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Population-Based Studies in Urologic Cancer

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Thesis by compilation

This thesis is submitted in full satisfaction of the requirements for the degree of Doctor of
Medical Science

Faculty of Medicine, University of Melbourne
Department of Surgery, Austin Health, Heidelberg
July 2019

2. Declaration

This thesis is submitted to the University of Melbourne in fulfillment of the requirements for the Degree of Doctor of Medical Science. The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text and journal articles.

This thesis is fewer than the maximum word limit.

Dr Anthony Ta

Date: 18/7/19

3. Preface

The works included in this thesis contains a selection of articles published in international journals of urology during my clinical research years under the supervision of Professor Damien Bolton. Although I was the primary author in all of thesis studies, all of the included work was done in collaboration with other co-authors. However, the majority of the work (i.e. more than 50%) required for each publication, including literature review, data collection and analysis, writing and submission, was performed by myself. The nature of the contributions from other co-authors included some data provision, complex statistical data analysis where required, and reviews of draft publications.

All the included articles were accepted for publication and have since been published. The relevant journal articles and dates of acceptance and publication are listed below. No third party editorial assistance was provided. None of this work has been submitted for other qualifications.

The Australian Postgraduate Scholarship provided a personal source of funding during my enrolment. Study grants and sources of funding for the development and maintenance of the cancer registries used in the included studies are outlined in each of the articles.

The appendix of the thesis contains a set of published articles where I was a co-author, but not the primary author and contributed less than 50% of the work required. The work in these articles both arose directly and indirectly from this thesis.

Contemporary Management of Renal Cell Carcinoma in Victoria

Journal: British Journal of Urology International

Date of acceptance: May 2013

Date of publication: November 2013

Interval to Biochemical Recurrence Following Radical Prostatectomy Does Not Affect Survival in Men with Low-risk Prostate Cancer

Journal: World Journal of Urology

Date of acceptance: 24th June 2013

Date of publication: 4th July 2013 (online)

Increased Prostate Cancer Specific Mortality Following Radical Prostatectomy in Men Presenting with Voiding Symptoms – A Whole of Population Study

Journal: Prostate International

Date of acceptance: 4th June 2015

Date of publication: 17th July 2015 (online)

Testicular torsion and the acute scrotum: current emergency management.

Journal: European Journal of Emergency Medicine

Date of acceptance: 6th July 2015

Date of publication: June 2016

4. Acknowledgements

I would like to acknowledge the Cancer Council Victoria for their resources and collaboration, which allowed my work to progress and reach a level of quality and relevance for publication. Furthermore, this work was of sufficient importance that it produced several presentations at international conferences.

Similarly, I would like to acknowledge the Department of Surgery at Austin Health for its resources and support, especially with regards to conference presentation materials.

And finally, I would like to thank and acknowledge my supervisor, Professor Damien Bolton, for being an eternal source of inspiration and support.

5. Introduction

This thesis represents a body of work in the subject of urology completed during my clinical research years. Whilst the main focus of this thesis included urologic oncology, namely population-based studies of prostate and renal cell cancer, some of the included published work focuses on common and benign urological conditions.

Long-term data on cancer outcomes are frequently based on large series from single- or multi-institutional databases, and whilst study numbers may be large, the study population and outcomes are often not truly reflective of community practice. Furthermore, very few of these studies, especially in urologic oncology, include patients diagnosed and treated in Australia. Statewide cancer registries rely on compulsory notification of all diagnoses of cancer, hospital admissions and causes of death. Therefore, such registries have the advantage of capturing whole-of-population data that may be missing from large institutional- or surgeon-based series.

Prostate cancer (PCa) is the most common non-cutaneous malignancy affecting men in Australia. Following the availability of prostate specific antigen (PSA) as a modality for PCa detection in the early 1990s, PCa underwent a dramatic shift from a disease often diagnosed at an advanced stage in elderly men who are symptomatic, to one that is usually detected early in asymptomatic men. Unlike many other neoplastic processes, PCa has a wide spectrum of grade and aggression, ranging from relatively indolent disease to rapidly progressive disease with high mortality. Even with advancing diagnostic and therapeutic

advances, there remains controversy over screening and treatment algorithms. Most men with PCa have long life expectancies, and whilst a significant paradigm shift has occurred towards observation and surveillance, radical prostatectomy (RP) remains the mainstay of treatment for men with localised disease and adequate life expectancy.

The premise of the Victorian Radical Prostatectomy Register, established under the guidance of the Cancer Council Victoria, was to represent a whole-of-population registry of all men diagnosed and treated with RP in Victoria, Australia. Men underwent follow-up for a 10 year period over a defined interval of 5 years, with a view to assess the long term outcomes of RP, including survival. This database has formed the basis for multiple publications, and a selection of these manuscripts is presented to comprise this thesis. Our study confirmed that high Gleason sum and pathological stage was associated with high risk of prostate cancer-specific mortality (PCSM). We also noted high PCSM in men with high risk PCa at diagnosis who developed early recurrence compared to men who develop late recurrence, whereas men with lower risk PCa have low PCSM regardless of when PSA recurrence occurs. Additionally, we found that men presenting with lower urinary tract symptoms at the time of diagnosis had higher PCSM.

Renal cell carcinoma (RCC) represents the most common malignancy affecting the kidney, and accounts for approx. 2-3% of all cancers. It is the second most common urological malignancy in Victoria. Increased use of abdominal imaging has resulted in stage migration at time of diagnosis, from late stage symptomatic renal masses with high mortality to small asymptomatic masses with low mortality. For many decades, the mainstay of treatment of localised RCC was to perform a radical nephrectomy (RN). However, partial nephrectomy

(PN) has been demonstrated to provide equivalent oncological control to RN for appropriately selected renal masses, with the benefit of renal preservation.

Given the rise of incidentally diagnosed small renal masses, and the low mortality associated with early stage RCC, PN is recommended as first line treatment. However, its utilisation has been questioned, and studies from the United States have shown underutilisation of this modality. However, such studies have never been conducted on an Australian population.

Using whole-of-population data from a statewide cancer registry maintained by the Cancer Council Victoria, we demonstrated that the majority of small renal masses in Victoria in 2009 were treated with RN, suggesting potential overtreatment of early stage RCC. This effect was more pronounced in cases diagnosed in regional centres of Victoria, and those treated in private hospitals.

In addition to the study of urologic malignancies, evaluation and management of common and benign urological conditions, such as acute scrotal pain, also contributed in part to this thesis.

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BJU Int. 2015 Oct;116 (3): 66-72

- b. *Rural residency and prostate cancer specific mortality: results from the Victorian Radical Prostatectomy Register.*

Papa N, Lawrentschuk N, Muller D, MacInnis R, Ta A, Severi G, Millar J, Syme R, Giles G, Bolton D.

Aust N Z J Public Health. 2014 Oct;38(5):449-54

6. Literature Review

Prostate Cancer

Introduction

Prostate cancer (PCa) is the most common urological malignancy affecting males, and is a serious disease with significant impact on mortality and quality of life. Studies have shown that PCa represents approximately 15% of male malignancies in developed countries, compared to 4% in underdeveloped countries.^{1,2}

The prostate gland can be described as having zonal anatomy, a concept first described by McNeal in 1968.³ He described four distinct zones in a landmark paper published in 1981⁴, each with distinct ductal systems, and importantly, affected by different neoplastic processes. Unlike benign prostatic hyperplasia (BPH) which uniformly originates the transition zone of the prostate, approximately 60-70% of carcinomas of the prostate originate in the peripheral zone of the prostate, compared to 10-20% in the transition zone and 5-10% in the central zone.^{5,6}

Over 95% of cancers arising in the prostate are adenocarcinomas, arising from glandular cells in the prostate. The histology of the remaining 5% of PCa is heterogenous, arising from stromal, epithelial or ectopic cells. Under the influence of androgens, namely testosterone which is converted into the more active androgen dihydrotestosterone (DHT) within prostatic cells, these glandular cells within the prostate undergo cell division and growth. Dysplastic growth of these cells eventually gives rise to adenocarcinoma.⁷ High-grade prostatic intraepithelial neoplasia (PIN) observed on prostate biopsies is considered a histologic precursor to PCa, however, PCa frequently arises in the absence of PIN.^{8,9}

Non-adenocarcinoma variants (epithelial and non-epithelial) are uncommon. Epithelial variants include endometrioid, mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell and neuroendocrine carcinomas. Non-epithelial variants

include sarcomas (rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma), malignant lymphoma and metastatic neoplasms. These rare variants of PCa will not be discussed in this thesis.

The Gleason grading system was introduced in the 1960s by Donald Gleason. The Gleason grading system is based on the architectural pattern of the prostate glands, and the two most abundant patterns of tumour are graded from 1 to 5. The Gleason score or Gleason sum represents the most abundant grade plus the second most abundant grade. In 2005, the International Society of Urological Pathology (ISUP) altered the Gleason system (then known as the “modified Gleason score”), refining the criteria and changing attribution of certain patterns.¹⁰ Following this, Gleason grades 1 and 2 were removed as they no longer met pathological criteria for carcinoma. Higher Gleason sum is associated with increased prostate cancer-specific mortality (PCSM), which will be discussed in this thesis. More recently, a new grading system was proposed by the International Society of Urological Pathology, and was accepted by the World Health Organisation in 2016. This grading system, consisting of Grade Groups 1-5, will not be used as part of this thesis.¹¹

Similarly, adverse pathological stage is associated with increased mortality from PCa. At the time of this study, the most commonly used staging system was the seventh edition of the American Joint Committee on Cancer, published in 2010.¹²

TABLE 1: 2010 TNM staging system of prostate cancer

Localized disease	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in ≤ 5% of resected tissue
T1b	Tumor incidental histologic finding in > 5% of resected tissue
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
T2	Tumor confined within prostate
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
Local extension	
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures
Metastatic disease	
N1	Positive regional lymph nodes
M1	Distant metastasis

PCa is a disease of older men, as approximately 2/3rds of cases of PCa are diagnosed in men aged 65 years and over.¹³ Australia has a current population of over 22.7 million people.¹⁴ In 2007, people aged 65 years and over made up 13% of the total population in Australia. By the year 2056, this proportion is expected to increase to between 23-25%.¹⁵ The incidence of PCa has increased dramatically over the last 20 years due to the advent of prostate-specific antigen (PSA) testing, and this trend is set to continue given the increasing public awareness of PCa. The costs associated with the diagnosis, treatment and on-going management of PCa is significant.¹⁶⁻²⁰

Of further significant importance is the recognition that PCa represents a spectrum of disease. An increasing wealth of studies have demonstrated, and continue to demonstrate, low lethality from favourable-risk PCa, and conversely significant mortality from high-risk PCa. The key for treating clinicians is the identification of men with PCa who are at greatest long-term risk of adverse outcomes, such as mortality from PCa, who may benefit from best-evidence management. Similarly, it is imperative to identify men who have an extremely low risk of long-term adverse outcomes, so that they can be appropriately counselled regarding their treatment options, which may include non-surgical management.

Epidemiology of Prostate Cancer

Incidence

In Australia, and in many parts of the developed world, PCa represents the most common malignancy affecting males, and is the second most common cause of death following lung cancer. In the last 30 years, there has been a gradual and significant increase in the incidence of PCa in Australia. The rate remained fairly stable in the 1980s, but was followed by a dramatic increase in the early 1990s associated with a peak age-standardised (AS) incidence rate of 184 cases per 100 000 males in 1994.²¹ This steep increase in the incidence of PCa was observed was due to the introduction and availability of PSA as a screening tool.^{22,23} Following this, a sharp reduction in the incidence of PCa ensued (AS

incidence rate of 130 per 100 000) in 1997, after which the rate was stable for several years. This dramatic reduction (Figure 1) can be attributed to the diagnosis of prevalent cases of PCa that had not yet been diagnosed prior to the advent of PSA screening. From 2002, the rate began to increase rapidly again. In 2006, there were 17 444 new cases of PCa in Australia, accounting for 29.5% of all cancers in men.¹³ In 2007, there were 19 403 newly diagnosed cases of PCa (AS incidence rate of 182.9 per 100 000), representing 31.3% of all male malignancies.

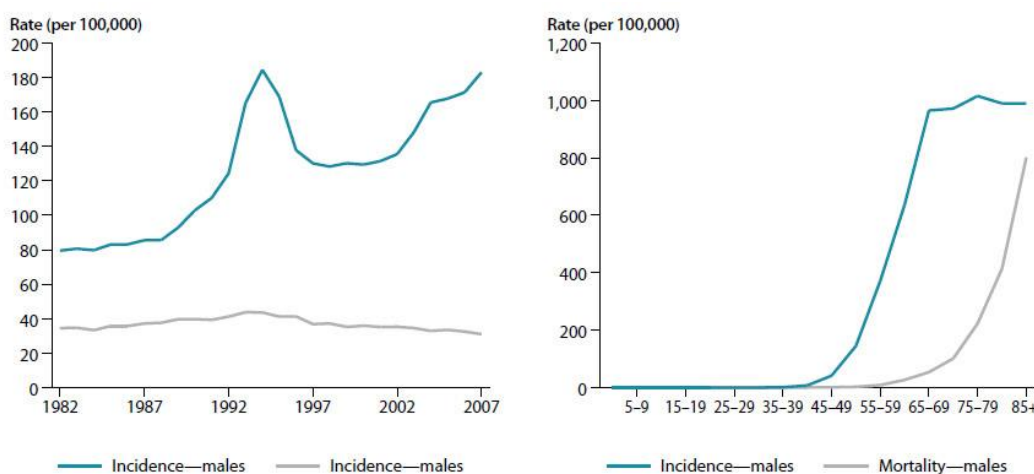


Figure 1. Trends in PCa incidence rates. Rates age-standardised to Australian population as at 30 June 2011 (Source: Australian Institute of Health and Welfare)

In 1982, the AS mortality rate of PCa was 35 deaths per 100 000 males. This increased to a peak incidence of 44 per 100 000 males in 1993 (Figure 2). Since this period, the mortality rate has slowly declined. In 2007, the mortality rate of PCa stood at 31 deaths per 100 000 males, indicating an overall decrease of 30% between 1993 and 2007.²¹ Similarly, the 5-year relative survival of PCa had improved from 57% to 85% when comparing men diagnosed between 1982-1986 and 1988-2004.

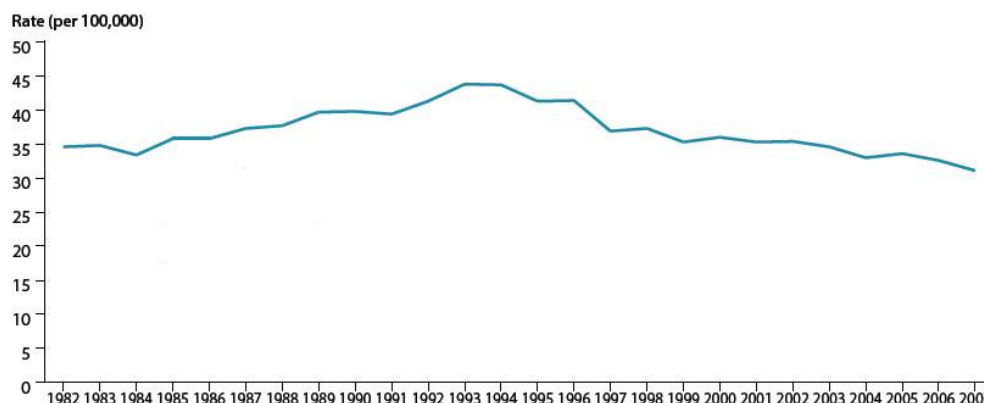


Figure 2. Trends in PCa mortality. Rates age-standardised to Australian population as at 30 June 2011 (Source: Australian Institute of Health and Welfare)

Comparatively, whilst in the AS incidence rate of lung cancer and bowel cancer in 2007 was 58 and 75 cases per 100 000 males, respectively, lung cancer was the leading cause of cancer-related death (4715 cases, AS mortality rate of 46.3 per 100 000 men), with bowel cancer as the third leading cause of cancer-related death (2191 cases, AS mortality rate of 21.7 per 100 000 men). Among males, PCa is the second leading cause of burden of disease due to cancer, following lung cancer.²¹

The state of Victoria has a population of over 5.6 million persons, representing nearly 25% of the national population.²⁴ In Victoria, there were 5609 new cases of PCa in 2009, representing an AS incidence rate of 134.6 cases per 100 000 men, and accounting for 35% of cancers in men. 816 of cancer-related deaths were attributable to PCa, representing the third leading cause of cancer-related deaths among males (AS mortality rate of 13.4 per 100 000 men) after lung (AS mortality rate 24.4) and bowel (AS mortality rate 15.5) cancer.²⁵

Similar trends in PCa incidence are seen in other developed parts of the world. In the US, PCa represents the most commonly diagnosed malignancy in men and the second most common cause of cancer-related death, based on data from the Surveillance Epidemiology and End Results (SEER) program.²⁶ The SEER cancer registry is an information system designed for the collection, storage and analysis of cancer statistics in the US. Americans of Black race (approximately 10% of total American population) have higher incidence and mortality compared to Americans of White race. The rise in incidence from 1975 to the late 1980s was approximately 2% per year, and likely influenced by incidental diagnosis of PCa

resulting from transurethral resection of prostate (TURP) for benign prostatic hyperplasia (BPH), which was increasingly being used during this period. Similar to trends observed in Australia, a sharp incline in the incidence of PCa in the early 1990s was subsequently followed by sharp decline (Figure 3)

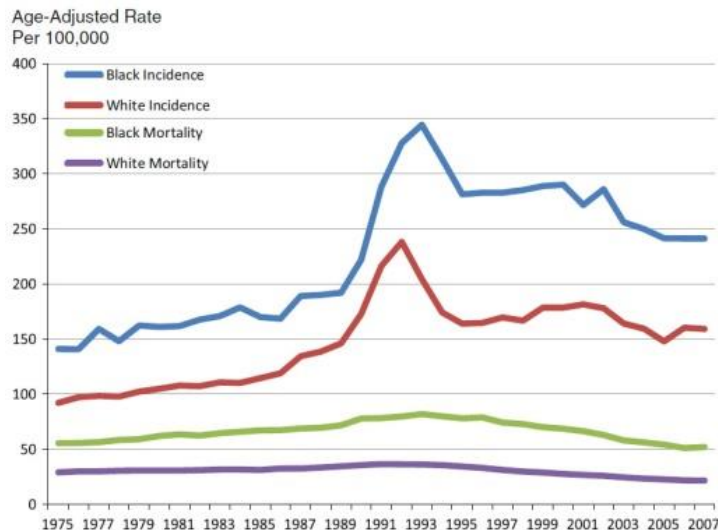


Figure 3. Trends in PCa incidence and mortality in the US.
Source: US SEER Program

In the UK, PCa is the most common cancer in men, accounting for one-quarter of all new cancer cases in males.²⁷ The AS incidence rate in the UK was 106.3 in 2009, with England and Wales having the highest incidence of PCa compared to Scotland. Similarly, PCa is the most common male malignancy across Europe, with deaths from PCa being the third most common cause of cancer death among men after lung and bowel cancer. Mortality rates from PCa in Europe have been decreasing, but mostly in higher-resourced countries in Western Europe (e.g. UK, France, Germany, Netherlands) and the Nordic Countries (e.g. Finland and Norway).²⁸ However, there is little correlation between incidence and mortality in Europe following the introduction of PSA testing, suggesting that PSA testing is associated with overdiagnosis or detection of indolent tumours (this will later be discussed in further detail).

According to data from the International Agency for Research on Cancer, PCa incidence rates are highest in Australia/New Zealand, and lowest in South-Central Asia (Figure 4).

Globally, however, PCa is a less prominent cause of cancer death, contributing approximately 5.8% of cancer deaths in men.²⁹

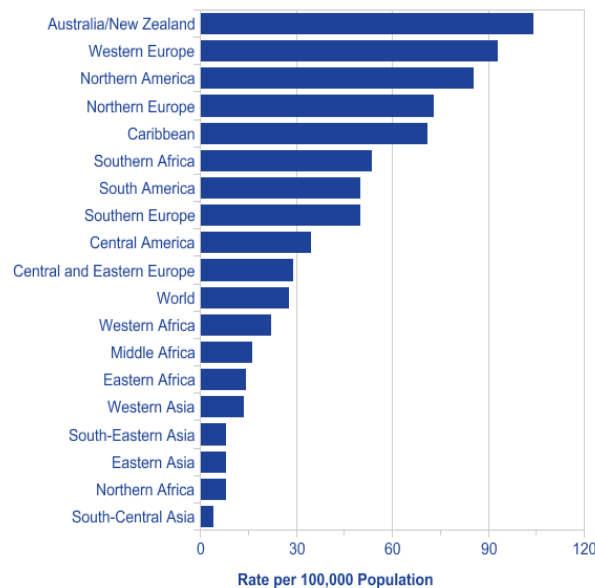


Figure 4. International PCa incidence Rates
Source: Cancer Research UK

Lifetime Risk

PCa is invariably a disease of old age. In the UK, approximately three-quarters of new diagnoses between 2007 and 2009 were in men aged 65 years and older, and age-specific incidence rates increase sharply from around age 50, peaking in men aged 75 and over.²⁷ In the US where the median age at diagnosis of PCa is 67 years, nearly 60% are diagnosed at the age of 65 or older, and less than 10% of new cases are diagnosed in men under the age of 55.^{26,30} In Australia, approximately two-thirds of new PCa diagnoses occur in men aged 65 or older. In Victoria, four out of five men with new diagnoses of PCa in 2009 were aged 60 or older.²⁵

As PCa is a relatively highly prevalent malignancy, the lifetime risk of being diagnosed with this disease is also unfortunately high. The lifetime risk of developing PCa in the UK is estimated to be 1 in 9 based on data from 2008.²⁷ Based on SEER data, it is estimated that 1 in 6 American men will be diagnosed with PCa during their lifetime.²⁶ Similarly, it is estimated that 1 in 7 Australian men will be diagnosed with PCa.¹³

Influence of Demographic and Socioeconomic Variables on Prostate Cancer

Other than clinicopathologic factors, socioeconomic status (SES) and other demographic factors may play a role in PCa screening, incidence, management and outcomes following treatment.

Miller et al evaluated trends in PCa severity in a study of 570 disadvantaged men treated by a state funded public health program in California between 2001 and 2006, which included 79% of men being of a racial/ethnic minority group. The authors found that compared to men in the general US population, disadvantaged men presented with higher PSA levels, greater intermediate or higher risk Gleason score, and later stage disease.^{31,32} Among men with non-metastatic cancers, only 24% had low risk tumours, compared to approximately 45% as seen in SEER data from 1999 to 2001. Similarly, a prevalence of 19% of metastatic disease at diagnosis in this study was substantially higher than a prevalence of 4% seen in SEER data from 2000 to 2005.²⁶ During the duration of the study, the proportion of men presenting with metastatic disease or low risk PCa did not change, suggesting that PSA screening patterns in disadvantaged men did not improve over time. Similarly, other studies have demonstrated that men with lower SES, as evidenced by lower income or insurance status, have lower participation rates in PCa screening programs or examinations.^{33,34}

Using data from a population-based cancer registry in Los Angeles, Liu et al compared the relationship between SES (based on education and income) and PCa incidence before and after the introduction of PSA testing. The authors found that for men diagnosed prior to widespread PSA testing there was no association between SES and PCa incidence among racial/ethnic subpopulations (including 72% white, 14.1% black, 9.9% Hispanic and 3.3% Asian men), and no association between SES and stage of disease at diagnosis.³⁵ In contrast, SES was statistically significantly and positively associated with PCa incidence in all racial/ethnic subpopulations (except Asians) in men diagnosed with PCa after 1987, when PSA testing was more widely available. Furthermore, higher SES was associated with cancers of earlier stage in these men. These results suggested increased PSA screening among men with less socioeconomic disadvantage.

Black men in the US have been shown to have the highest incidence and mortality from PCa in the world.³⁶ Based on data from 1999 to 2003, black men were 1.5 times more likely to develop PCa and 2.4 times more likely to die from PCa compared to white men.³⁷ The reasons for this are thought to be multifactorial, and include access to care, attitudes about care, socioeconomic and educational differences, potentially less aggressive treatment by black men, and genetic factors.³⁸ However, black men undergoing RP have also been shown to have poorer outcomes compared to non-Hispanic whites, this has been thought to be due to more advanced disease upon diagnosis.^{39,40} Interestingly, other studies have demonstrated that when stage, grade, PSA and treatment modalities are controlled for, black and white men have similar outcomes⁴¹⁻⁴⁴, suggesting that other factors, such as socioeconomic variables, may influence mortality.^{45,46}

The effect of socioeconomic and demographic variables on PCa detection, management and outcomes has also been investigated in Australian populations. Several studies have attempted to evaluate the difference in outcomes in rural and urban patients with PCa. In a study from Western Australia of men diagnosed with PCa between 1982 and 2001, the authors found that men were less likely to be treated with RP if they were from a rural location, non-privately insured and had lower SES.⁴⁷ Men also had a greater likelihood of death within 3 years if their first post-operative admission was to a rural hospital or they had lower SES. Another study from New South Wales of men diagnosed with PCa between 1985 and 2002 showed similar findings. Compared to men from capital cities, men from regional/rural areas experienced a mortality excess of 21%, a 29% lower rate of RP, and a 16% lower rate of PSA testing.⁴⁸ Such differences in outcomes may in part be explained by more limited access to urologists in rural areas.

In a larger and more recent study, Baade et al⁴⁹ used population-based data for Australian men aged 50-79 and diagnosed between 1982 and 2009 to assess urban-rural differences in PSA testing, PCa incidence, RP and PCa mortality. The investigators noted that overall rates of PSA screening and RP increased, and was accompanied by reductions in mortality throughout Australia. However, they noted that PCa mortality continued to be higher in

men from regional/rural areas, and that rates of RP and PSA screening continued to be lower. Furthermore, their mortality remained higher and survival outcomes continued to be poorer. Data published by the Australian Institute of Health and Welfare examining cancer statistics in Australia between 2003 and 2007 similarly demonstrated that people living in areas with the highest socioeconomic status group had a significantly higher incidence rate of PCa than people living in all other areas.²¹ Furthermore, mortality rates from PCa were lower in people with least socioeconomic disadvantage, suggesting that people with higher SES are more likely to undergo PSA testing and be diagnosed with earlier stage disease.

Risk Factors for Prostate Cancer

The only well-established risk factors for PCa are age, family history of the disease and race/ethnicity. However, rare inherited forms of PCa exist and will be described later. Age is by far the strongest risk factor for PCa and death. However, having a father or brother with PCa more than doubles a man's risk of developing PCa. The risk is higher for men with several affected relatives, particularly if the relatives were young at the time of diagnosis. For example, if two or more first-line relatives are affected, the risk increases 5- to 11-fold.⁵⁰

Genetic studies suggest that strong familial predisposition may be responsible for about 5-10% of PCa.^{51,52} Although no known genes responsible for the development of PCa have been identified, several known susceptibility genes have been investigated, including RNaseL and ELAC2, which may be associated with small increases in PCa risk.^{53,54} Mutations in BRCA1 or BCRA2 genes and their link to breast and ovarian cancer have been well recognised for over a decade^{55,56}, but male carriers of these mutations are also at increased risk of PCa and certain other cancers, including breast cancer for BCRA1 mutations, and breast and pancreatic cancer for BCRA2 mutations.⁵⁷ However, mutations in BCRA2 appear to be more significant for the development of PCa, as evidenced by several studies of families or populations carrying BRCA2 mutations having an approximate 3 to 5-fold risk of developing PCa compared to non-carriers.⁵⁸⁻⁶⁰ However, these forms of PCa account for a small percentage of prevalent PCa, the large majority of which are sporadic and are on averaged diagnosed 6-7 years later than these hereditary forms of PCa.⁵² Mutations in

BCRA2 genes are thought to contribute only to approximately 1-2% of early-onset PCa diagnosed under the age of 55 years.^{61,62}

Diet

The role of diet in increasing the risk of PCa, and also in reducing risk, is largely unclear. To date, no well-designed trials with conclusive data have demonstrated an increased risk of developing PCa with certain foods. However, although the evidence is limited, certain diets have been implicated in potentially increasing the risk of developing PCa. These findings have largely been borne out in cross-sectional studies.

Development of aggressive forms of PCa have been associated with excessive use of high-dose vitamin supplements. The Carotene and Retinol Efficacy Trial (CARET) was a double-blind RCT investigating the effects of carotene and retinol supplementation on preventing lung cancer among high-risk patients, but an analysis of a potential association with PCa was performed. The study demonstrated that men in the interventional arm, who also used additional dietary supplements, had an increased risk of developing PCa.⁶³ Similarly, in the National Institutes of Health-AARP Diet and Health Study, the investigators found excessive multivitamin intake to be associated with an increased risk of developing advanced or fatal PCa.⁶⁴

Dairy products have also been thought to increase the risk of developing PCa through several possible mechanisms. Such mechanisms include high levels of saturated fats, relative suppression of 1,25 dihydroxyvitamin D3 (an active form of vitamin D shown to halt cellular proliferation and promote apoptosis in PCa cells) and higher levels of insulin growth factor 1 (which have been shown to increase risk of developing PCa).⁶⁵⁻⁶⁸ Several meta-analyses have demonstrated a small association between high a dairy and calcium diet and increased risk of developing PCa, although other large studies have failed to show any effect.⁶⁹⁻⁷¹

Similarly, high total fat and meat consumption, typical of the Western diet, have been implicated in increasing risk of PCa in several epidemiological studies. However, the data appears conflicting. With regards to fat consumption, the exact causal mechanism between high dietary fat and carcinogenesis remains unclear, and the level of evidence is generally poor. A meta-analysis by Dennis et al demonstrated a small but significant increase in the risk of developing PCa with a dietary fat consumption of >45g/day.⁷² More recent prospective trials, however, have failed to show any correlation.^{73,74} With regards to meat consumption, there is increasing evidence that heterocyclic amines (HCAs) in cooked meat have carcinogenic properties and have been associated with the development of several human cancers.⁷⁵ Several observational studies have demonstrated an association between increased meat consumption, high HCAs and well done meat and the development of PCa.^{75,76} However, a recently published US case-control study of over 4000 men from five different ethnicities found no association between well-done meat and increased risk of PCa.⁷⁷

Screening and Early Detection

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS). Definitive diagnosis relies on histopathological confirmation of adenocarcinoma in prostate biopsy cores, specimens from TURP or operative specimens.

Prostate-Specific Antigen

The availability of measurement of serum PSA levels has revolutionised the ability for clinicians to not only diagnose PCa, but measure response to treatment of PCa.⁷⁸ PSA is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. The level of PSA is a continuous parameter – thus the higher the value, the higher the likelihood of PCa. However, although PSA is organ-specific, it is not cancer specific. As a result, serum PSA levels may be elevated in a number of benign conditions, including BPH and prostatitis. However, an elevated PSA is a greater predictor of cancer than suspicious findings on DRE or TRUS alone.⁷⁹

Role of Screening

As a result of widespread adoption of PSA screening, earlier stage migration of PCa has been observed. US data has demonstrated in the last two decades, there has been a significant increase in American men diagnosed with organ-confined, low risk PCa.³²

Whilst PCa is a leading cause of cancer-related death in men, the role of screening for PCa remains a topic of major controversy. Several large randomised trials have attempted to answer the question of whether PCa screening results in reduced PCSM, but have largely failed to unite clinicians and health policy decision makers in common agreement. Some of the key trials will be discussed below, the results of which are mixed.

In the early 1990s, the European Randomised Study of Screening for Prostate Cancer (ERSPC)⁸⁰ enrolled 182 000 men aged between 50 and 74 years from seven European countries, who were randomly assigned to either a PCa screening group or a control group. The primary outcome of this study was PCSM. During a median follow-up of nine years, the cumulative incidence of PCa was 8.2%, compared to 4.8% in the control group, and was associated with a 20% relative risk reduction in PCSM with screening compared to no screening. The rates of death in the two study groups were shown to diverge after 7 to 8 years, and continued to diverge over time (figure 5). Somewhat alarmingly, the number needed to screen (NNS) and the number needed to treat (NNT) in order to prevent one death from PCa was 1410 and 48, respectively. However, a study update was published in 2015, and continued to demonstrate divergence between the two study groups over time. Subsequently, by 13 years the NNS and NNT had reduced to 781 and 27, respectively.⁸¹ Although screening was associated with a reduction in mortality from PCa, but the benefit was restricted to men between the ages of 55 and 69, and was associated with significant overdiagnosis and over-treatment of non-lethal cancers.

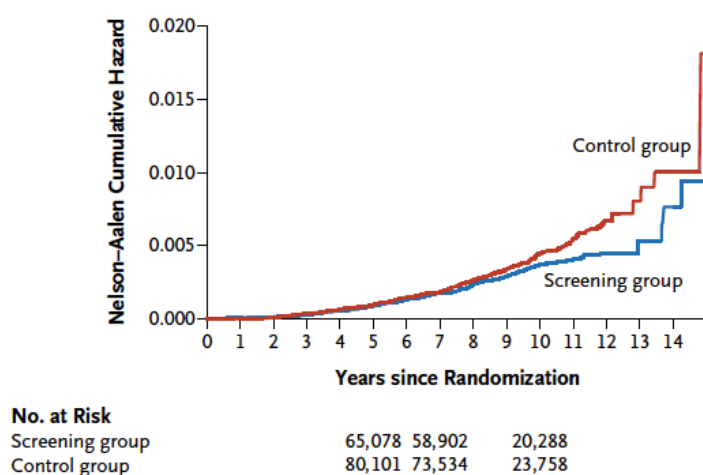


Figure 5. Mortality from prostate cancer (screening vs control)
Source: New England Journal of Medicine

The Göteborg PCa screening trial consisted of 20 000 men randomised in a 1:1 ratio to either a PSA screening group or a control group. The trial was designed and initiated independently from the ERSPC and the primary endpoint of the study was PCSM. After a median follow-up for 14 years, the relative risk of PCSM was 44% lower in the screening arm compared to the non-screening arm based on intention-to-screen analysis. Overall, an NSS and NNT of 293 and 12 men, respectively, was required to prevent one PCa death. These findings suggest a greater mortality benefit associated with PCa screening than what was observed in the ERSPC trial.

Published at the same time as the ERSPC study were the results from a randomised PCa screening trial from the US, which was part of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.⁸² From 1993 to 2001, the investigators randomly assigned 76 693 men at 10 US study centres to either screening or usual care control groups. After 7 years of follow-up, there was a 22% higher incidence of PCa in the screening group. However, no significant difference in mortality from PCa was detected between the two study groups during the first 7 years, with similar results at 10 years. Notably, this study was plagued by significant design flaws. Firstly, a significant rate of contamination of the control group was observed, approximately 45% and 52% of men having DRE and PSA testing, respectively, during the study. Importantly, approximately 44% of men in each group had one or more PSA tests prior to randomisation, which likely would have introduced a selection bias, as these men are at low risk of developing subsequent PCa. A subsequent

analysis of data from the PLCO trial by Crawford et al⁸³ revealed the NNS and NNT required to prevent one death at 10 years were 723 and five, respectively.

The findings of these three major trials has raised significant debate, as the NNS and NNT numbers are very high and associated with significant overdiagnosis of indolent tumours. However, it could be argued that such a high number of men requiring PCa screening to prevent one PCa-related death is not dissimilar to breast and colorectal screening. A meta-analysis of randomised trials of mammography for breast cancer screening demonstrated that 377 and 1339 women aged between 60-69 and 50-59, respectively, needed to be invited to screening to prevent one death from breast cancer.⁸⁴ Similarly, a recent Cochrane review showed screening to be associated with a 19% relative risk reduction of death from breast cancer, but was associated with 30% overdiagnosis and overtreatment, and that 2000 women overall would needed to be screened to prevent one death.⁸⁵ For colorectal cancer screening by faecal occult-blood test, meta-analyses have demonstrated the NNS required to prevent one death to be 1173 over 10 years, with a 16% relative risk reduction in death from colorectal cancer.^{86,87} Although these NNS numbers are very high, the risk of overdiagnosis and overtreatment is likely to be less compared to PCa.

Although widespread population-based screening cannot be recommended based on these study findings, PSA testing is still offered in an opportunistic fashion to well informed men at normal risk, or to other men with increased risk (e.g. family history). The Urological Society of Australia and New Zealand, the European Association of Urology, American Urological Association and the American Cancer Society generally agree and recommend annual PSA testing and DRE beginning at the age of 50 for men with a normal risk of PCa, and beginning at an earlier age for men at higher risk.⁸⁸⁻⁹⁰

Treatment of Localised Prostate Cancer

Although there are no randomised controlled trials comparing the efficacy of one curative treatment over another, radical prostatectomy (RP) is generally considered the treatment modality of choice for localised PCa in men considered medically fit for surgery. However,

active surveillance and radiotherapy are excellent alternatives to surgery for suitable patients. Greater understanding of the male pelvic anatomy and subsequent modifications to surgical techniques have allowed surgeons to perform RP with significantly reduced morbidity, allowing greater preservation of erectile function and urinary continence without compromising cancer control.^{91,92} However, surgery still remains a relatively morbid procedure.

