

https://dspace.org/

The pathological features of prostate cancer in South African men: what is the prevalence of local invasion at diagnosis?

Mathabe, Kgomotso Minah

2020
https://hdl.handle.net/10539/31692

Downloaded from a DSpace repository. https://dspace.org/

THE PATHOLOGICAL FEATURES OF PROSTATE CANCER IN SOUTH AFRICAN MEN: WHAT IS THE PREVALENCE OF LOCAL INVASION AT DIAGNOSIS?

Dr. Kgomotso Minah Mathabe

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of MMed (Urology).

Johannesburg 2020

TABLE OF CONTENTS

DECLARATION……v

DEDICATION……vi

PRESENTATION ARISING FROM THE REPORT……vii

ABSTRACT……viii

ACKNOWLEDGEMENTS……x

LIST OF FIGURES……xi

LIST OF TABLES……xii

ABBREVIATIONS……xiii

LIST OF APPENDICES……xvi

CHAPTER 1: INTRODUCTION 1

1.1. General introduction 1

1.2. Literature Review 4

1.2.1. Anatomy and physiology of the prostate gland 4

1.2.2. Risk factors for prostate cancer 6

1.2.3. Prostate cancer incidence and mortality in South Africa 12

1.2.4. Clinical presentation 13

1.2.5. Confirming the diagnosis on histology 23

1.2.6. The histology of prostate cancer 33

1.2.7. The clinical significance of prostate cancer using Epstein's criteria 41

1.2.8. Risk assessment tools: D'Amico and nomograms 42

CHAPTER 2: AIM AND OBJECTIVES 45

2.1. Aim 45

2.2. Objectives 45

CHAPTER 3: METHODS 46

3.1. Study design 46

3.2. Study population and sample 46

3.2.1. Site of study 46

3.2.2. Inclusion criteria 46

3.2.3. Exclusion 46

3.3. Variables....47
3.4. Ethics approval....48
3.5. Statistical analyses....48
CHAPTER 4: RESULTS....49
4.1. Indication for specimen....49
4.2. Type of specimen....50
4.3. Age....51
4.4. PSA level....51
4.5. Core needle biopsies....52
4.5.1. Completeness of reporting as per ICCR....52
4.5.2. Core biopsy protocol....52
4.5.3. Is either biopsy protocol superior in terms of information yielded?....54
4.5.4. Repeat biopsies....55
4.6. Gleason....56
4.6.1. Gleason grade....56
4.6.2. Gleason grade by decade....57
4.6.3. Gleason grade, tumour bulk and local infiltration.....58
4.6.4. ISUP grade groups....58
4.7. Local infiltration....59
4.8. HG-PIN and Prostatitis....59
4.9. Immunohistochemical staining....60
CHAPTER 5: DISCUSSION....61
5.1. Summary....61
5.2. Needle biopsies....61
5.2.1. Adequacy of reporting as per ICCR....61
5.2.2. Superiority of particular biopsy protocol....63
5.2.3. Systematic biopsy protocol....63
5.2.4. Repeat biopsies....64
5.3. Specimens other than core needle biopsies....65
5.4. Biochemistry and histology....66
5.4.1. Aggressive disease....66
5.4.2. Other histological findings....68
5.4.3. Immunohistochemistry and unusual histological findings....69
5.5. Age....70

5.5.1. Age at diagnosis 70
5.5.2. Early onset disease 71
5.6. Clinically insignificant disease, localised disease and nomograms 71
5.6.1. Indolent disease and Epstein 71
5.6.2. Localised disease and D'Amico 72
5.6.3. Nomograms 73
5.7. Screening 74
5.8. Race 74
CHAPTER 6: CONCLUSION AND RECOMMENDATIONS 77
6.1. As per the 6 objectives 77
1. Determine if PCa histology reports meet the International Collaboration on Cancer Reporting (ICCR) 77
6.2. Limitations of the Study 78
6.3. Recommendations and questions stemming from the study 78
6.3.1 Clinical recommendations and future studies 78
6.3.2 Practical recommendations for implementation 79
REFERENCES 81
APPENDICES 90

DECLARATION

I, Kgomotso Minah Mathabe declare that this research report is my own work. It is being submitted for the degree of M.Med (Urology) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……..

On the 9th day of August 2020 in Johannesburg.

DEDICATION

I dedicate this research report to Marumo Mothuloe, Setumo S. Mathabe, Daphne Mathabe, Setumo Mathabe, Mogolodi O. Mathabe, Dr. Selaelo Mametja, Dr. Janeshree Govindsamy and Dr. Evelyn Moshokoa. At various points along the journey, you kept helping me to find the light. My rocks. My anchors. My heroes.

PRESENTATIONS ARISING FROM THE REPORT

Wits Donald Gordon Medical Centre Research Day 2013 poster presentation: Prostate Biopsy results over a five-year period at Charlotte Maxeke Johannesburg Academic Hospital.

ABSTRACT

Background

Prostate cancer is the most common solid organ cancer amongst South African men. It poses a risk to life and is a significant public health burden. The management of patients affected by this disease who have access to tertiary hospitals includes a measurement of the serum prostate specific antigen level and a prostate biopsy. Data gathered from histology reports that are currently not used in the prognostication and risk stratification models have the potential to refine these tools. The prevailing view in current literature is that prostate cancer in Black men is more aggressive than in other races, and studies are being performed to determine the possible genetic basis for this.

Methods

A retrospective, observational, cross- sectional study of the histology reports of prostate biopsy specimens received by the NHLS from Charlotte Maxeke Johannesburg Academic Hospital from 01 January 2004 to 31 December 2009, which were positive for PCa, was conducted.

Results

Histology reports on 726 biopsy specimens were available for assessment. Race and clinical data were not available. The histology reports are of a high quality. The majority of specimens came from by core needle biopsies using the systematic technique, which provided superior information when compared to the other techniques. The majority of patients presented with advanced disease as shown by a high PSA >20ng/ml in 70%, high-grade disease with Gleason grade ≥ 7= 4 + 3 and evidence of locally advanced disease in all but 3 specimens, specifically perineural spread in 54%. The majority of patients were in the 7^{th} and 8^{th} decade of life.

Conclusion

The quality of our histology reports is high and provides data that can be used to optimally risk stratify and prognosticate patients. The majority of patients in the study presented with

advanced disease. The inaccessibility of clinical records and unavailable race data added a perspective to the understanding of PCa in this institution.

ACKNOWLEDGEMENTS

Various people have contributed to this research report, which was a marathon and not a sprint. I would like to heartily thank the following people:

Drs. Obakeng Mookeletsi, Vuyolethu Keti and Palesa Mogane. The beginning.

Prof. Mohamed Haffejee for giving me a chance.

Prof. Alison Bentley for getting me off the starting blocks.

Drs. Mmatsie Manentsa and Limakatso Lebina for helping in the middle where there was no turning back, but the end seemed and was so far off.

Dr. Bayanda Mbambisa who quietly carved a trail.

Dr. Lesiba Mogotlane, for the histology distinctions and painting pictures with words.

Dr. Sean Patrick for helping me across the finish line, without your patience and commitment this dissertation would quite simply never have come together. Here is to the next one!!!

Sr. Rosina Motingwa for finding information that no one else could.

Ms. Amitha Betchan, for your constant encouragement and faith.

Ms. Nthabiseng Matjomane, thank you for having a great idea on how to proceed and for advocating for the idea and thus my best outcome.

Dr. Layla Cassim for lifting the veil.

Prof. Mamokgethi Phakeng. Ulala kanjani?

Ms. Savannah Maziya. Phenomenally.

Letta Mbulu and Caiphus Semenya. Hareje. Ha re sa kotule hareje.

My gratitude knows no bounds.

LIST OF FIGURES

Figure 1.1: Anatomical relations of the prostate…… …….4

Figure 1.2: Zones of the prostate……..……5

Figure 1.3: Histology of the prostate……..……5

Figure 1.4: The original sextant technique and other reported systematic biopsy schemes....28

Figure 1.5: Microscopy patterns for Gleason pattern……35

Figure 4.1: Indications for prostate histology……50

Figure 4.2: Distribution of types of specimen……51

Figure 4.3: Age distribution……51

Figure 4.4: Distribution of PSA level……52

Figure 4.5: Core needle biopsy protocols……53

Figure 4.6: Distribution of Gleason grade……57

Figure 4.7: Distribution of grade of disease per decade……..58

Figure 4.8: Distribution of the ISUP grade groupings……59

Figure 4.9: Distribution of local spread within the sample……60

LIST OF TABLES

Table 1.1: Family history and risk of prostate cancer……8

Table 1.2: Prostate cancer incidence by race in South Africa, CANSA (2008)……..13

Table 1.3: South Africa incidence and comparative mortality……13

Table 1.4: Risk of detecting prostate cancer on prostate biopsy based on PSA……17

Table 1.5: PSA reference ranges by age and race……17

Table 1.6: Other factors that affect PSA……18

Table 1.7: Typical distribution of metastatic sites in patients with hormone-resistant prostate cancer entered in clinical trials……20

Table 1.8: TNM staging 2009 description……22

Table 1.9: Indications for TRUS directed prostate biopsy……25

Table 1.10: Increasing prostate cancer detection rates with extended core biopsy techniques……28

Table 1.11: ISUP 2014 grade groups……36

Table 1.12: Summary of immunohistochemical staining pattern in prostate cancer and benign disease……39

Table 1.13: ICCR criteria for core needle biopsy reports……40

Table 1.14: Epstein's criteria for clinically insignificant disease……42

Table 1.15: D'Amico risk stratification……43

Table 4.1: Comparing different biopsy protocols……54

Table 4.2: Comparing first time biopsies to repeat biopsies……56

Table 4.3: Showing the association of high Gleason score with high tumour bulk and local infiltration……59

ABBREVIATIONS

34BE12	34 beta E 12
AMACR	alpha methyl co-A racemase
ASAP	atypical small acinar proliferation
AUR	acute urinary retention
BPH	Benign Prostatic Hypertrophy
CANSA	Cancer Association of South Africa
CAP	College of American Pathologists
CAPRA	Cancer of the Prostate Risk Assessment
CARISA	Cancer Research Initiative of SA
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DHT	dihydrotestosterone
DoH	Department of Health
DRE	digital rectal examination
ECOG	Eastern Cooperative Oncology Group
ERSPC	European Randomised Study for Screening of Prostate Cancer
GnRH	gonadotrophin releasing hormone
HG	high-grade
HMWCK	high molecular weight cytokeratin
HPV	human papilloma virus
ICCR	International Collaboration on Cancer Reporting
IHC	immunohistochemistry

IPSS	international prostate symptom score
LH	luteinising hormone
LUTS	lower urinary tract symptoms
MRI	Magnetic Resonance Imaging
NCR	National Cancer Registry
ng/ml	nanograms per milliliter
NHLS	National Health Laboratory Services
OP	open prostatectomy
PAP	prostatic acid phosphatase
PCA 3	Prostate Cancer Antigen 3
PCa	prostate cancer
PIN	prostatic intraepithelial neoplasm
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PSA	prostate specific antigen
RCP	radical cystoprostatectomy
RP	radical prostatectomy
SA	South Africa
TNM	Tumour Node Metastasis
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UCSF	University of California, San Francisco

UK	United Kingdom
USA	Unites States of America

LIST OF APPENDICES

Appendix A Full datasheet

Appendix B Data collection sheet

Appendix C Charlotte Maxeke Johannesburg Academic Hospital patient admission form

Appendix D Steve Biko Academic Hospital patient admission form

Appendix E Template: Prostate biopsy request form

Appendix F Template: Prostate biopsy reporting form

Appendix G TurnitIn report

Appendix H Ethics Clearance

Appendix I Letter to Dr Elvira Singh, National Cancer Registry

Appendix J Letter to Dr Yvonne Perner, Department of Anatomical Pathology, Wits University

CHAPTER 1: INTRODUCTION

1.1. General introduction

Prostate cancer (PCa) poses a significant public health problem, causing morbidity and mortality in men older than 50 years around the world. It places a strain on the physical, psychological and financial resources of individuals and their families and places a financial burden on the state. It is the most common solid organ malignancy in men and the second most common cause of cancer related death after lung cancer [1]. The South African statistics from the National Cancer Registry report a lifetime risk of 1:28 [2]; while the American statistics report that 1:6 American males will get PCa. The prevalence of indolent PCa, which are small, well differentiated, low-risk tumours, at autopsy is similar throughout the world. However, the incidence of clinically apparent PCa during an individual's lifetime varies greatly across the world, as shown by global cancer statistics reporting the highest incidence amongst men of African origin, especially Afro-Caribbean men and lowest in Asian men [1 3]. The possible contributing factors for the difference in the incidence of clinically manifested PCa and indolent cancer include genetics and environmental influences, such as health seeking behaviour and diet [4].

As routine screening for PCa is not practiced nationally, patients who present to state facilities are screened opportunistically, or otherwise tested when they present with symptoms. Two papers published in May 2009 [5 6] from opposite sides of the Atlantic, which sought to lay to rest the debate on whether routine screening results in an improvement in mortality, reached opposing conclusions. The European Randomised Study for Screening of Prostate Cancer (ERSPC), which had enrolled just over 182,000 men, concluded that screening results in a decrease in PCa specific mortality [6]. The American- based study, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), which had enrolled 76,693 men, concluded that routine PSA (Prostate Specific Antigen) screening does not have an impact on PCa mortality [5]. In each of these two studies, the patients were randomised into two arms, one that was screened routinely for the development of PCa and the other that was subjected to the prevailing standard of care. The mortality trends between the two arms were monitored and conclusions drawn at the end of the data collection period. A further revision of the data collected in the two studies was carried out by Tsodikov et al. who aimed to evaluate whether the conclusions reached by the two studies were truly opposed after accounting for the

differences in implementation and settings of the two studies. The findings suggest that the ERSPC and PLCO provide compatible evidence that screening reduces PCa mortality [7].

A paucity of local data, specialist training in the country based on mostly American and European textbooks and materials, the ease of access of international journals as well as the ongoing interaction of local urologists with international urology bodies and associations suggests that the approach to patients in Africa is inferred from American and European data. Thus, an assumption is being made that Black patients in South Africa are like Black patients in America and the UK.

If the expression and clinical manifestation of PCa were a function of genes alone then that statement may possibly hold true. However, the environment plays a role the manifestation of the cancer. The Black patients contributing to both the USA and UK data are a vastly heterogeneous group; with some originating from West Africa or the Caribbean as slaves and living in those countries for many generations. Others are new immigrants who moved to the USA and UK having grown up in their native countries throughout the African continent and others reside in those countries for short-term reasons such as further education or work. Therefore, they cannot be grouped to a specific part of Africa, nor assumptions made about what they have in common, least of all their diet. These various groups may have a similar genetic makeup. However, their greatly varied environmental influences including diet, education level, income level, health seeking behaviours, as well as cultural and personal beliefs are such that the epigenetic impacts on those genes would result in differences in expression [8]. White patients in Africa are also a heterogeneous group. This begs the question whether data can be extrapolated from America and Europe to the White population in South Africa.

The South African National Cancer Registry (NCR) PCa data is histology based and anonymised [9]. Both of these are undesirable characteristics of a cancer registry. In order for a cancer registry to be robust, it should be population based taking into account a variety of factors such as histology, clinical findings, laboratory results and radiological features. It also should have patient names in order to prevent the same patient being captured twice for the same condition [10]. The South African population in the 2011 census was just over 51 million people, of which Black people made up 78.9% and White people made up 8.9% [11]. The NCR statistics for 2008 showed that 1899 Black men were recorded with PCa and 1809 White men. The

statistics for 2014 showed 2832 and 3237 for Black men and White men respectively. The internationally reported incidence of PCa in Black men is 47% higher than in White men [1], in a country where the population of Black people is 8 times more, these figures cast doubt on the process of data collection which feeds into the NCR statistics.

This study aimed to explore the incidence of PCa in sub-Saharan Africa, with specific reference to a tertiary academic hospital in an urban setting in South Africa. Within the resource constraints of both human and financial capital and the inequitable distribution of the available resources, the absence of a routine screening programme is a grave concern. The hospital records do not reflect race of the patients, it was not possible to explore the distribution of PCa incidence across the different race groups.

Hospital record keeping during the period of the study was on microfiche, with its inherent challenges. This made clinical information on treatment and follow up difficult to access. All that remained intact, complete and accessible were the National Health Laboratory Services (NHLS) biochemistry results and histology reports; these formed the basis of this study.

1.2. Literature Review

1.2.1. Anatomy and physiology of the prostate gland

The prostate gland, along with the paired seminal vesicles and the paired bulbourethral (Cowper's) glands are accessory sex glands found only in males. The prostate anatomy and physiology are well integrated to optimise its role in voiding, sexual function and fertility.

1.2.1.1. Anatomy

a. Surface anatomy

The prostate is an inverted pyramid-shaped gland with a base that sits against the bladder neck and an apex that rests on the pelvic floor, as shown in Figure 1.1.[12]. It lies caudal to the urinary bladder and anterior to the rectum. The prostatic part of the urethra runs through the middle of the prostate and bisects it into a left and right lobe and the prostatic ducts open into the urethra. The normal prostate weighs about 20g and the location of the prostate lends itself to transrectal, transperineal and transurethral routes for sampling.

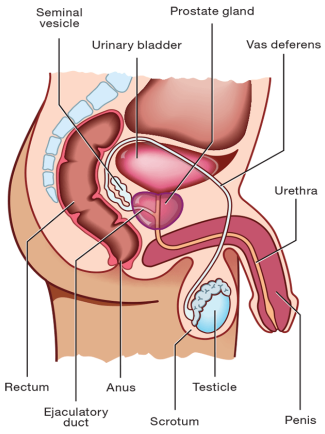


Figure 1.1: Anatomical relations of the prostate [12]

b. Gross anatomy

The prostate is made up of three zones: the peripheral zone, central zone and transitional zone as shown in Figure 1.2 [13]. The majority of prostate cancers arise in the peripheral zone [5].

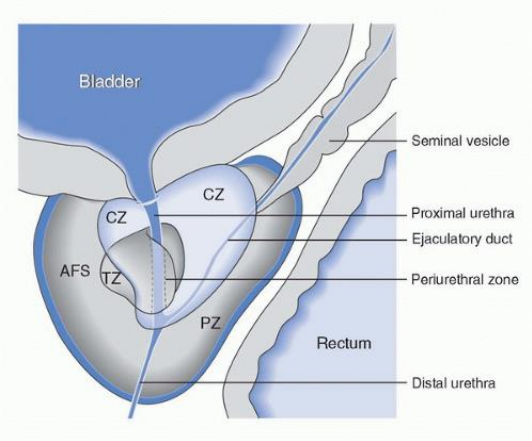


Figure 1.2: Zones of the prostate [13]

c. Histology of the prostate gland

The prostate gland is made up of tubulo-alveolar glands comprised of ducts and acini that are surrounded by a fibromuscular stroma, as shown in Figure 1.3 [14]. The glands are lined with columnar epithelium, which has a secretory function and rests on a basal cell layer. The fibromuscular stroma makes up 70% of the prostate gland and consists of connective tissue and smooth muscles [15].

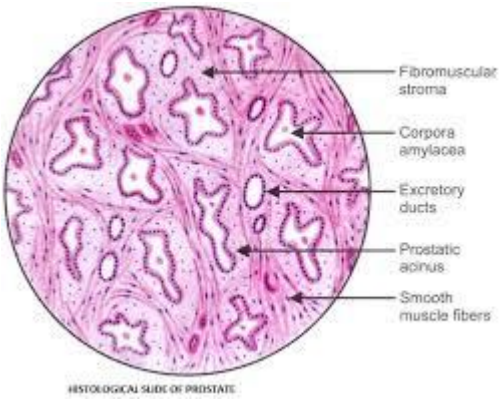


Figure 1.3: Histology of the prostate [14]

1.2.1.2. Physiology

Prostatic development, growth, maintenance and secretory function are under the influence of testosterone, which is produced by the Leydig cells of the testes.

The enzyme 5-alpha reductase is found in the prostate and converts testosterone to dihydrotestosterone (DHT). DHT is 5 times more potent than testosterone and is found at concentrations of 1.5 to 2.5 times those of testosterone. DHT is the major androgen within

the prostate, regulating growth, differentiation and function [16]. The adrenal gland also produces androgens that circulate in the serum at low concentrations. These include dehydroepiandesterone and androstenedione, which contribute less than 1% of the circulating androgens in the male and have been shown to have no effect on prostatic growth and function [17].

Prostatic fluid makes up about 20% of semen volume. It is secreted by the glandular cells within the prostate and is responsible for liquefaction of the coagulum following ejaculation. It is slightly acidic with a pH of 6.4 and contains spermine for the motility of sperm, spermidine, prostaglandins for uterine stimulation, zinc which affects testosterone metabolism within the prostate, citric acid which is a buffer, immunoglobulins, phosphatases and proteases. The prostate and the bladder neck control the flow of urine and semen during ejaculation. During micturition, the bladder neck, prostatic urethra and pelvic floor (striated sphincter) relax under parasympathetic regulation to allow the antegrade flow of urine. During ejaculation, which is under sympathetic control, the smooth muscles within the prostate contract leading to expulsion of prostatic fluid, the smooth muscles of the bladder neck also contract to prevent the flow of urine and ensure antegrade ejaculation.

1.2.2. Risk factors for prostate cancer

Risk factors within the environment or innate within a person, increase the likelihood of having an event occur, such as developing PCa. Having a risk factor does not guarantee that a person will get cancer, nor does the absence of any identifiable risk factors ensure that a person will not get PCa. At present three non-modifiable and established risk factors for PCa are recognized. These are age, race and family history. Other potential risk factors are less well established and potentially modifiable. These include circulating reproductive hormones and lifestyle habits such as diet, the use of cigarettes, the consumption of alcohol and the frequency of ejaculation [18].

1.2.2.1. Age

Prostate cancer is rarely diagnosed in males younger than 50 years of age. People younger than 50 years of age account for only 2% of all cases of PCa [19]. This incidence marks a ten-fold increase in the reported incidence in this age group over a 29-year period, from 1974 to 2003. This can be partially attributed to an increase in the screening for PCa, which has led to a 50% increase in the incidence between 50 and 59 years of age [20]. The peak incidence typically

occurs between the ages of 70 and 74 years, with the mean age at diagnosis being 68 years, with 63% diagnosed after age 65 years [21]. At age 85 years, between 0.5 and 20% of men worldwide will have been diagnosed with clinically significant PCa, yet at autopsy over 75% have microscopic evidence of PCa [22].

1.2.2.2. Race and ethnicity

African-Americans and Caribbean men of African ancestry have the highest incidence of PCa in the world. African-Americans are twice as likely to die from the disease as their White counterparts are. Asians in Asia have the lowest incidence in the world. However, Asians in America and those adopting a more Western lifestyle have a higher incidence than native Asians do, which is still lower than that of African-Americans. This calls into question the role that the environment has on this disease, including lifestyle and diet. [1].

Based on their seminal study Kheirandish and Chinegwundoh [23] proposed other possible explanations to account for the differences in the clinical course of the disease from presentation, through treatment and finally onto mortality between the races in America. These include health education and access to quality healthcare. In their study, they showed that there were no differences in these parameters between the races in the United Kingdom, where there is a National Healthcare Insurance, ensuring equal access to quality care regardless of race or socioeconomic status [23].

Studies by Fowler et al. (2000) and Powell (1998), evaluating the histological features, stage and response to treatment of the different races within the Veterans Administration in the USA found no difference when personal finances and level of education were accounted for. A study in South Africa by Slabber (1992) found that White South Africans had PCa rates similar to men living in Britain and that this could in part be due to White South Africans being wealthier and having greater life expectancies than Black South Africans [24]. Biologic, genetic and environmental factors influence the manifestation of cancer. As do access to health and socioeconomic status, the so-called social determinants of health. Some studies have suggested that social factors such as willingness to seek treatment besides may also contribute to the poorer outcomes for PCa in Black Americans compared to White Americans [1].

1.2.2.3. Familial and genetic influences

For investigative purposes, PCa is divided into three phenotypes: sporadic, familial, and hereditary. Sporadic cancers occur in individuals with no family history of PCa. Familial PCa is

defined as cancer in a man with one or more affected relatives. Hereditary PCa is a subset of the familial form and has been operationally defined as nuclear families with three or more affected members, PCa in three successive generations, or two affected individuals diagnosed with cancer before the age of 55 years [25].

Epidemiological evidence supports the assertion that PCa has a genetic and familial component as shown in Table 1.1 [26]. The relative and absolute risk of PCa increases if there is a family history of PCa. Up to 10% of PCa cases and 30-40% of cases of early onset of disease are inherited in a dominant pattern. Hereditary PCa presents on average 6-7 years earlier than sporadic PCa, with the result that a greater proportion of these patients die of the disease [27].

Table 1.1: Family history and risk of prostate cancer [26]

FAMILY HISTORY	RELATIVE RISK	ABSOLUTE RISK (%)
None	1	8
Father or brother	2	15
Father or brother affected < 60 years	3	20
Father and brother	4	30
Hereditary prostate cancer	5	35-45

The earliest reports of familial clustering of PCa, with a higher incidence in men with a first-degree relative, either a brother or father with the disease, came out in the 60's [28]. These have subsequently been confirmed in case-control and cohort studies, including twin studies of both monozygotic and dizygotic twins. The relative risk increases according to the number of affected family members, their degree of relatedness, and the age at which they were affected [27].

