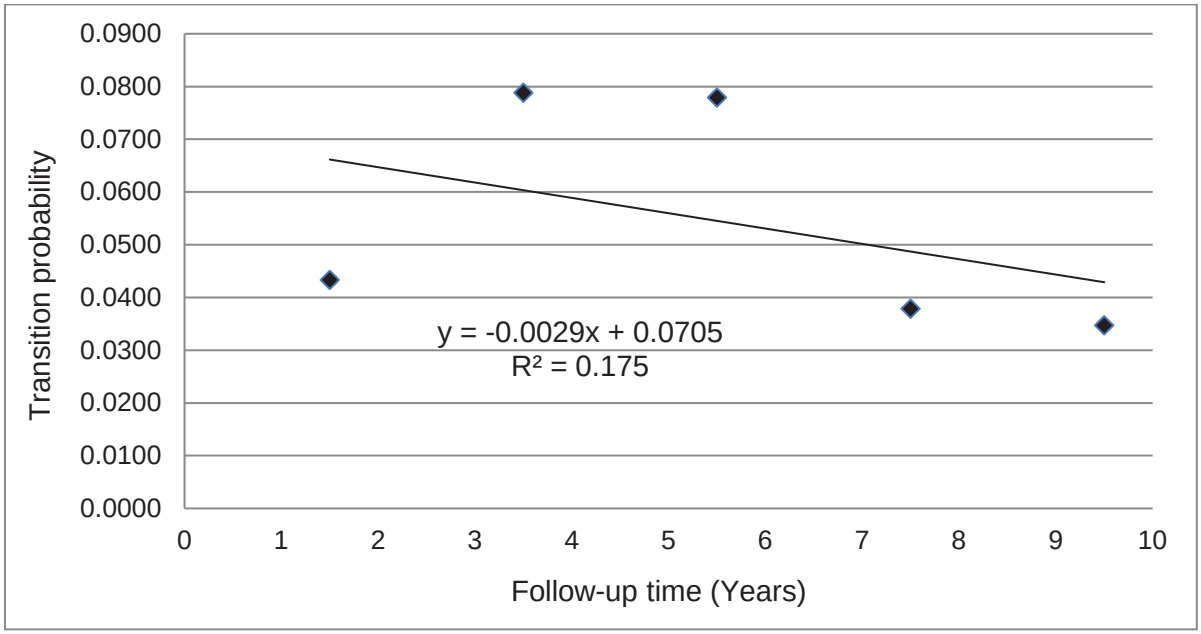
The emerging new treatments for metastatic prostate cancer might revolutionize the treatment pathway for metastatic prostate cancer, especially the treatment phase. The costs of pharmaceuticals are expected to increase substantially, and economic evaluation studies would be needed to critically appraise the value of new treatments.

Appendices

Appendix 1. The impact of each parameter on the screening costs: increased by 20% of the original value

Parameter		Proportion of initial general practitioner consultation cost included		
		20%	50%	100%
Quantity				
	Number of cancer cases identified	20.0%	20.0%	20.0%
	PSA test ordered by general practitioner	5.8%	3.7%	2.3%
	Initial general practitioner consultation	7.5%	12.0%	15.0%
	Follow up general practitioner consultation	0.9%	0.6%	0.4%
	First specialist assessment	1.2%	0.8%	0.5%
	Follow-up specialist consultation	1.2%	0.7%	0.5%
	PSA test ordered by specialist	0.0%	0.0%	0.0%
	Biopsy	1.3%	0.8%	0.5%
	Pathology report	2.1%	1.3%	0.8%
	Hospitalization after biopsy (bed days)	0.1%	0.1%	0.0%
Unit cost				
	PSA test	5.8%	3.7%	2.3%
	General practitioner consultation	8.4%	12.6%	15.3%
	First specialist assessment	1.2%	0.8%	0.5%
	Follow-up specialist consultation	1.2%	0.7%	0.5%
	Biopsy	1.3%	0.8%	0.5%
	Pathology report	2.1%	1.3%	0.8%
	Hospitalization after biopsy (bed days)	0.1%	0.1%	0.0%

Note: By decreasing 20% of the original value of each parameter, the screening costs decreased the same percentage as above.



Appendix 2. Correlation between follow-up time and transition probability to 'Local progression' from 'Localised' in the watchful waiting arm in the SPCG-4 study

Appendix 3. Life table in New Zealand

Age (years)	Probability of death	Age (years)	Probability of death
50	0.00317	76	0.0399
51	0.00347	77	0.04423
52	0.0038	78	0.04893
53	0.00417	79	0.05404
54	0.00457	80	0.05977
55	0.00501	81	0.06634
56	0.00549	82	0.07399
57	0.00602	83	0.08292
58	0.0066	84	0.09334
59	0.00725	85	0.10533
60	0.00797	86	0.11863
61	0.00877	87	0.13286
62	0.00965	88	0.14769
63	0.01063	89	0.1628
64	0.01172	90	0.17787
65	0.01291	91	0.19267
66	0.01424	92	0.20946
67	0.01569	93	0.2271
68	0.01732	94	0.24541
69	0.01914	95	0.26483
70	0.02119	96	0.28527
71	0.02351	97	0.30667
72	0.02612	98	0.3289
73	0.02905	99	0.35185
74	0.03232	100	0.37537
75	0.03593		