Active Surveillance of Localised Prostate Cancer

The notion of clinically insignificant PCa has progressively emerged in the past two decades resulting from widespread use of PSA testing and improved prostate biopsy techniques and strategies. This has led to overall stage and volume migration of prostate cancers towards small and non-aggressive tumours, which may otherwise have been undetected. Such tumours may be indolent in nature and likelihood of progression to clinically significant disease is low in the absence of definitive treatment. The most commonly used criteria to define clinically insignificant prostate cancer are based on the pathologic assessment of the radical prostatectomy specimen and were originally defined by Epstein and Ohori: 1) Gleason score ≤ 6 (without evidence of pattern 4 or 5), 2) organ-confined disease, and 3) tumour volume $< 0.5\text{cm}^3$.⁹³⁻⁹⁵ Most published active surveillance series have used entry criteria similar to this, but are frequently more liberal with regards to certain parameters such as tumour volume, which is difficult to estimate from prostate biopsies.

Several studies with long-term follow-up have confirmed the low lethality of low risk PCa. Albertsen et al reported on 20-year outcomes following conservative management of clinically localised prostate cancer in 767 men.⁹⁶ Patients in this study received either observation or immediate or delayed androgen withdrawal therapy, and we observed over a median period of 24 years (longer than 20 years for 87% of men). The PCa mortality rate was low, with 33 per 1000 person-years during the first 15 years of follow-up on Poisson regression and 18 per 1000 person-years after 15 years of follow-up. The authors concluded that men with low-grade PCa have minimal risk of dying from PCa during 20 years of follow-up, as evidenced by 6 deaths per 1000 person-years for men with Gleason score of 2-4.

Conversely, men with high-grade PCa of Gleason score 8-10 have significant risk of death within 10 years of diagnosis (121 deaths per 1000 person-years), and men with Gleason score of 5-6 had an intermediate risk of death. Comparisons with contemporary patients diagnosed with PCa may be limited by the unscreened population of men, with only a minority diagnosed on needle biopsy of the prostate (only 26%), and the then outdated Gleason scoring system, as very few contemporary patients are diagnosed with Gleason 5 or less.

In another study evaluating the natural history of early, localised PCa, Johansson et al found that most early stage cancers have an indolent course, however, local tumour progression and aggressive metastatic potential still exists with longer follow-up.⁹⁷ The study cohort consisted of 223 men with localised organ-confined disease (T0-T2) who were followed up over a mean period of 21 years. Approximately two-thirds of patients had highly differentiated tumours (4% had poorly differentiated). Following an indolent period during the first 10 to 15 years, the authors found a substantial decrease in cumulative progression-free survival (45.0% to 36.0%), survival without metastases (76.9% to 51.2%) and PCa-specific survival (78.7% to 54.4%) after 15 years of follow-up. On Poisson analysis, the PCSM rate increased from 15 per 1000 person-years (95% CI 10-21) during the first 15 years to 44 per 1000 person-years (95% CI 22-88) beyond 15 years of follow-up. Although this population cannot be compared to contemporary cohorts (unscreened population, WHO classification rather than Gleason score was used for tumour grading), these findings confirm the slow natural progression of PCa.

Given the low PCSM associated with observation and the morbidity associated with surgery or radiotherapy, active surveillance for suitable patients may reduce the risk of overtreatment of clinically insignificant prostate cancer, while retaining the option of surgical intervention for patients who demonstrate evidence of disease progression over time.

Klotz et al performed a prospective single-arm cohort study to assess long-term outcomes in patients managed with a watchful-waiting protocol, and confirmed its safety for

appropriately selected patients.⁹⁸ Selective delayed intervention was performed for patients with evidence of clinical, biochemical or biopsy-proven histological progression. 450 patients were included in the study, which included 83% with Gleason sum ≤ 6 and 85% with PSA ≤ 10 ng/mL. At a median follow-up of 6.8 years, overall survival was 78.6% and the 10-year PCa-specific survival on actuarial analysis was 97.2%. Only five deaths occurred in the study, all of which occurred in patients who were later reclassified as higher risk and offered radical treatment. The hazard ratio of non-PCa to PCa death was 18.6 at 10 years, and 8.8 vs 33.3 when stratified by age ≥ 70 or <70 , respectively. This demonstrated that at all ages, the risk of death from other causes far outweighed the risk of death from PCa. Given longer follow-up, the mortality rate from PCa is likely to increase, but the likelihood of death from competing causes is also likely to increase.

Comparisons of Surgery, Radiotherapy and Surveillance for Localised Prostate Cancer

The long-term outcomes of RP compared to surveillance have been assessed in several prospective randomised trials. The available evidence suggests that patients who are most likely to benefit from surgery include those with intermediate- or high-risk disease. Prior studies using population-based cohorts, whilst larger in number, have generally shown a benefit for surgery in all risk groups, including those with low-risk disease.

The Scandinavian Prostate Cancer Group study number 4 (SPCG-4) represents the first randomised trial comparing long-term outcomes in patients with clinically localised PCa managed with either RP (N = 347) or watchful waiting (N = 348). After a median follow-up of 10.8 years, 13.5% and 19.5% of men died due to PCa in the RP and surveillance arms, respectively.⁹⁹ The cumulative incidence of distant metastases did not increase beyond 10 years of follow-up (19.3% for RP group vs 26% for watchful waiting). The authors concluded that at 12 years, RP reduces PCSM and risk of distant metastases both by 35%, with little or no further increase in benefit seen 10 or more years after surgery. However, the patients included in the study predominantly included men whose cancer was not detected by PSA screening, with 46% of patients in the RP group having extracapsular disease. Thus the high mortality rates seen in the study are a reflection of their overall higher risk PCa, as only two

deaths occurred in patients with organ-confined disease (both after 11 years of follow-up) and no deaths occurred in men with Gleason 2-6 on RP specimens.

In the Prostate cancer Intervention Vs Observation Trial (PIVOT), Wilt et al conducted the second randomised trial comparing surgery and watchful waiting for men with localised PCa.¹⁰⁰ This study of 731 men perhaps more truly reflects contemporary population as the majority of patients had screen-detected disease, non-palpable disease and PSA <10ng/ml. Overall, the authors found no significant differences in overall or cancer-specific survival between men who had undergone surgery or watchful waiting, although surgery reduced the development of bone metastases (10.6% vs 4.7%). In men with low- or intermediate-risk disease, there was no difference in overall or cancer-specific survival at 12 years. However, in the highest risk group of men, RP significantly reduced the risk of death from prostate cancer by 33%.

The most recently published prospective trial comparing treatment modalities for prostate cancer is the Prostate Testing for Cancer and Treatment (ProtecT) study. In this study, 1643 men were randomised to RP, external beam radiotherapy or surveillance and followed-up for ten years. At the end of the study, there was no difference in either PCSM or overall survival between the three groups.¹⁰¹ However, men undergoing surveillance were more likely to experience disease progression and develop metastases. Whilst the study suggests that radical treatment with either surgery or radiotherapy may be unnecessary in many patients, it should be noted that 80% of men in the study had Gleason 6 disease, many of whom would be suitable for surveillance in contemporary urological practice.

Retrospective studies of large populations, whilst limited by their inherent study design, have shown differing outcomes to the aforementioned randomised trials. A nationwide population-based register of Swedish patients diagnosed with localised PCa included 6849 patients with low- or intermediate-risk PCa managed with either RP, radiotherapy or active surveillance. Median follow-up time was 8.2 years. Overall mortality was 8.4%, 13.7% and 20.4% for patients treated with RP, radiation therapy and active surveillance, respectively.¹⁰² Prostate cancer-specific mortality was 1.7%, 2.8% and 2.9%, respectively, for the three groups. On multivariate analysis, the authors found lower risk of PCSM in patients

treated with RP than radiation therapy or active surveillance, after controlling for risk category, Charlson index (co-morbidity status) and socio-economic status (SES).

Long-term outcomes of patients diagnosed with localised PCa between 1990 and 1992, and managed with either RP, external beam radiation or watchful waiting, were compared in a population-based retrospective study of 1,618 patients from Connecticut. The survival advantage offered by RP over radiation and watchful waiting appeared to occur across all risk groups, including patients with high-grade disease.¹⁰³ The estimated 10-year PCa-specific survival in patients with RP, radiation therapy or observation was 97%, 93% and 90%, respectively, in the lowest risk group. Similar results were seen in the intermediate-risk (94% vs 88% vs 81%) and high-risk groups (90%, 80% and 70%).

Biochemical Recurrence Following Radical Prostatectomy

Biochemical recurrence is reported to occur in between 17-40%¹⁰⁴⁻¹⁰⁷. The slow clinical progression of prostate cancer necessitates the use of PSA as a surrogate end point for evaluating the outcome of treatment. Biochemical recurrence or PSA failure following RP is frequently defined as two consecutive PSA rises of >0.2ng/ml, although definitions vary among studies.

Natural History of Biochemical Recurrence

Recurrence of PSA alone does not necessary portend a poor prognosis, and many men with biochemical recurrence (BCR) have long survival. However, PSA velocity and doubling-time are stronger predictors of PCSM than the recurrence of PSA alone.

Pound et al assessed the natural history of progression to distant metastases and death due to PCa in men who developed an elevated PSA following RP.¹⁰⁸ In this series of 1997 men treated between 1982 and 1997, mean follow-up was 5.3 years and men treated with adjuvant hormonal therapy were excluded. Overall, 315 (15%) men demonstrated evidence of PSA recurrence (defined as PSA >0.2ng/mL), with 23% of these men having undetectable

PSA levels for 5 years. Of these men with PSA recurrence, 103 (34%) progressed to metastatic disease over a median actuarial time of 8 years post-PSA recurrence. Once men developed metastatic disease, median actuarial time to death was 5 years, and earlier time to appearance of metastatic disease post-surgery was predictive of time until death. On multivariate analysis, predictors of development of metastatic disease were time to biochemical progression, Gleason score and PSA doubling time.

Antonarakis et al evaluated the metastasis-free survival in men with BCR following RP in a retrospective analysis of 450 men treated between a single institution between 1981 and 2010.¹⁰⁹ None of the men in the study received adjuvant or salvage therapy following BCR. Median follow-up after RP and BCR was 8.0 years and 4.0 years, respectively. At last follow-up, 134 of 450 patients (29.8%) had developed metastases, while median metastasis-free survival was 10.0 years on Kaplan-Meier analysis. On multivariate analysis, the authors found PSA doubling-time (<3.0 years) to be the strongest predictor of metastasis-free survival, followed by high-grade Gleason score 8-10. Time to PSA recurrence was not shown to be a predictor.

Timing of Biochemical Recurrence

The majority of BCR following RP occurs within the first five years, however it has been reported to occur in approximately 6-10% of patients more than five years after surgery.^{107,110} Whilst these patients with delayed recurrence are more likely to have more slowly developing disease, it suggests that follow-up of men post-RP should occur beyond five years, and in some cases ten years. The influence of timing of BCR on survival has also been evaluated, although results are mixed.

In one of the earlier studies investigating delayed onset (>5 years) of disease progression post RP, Amling et al examined a cohort of 2,782 men with clinically localised PCa who underwent RP in the early PSA era between 1987 and 1993. PSA recurrence in this study was defined as PSA greater than 0.4ng/mL. Overall, 29% of patients experienced BCR, including 6% of patients who experienced recurrence after 5 years.¹¹⁰ Annual hazard rates

were highest during the first 2 years. Patients with adverse prognostic features (pT3b, PSA >10ng/mL, Gleason score ≥ 8) had high initial hazard rates that decreased with time to lower levels, but patients with pathologically organ confined cancer had low but constant hazard rates throughout follow-up. Furthermore, hazard rates for progression in this group of pathologically organ-confined disease never reached zero even after 5 years, suggesting that there is a continued low risk of failure with time.

Ward et al investigated the significance of late biochemical recurrence (≥ 5 years after surgery) in their series of 3,903 men who underwent RP. Median length of follow-up was 8.8 years, with 98% of men having at least 6 years of follow-up. Biochemical recurrence occurred in 33% of men, of which 73% occurred before and 27% after 5 years of post-surgery follow-up.¹¹¹ Of the patients with BCR, only 29% progressed to develop clinical failure (local recurrence or distant metastases), however, the risk of progression to clinical failure was demonstrated to never reach zero on actuarial analysis, even after 8 years. Only 8% of men with BCR eventually died of prostate cancer. Interestingly, there was no difference in progression to clinical disease, PCa-specific or overall survival between men with early or late BCR. On multivariate analysis, PSA doubling-time was the only independent predictor of clinical disease progression, after accounting for Gleason score, early PSA failure and pre-operative PSA.

In a retrospective review of 379 patients treated with radical prostatectomy between 1982 and 2000 who experienced BCR, Freedland et al examined the association between time of surgery to BCR and PSADT, and risk of PCSM.¹¹² Mean follow-up was 10.8 years, and mean follow-up after BCR was 7.3 years. During this time, 76 men (20%) died of PCa. The authors found increasing interval to BCR to be associated with slow PSADTs and decreased risk of PCSM. The estimated 15-year actuarial PCa-specific survival rate after BCR in patients with recurrence at 3 years or less was 41% compared to 87% in patients with recurrence after 3 years. On multivariate analysis, shorter interval to BCR (<3 years) was associated with a near three-fold increased risk of PCSM, after adjusting for PSADT and high Gleason score ≥ 8 , which were also strong independent predictors. Furthermore, time to BCR was associated

with PCSM when analysed as a continuous variable. Only one death was noted among patients who BCR after 5 years.

In an attempt to identify factors that predicted delayed BCR after RP, Caire et al examined a cohort of 4,561 men who underwent RP between 1988 and 2008. Of these men, 26.5% (1,207 men) experienced BCR (defined as PSA >0.2ng/mL) and were divided into two groups; early (before 5 years) and delayed (after 5 years). Approximately 90% of PSA recurrence occurred within 5 years after RP.¹¹³ Although there was no statistically significant difference in metastasis-free survival between the men with early vs late BCR, men with late BCR had increased PCa-specific survival. On multivariate analysis, the factors associated with delayed PSA recurrence included Gleason sum <7 (vs Gleason sum >7) and PSA <10ng/mL (vs PSA >20ng/mL).

Debate remains as to the frequency and duration of surveillance PSA testing after a certain period of PSA recurrence-free survival. Whilst it is clear that BCR occurs after a prolonged period (>5 years) of undetectable PSA levels, no guidelines exist to help clinicians stratify patients into groups that require yearly PSA testing and those that may require less frequent testing, such as biannual PSA tests.

Above et al attempted to address this concern by evaluating risk factors for BCR in 505 men with a ≥ 5 year history of undetectable PSA readings following RP.¹¹⁴ Median post-surgery follow-up was 10.7 years. Using Kaplan-Meier analysis, PSA failure-free survival in this group of patients was estimated to be 88% after 10 years and 82% after 13 years, suggesting that a sizeable minority of men are still at risk of very late failure. On multivariate analysis, the authors found higher Gleason score (Gleason sum 7 and 8-10) and extracapsular extension to be associated with BCR after 5 years. No patients with Gleason 6 disease developed distant metastases, suggesting that these men would be candidates for less intense follow-up after a 5-year disease-free interval, compared to patients with high risk disease who should continue to undergo yearly PSA testing.

Loeb et al investigated predictors of late BCR and the relationship between timing of BCR and survival outcomes in a retrospective review of 10,609 men who underwent RP between

1978 and 2009.¹¹⁵ Overall, 1684 men experienced BCR, including 77% before 5 years post-RP, 16.6% between 5 and 10 years, 4.9% between 10 and 15 years, and 1.5% after 15 years. Late recurrence was found to be associated with more favourable pathological features, as well as higher metastatic-free and cancer-specific survival rates on Kaplan-Meier analysis. In men with no evidence of BCR at 10 years, the risk of developing subsequent BCR was low, no progression to metastatic disease was observed with Gleason 6 disease, and only one death within 20 years of radical prostatectomy was noted in this subgroup (this patient had Gleason 7 and pT3b disease). The authors concluded that annual PSA testing may not be necessary for men with Gleason 6 or less and/or limited life expectancy.

In a retrospective analysis of 2,219 men with low-risk PCa managed with RP between 1994 and 2004, Tollefson et al investigated the risk of developing PSA recurrence following a defined period of undetectable PSA levels post-surgery. Biochemical recurrence was low (6.4%) in this low-risk cohort, and only 1.4% of experienced BCR after 5 years.¹¹⁶ Using Kaplan-Meier analysis, the risk of developing BCR at any stage following a 5-year PSA recurrence-free interval post-surgery was very low, with 1, 3 and 5-year BCR rates predicted to be 0.0%, 0.7% and 1.3%, respectively. Similarly, the authors demonstrated that after a PSA recurrence-free period of 3 years, the risk of developing PSA failure within the next year was 0.2%. The authors thus concluded that PSA measurements need only be performed every 2 years following a PSA recurrence-free interval of 3 years in low-risk men, alleviating the costs and patient anxiety associated with yearly and intensive PSA testing.

Predictors of Increased Prostate Cancer-Specific Mortality Following Radical Prostatectomy

Positive Surgical Margins

Studies have demonstrated that positive surgical margins following RP are associated with increased risk of BCR. However, BCR represents an early event in the natural history of PCa recurrence, and the outcomes are variable. The rate of BCR for patients with a positive surgical margin is variable, with rates reported to be between 19% and 50%.^{117,118} The

relatively low mortality rate from PCa overall perhaps precludes positive surgical margins from having an impact on mortality except in studies with very large populations, given that adverse pathological features such as high grade Gleason score and extraprostatic disease are very strong predictors of mortality (discussed later).

In a large study of 65,633 patients from the SEER registry who underwent RP between 1998 and 2006, with follow-up of 50 months, positive surgical margins were reported in 21.2% of cases and were more common in pT3a than pT2 tumours (44% vs 18%, $p<0.001$) and higher grade tumours (28% vs 18%, $p<0.001$).¹¹⁹ On multivariate analysis, positive surgical margins were shown to be an independent predictor of PCSM (HR 1.70, 95% CI 1.32-2.18). However, limitations of this study included lack of PSA data and location of positive surgical margins, which can influence BCR.

Other studies have shown BCR to not have significant influence on mortality outcomes. Boorjian et al assessed the impact of positive surgical margins following RP using data from 11,729 patients treated at the Mayo Clinic between 1990 and 2006. Median post-operative follow-up was 8.2 years. In this study, 3,651 (31.1%) men were identified with a positive margin, and these men had significantly decreased 10-year BCR-free (56% vs 77%, $p<0.001$) and local recurrence-free survival (89% vs 95%, $p<0.001$).¹²⁰ On multivariate analysis, presence of a surgical margin was associated with increased risk of BCR (HR 1.63, 95% CI 1.47-1.80, $p<0.0001$), local recurrence (HR 1.78, 95% CI 1.45-2.19, $p<0.0001$) and receipt of salvage therapy (HR 1.79, 95% CI 1.58-2.02, $p<0.0001$). However, it was not a significant predictor of systemic progression, cancer-specific death or overall mortality.

PSA, Gleason Score and Pathological Stage

Men with high-risk PCa, as evidenced by high pre-operative PSA, advanced pathological stage and high Gleason score, have been consistently shown to have adverse survival outcomes following RP. However, men with intermediate-risk disease can have heterogenous outcomes, which will be discussed below and as part of this thesis. Men with

low-risk disease, namely those with Gleason 6 PCa, have been consistently shown to have excellent survival following RP, and following surveillance (as discussed previously).

Stephenson et al reported 15-year outcomes following RP in a multi-institutional cohort of 6,398 patients treated between 1987 and 2005 and demonstrated 15-year PCSM and all-cause mortality to be 12% and 38%, respectively.¹²¹ Biopsy Gleason grade and year of surgery were associated with PCSM. Low lethality from good risk PCa (cT1c or T2a, PSA <10, Gleason ≤ 6) was noted with a PCSM of 2%, and these men comprised 46% of patients in the study. The authors developed a nomogram to allow estimates of death from PCa at 10 and 15 years. Based on this model, the authors concluded that few contemporary patients have an estimated 15-year PCSM risk of over 5% (only 4% of patients in their study met this risk), and that the long-term risk of PCSM among patients treated with RP is low, even for patients with adverse clinical features.

Long-term outcomes from 787 patients treated with RP from a single centre in Seattle were reported by Porter et al, and represents one of the most mature series in the literature. Men in the cohort were treated between 1954 and 1994 and follow-up ranged from 0.1-40.5 years (mean 11.7, median 11.4). PSA recurrence occurred in 31.4% of men (601 evaluable), with local and distant recurrence noted in 8.4% and 11.3%, respectively.¹²² Of the deaths, 6.6% were attributable to PCa and overall 39.6% of men died due to any cause. On actuarial survival analysis, estimated probabilities of PCa-specific survival at 10-years for patients with Gleason 6, 7 and 8-10 were 95.1%, 94.5% and 82.6%, respectively. On multivariate analysis, the strongest predictors of increased risk of PCSM were high-grade Gleason score ≥ 8 and hormonal therapy after surgical treatment. Interestingly, adverse pathological stage was not found to be associated with increased PCSM.

A large single surgeon series of 3,478 patients treated with RP between 1983 and 2003 with mean follow-up of 65 months showed 10-year Kaplan-Meier estimates of PCa-specific survival and overall survival to be 97% and 83%, respectively.¹⁰⁵ The 10-year biochemical progression-free survival was estimated to be 68%. On multivariate analysis, factors associated with increased risk of BCR included PSA, clinical stage, Gleason sum, pathological

stage and era of treatment. When death from PCa was addressed, factors associated with increased risk of death were pathological stage, Gleason sum and pre-PSA era of RP.

Other large studies have evaluated the predictive value of multiple adverse pathological risk factors. Han et al reported 15-year post-RP outcomes in a single surgeon series of 2,494 patients from John Hopkins, where mean follow-up was 6.3 years, and 26% of patients having 10 or more years of follow-up. Kaplan-Meier estimates of 10-year and 15-year PCa-specific survival were 96% and 90%, respectively.¹²³ A statistically significant difference was seen in actuarial PSA progression-free probabilities between men with Gleason 3+4 versus 4+3 tumours, but no difference was observed between men with Gleason 4+3 vs Gleason sum 8-10, highlighting the importance of the primary disease pattern. PSA progression-free survival probabilities were similar for men with seminal vesical invasion (T3b disease) and men with a combination of T3a disease, positive surgical margins and Gleason score ≥ 7 .

Lodde et al also analysed the effect of none, single or multiple high-risk factors (PSA ≥ 20 or cT $\geq 2c$ or Gleason ≥ 8) on BCR and PCSM. The study included 1,109 men treated with RP between 1989 and 2005, with median follow-up of 8.18 years. The authors found high-risk patients with 1 or ≥ 2 high-risk criteria to have a 2.6 and 3.9 times risk of BCR, respectively, when compared to low- or intermediate-risk patients.¹⁰⁶ When addressing PCSM, risk was increased by 9.2 times for ≥ 2 high-risk factors and by 4.7 times for one high-risk factor, respectively, when compared to no high-risk factors. PSA ≥ 20 was found to have the lowest estimated 10-year PCSM on actuarial analysis (4.5%), followed by cT $\geq 2c$ (9.2%) and Gleason score ≥ 8 (18.2%).

Influence of Socioeconomic Factors on Prostate Cancer Management and Outcomes

Other than clinicopathologic variables, and PSA patterns and kinetics, socioeconomic factors may play a role in promoting poorer outcomes in men with localised PCa managed with surgery. Several studies from the US have demonstrated that black men undergoing RP have poorer outcomes compared to non-Hispanic whites, likely due to more advanced disease upon diagnosis.^{39,40} Others have also confirmed a difference between the two

groups, however, when socioeconomic status (SES) is added to the multivariate models, very little difference is seen, suggesting that the disparity in outcomes between black and non-Hispanic white men may be largely explained by socioeconomic factors.^{45,46}

Such findings, however, may not be applicable to an Australian population given the difference in demographic status. Although the Australian land mass is significant, much of the population resides near major cities and results in a mal-distribution of health care resources to rural locations. Several studies have attempted to evaluate the difference in outcomes in rural and urban patients with PCa. In a study from Western Australia of men diagnosed with PCa between 1982 and 2001, the authors found that men were less likely to be treated with RP if they were from a rural location, non-privately insured and had lower SES.⁴⁷ Men also had a greater likelihood of death within 3 years if their first post-operative admission was to a rural hospital or they had lower SES.

Another study from New South Wales of men diagnosed with PCa between 1985 and 2002 showed similar findings. Compared to men from capital cities, men from regional/rural areas experienced a mortality excess 21%, a 29% lower rate of RP, and a 16% lower rate of PSA testing.⁴⁸ Such differences in outcomes may in part be explained by more limited access to urologists in rural areas.

Renal Cell Carcinoma

Introduction

Renal cell carcinoma (RCC) accounts for approximately 95% of primary malignant tumours affecting the kidney in adults. Other primary malignant renal tumours include transitional cell carcinomas and sarcomas. Several risk factors have been demonstrated for sporadic RCC, including smoking, obesity and hypertension.¹²⁴

The most common histological subtype of RCC is clear cell (or conventional) RCC. This is followed by papillary RCC and chromophobe RCC. Rare highly malignant variants include collecting duct carcinoma, renal medullary carcinoma and unclassified RCC. Although the vast majority of RCCs are sporadic, various acquired RCC diseases have been classified, including RCC associated with end-stage renal disease (acquired cystic disease-associated RCC).¹²⁵

Several inherited RCC syndromes have been identified, which comprise 5-8% of all RCCs. These syndromes include hereditary clear cell RCC, hereditary papillary RCC, von Hippel Lindau syndrome, Tuberous sclerosis and Birt-Hogg Dubé syndrome. In sporadic RCC, clear cell RCC appears to have a worse prognosis than papillary or chromophobe RCC, with the latter having the best prognosis.¹²⁶

Apart from RCC subtype, evaluation of nuclear grade, presence of sarcomatoid elements and clinical and pathological stage provide valuable prognostic information. At the time of this study, the most commonly used staging classification for RCC is the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, published in 2010.¹²⁷

Staging	Criteria
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤ 4.0 cm
T1b	Tumor > 4.0 cm but ≤ 7.0 cm
T2	Tumor > 7.0 cm in greatest dimension, limited to the kidney
T2a	Tumor > 7 cm but ≤ 10 cm
T2b	Tumor > 10 cm, limited to the kidney
T3	Tumor extends to major veins or peri-nephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades peri-renal and/or renal sinus fat (peri-pelvic) but not beyond Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes (N)	
NX	Regional node metastasis cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Epidemiology

Renal cell carcinoma (RCC) is the second most common urological malignancy diagnosed in Victoria, Australia, following prostate cancer in men.¹²⁸ There is a 1.5:1 male predominance, with a peak incidence in the 6th and 7th decades of life.

In Europe, overall mortality rates for RCC increased up to the early 1990s, and stabilised or declined thereafter, likely reflecting stage migration of RCC at diagnosis to earlier localised disease due to the increasing use of abdominal imaging, such as computerised tomography or ultrasound.¹²⁹ A similar trend in increasing incidence in the 1990s and an associated decline in mortality was also seen in the United States.^{130,131}

Trends in Diagnosis and Presentation

The widespread use of imaging has in large part contributed to a steady increase in the incidence of renal cancer in the last two decades. Additionally, the largest increase has been demonstrated for localised renal tumours.^{13,130,132} Consequently, the most common presentation of renal cell carcinoma is that of an incidental finding; an asymptomatic renal mass most typically discovered by ultrasound, CT or MRI. This represents approximately 60% of all presentations.¹³³ The 'classic triad' of haematuria, flank pain and a palpable abdominal mass is now rare.

Using the SEER database, Nguyen et al analysed trends in presentation of RCC in 29,053 patients diagnosed with a primary renal cancer between 1988 and 2002. Throughout this period, mean tumour size at diagnosis decreased from 66.8mm in 1988 to 58.6mm in 2002, while the age-adjusted incidence of renal cancer increased from 8.6 to 11.2 cases per 100,000 individuals.¹³ Using Kaplan-Meier analysis, increased renal cancer size above 4cm was associated with decreasing survival, whilst tumours less than 4cm demonstrated uniform survival. Patients diagnosed towards the latter part of this period were also shown to have improved survival compared to those diagnosed in the earlier part after adjusting for tumour size on multivariate analysis. However, the effect was no longer statistically significant after 1998, suggesting that despite an increase in proportion of smaller renal masses (39% < 4cm between 1998-2002 vs 30% between 1988 and 1992), other factors lead to an improved survival in patients diagnosed more recently.

Cooperberg et al performed an analysis of 104, 150 patients diagnosed with stage I RCC between 1993 and 2004 from the US National Cancer Data Base. During this period, a statistically significant increase in the proportion of renal masses 3.0cm or less (32.5% in 1993 vs 43.4% in 2004) was noted.¹³² Of these tumours, a corresponding increase in tumours less than 2.0cm was also demonstrated (24.1% in 1993 vs 29.4% in 2004). Overall, mean tumour size decreased from 4.1cm to 3.6cm.

In a similar and more recent study, Kane et al¹³⁴ assessed patterns of disease presentation and outcomes for RCC using the National Cancer Database, which included 205 963 cases of RCC diagnosed between 1993 and 2004. Comparisons between 1993 and 2004 demonstrated an increase in stage I disease, and decreases in stage II, III and IV disease. The size of stage I tumours also decreased from a mean of 4.1cm in 1993, to 3.6cm in 2003. In multivariate analysis, stage (but not histology) and age was predictive of survival. For all stages combined, overall survival for patients diagnosed in 1998 was slightly higher than for patients diagnosed in 1993, but stage-specific survival was similar, suggesting that the improvement in overall survival were due to the decrease in proportion of stage II and III patients over time.

To evaluate whether or not stage migration of RCC was also occurring in Australia, Doeuk et al retrospectively analysed 547 nephrectomies (499 for RCC) performed in several private and public western Sydney hospitals between 1993 and 2007.¹³⁵ Median age was 62 years, with a male to female ratio of 1.9:1. Pathological stage II disease decreased from 18.1% to 11.1%, but stage III disease showed an increase from 13.9% to 21.5% over that time period. The proportion of stage I and IV disease remained relatively the same. There was also a decrease in the number of benign tumours originally thought to be malignant on imaging. The authors concluded that the phenomenon of RCC migration towards earlier stage and smaller tumours, as well as an increase in benign tumours, was not observed in this Australian study.

Several studies have demonstrated an improvement in survival from RCC due to the increase in incidental RCC diagnoses and stage migration. Chow et al demonstrated an improvement in 5-year relative survival rates in patients with RCC diagnosed between 1975 and 1995 across all racial and sex groups.¹³⁰ In a population study of 205,963 patients from the US National Cancer Data Base (NCDB), Kane et al were also able to demonstrate a 3.3% improvement in survival for patients diagnosed in 1998 vs 1993, and that stage migration was predictive for improved survival.¹³⁴

Treatment of Localised Renal Cell Carcinoma

For many decades, radical nephrectomy (RN) remained the mainstay for surgical treatment of renal cell carcinoma¹³⁶. Traditionally, the procedure was performed with an open approach. However, this approach was fraught with significant complications and morbidity, including post-operating pain, prolonged recovery, excessive blood loss and wound related complications. Subsequent development of minimally invasive laparoscopic techniques allowed a similar operation to be performed with comparable oncologic outcomes and significantly less morbidity.¹³⁷⁻¹³⁹

Similarly, open partial nephrectomy (PN) was traditionally the gold standard nephron-sparing approach for amenable renal tumours, either for absolute indications (bilateral RCCs, tumour in single kidney, inheritable RCC syndromes) or relative indications (small tumour, chronic kidney disease, high likelihood of benign tumour). But advancing surgical techniques have allowed this operation to be performed with minimally invasive approaches, such as laparoscopic or robotic-assisted, therefore reducing patient morbidity.¹⁴⁰⁻¹⁴² Preservation of renal function following surgery also has significant potential long-term benefits, which will be discussed below.

However, given the stage migration of RCC and increasing diagnosis of smaller and potentially more indolent renal masses, both partial and radical nephrectomy may be considered excessively morbid and unnecessary treatment options in certain patient groups, such as the elderly or those with significant comorbid disease. Thus increasing evidence has accumulated to support the use of observation.

The natural history of small renal masses, as demonstrated in several observational studies, is that the vast majority grow at a slow rate, and have little metastatic potential or cancer-related mortality.^{143,144} Chawla et al performed a meta-analysis of single-institution series reporting data on solid and localised renal masses managed with observation.¹⁴⁵ A total of 286 lesions were analysed, representing the largest dataset of this kind in the literature, of which 234 could be included in the meta-analysis. Pathological information was available in

46% of the cases, of which 92% were demonstrated to be RCC variants. Mean lesion size at presentation was 2.60cm (median 2.48cm, range 1.73-4.08). Meta-analysis demonstrated a mean growth rate of 0.28cm yearly at a mean follow-up of 34 months. When the subset of pathologically confirmed RCC was analysed, a mean growth rate of 0.40cm was noted. No correlation between lesion size at presentation and overall growth rate was identified ($p=0.46$). Only 1% of the lesions (3 of 286) progressed to metastatic disease.

Rationale for Partial Nephrectomy

Equivalence of Oncological Control Between Partial and Radical Nephrectomy

Several studies with intermediate- to long-term follow-up have confirmed PN to be a safe option for suitable patients with RCC, with very low rates of local or distant recurrence. Lee et al compared the use of RN and PN in a retrospective review of patients with RCC tumours <4cm treated between 1989 and 1997.¹³⁹ The authors included 183 patients who underwent RN (median size 3.0cm), and 79 patients who underwent PN (median size 2.5cm), and median follow-up in this study was 40 months. Partial nephrectomy was elective in 47% of cases. No local recurrence was observed in either group, and no significant differences in overall or cancer-specific survival were observed on Kaplan-Meier analysis. Of the patients who had elective PN, no cases of disease recurrence were reported and disease-free survival rate was 100%. On univariate analysis, only pathological stage was predictive of disease-specific or overall survival, and operation type was not predictive of survival on multivariate analysis.

Using SEER data, Crépel et al assessed cancer-specific mortality after PN or RN for T1a RCC using competing-risks models.¹⁴⁶ The investigators identified 1622 (22.3%) and 5658 (77.7%) patients who underwent PN and RN, respectively, between 1988 and 2004. The competing-risks regression models addressed the effect of nephrectomy type on cancer-specific mortality, and controlled for other-cause mortality and matched for age, year of surgery, tumour size and Furrman grade. Overall, 1564 of the PN patients (96.4%) were matched with 3955 (69.9%) of the RN patients. No significant difference in survival was observed

between PN and RN groups for both matched cohorts. The investigators found at five years, cancer-specific mortality after PN and RN was 1.8% vs 2.5% ($p=0.5$).

More advanced and larger tumours may be amenable to PN, however, outcomes may be poorer, especially for larger tumours. Jeldres et al analysed long-term outcomes in a multi-institutional cohort of patients with localised RCC treated with surgery between 1984 and 2001, with mean follow-up of 4 years.¹⁴⁷ Of 4072 patients, 925 (22.7%) had tumours >7cm, 973 (23.9%) had Furhman grades III or IV, and 861 (21.1%) had stage pT3a. Patients receiving either PN or RN were matched for age, gender, tumour size, T stage, tumour histologic subtype and Furhman grade). No significant differences in cancer-specific survival was noted between PN and RN for tumours with Fuhrman grade III-IV or for pT3a tumours based on matched Kaplan Meier or unmatched multivariate analysis. However, PN for tumours >7cm was associated with higher mortality than RN on matched Kaplan Meier analysis and on unmatched multivariate analysis (HR 5.3, $p=0.25$).

Prevention of Chronic Kidney Disease Associated with Radical Nephrectomy

Radical nephrectomy has been clearly shown in several large retrospective case matched studies to be associated with chronic kidney disease (CKD) compared to PN. On multivariate analysis, after controlling for other risk factors for CKD such as diabetes and hypertension, RN consistently predicts worsening renal function after surgery.

Lau et al performed a retrospective matched cohort analysis of patients with localised renal tumours (97% pT1) and normal contralateral kidneys treated with PN or RN and followed up for 4 years.¹⁴⁸ Overall, 164 patients from each group were matched for age, sex, tumour size, pathological T-stage and grade, and year of surgery. No significant difference in overall or cancer-specific survival or rates of contralateral recurrence and metastases between the two groups was demonstrated, although the rate of ipsilateral recurrence was slightly higher in the PN group. When the authors assessed long-term renal function, the cumulative incidence of chronic renal insufficiency (defined as creatinine >2.0mg/dL) was

22.4% and 11.6%, respectively, for the RN and PN groups (risk ratio 3.7). Patients managed with RN were also at significantly higher risk for proteinuria.