Eight PCa susceptibility genes have been identified thus far, from genome-wide scanning of familial clusters. Linkage studies have mapped hereditary PCa to the long arm of chromosome 1, Hereditary Prostate Cancer (HPC1 on 1q24–25), as well as other loci, namely Predisposing for Cancer Prostate (PCAP on 1q42.2–43), Cancer Prostate and Brain (CAPB on 1p36), HPCX (Xq27–28) on the long arm of chromosome X and 16q [29]. The best studied and characterized of the susceptibility genes is HPC1. It is a rare, autosomal dominant gene with high penetrance, meaning that although it does not account for many prostate cancers, an individual who is a

carrier is highly likely to be affected by PCa. Cancers linked to HPC1 have been reported to present with higher grade and more advanced stages, although there are no reported histologic differences when compared with sporadic cancers [30].

Regarding the clinical course, there are opposing findings in various studies. Some concluded that there is no difference in outcomes between the sporadic and the hereditary forms of the disease [26] [2016], while others found hereditary forms of PCa to behave more aggressively including those with low Gleason score [31].

1.2.2.4. Reproductive hormones

Both testosterone and estrogens have a direct and indirect influence on the development and functioning of the prostate, starting in utero and continuing into adult life. An alteration in their ratio following andropause, when testosterone levels decline but estrogen levels remain stable, is proposed as a possible contributor to the development of PCa [32].

a. Testosterone and other androgens

Androgens, namely testosterone and its metabolite DHT play a role in the development, maturation and maintenance of the prostate. Testosterone is produced by the Leydig cells within the testes. It is converted to the active form DHT within the prostate under the influence of the enzyme 5-alpha reductase. These androgens influence the proliferation and differentiation of the luminal epithelium where PCa occurs and play a role in prostate carcinogenesis [33].

One hypothesis attempting to explain the higher incidence of PCa observed in African Americans suggests that this may be related to elevated levels of circulating androgen. A study by Ross et al. (1992) demonstrated that young African American men have a 15% higher total circulating testosterone level compared to Whites of similar age [34]. Japanese men have amongst the lowest incidences of PCa. Ross and Bernstein also showed that young Japanese men had androgenic evidence of reduced 5-alpha reductase activity compared with young Black and White men and raised the possibility that this reduced activity may play a role in the low cancer rates amongst the Japanese [34]. Further support for the role of androgens in the PCa pathway is the absence of PCa in eunuchs. These men, whose testes have been removed, do not develop PCa [1].

b. Estrogen

Studies on the role of estrogens in PCa have shown conflicting results. The work by Prezioso et al. (2007) suggests that they protect against PCa by inhibiting prostate epithelial cell growth and that PCa is rare in communities whose diet is rich in phytoestrogens [32]. While the findings of a study by Naslund and Coffey (1986) suggests the opposite; that by acting in concert with androgens, estrogens elicit inflammation and thus increase the risk of PCa [35]. Estrogen has a physiological effect on the development of the prostate. A study by Prins et al. (2006) using a rat model showed that in high doses at a critical developmental period, estrogen causes a disruption in prostatic morphogenesis, a process known as neonatal imprinting or developmental estrogenisation. This results in prostate growth and differentiation being under the influence of estrogen, rather than androgens; leading to an abnormal and pathological response to androgens in later life including hyperplasia, inflammation, dysplasia and potentially neoplasia [36].

1.2.2.5. Lifestyle habits

Lifestyle factors such as diet, the use of cigarettes, the consumption of alcohol and frequency of ejaculation may influence the development of PCa. Some of these factors may also have an impact on treatment choices and thus survival outcomes; for example, respiratory insufficiency secondary to smoking will influence the patient's ability to tolerate radical surgery with curative intent.

a. Dietary Factors

Diet has been shown to have an influence on PCa. The diet of men is influenced by, among others geography, culture, socioeconomics and urbanization [37]. Foods may be metabolised to carcinogens, they may interfere with the balance of hormones and they may contain minerals, vitamins and other protective nutrients. Diet impacts on levels of circulating androgens, high fibre and vegetarian diets are associated with lower testosterone levels. Nutrients such as lycopene and selenium have a protective effect, while poly- unsaturated fats have a harmful effect. Migration studies offer the best evidence for the role that diet and other environmental factors contribute to the development of PCa. The level of fat consumption has been shown to correlate positively with PCa incidence and mortality in Black, White and Asian Americans. High fat intake stimulates growth of PCa cells both in vivo and in vitro. However, the high fat diets may be deficient in other products such as vegetables, which may play a protective role against PCa [38].

The rate of latent or indolent cancer is the same throughout the world, yet the incidence of clinically manifest cancer varies. Asians from Japan and China, have very low rates of PCa. The higher rate of clinically apparent PCa as seen in first-generation Asian immigrants to America, who are exposed to diet high in saturated fats and meat products compared to their counterparts who do not emigrate, favours the theory of a Western diet as a possible contributor to the carcinogenic process [39]. This theory is further supported by the increasing rate of PCa in both Japan and China with the introduction of Western diet [1].

b. Smoking and Alcohol

Smoking and moderate alcohol consumption have not been shown to cause PCa. There is no evidence showing that smoking directly causes PCa [40]. However, it has been shown that smokers have higher rates of PCa and a higher mortality from PCa [41]. Smoking may indirectly worsen the outcomes from PCa in a number of ways:

- Cadmium, which is found in cigarettes, is a carcinogen and may play a role in the development of the more aggressive type of PCa found in smokers.
- Smoking causes significant cellular oxidative stress.
- Smokers have higher levels of circulating testosterone.
- Smokers tend to be less healthy than non-smokers and may thus not present for screening.
- Smokers may have other co-morbidities that may make some treatment options more risky to their health.

A review of relevant epidemiologic studies by Breslow and Weed showed no increased risk for the development of PCa among light to moderate drinkers [42]. A prospective cohort study by Sesso et al. (2001) showed a dose-dependent increase in PCa risk. This was highest in those imbibing more than three hard liquor drinks per day (relative risk, 1.85) over a period of 11 years [43]. There was no association with intake of beer or wine, and in fact the consumption of moderate amounts of red wine, 1 -3 units per week, seemed to confer a protective effect even when adjusted for age, PSA screening, total lifetime number of female sexual partners, and smoking [44].

c. Sexual Activity

One of the theories of the development of PCa looks into the possibility of an infectious causative agent being involved, like human papilloma virus (HPV) in cervical cancer in females.

It looks at the role of early sexual activity and thus exposure to the agent. Some studies have found a link between early sexual intercourse, number of sexual partners and PCa [45]. These findings have however been inconsistent [46].

Frequent ejaculation has been shown to have a protective effect against PCa. A study by Giles et al. (2004) showed that men who reported more than five ejaculations per week in their early 20's were protected [47]. A large prospective cohort study by Leitzmann and Rohrmann (2012) demonstrated a protective effect for men reporting 21 or more ejaculations per month in their 20s, in their 40s, in the previous year and as a lifetime average [18]. The biologic basis for this effect is unknown.

1.2.3. Prostate cancer incidence and mortality in South Africa

Cancer surveillance takes into account incidence data, i.e. new diagnosis and mortality data as per death certificates. The ratio of mortality to incidence gives a measure of the lethality of a particular cancer. Highly lethal cancers such a liver, pancreas, esophagus and lung have mortality rates close to incidence rates, whereas breast, colon and prostate have considerably lower ratios of 0.36, 0.51 and 0.32 respectively, i.e. 3 of 10 patients with PCa will die of the disease. [48].

In South Africa, the incidence data as supported by histological confirmation and demographic data is sent to the National Cancer Registry (NCR) by the National Health Laboratory Services (NHLS), universities, military services and private pathology laboratories. This is done in an anonymised format as in the past concerns over patient confidentiality and data security lead some of the contributors to discontinue participating in the surveillance data collection programme. The anonymisation of identifying data has, however, had the unintended consequence of some patients being entered into the registry more than once, for example in a case of PCa, initially the positive core needle biopsy is captured and later the positive radical prostatectomy or channel TURP specimen is also captured. The Medical Research Council (MRC) Burden of Disease unit collects the mortality data. The incidence data as held by CANSA for 2008 is shown in Table 1.2. According to Statistics SA, 8% of deaths in SA are due to cancers. The mortality data as reported in the document for the activation of Cancer Research Initiative of SA (CARISA) and how South Africa compare to USA and world figures is shown in Table 1.3 [48].

Table 1.2: Prostate cancer incidence by race in SA, CANSA (2008) [48]

	NUMBER OF CASES	LIFETIME RISK
All men	4,307	1:28
Asian men	118	1:36
Black men	1,899	1:41
Coloured men	481	1:23
White men	1,809	1:15

Table 1.3: SA incidence and comparative mortality [48]

SA INCIDENCE PER 100,000	SA MORTALITY PER 100,000	USA MORTALITY PER 100,000	WORLD MORTALITY PER 100,000
24	27	29	25

When the South African mortality data from 2000 was studied against the NHLS incidence data of 1999, it was found unexpectedly and impossibly that the mortality rates of 6 of the top 10 most common cancers (lung, esophagus, stomach, non-Hodgkin's lymphoma, liver and bladder) were significantly higher than the incidence rates, i.e. there were more people dying of the disease than there were people reported with the disease. This points to a suboptimal functioning and thus unreliability of the registry with probable large scale under-reporting. It is important to determine the reasons why details of known cancer patients do not reach the NCR and to address them in order to optimise the cancer surveillance infrastructure in South Africa and to create a strong foundation for cancer research and control. In the absence of such we cannot win the war against cancer.

1.2.4. Clinical presentation

More men are said to die with PCa, rather than because of it [49]. Patients with PCa are often asymptomatic. Prostate cancer has an average symptom free lead-time of 10 to 12 years, prior to diagnosis [50].

The presence of symptoms, specifically lower urinary tract symptoms (LUTS) indicates either locally advanced disease or concurrent benign prostatic hyperplasia (BPH). Locally advanced

disease may present with obstruction of the adjacent structures. Alternatively, the patient may present with evidence of distant, systemic metastases.

The discovery and use of tumour markers have positively influenced early detection, diagnosis and staging for many malignancies. The use of tumour markers for screening can lead to earlier detection of malignancies while still localised, which in turn leads to an improved cure rate [51].

Tumour markers also influence another aspect of optimal management of cancer, in that they allow reliable follow-up for detection of biochemical recurrence. As we identify and develop new and more sensitive markers, this will hopefully further improve diagnosis, risk stratification and subsequently cure rates. The flipside of the role played by early detection and treatment based on tumour marker results, especially as used in screening programmes, is the psycho-emotional impact of diagnosing potentially insignificant tumours, as well as the physical and financial impact of treating them. Even though a consensus has been reached on the value of PSA screening on PCa mortality [7], the management options must be individualised in consultation with the patient within the resources available.

1.2.4.1. Prostate Specific Antigen

a. The discovery of PSA

Prostate cancer biomarkers can be divided into tissue, blood, urine and cellular biomarkers. The most commonly used is PSA, which is a serum biomarker. PSA was first discovered in 1979, and clinically applied in 1986 for monitoring men with PCa and in 1994 for screening for PCa [52 2001a]. PSA is produced by the epithelium of the prostate, secreted by the prostatic ducts and makes up part of semen. PSA plays a role in the liquefaction of the ejaculate and is most plentiful within the prostate, but can be detected in blood.

PSA is produced from transcription and translation of genes that belong to the human kallikrein family. Three genes from this family were first identified pancreatic/ renal kallikrein (HKLK1), human kallikrein 2 (HKLK 2) and PSA (HKLK3). Twelve other kallikrein genes have been identified, bringing the total number to fifteen [53]. They are located on the long arm of chromosome 19. HKLK 2 has a regulatory function on PSA activity; it cleaves pro-PSA to the PSA active form. PSA is a 33 kDa androgen-regulated glycoprotein made up of 237 amino acids and acts as a serine protease.

In 1987, Stamey et al. conducted one of the first large studies to determine if PSA was an adequate tumour marker [54]. Their findings showed a correlation between a worsening pathological grade of cancer with an increasing PSA level, i.e. the worse the grade the higher the PSA. They also found that PSA was undetectable following prostatectomy.

At that time, prostatic acid phosphatase (PAP) analysis was being used as a marker for PCa [55]. It is raised in bone pathology, including bony metastases of PCa and Paget's disease of the bone. In the setting of PCa, raised PAP levels imply bone metastases and the disease process is thus no longer localised to the prostate and therefore no longer amenable to curative therapy [54].

Since that time, the role of PSA in the management of PCa has evolved as approval from the Food and Drug Administration evolved. It was initially used in patients who had already been diagnosed with cancer and from 1994 was used as a screening tool for patients suspected of having PCa. In 1998, the free-PSA test was approved to help determine the risk of PCa in men with a total PSA value found to be between 4 and 10ng/ml [52].

In the 1980's and early 1990's the majority of PCa were diagnosed based on the presence of either an abnormal digital rectal examination (DRE) or a raised PSA or both. The two together are 25% more sensitive for picking up early PCa, than either one alone [52]. Today most PCa is diagnosed as stage T1c, i.e. clinically undetectable disease, with a normal DRE and PSA levels between 2.5 and 10ng/ml. This has led to a downward stage migration in PCa diagnosis, as well as a corresponding reduction in mortality [56].

Currently the PSA value that triggers a prostate biopsy is 4ng/ml. However, the American Urology Association (AUA) guidelines recommend that a cut- off value of 2,5ng/ml be used if the patient has risk factors for PCa such as ethnicity (African descent) or a family history of PCa [57], as per the race based cut-offs [58].

Furthermore, PSA derivatives and isoforms, such as PSA velocity, PSA density and PCA3 may be used to better define a patient's risk and thus the need for further invasive testing.

b. The lower limit of PSA

For many years, PSA values ranging between 0 and 4ng/ml were regarded as normal. This assumed that men with a PSA of less than 4ng/ml had a negligible chance of having PCa. It was not recommended for those men to undergo prostate biopsy. The findings of the Prostate

Cancer Prevention Trial (PCPT) however, changed this thinking [59]. The aim of the 7-year trial which concluded in 2003, and had enrolled 18,882 men was to determine if the daily use of finasteride would lead to a decrease in the prevalence of PCa, as opposed to those men who took a placebo. The study concluded that finasteride did confer protection from PCa and found that those men who developed PCa while on finasteride had higher grade disease. Further evaluation of the study concluded that those high-grade cancers were unmasked, rather than caused by the finasteride [59].

Further findings of the PCPT study indicated that there was no PSA value at which a man had a 0% chance of having PCa. Additionally, of the 2,950 participants whose PSA level never rose above 4ng/ml, 449 (15.2%) were found to have PCa, half of whom had intermediate or high-grade disease with a Gleason score of ≥7. A further 1,246 (6.6%) with PSA ≤ 0.5ng/ml also had PCa on biopsy. The researchers then divided the PSA values into seven strata, where they matched PSA values that were previously thought to be normal at < 4ng/ml with a numerical figure of risk of PCa biopsy, as shown in Table 1.4 [60 61].

Table 1.4: Risk of detecting prostate cancer on prostate biopsy based on PSA[60-61]

TOTAL SERUM PSA LEVEL (ng/mL)	RISK OF PROSTATE CANCER PER BIOPSY (%)
≤ 0.	6.6
0.6–1.0	10.1
1.1–2.0	17
2.1–3.0	23.9
3.1–4.0	26.9
4.1–10.0	47
>10.0	58.2

c. Age and race/ ethnicity-based PSA reference ranges

It is commonly accepted that as a man ages his PSA will increase. This increased value is attributed to an increase in the size of the prostate over time. A review by Richardson and Oesterling (1997), set out to determine age-specific reference ranges for PSA in men of different races. The men were grouped into four decades and the acceptable, not normal as there is no normal value for PSA at which the risk of cancer is zero, ranges were determined and found to be lower for Asians and African-Americans than Caucasians and are shown in Table 1.5 [62].

Table 1.5: PSA reference ranges by age and race [62]

UPPER LIMIT OF PSA LEVEL (ng/mL)			
AGE (YEARS)	BLACK	ASIAN	WHITE
40–49	2	2	2.5
50–59	4	3	3.5
60–69	4.5	4	4.5
70–79	5.5	5	6.5

d. Factors other than cancer which affect PSA

Changes in PSA are specific to the prostate gland and not to PCa. Thus, it may be increased by factors other than PCa. Its value fluctuates on a day-to-day basis. Table 1.6 [63] below shows a list of other factors that can influence the PSA value.

Table 1.6: Factors that influence PSA levels [63]

Factors affecting PSA levels
Age
Race and ethnicity
Medication, including treatment for balding
Prostatic inflammation (integrity of prostatic cellular architecture)
Benign prostatic hyperplasia
Digital rectal examination
Urological instrumentation
Ejaculation
Treatment of prostatic disease
Androgens
Body mass index (BMI)
Laboratory kit

1.2.4.2. Localised disease

The assessment of both a DRE as well symptoms will point to the possibility of PCa being present in a patient. Localized disease typically presents with LUTS much like in patients with prostatic enlargement due to BPH.

Lower urinary tract symptoms comprise of the storage symptoms of frequency, urgency, nocturia and the voiding symptoms of weak stream, incomplete emptying, intermittency and straining. These are quantified using the international prostate symptom score (IPSS) questionnaire [64]. Prostate cancer involves the periphery of the gland in 70- 85% of cases [65]. Compression of the prostatic urethra by prostatic cells in the transitional and central zones causes LUTS, which could indicate locally advanced tumour with a large tissue bulk. They could also indicate a tumour which primarily involves the transitional zone, these account for about 5-15% of PCa, or very rarely central zone involvement which account for up to 2.5% of all PCa [66].

Prior to the biochemical era with the use of PAP and later PSA, clinicians depended solely on the abnormalities palpated on DRE to determine the presence of PCa. Any abnormalities on DRE such as nodules, irregularity, asymmetry, hardness or cragginess mandate further evaluation for the possibility of PCa [67]. Biochemical testing alone is more sensitive than DRE alone, however DRE is simple to do and palpable abnormalities correlate highly with PCa, such that most urologists perform it together with PSA. A raised PSA increases the positive predictive value of DRE. On its own PSA has a greater detection rate than DRE, but the two together have the highest detection rate [68]. Due to PSA and DRE not always detecting the same cancers, the tests are considered complementary and are recommended in combination as methods of assessing PCa risk [69].

Locally advanced PCa cancer can invade the bladder neck causing LUTS; the trigone and ureteric orifices leading to hydronephrosis and renal failure; the ejaculatory ducts causing haematospermia, decreased ejaculatory volume and dyspareunia; as well as the periprostatic neurovascular bundles that innervate the corpora leading to erectile dysfunction or dyspareunia as dictated by the anatomy of the adjacent structures.

1.2.4.3. Metastatic disease

Over 80% of distant metastases from PCa are to bone. This may lead to systemic manifestations such as anaemia due to bone marrow suppression; hypercalcaemia due to bone destruction; bone pain, immobility and spinal instability secondary to pathological fractures and neurological fall-out due to nerve root impingement or spinal compression [70].

The vascular spread of cancer leads to bony and soft tissue metastases as shown in Table 1.7[71] Prostate cancer most commonly metastasizes to the skeleton and later to the soft tissues such

as lung and liver. It initially spreads to the axial skeleton and later the appendicular skeleton, presumably via retrograde haematogenous spread through Batson's plexus [72]. The possibility of skeletal metastases is raised by a history of bone pain, the biochemical finding of a PSA greater than 20ng/ml [73] and a raised serum calcium or raised serum alkaline phosphatase [74]. Suspected bone metastases are confirmed on radionuclide bone scan [75]. Bone metastases in PCa are typically osteoblastic/osteosclerotic in nature and can be detected on radionuclide bone scan. A study by Kamaleshwaran et al. (2012) showed that 98% of patients with PCa and a PSA of ≥ 20ng/ml had a bone scan positive for metastatic disease, 28% had a PSA between 20 & 100, and 70% had PSA ≥ 100. In their study patients with PSA >100ng/ml were found to have multiple bone metastases [76].

Table 1.7: Typical distribution of metastatic sites in patients with hormone-resistant prostate cancer entered in clinical trials [71]

INVESTIGATOR	TOTAL NO. OF PAT IENTS	BONE	SOFT TISSUE– NODAL	LUNG	LIVER
Pienta (1994)	42	42 (100%)	13	3	5
Sella (1994)	39	36 (92%)	9	3	3
Moore (1994)	27	22 (81%)	10	2	2
Eisenberger (1995)	109	108 (99%)	15	6	4
Hudes (1992)	36	36 (100%)	7	0	2
Tannock (2004)	1,006	915 (91%)			
Petrylak (2004)	674	579 (86%)	168	67	57

Infrequently, PCa may spread to the soft tissues, such as lung, liver and brain, in this order of frequency, through antegrade venous spread via the inferior vena cava into the systemic circulation [72]. This may also be a sign of neuroendocrine transformation of the adenocarcinoma [77]. Only 10% of patients with PCa have soft tissue metastases, with about 20% having demonstrable nodal metastases [78]. In the lungs, PCa causes the typical appearance on chest x-ray of lymphangiitis carcinomatosis, which may be associated with respiratory embarrassment [79]. In the liver, it causes raised bilirubin levels and raised alanine transaminase and aspartate aminotransferase secondary to the destruction of normal hepatocytes with

release of these intracellular enzymes into the circulatory system [80]. In the brain, PCa causes symptoms and signs related to the presence of a space - occupying lesion in a confined space, including confusion and delirium, raised blood pressure, coma, coning and death. Brain metastases are more common in an adenocarcinoma of the prostate which has undergone neuroendocrine differentiation [81].

Rarely, PCa can cause paraneoplastic phenomena from ectopic hormone production. These are signs and symptoms caused by the tumour producing hormone-like substances that have an effect distant from the primary tumour and are not due to metastatic disease. The dysfunction can be endocrine or neurological in nature and includes hypercalcaemia, hypertension, polycythaemia and peripheral neuropathy. Prostate cancer is the second most common urological malignancy to cause paraneoplastic phenomena, after renal cell carcinoma. [82].

1.2.4.4. Tumour, Nodes and Metastases staging in prostate cancer

The tumour, node and metastases (TNM) classification is applied to malignant tumours. It takes those three parameters into account and is used to clinically stage patients with suspected cancer. It is also used in research to prognosticate patients, allocate treatment, for enrolment into trials and for data collection by cancer registries around the world. In the setting of PCa, histological confirmation together with this information as shown in Table 1.8 [83], is used to determine the extent and severity of the disease, and used to guide treatment. Various clinical tools are used to determine the TNM stage, the clinical significance of the disease and to risk stratify the patients. These clinical findings including DRE, laboratory and radiological findings. If a radical prostatectomy is performed to treat the cancer, the TNM stage can be further refined using the post-operative histology [84].

Table 1.8: TNM staging for prostate cancer, 2017 classification [83]

TUMOUR
TX Primary tumor cannot be assessed T0 No evidence of primary tumor T1 Non-palpable tumor—not evident by imaging: T1a - Tumor found in tissue removed at TUR; 5% or less is malignant and histologic grade <7 T1b - Tumor found in tissue removed at TUR; >5% is malignant or histologic grade >7 T1c - Tumor identified by prostate needle biopsy due to elevation in PSA T2 Palpable tumor confined to the prostate: T2a - Tumor involves one lobe or less T2b - Tumor involves more than half of one lobe T2c - Tumor involves more than one lobe T3 Palpable tumor beyond prostate: T3a - Uni or bilateral Extra-capsular extension T3b - Tumor invades seminal vesicle(s) T4 Tumor is fixed or invades adjacent structures (not seminal vesicles): T4a - Tumor invades bladder neck, external sphincter, and/or rectum T4b - Tumor invades levator muscle and/or fixed to pelvic wall
REGIONAL NODES
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastases

N1 Regional lymph node metastases
DISTANT METASTASES
M0 No evidence of distant metastases
M1 Distant metastases
M1a Non-regional lymph nodes
M1b Bones
M1c Other sites

1.2.5. Confirming the diagnosis on histology

The triad of abnormal DRE, raised serum PSA and a transrectal ultrasound (TRUS) guided biopsy is used to make the diagnosis of PCa. The combination of DRE and serum PSA is the most useful first-line test for assessing the risk of PCa being present in an individual [68].

In most cases, the diagnosis of PCa is confirmed on the histology features found on a prostate biopsy. A raised PSA or an abnormal DRE raise the suspicion of PCa and trigger the clinician to perform a prostate biopsy to confirm the diagnosis. In some instances, the diagnosis may be made on the histology of prostatic tissue removed by transurethral resection of the prostate or open prostatectomy in which case there was no suspicion of cancer prior to going to the surgical procedure. In yet other instances, the diagnosis may be made following assessment of metastatic lesions.