Source: Statistics New Zealand

Appendix 4. Number of life-years per man with low risk localised prostate cancer

Age at diagnosis	Watchful waiting (life-years)	Active surveillance (life-years)	Radical prostatectomy (life-years)
45 years	17.64	18.48	18.45
50 years	16.55	17.23	17.22
55 years	15.26	15.79	15.79
60 years	13.77	14.14	14.16
65 years	12.09	12.33	12.37
70 years	10.27	10.38	10.45

Appendix 5. Scenario analysis for men with low risk localised prostate cancer: Number of life-years per man by using the 5% conversion rate

Age at diagnosis	Watchful waiting (life-years)	Active surveillance (life-years)	Radical prostatectomy (life-years)
45 years	17.63	18.43	18.45
50 years	16.54	17.20	17.22
55 years	15.25	15.77	15.79
60 years	13.76	14.14	14.16
65 years	12.09	12.33	12.37
70 years	10.27	10.39	10.45

Appendix 6. Scenario analysis for men with low risk localised prostate cancer: Number of QALYs per man by using the 5% conversion rate

Age at diagnosis	Watchful waiting (QALYs)	Active surveillance (QALYs)	Radical prostatectomy (QALYs)
45 years	15.43	16.34	16.43
50 years	14.49	15.26	15.35
55 years	13.37	13.99	14.08
60 years	12.07	12.55	12.65
65 years	10.62	10.94	11.05
70 years	9.03	9.20	9.35

Appendix 7. Scenario analysis for men with low risk localised prostate cancer: Life-time costs per man by using the 5% conversion rate

Age at diagnosis	Watchful waiting	Active surveillance	Radical prostatectomy
45 years	$15,880	$28,028	$22,321
50 years	$14,187	$25,948	$20,988
55 years	$12,254	$23,378	$19,610
60 years	$10,119	$20,206	$18,251
65 years	$7,835	$16,174	$16,962
70 years	$5,557	$10,850	$15,821

Appendix 8. Scenario analysis for men with low risk localised prostate cancer: Number of QALYs per man by changing quality of life values

Age at diagnosis	Watchful waiting (QALYs)	Active surveillance (QALYs)	Radical prostatectomy (QALYs)
45 years	14.52	15.20	14.73
50 years	13.63	14.18	13.75
55 years	12.57	12.99	12.61
60 years	11.35	11.65	11.31
65 years	9.97	10.16	9.88
70 years	8.48	8.57	8.35

Appendix 9. Scenario analysis for men with low risk localised prostate cancer: Life-time costs per man by changing costing values

Age at diagnosis	Watchful waiting	Active surveillance	Radical prostatectomy
45 years	$15,838	$23,491	$21,162
50 years	$14,144	$21,229	$19,831
55 years	$12,214	$18,618	$18,457
60 years	$10,066	$15,622	$17,095
65 years	$7,805	$12,210	$15,810
70 years	$5,520	$8,231	$14,668

Appendix 10. Scenario analysis for men with low risk localised prostate cancer: Number of QALYs per man by changing quality of life values and the 5% conversion rate

Age at diagnosis	Watchful waiting (QALYs)	Active surveillance (QALYs)	Radical prostatectomy (QALYs)
45 years	14.52	15.00	14.73
50 years	13.63	14.02	13.75
55 years	12.57	12.87	12.61
60 years	11.35	11.56	11.31
65 years	9.97	10.10	9.88
70 years	8.48	8.53	8.35

Appendix 11. Scenario analysis for men with low risk localised prostate cancer: Life-time costs per man by changing costing values and the 5% conversion rate

Age at diagnosis	Watchful waiting	Active surveillance	Radical prostatectomy
45 years	$15,847	$26,841	$21,167
50 years	$14,132	$24,812	$19,829
55 years	$12,213	$22,350	$18,458
60 years	$10,076	$19,335	$17,097
65 years	$7,789	$15,559	$15,810
70 years	$5,524	$10,592	$14,668

Appendix 12. Number of PSA tests for prostate cancer patients ordered by GP

	Number of patients	Mean	SD
Localised			
First year			
Watchful waiting	29	1.1	1.0
Active surveillance	26	1.0	1.9
Radical prostatectomy	127	0.4	0.7
Subsequent years			
Watchful waiting	17	1.8	1.8
Active surveillance	19	1.7	1.9
Radical prostatectomy	77	1.1	1.5
Metastatic	33	1.8	2.2

Appendix 13. Number of life-years per man with intermediate risk localised prostate cancer

Age at diagnosis	Watchful waiting (life-years)	Active surveillance (life-years)	Radical prostatectomy (life-years)
60 years	12.18	13.07	13.06
65 years	10.94	11.54	11.60
70 years	9.50	9.81	9.94

Appendix 14. Scenario analysis for men with intermediate risk localised prostate cancer: Number of QALYs per man by changing quality of life values

Age at diagnosis	Watchful waiting (QALYs)	Active surveillance (QALYs)	Radical prostatectomy (QALYs)
60 years	9.92	10.63	10.40
65 years	8.92	9.40	9.23
70 years	7.76	8.00	7.92

Appendix 15. Scenario analysis for men with intermediate risk localised prostate cancer: Life-time costs per man by changing costing values

Age at diagnosis	Watchful waiting	Active surveillance	Radical prostatectomy
60 years	$25,789	$25,695	$26,075
65 years	$20,849	$21,386	$22,713
70 years	$15,305	$16,199	$19,483

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