Huang et al assessed the development of CKD in a retrospective review of 662 patients treated at Memorial Sloan-Kettering Cancer Centre between 1989 and 2005 with normal serum creatinine levels and two healthy kidneys undergoing elective PN or RN for solitary renal cortical tumours <4cm.¹⁴⁹ The investigators defined CKD as estimated GFR < 60mL/min/1.73m² and < 45mL/min/1.73m². Using these GFR thresholds, the authors found that 26% of patients with normal serum creatinine levels in fact had pre-existing chronic kidney disease before surgery. Following surgery, 5-year probability of freedom from new onset GFR < 60 was 67% following PN (95%CI 57-75) and 23% following RN (95% CI 16-30). Median time to development of GFR < 60 was 18 months for the RN group (not reached for the PN group). Similarly, 5-year probability of freedom from new onset GFR < 45 was 93% (95%CI 87-96) and 57% (95%CI 50-64) for PN vs RN groups, respectively. Radical nephrectomy was confirmed as an independent risk factor for CKD on multivariate analyses, after controlling for age and co-morbidities such as diabetes and hypertension.

Similarly, Malcolm et al demonstrated increased risk of CKD, proteinuria and metabolic acidosis following RN compared to PN.¹⁵⁰ This study included 749 patients who underwent RN (n=499) or PN (n=250) for renal tumours between 1987 and 2006, with the primary outcome of CKD defined as estimated GFR <60mL/min/1.73m.² Tumours of all sizes were included in this study. Secondary outcomes included the development of a serum creatinine level of ≥ 2.0 mg/dL, metabolic acidosis and proteinuria (on dipstick testing). Following surgery, a significantly greater proportion of patients who had RN had CKD (44.7% vs 16.0%), metabolic acidosis (12.8% vs 7.2%), proteinuria (22.2% vs 13.2%) and elevated creatinine (14.2% vs 8.4%) compared to patients who had PN. On multivariate analysis, RN was shown to be an independent risk factor for the development of CKD.

Chronic Kidney Disease Following Radical Nephrectomy May be Associated with Adverse Survival Outcomes

The development of CKD is associated with adverse health outcomes, including the requirement for dialysis in severe cases. Other complications of CKD include hypertension, anaemia, malnutrition, neuropathy and reduced quality of life. Strong evidence exists for CKD to be an independent risk factor for cardiovascular disease, as well as increasing risk of post-operative mortality in non-cardiac surgery and overall death.¹⁵¹ Therefore, the preservation of renal function in patients with RCC is an important consideration when counseling patients about treatment options. Several retrospective studies have demonstrated improved survival outcomes in patients undergoing nephron-sparing surgery, but such findings have not been borne out in any prospective randomised studies.

In a landmark study, Go et al assessed the associated between CKD and risks of deaths, cardiovascular events and hospitalisation in a large community based cohort of over 1.1 million patients. On multivariate analysis, risk of overall death increased inversely with estimated GFR levels below 60 ml/min/1.73m², with the highest risk seen in patients with estimated GFR below 15. In this group, the risk of death was nearly six times greater than in patients with normal renal function (estimated GFR greater than 60).¹⁵² Similarly, patients with declining renal function were more likely to experience cardiovascular events and hospitalisation.

Weight et al assessed compared overall survival, cancer-specific survival and cardiac specific survival in patients undergoing PN or RN for cT1b tumours.¹⁵³ The study included 1004 patients treated with PN (n=524) or RN (n=480) between 1999 and 2006 at Cleveland Clinic. Cancer-specific survival was equivalent between the two groups at 5 years for patients with malignant tumours on Kaplan Meier analysis, and surgical approach was not predictive of cancer-specific survival in multivariate Cox regression model. Patients who underwent RN, however, had significant deterioration in renal function compared to patients who had PN, with the average decrease in estimated GFR being 23.5 and 16.6 for RN vs PN, respectively. Post-operative renal insufficiency was a significant independent predictor of overall and

cardiovascular specific survival. On Kaplan Meier analysis, a decrease in overall survival and cardiovascular-specific survival was observed with decreasing renal function. The average excess loss of renal function observed with RN was associated with a 25% (95% CI 3-73) increased risk of cardiac death and 17% (95% CI 12-27) increased risk of death from any cause.

Overall survival outcomes were also compared by Thompson et al using the Mayo Clinic tumour registry, and the study included 648 patients with renal masses ≤ 4 cm who underwent RN or PN between 1989 and 2003, with pathologically confirmed pT1a RCC.¹⁵⁴ RN and PN was performed in 290 (44.8%) and 358 (55.2%) patients, respectively, and median follow-up was 7.1 years. RN was not associated with increased overall mortality, however, when a subgroup analysis of patients < 65 years was performed, the investigators observed increased risk of mortality in younger patients who received RN (RR 2.16, $p=0.02$). The increased risk of death persisted after adjusting for year of surgery, pre-operative creatinine, co-morbidity, symptoms at presentation and histology. These findings implicate the potential adverse effects of CKD on overall survival.

To address some of the limitations of hospital-based series, several authors have used SEER data to demonstrate similar findings. Huang et al performed a retrospective analysis of 2,991 patients older than 66 years who were treated with either PN ($n=556$ or 19%) or RN ($n=2,547$ or 81%) between 1995 and 2002 using the SEER database. Tumour size was limited to 4cm or less. Median overall length of follow-up was 43 months. On Kaplan-Meier analysis, the 3 and 5-year probability of freedom from a CV event was 86% and 82%, respectively, compared to 82% and 75% following radical nephrectomy.¹⁵⁵ After adjusting for preoperative demographic and comorbid variables, radical nephrectomy was associated with an increased risk of overall mortality (HR 1.38, $p<0.01$) and a 1.4 times greater number of cardiovascular events after surgery ($p<0.05$). A limitation of this study was that the SEER database did not contain information pertaining to pre- and post-surgery renal function, thus CKD acting as a risk factor for subsequent cardiovascular events could only be inferred but not directly observed.

In a similar study, Zini et al used SEER data to compare overall mortality and non-cancer death rate in patients who underwent PN and RN for T1a RCC between 1988 and 2004. During the study period, 2198 (22.4%) and 7611 (77.6%) of patients underwent PN and RN, respectively, with median follow-up of 35 and 46 months.¹⁵⁶ Patients were matched for age, year of surgery, tumour size, and Furhman grade (where available). RN was found to be associated with a 1.23-fold increased overall mortality rate, with estimated 5- and 10-year survival rates of 89.3% and 71.3% for PN, compared to 84.4% and 68.2% for RN. This translated into a 4.9% and 3.1% absolute increase in mortality at 5 and 10 years after surgery.

Several confounders may exists in these retrospective studies, and factors influence choice of either PN or RN may not be recorded. Such confounders may include access to surgeons who perform PN. Tan et al addressed this concern by using SEER data to evaluate overall survival among patients with clinical stage T1a RCC treated with PN or RN.¹⁵⁷ This study of 7138 patients included 1925 (27.0%) patients treated with PN and 5213 (73.0%) treated with RN. Median follow-up in this study was 62 months. The investigators employed an instrumental variable approach to account for measured and unmeasured differences between treatment groups, and fitted a 2-stage residual inclusion model to estimate the treatment effect of PN on long-term survival. Differential distance to a PN physician was employed as the instrumental variable, and patients living closer to a PN physician were shown to be more likely to receive this treatment. The second-stage model adjusted for patient-level covariates, surgical approach and post-operative complications. On multivariate analysis (including controlling for distance to PN physician), no difference was noted in kidney cancer-specific survival, but patients treated with PN had a significantly lower risk of overall death (HR 0.54, 95% CI 0.34-0.85). Although serum creatinine levels were not included in the analysis, the positive effect of renal preservation on overall survival is implied.

Although an increasing body of literature demonstrating adverse health outcomes following RN exists, a major limitation of available evidence is that the studies are retrospective in nature and therefore prone to unknown confounders. A large European study by the EORTC

group currently represents the only prospective and randomized trial comparing PN to RN for localised renal masses <5cm.¹⁵⁸ During the accrual period between 1992 and 2003, 268 and 273 patients were randomized to PN and RN respectively. Median follow-up was 9.3 years. Interestingly, intention-to-treat analysis showed superior 10-year overall survival rates for RN vs PN (81.1% vs 75.5%). However, following sub-group analysis of pathologically eligible patients (confirmed RCC <5cm), no difference in overall survival is seen. No significant difference in deaths from renal cancer was seen between the two groups, owing to the small number of renal cancer-related deaths overall (8 in NSS group, 4 in RN group). In terms of secondary end points, no significant difference in progression of disease was demonstrated between the two groups, again owing to the low number of recurrences overall (12 patients in NSS group, 9 patients in RN group). A slightly higher complication rate following NSS was seen. Some of the limitations of the study include a significant rate of contamination and cross-over (5.9% of patients randomized to RN received NSS, and 14.6% randomized to NSS received RN).

As mentioned above, CKD has been shown to be an independent risk factor for cardiovascular mortality and lower overall survival. However, patients with a normal contralateral kidney and surgically induced CKD following RN may not experience these adverse health outcomes. In 2015, Lane et al published a large series of 4299 patients who underwent renal surgery for cancer between 1999 and 2008, and evaluated aetiology of CKD (defined as post-surgical estimated GFR < 60ml/min/1.73m²) on overall and cancer-related mortality.¹⁵⁹ The authors noted patients with post-operative CKD who had co-existing medical renal diseases (such as hypertension, diabetes and cardiac disease) were more likely to have lower overall survival, compared to patients who developed post-operative CKD purely from surgery (either PN or RN). Importantly, functional decline and mortality was greatest for patients with new baseline GFR < 45, and patients with surgically induced CKD were less likely to reach this threshold of CKD, and were more likely to have stable renal function over time. Data from the EORTC 30904 randomised trial supports this, as both RN and PN groups had stable renal function after a decade of follow-up, although lower estimates of GFR were seen in the RN group.¹⁶⁰ Therefore, surgical technique may be less important provided that patients maintain an estimated GFR > 45, and patients without

pre-existing medical renal disease are more likely to achieve this. This bears important consideration in patients with larger tumours (for example, cT1b lesions) and a healthy contralateral kidney, as PN may expose them to unnecessarily higher risk and complex surgery without any long-term benefit.

Quality of Life

Several investigators have assessed quality of life (QOL) in patients who have undergone either radical or partial nephrectomy to determine if preservation of renal function following surgery leads to improved QOL. The data appears conflicting, but most studies show that patients have high QOL measures following either approach.

Lesage et al assessed health-related quality of life (HRQOL) after open PN and RN for renal tumours in a review of the literature. Although no statistical difference was found concerning perioperative complications, when considering HRQOL, a benefit was found after PN.¹⁶¹ Poulakis et al demonstrated similar findings in their comparison of patients who had undergone PN or RN. The authors noted that QOL correlates proportionally with the size of tumour and is significantly better for patients undergoing PN for tumours less than 4cm and with a normal contralateral kidney. These findings may be explained by patient reassurance that PN allowed maintenance of healthy renal parenchyma and bilateral renal units.

Conversely, Gratzke et al found no difference in QOL measures following laparoscopic RN, open RN and NSS, with patients reporting high QOL scores following all three approaches.¹⁶²

Trends in Utilisation of Partial Nephrectomy

The American Urological Association and the European Association of Urology both strongly advocate the use of PN to treat cT1a tumours, and for cT1b tumours where technically feasible.^{163,164} Although increasing evidence and international guideline recommendations support PN for management of small renal masses, the existing evidence points to general

underutilisation of this technique. Several explanations may exist to account for this general finding. Partial nephrectomy is a more complex procedure, especially when performed laparoscopically, thus limiting its use to surgeons with this particular skill set. Conversely, laparoscopic RN requires less advanced laparoscopic skills and can be performed by most urologists, and patient convalescence is rapid, especially when compared to open PN. A higher rate of positive margins has also been observed following PN. These barriers to PN will be discussed later in further detail. Furthermore, the available studies may not take into account important factors in treatment decision, such as patient preference and tumour location, as not all smaller tumours are suitable for PN if located close to the renal hilum or are endophytic in nature.

Underutilisation of Partial Nephrectomy in the United States

Several population based studies from the US have demonstrated underutilisation of PN for small renal masses. Using the SEER registry data, Yabroff et al evaluated surgical management and use of systemic treatments in a national population-based sample of 1,263 patients with newly diagnosed RCC in 2004. Of these patients, 429 (34.9%) had tumours <4cm. Radical nephrectomy was the most common surgical management for RCC (847 patients or 64.7%), with the majority of these being performed via an open rather than laparoscopic approach.¹⁶⁵ Partial nephrectomy was performed in 201 (18.3%) of patients, with 44.5% of patients with tumours <4cm receiving RN. Patients treated at hospitals without a residency training program were more likely to undergo RN rather than PN, and patients treated at smaller hospitals were more likely undergo an open rather than laparoscopic procedure.

Miller et al also observed similar trends in nationwide use of partial nephrectomy using SEER data. A total of 14,647 patients with renal tumours less than 7cm and managed with surgery were included, of which 9.6% were managed with PN. Among patients with renal tumours between 2 and 4cm, 20% underwent PN in 2000 and 2001.¹⁶⁶ Even more alarming was the finding that 42% of patients with tumours less than 2cm underwent partial nephrectomy in the same period, suggesting that over half of the patients underwent

extirpative surgery for very small and early stage renal masses. Using more recent SEER data, Dulabon et al identified 18,330 patients between 40-90 years who underwent surgery for kidney tumours ≤ 4 cm in the US between 1999 and 2006. In total, 11,870 patients (65%) underwent RN and 6,640 patients (35%) underwent PN.¹⁶⁷ Although PN was generally underutilised during this period, the ratio of PN to RN increased yearly ($p < 0.001$), and PN ultimately represented 45% of kidney surgeries in 2006 for small tumours. In multivariate analysis, male gender, age ≤ 70 years, urban residence, smaller tumour size and more recent year of treatment were predictors of PN.

Surgical Treatment Patterns Between Tertiary and Community Hospitals

Surgical complications of PN include a higher rate of vascular and urinary complications. Thus in the absence of readily available radiological and intensive care support, some surgeons may be less inclined to performed PN in certain hospital settings. Several studies have shown a significant disparity between high volume tertiary institutions and community non-teaching hospitals with regards to use of PN.

Hollenbeck et al performed a retrospective analysis of data from the Healthcare Cost and Utilization Projection Nationwide Inpatient Sample (NIS) to characterize practice patterns in the use of partial and radical nephrectomy. The NIS represents a 20% stratified sample of all hospital discharges in the US. A total of 66,621 patients treated between 1988 and 2002 were included in the analysis. Overall, 7.5% of patients treated underwent PN.¹⁶⁸ The authors noted that despite an increase in the use of PN during that period, there was a concurrent increase in the use of RN, suggesting an underuse of PN on a national level. The authors also demonstrated that patients were more likely to be treated with PN in teaching, high-nephrectomy volume hospitals in urban settings. This may reflect a disparity of ancillary and supportive health services, such as interventional radiology, between different centres, as well as perhaps selective referral of patients with renal tumours to high-volume institutions.

Also using data from the NIS from 1998 to 2002, Porter et al evaluated patient and provider factors associated with PN.¹⁶⁹ The authors found the number of nephrectomies performed in the US increased yearly, with an estimated 23,375 RNs and 4272 PNs performed in 2002, and the percentage of PNs performed also increased from 7.9% in 1998 to 15.5% in 2002. In multivariate analysis, patient and provider characteristics that were associated with PN included male sex, age (decreasing with increasing age), teaching hospital status, annual nephrectomy volume, annual surgeon nephrectomy volume and private insurance/health maintenance organization coverage (compared to Medicare).

Using data from the National Cancer Data Base (NCDB), which captures approximately 70% of all cancer diagnoses in the US, Cooperberg et al assessed treatment trends for Stage I RCC.¹⁷⁰ The advantages of the NCDB over SEER is that it represents a broader geographic representation and is not limited to patients older than 65 years. Patients diagnosed between 1993 and 2007 were included in the analysis, comprising 242 740 cases of RCCs, of which 127 691 were stage I. The number of stage I cases recorded annually in the database increased with time from 4274 in 1993 to 14 176 in 2007. During the study period, the use of RN for stage I RCC decreased from 88.3% in 1993 to 57.7% in 2007, PN increased from 6.3% to 32.2%, and focal ablative therapies increased from 1.0% to 6.8%. Predictors of decreased likelihood of receiving NSS (either PN or ablation) included female gender, black race, Hispanic ethnicity, lower income, older age and treatment at community hospitals. The authors also found that at all times, and for all tumour sizes, patients treated at teaching/research hospitals were more likely to undergo NSS than those treated at community hospitals. Between 2004-2007, tumours <3cm were treated with NSS in 47.8%, 53.5% and 66.8% of cases in community, comprehensive community and teaching/research hospitals.

Increasingly contemporaneous data may demonstrate an increasing use of PN for small renal masses less than 4cm, as well as renal masses between 4 and 7cm, as time may be required for the dissemination of technology and newer surgical techniques. However, rates of PN appear significantly higher in high volume tertiary centres compared to the rates reported above from cancer registries.

Thompson et al reported on the contemporary use of PN at Memorial Sloan-Kettering Cancer Centre, a high-volume hospital in New York.¹⁷¹ Between 2000 and 2007, 1,533 patients were treated for a sporadic and localised renal cortical tumour with pre-operative estimated GFR of $\geq 45 \text{ ml/min/1.73m}^2$. Patients with RCC or benign tumours on histology were included – 13% of patients had a benign tumour. Overall, 854 (55.7%) and 679 (44.3%) of patients were treated with partial and radical nephrectomy, respectively. Of the 820 patients treated electively for a tumour $\leq 4 \text{ cm}$, the frequency of PN increased from 69% in 2000 to 89% in 2007, which is significantly higher than the rates reported above. Similarly, among the 365 patients treated electively for a tumour 4-7cm, the frequency of PN increased from 20% in 2000 to 60% in 2007. The predictors of receiving PN in multivariate analysis included male gender, more contemporary year of surgery, younger age, smaller tumour size and open surgery. Significant independent predictors of RN included female gender, laparoscopic surgical approach and older age.

Zini et al compared PN to RN usage between 1987 and 2007 for stages T1-2 RCC in six high volume European institutions (patients with PN for lesions $> 7 \text{ cm}$ were excluded, and analyses were restricted to patients with T1a-b RCC).¹⁷² Overall, 597 (31.7%) of 1881 patients included were treated with PN, and an overall 4.5 fold increase in PN utilisation was observed during the study period. Tumour size was determined from imaging. The absolute increases in PN usage were 41.7 to 86.3% for lesions $\leq 2 \text{ cm}$, 14.9 to 69.3% for lesions 2-4cm, and 8.1-35.3% for lesions 4.1-7cm. Overall, PN was performed on 51.4% of tumours $\leq 4 \text{ cm}$, and 20.5% of tumours 4.1-7cm, which compares favourably to US population-based data. In multivariate logistic regression models, the authors found the following variables to be associated with greater likelihood of receiving PN: decreasing tumour size, younger age, more contemporary date of surgery, male gender and institutional PN rate. In the final study period between 2004-2007, the investigators observed a PN rate of 83.6% for tumours $\leq 2 \text{ cm}$, which compares similarly to US tertiary referral centres.

Increasing Popularity of Laparoscopic Radical Nephrectomy

In the past decade, the increased popularity of laparoscopic RN is a significant competing treatment option to open PN in patients with small renal masses.¹⁷³ Laparoscopic radical nephrectomy does not require highly advanced laparoscopic skills, and is associated with lower morbidity compared to open surgery, namely reduced blood loss and analgesic requirement, shorter hospital length of stay and more rapid convalescence.^{138,174,175} Conversely, laparoscopic PN is a technically challenging procedure to perform, and is generally the standard of care for small renal tumours in high-volume nephrectomy centres with experienced laparoscopic surgeons.

Abouassaly et al¹⁷⁶ examined the effect of laparoscopic RN on utilisation of PN over time using a population-based cohort. All patients treated surgically in Ontario (Canada) between 1995 and 2004 were included, and identified from a tumour registry (95% case ascertainment rate). Ontario represents approx. 1/3rd of Canadian population. In all, 7830 patients underwent surgery, of which 7042 (89.9%) and 788 (10.1%) underwent RN and PN, respectively. Laparoscopic codes were available in 2002. The authors found that introduction of laparoscopic RN coincided with decreased uptake and use of PN. Segmented regression analysis showed that odds of PN increased by 18% per year before January 2003 (OR 1.18, 95% CI 1.14-1.23) and subsequently decreased by 12% per year (OR 0.88, 95% CI 0.75-1.02). In the multinomial regression model, age and surgery year were independently associated with PN, but not gender.

Concerns and Barriers to Partial Nephrectomy

Inferior Surgical Oncological Control with Partial Nephrectomy

As partial nephrectomy involves removal of the tumour with a thin margin of normal parenchymal tissue, there remains some concern about the surgical oncological control compared to radical nephrectomy, which involves removal of the entire kidney and tumour, and the surrounding perinephric fat. Partial nephrectomy has been demonstrated to be

associated with a higher positive surgical margin (PSM) rate compared to RN. However, inferior cancer specific survival has not been borne out in studies with longer term follow-up. Another concern is the presence of satellite lesions adjacent to the index tumour, that may not be visible on pre-operative imaging.

Marszalek et al performed a review of the literature regarding PSM after PN.¹⁷⁷ PSMs are present in 0-7% of patients after open PN, 0.7-4% after laparoscopic PN, and in 3.9-5.7% after robot-assisted PN. Based on the available evidence, the authors concluded that thickness of normal parenchyma surrounding the tumour had no influence on outcomes, provided that complete tumour removal was achieved. The risk of local recurrence increased with the coincidence of a highly malignant tumour and PSM. Based on only intermediate follow-up data, the vast majority of patients with PSMs did not experience local or distant tumour recurrence. Furthermore, RN specimen after PNs associated with PSMs only contained tumour remnants in 6.9-15% of cases. Consequently, surveillance seems to be a viable option to salvage therapy in such patients, preventing potential overtreatment and further loss of functional renal tissue.

Another concern of PN relating to oncological control is the prevalence of malignancy in a synchronous satellite renal lesion. To address this concern, Raz et al examined the prevalence of malignancy in a synchronous ipsilateral renal lesion identified during PN and evaluated its clinical significance.¹⁷⁸ The authors performed a retrospective review of medical records of 112 patients (114 renal units) who underwent PN for a clinical localised sporadic mass between 1995 and 2005. In 37 patients (32%), an additional lesion was diagnosed and excised intraoperatively, whilst in 67% of cases these lesions were known before surgery and believed to be simple cysts. The mean size of the primary mass was 3.1cm. In 29 (78%) of cases, the primary mass was malignant, in 23 (79%) of these the second mass was benign and in the remainder RCC was diagnosed (7%). Of the 8 cases (22%) where the primary mass was benign, in 2 cases the secondary mass was malignant. Overall, 22% of all secondary masses were malignant, and of low grade and stage. The authors concluded that it is not fully clear whether microscopic satellite lesions to a major RCC mass and a secondary macroscopic mass are comparable biologically, but that it is

possible that macroscopic secondary lesions may arise from a small proportion of microscopic lesions. Given the low grade and low stage of secondary lesions, the authors did not recommend conversion to RN when these lesions were detected.

Richstone et al assessed tumour multifocality in 1071 RN specimens between 1989 and 2002 from a single institution.¹⁷⁹ The authors quoted the frequency of multifocal renal cortical tumours to be in the range of 6.5-25% in their review. 57 specimens (5.3%) had evidence of tumour multifocality. Of these, bilateral synchronous renal cortical tumours were present in 6 cases (11%; 28 patients of the entire group had bilateral synchronous tumours). Occult multifocality (cases where multifocality was not detected on imaging) was present in 3.5% of nephrectomy specimens, and 6.8% of tumours ≤ 4 cm had multifocality. Of the multifocal cases, 74% had the same histological subtype in all tumours. In multivariate analysis, predictors associated with tumour multifocality included papillary subtype, advanced tumour stage and lymph node metastasis.

Increased Risk of Complications Associated with Partial Nephrectomy

Partial nephrectomy for elective indications, especially when performed laparoscopically, is still a technically challenging and complex procedure. Potential perioperative complications following PN can also be a significant barrier to further adoption of this treatment modality. The main complications involve vascular complications, such as bleeding requiring embolization or re-exploration, or urinary leak requiring prolonged drainage and occasionally addition procedures such as ureteric stents or drains. Most studies show a slightly increased risk of complications with PN, although several other studies show comparable complication rates.

Stephenson et al compared complications of RN and PN using a large cohort of patients treated at Memorial Sloan-Kettering Cancer Centre between 1995 and 2002.¹⁸⁰ During the study period, 1049 patients were treated for a renal cortical neoplasm, including 66% who received RN and 34% who received PN. A total of 235 complications occurred in 180 patients (17%), including 3 perioperative deaths. PN was not associated with more

complications compared to RN when accounting for other variables, although PN cases had more procedure related complications compared to RN (9% vs 3%) due to complications of urinary leak. The reintervention rate was also subsequently higher (2.5% vs 0.6%), and were largely performed via endoscopy or radiology (only one patient who underwent PN required re-exploration for a complication).

In an update to this study, Lowrance et al¹⁸¹ compared complications after RN and PN as a function of age, as clinicians frequently have concerns regarding potentially higher complication rates following PN in this subgroup of patients. 1712 patients treated with RN (38%) and PN (62%) for tumours ≤ 10 cm at Memorial Sloan-Kettering Cancer Centre between 2000 and 2008 were included in the study. Overall, patients treated with PN had a higher complication rate compared to RN (20% vs 14%). In a multivariate model, age was significantly associated with a small increase in risk of complications regardless of procedure type, but when including an interaction term between age and procedure type, the interaction term was not significant. A similar pattern was seen when a subgroup of patients with tumours ≤ 7 cm were analysed. This indicated that elderly patients undergoing PN were no more likely to have complications compared to similarly aged patients undergoing RN. There was also no evidence that age was significantly associated with estimated blood loss or operative time.

In a study using the Nationwide Inpatient Sample data set, Joudi et al demonstrated low morbidity and mortality for PN and RN.¹⁸² In this study, 3,019 and 18,575 partial and total nephrectomies, respectively, were identified and performed between 2000 and 2003. Respiratory, digestive and bleeding complications were the most common, with patterns similar between PN and RN. Overall complication rates were similar for both groups (17.16% for PN and 18.20% for RN) and mortality rates were low for both groups. Predictors of complications following RN included age, male sex, comorbidity and hospital location (rural vs urban), while severe comorbidity was the only significant predictor for complications following PN. Hospital volume, bed size and teaching status were not significant factors for PN or total nephrectomy.

Lesage et al performed a review of the literature and meta-analysis and found no statistical difference concerning perioperative complications between PN and RN, although there appeared to be a trend towards a slightly higher complication rate after PN.¹⁶¹ Haemorrhage was shown to be the most common intraoperative complication (1.2-4.5%), and other common complications included urinary fistula formation (1.4-17%), acute renal failure (0.7-26%) and postoperative bleeding (0-4.5%). No statistical difference was noted amongst the included studies regarding hospital costs and length of stay.

Potential Risk of Developing Renal Cell Carcinoma in the Remaining Kidney

Proponents of RN argue that the risk of developing RCC in the remaining contralateral kidney following RN is exceptionally low, and therefore the vast majority of patients undergoing RN for elective indications are unlikely to experience disease in their remaining kidney. This is in contradistinction to patients with certain conditions such as inheritable RCC syndromes, which predispose patients to early development of RCCs, that are frequently bilateral. These patients have an absolute indication to undergo PN, due to the very high risk of development of RCC in the remaining kidney. For the vast majority of patients with sporadic RCC, although the risk of developing RCC in the contralateral kidney is low, a risk is still present. This risk must be considered, especially in younger patients with long life expectancy.

Rabbani et al evaluated the risk of developing a metachronous contralateral tumour after an initial diagnosis of RCC using SEER data from 1973 to 1997.¹⁸³ Of a total of 40 049 patients with available follow-up, 155 (0.4%) developed contralateral RCC (with no evidence of synchronous tumours at diagnosis). In the entire cohort, 357 patients were identified with synchronous bilateral tumours, the incidence of which was significantly higher in black men than white men. The authors found that the incidence of metachronous contralateral RCC to be stable on long-term follow-up, suggesting that surveillance of the contralateral kidney should remain rigorous on extended follow-up, even after 10 years of follow-up. Tumour stage was not found to have significant influence on the risk of developing a new contralateral tumour, which had been previously shown in other studies.

Patel et al evaluated survival of patients with bilateral non-familial sporadic renal tumours compared to patients with unilateral tumours using a database of 1082 patients with non-metastatic renal tumours.¹⁸⁴ From this database, 46 cases of bilateral tumours were identified (4.25%), including 33 and 13 with synchronous and asynchronous tumours, respectively. This rate is much higher than that observed in the aforementioned study by Rabbini et al. Of the 92 tumours in these 46 patients, 42% were managed with RN and 58% with PN; 7 underwent bilateral PN. Conventional clear cell RCC was the predominant histological subtype in 66%, and a 76.2% concordance was noted between the histologic subtypes of the two renal tumours in each patient. Following a median follow-up of 74 months, disease-free survival at 3- and 5-years post-surgery was similar patients with bilateral tumours compared to those with unilateral disease, and for those with synchronous and asynchronous tumours. Although the risk of developing a subsequent contralateral tumour was low (1.20%), this is likely to increase with further long-term follow-up.

7. First and Principal Authored Publications Arising Directly from this Thesis

a. Contemporary Management of Renal Cell Carcinoma in Victoria

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Summary

Objective

- To describe the contemporary patterns of care of renal cell carcinoma (RCC) using a whole of population series from Victoria

Patients and Methods

- Retrospective review of medical records of all cases diagnosed and treated for RCC in Victoria in 2009
- Cases were identified via the state-wide Victorian Cancer Registry
- Case demographic characteristics, symptoms, stage, and first-line treatment were assessed
- Associations between case residential location (metropolitan or rural) and treatment were examined using multivariate logistic regression after adjusting for age, sex, socioeconomic status, treatment in private or public hospital and comorbidity.

Results

- Data were obtained for 499 of 577 eligible cases
- Altogether, 413 cases (83%) underwent surgery
- Laparoscopic radical nephrectomy (RN) was the most common procedure for Stage I pT1a/pT1b tumours (51.2%); partial nephrectomy (PN) was performed for 27% of Stage I RCC
- In multivariate analysis, regional cases were less likely to receive PN (OR=0.39, 95% CI 0.18-0.85) for Stage I RCC, and less likely to receive systemic therapy for Stage IV RCC (OR=0.06, 95% CI 0.01-0.41)
- Multidisciplinary team meetings were recorded for only 25% of cases and 3% of cases were enrolled in a clinical trial

Conclusion

- Most contemporary patients diagnosed with RCC are still treated with RN, including those with smaller tumours amenable to PN

- This may impact future outcomes, including increased risk of chronic kidney disease and its potential financial healthcare burden
- Patterns of treatment also appear to differ between metropolitan and regional populations

Word Count: 250

Key Words

Renal cell carcinoma

Nephrectomy

Cancer registry

Victoria

Chronic kidney disease

Introduction

Renal cell carcinoma (RCC) represents the most common malignancy affecting the kidney, and accounts for approximately 2-3% of all cancers (1). Widespread use of abdominal imaging has in large part contributed to a steady increase in incidence of RCC over the last two decades, with the most rapid increase seen for the smallest tumours (2). Consequently, the majority of contemporary patients present with an asymptomatic renal mass (3).

Surgical management of localised RCC has traditionally been radical nephrectomy (RN) for patients with a normal contralateral kidney. However, over the last decade an increasing body of evidence has promoted the management of T1a RCC, and even T1b RCC where possible, with partial nephrectomy (PN) due to equivalent safety and oncological control, but superior preservation of renal function and reduced risk of longer-term chronic kidney disease (CKD) (4-8). The clinical sequelae and public health costs associated with CKD may be significant (9-10). Concurrently the development of laparoscopic techniques for renal surgery has seen a shift away from open surgery to less invasive approaches, with laparoscopic RN having equivalent oncological control to open RN, coupled with reduced blood loss, analgesic requirement and length of hospital stay (11-12). Minimally invasive focal ablative techniques, such as radiofrequency ablation and cryoablation, have also recently emerged as alternative treatment options for small renal masses and may be suitable for patients with tumours amenable to PN who are otherwise considered poor surgical candidates, either due to age or to pre-existing comorbidities (13-14).

Advances in molecular biology over the last decade have also led to the development of several novel targeted molecular therapies designed to inhibit tumour angiogenesis for patients with metastatic RCC. Commonly used agents include sunitinib and temsirolimus. Traditional immunotherapy agents, such as interferon-alpha and interleukin-2, are now only recommended in guidelines for select patient subgroups (1,15).

Currently there is a paucity of data regarding patterns of RCC management in Australia at a population level. Furthermore, regional differences in management, including the uptake of

newer medical and surgical treatments, are yet to be assessed. To address these concerns, we examined the contemporary clinical management of RCC in Victoria using a whole of population registry of patients diagnosed with RCC.

Subject/Patients and Methods

All cases of RCC (ICD-O-3 code C649) diagnosed in Victoria between 1 January 2009 and 31 December 2009 and registered with the Victorian Cancer Registry (VCR) were identified. Victorian residents treated in Victoria were eligible for inclusion. For each case the notifying hospital and/or clinician was identified from the VCR records. Public hospitals and private specialist clinics were approached regarding medical record review of the identified cases. Trained data managers extracted relevant data by retrospective review of medical records and pathology reports.

Data extracted included: mode of presentation, diagnostic and staging investigations, clinical and pathological disease stage, first line treatment, enrolment in clinical trials, and provision of multidisciplinary care. Comorbidity was assessed using the ACE-27, a validated comorbidity risk assessment tool developed for cancer cases. Patients were assigned a comorbidity score of 0 to 3 (0 = none, 1 = mild, 2 = moderate and 3 = severe). The area-based Index of Relative Socio-Economic Disadvantage (IRSD) was used as an indicator of socioeconomic status (SES). This measure was developed by the Australian Bureau of Statistics from 20 direct or indirect indicators of disadvantage obtained from census data. Examples of indicators used for this measure include education and income levels within a postcode, proportion of single parent families, proportion of males and females unemployed and proportion of rental properties within a postcode. The IRSD ranks postcodes from most disadvantaged to least disadvantaged. This ranking was collapsed into three levels to reflect the top 20%, middle 60% and bottom 20%.

Overall tumour stage was determined from pathological T stage, nodal and metastatic disease status. Pathological T stage (pT) was categorised according to the seventh edition (2009) of the American Joint Committee on Cancer (AJCC) staging system where

nephrectomy specimens were available for pathological review. Pathological data was not available for 100 cases, including 85 cases where surgery was not performed. For these cases, pT stage was supplemented by AJCC clinical stage group from imaging reports. Case residency was categorised as metropolitan or regional/rural based on the Department of Human Services Integrated Cancer Services regions.

The study gained ethical approval from the Cancer Council Victoria human research ethics committee and other ethics committees as required.

Data analysis

The χ^2 test was performed to examine differences in proportions; analysis of variance techniques were employed to examine differences in means and other linear variables. Bivariate analyses examined associations between patient residential location and disease characteristics at diagnosis as well as patient characteristics (such as age, treatment location, comorbidity levels). Bivariate and multivariate logistic regression models were employed to detect associations between patient residence and use of differing types of surgery. Metropolitan residence was the reference category in these models. For multivariate analyses, odds ratios (OR) were adjusted for age (≤ 54 , 55-64, 65-74, 75+), sex, ACE-27 comorbidity index (none, mild, moderate, severe), SES and treatment in private or public hospital (for analyses of surgical cases). When pT1a and pT1b tumours were combined for analyses, pT stage was included as a covariate in multivariate analyses. A two-sided statistical level of $p < 0.05$ was considered significant.

Statistical analyses were undertaken using Stata/SE 11.2 (Stata Corporation, College Station, Texas, US).

Results

A total of 577 cases were eligible for inclusion. Doctors declined consent for review of medical records for 49 (8.5%) cases. For another 29 (5.0%) cases no medical record could be located, including 14 cases where diagnosis of RCC was identified only by death certificate (2.4%). Data for 499 cases (86.5% of eligible cases) were analysed. Cases not included in record review were similar to those reviewed in terms of age, gender and residential location. However, cases not included were less commonly treated in the public setting.

Baseline Characteristics and Presentation

Baseline case characteristics and comparisons between metropolitan and regional/rural residency are shown in Table 1. The median age of cases at diagnosis was 63 years (range 14-97). Most cases were male and the most common residential location was metropolitan. The majority of cases managed with surgery (approximately two-thirds) were performed in a public hospital setting. A higher proportion of patients from metropolitan regions had no comorbidities at diagnosis (24.7% vs 14.8%) (Table 1).

Symptoms at presentation are also shown in Table 1. 302 (60.5%) cases presented with an asymptomatic renal mass diagnosed incidentally during investigation of other disease or non-specific symptoms. Residential location was not associated with incidental diagnosis. One or more of the 'classic' symptoms of RCC were present at diagnosis in 159 (31.9%) cases, but only three cases displayed the complete triad of flank pain, haematuria and a palpable abdominal mass. Symptoms suggestive of metastatic disease were present in 28 (5.6%) of cases at time of diagnosis.