A research group in Stellenbosch, South Africa, proposed another method to diagnose PCa based on clinical and biochemical findings without using histology to confirm the diagnosis. Their findings showed that the patients in whom the clinical suspicion of PCa was confirmed on histology and those in whom it was not, had similar outcomes in terms of mean follow-up (26.1 v. 26.8 months), documented PSA relapse (70% v. 67.7%) and patients alive at last follow-up (91.1% v. 95.8%). This approach was also associated with significant financial savings. ZAR1 068 200 (US$1 = ZAR8) was saved by treating the 218 men with advanced PCa diagnosed on the basis of a clinical (non-histological) findings only during the 11-year period of the study [85].

1.2.5.1. Prostate biopsy

Before the use of TRUS and PSA gained mainstream popularity, urologists relied on DRE to establish the suspicion of PCa and performed digitally directed biopsies of the lesions palpated. The availability of and improvements in TRUS technologies as well as PSA-based screening of asymptomatic men, have led to the TRUS biopsy being regarded as the standard of care for routine prostate biopsies [86]. The indications for prostate biopsy are shown in Table 1.9 [71]. These have expanded over time and are continually being refined. A few contra-indications to prostate biopsy also exist, namely significant coagulopathy, painful anorectal conditions, severe immunosuppression and acute prostatitis.

Table 1.9: Indications for TRUS directed prostate biopsy [71]

TRUS directed biopsy
• Diagnosis of suspected symptomatic PCa (i.e. bone metastasis, cord compression, haematuria) • Screening for PCa in asymptomatic patient > age 50 with > a 10-year life expectancy • If strong family history or of African descent, consider screening earlier at age 40 according to the AUA or 45 years according to the EAU • Prostate nodule or significant prostate asymmetry regardless of PSA level • PSA > 4.0ng/ml regardless of age • In men age 60 to 65 years, consider biopsy if PSA > 2.5ng/ml • If PSA > 0.6ng/ml at age 40 • Increased PSA velocity (>0.75ng/ml/year) • If PSA < 10ng/ml, measure free PSA to guide decision on biopsy: - >25% no biopsy - >10% and <15%, consider biopsy - <10%, biopsy • Prior to intervention in symptomatic benign prostatic hyperplasia (e.g., surgical therapy or initiation of 5α-reductase inhibitors) • Prior to cystoprostatectomy or orthotopic urinary diversion • To diagnose failed radiation therapy before use of second-line therapy • Follow-up biopsy (3-6 months) after diagnosis of high-grade PIN or ASAP

a. Transrectal Ultrasound

In the United States in 2008, the estimated number of deaths due to PCa was 29,000, which was 25% fewer deaths than a decade earlier. Amongst the factors purported to have led to this decrease in mortality is early detection as aided by the introduction and refinement of systematic transrectal ultrasound (TRUS) guided prostate biopsy techniques, PSA screening efforts and an increased public awareness about PCa [87].

Watanabe et al. (1974) first described TRUS of the prostate in 1974 [88]. Improvements in ultrasound technology and the introduction of the TRUS-guided systematic sextant biopsy protocol by Hodge and associates in 1989 led to its expansion and adoption into routine

clinical use. An estimated 500, 000 prostate biopsies are conducted annually in the USA [89]. With such large numbers of men undergoing TRUS guided biopsies it behooves the urological community to continuously work towards refining the indications and techniques to image and biopsy the prostate.

Other than in guiding prostate biopsies, TRUS has found applications in many image-guided prostate interventions; including brachytherapy, cryotherapy, high-intensity focused ultrasound in cases of PCa, as well as use in evaluating the appropriateness of various therapeutic options in benign prostatic disease as large prostates tend to fail medical therapy and need to be treated surgically [90].

The transrectal ultrasound is typically conducted either with the patient in the left lateral position or in lithotomy position depending on the procedure to be performed. The prostate is scanned in both the sagittal and transverse plane. Transrectal ultrasound may be done under local anaesthesia (topical intrarectal lubricant agents or nerve blocks administered via the periprostatic, pudendal or caudal routes) or systemic anaesthesia (oral/intravenous drug administration) as informed by the procedure being done [91].

b. Prostate biopsy routes

The majority of patients requiring a prostate biopsy will have a transrectal biopsy done. However, in some patients either the transperineal or the transurethral route may be indicated. Patients who do not have a rectum, usually due to surgical excision, are candidates for the use of the transperineal route. Patients whose clinical course leads the clinician to suspect a transitional zone (TZ) cancer may have their biopsy done via the endoscopic transurethral route. In the study by Pelzer et al, transitional zone cancers without concomitant peripheral zone involvement occurred in less than 5% of patients [92]. Improvements in the TRUS techniques and local anaesthesia techniques allow the transitional zone to be sampled adequately using the transrectal route as an office procedure, with a decreasing need to use the transurethral route, which is done in theatre [93].

c. Core needle biopsy technique: the number of cores on prostate biopsy

There have been continuous efforts to determine the ideal number of cores for collection. The original sextant biopsy scheme has been modified to the current systematic or extended biopsy technique [86].

The number of cores reportedly collected by the urologist do not always match the number of cores received by the pathologist. Possible reasons for this include the gun may be fired and no tissue is captured in the needle, which would result in fewer cores received than stated or the prostate cores may break during transport, handling and processing and this would result in more cores being received than stated.

Sextant biopsy technique

In this collection scheme, six cores are collected; one from the base, one from the middle and one from the apical part of each half of the prostate. The adoption of this scheme improved the rate of cancers detected compared to the preceding techniques of digitally directed biopsies of palpable nodules and ultrasound-guided biopsies of hypoechoic lesions [94]. This technique samples the peripheral as well as portions of the transitional zones of the prostate. Later studies of radical prostatectomy specimens showed that the vast majority of PCa originate in the posterolateral peripheral zones [15]. This accounts for the false negative biopsies taken using the standard sextant technique [95]. At present six cores are considered inadequate for routine prostate biopsy cancer detection.

Systematic biopsy technique

This is also called the extended sextant biopsy technique. With the findings from the radical prostatectomy studies by McNeal et al. (1988) showing that the majority of prostatic adenocarcinoma arose from the posterolateral peripheral zone region, the urology community had to design biopsy strategies that incorporated laterally directed cores into the standard sextant sampling techniques. This resulted in the number of cores sampled being increased from six to between eight and thirteen [95]. Various sampling patterns were attempted to maximise the cancer detection rate of the biopsy, as shown in Figure 1.4[71]. These all showed an increase in the cancer detection rate as the number of cores obtained increased as shown in Table 1.10 [71]

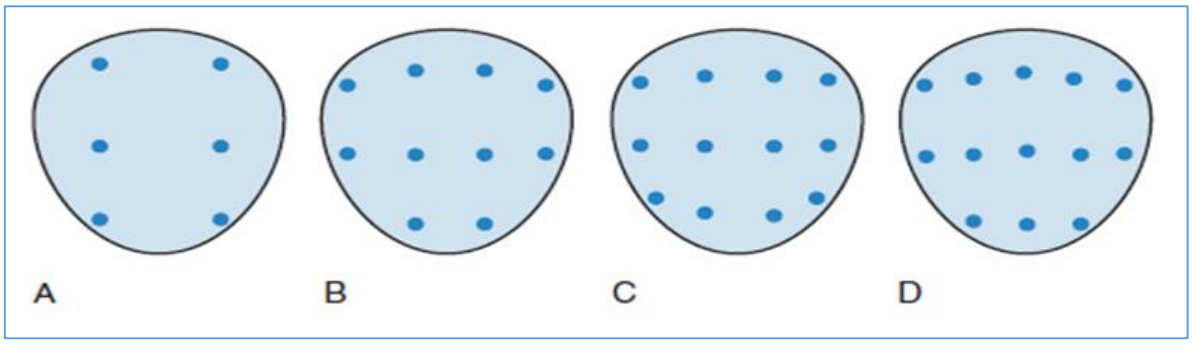


Figure 1.4: The original sextant technique and other reported systematic biopsy schemes [71]

Where the base is at the top of figure and the apex is at bottom.

A. Sextant biopsy

B. The 10-core biopsy

C. The 12-core, or double sextant, biopsy

D. The 13-core "5-region biopsy"

Table 1.10: Increasing prostate cancer detection rates with extended core biopsy techniques [71]

AUTHOR	NUMBER OF CORES	CANCER DETECTION RATE
Eskew et al, 1997	6	26.10%
	13	40.30%
Presti et al, 2000	6	33.50%
	8	39.70%
	10	40.20%
Babaian et al, 2000	6	20%
	11	30%

Turk et al. showed that for the initial biopsy there was no added benefit or increase in the cancer pick up rate when comparing a 12-core biopsy to a 20-core office biopsy. In their study, a 20-core biopsy did not lead to a higher PCa detection rate compared to a 10- to 12-core biopsy. Moreover, the cumulative detection rate of a 10- to 12-core biopsy and prompt repeat biopsy as needed was significantly higher compared to a single 20-core biopsy [96]. Currently

the 12-core biopsy, the systematic technique is the standard as it has been shown to increase the detection of PCa and the accuracy of Gleason score [97].

Limited biopsy

The concept of the limited biopsy does not appear in the literature. At our institution, this means a needle biopsy specimen comprising two - four cores of tissue. It is performed under specific circumstances, typically on a patient who clinically has evidence of PCa in the form of constitutional symptoms or signs of metastatic disease and a palpably abnormal DRE. In such cases the burden of the distant disease, local tumour bulk and PSA values are often high. The typical patient is often too sick and weak to have the biopsy performed at the biopsy clinic, often presenting with an Eastern Cooperative Oncology Group performance status of two or higher. The biopsy is performed with the sole intention of obtaining a histological confirmation of the clinically suspected diagnosis of PCa, especially if irreversible treatment such as bilateral orchidectomy is being considered. It is performed at the patient's bed, using a 16- gauge tru-cut biopsy needle that is not spring loaded and is digitally directed towards the most abnormal part of the prostate, using ramicaine jelly for local anaesthesia.

These patients may have a higher rate of localised complications, for the following reasons:

- Not being compliant with the procedure due to lack of understanding if cognitively impaired by the cancer or other co-morbidities.
- More advanced disease and thus potentially more haematological abnormalities due to bone marrow infiltration causing anaemia and thrombocytopaenia, which predispose to bleeding.
- The diameter of the needle used is wider than that used in the systematic biopsy, possibly causing more trauma.
- The needle is not spring loaded and is thus manually manipulated, leading to less smooth motion in obtaining the cores.
- The prostate being biopsied is macroscopically abnormal with probable neoangiogenesis and vessels invaded by tumour, making bleeding more likely.

Repeat and saturation prostate biopsies

Repeat Biopsy

Clinical decisions regarding the need for repeat biopsy can be difficult, where a clinician needs to balance pursuing the concern about possible PCa as driven by either a persistently raised PSA or persistently abnormal DRE, against patient comfort and the risks inherent in a prostate biopsy. In such cases the use of additional tests such as PSA derivatives or PCA 3 are helpful. In some situations, the decision may be to repeat the biopsy. There is a decrease in cancer detection rates with multiple repetitions of biopsies. A study of 1136 men by Keetch et al. (1994) showed the following detection rate associated with success of biopsies; biopsy 1 had a 34% pickup rate, biopsy 2 had 19%, biopsy 3 had 8% and biopsy 4 had 7% [98]. These results were supported by the findings of the European Cancer Detection Study [99] where the first biopsy had a 22% pickup rate, second biopsy 10%, third biopsy 5% and the fourth biopsy had 4%. These studies show that there is little clinical benefit and an increased morbidity of patients having more than three sets of biopsies [5].

Other findings from the European Cancer Detection Study [99] were that cancers found on a first and second biopsy had similar biochemical and pathological features, suggesting similar biological behaviour. Cancers diagnosed on the third and fourth biopsies had a lower grade, stage and volume. The morbidity of the first and second biopsies was similar, whereas the third and fourth biopsies had a slightly higher complication rate [100]. Thus, if a first biopsy is negative, one may justifiably proceed to the second biopsy. Should the second biopsy also be negative, the decision to proceed to a third must be carefully considered.

Saturation Biopsy

Historically saturation biopsies have been done in the subset of patients in whom the clinical suspicion of cancer persists with three negative biopsies from adequate, extended technique biopsies [5]. In these patients, a saturation biopsy strategy to obtain between 20 and 24 cores by extensively sampling the prostate is then employed. One of the drawbacks of a saturation biopsy is that it is done in theatre under regional or general anaesthesia, with the associated risks and the associated costs of hospital admission and theatre time.

The Mayo Clinic in reviewing the risks and expenses conducted a prospective study in 2008 comparing the cancer detection rates in a standard systematic biopsy scheme versus

saturation biopsy technique. They did not find a significantly improved PCa detection rate in the saturation biopsy arm [101].

Improved imaging techniques such as MRI, are being used with increasing frequency in cases where the clinical suspicion of a PCa remains high despite one or more negative biopsies, and thus replacing saturation biopsies as an option [102].

Transitional zone and seminal vesicle sampling

The transitional zone and seminal vesicles were shown by Epstein et al. (1997) and Terris et al. (1997) to consistently have low yields of detecting cancer at the initial biopsy, thus they are not routinely sampled [103].

Transitional zone and anteriorly direct biopsy may be necessary in the setting of a persistently raised PSA with a negative prior biopsy. Tumours in this region account for 5 to 10% of PCa [104]. There may also be a role for transitional zone biopsies in men with prostate glands greater than 50ml in size [105]. The seminal vesicles are not routinely sampled. However, the presence of seminal vesicle in the specimen additionally with evidence of involvement by cancer assigns a higher T stage to the specimen, making it a T3b lesion. When compared to a specimen which is positive for cancer in the absence of a palpable lesion which is a T1 lesion, or in the presence of a palpable lesion which makes it a T2 lesion as per the TNM classification.

d. Risks and complications of prostate biopsy

The two major risks of prostate biopsy are bleeding (haematuria, rectal bleeding or haematospermia) and infection. Other complications reported include vasovagal response, acute urinary retention [106] and perineal pain/ dyspareunia [86]. Heyns et al. (2014) showed that histological confirmation of PCa is not necessary to initiate treatment [85]. The performance of a prostate biopsy is not an innocuous process. The approach to diagnosis and treatment used by Heyns et al. may have additional benefits to the two major conclusions drawn in their study. They concluded that in patients suspected of having PCa on clinical grounds in whom a biopsy is not performed the treatment outcomes are comparable to those patients who had a biopsy and that there are significant financial savings in not performing biopsies on all patients. The additional benefit is that the potential complications of biopsy and attendant cost to treat are also obviated.

Bleeding

Bleeding is the most common complication seen after prostate biopsy. This can be in the form of haematuria which can be severe enough to cause clot retention, haematochezia or haematospermia. These complications of bleeding can occur in patients with normal clotting profiles. The incidences are higher in patients with abnormal coagulation due to congenital or acquired factors such as the use of warfarin, aspirin or non-steroidal anti-inflammatory drugs [107]. Haematuria occurs in 23 - 63% of patients, with <2% of patients experiencing clot retention [108]. Rectal bleeding is seen in 2.1 to 21.7% of patients and usually can be controlled by direct pressure either digitally or with the ultrasound probe. If it persists however, the patient may require further intervention in the form of a procoagulant anal plug such spongostan or endoscopic intervention [109]. Haematospermia is present in 9.8 - 50.4% of men and may persist for four to six weeks following biopsy. It is of minimal clinical consequence, but can be quite alarming for patients if they are not counselled about the possibility in advance [110 2002].

Infections

In those patients who get infectious complications following biopsy, the majority will have symptomatic urinary tract infection with a low-grade fever. These are normally adequately treated with oral antibiotics. Up to 2% of patients may develop infectious complications requiring hospital admission for intravenous therapy, including febrile urinary tract infections, bacteraemia or acute prostatitis.

Prior to the antibiotic era and the routine use of antibiotic prophylaxis, infectious complications rates were much higher, with bacteriuria present in 32 to 36% of patients and bacteraemia present and 48 to 69% of patients following TRUS biopsy [111]. Fatal infectious complications have been reported following TRUS biopsy [112] . Of current concern is the increasing incidence of community- acquired organisms that are resistant to fluoroquinolone prophylaxis as talk of the world entering the end of the antibiotic era intensifies [113].

Other complications

Other less frequently reported complications include moderate to severe vasovagal response in 1.4 - 5.3% of patients [110]. This may require the procedure to be terminated and resuscitation measures to be instituted, such as placing the patient in Trendelenburg position and administering intravenous fluids.

Acute urinary retention (AUR) occurs in 0.2 to 0.4% of patients [109]. It may require temporary urinary catheterisation. Men with BPH, as suggested by the size of the prostate gland or presence of LUTS prior to the procedure are at greater risk of developing AUR [114 1998].

1.2.6. The histology of prostate cancer

The most common primary prostatic malignancy is adenocarcinoma of the epithelium within the acini and ducts of the prostate glands. It accounts for over 95% of cases of PCa. The stromal component can also become malignant leading to sarcomas. Adults get leiomyosarcomas, whereas in the paediatric population rhabdomyosarcomas are more common [115]. Primary urothelial carcinoma of the prostate without bladder involvement accounts for 1- 4% of all prostatic carcinomas [116]. A few cases have neuroendocrine morphology. When present, they are believed to arise from the neuroendocrine stem cells normally present in the prostate or from aberrant differentiation programs during cell transformation [117]. Regarding the anatomical zone for the origin of the cancer, 70% arise in the peripheral zone, 15-20% in the central zone, and 10-15% in the transitional zone [118].

1.2.6.1. Premalignant lesions of the prostate

Two types of lesions found on prostate biopsy are considered premalignant, high-grade prostatic intraepithelial neoplasia (HG-PIN) and atypical small acinar proliferation (ASAP) [119]. Patients found to have either of these lesions on initial biopsy are at an increased risk of having PCa on subsequent biopsies. These are histological findings and cannot be predicted on the clinical, transrectal ultrasound or PSA findings. Schlesinger et al. (2005) found prostatic carcinoma in subsequent biopsies in 23% of cases when the initial finding was HG-PIN alone, in 33% of cases if the initial findings showed HG-PIN with ASAP and 37% of cases if the initial finding was ASAP alone [120].

In HG-PIN, the histological features show an abnormal cytology with normal architecture and an intact basement membrane. Whereas in ASAP both the cytological appearance and architecture of the glands show abnormalities. HG-PIN is found in 5 to 10% of prostate biopsies [121]. In Orozco's study in 1998 of 62, 537 patients, 4.1% had HG-PIN [122]. ASAP occurs in 2 to 5% of specimen [123]. Both are found the peripheral zone of the prostate. The current recommendations are to repeat prostatic biopsies in patients with HG-PIN or ASAP in the initial biopsy specimens within three to six months.

PIN was previously divided into low-grade and high-grade. However, it has been found that pathologists cannot reliably distinguish between low-grade PIN and benign prostatic tissue [124] and that patients found to have low-grade PIN on initial biopsy do not have an increased risk of having adenocarcinoma diagnosed on a follow-up biopsy [125]. Thus, the current recommendation is that histology report should no longer comment on low-grade PIN.

HG-PIN on the other hand, carries an increased risk of the finding of adenocarcinoma and a subsequent biopsy. The largest study reported a risk of 16 - 44.6% on subsequent biopsy. The mean risk was 26.4% from 11 studies [125]. In cases where HG-PIN is found to be focal on biopsy, be it a sextant or extended protocol specimen, and there is no ongoing clinical or biochemical suspicion of cancer there is no need for repeat biopsy. If, however HG-PIN is found to be multifocal, extensive and involves two or more cores, a repeat extended protocol prostate biopsy is warranted within a year [126]

Lefkowitz et al. (2002) found that patients who had HG-PIN on initial biopsy had a cancer pickup rate of 2.3% on repeat biopsy done within a year of the initial sampling, which rose to 25.8% if the follow-up interval was increased to three years. They hypothesised that small cancers that were not sampled during the initial biopsy grew large enough to be detectable on repeat biopsy in the intervening three years or alternatively that the areas that had initially harboured HG-PIN had progressed to carcinoma during the three-year interval. HG-PIN seems to be a precursor for intermediate to high-grade carcinomas of the prostate; however, it does not need to be present for carcinoma to arise [127].

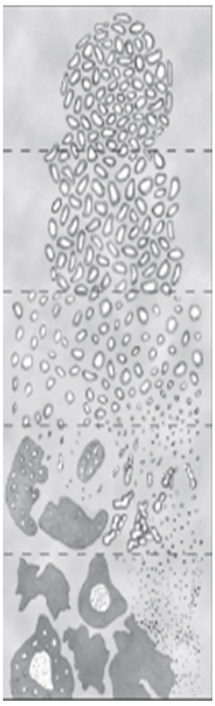
The natural history of ASAP is less well defined than HG-PIN, but if ASAP is present on initial biopsy the risk of diagnosing PCa on subsequent biopsy is significantly increased and therefore a repeat biopsy is indicated within 3 to 6 months [128].

1.2.6.2. Adenocarcinoma of the prostate, Gleason score and ISUP grade groups

Adenocarcinoma of the prostate arises in the glandular structures within the prostate. The Gleason grading system, which is the most widely used grading system for PCa, is then applied to the specimen [129]. It is based on the glandular pattern of the tumour as identified at relatively low magnification. It is used to assess how closely the carcinoma resembles normal prostate histology. The closer the microscopic appearance is to normal, the lower the number assigned to the pattern, as shown in Figure 1.5 [71].

The pattern is graded from 1 to 5, with worsening appearance due to poor differentiation of the glandular epithelium and architecture scoring higher. The specimen is assigned a major or primary pattern ranging from 1 to 5 for the predominant pattern and a minor or secondary pattern also from 1 to 5 being awarded to the second most commonly seen pattern. The numbers assigned to each of the major and minor patterns are then added together to provide a combined sum or score. The highest possible score is then major 5 + minor 5 = 10. The higher the score, the more aggressive the clinical behaviour of the carcinoma.

Sometimes a third pattern is quite prominent and it is then termed the tertiary pattern and is also given a score from 1 to 5. This is typically on radical prostatectomy specimens when more tissue is available for assessment [130].



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

Figure 1.5: Microscopy patterns for Gleason pattern [71]

The combined Gleason score is then assigned a grade based on the clinical behaviour of that score observed in many patients over many years in the past. A Gleason score of 6 or less, is considered low grade or well differentiated. The intermediate score of 7 was previously considered to be moderately differentiated. However, there are constant refinements to the diagnostic categories, based on ongoing studies and trials. Prostate cancers with Gleason score 7 composed of a major pattern = 4 plus a minor pattern = 3 were found to behave more aggressively than Gleason 7 composed of major pattern 3 plus minor pattern 4 following radical prostatectomy. They were found to have a higher PSA level at diagnosis, more extra-

prostatic extension, shorter time to progression and increased risk of developing metastatic disease [131]. Based on this difference in the behaviours and clinical outcomes of Gleason score 7= 3+4 compared to Gleason score 7= 4+3, the former is now classified as intermediate grade, and the latter as high-grade. Tumours scoring between 8 and 10 are poorly differentiated, and are considered high-grade disease. [132].

The International Society of Urological Pathology together with the World Health Organization in 2014 adopted ISUP grade groupings, which are shown in Table 1.11 [133]. This was done to categorize the Gleason score to make it easier for patients to understand the behaviour of their PCa, as described in the biopsy report. It also separated Gleason score 7 adenocarcinomas into grade group 2 for Gleason score 7= 3+4 and grade group 3 for Gleason score 7=4+3, which are 2 prognostically distinct categories [134].

Table 1.11: ISUP 2014 grade groups [133]

GLEASON SCORE	GLEASON GRADE	ISUP GRADE GROUP
2-6	Low	1
7=3+4	Intermediate	2
7= 4+3	High	3
8 (4+4 or 3+5 or 5+3)	High	4
9-10	High	5

1.2.6.3. Evidence of locally advanced PCa on biopsy

Evidence of locally advanced disease which can be identified on prostate biopsy includes invasion into the perineural space, lymphovascular space, extra-capsular space and the seminal vesicles. The presence of these is not factored in the risk stratification and prognostication models in common use. This omission presents an opportunity for the further refining of the current models or the creation of new models to risk-stratify and prognosticate the patients who demonstrate histological evidence of locally advanced disease at presentation.

Peripherally located adenocarcinomas extend out of the prostate through perineural extension [135]. Historically it was thought that perineural extension does not imply a worse prognosis, as it represents local extension along the path of least resistance [136]. However, new

studies support the negative impact of perineural invasion on various parameters such as biochemical recurrence, tumour progression and recurrence free survival [137] [138]. These clinical outcome studies are in turn supported by laboratory studies showing that quantitative perineural invasion is a poor prognostic marker in PCa [139]. The currently accepted route for PCa reaching the spinal cord is through retrograde haematogenous spread via Batson's valveless venous plexus [72]. The finding of perineural invasion on histology raises the scintillating possibility of an alternative route of PCa reaching the spinal cord via a perineural or neurogenic route. Laboratory studies by Ghinea et al. (2019) showing vasa nervorum neoangiogenesis in cases of perineural invasion [140] suggest an interesting interplay between the perineural and vascular routes of metastases.