Diagnostic and Staging Investigations

Computed tomography (CT) scan of abdomen (91.4%) was the most common imaging procedure followed by abdominal ultrasound (47.3%) and CT chest (37.3%). Full blood examination was performed for nearly all cases (96.4%). Corrected serum calcium (CSC) was

obtained for 40.5% of cases; a record of serum lactate dehydrogenase levels (LDH) was only found for 6.4% of cases.

Tumour Characteristics

The predominant histological subtype was clear cell RCC (59.1%), followed by papillary (10.8%) and chromophobe (6.4%) RCC. Sarcomatoid RCC (1.2%) was uncommon. Histological subtyping was not available for 61 (12.2%) cases and 33 (6.6%) cases had no histological confirmation of the tumour. Absence of histological confirmation was associated with older age ($p<0.001$) and higher comorbidity scores ($p=0.05$), suggesting increased usage of surveillance or watchful waiting amongst this patient subgroup.

The distribution of RCC stage groups is shown in Table 1. Pathological T stage was not available for 100 cases, including 85 who did not have surgery. The majority of tumours were Stage I pT1a/pT1b (57.1%). At diagnosis, 16.8% of cases had evidence of Stage IV disease.

Treatment of Renal Cell Carcinoma

82.9% of cases underwent surgical treatment. While treatment with surgery was not related to residential location, it was inversely associated with age ($p<0.001$) and comorbidities ($p<0.001$). Of the 413 cases where surgery was performed, RN was performed in 336 cases (81.2%), and the preferred operative approach for RN was laparoscopic, representing 61.3% of all cases of surgery. For pT1 and pT2 tumours, laparoscopic surgery was more common for smaller tumours, with 70.2% of pT1a tumours having laparoscopic surgery compared with 44.0% of pT2a and 28.6% of pT2b tumours. Overall, nine cases were converted from laparoscopic to open, and were classified as open. Only four cases of focal ablation were performed.

The surgical management of Stage I pT1a tumours is shown in Table 2. PN for stage I RCC (regardless of operative approach) was less common for cases from regional/rural areas (16.2%) than those from metropolitan regions (31.3%), and this difference was statistically significant in multivariate analyses (OR=0.39, 95% CI 0.18-0.85). Cases from regional/rural

areas were more likely to receive open RN for stage I RCC (OR=2.31, 95% CI 1.06-5.02). For the subgroup of Stage I pT1a tumours, the odds of cases residing in regional/rural areas receiving PN were about 50% less than the corresponding odds for metropolitan cases (OR=0.43, 95% CI 0.18-1.02), while a trend towards increasing likelihood of open RN was noted (OR=2.56 95%CI 0.84-7.80). However, residential location was not associated with treatment for Stage I pT1b tumours (data not shown).

The surgical treatment of Stage II and III tumours (excluding pT3b/T3c tumours) is shown in Table 3, comparing usage of laparoscopic to open surgery. No cases of PN were performed for these tumours. Although cases residing in regional/rural areas were more likely to be treated by open RN than those from metropolitan areas on unadjusted analysis, this difference did not remain statistically significant on multivariate analysis.

The treatment of Stage IV cases is shown in Table 4. Cases from regional/rural areas were less likely to receive systemic therapy (OR=0.06, 95% CI 0.01-0.41) compared to metropolitan cases. 32 cases with Stage IV disease received Sunitinib, representing 74.4% of all cases receiving systemic therapy. Radiotherapy was used for 26 cases (31.0%) with Stage IV disease, and this was not associated with case residential location.

Documented multidisciplinary team meeting review was noted in 124 (24.8%) of cases and was not associated with residential location or tumour stage. During the study period, 14 (2.8%) cases were enrolled in a clinical trial.

Discussion

This population-based study of the treatment patterns for RCC found that most cases diagnosed with RCC are asymptomatic at presentation and present with early-stage, localised disease. Although most RCC tumours were small at diagnosis, RN was the most common treatment with 60% of Stage I pT1a tumours managed with RN. Residential location was a significant predictor of treatment. We found that cases residing in regional/rural areas were less likely to be treated by PN, while those with Stage IV disease were less likely to receive systemic therapy.

Only 3 cases (0.6%) presented with the 'classic triad' of haematuria, flank pain and a palpable abdominal mass, which appears lower than an expected rate of approximately 6-10% as reported in the literature. While the reasons for this difference are not clear, it might reflect the increasing incidental diagnosis of RCC through the investigation of other medical conditions. Abdominal imaging and staging investigations were commonly performed and recorded. Conversely, CSC and LDH levels were not regularly undertaken, despite elevated CSC and LDH levels being independent predictors of poor prognosis from RCC (16,17).

Historically RN has been considered the standard treatment for localised RCC. More recent studies instead have offered support to nephron-preserving surgery through PN, and the demonstrated equivalence of oncological control (4,6) and superior preservation of renal function (5,7,8), has led to recommendations by various international guidelines for PN to be standard of care for T1a RCC, and for some T1b RCC where technically feasible. A notable finding in the current study was limited use of PN in the surgical management of pT1a RCC, where it represented approximately 40% of cases of pT1a RCC managed operatively. Furthermore, there was a significant trend towards regional/rural patients with pT1a tumours being less likely to receive PN (Table 2). Case suitability for PN could not be analysed in this study, but this trend remains clear despite controlling for important variables that may influence treatment choice, such as patient age, comorbid status, SES, and private or public hospital treatment. However, surgeons may prefer to avoid complex

renal surgery in regional centres where there may be a lack of ancillary services, such as intensive care or interventional radiography.

An ideal rate of PN for pT1a tumours remains unclear. Comparisons between population-based data and high-volume institutional series, where rates of PN for pT1a tumours approaches 90%, is inappropriate (15). However, patterns of utilisation of PN for pT1a tumours similar to those reported here have been observed in US population-based data, although some of these studies have used less contemporary population samples. Whilst more recent US data from the Surveillance Epidemiology and End Results Program (SEER) and the National Cancer Database have shown increasing utilisation of nephron-sparing surgery with PN and ablative techniques, significant underutilisation still exists according to the investigators (18,19). Interestingly, SEER data from 2006 demonstrated PN to represent 45% of kidney surgery for renal tumours ≤ 4 cm, a figure slightly higher than observed in our population. Whether or not true underutilisation of PN for pT1a RCC has taken place in this study remains unclear, as population-based data does not allow for control of important parameters that influence suitability for PN, such as tumour location within the kidney, patient preference, pre-existing renal function and surgeon experience.

The widespread adoption of PN as definitive surgical management of small renal masses has arguably been impeded by the incorporation of laparoscopic RN into the technical skill-set of urologists. This approach offers reduced blood loss and analgesic requirement, rapid convalescence, improved cosmesis and, importantly, equivalent cancer control to open RN (11,12). Furthermore, there is a lack of randomised prospective data comparing long-term outcomes of RN and PN. To date, only one such trial has been performed, and reported outcomes with median 9-year follow-up demonstrating no advantage of PN over RN in improving overall mortality. This may provide some explanation for the common usage of laparoscopic RN in this study, which represented half (49.7%) of all surgeries performed for pT1a tumours. Whilst this may arguably be regarded as potential over-treatment for these smaller tumours, longer-term follow-up of patients in this study is required to evaluate any associations between surgical treatment and mortality.

Although prospective data addressing mortality (both overall and cancer-specific) is limited, there is increasing evidence that the use of RN where PN may be appropriate increases the risk of long-term patient morbidity resulting from CKD (5,7,8). This risk is potentially increased in patients with diabetes and hypertension, who have been shown to receive similar rates of PN to patients without these comorbidities (20). CKD is associated with increased risk of cardiovascular morbidity, progression requiring dialysis, further hospitalisation and all-cause mortality (7,8,10). Furthermore, CKD is a significant contributor to healthcare related costs. Recent data from the US Renal Data System demonstrated that overall Medicare expenditure for CKD (excluding end-stage kidney disease) reached \$33.8 billion in 2009. The costs associated with CKD are also likely to continue to increase, as evidenced by the proportion of Medicare expenditure towards CKD increasing from 5.8% in 2000 to 15.9% in 2009.

Our use of pathological T stage may have over-estimated the number of small malignant tumours due to post-surgery tumour size reduction. However, as a similar proportion of cases were found to have RN when clinical T stage (based on imaging alone) was analysed, the use of pathological T stage does not appear to have overestimated usage of RN for small renal tumours (analyses not shown). Furthermore, the VCR does not contain information on benign tumours, which can represent up to 25% of small kidney tumours presumed to be RCC on imaging prior to surgery.

Whilst laparoscopic surgery was commonly employed in the treatment of Stage I RCC, we found that the uptake of this minimally invasive approach was not even across Victoria. For such tumours, cases from regional areas were twice as likely to receive open RN compared to metropolitan cases. This disparity might be partly explained by selective referral to metropolitan hospitals for laparoscopic surgery, individual surgeon experience or preference, or accessibility to the disposable equipment required for laparoscopic surgery in more regional hospitals. Unfortunately these variables were not captured in this study. US population-based data has similarly shown that PN or laparoscopic procedures are more likely to be performed in teaching, high-nephrectomy volume hospitals in an urban setting (21,22). Whilst laparoscopic PN has similar efficacy to open PN, it is a technically challenging

procedure most often performed in tertiary hospitals by experienced high-volume laparoscopic surgeons (23,24). In this study, we observed that all laparoscopic PNs for pT1a tumours were performed in metropolitan hospitals (data not shown). This disparity may become less significant with time with increased training and provision of resources to allow more complex surgery to be performed in more regional settings.

Half of the cases diagnosed with metastatic disease in this present study received systemic therapy with regional cases less likely to receive this therapy than those from metropolitan areas. Whilst these findings may raise some concern and potentially reflect a degree of inequality of access to newer and recommended therapies, the use of systemic therapies for RCC is complex and we cannot comment on individual clinician treatment decisions and case suitability for these systemic treatments. Furthermore, while Sunitinib was the most commonly used agent in this study, it was only listed for subsidy on the Australian Pharmaceutical Benefits Scheme in May 2009, thus potentially limiting its utilisation for cases diagnosed prior to this date (25).

We found less than 3% of subjects with RCC diagnosed in 2009 were involved in a clinical study of any type, including sponsored trials. A similarly low rate of 2% was also observed by Yabroff et al from SEER data (22). Several barriers to referral to clinical trials may have been present, such as accessibility for regional cases and likely pharmaceutical industry-driven promotional activity in larger metropolitan centres during the study period. Whilst efforts should be made wherever possible to promote participation in clinical trials, the significance of this finding is limited as we cannot comment on individual case eligibility.

This study has several strengths. Our observations from this state-wide whole of population dataset reflect contemporary patterns of care across Victoria, accounting for differing practice patterns by clinicians and treatment centres, limiting potential biases seen in institutional or sampled population studies locally or internationally. Whilst the dataset does not represent the entire Australian population, it reflects contemporary treatment patterns in a significant proportion of the Australian population. This study has significant importance as few previous studies have addressed patterns of modern RCC management in

Australia. However, the study was potentially underpowered to detect anything but large differences due to case residential location. Furthermore, we did not have information on surgeon or patient preferences for care, or surgeon experience, which may have significantly influenced treatment decision-making. Further work is required to examine the role of patients and clinicians in selecting surgical and medical therapies for the management of RCC.

In conclusion, contemporary population-based data shows that the most common treatment for localised renal cell carcinoma is RN, including for small tumours that may have been amenable to nephron-preserving surgery. This may have consequences in terms of the potential morbidity and treatment costs associated with CKD, but the role of PN in reducing overall mortality still remains controversial. Patterns of treatment appear to differ between metropolitan and regional populations following diagnosis, with a suggestion that patients from regional and rural locations in Victoria may be less likely to receive recognised contemporary best evidence-based management. Further work is needed to better understand the reasons for these differences, which are likely to be multifactorial and influenced by patient preferences for care. These findings should help develop and implement strategies for the diffusion and dissemination of newer surgical and medical treatment options throughout Victoria.

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Abbreviations

RCC = Renal cell carcinoma

RN = Radical nephrectomy

PN = Partial nephrectomy

CKD = Chronic kidney disease

VCR = Victorian Cancer Registry

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Disclosure of Interests

No conflict of interests requiring disclosure

Table 1 Demographic, tumour diagnostic and treatment characteristics of patients diagnosed and treated in Victoria for renal cell carcinoma In 2009.

		Total	Patients' Residential Location		How diagnosed	
		(n=499)	Metro (n=364)	Non-Metro (n=135)	Symptoms (n=197)	Incidental (n=302)
Patient Demographics						
Age	Mean (Years)	63 yr	62 yr	65 yr	63 yrs	63 yrs
Gender	% Male	65%	64%	70%	66%	65%
Co-morbidities (score)	None	22%	25%	15%	27%	19%
	Mild	44%	42%	50%	44%	44%
	Moderate	20%	21%	19%	17%	23%
	Severe	14%	13%	16%	12%	15%
Incidental finding	Yes	61	62%	56%		
Clinical T stage	1a	40%	40%	39%	30%	46%
	1B	29%	31%	24%	24%	33%
	2A	12%	11%	17%	16%	10%
	2B	5%	6%	4%	6%	4%
	3A	7%	6%	7%	11%	4%
	3B	1%	1%	2%	3%	0%
	3c	0%	0%	1	0%	0%
	4	2%	2%	4%	5%	1%
	X	3%	3%	4%	5%	2%
Pathological T stage	1a	34%	35%	32%	23%	41%
	1B	18%	17%	19%	14%	20%
	2A	5%	4%	10%	6%	5%
	2B	2%	2%	3%	3%	2%
	3A	18%	21%	12%	22%	16%
	3B	1%	1%	2%	2%	0%
	3c	0%	0	0	1%	0%
	4	1%	1%	2%	2%	1%
	X	20%	19%	22%	28%	15%
Investigations						
	Abdominal CT	91%	91%	93%		
	Abdominal Ultrasound	47%	50%	41%		
	Chest CT	37%	38%	36%		
	Full blood exam	96%	97%	95%		
	Corrected Serum Calcium	40%	41%	40%		
	LDH	6%	7%	4%		
Treatment						
Surgery	Yes	83%	84%	79%		
Type of surgery	Laposcopic^	59%	62%	51%*		
Procedure Type	Radical Nephrectomy	81%	79%	89%		
Systemic therapy	Yes	11%	12%	8%		
Radiotherapy	Yes	5%	5%	5%		

[‡]Staging of RCC follows the 2002 American Joint Committee on Cancer TMN staging system (presence of nodal and metastatic disease not presented)

*As confirmed from radiological examination (CT or ultrasound) prior to treatment

#As confirmed from histological examination

^ 9 cases where surgery was converted from laproscopic to open are classified as having open surgery.

3 cases defined as having treatment in both regional and metro hospitals have been excluded.

*Significantly different at $p < .05$

*Significantly different at $p < .01$

Table 2 Bivariate and multivariate associations between patient factors and tumour factors and having partial nephrectomy (PN) among cT1a and cT1b cases having surgery.

Predictor	Partial Nephrectomy (PN) among cT1a and cT1b tumours					
	N	Bivariate		Multivariate		
			p-value^	OR	95%	CI
Age (mean)						
Partial Nephrectomy	76	57.6	<.01	0.97	0.94	0.99
Radical nephrectomy	221	61.3				
		Yes PN %				
Sex						
Males	178	23.6				
Females	119	28.9	0.336			
Comorbidity score						
none	71	22.5				
mild	138	29.0				
Moderate &severe	88	22.7	0.458			
Where live						
Urban	227	28.6		1		
regional/ Rural	78	15.7	0.03	0.26	0.11	0.59
cT						
cT1a	173	38.2		1		
cT1b	124	8.1	<0.001	0.11	0.05	0.23
Surgery technique						
Open	92	41.3		1		
Lap	205	18.5	<0.001	0.23	0.19	0.43

Table 3: Surgical treatment of Stage II & III RCC (pT2 and pT3a)

	Metropolitan	Regional/Rural	Total	Unadjusted	Adjusted#
	(N=88)	(N=31)	(N=119)	OR (95% CI)	OR (95% CI)
Lap. radical nephrectomy	47.7	32.3	43.7	0.52 (0.22-1.23)	0.43 (0.15-1.19)
Open radical nephrectomy	46.6	67.7	52.1	2.41 (1.02-5.70)	2.25 (0.83-6.11)
Of those who have had surgery	(N=87)	(N=31)	(N=98)		
Laparoscopic surgery	50.6	32.3	45.8	0.47 (0.20-1.10)	0.43 (0.16-1.16)
Radical nephrectomy	95.4	100	96.6	0.52 (0.20-1.32)	

ORs are adjusted for age, sex, ACE-27 comorbidity index, SES level and hospital setting

Table 4: Treatment of Stage IV RCC

	Metropolitan	Regional/Rural	Total	Unadjusted	Adjusted#
	(N=59)	(N=24)	(N=83)	OR (95% CI)	OR (95% CI)
No surgery	66.0	79.2	69.9	1.95 (0.63-5.99)	1.62 (0.37-6.98)
Radical nephrectomy (laparoscopic)	11.9	0	8.4	0.24 (0-1.68)	0.25 (0-2.29)
Radical nephrectomy (open)	22.0	20.8	21.7	0.95 (0.30-3.04)	1.56 (0.34-7.20)
Any Systemic therapy	56.7	37.5	51.2	0.45 (0.17-1.21)	0.06 (0.01-0.41)

ORs are adjusted for age, sex, ACE-27 comorbidity index, SES level and hospital setting

**b. Interval to Biochemical Recurrence Following Radical Prostatectomy
Does Not Affect Survival in Men with Low-risk Prostate Cancer**

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Abstract

Objectives

- To evaluate the temporal relationship between interval to biochemical recurrence (BCR) following radical prostatectomy (RP) and prostate cancer-specific mortality (PCSM)

Patients and Methods

- The study comprised of 2116 men from the Victorian Radical Prostatectomy Register, a whole-of-population database all RPs performed between 1995-2000 in Victoria, Australia.
- Follow-up PSA and death data were obtained via record-linkage to pathology laboratories and the Victorian Registry of Births, Deaths and Marriages.
- Poisson regression models with PCSM as the outcome were fit to the data.
- Models included age at surgery, Gleason score, and tumour stage as covariates.

Results

- Median post-surgery and post-BCR follow-up was 10.3 and 7.5 years, respectively.
- 695 men (33%) experienced BCR during follow-up, of which 82% occurred within 5 years of RP; 66 men died from prostate cancer.
- Men with combined high Gleason sum ($\geq 4+3$) and extra-prostatic ($\geq pT3a$) disease had substantially increased mortality rate with early BCR, while those experiencing BCR after a longer interval had significantly lower mortality.
- Men with combined low Gleason sum ($\leq 3+4$) and organ-confined disease ($\leq pT2c$) risk disease were not at any substantial risk of death in this time frame regardless of timing of BCR following RP.

Conclusions

- This is the first study to evaluate the temporal relationship between BCR and PCSM using a whole-of-population cohort of men treated with RP.
- Men with low-risk features of prostate cancer at time of RP have low mortality even if they experience early BCR.
- This sub-group may be counselled regarding their favourable long-term prognosis.

Introduction

Prostate specific antigen (PSA) surveillance following radical prostatectomy (RP) provides an effective means of monitoring for disease recurrence (1). Approximately 17-31% of men may be expected to experience biochemical recurrence (BCR) during follow-up (2-4) and the risk of developing disease recurrence increases with adverse pathological findings, such as extra-prostatic extension, higher grade Gleason score and positive surgical margins (2, 4-6). However, the natural history of disease recurrence following RP can have a long and protracted course. Pound et al (7) demonstrated a median time of eight years to development of metastases following BCR, and a further median of five years until death from prostate cancer.¹⁰⁸ Compared to men with slow increases in PSA levels following BCR, men with rapid PSA doubling times (PSA DT) following BCR have increased risk of progression to metastatic disease and prostate cancer-specific mortality (PCSM) (7-8). PCSM following RP has been reported to be approximately between 2-7% in mainly large, high-volume institutional series (3,4,9-10).

The prognostic significance of interval from surgery to BCR on mortality from prostate cancer is unclear (7,8,11-16). Most studies evaluating this temporal relationship have defined early or late BCR as a categorical variable, which may have practical limitations when counselling men as the timing of BCR can be variable, and not all men who experience BCR before or after a certain point in time have similar outcomes. Furthermore, the majority of studies assessing this temporal relationship are based on data from high-volume institutional series, which may not reflect patient characteristics or outcomes seen on a community or population level. The majority of BCR occurs within two or three years, although a significant proportion of men, approximately 6-27%, will have BCR more than five years following surgery. Recurrence more than 10 years post-surgery has also been shown to occur in nearly 5% of men. Early BCR following RP is associated with earlier progression to metastatic disease and death (7,12,13). Conversely, men with delayed BCR have a more favourable long-term prognosis, and are more likely to have lower risk prostate cancer at the time of their surgery (14,16). Several large studies with long-term follow-up have demonstrated that mortality in men with low-risk disease is very low (10,17,18)

Whilst delayed BCR may be associated with a more favourable prognosis, it is unclear if all men in this subgroup have a similar prognosis. Additionally, whilst men with low-risk prostate cancer have low mortality overall, there is uncertainty whether early BCR in these men confers an increased risk of mortality. Using a prospective whole-of-population based series of men who underwent RP for localised prostate cancer during the PSA-era, we assessed the effect of timing of BCR on PCSM in men with post-RP follow-up of more than 10 years.

Patients and Methods

Patients

The Victorian Radical Prostatectomy Register (VRPR) is a whole of population series of men who underwent RP for the treatment of prostate cancer between 1995 and 2000 in Victoria, Australia. Eligible cases were men notified to the Victorian Cancer Registry (VCR) with a diagnosis of adenocarcinoma of the prostate (there is a statutory requirement that all diagnoses of invasive cancer, excluding non-melanoma skin cancer, be reported to the VCR). The VRPR was established within the VCR to record additional information on men who underwent radical prostatectomy. Details of VRPR registration and data collection have been reported previously (19). The VRPR was approved by the Human Research Ethics Committee of Cancer Council Victoria.

All men underwent prostate-specific antigen (PSA) testing prior to RP. Tumor details coded to ICDO-2 topography and morphology rubrics were abstracted from pathology reports submitted to the VCR, and record-linkage to the VRPR for both biopsies and radical prostatectomy specimens was subsequently performed. Total prostatectomies performed at cystoprostatectomy for bladder cancer were excluded.

Full follow-up PSA testing histories were obtained via record-linkage to pathology laboratories. BCR was defined as two consecutive PSA values $\geq 0.2\mu\text{g/L}$, with the date of BCR set to the latter of the two test dates. Deaths were coded by the VCR as either due to

prostate cancer or other causes, based on death records obtained from the Victorian Register of Births, Deaths and Marriages. Follow-up began at the date of BCR, and ended at the date of death, date of the last ascertained PSA test, or 1 January 2010, whichever occurred first.

Statistical Analysis

Poisson regression models, with prostate cancer cause-specific death as the outcome, were fit to the data. In order to obtain mortality rates per 10 person-years we included $\log(\text{follow-up time}/10)$ as an offset with its coefficient constrained to equal 1. All models included age at surgery (<55 , $55-65$, ≥ 65), Gleason score, and tumor stage as covariates.

We modeled time to BCR as continuous covariate, using restricted cubic splines with knots at the 25th, 50th, and 75th percentiles of time to BCR to allow for a non-linear relationship with the $\log(\text{mortality rate})$. Predicted marginal mortality rates were calculated from the fitted models for given values of time to BCR. Confidence intervals (CI) for the predicted log mortality rates were calculated and back transformed to the natural metric. In order to examine whether the predicted mortality rates depended on patient characteristics, we also fit models for low versus high Gleason score, low ($\leq \text{pT2c}$) versus high (pT3a , pT3b , pT4) tumor stage, and positive versus negative surgical margins. Low Gleason score was defined as less than or equal to Gleason 7 but with a predominance of Gleason 3 pattern (total $\leq 3+4$), and high Gleason score as greater than or equal to 7 but with a predominance of Gleason 4 pattern (total $\geq 4+3$). These models included the additional covariate of interest fully interacted with the restricted cubic spline basis functions of time to BCR.

Statistical analyses were performed using Stata 12.0 for Linux 64-bit (Stata corporation, College Station, TX, USA).

Results

During the accrual period, 2154 men underwent RP (baseline characteristics shown in **Table 1**). Median post-surgery follow-up was 10.3 years. Post-surgery PSA follow-up data was available for 2116 men, 695 of whom experienced BCR during their follow-up. 10 cases were performed via a perineal approach; the remainder were performed via a retropubic approach. The distribution of time between surgery and BCR is shown in **Figure 1**. 82% of men who experienced BCR did so within five years of surgery, 16% had BCR between five and 10 years post-surgery, and 2% had BCR more than 10 years after surgery. During a median post-BCR follow-up 7.5 years (4880 total person-years observed), 66 men (10%) who experienced BCR eventually died from prostate cancer. Of these deaths, 13 (20%) and six (9%) occurred following a PSA progression-free period of five and six years, respectively.

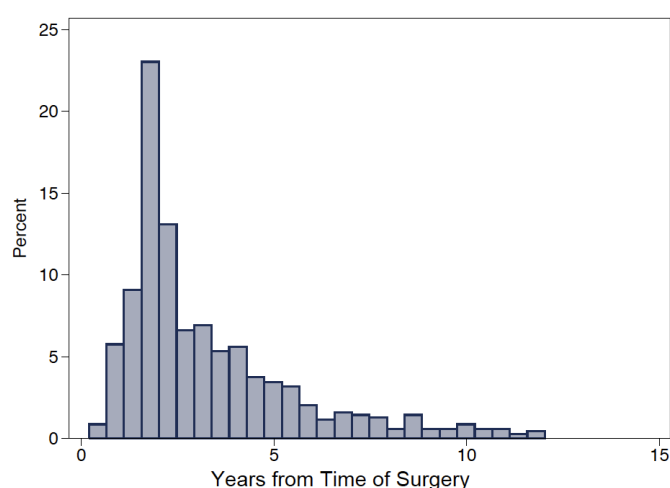


Figure 1. Distribution of time between surgery and BCR

Table 2 shows the characteristics of men who experienced BCR, comparing men who are surviving following disease recurrence to men who died of prostate cancer. There was no substantial difference between the age distribution of the two groups, nor was there any difference in the proportion of patients who underwent surgery in a private hospital, although a higher proportion of men who experienced PCSM were from a rural area compared to metropolitan areas (35% versus 17%). Men who experienced PCSM were also more likely to have a higher tumor stage and Gleason score at surgery, but not positive surgical margins.

Mortality Following Biochemical Recurrence

Figure 2a presents the predicted overall PCSM rate per 10 person-years for given values of the time between surgery and BCR. The mortality rate decreases with increasing time between surgery and BCR. For BCR at two years post-surgery the mortality rate is 0.14 (95% CI 0.11-0.19), compared to 0.06 at five years (95% CI 0.02-0.14).

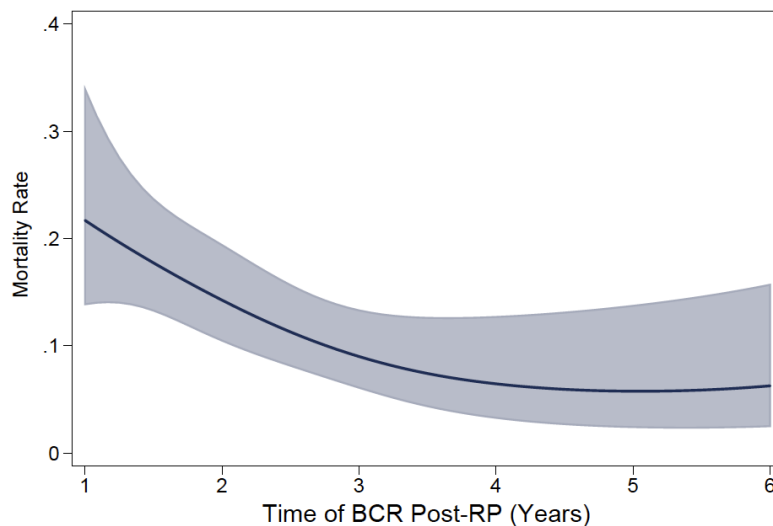


Figure 2a. Mortality rates for all men who experienced BCR

Predicted PCSM rates per 10 person-years are plotted by Gleason score group in **Figure 2b**. The predicted mortality rate for men with low Gleason sum ($\leq 3+4$) is low regardless of the time between surgery and BCR. With BCR at two and five years post-surgery, the predicted mortality rate is 0.07 (95% CI 0.04-0.11) and 0.05 (95% CI 0.02-0.13), respectively. Conversely, earlier BCR is associated with high predicted mortality rate for men with high Gleason sum ($\geq 4+3$), as evidenced by a predicted mortality rate of 0.42 (95% CI 0.28-0.63) with BCR at two years post-RP. However, the mortality rate reduces substantially with increasing interval to BCR, where a mortality rate of 0.08 (95% CI 0.02-0.27) with BCR at five years post-RP is comparable to men with low Gleason sum.

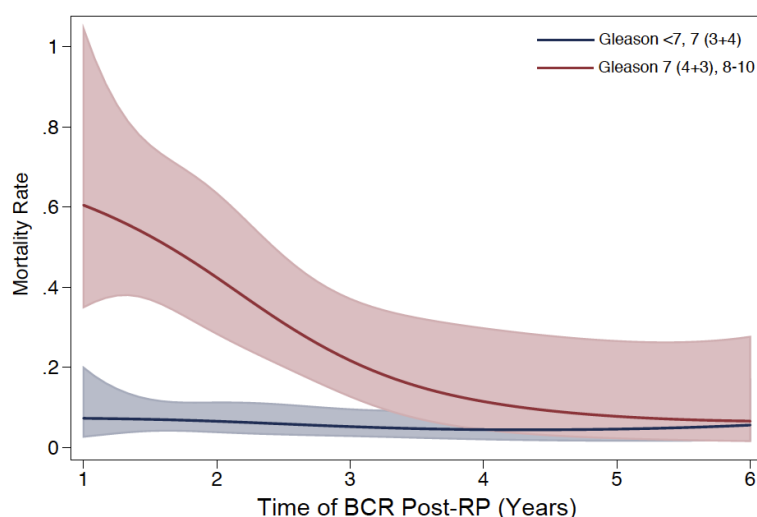


Figure 2b. Mortality rates stratified by Gleason sum

Analysis by tumor stage yielded similar results (**Figure 2c**). The mortality rate for BCR at two years post-surgery was substantially higher for men with extra-prostatic disease (0.33, 95% CI 0.23-0.49) compared to men with organ-confined disease (0.05, 95% CI 0.02-0.09). However, with delayed BCR at five years post-surgery, the mortality rates were more comparable as men with extra-prostatic disease and organ-confined disease had mortality rates of 0.08 (95% CI 0.03-0.21) and 0.05 (95% CI 0.02-0.18), respectively.

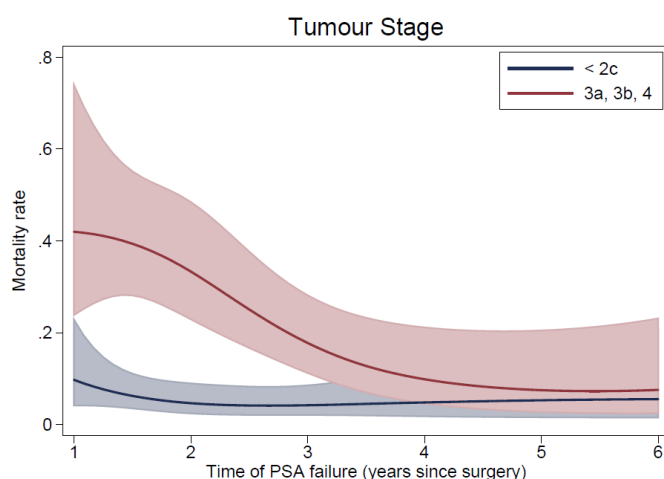


Figure 2c. Mortality rates stratified by tumour stage

Models including both Gleason score and tumor stage categorised into low-, intermediate- and high-risk showed a similar pattern (**Figure 2d**). Men with high-risk disease, as defined by high Gleason sum ($\geq 4+3$) and extra-prostatic disease, were shown to have significant risk of PCSM with early BCR. Similarly, men with intermediate-risk disease (either low Gleason sum and extra-prostatic disease, or high Gleason sum and organ-confined disease) had higher

PCSM with early recurrence. With late BCR, neither of these two groups had substantially increased risk of PCSM. Men with low-risk disease, as defined by low Gleason sum ($\leq 3+4$) and organ-confined disease, had low mortality rates regardless of early or late BCR.

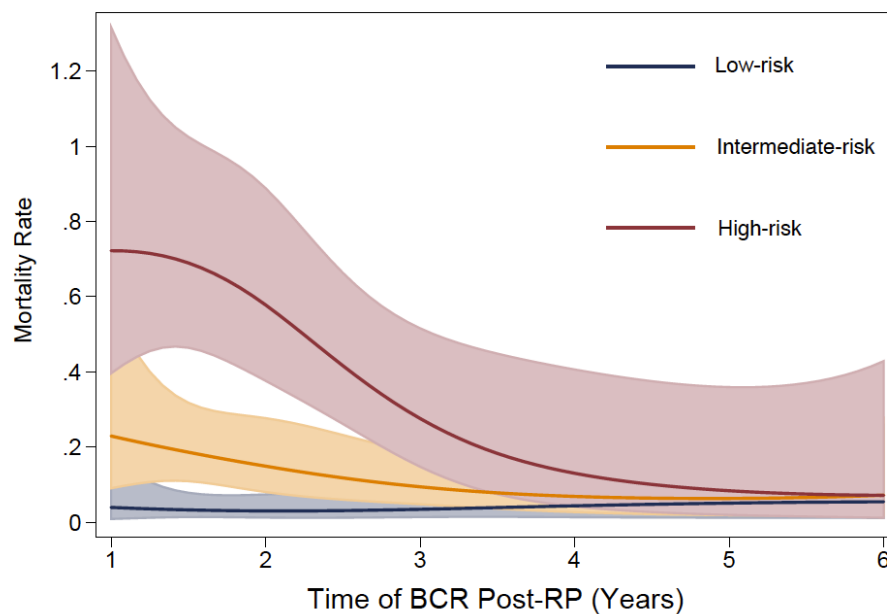


Figure 2d. Mortality rates stratified by risk

No substantial differences in predicted mortality rates by surgical margins status was observed (**Figure 2e**).

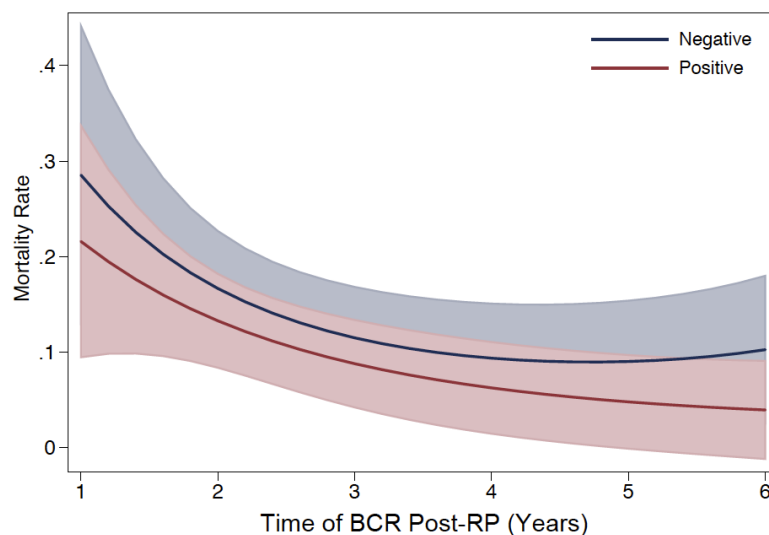


Figure 2e. Mortality rates stratified by surgical margin status

Discussion

In this whole-of-population series of men who underwent RP and subsequently experienced BCR, we found that the association between BCR and the rate of PCSM depended critically on the interval to BCR from surgery. Men with adverse pathological findings, such as high Gleason score and extra-prostatic disease, who experienced BCR shortly after surgery had a substantially increased mortality rate, while those experiencing BCR after a longer interval had a low mortality rate. Men with low risk disease were not at any substantial risk of death regardless of when their BCR occurred.

Interval to BCR has a time-varying effect on PCSM. The use of Poisson regression analysis in this study clearly demonstrates this interaction, which remains evident after adjusting for other known adverse prognosticators in our models, such as Gleason score, tumor stage and age. To our knowledge, this is the first study evaluating the temporal relationship between BCR and PCSM in a whole of population-based cohort outside of the United States.

Our analyses were performed on a prospective whole-of-population registry of men with localised prostate cancer managed with RP, encompassing a heterogeneous group of patients, surgeon volume and experience. Whilst our findings more truly reflect outcomes observed on a community and population level we are limited by the accuracy of cancer registry coding of deaths, although given the experienced and trained coding staff involved we presume a high degree of accuracy in this task. Furthermore, we were unable to obtain more than two post-operative PSA values in 38 men, who were subsequently excluded from the analysis. We did not adjust for PSA in our models, which is a previously established independent predictor of PCSM. (19,20). However, in a separate multivariate Cox regression analysis using this series, pre-operative PSA was not demonstrated to be predictive of PCSM (data not shown). We also have not assessed the association between PSA DT and PCSM. Our objectives, however, were not to demonstrate the effect of post-operative PSA kinetics on survival, but to observe the time-varying influence of PSA recurrence on survival among men with different risk profiles.

Recurrence of prostate cancer following attempted surgical cure with RP is detected by increasing levels of PSA during post-surgery surveillance, and follows a varying period of undetectable PSA levels (19). The clinical course of men who experience BCR varies, depending on the timing of BCR following surgery and the velocity of the PSA rise. It is important, however, to identify men who are at greatest quantifiable risk of PCSM in the event of early BCR following surgery. In this study, men with high-risk prostate cancer had substantial mortality with early BCR, and such men may benefit from the early institution of salvage radiotherapy or other additional treatment, especially those with a rapidly increasing PSA.

Studies of men with low-risk features of prostate cancer have demonstrated low PCSM where managed with watchful waiting and followed up for 20 years (20,21). Similarly, men undergoing RP with Gleason ≤ 6 and organ-confined tumors have very low mortality after 15 or more years of follow-up.^{121,183} Our population of men treated with RP support the evidence that this subgroup of men have low rates of PCSM, as men with low Gleason sum (≤ 7 with primary Gleason 3) and organ-confined disease had low mortality regardless of early or late BCR. Consequently, this subgroup of men may be counseled regarding their favorable long-term prognosis in the event of disease recurrence. We caution the advocacy for active surveillance for men with low-risk prostate cancer based on our findings, as we have not performed a subgroup analysis of PCSM in men who would have been suitable for active surveillance based on contemporary protocols (21-23).

Interval from surgery to first BCR is frequently analysed as a categorical variable in studies evaluating the effect of timing of BCR on PCSM. Defining early or late BCR as a point in time following surgery is also less helpful in clinical practice in regards to assessing prognosis, determining treatment options and counselling patients, as the timing of BCR after surgery is variable. Furthermore, no consensus exists on the definition of either early or late BCR, and current available evidence on the influence of interval to BCR following surgery on PCSM appears mixed (7,8,11-15).

Pound et al (7) found a shorter interval from surgery to first BCR (≤ 2 years) to be predictive of the development of metastases, but it did not significantly influence time until death. Freedland et al (13) found shorter interval to BCR (< 3 years) following RP was associated with increased risk of PCSM, after adjusting for PSADT and high Gleason score ≥ 8 . Similarly, Caire et al (14) were able to demonstrate a cancer-specific survival advantage in patients with delayed BCR (> 5 years post surgery). The authors also found Gleason sum < 7 and PSA < 10 ng/mL to be associated with delayed BCR.

Well established predictors of BCR include high Gleason score, extra-prostatic disease, positive surgical margins and elevated pre-biopsy PSA levels (14-16,24). Although we have not assessed for predictors of early or delayed BCR, men with adverse pathological features at time of RP have been previously shown to be at higher risk of early BCR (24). The majority of cases of BCR in our study occurred within 5 years of surgery. However, we observed that up to 2% of men who experienced BCR have a PSA progression-free period of 10 years. Similarly, Loeb et al demonstrated in their series very late recurrence with 4.9% and 1.5% of BCR occurring after 10- and 15-years of post-surgery follow-up, respectively (16).

At this stage there appears to be limited evidence and consensus regarding the frequency and intensity of PSA surveillance following a period of undetectable PSA levels. Current internationally accepted guidelines recommend life-long annual PSA testing after a PSA progression-free period of 3 to 5 years (25,26). However investigators have demonstrated low risk of delayed BCR in men with Gleason 6 disease and have consequently suggested less intense surveillance in men with low-risk disease after a similar PSA progression-free period (27,28). Loeb et al found that men with undetectable PSA levels for 10 years post-surgery were at low risk of developing subsequent BCR and had extremely low risk of PCSM. Within this subgroup, no men with Gleason 6 tumours progressed to metastatic disease, and the authors suggested that annual PSA testing may not be required in men with Gleason 6 disease and/or limited life expectancy after a progression-free period of 10 years (16).

Conclusions

Data from this whole-of-population registry of RP shows that time to BCR significantly influences prognosis for men with high-risk prostate cancer, who have significant mortality risk with early BCR. These men should undergo intense PSA surveillance following surgery and may be best managed with salvage therapy in the event of BCR. Men with low-risk prostate cancer have low mortality, and time to BCR following surgery does not alter their prognosis. Thus in the event of early BCR, this subgroup of men may be counseled regarding their favorable long-term prognosis.

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**Table 1. Characteristics of men in the Victorian Radical Prostatectomy Register
(n=2154)**

	Median (years)	Range (years)
<i>Age</i>	62	38-81
<i>Follow-up post-RP</i>	10.3	
<i>Follow-up post-BCR</i>	7.5	
	N	%
<i>PSA</i>		
<4 µg/L	214	10.0
4-10 µg/L	1180	54.9
>10 µg/L	754	35.1
<i>Gleason Sum at RP</i>		
≤6	1213	57.5
7	744	35.3
8-10	153	7.2
<i>Pathological Stage</i>		
<pT2c	1600	74.6
pT3a	319	14.9
pT3b	180	8.4
pT4	45	2.1
<i>Lymph Node Status</i>		
N ₀	1535	71.2
N ₁	23	1.1
N _x	596	27.7
<i>Surgical Margin Status</i>		
Negative	1468	68.3
Positive	681	31.7

RP = radical prostatectomy
BCR = biochemical recurrence

Table 2. Characteristics of the 695 men who experienced biochemical recurrence following radical prostatectomy

		Prostate Cancer Death				Total	
		No		Yes			
		N	%	N	%	N	%
<i>Age at surgery</i>							
	< 55	83	13	9	14	92	13
	55-65	339	54	33	50	372	54
	≥ 65	207	33	24	36	231	33
<i>Surgical margins status</i>							
	Negative	351	56	37	56	388	56
	Positive	278	44	29	44	307	44
<i>Pathological stage</i>							
	<pT2c	397	64	17	26	414	61
	pT3a	119	19	13	20	132	19
	pT3b	84	14	30	47	114	17
	pT4	20	3	4	6	24	4
<i>Gleason score</i>							
	≤ 6	256	42	11	17	267	39
	7 (3+4)	211	34	13	20	224	33
	7 (4+3)	86	14	18	28	104	15
	8-10	61	10	23	35	84	12

c. Increased Prostate Cancer Specific Mortality Following Radical Prostatectomy in Men Presenting with Voiding Symptoms – A Whole of Population Study

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Abstract

Purpose

Whole of population studies reporting long-term outcomes following radical prostatectomy are scarce. We aimed to evaluate the long-term outcomes in men with prostate cancer (PC) treated with radical prostatectomy (RP) in a whole of population cohort. A secondary objective was to evaluate the influence of mode of presentation on prostate cancer-specific mortality (PCSM).

Methods

A prospective database of all cases of RP performed in Victoria, Australia, between 1995-2000 was established within the Victorian Cancer Registry. Specimen histopathology reports and PSA values were obtained by record linkage to pathology laboratories. Mode of presentation was recorded as either PSA screened (PSA testing offered in absence of voiding symptoms) or symptomatic (diagnosis of PC following presentation with voiding symptoms). Multivariate Cox and competing risk regression models were fitted to analyse all-cause mortality, biochemical recurrence and PCSM.

Results

Between 1995-2000, 2154 men underwent radical prostatectomy in Victoria. During median follow-up of 10.2 years (range 0.26-13.5 years), 74 men died from prostate cancer. In addition to Gleason score and pathological stage, symptomatic presentation was associated with PCSM. After adjusting for stage and PSA, no difference in PCSM was found between men with Gleason ≤ 6 and Gleason 3+4 = 7. Men with Gleason 4+3 had significantly greater cumulative incidence of PCSM compared to men with Gleason 3+4.

Conclusions

Primary Gleason pattern in Gleason 7 PC is an important prognosticator of survival. Our findings suggest that concomitant voiding symptoms should be considered in the work-up and treatment of PC

Key Words

Prostate tumour

Mortality

Symptomatic

Whole of population

Pathology

Surgery

Introduction

Prostate cancer (PC) is the most commonly diagnosed male malignancy and the second most common cause of cancer-related death in Australia, and its incidence continues to increase in the Asia-Pacific region(1, 2). The use of open radical prostatectomy (RP) for the surgical management of localised PC increased dramatically during the 1990s subsequent to the increasing use of prostate-specific antigen (PSA) testing and improved operative techniques(3-5). In more recent years, advances in laparoscopic and robotic surgery have seen a significant fall in rates of open surgery for PC(6). Due to relatively recent uptake of robotic surgery, long-term survival data following surgery for PC is largely limited to open RP series.

PC is associated with a long natural history. Multiple studies of long-term follow-up data in patients managed with observation and surgery have been published, although few of these represent whole of population series(7-13). Lower PC-specific mortality (PCSM) observed in men with more low-risk disease has resulted in a shift towards increased use of active surveillance(14-16). Conversely, men with higher risk PC may have the greatest survival benefit from surgery, as those with aggressive disease may be cured by RP alone or as part multimodality treatment(9, 17, 18).

Presentation in men with PC is usually asymptomatic and based on serum PSA, but there is a subgroup of men presenting with lower urinary tract symptoms (LUTS) who potentially harbour a malignancy(19, 20).

In this study, we evaluate the long-term survival outcomes in prospective whole of population study of men treated with RP in the PSA era. Furthermore, we sought to identify the impact on PCSM of symptomatic presentation with voiding dysfunction leading to cancer diagnosis, as opposed to diagnosis based purely on PSA testing.

Subjects and Methods

Patient Population:

The Victorian Radical Prostatectomy Registry (VRPR) is a prospective whole of population series of men who underwent RP for the treatment of clinically localised prostate adenocarcinoma between 1995 and 2000 in Victoria, Australia. This database was established within the Victorian Cancer Registry (VCR), which documents all cancer cases in the state, excluding non-melanoma skin cancer, and is managed by the Cancer Council Victoria. Further details regarding patient registration and data collection have previously been published(3).

Clinical and Histopathological details:

The mode of presentation was recorded at registration as either PSA screened (PSA testing offered by a urologist or general practitioner in the absence of significant voiding symptoms), symptomatic or other. Symptomatic presentation was defined as patients who sought treatment for irritative or obstructive symptoms and were subsequently diagnosed with prostate cancer. Specimen histopathology reports, and pre- and post-RP PSA surveillance values were obtained by record linkage to pathology laboratories. Biochemical recurrence (BCR) post-RP was defined as two consecutive PSA values ≥ 0.2 ng/ml and the latter date taken as the time of recurrence. Deaths were recorded by the VCR as either death from PC, death from another cancer, or death from another cause. Men who received neoadjuvant therapy were excluded from all analyses.

Statistical Analysis:

Multivariate Cox proportional hazards models were fitted to analyse all-cause mortality and time to biochemical recurrence. Competing risks regression based on the Fine and Gray model, with other cause mortality as the competing risk, was fitted to analyse overall PCSM as well as subgroup PCSM and was used to generate cumulative incidence plots. In all

regressions, time from surgery was used as the time axis and all covariates were entered into the model simultaneously. Formal statistical testing of the proportional hazards assumption in the Cox models using Schoenfeld residuals found that it was not violated. Proportionality was assessed in the competing risks regression by including interactions with a time variable for all covariates and these were found to be non significant. In the symptomatic subgroup analysis, age at surgery and PSA were found to be not normally distributed by the skewness-kurtosis test and hence were compared with the Wilcoxon rank sum test. Grade and stage were compared with the Kruskal-Wallis test. All tests were two sided and significance level set at $p \leq 0.05$.

Analyses were performed with Stata 12.1 SE (Statacorp, College Station, TX, USA).

Results

The full registry comprises 2154 patients. Baseline characteristics are shown in Table 1. 2112 subjects had follow-up data available (98.1%). After excluding men who received neoadjuvant therapy, 1935 subjects had data available including grade, stage and PSA. These men constitute the population set analysed in this report. During a median follow-up of 10.2 years (range 0.26-13.5 years), 622 men experienced BCR and 233 men died, including 74 from prostate cancer.

Results of the multivariate Cox regression analysis used to model risk of BCR, all cause mortality and PCSM are shown in Table 2. Increasing Gleason grade and tumour stage were strongly associated with time to BCR and PCSM. The non-significant result for pT4 tumours in all-cause mortality was likely due to the small number of events in this series. A higher baseline PSA was associated with reduced time to BCR, but was not found to be predictive of PCSM or overall mortality. Older age at surgery predicted time to all-cause mortality but not PCSM.

Symptomatic presentation with subsequent diagnosis of prostate cancer was significantly associated with older age and higher PSA, grade and stage as shown in Table 3. After multivariate adjustment of these clinico-pathologic parameters, there was still an association between symptomatic presentation and time to PCSM ($p=0.036$, Figure 1).

There were 16 PC-specific deaths observed in men who had Gleason ≤ 6 disease and 14 in men with Gleason 3+4 = 7 disease. After adjusting for pathological stage, PCSM outcomes for Gleason ≤ 6 and 3+4 tumours did not significantly differ ($p=0.231$, Figure 2). In a low risk subgroup of men with PSA ≤ 10 ng/ml and pT1/T2 stage ($n=994$, 51.4%), 17 PC deaths were observed overall, including 11 and 4 men with Gleason score ≤ 6 and 3+4, respectively. Similarly, no significant difference in PCSM was observed between the two groups ($p=0.649$), although the number of events was small (Figure 3).

In the sub-group of men with Gleason 7 tumours (n=674), 35 deaths were observed, including 14 and 21 in men with Gleason 3+4 and 4+3 disease, respectively. Men with Gleason 7 disease and primary pattern 4 had significantly greater cumulative incidence of PCSM compared to men with Gleason 7 disease and primary pattern 3 as shown in Figure 4 (SHR = 2.79, 95% CI 1.40 – 5.54, p = 0.003).

Discussion

This study represents the largest reported whole of population cohort of men treated with radical prostatectomy with more than 10-years follow-up. Whilst evaluating the role of screening was not a primary endpoint in this study we found that in addition to previously demonstrated pathologic predictors of PCSM, mode of presentation influenced survival outcomes. We report a difference in survival between men who were diagnosed with PC following PSA testing offered by their family doctor or urologist, compared to men who had diagnosis of PC made following a presentation with symptoms of urinary obstruction.

Symptomatic presentation was associated with older age and higher PSA, grade and stage, but even after adjustment for these parameters, there was an association between symptomatic presentation and reduced time to PCSM. Minimal data studying this parameter has been published to date, possibly because this variable is less commonly noted now that most PC is PSA detected in North America and Europe. Data from The Swedish National Prostate Cancer Register has shown that most men with PC diagnosed after a health check-up, compared to men presenting with LUTS, have localised tumours of low or intermediate risk(20). Lee et al found that men with pre-operative LUTS as demonstrated by International Prostate Symptoms Score > 8 had a higher incidence of pathologic pT3a disease at time of RP compared to men with no LUTS(19).

A possible explanation for this finding may be prostate volume, as men with larger prostates are more likely to experience LUTS. However, data regarding prostate volume was not available for all patients in our study. Whilst a relationship between prostate volume and symptomatic presentation may exist based on our data, other factors may exist, such as prostate cancer arising from the transition zone. This requires further study. Nonetheless, our data suggests that men who present with voiding symptoms should be counseled about PSA testing as part of their work-up of BPH, as some of these men may harbour more aggressive PC.

A further notable finding was the good prognosis of the subgroup of men with Gleason 3+4 PC, especially those with low-risk features such as PSA $\leq$ 10ng/ml and organ-confined disease. These men had no increased risk of PCSM compared to men with Gleason $\leq$ 6. This suggests that in low-volume PC treated with RP, secondary Gleason pattern 4 confers little increased risk of mortality.

Part of this lack of variance in outcomes between Gleason $\leq$ 6 and Gleason 3+4 PC in this series where all men were treated by RP may be that although the number of PC-related deaths in both groups was small the crude mortality rate from Gleason $\leq$ 6 disease was higher than expected. In the subgroup of men with Gleason $\leq$ 6, PSA $\leq$ 10ng/ml and organ-confined disease, 11 deaths from PC were observed. This observation may be partly explained by the multi-center study design whereby deaths were coded by a centralised cancer registry based on information from death certificates rather than medical records, and it is possible but unlikely that a greater proportion of deaths may have been over-attributed to PC. Furthermore, prior to the modification of the Gleason scoring system by the International Society of Urological Pathology in 2005, it is possible that some of the Gleason $\leq$ 6 tumours may have represented Gleason 7 tumours(21, 22).

We found that the sub-group of men with Gleason 7 PC had heterogenous outcomes. It has been previously shown that primary Gleason pattern 4 in men with Gleason 7 PC is associated with greater biochemical recurrence following surgery compared to primary Gleason 3(23-26). However, the effect of primary Gleason pattern 4 on mortality outcomes in these men is less clear. Among men with Gleason 3+4 and 4+3 PC, Eggener et al found no difference in 15-year PCSM in over 20,000 men treated with RP treated at multiple large US institutions(10). Conversely, Wright et al demonstrated higher rates of BCR and PCSM in men with Gleason 4+3 compared to men with Gleason 3+4 in a population-based cohort of men with Gleason 7 PC and median 13-year follow-up, although the study was limited to 753 men from a single county under the age of 65 years(27). Stark et al similarly demonstrated a 3-fold increase in PCSM in men with Gleason 4+3 compared to men with Gleason 3+4 with 20-year follow-up, however, the analysis did not control for PSA or tumour

stage(28). Furthermore the study was limited to 693 RP specimens and all men were identified from health survey studies conducted on health professionals.

This heterogeneity in outcomes in men with Gleason 7 PC in our study may further be explained by tumour volume. A trend between increasing tumour volume and adverse pathological findings at radical prostatectomy was noted, but was not reported as tumour volume was not available for all men. It is possible that the presence of primary Gleason pattern 4 is associated with increased tumour volume, and this requires further evaluation. Nonetheless, the distinctions between the predominant Gleason patterns remains important. We confirm in a whole of population setting that amongst men with Gleason 7 PC treated with RP, primary Gleason pattern 4 confers significantly greater PCSM compared to primary Gleason pattern 3.

Some limitations of this study include potentially incomplete data regarding adjuvant or salvage radiation therapy, and an inability to comment on functional or quality of life measures, which are important outcomes following RP. Prostate volume and tumour volume data were also not available for all men. However, this prospective study represents a statewide whole of population register of RP performed by all urologists of varying experience in large tertiary and smaller community hospitals. By including men of varying pathology, socioeconomic status and residency, and all urologists undertaking RP regardless of their experience or surgical volume, this study is representative of long-term outcomes on a population and community level that may not be reflected in large series from high-volume institutions from the US and Europe.

Conclusion

In this whole of population based study there appears to be increased PCSM for men treated by radical prostatectomy for clinically localized disease where their presentation was with symptomatic voiding difficulty, in comparison to men who had their cancer diagnosed on the basis of PSA elevation alone. This finding should be considered in determining the most appropriate form of treatment for individual patients, including where active surveillance may be an option. Furthermore Gleason score 3+4 =7 PC has been shown in this whole-of-population series to have significantly less PCSM than 4+3=7 disease, and similar to that of Gleason score 6 disease, reinforcing the significance of this pathologic distinction.

Conflicts of Interest

No conflicts of interests to declare

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Tables

	Median (Mean)	Range
Age at surgery (years)	61.9 (61.4)	38.9-81.7
PSA (ng/ml)	8.4 (10.2)	0-112
Gleason grade	N	Percentage
2-6	1123	58.1
7 (3+4)	489	25.3
7 (4+3)	185	9.6
8-10	135	7.0
Pathological Stage	N	Percentage
T1/T2	1437	74.4
T3a	294	15.2
T3b	160	8.3
T4	41	2.1
Mode of Presentation	N	Percentage
Symptomatic	631	32.7
Non-symptomatic	1301	67.3
Urologist	(206)	(15.8)
GP screen	(1095)	(84.2)

ng/ml = nanogram/milliliter

Table 1. Baseline characteristics

	Biochemical Recurrence				All Cause Mortality			Prostate Cancer-Specific Mortality	
	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Baseline Characteristics									
Symptomatic (vs. not)	215	1.06 (0.90-1.25)	0.481	101	1.34 (1.03-1.74)	0.029	37	1.64 (1.04-2.60)	0.034
Age (per year)		1.00 (0.99-1.01)	0.997		1.07 (1.04-1.09)	<0.001		0.99 (0.95-1.03)	0.514
PSA (per 5 ng/ml)		1.09 (1.05-1.12)	<0.001		1.01 (0.94-1.07)	0.862		1.00 (0.90-1.10)	0.950
Gleason Score									
≤6 (ref.)	245			104			16		
7 (3+4)	203	1.90 (1.57-2.30)	<0.001	52	1.08 (0.77-1.52)	0.665	14	1.61 (0.79-3.30)	0.194
7 (4+3)	96	2.34 (1.83-3.01)	<0.001	37	1.72 (1.15-2.58)	0.008	21	4.75 (2.45-9.22)	<0.001
8-10	78	2.24 (1.69-2.98)	<0.001	40	2.36 (1.55-3.60)	<0.001	23	5.39 (2.61-11.11)	<0.001
Pathological Stage									
T1/T2 (ref)	369			139			23		
T3a	123	1.35 (1.09-1.67)	0.006	38	1.15 (0.79-1.66)	0.478	16	2.37 (1.23-4.55)	0.010
T3b	107	2.36 (1.86-2.98)	<0.001	49	2.25 (1.54-3.30)	<0.001	31	5.83 (3.18-10.69)	<0.001
T4	23	2.03 (1.29-3.19)	0.002	7	1.58 (0.73-3.42)	0.245	4	5.15 (1.88-14.06)	0.001

HR = hazard ratio, SHR = subhazard ratio, CI=confidence interval, ng/ml = nanogram/milliliter

Table 2. Multivariate Cox regression analysis

	Symptomatic	Not Symptomatic	P-value for
	Median (mean)	Median (mean)	Difference
Age (years)	62.78 (62.09)	61.66 (61.06)	<0.001
PSA (ng/ml)	7.9 (10.36)	8.2 (10.19)	0.017
Gleason Score			
≤6 (ref.)	374 (59.3%)	749 (57.6%)	0.038
7 (3+4)	138 (21.9%)	351 (27.0%)	
7 (4+3)	65 (10.3%)	120 (9.2%)	
8-10	54 (8.6%)	81 (6.2%)	
Pathological Stage			
T1/T2 (ref)	455 (72.1%)	982 (75.5%)	0.023
T3a	91 (14.4%)	203 (15.6%)	
T3b	68 (10.8%)	92 (7.1%)	
T4	17 (2.7%)	24 (1.8%)	

Table 3. Comparison of symptomatic vs non-symptomatic men

Figures

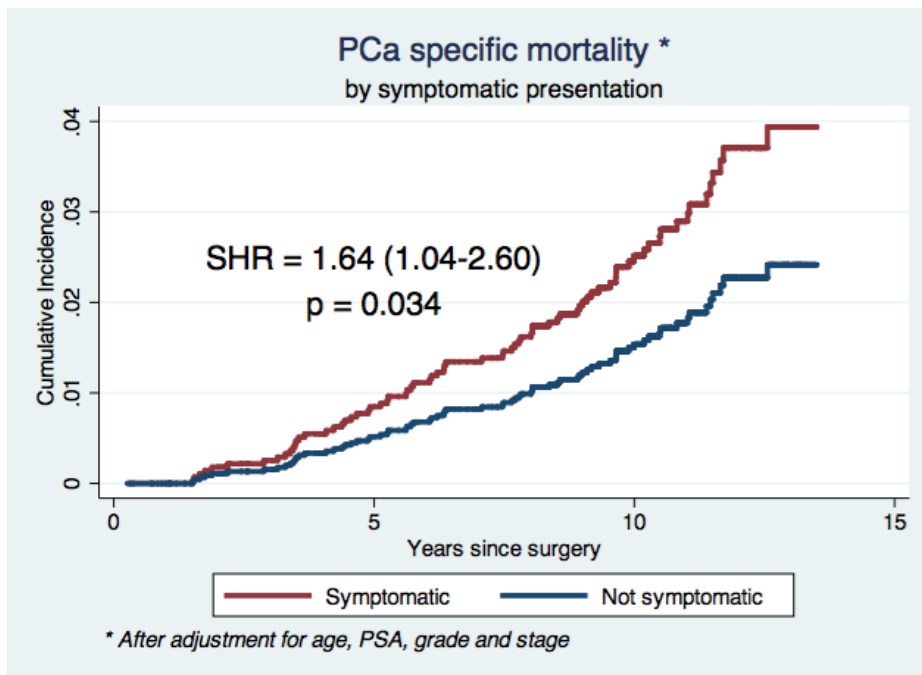


Fig. 1

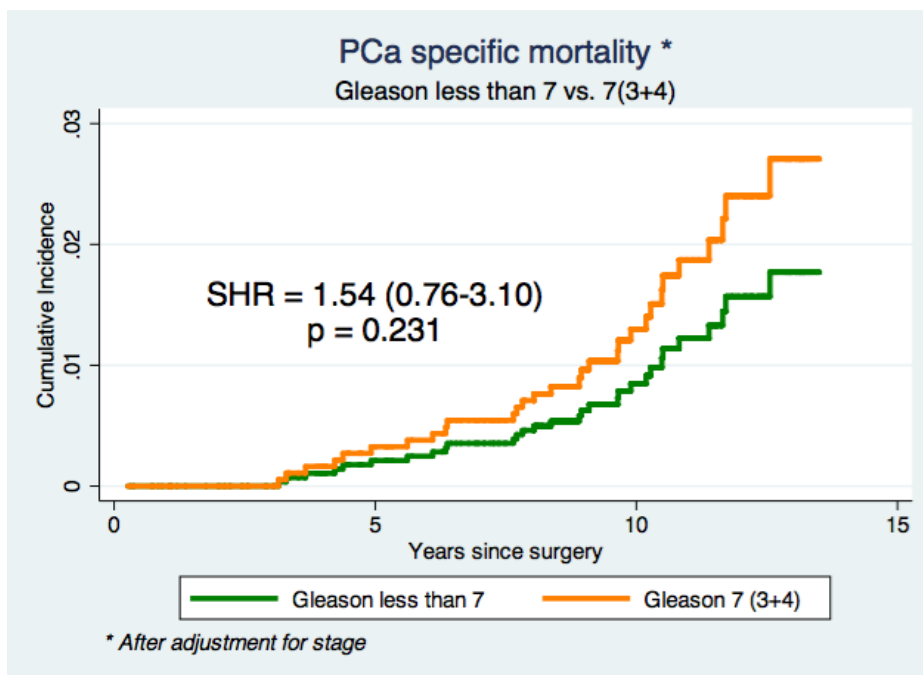


Fig. 2

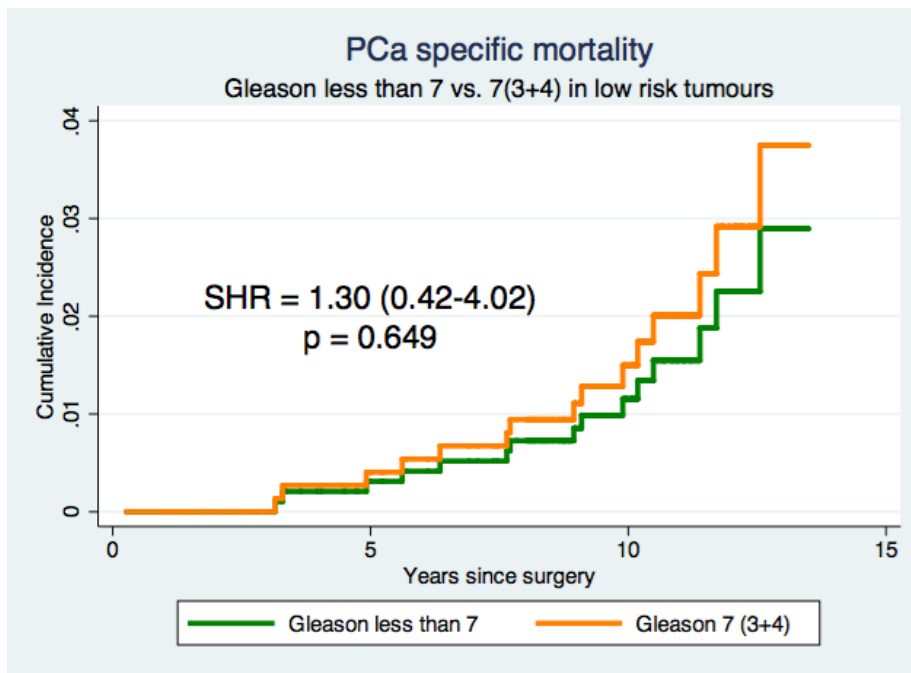


Fig. 3

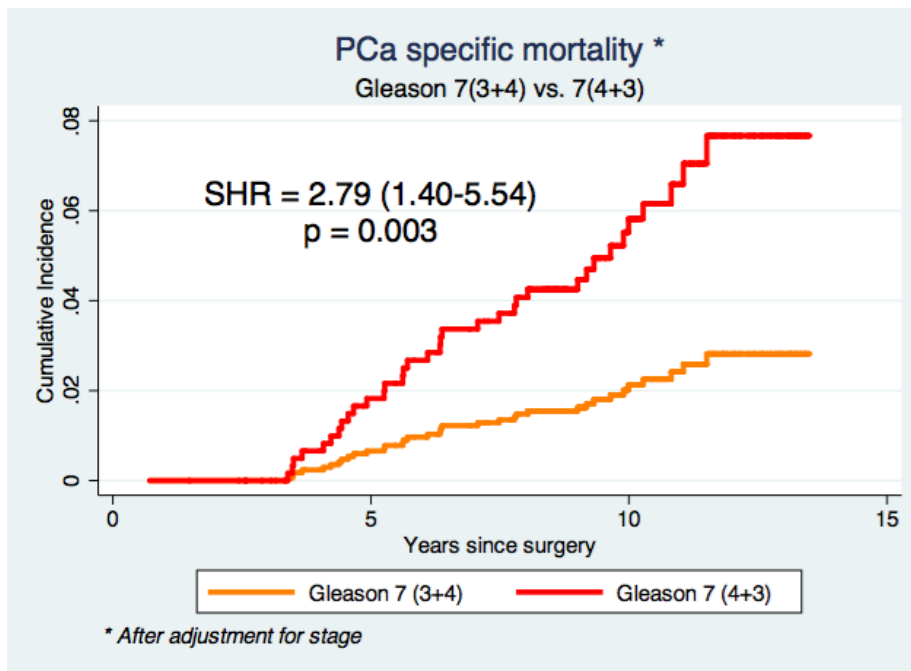


Fig. 4

Legends

Fig 1. Symptomatic presentation and prostate cancer-specific mortality

Fig 2. Comparison of Gleason ≤ 6 and 7 (3+4)

Fig 3. PCSM in lower risk prostate cancer (Gleason $\leq 3+4$, PSA ≤ 10 , pT1/2)

Fig 4. Effect of primary pattern on PCSM in Gleason 7 prostate cancer

8. First and Principal Authored Publications Arising Indirectly from this Thesis

a. Testicular torsion and the acute scrotum: current emergency management

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ABSTRACT

The acute scrotum is a challenging condition for the treating emergency physician requiring consideration of a number of possible diagnoses including testicular torsion. Prompt recognition of torsion and exclusion of other causes may lead organ salvage, avoiding the devastating functional and psychological issues of testicular loss and minimising unnecessary exploratory surgeries

This review aims to familiarise the reader with the latest management strategies for the acute scrotum, discusses key points in diagnosis and management, evaluates the strengths and drawbacks of history and clinical examination from an emergency perspective. It outlines the types and mechanisms of testicular torsion, and looks at the current and possible future roles of labwork and radiological imaging in diagnosis.

Emergency departments should be wary of younger men presenting with the acute scrotum.

Keywords: acute, pain, review, scrotal, testicular, torsion

Introduction

The acute scrotum in children and younger men is a challenging condition for emergency physicians, often hijacked by the term “potential testicular torsion” in recognition of the urgency to treat and not miss this time-critical condition. However, the acute scrotum should remain just that, allowing physicians to consider all potential diagnoses representing a constellation of symptoms and signs causing pain in the scrotum. In such situations the acute scrotum may be due to testicular torsion (TT) but a careful history and exam will elucidate many other potential causes. Understandably the spectre of a missed TT drives many to identify TT as a potential diagnosis even if low on the list of differentials, making referrals to surgical teams almost inevitable, perhaps driving explorations that are sometimes unnecessary. Accepting that imaging does not hold the key to delineating the acute scrotum, a heavy reliance on history and physical examination is often required. The object of this review is to outline presentation of the acute scrotum focusing on TT, the diagnosis that should not be missed.

Torsion of the testis is a common condition that accounts for approximately 20% of paediatric patients presenting to the emergency department with acute scrotal pain, with torsion of the testicular appendix representing the most common aetiology¹. Early presentation and recognition of key symptoms and signs are paramount in minimising the potentially devastating psychological and cosmetic issues associated with organ loss. Poorly managed TT is the third most common cause of malpractice cases in adolescent males presenting to ED departments². Delayed presentation contributes to risk of organ loss with a TT so emergency physicians need to be aware of the current management standards and role of early referral where TT is on the list of differentials for an acute scrotum.

Epidemiology

Causes of an acute scrotum vary with age (see Table 1). A bimodal peak in incidence of TT is seen, beginning in the neonatal period and early adolescence. Most boys who present with an acute scrotum (approximately 50%) will have torsion of the appendix testis (TAT).

However, around 13-20% will have TT, with epididymo-orchitis the most common of the other contributing conditions^{1, 3-5}. Other conditions to consider in the differential diagnosis range from mumps orchitis, haematoma, renal colic, appendicitis and strangulated inguinal hernias and, rarities like the scrotal manifestations of Henoch-Schonlein purpura and communicating haematocoeles following abdominal trauma^{6, 7}.

Age Group (years)	Testicular Torsion (%)	Torted Appendix Testis (%)	Epididymo-orchitis (%)
0-11	6.6	62	6
12-16	52	32	3
17-40	48	5	27

Table 1: Age distribution of the causes of an acute scrotum seen at surgical exploration⁸

Age of presentation can vary, but the age at which boys most commonly are affected with TT is between 12-18 years, with a peak between 13 and 16 years^{1, 4, 9}. In a retrospective analysis of 115 boys with an acute scrotum, of the 83 patients with TT, only 7% occurred in boys under the age of 11 years.¹⁰ Other series of the acute scrotum show a peak incidence of torsion of the testicular appendix of around 10 to 11 years of age.^{1, 8}

Anatomy and Mechanism of Infarction

TT can occur in several different ways, and can be classified as intravaginal, extravaginal or mesorchial (see Figure 1) A slight preponderance in left-sided TT has been noted in some series, although the mechanism for this is unclear.^{1, 9, 11}.