Lymphovascular invasion confers a worse prognosis as it represents invasion into the vascular system with the possibility of local and distant metastatic spread [141]. The prostate lacks a discrete histological capsule, thus the term extra-prostatic extension is preferred to extra-capsular invasion [142]. Seminal vesicle involvement by PCa may indicate local contiguous spread, retrograde extension through the ejaculatory ducts or haematogenous metastases. In the TNM classification, it confers a higher T stage to the disease process [143]. Currently, involvement of the seminal vesicles with cancer confers upon the specimen a T stage of T3b, which makes sense for contiguous spread. However, if the cancer reaches the seminal vesicles via haematogenous spread it should be categorized under M instead of T disease. Much like adrenal gland involvement with primary renal cell carcinoma, where direct spread is T4 disease, but a discrete non-contiguous lesion is considered M disease [144]. There are two clinical challenges here. Firstly, distinguishing between contiguous spread and haematogenous metastases is impossible on core needle biopsy. In time it will become easier to identify as the role of MRI prior to biopsy becomes better defined and more established. Secondly, assigning the appropriate TNM stage for retrograde invasion of the cancer into the seminal vesicles via the ejaculatory ducts will be a challenge, as this represents neither direct nor haematogenous spread. However, this distinction may be of no clinical relevance with respect to patient management.

Local spread may also involve rectum, in such cases it is difficult to distinguish from a primary rectal adenocarcinoma on microscopy and immunohistochemical stains must be applied to make the distinction [145] [1979].

1.2.6.4. Immunohistochemistry in prostate cancer

Immunohistochemistry (IHC), also known as immunostaining, is a biochemistry concept which applies to the use of antibody-based methods to detect specific proteins within a tissue sample [146].

The role of the immunohistochemistry in PCa is to distinguish it from benign mimickers and to confirm the diagnosis in equivocal cases, including those with ASAP on histology [147]. It is also used to further define local spread of the carcinoma or to determine neuroendocrine differentiation. It is used at the discretion of the pathologist.

No single marker or stain has absolute sensitivity and specificity for PCa, thus panels of markers are used. There are basal-specific markers, namely high molecular weight cytokeratin (HMWCK) and p63, and PCa-specific markers namely alpha methyl co-A racemase (AMACR), PSA and PAP. Jiang et al. recommend using a double-colour triple-cocktail of 34 Beta E 12 (34BE12), p63 and AMACR. The combination of results of the triple-cocktail which distinguish cancer from benign disease are shown in Table 1.12 [147]

MWCK

High Molecular Weight Cytokeratin (HMWCK) is also called 34BE12. It is expressed by all normal basal cells of the prostate. Normal prostate glands will have a continuous, intact, circumferential stain. Kahane et al. found that application of 34BE12 stain reduced the diagnosis of “atypical” findings from 8.3 to 0.4% [148]. Prostate cancer stains negative for 34BE12.

P63

The nuclear transcription factor p63 is important in the regulation of growth and development of epithelial organs. It is structurally homologous to p53 tumour suppressor gene and is expressed by basal cells of normal prostate glands. Prostate cancer stains negative for p63.

AMACR

AMACR is overexpressed in 60% of PCa and is low to undetectable in normal tissues. It must be interpreted with caution because of non-standardisation of immunostaining protocols and interpretation criteria and a heterogeneous staining pattern. AMACR has also been found to be positive in HG-PIN. The current recommendation is that AMACR be restricted to the

evaluation of foci which have a suspicious morphological appearance, but are negative for basal cell markers [146].

PSA and PAP

Immunohistochemistry for PSA includes the use of monoclonal and polyclonal antibodies. The niche role for these is in epithelial primary tumours of unknown origin in a metastatic site and in distinguishing between prostatic and urothelial tumours. Prostatic Alkaline Phosphatase IHC is less sensitive and specific for PCa. It also tests positive for rectal adenocarcinoma. These two markers are less sensitive in poorly differentiated adenocarcinoma.

Table 1.12: Summary of immunohistochemical staining patterns in prostate cancer and benign disease [147]

IMMUNOSTAINS	PROSTATE CANCER	BENIGN DISEASE
34BE12	(-)	(+)
P63	(-)	(+)
AMACR	(+)	(-)

1.2.6.5. The neuroendocrine subtype

Laboratory and clinical evidence indicates that neuroendocrine transformation of PCa typically occurs in patients with advanced disease [149]. The therapeutic implications of this finding are significant because tumours demonstrating the neuroendocrine phenotype usually represent inherently hormone-resistant disease and require separate therapeutic considerations.

These tumours express several biologic characteristics unique to neuroendocrine tumours. Neuroendocrine tumours are not limited to the prostate and can arise in other organs, most commonly the lung. In the prostate these tumours exhibit atypical clinical patterns, characterised by frequent visceral involvement and rapidly growing soft tissue metastases [117]. The clinical manifestations are suggestive of the clinical entity. These patients frequently present with subacute, rather than dramatic changes in their disease pattern characterized primarily by a rapidly growing soft tissue mass, frequently involving the primary site but also with retroperitoneal masses; rapid development of lung and liver involvement; osteolytic as opposed to the usual osteosblastic bone metastasis, and a high incidence of brain involvement

[81]. Histologic evaluation of the site demonstrating rapid clinical changes is strongly recommended. The tissue will show a small cell variant or a poorly differentiated neoplasm which stains positive for neuroendocrine markers on immunohistochemistry [149]. Typically, patients either stop expressing PSA in the face of major tumor progression or, more frequently, have undetectable levels at the time of this transformation [77].

1.2.6.6. Adequacy of histological reporting

The histology report together with the history provided by the patient and findings of the physical examination form the cornerstone of management of a patient with PCa. They inform additional special investigations for metastatic work-up and treatment strategies. An adequate histology report is critical in guiding decisions towards the most appropriate, individualised treatment plan. Institutions and countries around the world publish their own checklists and protocols for what they consider adequate histology reporting [150]. The College of American Pathologists (CAP) currently publishes more than 80 checklists for reporting of all major cancers. The intention is that the reports are complete, concise, reproducible and in line with international standards and current knowledge. The International Collaboration on Cancer Reporting (ICCR) is a collaborative project between the CAP, the UK Royal College of Pathology, the Royal Australasian College of Pathologists and the European Society of Pathology. Notably, all of these bodies represent first world countries. The ICCR issues datasets and guidelines for the standardisation of cancer reporting. With respect to the prostate, the ICCR has set out criteria which are required and those that are recommended for reporting on core needle biopsies, transurethral resection and enucleation specimens. The required and the recommended information for core needle biopsy reports is shown in Table 1.13 [150]

Table 1.13: ICCR criteria for core needle biopsy reports [150]

CLINICAL	MACROSCOPIC	MICROSCOPIC
Required		
	Specimen submitted Specimen/container identity	Histological tumour type
	Biopsy location	Histological grade (Gleason, ISUP)
	Total no. of cores	Tumour extent:
	Length of cores	- no. of cores positive/ total no. of cores
		- PLUS length of tissue involved in mm
		- OR linear extent as a percentage
		Extra-prostatic extension
Recommended		
Previous history of prostate cancer	Block identification key	Perineural invasion
Previous biopsy		Seminal vesicle or ejaculatory duct invasion
Pre-biopsy serum PSA		Lymphovascular invasion
Clinical stage		Extra-prostatic extension- location
		Intraductal carcinoma of the prostate
		Coexistent pathology

1.2.7. The clinical significance of prostate cancer using Epstein's criteria

Epstein developed criteria to determine whether PCa diagnosed on biopsy is clinically significant. One concern with routine screening for PCa using PSA is the over-diagnosis of

clinically insignificant cancer with the attendant morbidity [6]. The rate of clinically significant and overt PCa varies worldwide, however the prevalence of clinically insignificant or indolent PCa is similar throughout the world. The value of determining if PCa is clinically insignificant or not, is in adding active surveillance or watchful waiting to the management options and thus further individualizing treatment. Epstein's criteria for clinically insignificant PCa are 1) PSA density, which is calculated from laboratory and imaging results and 2) the volume of cancer as found on core biopsy and are shown in Table 1.14 [151].

Table 1.14: Epstein's criteria for clinically insignificant disease [151]

PSA DENSITY (ng/mL)	GLEASON SCORE	NUMBER OF CORES POSITIVE FOR TUMOUR	VOLUME OF CORE POSITIVE FOR TUMOUR
< 0.1	< 7	< 3	≤ 50%
0.1-0.15	< 7	1	< 3mm

Clinically insignificant PCa is cancer that is diagnosed during life and meets the criteria defined by Epstein. Indolent cancer is PCa that is discovered at autopsy having never caused clinical symptoms during life. Kattan et al defined indolent cancer as being organ confined, less than 0.5ml in volume, and without poorly differentiated elements on histology [152]. These cancers do not pose a risk to the patient's life and thus do not warrant active treatment. Recognising these cancers allows clinicians to better counsel patients regarding the risks vs. the benefits of treatment. Identifying these cancers will negate the various costs borne by the patient, their family and state in the course of treating a cancer, including the possible side effects or complications of therapy.

1.2.8. Risk assessment tools: D'Amico and nomograms

Risk stratification for PCa is a concept that correlates clinical outcomes with pretreatment findings. In the area of risk stratification, the dynamic nature of oncology diagnosis and management is appreciated. The number of tools available and the new tools being developed in an effort to better stratify and prognosticate speak to the complexity of this field and the amount of resources being applied to it. The older risk stratification tools are used to predict outcome following radical prostatectomy, that is surgical treatment done with intent to cure. The risk stratification tools in common use do not factor the findings of local invasion as seen on biopsy, which creates an opportunity for further refinement of these tools. Examples of

these include the D'Amico, Kattan and Partin nomograms [153]. The University of California San Francisco Cancer of the Prostate Risk Assessment (UCSF CAPRA) score introduces a new element, in that it can be used to assess outcomes following non-curative, non- surgical ones treatment options [154]. However, it also does not take into account evidence of local invasion as seen on biopsy.

1.2.8.1. D'Amico

The D'Amico classification is one of the more commonly used tool. It risk stratifies patients into low, intermediate and high risk, as shown in Table 1.15. Each risk category is associated with a percentage probability of freedom from PCa at 10 years following radical prostatectomy, where low risk is associated with an 83% probability, intermediate risk with 46% and high risk with 29% [155]. The utility of risk stratifying patients at diagnosis is in guiding treatment options including multimodal options and in counseling patients on treatment outcomes.

Table 1.15: D'Amico Risk Stratification [156]

LOW RISK	Clinical stage T1c-T2a PSA < 10 Gleason ≤ 6
INTERMEDIATE RISK	Clinical stage T2b PSA 10- 20 Gleason 7 (3+4)
HIGH RISK	Clinical stage T2c PSA > 20 Gleason ≥ 7 (4+3)

1.2.8.2. Nomograms

Nomograms are diagrams representing the relations between three or more variable quantities by means of a number of scales, so arranged that the value of one variable can be found by a simple geometrical construction for example by drawing a straight line intersecting the other scales at appropriate values [157]. Nomograms provide a visual, graphical calculation for complicated formulae, without the user having to solve algebraic equations to obtain the

results. They were most extensively used in the field engineering. In PCa, they were developed to predict the outcome of disease treatments in response to the increase in the information gathered from clinical databases over time, and to refine the staging of patients using more clinical parameters and risk factors.

a. Kattan nomogram and others

The use of these tools in PCa was pioneered by Kattan et al. to improve the ability to predict the likelihood of disease recurrence or progression. They are used to classify patients into risk groups, to inform patients and to help them in making treatment choices. The variables include DRE findings, PSA levels and Gleason grade. Each variable is assigned a score and from which a final score is calculated. The final scores have been shown to accurately predict the extent of a cancer and long-term outcomes following treatment [158]. Other similar instruments have been developed and validated in many settings. The limitation of nomograms is that they are typically developed using formulae based on data from high volume surgeons in high volume academic centres and thus may not be directly translatable to other settings. Some of the available and validated nomograms include Kattan, MSKCC, Steyerberg and Nakanishi. Their construction rests on combinations of the patient's age, PSA, prostate volume, Gleason score, number of cores positive and total volume involved with cancer.

b. CAPRA Score

The UCSF CAPRA instrument was developed to account for more variables contributing to PCa recurrence or progression, packaged in an easy to use format. It was developed using data from the cancer of the prostate strategic urologic research endeavour (CaPSURE) study. A CAPRA score predicts an individual's likelihood of metastasis, cancer-specific mortality, and overall mortality. Unlike other nomograms, it is valid across various treatment modalities including radical prostatectomy, radiation, primary androgen deprivation, cryoablation and active surveillance. Points are assigned to the following 5 variables; age at diagnosis, PSA at diagnosis, Gleason score of the biopsy, clinical stage and percent of cores involved with the cancer, a final score between 0 and 10 is then calculated. The cancer risk is indicated as low, intermediate or high risk based on the final score, where 0 -2 indicates low risk, 3-5 intermediate and 6-10 high risk [154]. This risk stratification informs treatment decisions.

CHAPTER 2: AIM AND OBJECTIVES

2.1. Aim

This study aimed to review histological features of PCa at Charlotte Maxeke Johannesburg Academic Hospital from 01 January 2005 to 31 December 2009 with specific reference to evidence of local invasion at diagnosis.

2.2. Objectives

The objectives of this study were to:

1. Determine if PCa histology reports meet the International Collaboration on Cancer Reporting (ICCR) criteria for reporting.
2. Describe the biochemical and histopathological features of prostate biopsies that were positive for PCa.
3. Compare the characteristics differentiating low grade vs. high-grade PCa.
4. Determine if a particular biopsy protocol is superior in terms of information yielded.
5. Determine the percentage of patients meeting the criteria for clinically insignificant cancer.
6. Determine the percentage of patients meeting the criteria for localised disease.

CHAPTER 3: METHODS

3.1. Study design

This study is a retrospective observational, cross- sectional study of the prostate biopsy specimens, which were positive for PCa, received by the NHLS anatomical pathology laboratory serving the Department of Urology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from 01 January 2005 to 31 December 2009).

3.2. Study population and sample

3.2.1. Site of study

The prostate specimens were obtained from patients seen at the Urology clinic at CMJAH, which is a quaternary, teaching hospital serving the population of Johannesburg. It is a state hospital serving patients who cannot afford private medical care and is also a referral hospital for surrounding primary and secondary hospitals.

All the patients who had biopsies done were first assessed by a urology consultant or registrar either as an out-patient or as in-patient and the indication for biopsy confirmed. Out-patients are booked for the prostate biopsy clinic, usually within a month; whereas in-patients have their biopsies performed within a day or two in the referring ward or at the end of the week at the out-patients if deemed fit enough to leave the ward.

The prostate biopsy clinic occurs weekly and all biopsies are done in the ward under local anaesthesia by a urology registrar. Saturation biopsies are carried out in theatre under regional or general anaesthesia and are supervised by a consultant.

3.2.2. Inclusion criteria

All prostate histology specimens processed by the NHLS Department of Anatomical Pathology which were positive for cancer, starting from January 2005 ending in December 2009 were included in the sample. The reports were accessed from the NHLS database.

3.2.3. Exclusion criteria

Prostate biopsy specimens which were negative for PCa.

3.3. Variables

The variables listed below, were obtained from the NHLS database and were entered onto an Excel spreadsheet.

1) Age: Age was captured as a continuous variable for purposes of mean and standard deviation, age was then categorized into decades (years).

2) PSA level (ng/ml). The PSA levels were available and categorised using D'Amico classification into <10ng/ml, 10-20ng/ml and > 20ng/ml. The categories were expanded to include three extra categories: ≤2.5ng/ml and ≤4ng/ml as well as category ≥100ng/ml as patient management and clinical presentation is different at these levels.

3) The type of specimen was entered as core biopsy, TURP, open prostatectomy, radical prostatectomy or radical cystoprostatectomy.

4) With regards to core biopsies,

    i. The core biopsies were categorised based on the number of cores as follows: limited <4 cores, sextant 5-7 cores, systematic 8-17 cores and saturation >18 cores.
    ii. The number of cores processed was noted.
    iii. The number of cores within each specimen that were found to be positive for cancer was noted.

5) The volume of the specimen involved by cancer expressed as a percentage.

6) Gleason score, reported by the laboratories include scores for the major and minor patterns. The categorization of the Gleason scores into low, intermediate and high categories as based on the sum of the major and minor scores was noted.

7) Presence or absence of high-grade prostatic intraepithelial neoplasia (HG-PIN) and prostatitis.

8) Presence of local infiltration by tumour as shown by any of lymphovascular, perineural spread, extra-capsular spread or seminal vesicle spread.

9) Use of immunohistochemical staining, as well as type of stain used.

The full datasheet is contained in Appendix A.

3.4. Ethics approval

Ethics approval was obtained from the Human Research Ethics Committee (medical) at the University of the Witwatersrand (Ethics clearance certificate M1911182). All data obtained was anonymised to protect the identity of the patients

3.5. Statistical analyses

For age, a mean and standard deviation were used for description. PSA values were skewed and therefore categorized according to median and ranges used for clinical significance. All other data was categorized and described using frequencies and percentages.

The significance level used was $p<0.05$.

Statistical package was Graphpad instat (Graphpad.com). Comparative statistics was done using Fisher's exact test/ Chi2, characterized data as appropriate for a Kruskal- Wallis analysis of variance (ANOVA) for numerical data to compare types of biopsies.

CHAPTER 4: RESULTS

The sample consisted of 680 male patients, and 726 histological specimens. A total of 38 (6%) men had repeat histology for various reasons.

4.1. Indication for specimen

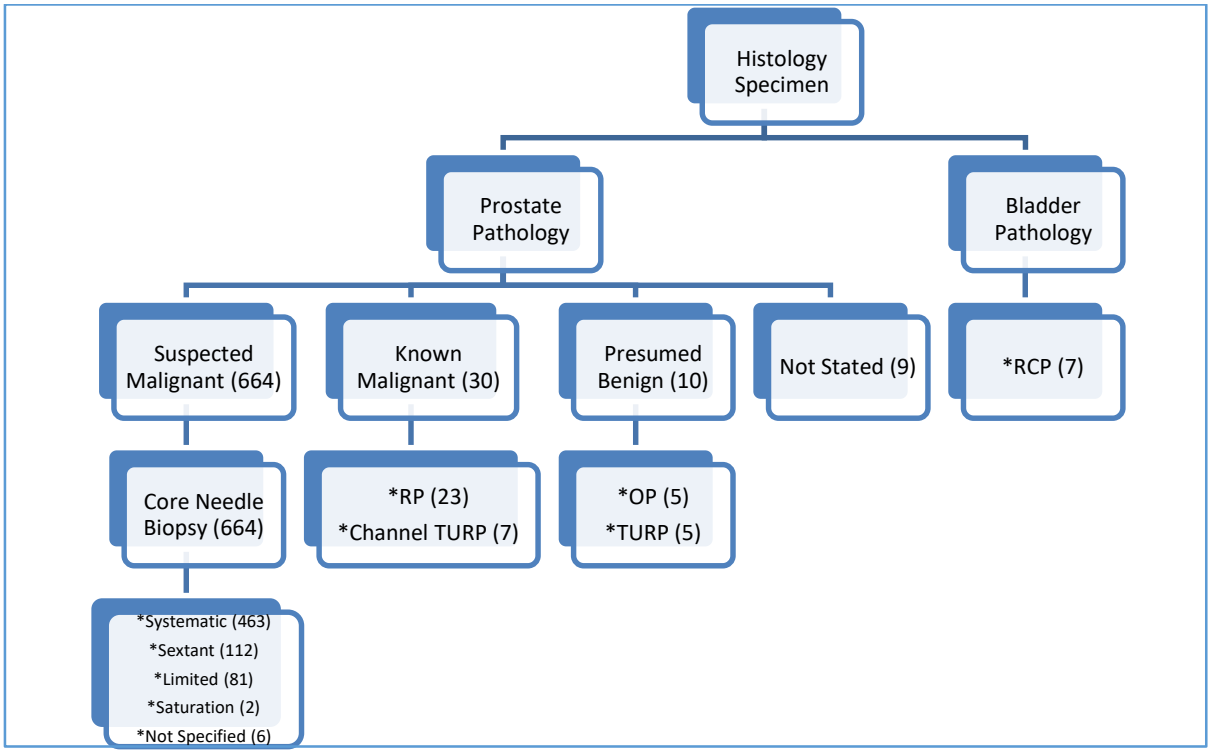


Figure 4.1: Indications for prostate histology

RCP = Radical Cystoprostatectomy

RP = Radical Prostatectomy

OP = Open Prostatectomy

TURP = Trans Urethral Resection of the Prostate

The majority of specimens, 99%, were obtained from patients with prostatic pathology, either known or suspected malignant disease. However, 1% were obtained from patients with bladder pathology.

4.2. Type of specimen

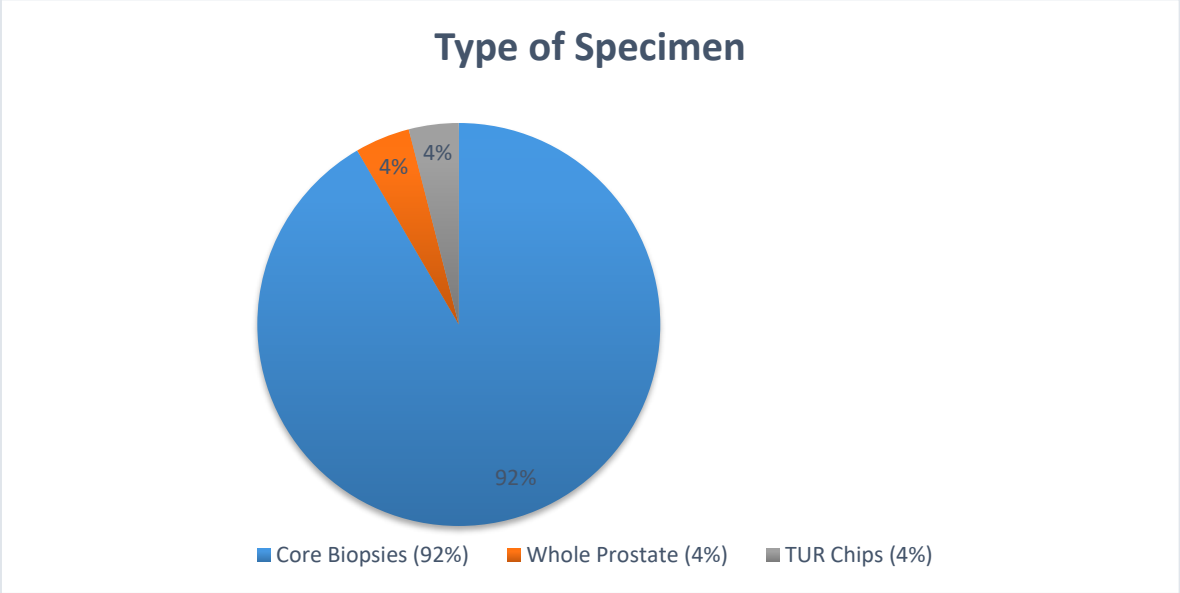


Figure 4.2: Distribution of types of specimen

Histological studies were conducted on prostate tissue acquired either as core biopsy, prostatic chips or whole prostate depending on the pathology at presentation. Core biopsies made up the majority of the specimens 664 (91.5%), whole prostates made up 32 (4.4%) and TUR chips made up the remainder of 29 (4.0%).

4.3. Age

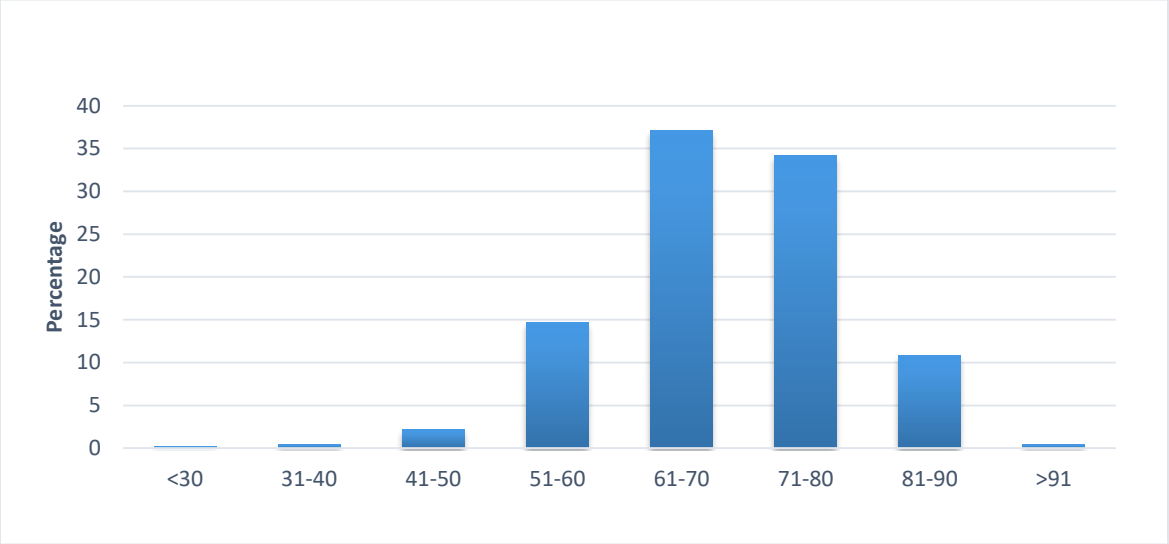


Figure 4.3: Age distribution

In our study, the mean (SD) age was 69.2 (9.5) years. The majority of patients (71%) were in the 7th and 8th decades, which had similar numbers; 16 (2.2%) were less than 50 years; and 203 (27.9%) were 75 years or older. The ages of 24 patients were not available.