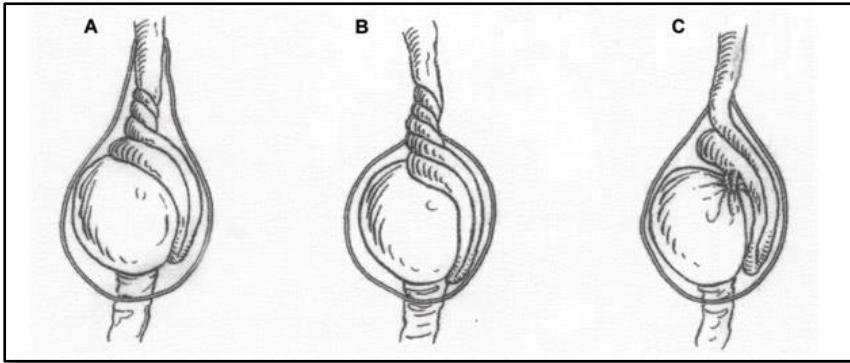


Figure 1: Diagram demonstrating (A)intravaginal (B)extravaginal and (C)mesorchial torsion

Intravaginal torsion most often occurs due to a congenital malformation of the processus vaginalis as the testis descends into the scrotal sac. This type of torsion accounts for the majority of testicular torsions, and is most often seen in pubertal boys, where rapid growth and increased vasculature may be a precursor. Under normal circumstances, the tunica vaginalis does not fully extend around the testicle, and attaches to the posterolateral scrotal wall allowing the testis to remain suspended in an upright vertical position (see Figure 2). However, in up to 12% of boys, the tunica vaginalis completely envelopes the testis and epididymis, resulting in a “bell-clapper” testicle that is more horizontally oriented, with greater ability to freely rotate around an axis.¹²

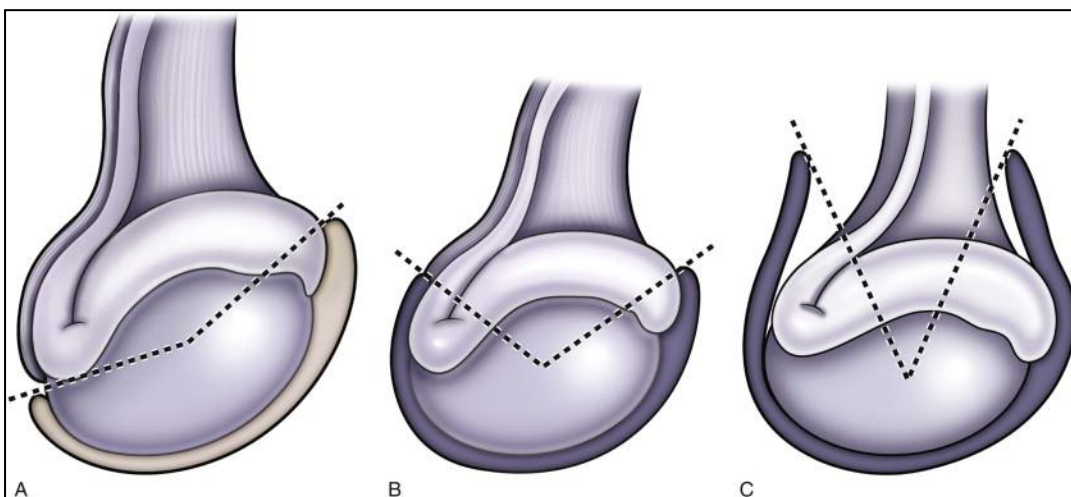


Figure 2. Mechanism of torsion with “bell-clapper” deformity

Extravaginal torsion, which is rare, occurs during the perinatal period and is due to a different mechanism. It occurs during descent of the testes into the scrotum before scrotal investment of the tunica vaginalis has taken place, where complete adhesion to the surrounding tissues is usually completed by six weeks age.¹³ Twisting of the processus vaginalis and its contents results in necrosis and absence of blood flow within the testis, epididymis and cord. If torsion has occurred in the prenatal period, the clinical presentation is a neonate with unilateral or bilateral blue non-tender hard masses in the scrotum.¹⁴ However, if it occurs in the postnatal period, the presentation is more classic with acute inflammation and erythema in a previously normal neonatal scrotum, requiring exploration and fixation.¹³

Mesorchial torsion is exceedingly rare and has an atypical presentation. It occurs due to anomalies in the mesothelium that covers the anterior half of the testis and suspends it from the vasculature and epididymis. When the attachment is narrow, mesorchial torsion can occur when there is a twist in the tissue overlying the vasculature (anteriorly) between the epididymis and parietal tunica vaginalis.¹⁵

In the majority of cases, rotation of the testes initially compromises venous return. However, as time progresses and oedema ensues, arterial flow is reduced or occluded.¹⁴ Whilst the majority of TT occurs in a medial direction, several studies have shown torsion in a lateral direction in up to 29-33% of cases.^{9, 16}

The degree of testicular rotation varies according to the literature. One retrospective study of 200 paediatric boys with testicular torsion showed a higher degree of rotation in non-salvageable (managed with orchidectomy) versus salvageable testes (median of 540 vs 360 degrees).⁹ However, the authors also noted that testicular infarction can occur with rotation as mild as 180 degrees.

Torsion of the appendix testis (TAT) results in infarction of the mesothelial remnant of the Müllerian (paramesonephric) duct on the superolateral surface of the testis. The appendix of the epididymis (remnant of mesonephric duct) has also been reported to twist¹⁷. This

results in a hard mass on the surface of the testicle with point tenderness, and a “blue dot” sign (a subtle blue-coloured mass viewed through the scrotal skin on examination). TAT occurs more commonly in the pre-pubertal age group⁸.

Diagnosis

History

A careful history is vital in the assessment of the acute scrotum. The classical presentation for TT is sudden onset severe unilateral pain. Early presentation is frequently seen compared to other causes of acute scrotal pain, which has been demonstrated in large retrospective studies^{1, 18}. The pain, being ischaemic in nature, typically requires opiate analgesia for effective pain relief. Persistent pain after opiate analgesia should arouse suspicion of TT. The pain may be accompanied by a history of previous bouts of intermittent testicular pain, which likely represents episodes of torsion and detorsion.

Duration of symptoms before presentation can vary significantly, ranging from several hours to several days. However, patients with TT tend to have a shorter duration of symptoms before presentation.^{1, 18} Early presentation in cases of TT is associated with higher likelihood of salvage, as will be discussed below.

The presence of nausea and vomiting, caused by reflex stimulation of the coeliac ganglion, can be a useful clue in diagnosing TT, but incidence varies significantly in the literature. Some series report nausea and vomiting in 57-69% of patients with TT, with positive predictive values for nausea and vomiting as high as 96% and 98%, respectively, compared with 8% and 4% in TAT and none in epididymo-orchitis.^{9, 10} Other series have shown that nausea and vomiting do occur in torsion of the testicular appendix and epididymo-orchitis, but the complaint is much rarer.^{1, 18}

Dysuria is an uncommon complaint in testicular torsion, and its presence likely indicates an alternate diagnosis such as epididymo-orchitis.¹⁹ A history of trauma should not discount

the possibility of TT. Although the large majority of cases of TT are unprovoked, 4-10% of cases have been reported to occur in the setting of trauma.^{4, 9, 20}

Physical Findings

In a normal scrotum, the testis is mobile, and the cord and epididymis are palpable posterior to the testis. In TT, the affected testis is usually riding high. The globe of the testis is very tender, and venous distension and transudate often result in a larger testis compared to the contralateral and unaffected testis. Focal areas of tenderness in the superior testis or caput epididymis may indicate a tortic testicular appendix or epididymitis. However, anatomical landmarks may be obliterated as oedema and erythema increase in later stages of torsion (see Figure 3).



Figure 3. Erythematous left hemiscrotum with high riding testicle in a TT

Assessment of the cremasteric reflex is important, and its absence is generally considered as one of the more reliable physical signs of the presence of TT (see Figure 4). The reflex is elicited by stroking or pinching the medial thigh. Contraction of the cremasteric muscle results in elevation of the testis, and the sign is considered positive if there is movement of less than 0.5cm on the affected side with a movement greater than 0.5cm on the unaffected side. One series of 245 boys presenting with acute scrotal swelling reported absence of the cremasteric reflex in 100% of patients with torsion.²¹ Similarly, in a large retrospective study of over 1200 cases over an 18 year period, 94% of boys with TT had an absent cremasteric reflex.¹⁸ Whilst the sign can be observer dependent and published reports have

demonstrated an intact cremasteric reflex in cases of TT, its absence should raise significant clinical suspicion of the diagnosis.^{4, 22, 23}

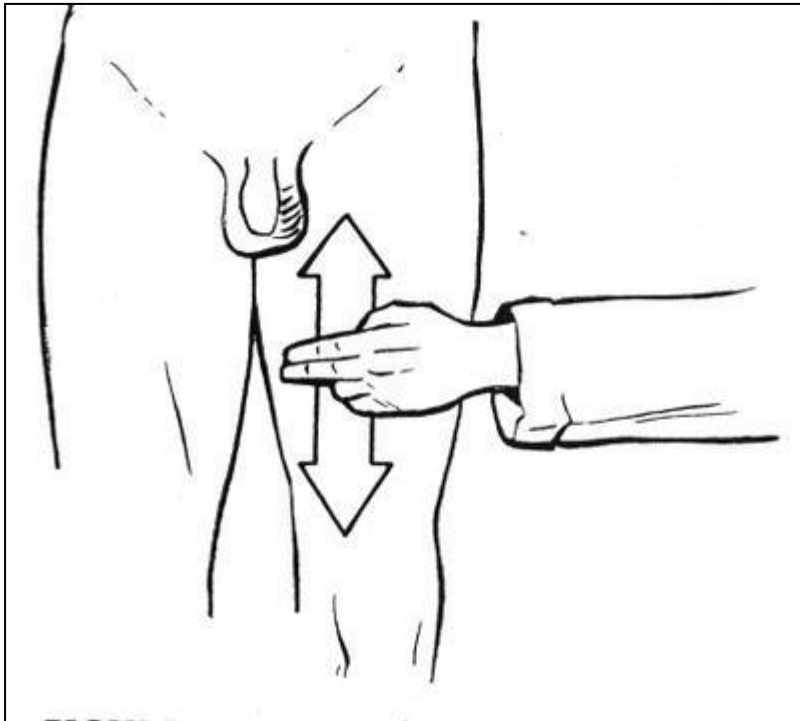


Figure 4: Eliciting the cremasteric reflex

The epididymis may be located medially, laterally or anteriorly, depending on the degree of torsion, but may appear normally located if there is 360 degree torsion, or may be difficult to palpate in a significantly oedematous scrotum. A reactive hydrocele may be present, as well as scrotal oedema.

A well performed clinical examination may not reliably exclude TT as a differential diagnosis and avoid scrotal exploration, but should raise significant concern where TT is likely and expedite management. Several studies have demonstrated that the most reliable physical signs of TT include (a) a high-riding testis, (b) absent cremasteric reflex, and (c) an anteriorly rotated epididymis or abnormally oriented testis.^{18, 19, 24}

A febrile patient, or erythema of the scrotum with or without a small hydrocoele may suggest an infective process. However, the treating physician should be aware these signs may be superimposed on an already infarcted and necrotic testes.

In children other clinical indicators such as easily jumping in and out of the bed, a normal appearance lacking distress and a healthy appetite although not pathognomonic of another cause, may be used to help place TT as a less likely diagnosis of the acute scrotum.

Laboratory Investigations

A urinalysis should be performed as part of the routine work-up. A positive dipstick result is more likely to be in keeping with epididymitis, especially in the setting of dysuria and other features of a urinary tract infection. However, a positive result does not exclude torsion, which can occur in rare instances.¹

Routine blood tests may not need to be performed if the clinical diagnosis is highly suspicious of TT, but may be useful in identifying other causes of the acute scrotum. An elevated C-reactive protein and white cell count for example would be consistent with infection.⁴

Role of Imaging

High-resolution ultrasound (HRUS) with colour-flow Doppler ultrasonography (CDS) and radionuclide imaging can provide information about blood flow to the testes.²⁵ Absent arterial flow within the suspect testis on CDS is indicative of testicular torsion. However, the availability of ultrasound in the emergency setting will vary between institutions, and the results will be dependent on the skill and experience of the radiographer or radiologist.

Many studies advocate CDS as a useful tool in excluding torsion and confirming other testicular pathology. However, the accuracy of CDS in diagnosing TT can vary significantly in the literature. In a recent retrospective study of 298 patients who underwent CDS followed

by surgery regardless of the result, CDS was shown to have a sensitivity and specificity for TT of 96.8% and 97.9%, respectively.⁴ Positive and negative predictive values were 92.1% and 99.1%, respectively. Other studies have also shown similarly high sensitivity (95.7-100%) and specificity (85.3-100%) for CDS in diagnosing testicular torsion.²⁶⁻²⁸ However, CDS can be inaccurate and false-negatives can occur, especially in cases of early TT, intermittent torsion or incomplete torsion of the spermatic cord. Several studies have demonstrated arterial flow in affected testes, which were subsequently shown to be torsed at surgery.^{29, 30} Thus delaying or avoiding surgery in a patient with torsion and a false-negative US can result in a missed diagnosis of TT, hence many treating clinicians prioritise a strong clinical suspicion over radiological findings in the decision of whether or not to perform scrotal exploration.

HRUS can be used to directly visualise the spermatic cord along its entire length (beginning at the inguinal canal to postero-superior border of testis, and assess for any degree of twisting. In a retrospective study of 44 patients with surgically confirmed testicular torsion, CDS detected absent blood flow in only 31 patients (70% sensitivity), but HRUS detected twisting of the spermatic cord in all 44 cases.³¹ The authors described the appearance as a snail shell-shaped mass, separated from the testis, and characterised by an abrupt change in course, size, shape and echo texture below the point of torsion. In a larger multicentre study of 919 patients with an acute scrotum, HRUS was used to detect spermatic cord torsion in 199 of 208 patients with surgically proven testicular torsion (96% sensitivity), compared with 158 confirmed on CDS (sensitivity 76%).³² Whilst HRUS revealed a linear cord in the remaining 711 patients (99% specificity), the authors did show that increasing reliability correlated with the degree of experience by the radiologist, and that visualisation of a spermatic cord twist is difficult in very high or inguinal testes.

In summary, the role of ultrasound still remains controversial in management of the acute scrotum. Although ultrasound can reliably detect cases of testicular torsion, the practice should be that if torsion is highly suspected on grounds of history and physical examination, there should be no delay to scrotal exploration. Furthermore, if an obvious alternate diagnosis cannot be achieved, scrotal exploration is recommended. However, ultrasound may be useful in confirming an alternate diagnosis when the clinical suspicion of TT is low.

Scintigraphy using technetium 99m pertechnetate can be used to evaluate the acute scrotum and has been shown to have superior sensitivity to CDS for detecting testicular torsion.^{33, 34} Reduced or absent uptake in the suspect testis is seen, with increased uptake seen in conditions such as infection. However, significant disadvantages of this modality include prolonged duration of the investigation compared to ultrasound and lack of availability especially after hours.

More recently, MRI has been advocated in some studies as a suitable and accurate test for diagnosis testicular torsion. Although human investigations are limited, several studies have shown that reduced testicular enhancement on dynamic contrast-enhanced subtraction MRI in combination with decreased signal on T2 and fat-saturated T2-weighted imaging to be a potentially accurate means for diagnosing testicular torsion and haemorrhagic necrosis, especially in equivocal cases.^{35, 36} However, its practice use in mainstream emergency management is likely to be very limited given its associated costs, limited availability and time delay.

Near infrared spectroscopy (NIRS) is a tool that may be of promise. It consists of a handheld device applied to the scrotal skin, is available at the bedside and operates using the same fundamentals as a pulse oximeter. Tissue saturation index of the affected testis is compared to the unaffected side, and a discrepancy is suggestive of torsion. To date, its usage has been limited to case reports and until it has been proven to be of use in well-designed clinical trials must be considered experimental.^{37, 38}

Management

Timing of Scrotal Exploration

TT is a true surgical and time-critical emergency. In patients with testicular pain that is highly suspicious of TT on clinical grounds, urgent exploration should be undertaken with minimal delay, although a risk of “overtreatment” must be accepted. Some series have reported surgical exploration for suspected TT to be unnecessary in up to 28% of cases, but

in 15% TT was found to be the cause of acute scrotal pain where the diagnosis was suspected to be torsion of the appendix testis.³⁹

Scrotal exploration within six hours of presentation is associated with a significantly higher rate of organ salvage. A large retrospective study showed median time between pain onset and presentation to 5 hours for cases managed with orchidopexy (organ salvage and fixation) compared to 2.2 days for those managed with orchidectomy.⁹ After 12 hours of pain, the salvage rate appears to reduce dramatically, but the reported salvage rate varies in the literature. One study of 83 boys with surgically confirmed torsion demonstrated no salvageable testes after 12 hours of pain.¹⁰ Other studies have demonstrated a rate of organ loss of 64%-90%.^{1, 40, 41}

Role of Manual Detorsion

Manual detorsion can lessen the severity of testicular torsion, if tolerated by the patient. The classical description is that detorsion should be performed with medial-to-lateral rotation of the testicle, likened to the action of “opening a book.” If successful, relief from pain is often immediate. As approximately two-thirds of torsions can be in a lateral direction, manual detorsion in a medial direction can be performed if the first attempt is unsuccessful.^{9, 16} However, relief of symptoms from manual detorsion can be misleading, as a degree of torsion may still be present. Residual torsion has been shown to be present in 27-32% of patients in who manual detorsion was attempted prior to surgery.^{9, 10} Thus manual detorsion can decrease the degree of ischaemia, but is not a substitute for exploration and orchidopexy.

Long-Term Follow-up

Testicular atrophy, as evidenced by reduced volume in the affected testis compared to the contralateral testis, has been shown to occur in up to 12% of patients, with increased risk if surgery is delayed for more than six hours after onset of symptoms.⁹ However, parents and patients should be aware of the risk of testicular atrophy despite earlier presentation, as it

can still occur in patients presenting within five hours.¹⁴ Long-term studies have shown that early intervention with surgery in patients with testicular torsion can reduce the risk of poorer semen quality, however, even patients diagnosed early and managed with orchidopexy to the affected testis can develop impaired spermatogenesis.^{42, 43}

If testicular pain occurs in a patient with previous torsion and orchidopexy, he should be treated with the same degree of clinical suspicion for torsion as other patients, as torsion has been shown to occur in patients who have undergone previous fixation.^{44, 45}

Conclusion

The diagnosis and management of acute scrotal pain remains a challenging problem for the emergency department physician. Early diagnosis of true testicular torsion is crucial as timely scrotal exploration may lead to salvage of the affected testis with the best outcomes reserved for those who present within a few hours of the onset of their pain. Clues in the history will often raise or increase suspicion of TT, and several features of physical examination may confirm the diagnosis. Urine dipstick is the standard initial investigation in all patients. Early consultation with specialist referral units is recommended prior to arranging imaging with modalities such as Doppler ultrasonography, as such tests may delay surgery or occasionally falsely exclude the diagnosis of testicular torsion. However, such investigations may be useful in confirming an alternative diagnosis, and may be performed if suspicion of testicular torsion is low. Whilst newer imaging modalities show some diagnostic promise, the cornerstone of diagnosis still remains a clinical assessment. Physicians working in emergency departments should be wary of the initial management of acute scrotal pain even in patients with a previous orchidopexy, as testicular loss as a result of a missed TT is a devastating and avoidable outcome.

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9. Discussion

At the time of this study, few whole of population datasets have been published in regards to prostate (PCa) cancer and renal cell carcinoma (RCC). Although several population-based data sets on both malignancies exist, very few are whole of population. For example, the Surveillance, Epidemiology, and End Results (SEER) Program dataset does not include patients under the age of 65. More importantly, very few large datasets in the literature are comprised of an Australian population. The findings presented in this thesis are unique, as the whole of population nature of the datasets capture practice patterns and outcomes across an entire state, which in our case is Victoria. Patients in our study reside in urban and rural locations, and are from high to low socioeconomic status (SES). Hospitals included vary from high volume tertiary referral centres to smaller regional hospitals, and from both private and public sectors. All surgeons with varying experience and high to low volume practices were included. Therefore, results are less likely to be confounded by institutional referral, treatment or selection biases.

Prostate Cancer

This study reports prostate cancer-specific mortality (PCSM) outcomes on all patients treated by RP in Victoria over a 5 year time frame. The purpose of the Victorian Radical Prostatectomy Register, at the time of its establishment, was to provide a detailed description of the whole of population patient casemix, and to identify correlations between baseline characteristics and outcomes from RP, and to assist in providing future direction as to the most appropriate strategies of PCa detection and treatment in order to optimise outcomes. Given the slow growth of PCa, time to recurrence and time to mortality, a long duration of follow-up is required. Median 10 year follow-up in this study allowed us to comment on PCSM outcomes, in addition to BCR outcomes, which have a variable association with PCSM. Although a significant body of literature exists for PCa outcomes post RP, PCSM data post RP based on 10 year median follow up have not previously been available for a whole of population series. A comparison between our study and previously published large series are shown in table 1.

Table 1. Comparison of Large Series of Radical Prostatectomy with Long-term Follow-up

	<i>Albertsen et al¹</i>	<i>Bill-Axelsson et al²</i>	<i>Stephenson et al³</i>	<i>Porter et al⁴</i>	<i>Han et al⁵</i>	<i>Roehl et al⁶</i>	<i>This Study</i>
<i>Number of patients</i>	596	347	6398	752	2404	3478	2154
<i>Study Design</i>	Population-based	Multi-institutional (randomised trial)	Multi-institutional	Single institution	Single surgeon	Single surgeon	Population-based
<i>Year of RP</i>	1990-1992	1989-1999	1987-2005	1954-1994	1982-1999	1983-2003	1995-2000
<i>Follow-up (months)</i>	159.6 (mean)	153.6 (median)	48 (median)	136.8 (median)	75.6 (mean)	65 (mean)	123.6 (median)
<i>Age (years)</i>	65	65	61 (median)	64.4 (median)	58.2 (mean)	61 (mean)	62 (median)
<i>PSA</i>		13 (mean)	6.3				8
<i>Pathological stage (%)</i>							
≤T2		53.2		54.6	51	68	74.6
T3a							14.9
T3b		46.8		45.3			8.4
T4							2.1
<i>Gleason score</i>							
≤6	61	31.0	64	69	62	63	57.5
7	27	55.2	29	22.6	31	30	35.2
≥8	12	13.4	6	8.4	7	7	7.3
<i>Pos. surgical margin</i>		35		37.6			31.7
<i>Definition of BCR</i>					PSA >0.2ng/mL	PSA >0.2ng/mL	PSA >0.2ng/mL
<i>Rate of BCR</i>				31.4	17	18	31.4
<i>Rate of PCSM</i>	6	14.6	2	6.6		2	3.8

¹Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293:2095-101.

²Bill-Axelsson A, Holmberg L, Fil, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. Journal of the National Cancer Institute 2008;100:1144-54.

³Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. Journal of Clinical Oncology 2009;27:4300-5.

⁴Porter CR, Kodama K, Gibbons RP, et al. 25-year prostate cancer control and survival outcomes: a 40-year radical prostatectomy single institution series. Journal of Urology 2006;176:569-74.

⁵Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urologic Clinics of North America 2001;28:555-65.

⁶Roehl KA, Han M, Ramos CG, Antenor JAV, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. Journal of Urology 2004;172:910-4.

Predictors of Increased Prostate Cancer-Specific Mortality

We observed a strong correlation in this study between PCSM and advanced pT stage of cancer at RP. This may be seen as a justification for PSA based detection of early stage prostate cancer, although the role of population-based PCa screening was not assessed in this study. At the time of this study, all patients underwent digital rectal examination and

transrectal ultrasound-guided biopsies. Newer techniques, such as prostate MRI and transperineal saturation biopsies, were not available at the time of this study. However, it remains clear that the role of early and accurate staging and grading of PCa is paramount, as patients with non organ-confined disease had poorer outcomes. These patients need counselling about their poorer prognosis, and increased potential need for additional treatments, such as adjuvant or salvage radiation therapy and systemic therapy.

Similar observations may be made about Gleason score at RP. Men with higher Gleason grade consistently had lower PCSM, after adjusting for all other variables. It is no surprise that men with Gleason 4+4 and above had the poorest survival. Similarly to men with advanced pT stage, these unfortunate men require counselling about their increased risk of need additional multimodal treatments.

Predictors of Overall Mortality

For overall mortality, both advanced pT stage and higher Gleason score were strong predictors. Analysis of locally advanced (pT4) disease did not reach significance probably due to the low numbers of subjects with this classification in the sample (n=42), and the low number of deaths (n=7). Men who underwent RP at an older age were more likely to experience death from any cause, but age at surgery did not significantly predict PCSM. Biochemical recurrence was significantly associated with a higher hazard of both overall mortality and PCSM. Compared to men residing in urban areas, men from rural areas did not experience increased overall mortality, although a difference was seen in regards to PCSM (discussed later).

Influence of Primary Gleason Pattern on Prostate Cancer-Specific Survival

We found that men with Gleason score 6 disease had very low PCSM following RP. Although this finding is not suggestive of overtreatment of this cohort of men with lower risk disease, it does clearly demonstrate that these men have very good prognosis. More recently

published randomised controlled trials have demonstrated that these men have low PSCM with surveillance, and that RP offers no survival benefit.^{100,101}

We observed 16 PCa-specific deaths in men who had Gleason ≤ 6 disease and 14 deaths in men with Gleason 3+4 = 7 disease. After adjusting for pathological stage, PSCM outcomes for Gleason ≤ 6 and 3+4 tumours did not significantly differ ($p=0.231$). When limited this group to men with PSA ≤ 10 ng/ml and pT1/T2 stage, 17 PCa deaths were observed overall, including 11 and 4 men with Gleason score ≤ 6 and 3+4, respectively. Similarly, no significant difference in PSCM was observed between the two groups ($p=0.649$), although the number of events was small.

The lack of variance in outcomes between Gleason ≤ 6 and Gleason 3+4 PCa in this series where all men were treated by RP is somewhat surprising. One potential explanation may be that although the number of PCa-related deaths in both groups was small, and also that the crude mortality rate from Gleason ≤ 6 disease was higher than expected. As mentioned above, we observed 11 deaths in men with Gleason ≤ 6 , PSA ≤ 10 ng/ml and organ-confined disease. This seem in contrast to large series, including a study published by Stephensen et al showing only 3 deaths in men with Gleason 6 disease out of a multi-institutional cohort of over 12,000 men.¹²¹ This observation may be partly explained by a centralised cancer registry where deaths are coded based on information from death certificates rather than medical records. It is possible, but unlikely, that a greater proportion of deaths may have been over-attributed to PCa. Furthermore, prior to the modification of the Gleason scoring system by the International Society of Urological Pathology in 2005, it is possible that some of the Gleason ≤ 6 tumours may have represented Gleason 7 tumours according to the newer classification, and were therefore more lethal.^{196,197}

We found that the sub-group of men with Gleason 7 PCa had heterogenous outcomes. In these men, 35 deaths were observed, including 14 and 21 in men with Gleason 3+4 and 4+3 disease, respectively. Men with primary pattern 4 had significantly greater cumulative incidence of PSCM compared to men with primary pattern 3. It has been previously shown that primary Gleason pattern 4 in men with Gleason 7 PCa is associated with greater

biochemical recurrence following surgery compared to primary Gleason 3.¹⁹⁸⁻²⁰⁰ Several other authors have published long-term data on men with Gleason 7 disease treated with RP, although the results are somewhat conflicting. Among men with Gleason 3+4 and 4+3 PCa, Eggener et al found no difference in 15-year PCSM in over 20,000 men treated with RP treated at multiple large US institutions.¹⁸⁵ Conversely, Wright et al demonstrated higher rates of BCR and PCSM in men with Gleason 4+3 compared to men with Gleason 3+4 in a population-based cohort of men with Gleason 7 PCa and median 13-year follow-up, although the study was limited to 753 men from a single county under the age of 65 years.²⁰² Stark et al similarly demonstrated a 3-fold increase in PCSM in men with Gleason 4+3 compared to men with Gleason 3+4 with 20-year follow-up, although the analysis did not control for PSA or tumour stage and was limited to 693 RP specimens.²⁰³ Our study of an Australian population of men treated with RP that primary Gleason pattern 4 disease confers significantly greater PCSM compared to primary Gleason pattern 3 disease in men with Gleason sum 7.

Influence of Regional Status of Mortality Outcomes

One of the interesting findings of our study was the effect of regional status on PCSM. The paper demonstrating this finding is included in the appendix of this thesis. Men living in a rural area were observed to have a greater risk of PCSM compared to men living in urban areas. This result persisted after adjustment for patient factors, adverse tumour factors and socioeconomic status. As mentioned above, rural men were not at greater risk of overall mortality, which suggests that rural men were not generally “unhealthier” than urban men. However, one of the study limitations was lack of data on pre-existing comorbid conditions.

Increasing remoteness appeared to amplify this effect, as men from “Outer regional or remote” areas had increased PCSM compared to men from urban areas, whereas men from “Inner regional” areas had similar PCSM.

This disparity between rural and urban men is complex and likely multifactorial. A delay between confirmatory biopsy date and date of RP for rural men was observed. However,

when we assessed lag time as a predictor of PCSM, no association was found ($p>0.20$). Men in urban areas were also significantly more likely to be operated on by an experienced surgeon, defined as one who had contributed more than 50 cases to the registry. Increased surgeon experience, as discussed later, was shown to be associated with reduced PCSM.

A reasonable assumption would be that men from rural areas presented with later stage or more adverse disease at the time of diagnosis. However, this assumption did not prove correct based on our analysis. Baseline characteristics of rural men showed higher median PSA, greater percentage of men with PSA $>10\text{ng/ml}$ and reduced likelihood of treatment in a private hospital compared to urban men. However, pre-operative PSA value has poor correlation with PCSM, and in our study it was not shown to predict overall or PCSM. Although the percentage of Gleason 8-10 tumours in rural men was slightly higher, this has been adjusted for in the multivariable regression analyses. Lastly, the distinction between treatment in private and public health care facilities also did not reach significance in predicting overall or PCSM.

It is reasonable to observe that patients living in rural areas may often have further to travel for post-operative review, thus potentially leading to late diagnosis of recurrence. Furthermore, such men may live in areas with reduced access to services such as radiotherapy or oncology, that may be required following recurrence of PCa. Unfortunately, we cannot comment the use of any adjuvant or salvage therapies. Interestingly, we found that rural men were followed less closely with repeat PSA measurements and that both the overall number and time between tests differ significantly. Of the 51 men who had only one recorded follow-up PSA, proportionately more of these were rural men. As there is no central database for biochemical testing data in Victoria, it is possible that full follow-up information on PSA testing, may be differentially incomplete for rural men due to logistical problems in obtaining the data.

Other potential explanations may exist to explain this disparity in PCSM outcomes between rural and urban men. Compared to surveillance, RP offers superior survival outcomes, especially in men with more adverse disease.^{100,190} However, Australian rural patients have

been shown to have comparatively fewer RPs and reduced frequency of PSA screening compared to urban men.^{48,49} Furthermore, men in Australia with low socioeconomic status have been shown to be less likely to receive RP as a treatment option, and Australian rural men are over-represented in the lowest quintiles of national SES.^{47,249}

Effect of Surgeon Experience on Prostate Cancer-Specific Mortality

An interesting and surprising finding of the study was the effect of involvement of a trainee surgeon at RP, which was associated with worse PCSM ($p=0.031$). Furthermore, we noted a relationship between surgeon RP volume and PCSM. The publication demonstrating these findings can be found in the appendix of this thesis. The negative impact of the involvement of a trainee surgeon at time RP on PCSM was independent of cancer stage, margin status and Gleason score. However, we were not able to comment on whether or not the trainee surgeon was the primary operator. Nonetheless, the finding does raise some concern, and suggests that the presence of a trainee surgeon may result in inferior surgical outcomes, perhaps due to lower surgeon experience and skill.

The impact upon PCSM noted for patients who had their RP performed by lower vs higher volume surgeons also is noteworthy. Using a cut off of 40 cases in total or 8 per year during the 5 year period, a lower risk ($p=0.025$) of PCSM was observed for higher volume surgeons, which demonstrates the positive impact of skill and expertise on long-term PCa outcomes. It is noteworthy, however, that in comparison to contemporary urological practices, most surgeons included in this study performed relatively low numbers overall as RP was still in the process of being popularized. Given the potential role of experience and skill in determining mortality outcomes in PCa, it seems appropriate that urologist subspecialisation into areas such as PCa may be required to promote better outcomes for patients.

Influence of Time to Biochemical Recurrence on Prostate Cancer Mortality

We found that the association between BCR and PCSM depended critically on the interval to BCR from surgery. To our knowledge, this is the first study evaluating the temporal relationship between BCR and PCSM in a whole of population-based cohort outside of the United States.

Interval to BCR had a time-varying effect on PCSM, which remained evident on Poisson regression analysis after adjusting for other known adverse prognosticators in our models, such as Gleason score, tumor stage and age. In this particular analysis, we did not include PSA in our models, as we had previously found pre-operative PSA to have no association with PCSM. However, PSA has been shown in other studies to be predictor of PCSM.^{106,121} Although rapid PSADT can predict PCSM, we chose to observe the time-varying influence of PSA recurrence on survival among men with different risk profiles.

Men with adverse pathological findings and a high risk profile, such as high Gleason score and extra-prostatic disease, who experienced BCR shortly after surgery had a substantially increased mortality rate. Conversely, high risk men experiencing BCR after a longer interval had a low mortality rate. As the clinical course of men who experience BCR varies, it is important to identify men who are at greatest quantifiable risk of PCSM. Therefore high risk men with early cancer recurrence are most likely to benefit from the early institution of salvage radiotherapy or other additional treatments.

Men with a low risk profile were not at any substantial risk of death regardless of when their BCR occurred. This finding is consistent with other large series, where men with Gleason ≤ 6 and organ-confined tumours at time of RP have very low mortality after 15 or more years of follow-up.^{121,185} Consequently, this subgroup of men may be counseled regarding their favorable long-term prognosis in the event of disease recurrence, and salvage or systemic therapies may not be warranted in many cases.

Other previously published studies have evaluated interval from surgery to first BCR is frequently as a categorical variable (for example, less than or greater than three years), which is less useful clinically as the timing of BCR after surgery is very variable. Furthermore, no consensus exists on the definition of either early or late BCR, and current available evidence on the influence of interval to BCR following surgery on PCSM appears mixed.^{108-113,250} Freedland et al found shorter interval to BCR (<3 years) following RP was associated with increased risk of PCSM, after adjusting for PSADT and high Gleason score ≥ 8 .¹¹² However, other studies have not shown shorter interval to BCR to influence PCSM.^{108,113}

The majority of cases of BCR in our study occurred within 5 years of surgery. However, we observed that up to 2% of men who experienced BCR have a PSA progression-free period of 10 years. These findings were similar to a study by Loeb et al, where late recurrences occurred in 4.9% and 1.5% of men after 10- and 15-years of post-surgery follow-up, respectively.¹¹⁵ Current guidelines recommend life-long annual PSA testing after a PSA progression-free period of 3 to 5 years, and our study supports these recommendations.^{50,251} However, it is clear that risk stratification is required.

Given men with low risk disease have low PCSM, even with early BCR, men without PSA progression after a certain number of years may benefit from less intense surveillance (for example, PSA testing every 2 years after BCR-free period of 3-5 years), which has been supported previously.¹¹⁴⁻¹¹⁶ However, it is clear that men with high risk disease need life-long annual surveillance.

Impact of Voiding Symptoms on Prostate Cancer Mortality

Presentation in men with PCa is usually asymptomatic and based on serum PSA, but some men presenting with lower urinary tract symptoms (LUTS) may harbour an aggressive malignancy. In this study, we reported a difference in survival between men who were diagnosed with PCa following PSA testing offered by their family doctor or urologist,

compared to men who had diagnosis of PCa made following a presentation with symptoms of urinary obstruction.

Symptomatic presentation was associated with older age and higher PSA, grade and stage, but even after adjustment for these parameters, the association between symptomatic presentation and PCSM remained. In our cohort, men with symptomatic presentation had over 1.5 times greater risk dying from PCa during their follow-up. This is supported by data from The Swedish National Prostate Cancer Register, which has shown that most men with PCa diagnosed after a health check-up, compared to men presenting with LUTS, have localised tumours of low or intermediate risk.¹⁹⁵ Similarly, Lee et al found that men with pre-operative LUTS as demonstrated by International Prostate Symptoms Score > 8 had a higher incidence of pathologic pT3a disease at time of RP compared to men with no LUTS.¹⁹⁴

One potential explanation for this finding is the presence of higher volume disease in men with symptomatic presentation. Disease volume may be inferred by number of positive cores involved on prostate biopsy and the percentage of core involvement, or measured when RP specimens are analysed histologically. Unfortunately, we were not able to comment on these variables as they are not routinely captured in cancer registries. Nonetheless, our study suggests that men who present with voiding symptoms should be counseled about the pros and cons of PSA testing, which should be done as part of their work-up of LUTS. Some of these men may have co-existing high grade PCa, and delayed diagnosis may result in adverse survival outcomes.

Limitations

One of the limitations of a centrally based data registry is lack of access to hospital medical records, and the reliance on the accuracy of death certificates for causes of death. Although mandatory notifications of new cancer diagnoses and deaths reduces loss to follow-up, certain datasets may be incomplete due to lack of centralisation of medical records, treatments, and biochemical and radiological testing. Therefore, we cannot report on non-mortality outcomes, such as the development of metastases. We also cannot comment on

the use of any salvage or adjuvant treatments, such as radiotherapy or use of androgen deprivation therapy.

Although quality of life and functional outcomes are important in the treatment of PCa, capturing such data would have required use of validated instruments administered in a standardised fashion, and this was felt to be beyond the funding and administrative capacity of this project at inception. A further limitation of our study is the method of capturing SES. The SEIFA metric uses postcodes to estimate SES, which do not account for the heterogeneity of the population within a postcode area. As a consequence there is also a correlation between SEIFA quintile and rural status.

Despite these limitations, the data captured in this study represented statewide whole-of-population PCa surgical treatment and outcomes, providing a more realistic measure of service provision to the general population compared to high volume centres in the US and Europe. Moreover, we were able to comment on long-term survival outcomes in an Australian cohort of men, who have unique sociodemographic patterns and profiles compared to men in other developed countries.

Renal Cell Carcinoma

This whole of population study of all renal cell carcinomas (RCCs) diagnosed in 2009 was conceived with a view to assess the patterns of care of this urological malignancy across the state of Victoria. We sought to evaluate the contemporary management of RCC, as such data in an Australian population was sorely lacking at the time of this study. RCC is a relatively common urological malignancy, representing the second most common urological malignancy following prostate cancer.¹⁸⁷ Radical nephrectomy (RN) is a commonly performed surgical treatment option for organ-confined RCC, but may represent overtreatment of some tumours that are amenable to partial nephrectomy (PN). Our study revealed several interesting findings.

Mode of Presentation of Renal Cell Carcinoma

We found that most cases of RCC at diagnosis were asymptomatic at presentation (60%) and were early stage, which can be attributed to the widespread use of abdominal imaging. This has been previously demonstrated in large population-based studies of patients from the US.^{13,130,132} We can confirm similar findings in an Australian population.

Rarely, in our study, did patients present with the 'classic triad' of haematuria, flank pain and a palpable abdominal mass. Only three out of 499 cases presented with this classic triad, which has previously been reported to occur in up to 10% of cases. However, nearly one-third of patients had at least one symptom from the classic triad. Approximately 17% of patients also presented with metastatic disease.

Given that our study took place over a 12 month period, we cannot comment on stage migration or changes in tumour size at presentation over a given period of time. However, several large population-based studies from the US have confirmed migration towards smaller tumour size at diagnosis. Using the SEER database, Nguyen et al analysed trends in presentation of RCC in 29,053 patients diagnosed with a primary renal cancer between 1988 and 2002. Throughout this period, mean tumour size at diagnosis decreased from 66.8mm

in 1988 to 58.6mm in 2002, while the age-adjusted incidence of renal cancer increased from 8.6 to 11.2 cases per 100,000 individuals.¹³ Cooperberg et al performed an analysis of 104 150 patients diagnosed with stage I RCC between 1993 and 2004 from the US National Cancer Data Base and found an overall reduction in mean tumour size from 4.1cm to 3.6cm during the study period. A statistically significant increase in the proportion of renal masses 3.0cm or less (32.5% in 1993 vs 43.4% in 2004) was noted, including a corresponding increase in tumours less than 2.0cm (24.1% in 1993 vs 29.4% in 2004).¹³²

Data assessing trends of RCC diagnosis over time in an Australian population are very limited. An Australian study of Doeuk et al, unlike the aforementioned studies, failed to demonstrate any stage migration of RCC due to increased use of abdominal imaging.¹³⁵ The authors retrospectively analysed 547 nephrectomies performed in several private and public western Sydney hospitals between 1993 and 2007 and found pathological stage II disease decreased from 18.1% to 11.1%, but stage III disease showed an increase from 13.9% to 21.5% over that time period. The proportion of stage I and IV disease remained relatively the same.

Patterns of Surgical Management

In our study, as most cases of RCC diagnosed were confined to the kidney, the majority of cases were unsurprisingly managed with surgery (83% overall). Most of these cases were performed in a public hospital setting. Although most RCC tumours were small at diagnosis, RN (either open or laparoscopic) was the most common treatment, representing 81% of all surgical procedures performed. Laparoscopic RN was the most common procedure overall, representing 61% of all cases of surgery. The significance of this finding will be discussed later.

Historically, RN has been considered the standard treatment for localised RCC. However, an increasing body of literature have offered support to nephron-preserving surgery through PN, citing superior preservation of renal function and equivalence of oncological control, at least in the short to intermediate term.^{139,150,153,155,252,253} Despite a single randomised

control trial showing a slight advantage to RN over PN with regards to overall survival, such mounting evidence of PN has led to recommendations by various international guidelines for PN to be standard of care for T1a RCC, and for some T1b RCC where technically feasible.^{163,164,252}

Underutilisation of Partial Nephrectomy for pT1a Tumours

A notable finding in the current study was the limited use of PN in the surgical management of pT1a RCC. We found that approximately 40% of cases of pT1a RCC were managed with PN. Whilst we cannot comment on factors that may have influenced surgical approach, such as tumour factors (location, technical feasibility for PN) or patient factors (preference, comorbidity), our findings suggests significant underutilisation of PN as a surgical approach for small and early stage RCC. Several international guidelines, including those published by the American Urological Association and the European Urological Association, strongly recommend that PN be offered to all Ta tumours that are amenable to PN.^{163,164}

The ideal rate of PN for pT1a tumours remains unclear. Not all tumours less than 4cm will be suitable for PN, especially tumours that may be centrally located, close to hilar structures or invading into the collecting system. Furthermore, comparisons between population-based data and high volume institutional series is not appropriate. High volume tertiary or quaternary centres with highly trained surgeons and excellent ancillary services can achieve PN rates of up to 90% for T1a tumours.¹⁷¹ However, it remains clear that there is a need to improve rates of nephron-sparing surgery in Victoria.

Interestingly, utilisation of PN for pT1a tumours in this study appear similar to those reported in US population-based data, although some of these studies have used less contemporary population samples. Yabroff et al evaluated surgical management and use of systemic treatments in a national population-based sample of 1,263 patients with newly diagnosed RCC in 2004. Partial nephrectomy was performed in 201 (18.3%) of patients, with 44.5% of patients with tumours <4cm receiving RN, a figure slightly better than observed in our population.¹⁶⁵ Whilst more recent US data from SEER and the National Cancer Database

have shown increasing utilisation of nephron-sparing surgery with PN and ablative techniques, significant underutilisation still exists according to the investigators.^{166,254}

The development of laparoscopic surgery in urology significantly changed the landscape of surgical management of RCC. Laparoscopy offers reduced blood loss and analgesic requirement, rapid convalescence, improved cosmesis and, importantly, equivalent cancer control when laparoscopic RN is compared to open RN.^{137,255} As laparoscopic RN became common place, surgeons with increasing skill transferred open PN skills to laparoscopy. However, laparoscopic PN remains a technically difficult and challenging procedure, limiting PN to an open approach for most urologists. Therefore, the widespread adoption of PN as definitive surgical management of small renal masses has been impacted by the widespread uptake of laparoscopic RN. This is further compounded by lack of randomised prospective data demonstrating superior survival with PN. In this study, approximately half of pT_a tumours were treated with laparoscopic RN, highlighting its popularity even for small tumours.

Recently, van Poppel et al published the only randomised controlled trial comparing RN to PN. After 9 year follow-up, the study failed to demonstrate equivalent overall mortality on intention to treat analysis, and in fact demonstrated RN to be superior.²⁵² However, when tumours were limited to pathologically proven RCC <5cm, this difference was no longer seen, suggesting that better patient and tumour selection was required.

Despite the lack of prospective data comparing PN and RN, there is a large body of retrospective data supporting PN with regards to preservation of renal function and superior survival outcomes. Progression to CKD following RN may have significant adverse health outcomes. Weight et al assessed compared overall survival, cancer-specific survival and cardiac specific survival in patients undergoing partial or radical nephrectomy for cT1b tumour. The study included patients treated with PN (n=524) or RN (n=480) between 1999 and 2006 at Cleveland Clinic. Cancer-specific survival was equivalent between the two groups at 5 years for patients with malignant tumours. Patients who underwent RN had significant deterioration in renal function compared to patients who had PN, and post-

operative renal insufficiency was a significant independent predictor of overall and cardiovascular specific survival. The average excess loss of renal function observed with RN was associated with a 25% increased risk of cardiac death and 17% increased risk of death from any cause.

These findings were supported by Huang et al who analysed 2,991 patients from the SEER database treated with either PN (n=556) or RN (n=2,547) between 1995 and 2002 for tumours 4cm or less. On Kaplan-Meier analysis, the 3 and 5-year probability of freedom from a CV event following PN was 86% and 82%, respectively, compared to 82% and 75% following RN.¹⁵⁵ After adjusting for preoperative demographic and comorbid variables, RN was associated with a 1.4 times greater risk of overall mortality and a 1.4 times greater number of cardiovascular events after surgery.

In a landmark study, Go et al demonstrated an association between worsening grades of CKD and increasing risk of deaths, cardiovascular events and hospitalisation. Using a large community based cohort of over 1.1 million patients, the authors demonstrated that risk of overall death increased inversely with estimated GFR levels below 60ml/min/1.73m², with the highest risk seen in patients with estimated GFR below 15. In this group, the risk of death was nearly six times greater than in patients with normal renal function.¹⁵² Similarly, patients with declining renal function were more likely to experience cardiovascular events and hospitalisation. Although this was not a study of PN and RN, these findings emphasise the importance of maintaining adequate renal function following surgery.

In addition to adverse health outcomes, CKD is a significant contributor to healthcare related costs. Data from the US Renal Data System demonstrated that overall Medicare expenditure for CKD (excluding end-stage kidney disease) reached \$33.8 billion in 2009.²⁵⁶ This figure was shown to have increased to \$50 billion in 2013.²⁵⁷ The costs associated with CKD are also likely to continue to increase, as evidenced by the proportion of Medicare expenditure towards CKD increasing from 5.8% in 2000 to 15.9% in 2009.²⁵⁶

However, patients with CKD following surgery are a heterogeneous group, and those with surgically induced CKD in the absence of pre-existing medical renal disease may have better survival outcomes. In a large retrospective analysis, Lane et al assessed the relationship between aetiology of post-operative CKD (estimated GFR < 60ml/min/1.73m²) and overall survival. The authors noted that patients with pre-existing CKD from conditions such as hypertension, diabetes and cardiac disease were more likely to have lower overall survival compared to patients with CKD resulting purely from either PN or RN.¹⁵⁹ Functional decline and mortality was also greatest in patients with new baseline GFR < 45, and patients without medical renal diseases were less likely to reach this threshold, regardless of surgical approach. Thus, the presence of medical renal diseases was shown to influence survival more than the amount of nephrons preserved after surgery, provided that patients maintain an estimated GFR > 45.

When considering surgical approaches for renal masses, clinicians must balance the risk of CKD following RN against the risks and potential complications of PN. Prevention of later stages of CKD may reduce hospital admissions, cardiovascular morbidity and overall mortality. However, patients without medical renal disease and normal renal function who undergo renal surgery are less likely to experience these adverse health outcomes regardless of the surgical approach, and this needs to be considered when considering PN for large and complex tumours.

Effect of Regional Residency on Surgical Patterns of Care

Our study set out to evaluate patterns of care of RCC across Victoria. In addition to general surgical and medical management patterns of RCCs, we sought to evaluate any potential differences using sociodemographic data. In our multivariate analysis, we included several potential predictors of treatment, including age, Charlson comorbidity index, residential location (regional or metropolitan), socioeconomic status and hospital type (public or private). Our study revealed several interesting findings with regard to residential location.

One major significant finding was that residential location was a significant predictor of treatment, as cases residing in regional/rural areas were less likely to be treated by PN. PN for stage I RCC (regardless of operative approach) was less common for cases from regional/rural areas (16.2%) than those from metropolitan regions (31.3%), and this difference was statistically significant in multivariate analyses (OR=0.39, 95% CI 0.18-0.85). When we evaluated the subgroup of pT1a tumours, the odds of cases residing in regional/rural areas receiving PN were about 50% less than the corresponding odds for metropolitan cases (OR=0.43, 95% CI 0.18-1.02). However, residential location was not associated with treatment for Stage I pT1b tumours.

Our findings raise some concern that patients residing in rural areas are less likely to receive nephron-sparing surgery, thus increasing their risk of CKD and its associated adverse health outcomes. These findings are consistent with US based studies, which have confirmed that PN is more commonly performed in teaching-based tertiary referral centres with high volume surgeons, given the increased difficulty associated with the procedure, and the potential need for ancillary services such as interventional radiology and intensive care.^{169,170,258} Our findings may lend support to centralisation of complex urological surgery, as surgeons may prefer to avoid complex renal surgery in regional centres where there may be a lack of ancillary and supportive services.

Whilst laparoscopic surgery was commonly employed in the treatment of Stage I RCC, we found that the uptake of this minimally invasive approach was not even across Victoria. For such tumours, cases from regional areas were twice as likely to receive open RN compared to metropolitan cases. This disparity may be explained by several factors, such as selective referral to metropolitan hospitals for laparoscopic surgery, individual surgeon skill and experience, or accessibility to the disposable equipment required for laparoscopic surgery. Unfortunately, we cannot comment about these potential confounders in this study. However, it is likely that laparoscopic surgery will become common place across Victoria with increasing training and education of surgeons with time, and further studies are required to confirm this.

Whilst laparoscopic PN has similar efficacy to open PN with regards to oncological control, it is a technically challenging procedure most often performed in tertiary hospitals by experienced high-volume laparoscopic surgeons.^{140,141} In our study, we observed that all cases of laparoscopic PNs for pT1a tumours were performed in metropolitan hospitals. This disparity may become less significant with time with increased training and provision of resources to allow more complex surgery to be performed in more regional settings.

Underutilisation of Partial Nephrectomy for Small Renal Masses Less than 3cm

In our study, we also assessed utilisation of PN in the subgroup of RCCs less than 3cm (performed as a separate analysis, data not included in the published study). As pT1a tumours may include tumours up to 4cm in size, such tumours can be typically less suitable for PN compared to tumours up to 3cm in size, as the volume difference can be more than double. Although we did not publish these findings in a manuscript, this data was presented at the annual Urological Society of Australia and New Zealand scientific meeting in 2013, which was held in Melbourne.²⁵⁹

In our cohort, 120 renal malignancies met the criteria of a localised small renal tumor (≤ 3 cm) based on size at pathology review. Overall, only 49% of these received PN, of which half (49%) were performed laparoscopically. Thus the remainder of tumours ≤ 3 cm were treated with RN, suggesting significant overtreatment of these small tumours, even accounting for an expected small proportion of these tumours to be not suitable for PN (based on location, endophytic nature etc).

This data does raise some significant concern, especially as cancer registries do not capture nephrectomies performed for benign tumours. Large studies of nephrectomies performed for renal tumours have demonstrated that up to 20% of small renal masses are in fact benign.^{260,261} Therefore, our study may have underestimated the degree of overtreatment of small renal masses with RN, as all RNs performed for histologically confirmed benign renal tumours during the study period have not been captured.

As our dataset contains only cancers identified from centralised registry notification, we cannot comment on the use of active surveillance or watchful waiting of small renal masses during our study period, which did not undergo biopsy. Therefore the rate of surveillance in our population remains unknown, and it is possible that small renal masses in our study managed even with PN were overtreated. Active surveillance is a safe and reasonable option for patients with small renal masses who chose not to have surgery, or may not be fit for surgery.^{164,262,263} Prospective studies with longer-term follow-up have shown very low rates of growth, development of metastases and equivalent cancer-related death compared to intervention.^{264,265} Furthermore, delayed intervention for small renal masses that have undergone a period of surveillance are usually amenable to nephron-sparing surgical techniques.²⁶⁶

During our study period, robotic PN was in its infancy across the world and not available in Australia, but in the last decade there has been rapid dissemination and uptake of this surgical technique for the treatment of RCC. Its popularity and availability in large tertiary centres has potentially seen the pendulum swing in the opposite direction, such that small renal masses may be overtreated in some centres. Shah et al evaluated the contemporary treatment of small renal masses (<4cm) in the United States between 2010 and 2014 using the National Cancer Database. The authors noted that the utilisation of robotic PN far outpaced the utilisation of active surveillance during the study period, as evidenced by an increase of 82% for robotic PN compared to 25% for active surveillance.²⁶⁷ Furthermore, even in the subgroup of patients aged > 75 years and multiple comorbidities, robotic PN utilisation increased 92-98%, which raises concern about potential overtreatment. In this subgroup of elderly patients, several previous studies have shown no survival benefit of PN over RN, and active surveillance having similar long-term survival to PN^{268,269}. Whether or not such trends are currently being seen in an Australian population warrants further investigation.

Treatment Patterns in Public vs Private Hospitals

In our further analysis of the subgroup of RCCs ≤ 3 cm, we performed a multivariate analysis on factors that may predict use of PN. In our analysis, we included age, Charlson comorbidity index, location of treatment (metropolitan or regional) and hospital type (public or private). As above, we did not publish this data in a manuscript, but our findings were presented at the Urological Society of Australia and New Zealand scientific meeting in 2013.²⁵⁹

We found on multivariate analysis that age, location of treatment (metropolitan or regional) and comorbidity were not associated type of nephrectomy. However, small tumours treated in a public hospital setting were significantly more likely to receive PN (OR 2.18, 95% CI 1.01-4.70, $p=0.047$), suggesting that uninsured patients were possibly more likely to receive evidence- and guideline-based treatment compared to insured patients.

As our study demonstrates a disparity in treatment patterns of small renal masses between patients undergoing surgery at a public vs private hospital, this finding raises concern about the possibility that in addition to the financial cost of surgery in private hospital, there may be a cost of renal function and its associated adverse health outcomes as discussed above. Such patients, despite paying more for their healthcare, may not be receiving optimal treatment.

When we assessed all pT1 tumours (i.e. tumours ≤ 7 cm), we similarly found that treatment in a public hospital was associated with increased likelihood of PN after controlling for comorbidity and tumor size (OR 2.24, 95% CI 1.19-4.24, $p=0.01$). However, whilst there may be further underutilisation of PN for tumours up to 7cm, the extent is likely to be less severe than for tumours ≤ 3 cm, as larger tumours are less likely to be amenable to PN. Unfortunately, we cannot account for suitability for PN in this group of potentially difficult tumours, as data such as tumour location, endophytic nature, collecting system involvement and proximity to hilar structures is not generally captured in cancer registries.

Management of Patients Diagnosed with Advanced Renal Cell Carcinoma

In addition to assessing patterns of care in patients with localised disease, we evaluated management of RCC in patients with advanced disease. Some interesting findings were observed in our population of patients with RCC.

Half of the cases diagnosed with metastatic disease in this present study received systemic therapy. However, regional cases were significantly less likely to receive this therapy than those from metropolitan areas (OR=0.06, 95% CI 0.01-0.41). Sunitinib, a first generation tyrosine kinase inhibitor, was the most commonly used systemic therapy, being utilised in 74% of cases. A disparity in the utilisation of radiotherapy between regional and urban cases was not seen, but use of radiotherapy in this setting was generally not common.

These findings raise some concern regarding access of regional patients to systemic therapies in the setting of metastatic RCC. However, the use of systemic therapies for RCC is complex and we cannot comment on individual clinician treatment decisions and case suitability for these systemic treatments. Furthermore, Sunitinib was only listed for subsidy on the Australian Pharmaceutical Benefits Scheme in May 2009, thus potentially limiting its widespread use prior to this date.²⁷⁰ The landscape of systemic therapy for metastatic RCC has changed dramatically in the last decade, with the introduction of numerous molecular targeted therapies, including second-generation tyrosine kinase inhibitors and checkpoint inhibitors.²⁶³ Further studies are required to ensure that these newer agents are readily accessible to patients living in more regional centres.

We also evaluated multidisciplinary management of RCC in Victoria. Documented multidisciplinary team meeting review was noted in 124 (24.8%) of cases and was not associated with residential location or tumour stage. Interestingly, we found less than 3% of subjects with RCC diagnosed in 2009 were involved in a clinical study of any type, including sponsored trials. A similarly low rate of 2% was also observed by Yabroff et al from SEER data.¹⁶⁵ Several barriers to referral to clinical trials may have been present, including the

general low rates of discussion at multidisciplinary team meetings, lack of clinician access to clinical trials, and distance of regional cases to tertiary centres participating in trials. Whilst efforts should be made wherever possible to promote participation in clinical trials, the significance of this finding is limited as we cannot comment on individual case eligibility or the number of clinical RCC trials open for recruiting at the time of this study.

Limitations

Some of our study limitations generally reflect the weaknesses associated with central registry-based data. We did not have access to detailed medical records, and therefore we cannot comment about suitability of individual cases for different surgical approaches, discussions between clinicians and patients about treatment decisions and surgeon experience. The central registry is also not notified about benign cases of renal tumours that have either been biopsied or treated with surgery, and therefore we could not truly evaluate the management of all renal masses, but only all cases of confirmed RCC. Although the data in this study are contemporary, we cannot comment about other outcomes of RCC, such as mortality, and therefore assess for any other disparities that may exist between subgroups of Victorian cases.

Given the relatively short accrual period of 12 months, overall study numbers were low and the study was potentially underpowered to detect anything but large differences. Our use of pathological T stage may have over-estimated the number of small malignant tumours due to post-surgery tumour size reduction. However, as a similar proportion of cases were found to have RN when clinical T stage (based on imaging alone) was analysed, the use of pathological T stage does not appear to have overestimated usage of RN for small renal tumours (analyses not shown).

Whilst the dataset does not represent the entire Australian population, it reflects contemporary treatment patterns in a significant proportion of the Australian population. Our observations from this statewide whole-of-population dataset reflect contemporary patterns of care across Victoria, accounting for differing practice patterns by clinicians and

treatment centres, limiting potential biases seen in institutional or sampled population studies locally or internationally.

10. Summary

Data from our whole-of-population registry of RP has shown several interesting findings. We emphasise the importance of primary Gleason pattern in predicting PCSM, as men with primary pattern 4 disease are at greater risk of PCa death and should therefore be appropriately counseled about their prognosis, treatment and follow-up options. Furthermore, men with high-risk disease should undergo frequent initial PSA surveillance, as early recurrence in these men is associated with poorer prognosis compared to men with late recurrence, and early institution of salvage radiotherapy may provide a survival benefit. In addition to adverse pathology at time of RP, rural residency and surgeon inexperience a confer a greater risk of PCSM, and measures to reduce this disparity are required, such as potential centralisation of RP or improvements in surgical training. Men who present with voiding symptoms should also be counseled about PSA testing, as some of these men will harbour clinically significant and aggressive PCa.

Contemporary whole-of-population data of RCC show that the most common treatment for localised renal cell carcinoma is RN, including tumours that may have been amenable to nephron-preserving surgical approaches. We observed potential underutilisation of PN for tumours less than 4cm, but also concerning for small tumours less than 3cm. Laparoscopic RN compared to PN, either open or laparoscopic, was the dominant surgical procedure for small RCCs, and its potential overuse in private hospitals raises some concerns about the delivery of evidence- and guideline-based care. Although patients from regional areas were less likely to undergo laparoscopic surgery for RCC, they were also less likely to receive PN for small RCCs. Underutilisation of PN may unnecessarily expose patients with small renal masses to the potential morbidity and treatment costs associated with chronic kidney disease. Further work is needed to better understand the reasons for these differences, which are likely to be multifactorial and influenced by patient and surgeon preferences for care. Our study should help clinicians develop and implement strategies to improve the management of RCC in Victoria.

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12. Appendices

a. Predictors of Prostate Cancer Specific Mortality after Radical Prostatectomy: 10 year oncologic outcomes from the Victorian Radical Prostatectomy Registry

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Abstract

Purpose: To identify the ability of multiple variables to predict prostate cancer specific mortality (PCSM) in a whole of population series of all radical prostatectomies (RP) performed in Victoria, Australia.

Materials & Methods: A total of 2,154 RPs were performed in Victoria between July 1995 and December 2000. Subjects without follow up data, Gleason grade, pathological stage were excluded as were those who had pT4 disease or received neoadjuvant treatment. 1,967 cases (91.3% of total) met the inclusion criteria for this study. Tumour characteristics were collated via a central registry. We used competing hazards regression models to investigate associations.

Results: At median follow up of 10.3 years pT stage of radical prostatectomy ($p < 0.001$) and high Gleason score of the RP specimen ($p < 0.001$ for ≥ 8 [Subhazard ratio (SHR) 11.19] and $4+3=7$ [SHR 7.10]) compared with Gleason score 6 disease were strong predictors of progression to PCSM. Gleason score $3+4=7$ was not at this time a significant predictor of PCSM ($p=0.08$, SHR 1.84). Predictors of PCSM, independent of stage and grade, included rural residency ($p=.003$), primary surgeon contributing less than 40 cases (low-volume) to the VRPR ($p=.025$) and the involvement of a trainee surgeon in the operation ($p=.031$).

Conclusion: The significant prediction of PCSM by pT cancer stage, Gleason score and primary Gleason pattern at RP in this whole of population study suggests a need to avoid understaging/grading in the process of cancer diagnosis and active surveillance protocols. Multi-modality therapy is likely to have a greater impact on PCSM in higher stage and Gleason grade disease. Identification of increased PCSM with rural residency and with involvement of a trainee urologist, and reduction in PCSM with higher surgeon volume all suggest potential for improved PC outcomes to be achieved with changes to surgical training and service delivery.

Introduction

Since the introduction of prostate specific antigen (PSA) testing in the early 1990s, radical prostatectomy (RP) has been the dominant procedure in urologic practice for the management of organ confined prostate cancer (PC) for men under 70 years of age. Although the number of RP performed has reduced over the past 5 years subsequent to the introduction of active surveillance protocols, this form of intervention remains central to the management of prostate cancer [1].

With the more widespread introduction of RP to standard urologic practice in the early 1990's the Urological Committee of the Victorian Cooperative Oncology Group initiated the prospective collection of data on all RPs performed in Victoria in order to ascertain in a whole of population setting the outcomes from the use of RP. As a consequence, the Victorian Radical Prostatectomy Registry (RPR) was established within the Victorian Cancer Registry (VCR), to which there is mandatory notification from all hospitals and pathology laboratories by law of all human malignancies diagnosed in the state of Victoria, Australia. The VCR is managed by Cancer Council Victoria, and the establishment of the RPR was approved by The Cancer Council of Victoria's Human Research Ethics Committee.

The purpose of this study was to determine outcomes following treatment by radical prostatectomy in a whole of population cohort, and to identify factors that may contribute to reduced prostate cancer specific mortality for patients being treated by radical prostatectomy.

Methods

Patient Population:

All cases of prostate adenocarcinoma diagnosed in Victoria over the period 1995 – 2000 were identified via mandatory notification by hospitals and pathologists to the VCR. All radical prostatectomies performed in the period from July 1995 to December 2000 were identified and followed up with the assistance of all urologists practising in the state of Victoria over that time. All patients were treated via an open retroperitoneal approach as laparoscopic and robotic technology for this procedure had not been introduced at that time. Patients who had undergone total prostatectomy as part of a cystoprostatectomy for bladder cancer were excluded from the study.

Registry Data-Collection:

All notifications of prostate cancer by hospitals and pathologists were fast-tracked within the VCR to minimise the time lag between treatment and registration. Once the data were coded and registered on the cancer registry, if a radical prostatectomy had been performed a VRPR registration form was sent to the treating urologist for completion. For 5 successive years, on the anniversary of each registration, a follow-up form was sent to the treating urologist for completion. A health information manager was provided as required to visit the practices of participating urologists to assist with completing registration and follow-up forms, and to assist with data collection beyond 5 years of follow-up. If a patient ceased being followed post surgery by their primary treating urologist the doctor responsible for ongoing care was identified and requests for follow up information were made. Information on deaths was obtained from the VCR that receives notifications of all deaths in Victoria, and which is matched against the National Death Index on regular basis to capture deaths that occur outside of the state. Prostate cancer specific mortality (PCSM) was recorded where prostate cancer was noted as the primary cause of death.

For each registrant the data held by the VCR included demographic details as well as data on the individual cancer coded to ICDO-2. This included Gleason scores for both the biopsy and

resection specimens, margin positivity status and TNM staging. The registration form captured additional information on mode of presentation, health system used for treatment (i.e. private or public), use of neo-adjuvant therapy; clinical stage; PSA test method and level at biopsy; biopsy method; operation type; surgeon ; laboratory that analysed the prostatectomy specimen and preoperative level of sexual function.

Patient Follow-up Data

The follow up form captured information relevant to the status of PC after initial surgery, including most recent PSA level and test method out to 13.5 years post surgery, adjuvant therapy, level of sexual function and continence post surgery and any further surgical intervention required (bladder neck incision, artificial sphincter, etc). Additional follow up included record linkage to Victorian pathology laboratories and radiotherapy facilities in order to collect full PSA testing histories (to identify time of any PSA failure) and salvage radiotherapy, respectively.

Exclusion criteria

Men without follow-up data were excluded. Subjects without a recorded pathological Gleason grade or T-stage were also excluded as were 50 men who received neoadjuvant therapy. Men with pT4 disease were also excluded as their postoperative treatment profile was sufficiently different from men with pT2-pT3 disease to preclude a reasonable comparison.

Socio-economic and Geographic Data:

In order to classify individual subjects with respect to their socioeconomic status (SES), their usual residential address at time of surgery was coded to a geographic area indicator that was then used to assign the Index of Relative Disadvantage, a Socio-Economic Index For Area (SEIFA) – derived from five yearly national census data and published by the Australian Bureau of Statistics (ABS) [2]

Rural status was defined using the ABS remoteness structure, part of the 2001 Australian Standard Geographical Classification. This categorised census collection districts for Victoria into four classifications: Major cities, Inner regional, Outer Regional and Remote [3]. We defined rural as not residing in the “major cities” classification. The usual residential addresses of registrants were geocoded with latitude and longitude co-ordinates accurate to five decimal places which allowed categorisation into urban and rural residence.

Statistical analysis

Univariable and multivariable competing risks regressions based on the Fine and Gray method were fitted to analyse PC specific mortality with other-cause-mortality as the competing hazard [4]. Formal statistical testing of the proportional hazards assumption by including interactions with a time variable found that it was not violated. Factors associated with mortality in univariate analyses were included simultaneously in multivariable regression models with stage and grade to identify independent predictor variables. Time from surgery was used as the time axis. All tests were two sided and significance level set at $p \leq 0.05$. Analyses were performed with Stata 12.1 SE (Statacorp, College Station, TX, USA).

Results

Between 1st July 1995 and 31st December 2000, 2154 eligible subjects were identified from pathology reports to the VCR as having had a RP, with 53 surgeons (excluding trainees) having been the primary surgeon for at least one operation. Demographic and baseline data together with detailed information on stage and grade of prostatectomy specimens for these subjects have been previously published, and provide insight into the clinical, biochemical and socio-economic features of men with PC treated by radical prostatectomy in this period [5].

With on-going follow up of this patient group, information was available for 2,113 men (98.1%) with median time of follow up being 10.3 years (range 0.3 – 13.5 years). 1,967

(91.3%) men met the inclusion criteria for this study. At this duration of follow up there had been 75 deaths from PC (prostate cancer specific mortality, PCSM) in this cohort and 172 deaths from other causes. Table 1 shows the breakdown of this cohort according to the variables included in this study.

As expected, pathologic T stage was a strong predictor of prostate cancer specific mortality for patients undergoing radical prostatectomy (figure 1). Subhazard ratios of 13.8 and 3.5 in univariable analysis were observed for T3b and T3a disease respectively ($p<0.001$) compared with patients with T2 (organ confined) disease.

Similar risks were associated with the Gleason score of the primary tumour (figure 2). Subhazard ratios of 11.2 and 7.10 ($p<0.001$) in univariable analysis were noted for Gleason score ≥ 8 and $4+3=7$ compared with Gleason score 6 disease at total prostatectomy. A trend toward increased PCSM was noted, but statistical significance was not achieved, for patients with Gleason score $3+4=7$ disease at this time (SHR 1.84, $P=0.08$), suggesting that primary Gleason pattern at total prostatectomy is a key factor in determining patient outcomes after radical prostatectomy. The significant risks maintained statistical significance ($p<0.005$) when both stage and grade were entered simultaneously in a multivariable model.

Other factors also appear to influence progression to PCSM after radical prostatectomy. After adjustment for stage and grade, rural residence was a strong independent predictor of PCSM ($p=0.003$), as was involvement of a trainee surgeon in the operation ($p=0.031$). This latter feature also may have been reflected in a non-significant trend for progression to PCSM after radical prostatectomy for patients treated in public compared with private hospitals ($p=0.084$).

The volume of RPs performed by individual surgeons was also evaluated as a predictive factor (an arbitrary number of 40 cases (8 per year) contributed to the RPR being chosen to

distinguish higher from lower volume radical prostatectomy surgeons). Using this cut off, a lower risk ($p=0.025$) of PCSM was observed for surgeons handling a higher volume of RPs.

Other factors were evaluated for possible associations with risk of PCSM independent of stage and grade. No significant associations were identified with socio-economic status of patients undergoing radical prostatectomy ($p=0.21$) and number of radical prostatectomy specimens evaluated by the reporting pathology laboratory (<100 specimens vs >100 specimens $p=0.26$). Age at surgery greater than 65 years was also found to be a non-significant predictor of PCSM ($p=0.95$). Using univariate analysis, PSA level at diagnosis and margin positivity status were strong predictors of PCSM but these factors were strongly correlated with stage and grade. Margin status is correlated on univariate analysis with stage and grade to a level of $p<0.0001$ for both variables, but was not associated with pcsm independent of these variables ($p=0.901$). The practical reason for this finding may be that margin status may matter at the individual surgeon level, but at the population level where this analysis is primarily directed the individual surgeon contribution to quality of surgery is averaged out. Consequently the main driver of margin status in this study is the tumours themselves rather than an effect by any outlying surgeon.

Discussion

Few whole of population datasets have been published in reference to radical prostatectomy. Although the significance of data from multi-centre or centre of excellence series is unquestioned, whole of population series provide a real-life evaluation of treatment, including that delivered by surgeons in regional and remote locations and by those with all levels of post-certification training and experience, with reduced potential for results to be confounded by institutional referral, treatment or selection biases. This study reports PCSM outcomes on all patients treated by RP in Victoria over a 5 year time frame.

The purpose of the VRPR when it was established was to provide a detailed description of the whole of population patient casemix, and to identify correlations between baseline characteristics and outcomes from radical prostatectomy, and to assist in providing future direction as to the most appropriate strategies of PC detection and treatment in order to optimise outcomes. The availability at this time of 10 year median follow up data permits us the opportunity to make valid observations in regard to these aims based on PCSM rather than upon PSA detected biochemical recurrence. Although biochemical recurrence may necessitate treatment using salvage radiation or androgen deprivation therapy with consequent side effects, cost and impact upon quality of life, PCSM remains the ultimate measure of the impact of prostate cancer. Measures ideally should be taken to treat otherwise healthy patients before they reach high risk groups for PCSM, or to initiate personalised treatment plans including the option for multi-modality therapy in this setting. Despite extensive work on PC biometrics, PCSM data post RP based on 10 year median follow up have not previously been available for a whole of population series.

The strong correlation observed in this study between PCSM and advanced pT stage of cancer at radical prostatectomy may be seen as a justification for PSA based detection of early stage PC. In a situation where PC has been diagnosed it also suggests potential value for detailed evaluation using radiologic or template biopsy techniques in order to avoid clinically understaging or undergrading PC, especially where consideration is being given to

management in an active surveillance protocol. It is logical to assume that improvements in PCSM could be made by treating at an earlier stage those patients who subsequently were noted to have pT3 disease at RP.

Similar observations may be made about Gleason score at RP. In this study the primary Gleason pattern appears to have major significance in predicting for PCSM. This is of relevance contemporaneously as some active surveillance protocols have suggested the potential for inclusion of Gleason score 3+4=7 disease for such management [6]. While this may be appropriate for some instances of small volume disease it would seem imperative that definitive intervention be considered before disease progression to 4+3=7 cancer, which is clearly associated with increased PCSM after RP at 10 year follow up in this series.

Rural residence of patients which also was identified as a strong predictor of PCSM in this study is a multifactorial issue. Although living in smaller rural communities most of these patients were treated surgically at larger regional and urban centres. More detailed assessment of this association will be the subject of further analysis, but it is reasonable to observe that patients living in rural areas may often have further to travel for post operative review and may live in areas with reduced access to ancillary services and salvage therapy even after having had an RP at the same institution as a patient who lives in an urban area. Progress towards availability of telemedicine and regional facilities for salvage therapy such as external beam radiation/ IMRT therefore may assist in optimizing disease control in this setting.

The impact upon PCSM noted for patients who had their RP performed by lower vs higher volume surgeons also is noteworthy. While several publications have reported an association between surgeon volume and margin status, this study demonstrates this to extend to an independent influence upon PCSM [7-9]. Such a finding may be of further significance contemporaneously given that the number of RP procedures undertaken has reduced since its peak, that there has been an increase in the number of urologists trained to perform this procedure, and that there has been progression towards RP being

undertaken by robot assisted methods which have themselves been associated with a long learning curve and an increased risk of positive surgical margin for cases early in an individual surgeon's experience. Consideration may need to be given in time to consolidating performance of RP to those surgeons who fall into a higher volume group in order to limit the potential for avoidable PCSM [10].

A similar issue is the increased PCSM associated with involvement of a trainee surgeon at RP ($p=0.031$). This finding is independent of cancer stage, margin status and Gleason score, and suggests a requirement to modify teaching strategies. No trainee urologist can be an assistant forever, but clearly this issue must be addressed to limit unnecessary PCSM. Given that surgeon volume was also identified as a risk factor for PCSM it may be that measures such as earlier streaming of trainees into uro-oncologic vs other subspecialties where RP is not undertaken may be warranted, as may be introduction of modulated teaching programs which require competence in one area of RP to be demonstrated before more complex components of RP are undertaken. It may be of significance that when the RP in this series were undertaken this procedure was being widely popularized, and most urologists including those later characterised as high volume were at a comparatively early point in their learning curve.

Although the results reported by this study reflect outcomes post RP rather than Robot Assisted Radical Prostatectomy (RARP) the development of dual console systems for this procedure may be seen as progress in this regard that is worthy of evaluation with respect to PCSM. It may well be that with increased experience in directly supervised RARP in training, as opposed to assisting at RP, that the difference in PCSM seen for higher volume vs lower volume surgeons in this study reduces or only becomes apparent at a greater case load. Other aspects of prostate cancer management also have evolved over this period of extended follow-up, including greater usage of active surveillance protocols, MRI and multidisciplinary panel assessment in patient selection for RP [11-14]. Despite these adjustments impacting the type of patient who proceeds to surgery, especially by reducing the number of Gleason score 6 patients, these factors would not be expected to have

influenced stage and Gleason score specific PCSM. Similarly the results of this study would be expected to be independent of the variability in methods of contemporaneously assessing prostate tumour volume [15].