4.4. PSA level

Most of the patients (70%) had a PSA level greater than 20ng/ml indicating locally advanced or metastatic disease at time of biopsy, as seen in Figure 4.4. Seventy- two patients (10%) had PSA ≥ 1000ng/ml**.**

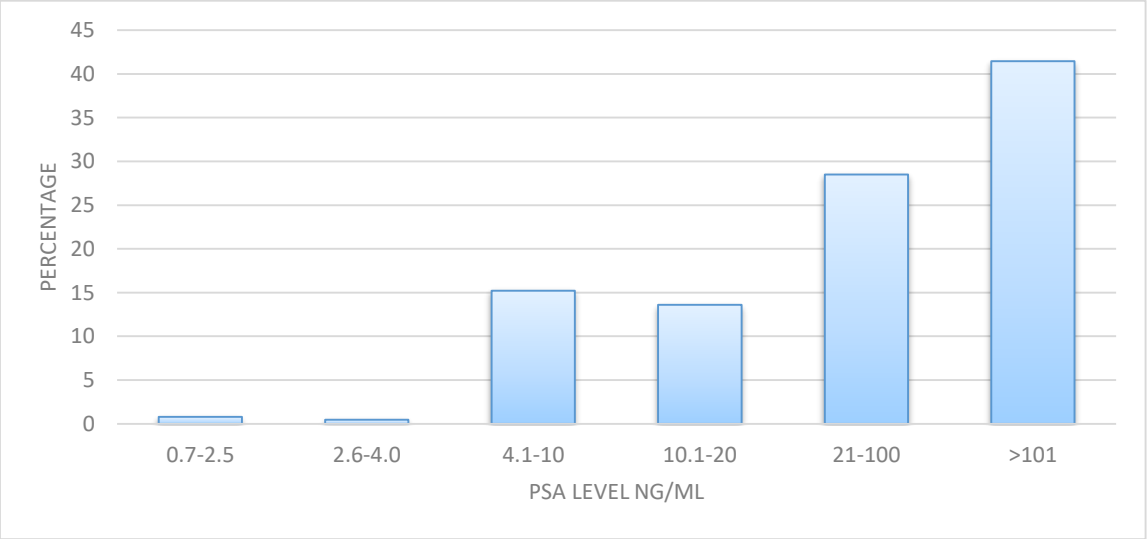


Figure 4.4: Distribution of Prostate-specific antigen (PSA) level

4.5. Core needle biopsies

4.5.1. Completeness of reporting as per ICCR

Regarding the criteria for completeness of histology reporting of the microscopic findings of the core needle biopsies as per the ICCR:

- With reference to required criteria, in 644 core needle biopsies the histological tumour type was reported in 644 (100%); the histological grade in 644 (100%) and the tumour extent based on number of cores positive/ total no of cores in 408 (63.4%).
- Our reports also reported on the tumour extent as a percentage of the entire specimen in 577 (89.6%).
- With reference to the recommended criteria, specifically the presence or absence of local invasion was reported in 560 specimens (87%).

4.5.2. Core biopsy protocol

The majority of specimens came from systematic biopsy (66.9%) with smaller numbers from sextant, limited and saturation biopsies, as shown in Figure 4.5

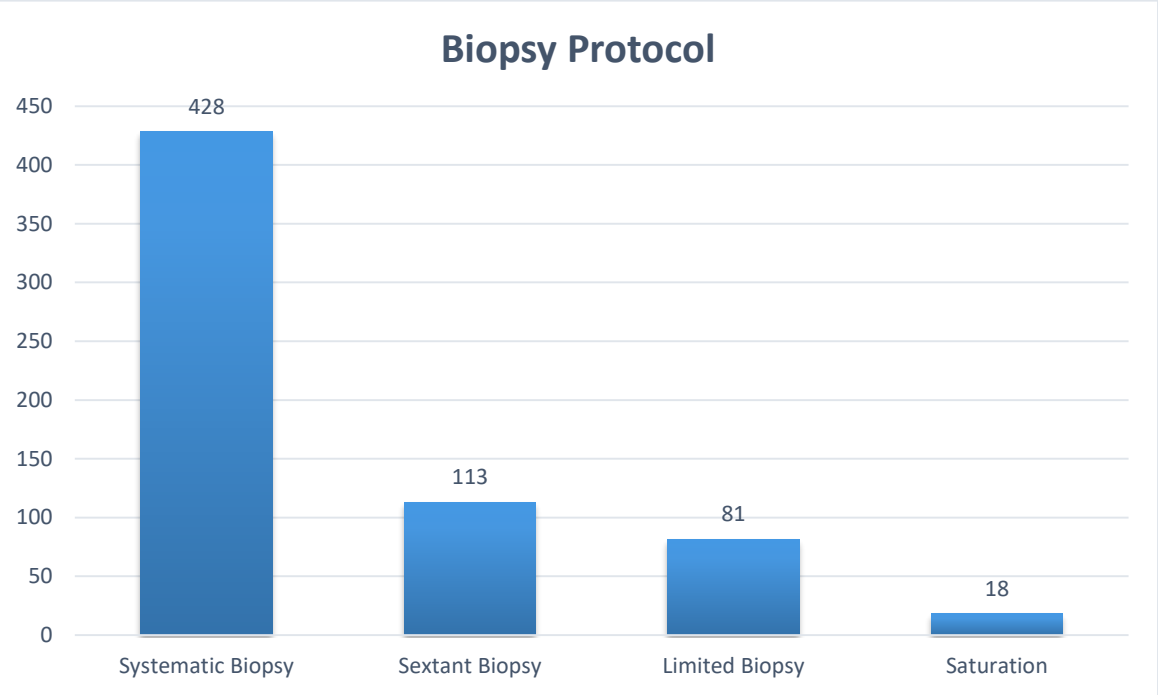


Figure 4.5: Core needle biopsy protocols

The number of cores received ranged from 1 to 26, with a median of 13.5. Of the total 664 core biopsies in the study population, 653 had the number of cores received recorded and of those 410 had the number of positive cores recorded. A total of 128 specimens had two or

fewer cores positive. Two patients had a saturation biopsy; they were included in the descriptive data, but excluded for comparison between types of biopsy.

Of the specimens in which the percentage of the specimen involved by carcinoma was reported, 354 (57%) had less than 50% involvement by the carcinoma. 128 (16.6%) of the core needle biopsy specimens had two or less cores positive.

4.5.3. Is either biopsy protocol superior in terms of information yielded?

Table 4.1: Comparing different biopsy protocols

	LIMITED (80)	SEXTANT (108)	SYSTEMATIC (454)	P VALUE
PSA (ng/ml)				
<2.5	0	1 (0.9)	3 (0.66)	Chi^2 = 68.93
<4	0	0	1 (0.22)	P=<0.0001
<10	2 (2.5%)	7 (6.5)	71 (15.6)	
<20	11 (13.8)	5 (4.6)	66 (14.5)	
<100	11 (13.8)	36 (35.1)	124 (27.3)	
≥100	28(35)	20 (18.5)	121 (26.7)	
≥1000	16 (20)	27 (29.1)	27 (6)	
Unspecified (DNI)	11 (13.8)	10 (9.25)	41 (9.0)	
Median	116 (7-6519)	100 (4.5-20000)	50 (0.7-23000)	Kruskal-Wallis ANOVA
	V sex - ns	V sys p<0.001	V lim p<0.001	P=<0.0001
Age (Youngest)	41	23	34	ANOVA
Mean (SD)	69.3(11.6)	69.7(9.9)	69.7(8.9)	P=0.9523
Immunohistochemistry used	10 (12.5)	12 (11.1)	55 (12.1)	Chi^2 0.1054
				P=0.9487
Gleason grade				
Low	13 (16.25)	13 (12)	82 (18.6)	Chi^2 = 3.2
Intermediate	8 (10)	15 (13.8)	67 (14.8)	P= 0.5243
High	56 (70)	74 (68)	297 (65.4)	
Indeterminate (DNI)	3 (3.8)	6 (5.5)	8 ((1.8)	
HG-PIN present	11 (13.8)	20 (18.5)	100 (22)	Chi^2 = 3.153
				P=0.2067
Local spread				
Perineural	38 (47.4)	66 (61)	265 (58.3)	Chi^2 =12.61

Lymphovascular	5 (6.3)	13 (12)	43 (9.47)	P= 0.0497
Extra-capsular	5 (6.3)	8 (7.4)	19 (4.19)	
Seminal vesicle	2 (2.5)	2 (1.9)	44 (9.7)	
Prostatitis	8 (10)	5 (4.6)	80 (17.6)	Chi^2 13.37
				P=0.0012
Repeat biopsy	14 (17.5)	6 (5.5)	44 (9.7)	Chi^2 7.438
				0.0243

There were significantly more specimens with seminal vesicle spread and prostatitis in the systematic biopsy protocol compared to the other two protocols. The PSA for the patients with systematic biopsies was significantly lower than both limited biopsies ($p<0.001$) and sextant biopsies ($p<0.001$). There was no significant difference between the PSA values between limited and sextant biopsies. There were no significant differences in age, whether immunohistochemistry was done, Gleason score or whether HG-PIN was present between the three types of biopsy protocols. Only two patients had saturation biopsies, which were thus not included in the comparison.

4.5.4. Repeat biopsies

Table 4.2: Comparing first time biopsies to repeat biopsies

	FIRST BIOPSIES		**REPEAT BIOPSIES**		**P VALUE**	**CHI COEFFICIENT**
	n =510		n =72			
	n	%	n	%		
Prostatitis	73	14.4	18	25	0.0244	
HG-PIN	112	21.9	22	30	0.1336	
Staining	26	5	15	20.8	0.0001	
Gleason Grade:						
Low	79	15.5	26	36.1	0.001	18.6
Intermediate	79	15.5	8	11.1		
High	343	67.3	37	51.4		

In n= 72 (9.9 %) of patients the biopsy was repeated, with the majority n= 54, having a second biopsy. The rest n= 18 had three or more biopsies, all of them showing cancer. The reasons for the repeat biopsies subsequent to a positive biopsy are unclear from the histology reports. The incidences of prostatitis, staining and low Gleason grade were statistically different ($p < 0.001$) between first and repeat biopsy, all were more frequently found in the repeat biopsies.

4.6. Gleason

4.6.1. Gleason grade

The distribution of high, intermediate and low Gleason grade in the sample is shown in Figure 4.6. The majority (n=447) of specimens in this study showed high-grade disease at presentation. Specimens with an indeterminate Gleason score (n=42) were excluded from the chart.

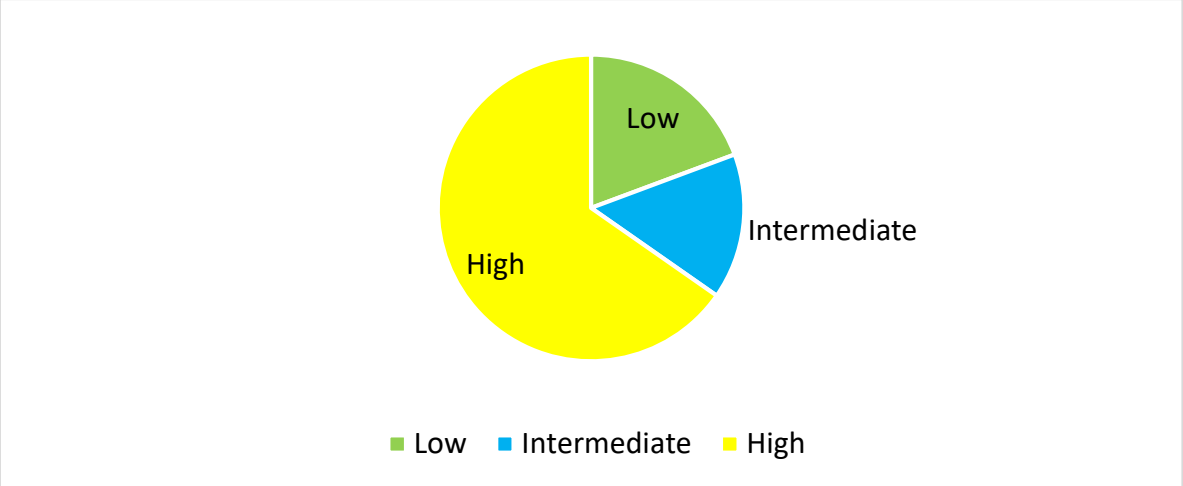


Figure 4.6: Distribution of Gleason grade

4.6.2. Gleason grade by decade

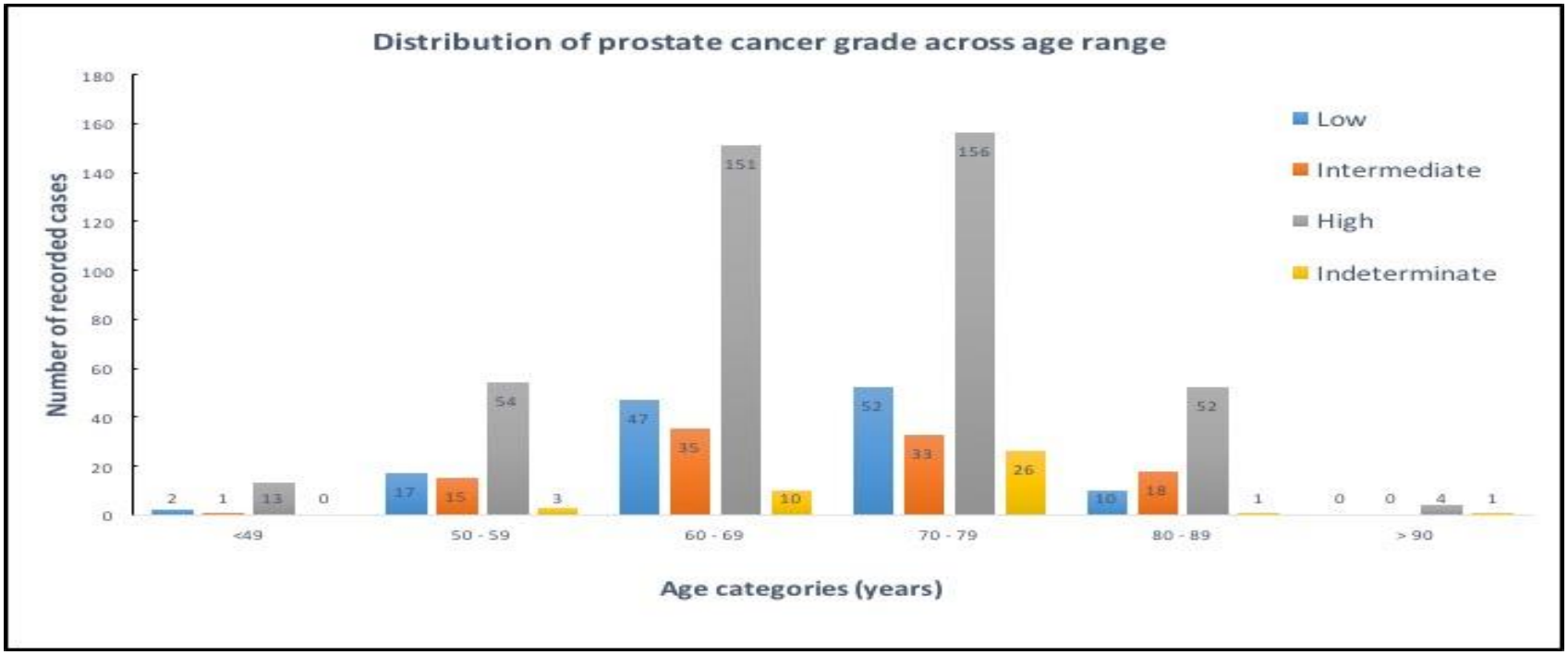


Figure 4.7: Distribution of grade of disease per decade

Consistently, the majority of patients in all of the age categories showed high-grade disease at presentation, especially in the two decades in which cancer occurred most commonly, the 6th and 7th decade. The age extremes, <49yrs and >90, both had low numbers but also had majority high-grade disease.

4.6.3. Gleason grade, tumour bulk and local infiltration.

Table 4.3: Showing the association of high Gleason score with high tumour bulk and local infiltration

VARIABLE	HIGH GLEASON	LOW GLEASON	P VALUE
Total biopsy area affected >50%	196	74	
Total biopsy area affected <50%	193	222	<0.001
Local infiltration present	284	142	
Local infiltration absent	105	154	<0.001

There was a statistically significant difference between high and low Gleason score, with a low Gleason score found in association with low tumour bulk and less local infiltration.

4.6.4. ISUP grade groups

The distribution of the ISUP grade groups is shown in Figure 4.8. Grade groups 4 and 5 made up 49.5% of the sample, and consisted of 128 and 232 specimens respectively

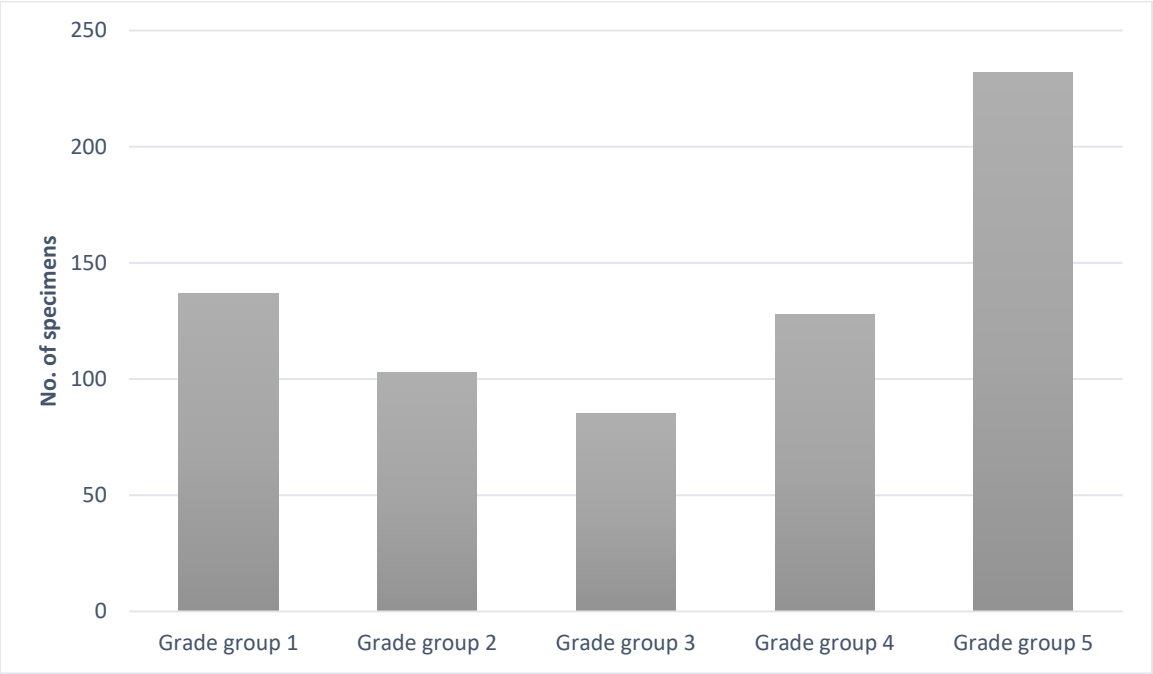


Figure 4.8: Distribution of the ISUP grade groups

4.7. Local infiltration

Local infiltration is evidenced by any of perineural spread, lymphovascular spread, extracapsular spread and seminal vesicle spread. There was one or more forms of local infiltration in 430 specimens. The distribution of perineural, lymphovascular, extra-capsular and seminal vesicle spread is shown in Figure 4.9. The data on evidence of local infiltration was missing on 296 specimens. Only three specimens had no evidence of any local spread at all on histology. Of the 114 specimens on which the presence of seminal vesicles was reported, whether they were infiltrated by or free of cancer, 90 were from core biopsies and 22 from radical surgery specimens.

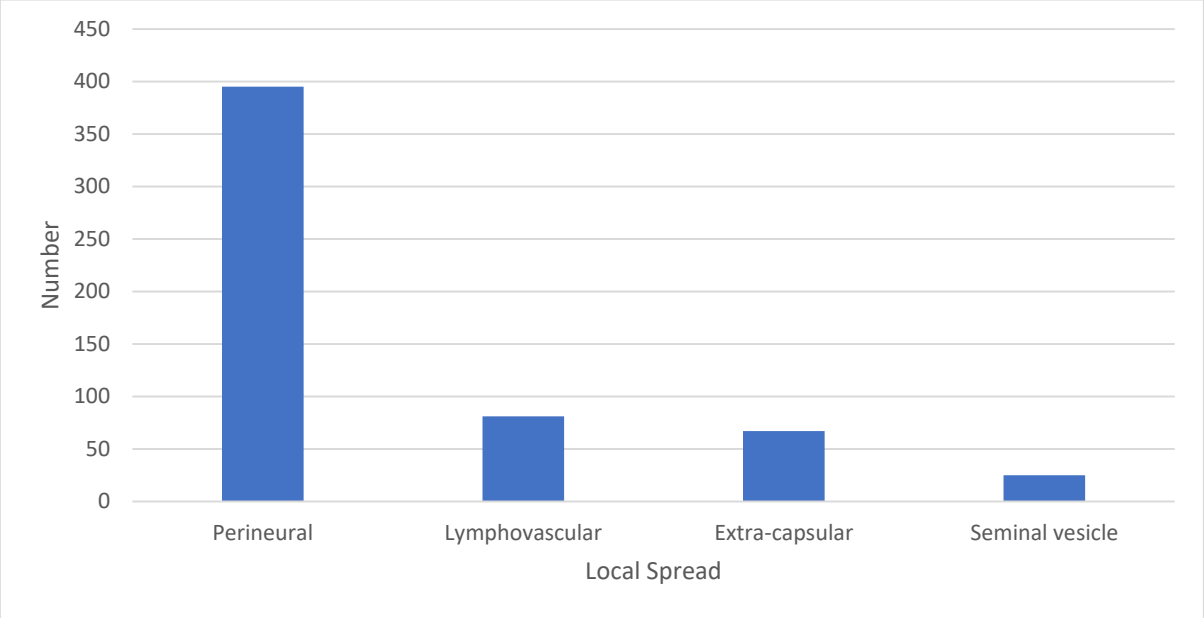


Figure 4.9: Distribution of local spread within the sample

4.8. HG-PIN and Prostatitis

The presence or absence of HG-PIN was reported in 242 (33.3%) specimens of the study population. It was not reported in 484 (66.7%) specimens. It was present in 162 (22%) biopsies, of which 78 had high-grade disease, 33 intermediate grade disease, 46 low-grade disease and in five, the grade was indeterminate. In 80 (11%) specimens, it was noted as absent. Of these 242 specimens 34 (14.5%) underwent immunohistochemical staining.

The presence of prostatitis was reported in 116 (16%) biopsies, of which 38 had high-grade disease, 23 intermediate, 54 low grade and in one, the grade of disease was indeterminate.

Of the specimen with prostatitis, 23 had immunohistochemical staining. Ten specimens were negative for prostatitis. In 600 (82.6%) specimens, the presence or absence of prostatitis was not reported.

4.9. Immunohistochemical staining

Regarding immunohistochemistry, 92 specimens were stained. The basal stains applied were 34BE12 in 51 specimens and p63 in 47. The PCa specific stains applied were PSA in 17 specimens and AMACR in six. The triple cocktail was used in four specimens.

Of the 92 specimens which were stained, 67 (78%) had more than one stain used. In 13, a single stain was used and in another 12, the stain(s) used were not specified in the report. Two of the specimens had neuroendocrine differentiation as supported by the staining results, where NSE, synaptophysin and chromogranin stains were positive.

CHAPTER 5: DISCUSSION

5.1. Summary

In this study, a variety of results was found among patients in whom adenocarcinoma of the prostate was proven on histology. The clinical data was unobtainable and the race data was unavailable, leaving gaps in our ability to analyse all of the data gathered. The missing data still provided useful insights into this disease at Charlotte Maxeke Johannesburg Academic Hospital. The majority of patients presented with advanced disease as per the PSA, Gleason grade and evidence of local spread on biopsy. Very few patients potentially met Epstein's criteria for clinically insignificant or indolent disease. A small percentage of patients potentially met D'Amico's criteria for localised disease, and only 20 radical surgeries with intention to cure were performed.

The histological samples showing adenocarcinoma of the prostate were obtained from specimens of men presenting with either prostate pathology, who made up the great majority, or those presenting with bladder pathology. The majority of the patients with prostate pathology, had a suspicion of PCa based on an abnormal DRE or a raised PSA, and a core needle prostate biopsy was performed. In a minority of patients with known PCa, the prostate was either completely removed, with the intention to cure the cancer, or in fragments, with the intention to relieve the symptoms of urinary obstruction.

5.2. Needle biopsies

The current standard manner of confirming PCa is to perform a core needle biopsy, in response to either a raised PSA or an abnormal DRE. In this study, the vast majority (91.5%) of positive PCa histology came from core needle biopsies.