PCSM was noted in this study where it was listed as the primary cause of death. Instances where longer term consequences of treatment of prostate cancer may have contributed to a reduction in life-expectancy were not recorded as PCSM. Such instances may include where a patient dies from cardiovascular disease after some years of treatment with anti-androgen therapy. Accordingly the impact of PC on patient mortality may be greater than that identified in this series. The low PCSM for Gleason score 6 disease treated by RP would appear to justify the more conservative approach to management of this form of PC that has been advocated since the commencement of this study [16].

Many radical prostatectomy databases have been established worldwide to evaluate RP as treatment for PC. In order to provide a broad based assessment these are often based upon multiple hospitals from different areas or major centres serving a wide referral base [17-19]. Much of the established data underpinning our assumptions on RP at different cancer stage and Gleason score is drawn from such patient databases. The hospitals coordinating these series are often centers of excellence, and referral patterns and case selection for RP may differ from smaller urban centres or hospitals in rural/regional areas. The availability of a whole of population series such as the VRPR invites comparison with alternative approaches to this question.

One of the limitations of a whole of population study is that end points for outcome measures are necessarily defined to reduce subjectivity, in order to provide for accuracy across multiple locations of treatment. Hence in this study secondary effects of PC treatment may be reflected in patient deaths from other causes but not PCSM. Similarly quality of life outcomes would have required use of validated instruments administered in a standardised fashion, and this was felt to be beyond the funding and administrative capacity

of this project at inception. Consequently we have examined only those objective measures with potential to have impacted upon PCSM.

Although multiple variables assessed in this study appear to have an association with PCSM independent of stage and grade, in this whole of population study the nature of the primary tumour at the time of treatment by RP appears to have the greatest correlation with PCSM. This analysis should assist patients and clinicians in making decisions about staging, surveillance, and timing of surgical intervention in PC treatment.

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Ethical Consideration:

As detailed in the manuscript this project was approved by the ethics committee of Cancer Council Victoria in accordance with the standards prescribed and reported annually to the Australian National Health and Medical Research Committee.

Conflict of Interest Statement:

No author of this manuscript has any financial, regulatory or governance conflict of interest pertaining to the publication of this article.

Author Contribution Statement:

All coauthors of this publication have contributed to its construction by means of one or more of project development and oversight, data collection and analysis, and manuscript production and review, and all authors offer their consent for its publication

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Figure 1.

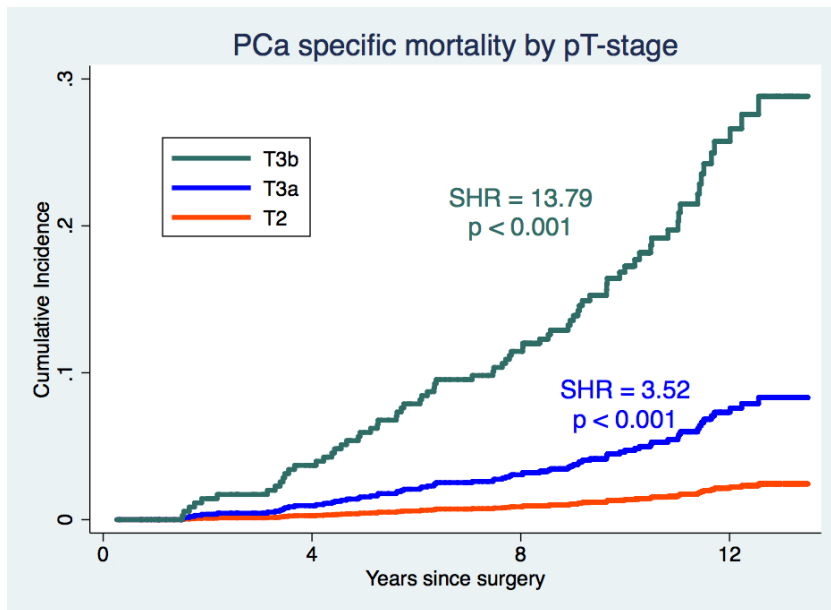


Figure 2

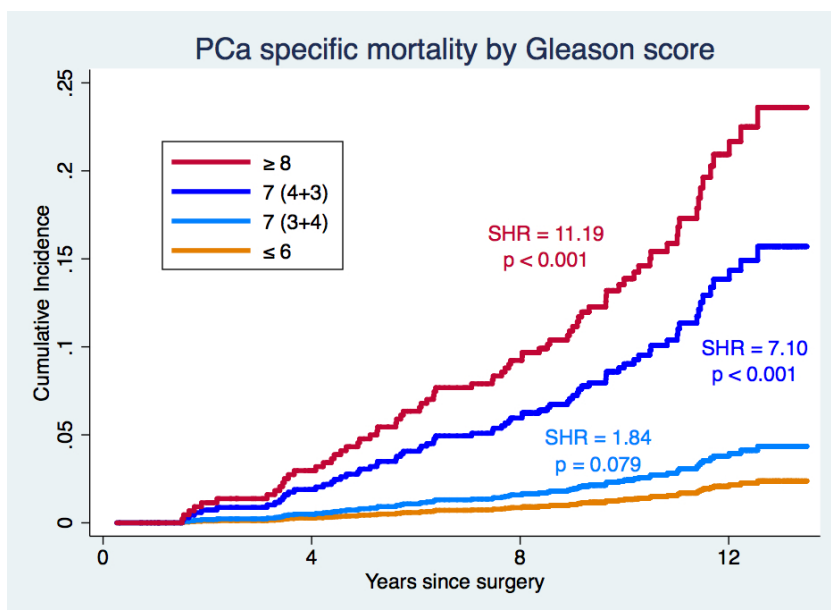


Table 1: Breakdown of patients in the study

	Total patients n=1967 (% of total)	Other cause mortality n=172 (% of category)	PCSM n=75 (% of category)
Gleason grade			
6	1147 (50.3)	94 (8.2)	19 (1.7)
7 (3+4)	500 (25.4)	43 (8.6)	14 (2.8)
7 (4+3)	186 (9.5)	17 (9.1)	20 (10.8)
8-10	134 (6.8)	18 (13.4)	22 (16.4)
pT-stage			
T2	1499 (76.2)	127 (8.5)	25 (1.7)
T3a	305 (15.5)	26 (8.5)	17 (5.6)
T3b	163 (8.3)	19 (11.7)	33 (20.2)
Residence			
Urban	1532 (77.9)	135 (8.8)	47 (3.9)
Rural	435 (22.1)	37 (8.5)	28 (6.4)
Surgeon			
Consultant only	1583 (82.5)	146 (9.2)	57 (3.6)
plus Trainee	335 (17.5)	22 (6.6)	16 (4.8)
Surgeon volume			
≥ 40 cases	1572 (79.9)	135 (8.6)	54 (3.4)
< 40 cases	395 (20.1)	37 (9.4)	21 (5.3)
Hospital system			
Private	1531 (77.8)	139 (9.1)	54 (3.5)
Public	436 (22.2)	33 (7.6)	21 (4.8)
Laboratory			
≥ 100 cases	1496 (76.1)	137 (9.2)	55 (3.7)
< 100 cases	471 (23.9)	35 (7.4)	20 (4.2)
SES quintile (17 missing)			
Q5 (most advantaged)	682 (34.7)	59 (8.7)	22 (3.2)
Q4	394 (20.0)	34 (8.6)	8 (2.0)
Q3	292 (14.8)	23 (7.9)	8 (2.7)

Q2	307 (15.6)	31 (10.1)	22 (7.2)
Q1 (least advantaged	275 (14.0)	23 (8.4)	14 (5.1)
Age at surgery			
≥ 65	597 (30.4)	91 (15.2)	28 (4.7)
< 65	1370 (69.6)	81 (5.9)	47 (3.4)

b. Rural residency and prostate cancer specific mortality: results from the Victorian Radical Prostatectomy Register

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Abstract:

Objective:

Rural residency has been suggested to be a risk factor for prostate cancer specific mortality in North American studies. This may be related to choice or timing of treatment, as well as factors specific to this disease. We sought to ascertain if this mortality risk was apparent for men all of whom had been treated by radical prostatectomy in a whole of population series.

Methods:

Using census data patients were assessed as residing in either outer regional, inner regional or metropolitan locations. Additional cross referencing by socio-economic status of these areas also was undertaken. Details of all patients' prostate cancer subtypes and treatment outcomes including prostate cancer specific mortality was obtained via the Victorian Radical prostatectomy Registry. Statistical analysis between the urban and rural cohorts was undertaken using chi-square tests, Kruskal-Wallis tests and the Wald test from linear or logistic regressions. A multivariable Cox regression model was fitted to analyse all-cause mortality, and competing risks regression based on the Fine and Gray method.

Results:

Men from rural subgroups had higher median PSA values prior to surgery and were less likely to be treated in the private system ($P < 0.001$) than urban males. The effect of living in a rural area was observed to confer a greater hazard of prostate cancer specific mortality and that increasing remoteness amplified this, "Inner regional" subdistribution hazard ratio (SHR) = 1.64, $p = 0.154$, "Outer regional / Remote" SHR = 4.09, $p = 0.004$. This result is after adjustment for individual patient and tumour factors and socioeconomic status.

Conclusion:

Men from rural areas who have undergone open Radical Prostatectomy for localised prostate cancer have a shorter time to prostate cancer specific mortality than urban men even after adjustment for socioeconomic status and individual tumour factors. This effect is more pronounced with greater remoteness from major metropolitan centres.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy in Australian males and causes the second highest number of cancer-related deaths behind lung cancer with 3,235 deaths in 2010 (1). Australian men from regional areas have a twenty percent higher PCa mortality rate than those residing in a major city which corresponds to 182 'excess' deaths per year (reporting period 2002-2004) (2). This disparity is also evident in population-wide surveys in the USA (3) and Canada (4) with the respective mortality rate increases being 6% and 9% for the rural population relative to the urban population.

Several plausible explanations have been put forward to account for this reproducible difference in disease-specific mortality. The published SPCG-4 randomised controlled trial has shown the superiority of radical prostatectomy (RP) as a curative treatment for early stage PCa (5), and Australian rural patients have had comparatively fewer RPs since the treatment became commonplace (6) : in 2007-08, there was a difference of 57/100,000 men in the age-standardised rate of RP (7). Additionally, prostate-specific antigen (PSA) testing overall is lower with the rural:urban rate ratio of 0.93 reported in 2008-09 and the PSA screening specific ratio 0.86 (7). Furthermore a link between low socioeconomic status (SES) and adverse PCa specific outcomes has previously been reported in other developed countries (8-10), and in our sample, Australian rural men are over-represented in the lowest quintiles of national SES.

While rural residency appears to affect the choice of treatment (11) or perhaps its timing, it is unknown whether rural men do worse than urban counterparts following definitive treatment for localised PCa. We sought to identify if rural residency is a risk factor for PCa specific mortality using outcomes data from the Victorian RP register (VRPR), a whole of population series of men from both urban and rural areas of Victoria who have all undergone treatment by open RP.

Methods

The VRPR is a prospective whole of population series of all men who underwent open RP for the treatment of localised prostate adenocarcinoma between 1995 and 2000 in Victoria, Australia. It was established within the Victorian Cancer Registry (VCR), which documents all cancer cases in the state, excluding non-melanoma skin cancer. The VCR is managed by The Cancer Council of Victoria and the VRPR was approved by the Cancer Council of Victoria's Human Research Ethics Committee and established within the VCR. Further details regarding patient registration and data collection have been previously described (12).

Rural status was defined using the Australian Bureau of Statistics (ABS) remoteness structure, part of the 2001 Australian Standard Geographical Classification. This categorised census collection districts for Victoria into four classifications: Major cities, Inner regional, Outer Regional and Remote (13). The subjects in our register were geocoded with latitude and longitude co-ordinates accurate to five decimal places. Mapping of subjects to the ABS classifications was performed using the open source geographic information system QGIS. There were only four subjects who were classified as "Remote" hence "Outer regional" and "Remote" patients were combined for the analysis. This created three classifications: "Major Metropolitan" or urban which encompasses metropolitan Melbourne and Geelong and two rural subgroups: "Inner regional" which includes Ballarat, Bendigo and Shepparton and "Outer regional / Remote" which includes towns such as Portland, Mansfield and Bairnsdale.

Socioeconomic status was defined by the ABS Socioeconomic index for areas (SEIFA) "Index of relative disadvantage" score (14). This score is based on census derived data with each postcode's score re-evaluated at each census date. Men in our series who had surgery prior to 30th June 1998 were coded with data from the 1996 census year, men who had surgery on or after this date were coded with the index score corresponding to the 2001 census year. These scores are then transformed into quintiles with "Quintile 1" being the most disadvantaged and "Quintile 5" being the least disadvantaged.

All subjects had a recorded PSA test prior to surgery and operative histology reports plus follow-up PSA testing histories were obtained by record linkage to the pathology laboratories, with staging based on prostate specimen histology. Biochemical recurrence post RP was defined as two consecutive PSA values ≥ 0.2 ng/ml as per the American Urological Association guidelines (15) and the latter date taken as the time of recurrence. Deaths were recorded by the VCR as either prostate cancer death, other cancer death or death from another cause. Subjects exited the study at the date of death or 1 January 2009, whichever occurred first. Men who had neoadjuvant therapy were excluded from the multivariable analyses.

Baseline data between the urban and rural cohorts were compared with chi-square tests, Kruskal-Wallis tests and the Wald test from linear or logistic regressions. A multivariable Cox regression model was fitted to analyse all-cause mortality. Competing risks regression based on the Fine and Gray method (16) was fitted to analyse prostate specific mortality with other cause mortality as the competing hazard. Covariates were selected for the model *a priori* as those that were thought to be associated with survival. Socioeconomic status was also included as it has, by definition, an association with our rural groupings as both are defined by location. Formal statistical testing of the proportional hazards assumption was performed by analysing Schoenfeld residuals for the Cox regressions and interacting covariates with a time variable for the competing risks regression. In both cases the assumption was not violated. In the two regressions, time from surgery was set as the time axis, covariates were entered simultaneously and biochemical failure included as a time varying covariate. Post prostatectomy follow up comparisons were adjusted for socioeconomic status by its inclusion in a multivariable model with rural residence. All tests were two sided and significance level set at $p \leq 0.05$.

Analyses were performed with Stata 12.1 SE (Statacorp, College Station, TX, USA).

Results

During the accrual period 2154 men underwent RP. Follow-up information was available for 2115 men. Men who had neoadjuvant therapy were excluded (n=50) as were men with missing data for SES status, grade and stage. There were a total of 1984 patients (92.1% of total) available for the analyses, 348 of which were classified “Inner regional” (17.5%) and 72 “Outer regional / Remote” (3.6%). The median time of follow up was 10.3 years (range 0.3 – 13.5 years). Demographic characteristics and prostate cancer status of these men at RP are shown in Table 1. The geographic distribution of patient origin is shown in Figure 1 and distribution with respect to SES status is shown in Figure 2.

There were 238 deaths observed in this sample (180 “Major metropolitan”, 47 “Inner regional”, 11 “Outer regional / Remote”). This included 77 PCa specific deaths (“Major metropolitan” 50 deaths, 3.20% of this classification, “Inner regional” 21 deaths, 6.03%; “Outer regional / Remote” 6 deaths, 8.33%), score test for trend in odds, $p < 0.001$.

In this whole of population based series, 35% of men were from the most advantaged quintile of SES and in excess of 95% of this subgroup was urban based. 431 RP's were done in the public health system and 1533 in the private system. Significant differences were present between urban and rural subgroups in regard to median PSA values prior to surgery and whether they were treated in the private system OR 0.43 (95% CI 0.34 – 0.56, $P < 0.001$). The percentage with PSA > 10 ng/ml prior to surgery was higher in the rural subgroups, almost reaching significance, $p = 0.056$. Tumour stage, grade and age at surgery were not significantly different between groups.

The effect of living in a rural area was observed to confer a greater hazard of prostate cancer specific mortality and that increasing remoteness amplified this, “Inner regional” subdistribution hazard ratio (SHR) = 1.64, $p = 0.154$, “Outer regional / Remote” SHR = 4.09, $p = 0.004$. This result is after adjustment for individual patient and tumour factors and socioeconomic status. There was not a significantly greater hazard for overall mortality in men who underwent RP. Table 2 demonstrates the results of the regressions for the urban

and rural groups described above with hazard ratios, subdistribution hazard ratios, confidence intervals and associated p-values presented. The cumulative incidence plot for this increased risk of PCa specific mortality in rural men treated by RP is shown in Figure 3. There is a clear and continuing separation of the plots with the curve for the most remote classification noticeably divergent from the urban plot.

Tumour grade and stage were both observed to be associated significantly with PCa mortality shown in Table 2. In our study, there was a clear difference between men with Gleason 7 disease when separated according to dominant pathological pattern. Men with Gleason grade 3+4 did not have a significantly different SHR than those with grade 6 or less (SHR 1.08, 95% CI 0.55 – 2.13) while men with 4+3 disease had SHR = 3.21 (95% CI 1.65 – 6.23) compared to Gleason grade 6 or less. For overall mortality, T4 stage disease did not reach significance probably due to the low numbers of subjects with this classification in the sample (n=42) and deaths (n=7). We note that men who underwent RP at an older age were more likely to die sooner than younger men from competing causes but age at surgery did not significantly predict PCa specific mortality (SHR 0.98 95% CI 0.94 – 1.02). Biochemical recurrence was significantly associated with a higher hazard of both overall and PCa specific mortality.

Further comparisons between urban and rural cohorts after adjusting for SEIFA are presented in Table 3. Men in urban areas were significantly more likely to be operated on by an experienced surgeon, defined as one who had contributed more than 50 cases to the registry. In a univariable analysis, however, surgeon experience alone did not significantly predict PCa mortality (SHR 0.74, p=0.177). The follow-up PSA measures only include men who were alive at the conclusion of the study. Rural men were observed to be followed less closely with repeat PSA measurements and that both the overall number and time between tests differ significantly. 51 men had only one recorded follow-up PSA, proportionately more of these were rural men. There was also a longer lag time between confirmatory biopsy date and date of RP for rural men though this did not reach significance and in univariable analysis, lag time was not predictive of PCa specific mortality (p>0.20).

Discussion:

In our state-wide, population based series of men who underwent RP between 1995 and 2000, we found an association between patients who lived in a rural location and PCa specific mortality even after adjustment for socioeconomic status, age at surgery, private or public hospital treatment and biochemical (PSA) and tumour factors (Gleason grade and tumour stage). Previously published studies (6,8,17) have noted rural men are less likely to be screened as often and/or undergo RP, but to our knowledge this is the first population wide study that demonstrates rural disadvantage persists even after definitive treatment and that it affects PCa specific mortality. The register incorporates a heterogeneous patient and urologist population, with 54 surgeons contributing data. This further removes any outcomes bias that may be associated with a more highly selected patient cohort, or from absence of a learning curve in a high volume, single institution series.

Baseline characteristics show significant differences only in median PSA prior to surgery and whether the patient was treated in the private or public health system. The higher median PSA and greater percentage of men with PSA > 10ng/ml may indicate a later presentation or be a consequence of less frequent screening leading to rural men having a slightly higher value when plans for definitive treatment are initiated. The difference is, however, unlikely to be clinically significant as the pre-operative PSA value was not shown to predict overall or PCa specific mortality between these groups in the regression analyses. The percentage of Gleason 8-10 tumours in rural men was slightly higher, the reason for this is unclear, though this has been adjusted for in the multivariable regressions.

For biopsy confirmed PCa the time from biopsy to surgery is comparable for both groups though there is a small difference in medians. There was a greater percentage, around 3% more, of rural men with long delays (>100 days) to surgery. This is in contrast to an American study which demonstrated distance from treating hospital to be predictive of shorter time to surgery (18), although our data does not specifically include information about distances from hospital. The distinction between treatment in private and public health care facilities also did not reach significance in predicting mortality in keeping with a

recent Australia-wide breast cancer study (19). Tumour factors have been shown in other prospective studies to be predictive of mortality (20,21) and it is also true in our series but no baseline differences between the groups were observed and even after adjustment for these factors, the rural effect remained. Age at surgery was not observed to be associated with PCa mortality after RP. This suggests RP remains an effective treatment for men of advanced age. In our registry, 31% of men were aged over 65 with 5.2% over 70.

The frequency of PSA testing following RP was significantly less for rural men. However the consequence of this is unclear. There is some controversy about how often men should be tested after RP, Ciezki et al (22) found that lower testing intensity is associated with clinical failure while another study suggests no survival benefit (23) and that clear, evidence based guidelines are lacking. In our study, full follow-up information on PSA testing, despite the best efforts of investigators may be differentially incomplete for rural men due to logistical problems in obtaining the data.

A limitation of our study is the method of capturing SES. The SEIFA metric uses postcodes which do not account for the heterogeneity of the population within a postcode area. As a consequence there is also a correlation between SEIFA quintile and rural status. This is adjusted for in the regressions and we found no significant evidence for heterogeneity of the effect of rural status on PCa specific mortality across the SES quintiles (data not shown). Co-morbidities have not been recorded and these may be higher in the rural population. Our results suggest overall mortality to be not significantly different between rural and urban cohorts. We would expect a much larger hazard ratio, closer to the cancer specific figure, if co-morbidities alone explained the poorer PCa survival statistic for rural men. Salvage treatments were also not recorded in our register. Inadequate access to radiotherapy (RT) centres may account for the relative increased mortality. An Australian survey (24) noted the paucity of rural medical and radiation oncological services, multidisciplinary clinics and access to psychosocial care. But this in itself should not necessarily lead to worse outcomes. In Canada (25) radiotherapy rates did not differ between urban/rural patients for treatment of PCa (though they did for breast and lung cancer). In Scotland (26) a study describes minimal, if any impact of distance to RT centre for

lung and colorectal cancer. In 8 states of the USA (27) rural/urban differences in RT utilisation were observed only for breast cancer with no difference for lung, cervical, anal and rectal cancer. It has been observed that rural Australian patients are reluctant to travel to urban centres for treatment (28) and the current paradigm of rural health service delivery is to place high quality services closer to the rural populace (29). However it is also noted that evidence that this leads to improved cancer outcomes is lacking (29).

The management of prostate cancer has changed somewhat in the years since our study period. The percentage of Victorian men with PCa undergoing RP has increased from 13.5% in 1993 to 43.9% in the period 2008-2011 (30). A considerable amount of patient follow-up is done by their general practitioner (GP) and the distribution of GP's over Victoria has altered minimally from 1999-2000 to 2011-2012. The percentage of total full-time workload equivalents done in the "Inner regional" category of Victoria increased from 15.6% to 18.9% and from 4.19% to 4.35% in the "Outer regional" category (31). It is our experience that the distribution of consultant urologists has also changed minimally over the same period. As the number of operations increases while the allocation of the medical workforce over the state remains constant, it is likely our findings remain valid in a contemporary context.

In conclusion, this population-wide study has demonstrated men from rural areas who have undergone open RP for localised PCa have a shorter time to PCa specific mortality than urban men even after adjustment for socioeconomic status and individual tumour factors. This effect is more pronounced with greater remoteness from major metropolitan centres. The precise reasons for this result remain unclear though it is certain a co-ordinated response across surgical, oncological, general practice and allied health disciplines is required.

Fig. 1 - Location of VRPR cohort. Each yellow dot represents the location of residence of a patient who underwent radical prostatectomy in Victoria from 1995-2000. The shaded areas grow darker with increasing remoteness, as defined by the Australian Bureau of Statistics in 2001. (Created with the open source software QGIS).

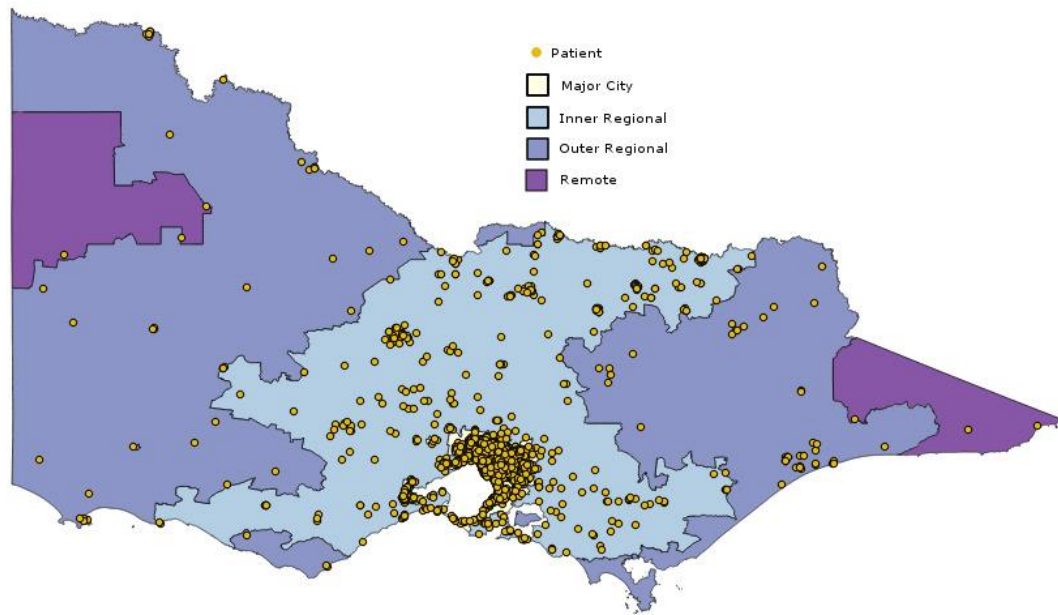


Fig. 2 – Distribution of SEIFA quintiles by residence. Socioeconomic index for areas scores were divided into fifths. Quintile 1 represents the fifth of all patients with the lowest (SEIFA) score, indicating most disadvantaged. The coloured areas, blue for major metropolitan, red for inner regional and green for outer regional/remote represent the absolute numbers of patients in each fifth.

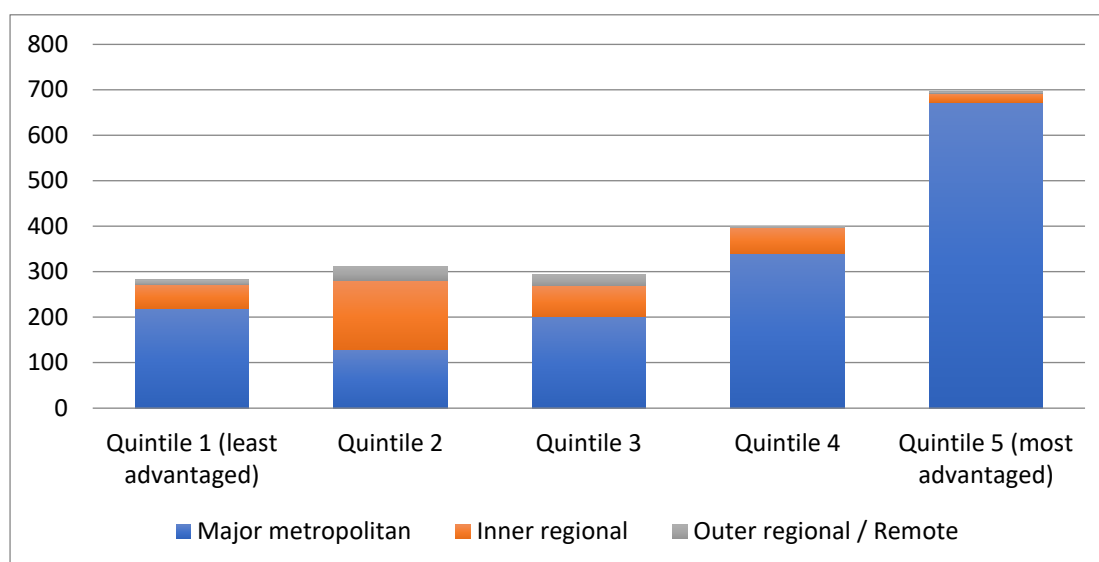


Fig. 3 – Cumulative incidence plots of prostate cancer specific mortality (PCSM). The plots represent incidence of PCS, cumulative over the follow-up period and adjusted for all other variables in the multivariable model. The red line represents outer regional/remote men, the green line inner regional and solid blue line, major metropolitan. The subhazard ratios (SHR) and associated p-values are for each rural group relative to major metropolitan.

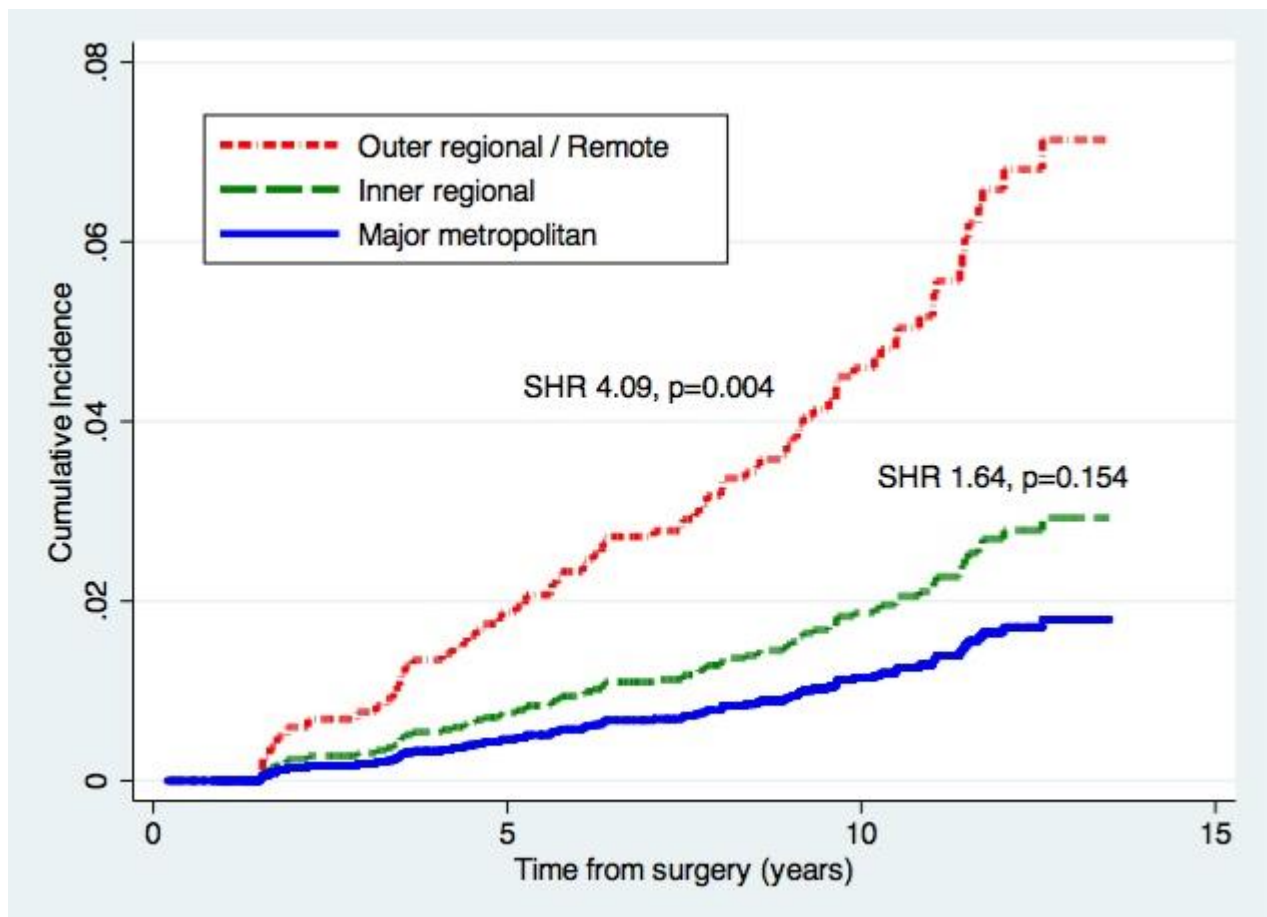


Table 1 – Baseline data for covariates entered into multivariable models according to residence. The p-value indicates overall difference between the three groups.

	Major metropolitan N=1564	Inner regional N=348	Outer regional / Remote N=72	P-value (difference between groups)
Age at surgery, years: median (IQR)	62.0 (57.1 – 65.9)	61.5 (57.1 – 65.4)	62.1 (58.3 – 65.5)	0.582
PSA prior to RP, ng/ml: median (IQR)	7.9 (5.7 – 11.8)	8.8 (6.1 – 13.4)	8.2 (5.4 – 12.8)	0.029
% PSA>10 ng/ml	33.8%	40.5%	36.1%	0.056
Private system: %	81.4%	66.1%	69.4%	<0.001
Gleason score: %				
6 or less	58.6%	57.8%	54.2%	0.490
7 (3+4)	25.3%	25.9%	23.6%	
7 (4+3)	9.7%	8.3%	9.7%	
8 or greater	6.4%	8.1%	12.5%	
Tumour stage: %				
T1/T2	74.6%	74.7%	77.8%	0.299
T3a	15.1%	17.0%	8.3%	
T3b	7.9%	7.5%	11.1%	
T4	2.4%	0.9%	2.8%	

IQR = interquartile range

Table 2 - Multivariable analysis: Cox regression and competing-risks regression. N indicates the number of deaths (overall or prostate cancer specific) for each category of the variable. The p-value is in reference to the base case for categorical variables of for each unit increase in continuous variables.

	Overall mortality			Prostate cancer specific mortality		
	N	HR (95% CI)	P-value	N	SHR (95% CI)	P-value
Location of residence						
Major metropolitan	180	1.0		50	1.0	
Inner regional	47	1.09 (0.75-1.57)	0.659	21	1.64 (0.83-3.23)	0.154
Outer regional / Remote	11	1.34 (0.70-2.57)	0.382	6	4.09 (1.56-10.7)	0.004
SEIFA						
Quintile 1 (least advantaged)	39	1.0		15	1.0	
Quintile 2	50	1.05 (0.67-1.64)	0.846	22	1.01 (0.46-2.22)	0.972
Quintile 3	28	0.73 (0.45-1.20)	0.214	9	0.69 (0.28-1.69)	0.417
Quintile 4	39	0.79 (0.51-1.24)	0.312	8	0.55 (0.22-1.38)	0.204
Quintile 5 (most advantaged)	82	0.88 (0.59-1.31)	0.530	23	0.90 (0.45-1.82)	0.776
Private system (vs. public)	188	0.97 (0.70-1.35)	0.859	56	0.65 (0.37-1.16)	0.144
Age at surgery (per year)		1.07 (1.04-1.09)	0.001		0.98 (0.94-1.02)	0.376
PSA at RP (per 5 ng/ml)		0.99 (0.94-1.05)	0.824		1.01 (0.93-1.10)	0.845
Gleason score						
Less than 6	107	1.0		18	1.0	
7 (3+4)	53	0.93 (0.66-1.31)	0.668	14	1.08 (0.55-2.13)	0.828
7 (4+3)	37	1.44 (0.95-2.16)	0.083	20	3.21 (1.65-6.23)	0.001
Equal or greater than 8	41	1.94 (1.28-2.98)	0.002	25	3.48 (1.79-6.78)	0.001
Tumour stage						
T1/T2	144	1.0		25	1.0	
T3a	39	1.11 (0.77-1.60)	0.583	17	2.43 (1.27-4.62)	0.007
T3b	48	1.83 (1.24-2.72)	0.003	31	4.62 (2.52-8.47)	0.001
T4	7	1.26 (0.58-2.73)	0.551	4	3.69 (1.29-10.6)	0.015
Biochemical recurrence (yes vs. no)	120	2.41 (1.81-3.21)	0.001	58	5.33 (3.00-9.45)	0.001

HR = hazard ratio, SHR = subdistribution hazard ratio, ng/ml = nanogram/millilitre

Table 3 – Comparison of lag time to surgery, surgeon experience and follow-up PSA testing post radical prostatectomy. PSA follow-up variables exclude men who had died from any cause. P-values are for comparison to metropolitan men.

	Major metropolitan	Inner Regional	Outer regional / Remote
Time between biopsy and surgery dates, days: median (IQR)	54 (39 – 76)	59 (42 – 83) p=0.199 [^]	65 (42 – 83) p=0.121 [^]
Delay >100 days	12.5%	15.3% p=0.190	15.5% p=0.466
High volume surgeon, >50 cases in our cohort (%)	72.2%	44.0% p<0.001	51.4% p=0.017
Mean number of PSA follow-ups	7.33	5.49 p<0.001	5.0 p<0.001
Mean length of PSA follow-up (years) *	6.38	6.09 p=0.125	5.76 p=0.076
Pt. with only a single follow-up PSA (%)	2.47%	5.41% p=0.068	4.92% p=0.569
Ave. time between PSA readings (years)	1.13	1.35 p<0.001	1.45 p=0.003

** In men with more than one follow-up PSA.*

[^] following log transformation

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