5.2.1. Adequacy of reporting as per ICCR

The International Collaboration on Cancer Reporting sets forth, by consensus, the features that are required and those that are recommended for histology reporting. The choice of the word "required" as against "mandatory" is of interest. It indicates the caution of international collaborators to be prescriptive. However, it lacks authority. The European Urology guidelines use the words "mandatory" or "optional", which are authoritative and commanding without being prescriptive.

Regarding the microscopic features that are required in reporting, the histological tumour type and the histological grade as per Gleason were reported in 100% of cases. The ICCR requires that the tumour extent be reported using number of cores positive/ number of cores and the linear extent of the tumour involvement of each core that is involved with tumour. In this study the extent of tumour was reported on in two ways; the number of cores received and involved with cancer were reported, each as discrete number in 63.4% of cases, and the percentage of the entire specimen received involved with cancer, in close to 90% of the core needle biopsies.

The microscopic findings that are recommended in reporting by the ICCR include histological grade 4 or 5 as a percentage of the whole, perineural spread, seminal vesicle spread, lymphovascular spread, extra-prostatic spread, intraductal carcinoma and other co-existing pathology. In this study, the pathology reports often commented on evidence of local spread in the specimen, especially perineural infiltration. In 560 specimens, comment was made on either the presence or absence of local spread. In 395 (54%) specimens, there was evidence of perineural spread, i.e. more than half of our patients had perineural spread at presentation. This is currently only a recommended criterion according to the ICCR. It offers an opportunity to customize reporting templates to be locally relevant and to reflect the unique features found in our setting.

There is a growing interest in local invasion of PCa seen on histology and studies looking into its implications have recently exploded in number. There are features found on histology that are currently not being factored in risk stratification and prognostication models. The urology, oncology and pathology communities are delving deeper into their possible implications.

Perineural infiltration was the form of local invasion observed most often in this study, and deserving of further study as shown by the conclusions reached by various researchers which include the following: there is vasa nervorum neoangiogenesis in patients with PCa with perineural invasion (Ghinea et al., 2019), this indicates interplay between haematogenous and perineural spread in PCa; perineural invasion has prognostic significance for biochemical recurrence after radical prostatectomy [159]; quantitative perineural invasion is a poor prognostic marker in PCa [139]; perineural invasion on biopsy is a predictor of biochemical recurrence and tumour progression [160 2019] and that perineural invasion positivity on biopsy is

an important predictive factor for increased T3 disease, biochemical recurrence and reduced recurrence free survival [138].

Ahmad et al. questioned whether the reporting of perineural invasion should be mandatory and concluded that it should not [161]. However, the findings of this study support the need for further evaluation of the importance of perineural invasion and the possible clinical implications thereof specifically on spinal cord compression.

5.2.2. Superiority of particular biopsy protocol

In this study the number of cores intended by the clinician as per the biopsy protocol specified in the request form were matched as closely as possible with the number of cores received by the pathologist. The intended number of cores taken by the urologist may differ from the number of cores received by the pathologist for several reasons. Technical aspects of the specimen acquisition may result in fewer cores received by the pathologist than the number stated by the urologist. The pathologist may also receive more cores than reported by the urologist. This is possible if cores fragment during transport or preparation for histological assessment.

Eskew et al. (1997) and Chang et al. (1998) showed that a 12-core needle biopsy has a higher cancer detection rate than the sextant biopsy protocol [95] (Chang, 1998). Turk et al. (2015) showed that a 20-core needle protocol was not better at cancer detection than a 12-core needle biopsy [96]. This study was unable to answer if either biopsy protocol was superior regarding cancer detection as the inclusion criterion for the study was all specimens received by the NHLS that were positive for PCa. However, we could assess the biopsy findings to see if more of the biopsy questions such on features such as Gleason score, presence of prostatitis, HG-PIN, evidence of local spread were better answered by one protocol compared to another. There was significantly more prostatitis in the systematic protocol. There was also more seminal vesicle tissue represented in the systematic protocol, although not significant. The limited biopsy protocol had notably more repeat biopsies than the other two protocols, but also not significant.

5.2.3. Systematic biopsy protocol

The systematic 12-core needle biopsy was the most commonly employed technique for prostate biopsy in our study. This approach is supported by a few studies. Elabaddy and Khedr showed that it increases both the detection of PCa and the accuracy of Gleason score [97]. In

this study, we could not show superiority regarding the detection rate of PCa nor the accuracy of the Gleason score needle, compared to the limited and sextant. However, the higher representation of seminal vesicle tissue in the systematic technique enabled a more accurate T- staging of the cancer. A specimen showing PCa in the seminal vesicles is assigned a higher T- stage than one without.

There was more prostatitis in the systemic biopsies. If the prostatitis was present prior to the biopsy, it reflects the superiority of the systematic technique in enabling prostatitis to be identified in the specimen. However, the possibility also exists that the prostatitis may be a function of the longer time taken to collect the 12 cores with sufficient time for the body to launch an inflammatory reaction in response to the trauma of the biopsy needle passing through the tissue. A distinction between the two would be found in the type of inflammatory cells present within the specimen, whether the lymphocytes, macrophages and plasma cells of chronic inflammation or the neutrophils and monocytes of acute inflammation.

Eskew et al. (1997) and Serefoglu et al. (2013) showed that the systematic biopsy provides a good balance between adequate tissue for histological assessment and acceptable level of complications and gives a superior yield compared to the sextant biopsy [95 2013,162]. Berger et al. concluded that obtaining more cores than the 12 cores of the systematic approach does not increase the yield but may increase minor, self-limiting complications such as post biopsy fever, rectal bleeding, haematuria and haematospermia [163]. In this study, we reviewed only the histological reports and thus cannot comment on the acceptability of the level of complications, which would be recorded in the clinical notes, if they were severe enough to warrant a return to the hospital. Minor complications would not have been reported or recorded.

5.2.4. Repeat biopsies

Seventy-two patients had repeat biopsies with the majority (75%) having a second biopsy. The rest had three [5] or more biopsies. The rates of prostatitis, staining and low Gleason grade were statistically different between first and repeat biopsy; all were higher in the repeats.

The possible causes of the prostatic inflammation seen on biopsy include pre-existing prostatitis, microbial infection introduced by the earlier biopsy, chemical irritation secondary to reflux of urine with urethral obstruction, as may happen with BP and the repeated trauma of the biopsy itself [114]. A study by Djavan also showed a higher rate of prostatitis in repeat

biopsies, [99]. If there is a high clinical suspicion of PCa but the initial biopsy results are equivocal or other histological features uncertain, and a repeat biopsy is done, in such a situation the pathologist may feel compelled to use stains to gain clarity and report with confidence. That would account for the higher rate of staining in the repeat biopsies.

Djavan and colleagues showed that the pick-up rate for PCa decreases with further repeats of the biopsy. They also showed that cancers from the third and fourth biopsies had a lower grade, stage and volume. They concluded that there was no clinical benefit for the patient in doing more than three biopsies and that in fact there is an increase in morbidity in doing so, [99]. In our study, there was a statistically significant difference in the rate of low grade disease. The repeat biopsies picked up lower grade disease, as in Djavan's study. Thus, we can conclude that in our setting we also should not repeat biopsies beyond three negative specimens, even if the clinical suspicion remains high. MRI now offers an alternative route for diagnosing hidden PCa, although with the condition for correct interpretation and superior results being that the patient preferably not have had a biopsy in the 6 months preceding the MRI [75].

There were more repeat biopsies in the limited biopsy protocol group, although not statistically significant. The limited biopsy is conducted differently to the other two in that it is performed with a manual tru-cut biopsy needle and is digitally directed, i.e. not on a spring loaded biopsy gun and not under ultrasound guidance, thus making it more likely that an inadequate specimen for histological study is obtained and the need for a repeat biopsy.

5.3. Specimens other than core needle biopsies

Some of the positive histology was found on prostatic tissue from patients with known PCa, including at radical prostatectomy to treat the cancer definitively or a channel TURP to relieve LUTS. Others came from pathology unrelated to the prostate.

In 30 patients, the finding of PCa was incidental, where a patient had a surgical procedure for presumed benign prostatic disease, and a subsequent finding of cancer on the histology of tissue routinely sent to the pathology laboratory was made. These include seven patients in whom the PCa was discovered at radical cystoprostatectomy for transitional cell carcinoma of the bladder, 13 who had a TURP and five who had an open prostatectomy.

In Perera's study of the incidental finding of PCa at TURP n= 925, he found PCa in 24.9%. This means that almost 1 in 4 of his presumed benign disease was found to harbour malignant

disease in the transitional zone. [164]. Our incidence differs from his. He looked at all TURP specimens and sought out those with cancer on histology. In this study, we looked at all histology positive for cancer and report on those that came from TURP specimens. In our study, only 13 cases of PCa were found on TURP over 5 years. This indicates adequate pre-operative work-up so that patients with cancer are offered appropriate cancer therapy, such that there are no surprise post-operative findings of unsuspected cancer.

In seven of the patients, the PCa was discovered on radical cystoprostatectomy for transitional cell carcinoma of the bladder. In Chun's study of the coincidental finding of both prostate and bladder cancer over five years, he had 100 patients who presented with bladder cancer, five (5) of whom had an incidental finding of PCa on histology [165]. In his study, 5% had incidental PCa, whereas in our study less than 1% of the PCa diagnosed was found to co-exist with bladder cancer. The differences in incidences can be attributed to the differing starting points. Chun started with radical cystoprostatectomy specimens and determined which of the total number done over a period of time had PCa at histology. Our starting point was PCa incidentally found on RCP specimens, without the total number of RCP done in that period.

5.4. Biochemistry and histology

5.4.1. Aggressive disease

A high PSA, a high Gleason score and evidence of local invasion on biopsy all suggest advanced and possibly aggressive disease, depending on the period since the onset of disease, which is a parameter that is currently not possible to determine. In this study 70% of patients had PSA ≥20ng/ml, 61.4% had high-grade disease and only three specimens showed no evidence of any form of local invasion.

5.4.1.1. PSA

The median PSA in this study was 1148.35ng/ml (0.7 – 22,978). In the sample 72 (10%) patients had PSA of more than 1000ng/ml; 66 (90%) of those had high-grade disease, five had intermediate grade and one was indeterminate. A higher PSA correlates positively with greater cytological and architectural disorganisation within the prostatic tissues, and thus a higher Gleason score [166].

Koo and colleagues studied patients with PSA ranging from 20 – 10,000ng/ml in an attempt to determine if there were differences in survival outcomes based on the level of PSA. The patients were stratified into categories of PSA < 20ng/ml, 20- 100ng/ml, 100 - 1000ng/ml and

1000 - 10,000ng/ml. Their study showed that patients with very high PSA levels develop bony metastases during follow up, however there was no difference in castrate resistant PCa – free survival or in cancer specific survival in patients in the various categories. The patients were given active treatment at the discretion of the treating physician, which included the following, intermittent or continuous androgen-deprivation therapy, secondary hormonal manipulations, and cytotoxic chemotherapy. They concluded that patients with extremely high PSA levels should not be denied active treatment for fear of poor response or even failure of response to treatment [167].

Close to 60% of patients (n = 424) presented with PSA ≥ 20ng/ml indicating locally- advanced disease at the time of diagnosis. Khalid et al showed that 50% of their patients with PSA ≥ 20ng/ml had bone metastases evident on bone scan [168]. Kamaleshwaran and colleagues showed that 95% of patients with PSA ≥ 20ng/ml had bone metastases, and that those with PSA ≥ 100ng/ml had multiple bone metastases [76]. In this study, n= 424 had PSA ≥20ng/ml and of those n = 245 presented with PSA ≥ 100ng/ml and 72 had PSA ≥1000ng/ml. Bone metastases in PCa pose a risk for spinal cord compression and resultant neurological fall-out. [70]. Our data did not include scintigraphic or radiological imaging and thus commentary cannot be made on the prevalence of bony metastases, or on the incidence of subsequent spinal cord compression.

5.4.1.2. Gleason grade

In this study, n = 446 (61.4%) had high-grade disease at presentation. When the age groups of patients were divided into decades, our results showed consistently that > 50% of all age groups, had high-grade disease. The age group with the lowest percentage of high-grade disease was the 70 – 79 years group which showed a 58.4% involvement, all the others had >60% of high-grade disease. At the extremes of age, those under 49 years and those over 90 years, which were small groups of 16 and 5 respectively, showed ≥ 80% high-grade disease. In this study, the majority of the patients presented with high-grade disease at diagnosis, regardless of age. This was also the case in the subgroup of early onset PCa (n= 19), where 73.6% of the specimens showed high-grade disease.

In this study, a high Gleason score was more often associated with high tumour bulk and more local spread. There was a statistically significant difference in the number of cases with tumour bulk occupying more than 50% of the specimen received and evidence of locally advanced

tumour in high-grade disease compared to low grade disease. This is in keeping with the natural history of PCa, which is characterised by progressive disorganisation of the cellular component and architecture of the glands, increase in the tumour size replacing normal tissue and also breaching of natural barriers with encroachment into the surrounding structures by contiguous spread and into distant structures via haematogenous and lymphogenous routes 169 1991, Gonzalgo and Isaacs, 2003

5.4.1.3 Local invasion within the specimens

Perineural spread was the most common form of local invasion identified. This route represents the path of least resistance where no natural barriers to spread are met, the cancer simply grows along paths adjacent to the nerve fibers. This was followed, in order, by lymphovascular, extra-capsular and seminal vesicle spread. Seminal vesicle infiltration is more easily and more commonly identified on radical prostatectomy specimens as these contain the excised seminal vesicles. It may also be identified on radical cystoprostatectomy specimens. Due to technical factors of obtaining the prostatic tissue, there should be no seminal vesicle tissue present on a TURP or on an open prostatectomy specimen. It is possible for seminal vesicle tissue to be found on a core of the prostate obtained during core needle biopsy.

Of the more commonly used tools in prognostication and risk stratification such as Epstein's criteria for clinically insignificant disease and D'Amico's criteria for localised disease, neither take evidence of local spread into account. Various authors have shown that the presence of perineural invasion on biopsy has a negative impact on PCa outcomes including biochemical recurrence, tumour progression and recurrence free survival [138]. Thus, a greater weight should be placed upon evidence of local invasion when prognosticating or risk stratifying. These variables must be factored in such tools including in nomograms.

5.4.2. Other histological findings

The presence of either HG-PIN or prostatitis was infrequently reported. HG-PIN was more often associated with high-grade disease (78 of 162), whereas prostatitis was more often associated with low-grade disease (54 of 116), IHC was infrequently used.

5.4.2.1. HG-PIN

In the study, the presence or absence of HG-PIN was reported in 242 specimens, a third of the sample. HG-PIN is a morphological diagnosis and is not dependent upon staining. It was

present in 162 (67%) and absent in 80 (33 %.) It was present in 22.3% of the study population, which is higher than the expected incidence reported by Epstein and Herawi of 5 - 8 % of biopsy specimens having HG-PIN [125]. However, in their review they considered all prostatic needle biopsies which included both benign and malignant disease. Their sample would show a lower rate due to the dilution effect of the samples showing benign disease. They also showed that the subsequent pick-up rate of cancer following HG-PIN is decreasing, in part due to extended biopsy techniques where the co-existing cancer is diagnosed at the same time as the HG-PIN and thus a re-biopsy is not needed.

The value of HG-PIN is in prostate biopsy specimens that do not show any cancer and can then guide the decision on repeat biopsy. The inclusion criteria for this study were biopsies that showed cancer, thus, there is no additional value in the finding of HG-PIN in this population. This raises the question of whether there is a need to routinely report on HG-PIN where cancer is evident on the biopsy, or only in those specimens in which only benign disease is found, in the presence of a high clinical suspicion of PCa.

5.4.2.2. Prostatitis

Prostatitis was reported on 126 specimens and found to be present in 116 of those. It was not reported in more than 80% of the specimens. It is neither a required nor a recommended finding according to the ICCR. However, it can lead to a raised PSA and this has clinical implications in both malignant and benign disease. The finding of prostatitis can influence diagnosis and treatment. For this reason, it is the opinion of the author that it should be mandatory for pathologists to report whether it is present or absent. In benign disease, the treatment of prostatitis should result in a lowering of the PSA to values within the reference range for the patient's age and race, thus reassuring the patient and the clinician of the absence of cancer. In malignant disease the treatment will enable the clinician to initiate management of the patient from a baseline PSA which is attributable only to the cancer and not to inflammation and to correctly ascribe further raises in PSA to cancer progression and thus to institute appropriate treatment.

5.4.3. Immunohistochemistry and unusual histological findings

The role of immunohistochemistry is typically in cases where the diagnosis is equivocal. Neuroendocrine tumours are inherently hormone resistant and rapidly metastatic. They do not respond well to standard adenocarcinoma treatment in the form of radical surgery or

hormonal manipulation. Instead, they respond to combination chemotherapy with agents such as cisplatin, carboplatin and etoposide [170]. In the two cases in this cohort, the confirmation of neuroendocrine histology would have had a direct impact on the management of the patients so it was important to make the specific diagnosis.

Two specimens had Schistosomiasis coexisting with the adenocarcinoma. Another two had co-existing granulomatous prostatitis, which in our setting is most commonly due to tuberculosis. Both Schistosomiasis and tuberculosis can affect the pulmonary system, thus if found on prostate histology a pulmonary assessment is mandated and treatment as indicated. This must be done regardless of the treatment decisions specific to the cancer.

5.5. Age

The age of diagnosis in our cohort is similar to what is being reported in the United States. However, the majority of our patients have locally advanced disease and high-grade disease at diagnosis. Should a case be made for routine screening in younger men in order to make the diagnosis while the disease is less advanced and less aggressive? Our results also showed a potential pool of hereditary PCa based on early onset at age younger than 50 years. In fact, the youngest patient in this study was 25 years old.

5.5.1. Age at diagnosis

The majority of prostate cancers are diagnosed between the ages of 70 and 74 years, the mean age at diagnosis being 68 years [21]. Our results are similar to these. Shao and colleagues showed that in the United States between 1988 – 1989 and 2004 – 2005, the average age at PCa diagnosis decreased from 72.2 to 67.2 years. This followed the approval and subsequent introduction of PSA testing for PCa in 1986 [87]. Shao found that 63% of patients diagnosed with PCa were over the age of 65 years. In our sample 493 (67.9%) were over age 65 years. Of the 726 patients, 16 (2.2%) were below age 50 years, which is similar to Jani's figure of 2% [19].

Community-wide PCa screening is not practiced in our catchment area or in the country as a whole, thus patients >75 years of age are biopsied based on symptomatic presentation. In our sample, 27.9% of patients were older than 75 years. Typically, patients above this age are considered not suitable for curative treatment in the form of radical surgery and thus are not routinely screened [171] [2015]. In our institution, patients above this age are biopsied if they present with symptoms and signs suggestive of PCa, typically spinal cord compression or

severe haematuria. In such cases, a diagnosis is sought in order that the appropriate treatment for the relief of symptoms can be initiated, not for cure.

5.5.2. Early onset disease

Hereditary PCa is a subtype of familial PCa. According to Carter, one of the criteria for its diagnosis is the occurrence of PCa at an age of 55 years or less, so called early- onset PCa. In this sample, 34 (4.7%) patients had early onset PCa. Carter and colleagues showed that up to 43% of early onset cancers are hereditary in nature [27]. Thus, potentially 15 families in our sample could have harboured a hereditary form of PCa. As this was a retrospective study assessing histological and biochemical features of PCa, we could not establish if any of these patients had any relatives with PCa [172]. In the literature, the reported figure of familial PCa is up to 10% of PCa overall and 43% of early onset [27]. The literature is contradictory as to whether hereditary PCa is more biologically aggressive than sporadic PCa. Cremer and colleagues and Keetch and colleagues showed that hereditary PCa had favourable clinical phenotype compared to sporadic PCa; had lower Gleason scores, and was more often organ confined [173] [2016]. The cases of hereditary PCa in the study by Kupelian and colleagues were found to behave more aggressively including those with low Gleason score [31].

5.6. Clinically insignificant disease, localised disease and nomograms

5.6.1. Indolent disease and Epstein

If we apply Epstein's histological criteria of number of cores in the specimen and number of cores positive to the data set and not the clinical criterion of PSA density, in our sample 534 specimens had more than six (6) cores available for histological assessment. Of those 82, had two (2) or fewer cores positive for cancer. Of those, 48 had a Gleason score of 6 or less with no Gleason 4 score. Thus, only 6.6% of the sample had potentially clinically insignificant cancer, provided the PSA densities also met the criteria. In his seminal study into the clinical significance of PCa found at screening, Epstein found that 16% of cancers detected were clinically insignificant (Epstein et al., 1994). This was in screened patients, whereas our patients represent a spectrum of presentation from opportunistic screening to symptomatic to metastatic. In a screened population, the men are asymptomatic and thus more likely to have a higher rate of clinically insignificant disease.

The PSA range in the 48 patients with favourable histological features was 2.4 to 862.4. Epstein's criteria do not specifically mention a PSA cut-off value, only PSA density. Using the

higher acceptable density of 0.15ng/ml per gram of prostate, as per the criteria, then the maximum PSA allowable in a 100g prostate would be 15ng/ml and in a 50g prostate would be 7.5ng/ml. If we assume an average prostate size of 100g, the 48 potentially clinically insignificant cancers, i.e. those with PSA ≤ 15ng/ml, would be decreased to 27 (3.58%). If we assume an average prostate size of 50g, with a PSA ≤ 7.5ng/ml the potentially clinically insignificant cancers would be reduced to 13 (1.79%). Gosselaar et al. found the following rates of clinically unsuspected PCa: 15 - 54% in an autopsy series, 23 - 46% in a cystoprostatectomy series and 15.2% in the PCPT trial. The higher rates in the autopsy and cystoprostatectomy studies may be explained in part because the entire prostate was examined, whereas in the PCPT only a biopsy specimen was studied [174]. All are much higher than the potential 6.6% in this study in which most cases of PCa were clinically significant by Epstein's criteria.

All seven cases of PCa discovered incidentally at RCP, met the histological criteria for clinical insignificance. Whether they met the clinical criteria for clinical insignificance, i.e. on DRE and PSA density cannot be determined, as the clinical information was not available. Aytac and Vuruskan, in their series of 60 cases of incidentally diagnosed PCa from 300 RCP, found that 66.7% of those had clinically significant PCa [175]. Our sample size is not comparable with theirs and their point of departure was RCP performed over 8 years in which the prostate was incidentally found to harbour adenocarcinoma. We commenced with all prostates positive for adenocarcinoma over 5 years and found seven of them to have been removed at radical cystoprostatectomy.

5.6.2. Localised disease and D'Amico

In this study n= 191 had PSA of ≤ 20ng/ml indicative of localised disease according to D'Amico's risk stratification, thus potentially amenable to radical treatment with the intention to cure. The T-staging as per DRE and the Gleason score make up part of the D'Amico classification [176]. However, the total number of patients in the study potentially suitable for curative treatment would not be impacted by factoring in the Gleason score, as no Gleason score is excluded from the D'Amico classification. A high Gleason score with a PSA within the stipulated range would qualify the patient as having localised disease even if at high risk of future metastatic disease. A DRE finding of greater than T2c would disqualify the patient from being considered to have localised disease. Thus if clinical records were included in this study and showed that any of the 191 patients had an abnormal DRE beyond T2c, the number of patients with localised

disease would decrease and the proportion of our patients meeting the criteria for localised, potentially curable disease as per D'Amico and thus qualifying for curative therapy would be less than 26%. Thus 74% of patients presented with locally advanced disease, some of whom were likely metastatic. During this time, 20 patients had radical prostatectomies.

5.6.3. Nomograms

Nomograms are commonly used to predict the risk of cancer recurrence after radical prostatectomy. Jeong and colleagues developed a nomogram using TRUS derived information for predicting high-grade disease on initial biopsy. Neither the older, traditionally accepted nomograms such as the Kattan or Partin nor the newer, novel nomograms such as UCSF CAPRA score incorporate local invasion such as perineural or lymphovascular spread into their prognostication and risk stratification processes. These factors speak to the aggressiveness of the cancer at diagnosis and the likelihood of recurrence following definitive surgical treatment. In resource-constrained environments, TRUS may not be available and therefore it is impossible to determine the PSA density, a clinical parameter often used to determine a nomogram score.

In our setting radical surgical therapy is not always possible due to patient or resource constraint factors such as late presentation, unfitness for surgery due to co-morbidities, long waiting periods or scarcity of ICU beds in government facilities. In this study, 20 radical prostatectomies were done over a period of 5 years. In a setting with low numbers of radical prostatectomies, risk stratification and prognostication tools which do not depend upon the findings of radical surgery, but are able to make optimum use of all biochemical and histological information which is available at diagnosis would be ideal. Most patients had advanced disease with perineural and lymphovascular infiltration on biopsy, and because these are not incorporated into prognostication tools it leaves a gap in our ability to risk stratify and prognosticate these patients at diagnosis. This extra information provides an avenue to explore to help with individualising counselling and treatment of patients. For example if perineural invasion is a risk factor for spinal cord compression and the resultant faecal incontinence, urinary incontinence and paraplegia, these patients can be counselled more specifically on the signs and symptoms of impending spinal cord compression and prompt actions they should take should these appear.

5.7. Screening

Sanyal et al. showed that the lifetime costs of managing high-grade disease are greater than for managing intermediate and low grade disease [177]. Therefore, within our resource constrained environment, earlier diagnosis in the less advanced stage of the disease process should be more cost effective.

Catalona showed that the detection of organ confined and thus less advanced disease is improved by PSA screening [178]. However, routine screening had until recently, not been shown to conclusively lower PCa related mortality but caused an increase in cost of managing the disease through unnecessary treatment of indolent or clinically insignificant cancers [6]. However, upon further review of the ERSPC and PLCO trials which had reached opposing conclusions regarding the impact of screening on PCa specific mortality, Tsodikov and colleagues have shown that the two trials concur that screening does reduce mortality.

To restrict screening, as recommended by the AUA to men of African descent from age 40 years and those with a positive family history, in our country is unlikely to have a great impact on resource preservation. Firstly, our population is 80% Black and secondly 90% of prostate cancers are sporadic, not familial [179]. Point of care PSA testing is now available and is likely to be a cheaper alternative for screening than formal laboratory PSA testing. If so and it is available on the market, can the state justify not having a screening programme? Is it ethical to not offer screening currently, with the knowledge of the long lead period of the disease, its asymptomatic nature and its lethal outcome? Other factors may be considered, such as health economics for example if routine screening was offered might there be an overwhelming number of early cancers detected; do the state facilities have the capacity to manage these and what are the comparative costs of managing patients with early localised disease vs. advanced disease?

5.8. Race

The admission forms at the Charlotte Maxeke Johannesburg Academic Hospital do not provide for the self- identification of race. Thus, no insights could be gained regarding the racial distribution pattern of PCa or the characterisations of cancer within the different races.

The scientific community currently considers that PCa in Black men occurs with greater frequency, is more aggressive and more advanced at presentation [180] African race, age and a positive family history are established risk factors for PCa. There has been an explosion of

research studying the genes of Black men trying to identify the genetic basis for such aggressive disease. It could be argued that in the absence of a national screening programme in South Africa our patients are presenting with advanced disease when symptomatic, much like in the USA prior to PSA testing. There are validated, age and race specific cut-offs for PSA values, which if applied through a national screening programme would allow the diagnosis of early phase PCa and thus provide insights into whether PCa in Black South African men is truly aggressive in the early stages. If the race based reference ranges are not being applied and the cut-off value of 4ng/ml is being applied to African and Asian patients whose cut-off ranges have been shown to be lower than for Caucasians, is the medical fraternity not also inadvertently contributing to the high numbers of advanced disease seen in Africans?

The incompleteness of the South African data as captured by the cancer registry, as it is histology based, raises a concern. According to the NCR statistics in 2008 there were 1899 cases of PCa in Black men and 1809 cases in White men. The population of South Africa is approximately 80% Black and 10% White, with the remaining 10% made up of Coloured and Asian populations. With the 8 times larger Black population and yet similar incidences of PCa, this implies that based on the available statistics PCa the llikelihood of developing PCa in South Africa is greater in White males than in Black males. This is contrary to the international literature, which reports an incidence of PCa which 47% higher in Black males [1]. It is possible that local circumstances differ markedly from international circumstances. However, the other reasons that may possibly explain this discrepancy must be explored. It behooves us as healthcare practitioners to fully explore the truth behind these statistics in order to correctly guide the Ministry of Health to judiciously and equitably allocate resources to serve the nation and adequately prepare for the National Health Insurance programme based on truth not just statistics. In South Africa, many men in rural areas do not have access to basic urological care such as PSA testing, let alone more advanced care such as prostate biopsies and urologists. Thus, those cases of PCa are never diagnosed or captured on national records. There are also men who, due to personal and cultural beliefs, will not seek Western healthcare even when it is available.

Do Black South African men have aggressive disease or advanced disease at diagnosis? When treating individual patients as healthcare practitioners we know to first make the correct diagnosis before we prescribe treatment. We must not forget these same principles when dealing the issue of men's health and prostate cancer. If Black men are presenting with

aggressive disease which from the onset of the malignant process had high PSA values and high Gleason scores, if in Black men those parameters do not gradually worsen over time but are high from the beginning, then genetic testing should be done to determine the genetic and molecular basis of aggressive disease in men of African ancestry. If, however they present with advanced disease, then the remedy for this lies not in genetic testing but rather like the approach in America following the discovery and approval of PSA testing, namely, community education and community wide screening, supported by a robust national cancer registry.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

6.1. As per the 6 objectives

The conclusions reached are presented against the objectives of the study below.

1. Determine if PCa histology reports meet the International Collaboration on Cancer Reporting (ICCR) criteria for reporting.

   In this study, we showed that regarding the ICCR criteria, our histology reports acceptably cover the required criteria and that our reports "over-report" on evidence of local spread, which is not required. This is locally relevant information and holds the promise of unlocking further insights into the pathological process of systemic metastases especially to the skeletal and central nervous systems.

2. Describe the biochemical and histopathological features of prostate biopsies that were positive for PCa.

   Biochemically, almost 2/3 of patients in the study had PSA >20ng/ml, which is associated with skeletal metastases in 50% of cases, thus advanced disease. Many patients had PSA > 100ng/ml which poses a risk for multiple skeletal metastases and spinal cord compression. Histopathologically, our patients presented with high grade disease across the decades, with evidence of locally advanced disease in the form of perineural invasion in more than half of the specimens reviewed and very few patients meeting Epstein's criteria for insignificant disease and very few meeting D'Amico's criteria for low risk disease.

3. Compare the characteristics differentiating low-grade vs. high-grade PCa.
   Most patients in this study presented with high-grade disease, which was shown to be associated with a high PSA, more likely to have a greater volume of the specimen involved with cancer and more likely to have local spread on biopsy. Low grade disease was more often found in repeat biopsies.

4. Determine if a particular biopsy protocol is superior in terms of information yielded.
   The systemic biopsy was the most commonly used biopsy technique and showed superiority regarding seminal vesicle sampling and thus T staging and identifying prostatitis, both of which have clinical and treatment implications.

5. Determine the percentage of patients meeting the criteria for clinically insignificant cancer.

   The vast majority of patients in the study had clinically significant disease. At best, with favourable clinical criteria in all patients, the maximum number of the study population fulfilling the criteria for clinically insignificant disease was 6.6%.

6. Determine the percentage of patients meeting the criteria for localised disease.

   At best, with ideal clinical findings, ¾ of the study population did not meet the criteria for localised disease as per D'Amico's classification. In our setting at presentation, the patients already have advanced disease with probable distant metastases based on the PSA values.

6.2. Limitations of the Study

The race of the patient is not available from the patient admission forms. Thus, it was not possible to comment on the characteristics of PCa in our study regarding race. Race is one of the most important demographic data in the discussion on PCa.

The clinical records of the patients being studied were unobtainable. Thus, local insights could not be made on the tools that take clinical criteria into account such as D'Amico risk stratification and Epstein's determinants of clinically insignificant disease. Tools such as these are important for determining which patients to treat and how to treat them. These impact on budgeting for oncology services.

6.3. Recommendations and questions stemming from the study

6.3.1 Clinical recommendations and future studies

- Is spinal cord compression secondary to PCa a consequence only of haematogenous spread to the vertebrae or does perineural invasion on biopsy also herald future spinal cord compression due to perineural spread? Is it possible to tell if a mass that is compressing the spinal cord originates from the vertebral body having spread there haematogenously or spinal cord having spread there perineurally?

If perineural invasion is a precursor of spinal cord compression, this can influence how clinicians counsel patients at diagnosis about their response to leg weakness, perhaps to create a separate follow up pathway to include regular serum calcium and ALP, a lower threshold for doing a bone scan and/ or MRI lumbar spine, and determining criteria for prophylactic lumbar spine radiation.

- A future study exploring how strictly race based PSA cut-offs are applied in the private sector to negate arguments about of level of education and income. For example, in the age category of 40 – 49 years, what proportion of Black patients with a PSA of 2.5ng/ml have had a prostate biopsy done? What proportion of White patients with a PSA 2ng/ml have had a prostate biopsy done?

- Studies looking at the adaptation of nomograms so that they incorporate biopsy findings of local invasion.

- Should routine nationwide screening for PCa be implemented, perhaps by using Point of Care PSA testing to keep costs down, as for glucose, cholesterol and HIV testing?

- Will the use of MRI in the diagnosis of PCa enable the distinction between contiguous seminal vesicle involvement (T stage) and haematogenous spread (M stage)? Will this distinction be of any clinical benefit?

6.3.2 Practical recommendations for implementation

- To engage the MEC for health in Gauteng Dr. Bandile Masuku on 1) community wide men's health education initiatives, 2) the feasibility of community wide prostate cancer screening, 3) the standardizing of provincial hospital admission forms such that patients can enter their self- assigned race, with a brief reason for this provided in brackets as well as the option to leave the space blank if patients prefers, by creating new admissions form for CMJAH/ DoH hospitals. The patient admission from at Steve Biko Academic Hospital provides space for this. See Appendix C and D, for the CMJAH and SBAH admission forms respectively.

- To approach Dr. Yvonne Perner, the head of department of Anatomical Pathology at the University of the Witwatersrand with the aim of facilitating engagement between the South African Urology Association and the National Pathology Group, the association of

pathologists in South African to 1) work on a template for pathology reporting which includes prostatitis as a mandatory feature to report, 2) if there is agreement on this, to jointly approach the ICCR on the issue of the elevating the reporting of either all evidence of local invasion on biopsy from being recommended to being required. Alternatively, the elevation of only the finding of perineural invasion unless dictated by the findings of further studies. See appendix J.

- To engage with the American Urological Association and the European Association of Urology about the D'Amico risk stratification system for localised disease: a change in the upper limit of the PSA value in the intermediate category to 19ng/ml, thus PSA 10-19ng/ml; also a change in the symbol preceding the PSA values in the high risk category to be an equal sign instead of a greater than sign, thus =20ng/ml rather than >20ng/ml. A PSA of 21ng/ml fits the criteria, as does a PSA of 100ng/ml or 1000ng/ml.

- The addition of a clinical component to the notification of cancer towards a more robust National Cancer Registry, much like the booklets for notification of tuberculosis in the wards, but using the technological advances available. Notification of TB by clinicians enabled the South African health authorities to have a clearer picture of this disease. Without a clear picture of the state of cancer in the country, we will not be able to plan adequately. The technological advances allow clinicians to capture critical information to guide in planning for health care needs of the country wherever they are in the country, including far-flung rural areas. See appendix I.

- A template for biopsy request: name, age, DoB, race, height and weight for BMI, PSA, DRE, use of alpha reductase inhibitors, indication, previous biopsy and date, number of cores taken. See Appendix E.

- A template for biopsy reporting: name, age, DoB, race, PSA, DRE, number of core received, number of core positive, percentage of core needle positive vs. percentage of specimen positive, Gleason/ ISUP, tertiary pattern, prostatitis, HG-PIN, local infiltration (perineural, lymphovascular, extra capsular extension, seminal vesicles). See Appendix F.

- Electronic storage of clinical files for ease of reference rather than the current system of microfiche.

REFERENCES

1. Haas GP, Sakr WA. Epidemiology of prostate cancer. CA Cancer J Clin. 1997; 47(5):273-87. doi:10.3322/canjclin.47.5.273
2. Herbst M. Fact sheet on the top ten cancers per population group. 2014.
3. Mutetwa B, Taioli E, Attong-Rogers A, Layne P, Roach V, Ragin C. Prostate cancer characteristics and survival in males of african ancestry according to place of birth: Data from brooklyn-new york, guyana, tobago and trinidad. Prostate. 2010; 70(10):1102-9. doi:10.1002/pros.21144
4. Bangma CH, Roobol MJ. Defining and predicting indolent and low risk prostate cancer. Critical Reviews in Oncology/Hematology. 2012; 83(2):235-41. doi:https://doi.org/10.1016/j.critrevonc.2011.10.003
5. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009; 360(13):1310-9. doi:10.1056/NEJMoa0810696
6. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized european study. N Engl J Med. 2009; 360(13):1320-8. doi:10.1056/NEJMoa0810084
7. Tsodikov A, Gulati R, Heijnsdijk EAM, Pinsky PF, Moss SM, Qiu S, et al. Reconciling the effects of screening on prostate cancer mortality in the erspc and plco trials. Ann Intern Med. 2017; 167(7):449-55. doi:10.7326/m16-2586
8. Kleier JA. Prostate cancer in black men of african-caribbean descent. J Cult Divers. 2003; 10(2):56-61.
9. Babb C, Urban M, Kielkowski D, Kellett P. Prostate cancer in south africa: Pathology based national cancer registry data (1986-2006) and mortality rates (1997-2009). Prostate Cancer. 2014; 2014:419801. doi:10.1155/2014/419801
10. Freddie Bray AZ, Patricia Cueva, Anne Korir, Rajaraman Swaminathan, Andreas Ullrich, Susan A. Wang, And Donald Maxwell Parkin. Planning and developing population-based cancer registration in low- and middle-income settings. Lyon, France: International Agency for Research on Cancer; 2014.
11. Lehohla PSSA. Census 2011 statistics release. Pretoria, South Africa: 2011.
12. PCFA. Prostate anatomical relations. 2020. p. Anatomical relations of the prostate.
13. Oncohema Key. Zones of the prostate.
14. Horizon. Histology of the prostate 20 Feb 2020.
15. McNeal JE. Normal histology of the prostate. Am J Surg Pathol. 1988; 12(8):619-33. doi:10.1097/00000478-198808000-00003
16. Wright A, Thomas L, Douglas R, Lazier C, Rittmaster R. Relative potency of testosterone and dihydrotestosterone in preventing atrophy and apoptosis in the prostate of castrated rat. The Journal of clinical investigation. 1997; 98:2558-63. doi:10.1172/JCI119074
17. Oesterling JE, Epstein JI, Walsh PC. The inability of adrenal androgens to stimulate the adult human prostate: An autopsy evaluation of men with hypogonadotropic hypogonadism and panhypopituitarism. J Urol. 1986; 136(5):1030-4. doi:10.1016/s0022-5347(17)45198-6
18. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: Age, location, and behavioral correlates. Clin Epidemiol. 2012; 4:1-11. doi:10.2147/clep.S16747
19. Jani AB, Johnstone PA, Liauw SL, Master VA, Brawley OW. Age and grade trends in prostate cancer (1974-2003): A surveillance, epidemiology, and end results registry analysis. Am J Clin Oncol. 2008; 31(4):375-8. doi:10.1097/COC.0b013e3181637384
20. Etzioni R, Legler JM, Feuer EJ, Merrill RM, Cronin KA, Hankey BF. Cancer surveillance series: Interpreting trends in prostate cancer--part iii: Quantifying the link between population prostate-specific antigen testing and recent declines in prostate cancer mortality. J Natl Cancer Inst. 1999; 91(12):1033-9.
21. Shao YH, Demissie K, Shih W, Mehta AR, Stein MN, Roberts CB, et al. Contemporary risk profile of prostate cancer in the united states. J Natl Cancer Inst. 2009; 101(18):1280-3. doi:10.1093/jnci/djp262
22. Grönberg H. Prostate cancer epidemiology. The Lancet. 2003; 361(9360):859-64. doi:http://dx.doi.org/10.1016/S0140-6736(03)12713-4

23. Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. Br J Cancer. 2011; 105(4):481-5. doi:10.1038/bjc.2011.273
24. Slabber CF. A new south africa--a new health care strategy. S Afr Med J. 1992; 82(6):388-91.
25. Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, et al. Hereditary prostate cancer: Epidemiologic and clinical features. J Urol. 1993; 150(3):797-802.
26. Bratt O. Hereditary prostate cancer. BJU Int. 2000; 85(5):588-98.
27. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A. 1992; 89(8):3367-71.
28. Woolf CM. An investigation of the familial aspects of carcinoma of the prostate. Cancer. 1960; 13:739-44. doi:10.1002/1097-0142(196007/08)13:4<739::aid-cncr2820130414>3.0.co;2-e
29. Gillanders EM, Xu J, Chang BL, Lange EM, Wiklund F, Bailey-Wilson JE, et al. Combined genome-wide scan for prostate cancer susceptibility genes. J Natl Cancer Inst. 2004; 96(16):1240-7. doi:10.1093/jnci/djh228
30. Gronberg H, Isaacs SD, Smith JR, Carpten JD, Bova GS, Freije D, et al. Characteristics of prostate cancer in families potentially linked to the hereditary prostate cancer 1 (hpc1) locus. Jama. 1997; 278(15):1251-5. doi:10.1001/jama.1997.03550150055035
31. Kupelian PA, Kupelian VA, Witte JS, Macklis R, Klein EA. Family history of prostate cancer in patients with localized prostate cancer: An independent predictor of treatment outcome. J Clin Oncol. 1997; 15(4):1478-80. doi:10.1200/jco.1997.15.4.1478
32. Prezioso D, Denis LJ, Klocker H, Sciarra A, Reis M, Naber K, et al. Estrogens and aspects of prostate disease. Int J Urol. 2007; 14(1):1-16. doi:10.1111/j.1442-2042.2006.01476.x
33. Debes JD, Tindall DJ. The role of androgens and the androgen receptor in prostate cancer. Cancer Lett. 2002; 187(1-2):1-7. doi:10.1016/s0304-3835(02)00413-5
34. Ross RK, Bernstein L, Lobo RA, Shimizu H, Stanczyk FZ, Pike MC, et al. 5-alpha-reductase activity and risk of prostate cancer among japanese and us white and black males. Lancet. 1992; 339(8798):887-9. doi:10.1016/0140-6736(92)90927-u
35. Naslund MJ, Coffey DS. The differential effects of neonatal androgen, estrogen and progesterone on adult rat prostate growth. J Urol. 1986; 136(5):1136-40. doi:10.1016/s0022-5347(17)45239-6
36. Prins GS, Huang L, Birch L, Pu Y. The role of estrogens in normal and abnormal development of the prostate gland. Ann N Y Acad Sci. 2006; 1089:1-13. doi:10.1196/annals.1386.009
37. Medicine Io. Genes, behavior, and the social environment: Moving beyond the nature/nurture debate. Hernandez LM, Blazer DG, editors. Washington, DC: The National Academies Press; 2006.
38. Kapiszewska M. A vegetable to meat consumption ratio as a relevant factor determining cancer preventive diet. The mediterranean versus other european countries. Forum Nutr. 2006; 59:130-53. doi:10.1159/000095211
39. Zaridze DG, Muir CS, McMichael AJ. Diet and cancer: Value of different types of epidemiological studies. Nutr Cancer. 1985; 7(3):155-66. doi:10.1080/01635588509513850
40. Stocks P. Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. Br J Cancer. 1970; 24(2):215-25. doi:10.1038/bjc.1970.25
41. Jones MR, Joshu CE, Kanarek N, Navas-Acien A, Richardson KA, Platz EA. Cigarette smoking and prostate cancer mortality in four us states, 1999-2010. Prev Chronic Dis. 2016; 13:E51. doi:10.5888/pcd13.150454
42. Breslow RA, Weed DL. Review of epidemiologic studies of alcohol and prostate cancer: 1971-1996. Nutr Cancer. 1998; 30(1):1-13. doi:10.1080/01635589809514633
43. Sesso HD, Paffenbarger RS, Jr., Lee IM. Alcohol consumption and risk of prostate cancer: The harvard alumni health study. Int J Epidemiol. 2001; 30(4):749-55. doi:10.1093/ije/30.4.749
44. Schoonen WM, Salinas CA, Kiemeney LA, Stanford JL. Alcohol consumption and risk of prostate cancer in middle-aged men. Int J Cancer. 2005; 113(1):133-40. doi:10.1002/ijc.20528
45. Honda GD, Bernstein L, Ross RK, Greenland S, Gerkins V, Henderson BE. Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. Br J Cancer. 1988; 57(3):326-31. doi:10.1038/bjc.1988.74
46. Giles GG, Severi G, English DR, McCredie MR, Borland R, Boyle P, et al. Sexual factors and prostate cancer. BJU Int. 2003; 92(3):211-6. doi:10.1046/j.1464-410x.2003.04319.x

47. Giles GG, Severi G, English DR, Hopper JL. Frequency of ejaculation and risk of prostate cancer. Jama. 2004; 292(3):329; author reply doi:10.1001/jama.292.3.329-a
48. Engelbrecht C. South Africa: 2006 Downloaded 8 Jan 2020, Released August 2006. Report No.
49. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among swedish and us men with prostate cancer. J Natl Cancer Inst. 2012; 104(17):1335-42. doi:10.1093/jnci/djs299
50. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic incidence and duration of prostate cancer. Am J Epidemiol. 1998; 148(8):775-85.
51. Duffy MJ. Tumor markers in clinical practice: A review focusing on common solid cancers. Med Princ Pract. 2013; 22(1):4-11. doi:10.1159/000338393
52. Charatan FB. Fda approves test for prostatic cancer. BMJ. 1994; 309(6955):628-9. doi:10.1136/bmj.309.6955.628a
53. Yousef GM, Diamandis EP. The new human tissue kallikrein gene family: Structure, function, and association to disease. Endocr Rev. 2001; 22(2):184-204. doi:10.1210/edrv.22.2.0424
54. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987; 317(15):909-16. doi:10.1056/nejm198710083171501
55. Papsidero LD, Kuriyama M, Wang MC, Horoszewicz J, Leong SS, Valenzuela L, et al. Prostate antigen: A marker for human prostate epithelial cells. J Natl Cancer Inst. 1981; 66(1):37-42.
56. Stephenson RA, Stanford JL. Population-based prostate cancer trends in the united states: Patterns of change in the era of prostate-specific antigen. World J Urol. 1997; 15(6):331-5. doi:10.1007/bf01300179
57. Carter HB. American urological association (aua) guideline on prostate cancer detection: Process and rationale. BJU Int. 2013; 112(5):543-7. doi:10.1111/bju.12318
58. Oesterling JE. Age-specific reference ranges for serum psa. N Engl J Med. 1996; 335(5):345-6. doi:10.1056/nejm199608013350511
59. Hamdy FC. The prostate cancer prevention trial and its messages. Eur Urol. 2007; 51(1):6-8. doi:10.1016/j.eururo.2006.09.013
60. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004; 350(22):2239-46. doi:10.1056/NEJMoa031918
61. Lucia MS, Darke AK, Goodman PJ, La Rosa FG, Parnes HL, Ford LG, et al. Pathologic characteristics of cancers detected in the prostate cancer prevention trial: Implications for prostate cancer detection and chemoprevention. Cancer Prev Res (Phila). 2008; 1(3):167-73. doi:10.1158/1940-6207.Capr-08-0078
62. Richardson TD, Oesterling JE. Age-specific reference ranges for serum prostate-specific antigen. Urol Clin North Am. 1997; 24(2):339-51. doi:10.1016/s0094-0143(05)70381-5
63. Kim JS, Ryu J-G, Kim JW, Hwang EC, Jung SI, Kang TW, et al. Prostate-specific antigen fluctuation: What does it mean in diagnosis of prostate cancer? International braz j urol : official journal of the Brazilian Society of Urology. 2015; 41(2):258-64. doi:10.1590/S1677-5538.IBJU.2015.02.11
64. Barry MJ. Evaluation of symptoms and quality of life in men with benign prostatic hyperplasia. Urology. 2001; 58(6 Suppl 1):25-32; discussion doi:10.1016/s0090-4295(01)01300-0
65. McNeal JE. Origin and development of carcinoma in the prostate. Cancer. 1969; 23(1):24-34. doi:10.1002/1097-0142(196901)23:1<24::aid-cncr2820230103>3.0.co;2-1
66. Grignon DJ, Sakr WA. Zonal origin of prostatic adenocarcinoma: Are there biologic differences between transition zone and peripheral zone adenocarcinomas of the prostate gland? J Cell Biochem Suppl. 1994; 19:267-9.
67. Palmerola R, Smith P, Elliot V, Reese CT, Mahon FB, Harpster LE, et al. The digital rectal examination (dre) remains important - outcomes from a contemporary cohort of men undergoing an initial 12-18 core prostate needle biopsy. Can J Urol. 2012; 19(6):6542-7.
68. Andriole GL, Catalona WJ. The diagnosis and treatment of prostate cancer. Annu Rev Med. 1991; 42:9-15. doi:10.1146/annurev.me.42.020191.000301

69. Okotie OT, Roehl KA, Han M, Loeb S, Gashti SN, Catalona WJ. Characteristics of prostate cancer detected by digital rectal examination only. Urology. 2007; 70(6):1117-20. doi:10.1016/j.urology.2007.07.019
70. Tsuzuki S, Park SH, Eber MR, Peters CM, Shiozawa Y. Skeletal complications in cancer patients with bone metastases. Int J Urol. 2016; 23(10):825-32. doi:10.1111/iju.13170
71. Wein AJ. Campbell-walsh urology ninth edition review. Philadelphia: Saunders/Elsevier; 2007.
72. Bubendorf L, Schopfer A, Wagner U, Sauter G, Moch H, Willi N, et al. Metastatic patterns of prostate cancer: An autopsy study of 1,589 patients. Hum Pathol. 2000; 31(5):578-83. doi:10.1053/hp.2000.6698
73. Rhoden EL, Torres O, Ramos GZ, Lemos RR, Souto CA. Value of prostate specific antigen in predicting the existence of bone metastasis in scintigraphy. Int Braz J Urol. 2003; 29(2):121-5; discussion 6.
74. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006; 12(20 Pt 2):6243s-9s. doi:10.1158/1078-0432.Ccr-06-0931
75. Taneja SS. Imaging in the diagnosis and management of prostate cancer. Rev Urol. 2004; 6(3):101-13.
76. Kamaleshwaran KK, Mittal BR, Harisankar CN, Bhattacharya A, Singh SK, Mandal AK. Predictive value of serum prostate specific antigen in detecting bone metastasis in prostate cancer patients using bone scintigraphy. Indian J Nucl Med. 2012; 27(2):81-4. doi:10.4103/0972-3919.110683
77. Pezaro C, Omlin A, Lorente D, Rodrigues DN, Ferraldeschi R, Bianchini D, et al. Visceral disease in castration-resistant prostate cancer. Eur Urol. 2014; 65(2):270-3. doi:10.1016/j.eururo.2013.10.055
78. Drake CG. Visceral metastases and prostate cancer treatment: 'Die hard,' 'tough neighborhoods,' or 'evil humors'? Oncology (Williston Park). 2014; 28(11):974-80.
79. Klimek M. Pulmonary lymphangitis carcinomatosis: Systematic review and meta-analysis of case reports, 1970-2018. Postgrad Med. 2019; 131(5):309-18. doi:10.1080/00325481.2019.1595982
80. Deng Y, Bi R, Zhu Z, Li S, Xu B, Rather WA, et al. A surveillance, epidemiology and end results database analysis of the prognostic value of organ-specific metastases in patients with advanced prostatic adenocarcinoma. Oncol Lett. 2019; 18(2):1057-70. doi:10.3892/ol.2019.10461
81. Hatzoglou V, Patel GV, Morris MJ, Curtis K, Zhang Z, Shi W, et al. Brain metastases from prostate cancer: An 11-year analysis in the mri era with emphasis on imaging characteristics, incidence, and prognosis. J Neuroimaging. 2014; 24(2):161-6. doi:10.1111/j.1552-6569.2012.00767.x
82. Sacco E, Pinto F, Sasso F, Racioppi M, Gulino G, Volpe A, et al. Paraneoplastic syndromes in patients with urological malignancies. Urol Int. 2009; 83(1):1-11. doi:10.1159/000224860
83. Buyyounouski MK, Choyke PL, McKenney JK, Sartor O, Sandler HM, Amin MB, et al. Prostate cancer - major changes in the american joint committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017; 67(3):245-53. doi:10.3322/caac.21391
84. Bertero L, Massa F, Metovic J, Zanetti R, Castellano I, Ricardi U, et al. Eighth edition of the uicc classification of malignant tumours: An overview of the changes in the pathological tnm classification criteria-what has changed and why? Virchows Arch. 2018; 472(4):519-31. doi:10.1007/s00428-017-2276-y
85. Heyns CF, Basson J, van der Merwe A, Zarrabi AD. Clinical (non-histological) diagnosis of advanced prostate cancer: Evaluation of treatment outcome after androgen deprivation therapy2014.
86. Matlaga BR, Eskew LA, McCullough DL. Prostate biopsy: Indications and technique. The Journal of Urology. 2003; 169(1):12-9. doi:http://dx.doi.org/10.1016/S0022-5347(05)64024-4
87. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics, 2008. CA: a cancer journal for clinicians. 2008; 58:71-96. doi:10.3322/CA.2007.0010
88. Watanabe H, Igari D, Tanahashi Y, Harada K, Saito M. Measurements of size and weight of prostate by means of transrectal ultrasonotomography. Tohoku J Exp Med. 1974; 114(3):277-85. doi:10.1620/tjem.114.277
89. Halpern EJ, Strup SE. Using gray-scale and color and power doppler sonography to detect prostatic cancer. AJR Am J Roentgenol. 2000; 174(3):623-7. doi:10.2214/ajr.174.3.1740623
90. Beerlage HP. Alternative therapies for localized prostate cancer. Curr Urol Rep. 2003; 4(3):216-20. doi:10.1007/s11934-003-0072-5

91. Maccagnano C, Scattoni V, Roscigno M, Raber M, Angiolilli D, Montorsi F, et al. Anaesthesia in transrectal prostate biopsy: Which is the most effective technique? Urol Int. 2011; 87(1):1-13. doi:10.1159/000327827
92. Pelzer AE, Heinzelbecker J, Weiss C, Fruhbauer D, Weidner AM, Kirchner M, et al. Real-time sonoelastography compared to magnetic resonance imaging using four different modalities at 3.0 t in the detection of prostate cancer: Strength and weaknesses. Eur J Radiol. 2013; 82(5):814-21. doi:10.1016/j.ejrad.2012.11.035
93. Bratt O. The difficult case in prostate cancer diagnosis--when is a "diagnostic turp" indicated? Eur Urol. 2006; 49(5):769-71. doi:10.1016/j.eururo.2006.01.010
94. Hodge KK, McNeal JE, Stamey TA. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol. 1989; 142(1):66-70. doi:10.1016/s0022-5347(17)38663-9
95. Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. J Urol. 1997; 157(1):199-202; discussion -3.
96. Turk Z, Hollberg H, Dill T, Kaspers I, Isbarn H. [prostate cancer detection rates: Comparison of standard biopsy with prompt rebiopsy and a one-time extended biopsy]. Urologe A. 2015; 54(1):28-33. doi:10.1007/s00120-014-3648-4
97. Elabbady AA, Khedr MM. Extended 12-core prostate biopsy increases both the detection of prostate cancer and the accuracy of gleason score. European Urology. 2006; 49(1):49-53. doi:http://dx.doi.org/10.1016/j.eururo.2005.08.013
98. Keetch DW, Catalona WJ, Smith DS. Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. J Urol. 1994; 151(6):1571-4.
99. Djavan B, Ravery V, Zlotta A, Dobronski P, Dobrovits M, Fakhari M, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: When should we stop? J Urol. 2001; 166(5):1679-83.
100. Djavan B, Remzi M, Schulman CC, Marberger M, Zlotta AR. Repeat prostate biopsy: Who, how and when?: A review. European Urology. 2002; 42(2):93-103. doi:http://dx.doi.org/10.1016/S0302-2838(02)00256-7
101. Ashley RA, Inman BA, Routh JC, Mynderse LA, Gettman MT, Blute ML. Reassessing the diagnostic yield of saturation biopsy of the prostate. Eur Urol. 2008; 53(5):976-81. doi:10.1016/j.eururo.2007.10.049
102. Drost FH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate mri, with or without mri-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database Syst Rev. 2019; 4:Cd012663. doi:10.1002/14651858.CD012663.pub2
103. Epstein JI, Walsh PC, Sauvageot J, Carter HB. Use of repeat sextant and transition zone biopsies for assessing extent of prostate cancer. J Urol. 1997; 158(5):1886-90. doi:10.1016/s0022-5347(01)64159-4
104. Mazal PR, Haitel A, Windischberger C, Djavan B, Sedivy R, Moser E, et al. Spatial distribution of prostate cancers undetected on initial needle biopsies. Eur Urol. 2001; 39(6):662-8. doi:10.1159/000052524
105. Chang JJ, Shinohara K, Hovey RM, Montgomery C, Presti JC, Jr. Prospective evaluation of systematic sextant transition zone biopsies in large prostates for cancer detection. Urology. 1998; 52(1):89-93. doi:10.1016/s0090-4295(98)00116-2
106. Peyromaure M, Ravery V, Messas A, Toublanc M, Boccon-Gibod L, Boccon-Gibod L. Pain and morbidity of an extensive prostate 10-biopsy protocol: A prospective study in 289 patients. J Urol. 2002; 167(1):218-21.
107. Quinlan MR, Bolton D, Casey RG. The management of rectal bleeding following transrectal prostate biopsy: A review of the current literature. Can Urol Assoc J. 2018; 12(3):E146-e53. doi:10.5489/cuaj.4660
108. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. Eur Urol. 2013; 64(6):876-92. doi:10.1016/j.eururo.2013.05.049
109. Enlund AL, Varenhorst E. Morbidity of ultrasound-guided transrectal core biopsy of the prostate without prophylactic antibiotic therapy. A prospective study in 415 cases. Br J Urol. 1997; 79(5):777-80. doi:10.1046/j.1464-410x.1997.00144.x

110. Djavan B, Waldert M, Zlotta A, Dobronski P, Seitz C, Remzi M, et al. Safety and morbidity of first and repeat transrectal ultrasound guided prostate needle biopsies: Results of a prospective european prostate cancer detection study. J Urol. 2001; 166(3):856-60.
111. Brown RW, Warner JJ, Turner BI, Harris LF, Alford RH. Bacteremia and bacteriuria after transrectal prostatic biopsy. Urology. 1981; 18(2):145-8. doi:10.1016/0090-4295(81)90425-8
112. Breslin JA, Turner BI, Faber RB, Rhamy RK. Anaerobic infection as a consequence of transrectal prostatic biopsy. J Urol. 1978; 120(4):502-3. doi:10.1016/s0022-5347(17)57246-8
113. Frieden T. Antibiotic resistance threats in the united states, 2013. Centre for Disease Control, US, 2013.
114. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schrder FH. Complication rates and risk factors of 5802 transrectal ultrasound-guided sextant biopsies of the prostate within a population-based screening program. Urology. 2002; 60(5):826-30. doi:10.1016/s0090-4295(02)01958-1
115. McKenney JK. Mesenchymal tumors of the prostate. Mod Pathol. 2018; 31(S1):S133-42. doi:10.1038/modpathol.2017.155
116. Sawczuk I, Tannenbaum M, Olsson CA, deVere White R. Primary transitional cell carcinoma of prostatic periurethral ducts. Urology. 1985; 25(4):339-43. doi:10.1016/0090-4295(85)90481-9
117. Berman-Booty LD, Knudsen KE. Models of neuroendocrine prostate cancer. Endocr Relat Cancer. 2015; 22(1):R33-49. doi:10.1530/erc-14-0393
118. McNeal JE, Redwine EA, Freiha FS, Stamey TA. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. Am J Surg Pathol. 1988; 12(12):897-906. doi:10.1097/00000478-198812000-00001
119. Zynger DL, Yang X. High-grade prostatic intraepithelial neoplasia of the prostate: The precursor lesion of prostate cancer. International Journal of Clinical and Experimental Pathology. 2009; 2(4):327-38.
120. Schlesinger C, Bostwick DG, Iczkowski KA. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: Predictive value for cancer in current practice. Am J Surg Pathol. 2005; 29(9):1201-7. doi:10.1097/01.pas.0000168178.48535.0d
121. Bostwick DG, Liu L, Brawer MK, Qian J. High-grade prostatic intraepithelial neoplasia. Rev Urol. 2004; 6(4):171-9.
122. Orozco R, O'Dowd G, Kunnel B, Miller MC, Veltri RW. Observations on pathology trends in 62,537 prostate biopsies obtained from urology private practices in the united states. Urology. 1998; 51(2):186-95. doi:10.1016/s0090-4295(97)00620-1
123. Iczkowski KA, Chen HM, Yang XJ, Beach RA. Prostate cancer diagnosed after initial biopsy with atypical small acinar proliferation suspicious for malignancy is similar to cancer found on initial biopsy. Urology. 2002; 60(5):851-4. doi:10.1016/s0090-4295(02)01981-7
124. Epstein JI, Grignon DJ, Humphrey PA, McNeal JE, Sesterhenn IA, Troncoso P, et al. Interobserver reproducibility in the diagnosis of prostatic intraepithelial neoplasia. Am J Surg Pathol. 1995; 19(8):873-86. doi:10.1097/00000478-199508000-00002
125. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: Implications for patient care. J Urol. 2006; 175(3 Pt 1):820-34. doi:10.1016/s0022-5347(05)00337-x
126. Merrimen JL, Evans AJ, Srigley JR. Preneoplasia in the prostate gland with emphasis on high grade prostatic intraepithelial neoplasia. Pathology. 2013; 45(3):251-63. doi:10.1097/PAT.0b013e32835f6134
127. Lefkowitz GK, Taneja SS, Brown J, Melamed J, Lepor H. Followup interval prostate biopsy 3 years after diagnosis of high grade prostatic intraepithelial neoplasia is associated with high likelihood of prostate cancer, independent of change in prostate specific antigen levels. J Urol. 2002; 168(4 Pt 1):1415-8. doi:10.1097/01.ju.0000028091.36436.21
128. Adamczyk P, Wolski Z, Butkiewicz R, Nussbeutel J, Drewa T. Significance of atypical small acinar proliferation and extensive high-grade prostatic intraepithelial neoplasm in clinical practice. Cent European J Urol. 2014; 67(2):136-41. doi:10.5173/ceju.2014.02.art4

129. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J Urol. 1974; 111(1):58-64. doi:10.1016/s0022-5347(17)59889-4
130. Pan CC, Potter SR, Partin AW, Epstein JI. The prognostic significance of tertiary gleason patterns of higher grade in radical prostatectomy specimens: A proposal to modify the gleason grading system. Am J Surg Pathol. 2000; 24(4):563-9. doi:10.1097/00000478-200004000-00011
131. Chan TY, Partin AW, Walsh PC, Epstein JI. Prognostic significance of gleason score 3+4 versus gleason score 4+3 tumor at radical prostatectomy. Urology. 2000; 56(5):823-7. doi:10.1016/s0090-4295(00)00753-6
132. McNeal JE, Villers AA, Redwine EA, Freiha FS, Stamey TA. Histologic differentiation, cancer volume, and pelvic lymph node metastasis in adenocarcinoma of the prostate. Cancer. 1990; 66(6):1225-33. doi:10.1002/1097-0142(19900915)66:6<1225::aid-cncr2820660624>3.0.co;2-x
133. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 international society of urological pathology (isup) consensus conference on gleason grading of prostatic carcinoma: Definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016; 40(2):244-52. doi:10.1097/pas.0000000000000530
134. Egevad L, Delahunt B, Srigley JR, Samaratunga H. International society of urological pathology (isup) grading of prostate cancer - an isup consensus on contemporary grading. Apmis. 2016; 124(6):433-5. doi:10.1111/apm.12533
135. Villers A, McNeal JE, Redwine EA, Freiha FS, Stamey TA. The role of perineural space invasion in the local spread of prostatic adenocarcinoma. J Urol. 1989; 142(3):763-8. doi:10.1016/s0022-5347(17)38881-x
136. Hassan MO, Maksem J. The prostatic perineural space and its relation to tumor spread: An ultrastructural study. Am J Surg Pathol. 1980; 4(2):143-8. doi:10.1097/00000478-198004000-00006
137. Vukovic M, Kavaric P, Magdelinic A, Nikomanis P, Tomovic S, Pelicic D. Perineural invasion on biopsy specimen as predictor of tumor progression in aging male treated with radical prostatectomy. Could we use it for pre-surgical screening? Aging Male. 2019:1-6. doi:10.1080/13685538.2019.1581758
138. Celik S, Bozkurt O, Demir O, Gurboga O, Tuna B, Yorukoglu K, et al. Effects of perineural invasion in prostate needle biopsy on tumor grade and biochemical recurrence rates after radical prostatectomy. Kaohsiung J Med Sci. 2018; 34(7):385-90. doi:10.1016/j.kjms.2017.12.014
139. Lubig S, Thiesler T, Muller S, Vorreuther R, Leipner N, Kristiansen G. Quantitative perineural invasion is a prognostic marker in prostate cancer. Pathology. 2018; 50(3):298-304. doi:10.1016/j.pathol.2017.09.013
140. Ghinea N, Robin B, Pichon C, Leclere R, Nicolas A, Chnecker C, et al. Vasa nervorum angiogenesis in prostate cancer with perineural invasion. Prostate. 2019; 79(6):640-6. doi:10.1002/pros.23771
141. Baydar DE, Baseskioglu B, Ozen H, Geyik PO. Prognostic significance of lymphovascular invasion in clinically localized prostate cancer after radical prostatectomy. ScientificWorldJournal. 2008; 8:303-12. doi:10.1100/tsw.2008.49
142. Ayala AG, Ro JY, Babaian R, Troncoso P, Grignon DJ. The prostatic capsule: Does it exist? Its importance in the staging and treatment of prostatic carcinoma. Am J Surg Pathol. 1989; 13(1):21-7.
143. Ohori M, Scardino PT, Lapin SL, Seale-Hawkins C, Link J, Wheeler TM. The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. Am J Surg Pathol. 1993; 17(12):1252-61. doi:10.1097/00000478-199312000-00006
144. Trpkov K, Grignon DJ, Bonsib SM, Amin MB, Billis A, Lopez-Beltran A, et al. Handling and staging of renal cell carcinoma: The international society of urological pathology consensus (isup) conference recommendations. Am J Surg Pathol. 2013; 37(10):1505-17. doi:10.1097/PAS.0b013e31829a85d0
145. Lane Z, Epstein JI, Ayub S, Netto GJ. Prostatic adenocarcinoma in colorectal biopsy: Clinical and pathologic features. Hum Pathol. 2008; 39(4):543-9. doi:10.1016/j.humpath.2007.08.011
146. Varma M, Jasani B. Diagnostic utility of immunohistochemistry in morphologically difficult prostate cancer: Review of current literature. Histopathology. 2005; 47(1):1-16. doi:10.1111/j.1365-2559.2005.02188.x

147. Jiang Z, Li C, Fischer A, Dresser K, Woda BA. Using an amacr (p504s)/34betae12/p63 cocktail for the detection of small focal prostate carcinoma in needle biopsy specimens. Am J Clin Pathol. 2005; 123(2):231-6.
148. Kahane H, Sharp JW, Shuman GB, Dasilva G, Epstein JI. Utilization of high molecular weight cytokeratin on prostate needle biopsies in an independent laboratory. Urology. 1995; 45(6):981-6.
149. di Sant'Agnese PA, Cockett AT. Neuroendocrine differentiation in prostatic malignancy. Cancer. 1996; 78(2):357-61. doi:10.1002/(sici)1097-0142(19960715)78:2<357::Aid-cncr27>3.0.Co;2-u
150. Egevad L, Judge M, Delahunt B, Humphrey PA, Kristiansen G, Oxley J, et al. Dataset for the reporting of prostate carcinoma in core needle biopsy and transurethral resection and enucleation specimens: Recommendations from the international collaboration on cancer reporting (iccr). Pathology. 2019; 51(1):11-20. doi:10.1016/j.pathol.2018.10.003
151. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage t1c) prostate cancer. Jama. 1994; 271(5):368-74.
152. Kattan MW, Eastham JA, Wheeler TM, Maru N, Scardino PT, Erbersdobler A, et al. Counseling men with prostate cancer: A nomogram for predicting the presence of small, moderately differentiated, confined tumors. J Urol. 2003; 170(5):1792-7. doi:10.1097/01.ju.0000091806.70171.41
153. Chun FK, Karakiewicz PI, Huland H, Graefen M. Role of nomograms for prostate cancer in 2007. World J Urol. 2007; 25(2):131-42. doi:10.1007/s00345-007-0146-y
154. Brajtbord JS, Leapman MS, Cooperberg MR. The capra score at 10 years: Contemporary perspectives and analysis of supporting studies. Eur Urol. 2017; 71(5):705-9. doi:10.1016/j.eururo.2016.08.065
155. D'Amico AV, Desjardin A, Chen MH, Paik S, Schultz D, Renshaw AA, et al. Analyzing outcome-based staging for clinically localized adenocarcinoma of the prostate. Cancer. 1998; 83(10):2172-80. doi:10.1002/(sici)1097-0142(19981115)83:10<2172::aid-cncr16>3.0.co;2-k
156. D'Amico AV, Desjardin A, Chung A, Chen MH, Schultz D, Whittington R, et al. Assessment of outcome prediction models for patients with localized prostate carcinoma managed with radical prostatectomy or external beam radiation therapy. Cancer. 1998; 82(10):1887-96.
157. Evesham HA. The history and development of nomography.: University of London; 1982.
158. Kleer E, Larson-Keller JJ, Zincke H, Oesterling JE. Ability of preoperative serum prostate-specific antigen value to predict pathologic stage and DNA ploidy. Influence of clinical stage and tumor grade. Urology. 1993; 41(3):207-16. doi:10.1016/0090-4295(93)90558-r
159. Liu H, Zhou H, Yan L, Ye T, Lu H, Sun X, et al. Prognostic significance of six clinicopathological features for biochemical recurrence after radical prostatectomy: A systematic review and meta-analysis. Oncotarget. 2018; 9(63):32238-49. doi:10.18632/oncotarget.22459
160. Zhang LJ, Wu B, Zha ZL, Qu W, Zhao H, Yuan J, et al. Perineural invasion as an independent predictor of biochemical recurrence in prostate cancer following radical prostatectomy or radiotherapy: A systematic review and meta-analysis. BMC Urol. 2018; 18(1):5. doi:10.1186/s12894-018-0319-6
161. Ahmad AS, Parameshwaran V, Beltran L, Fisher G, North BV, Greenberg D, et al. Should reporting of peri-neural invasion and extra prostatic extension be mandatory in prostate cancer biopsies? Correlation with outcome in biopsy cases treated conservatively. Oncotarget. 2018; 9(29):20555-62. doi:10.18632/oncotarget.24994
162. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Can Urol Assoc J. 2013; 7(5-6):E293-8. doi:10.5489/cuaj.11224
163. Berger AP, Gozzi C, Steiner H, Frauscher F, Varkarakis J, Rogatsch H, et al. Complication rate of transrectal ultrasound guided prostate biopsy: A comparison among 3 protocols with 6, 10 and 15 cores. J Urol. 2004; 171(4):1478-80; discussion 80-1. doi:10.1097/01.ju.0000116449.01186.f7
164. Perera M, Lawrentschuk N, Perera N, Bolton D, Clouston D. Incidental prostate cancer in transurethral resection of prostate specimens in men aged up to 65 years. Prostate International. 2016; 4(1):11-4. doi:10.1016/j.prnil.2015.10.016
165. Chun TY. Coincidence of bladder and prostate cancer. J Urol. 1997; 157(1):65-7.

166. Okolo C, M. Akinosun O, B. Shittu O, O. Olapade-Olaopa E, Okeke L, Akang E, et al. Correlation of serum psa and gleason score in nigerian men with prostate cancer2008.
167. Koo KC, Park SU, Kim KH, Rha KH, Hong SJ, Yang SC, et al. Predictors of survival in prostate cancer patients with bone metastasis and extremely high prostate-specific antigen levels. Prostate Int. 2015; 3(1):10-5. doi:10.1016/j.prnil.2015.02.006
168. Khalid KE, Brair AI, Elhaj AM, Ali KE. Prostate-specific antigen level and risk of bone metastasis in sudanese patients with prostate cancer. Saudi J Kidney Dis Transpl. 2011; 22(5):1041-3.
169. Tubiana M. Tumor cell proliferation kinetics and tumor growth rate. Acta Oncol. 1989; 28(1):113-21. doi:10.3109/02841868909111193
170. Frank S, Amsterdam A, Kelly W, Netto G, Liebertz C, Reuter V, et al., editors. Platinum-based chemotherapy for patients with poorly differentiated hormone-refractory prostate cancers (hrpc): Response and pathologic correlations. Proc Am Soc Clin Oncol; 1995.
171. Barry MJ. Screening for prostate cancer among men 75 years of age or older. N Engl J Med. 2008; 359(24):2515-6. doi:10.1056/NEJMp0807209
172. Potter SR, Partin AW. Hereditary and familial prostate cancer: Biologic aggressiveness and recurrence. Reviews in Urology. 2000; 2(1):35-6.
173. Keetch DW, Humphrey PA, Smith DS, Stahl D, Catalona WJ. Clinical and pathological features of hereditary prostate cancer. J Urol. 1996; 155(6):1841-3.
174. Gosselaar C, Roobol MJ, Schroder FH. Prevalence and characteristics of screen-detected prostate carcinomas at low prostate-specific antigen levels: Aggressive or insignificant? BJU Int. 2005; 95(2):231-7. doi:10.1111/j.1464-410X.2005.05324.x
175. Aytac B, Vuruskan H. Clinicopathologic features of incidental prostatic adenocarcinoma in radical cystoprostatectomy specimens. World Journal of Surgical Oncology. 2011; 9:81-. doi:10.1186/1477-7819-9-81
176. Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo clinic validation of the d'amico risk group classification for predicting survival following radical prostatectomy. J Urol. 2008; 179(4):1354-60; discussion 60-1. doi:10.1016/j.juro.2007.11.061
177. Sanyal C, Aprikian AG, Cury FL, Chevalier S, Dragomir A. Management of localized and advanced prostate cancer in canada: A lifetime cost and quality-adjusted life-year analysis. Cancer. 2016; 122(7):1085-96. doi:10.1002/cncr.29892
178. Catalona WJ, Smith DS, Ratliff TL, Basler JW. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. Jama. 1993; 270(8):948-54.
179. SA S. Census 2011. Pretoria: 2012 30 Oct 2012. Report No.
180. Tindall EA, Monare LR, Petersen DC, van Zyl S, Hardie R-A, Segone AM, et al. Clinical presentation of prostate cancer in black south africans. The Prostate. 2014; 74(8):880-91. doi:10.1002/pros.22806

APPENDICES