Exploring racial differences in disease stage and risk profile at presentation, and its influence on outcome in men with prostate cancer in Kwazulu Natal.

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By

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As the candidate's supervisor, I agree/do not agree to the submission of this dissertation.

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To my loving wife, Kerishma, who knowingly married a nerd and has yet to regret that day. Thank you for your support and encouragement.

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List of Abbreviations

AAM	**African American men**
ASTRO	**American Society for Therapeutic Radiology and Oncology**
DRE	**Digital rectal examination**
EAM	**European American men**
ECOG	**European Cooperative Oncology Group**
GNP	**Gross National Product**
KZN	**Kwazulu Natal**
PCa	**Prostate cancer**
PFS	**Progression free survival**
PNI	**Perineural invasion**
PSA	**Prostate specific antigen**
SA	**South Africa**
SEER	**Surveillance, Epidemiology, and End Results**
TTBR	**Time to biochemical response**
TTHRD	**Time to hormone refractory disease**
USA	**United States of America**

Abstract

Introduction

Prostate cancer (PCa) is the most commonly diagnosed male malignancy and the second leading cause of male cancer death in the Western world. In the United States of America (USA), African American men (AAM) have among the highest rates of PCa in the world. They develop the disease 1.5 times more frequently than European American men (EAM) of the same age .The mortality rate is approximately two to three times higher for AAM compared to EAM.

There is a dearth of literature exploring the incidence and treatment outcomes of this disease based on racial profiling in a South African population. This study aims to evaluate racial disparities with a focus on patients with PCa managed in the public health care sector in the province of Kwazulu Natal (KZN).

Patients and methods

The study was a retrospective analysis of patients with PCa treated at Inkosi Albert Luthuli Central Hospital and Addington Hospital, which are both based in the Durban Metropolitan area in the province of KZN. Data extracted from the folders of patients with PCa who presented between March 2003 and December 2007 were collated onto a data capture form and analysed. Patient data were analysed according to the following categories:

- Patient demographics;

- Patient follow-up period;
- Disease risk profile;
- Response to treatment;
- Compliance on treatment.

SPSS version 15.0 was used to analyse the data. Within each disease category, the response variables were analysed by race group using non-parametric Kruskal-Wallis tests. Multiple comparisons were made using pairwise Mann-Whitney tests and Bonferroni adjusted significance levels according to the number of multiple comparisons made. In order to control for other confounding factors such as age, serum PSA levels and compliance, Cox proportional hazards models were used. Hazard ratios and 95% confidence intervals were also reported.

Results

In KZN, the majority of the population is classified as blacks (82.9%). The Indian population group makes up 9.0% of the provincial population while white and coloured people make up 6.1% and 2.0% of the provincial population respectively. In this study population, Blacks made up 57.7% and whites made up 27.5%, followed by 11.4% of Indians and 3.4% of coloureds. The racial frequency distribution of the study population demonstrated that whites had a higher incidence of PCa when analysing their demographic profile in the province. Blacks had the highest median total serum prostate specific antigen (PSA) levels on presentation. When compared to that of the white study population, this was found to be statistically significant ($p < 0.001$). There was a significant association between stage of

disease and race (p = 0.001). In the black group, a greater proportion had metastatic rather than localised or locally advanced disease, and in the white group the converse was seen, whereas in the Indian and coloured groups an almost equal proportion had localised or locally advanced disease versus metastatic disease. A crude analysis of progression free survival (PFS) data in patients with metastatic disease demonstrated that PFS was significantly (p = 0.003) longer for whites compared to blacks. Cox regression analysis did not confirm the influence of race on disease progression but this was confounded by incomplete data.

Discussion

The high incidence of whites in our study population relative to their racial distribution in the province may be explained by better educational and awareness levels of PCa and better access to healthcare facilities in this race group as compared to blacks. The data demonstrating a more advanced stage of disease presentation and higher median PSA levels in the black population may be reflective of an informational void on screening and awareness of PCa and/or a more aggressive disease course in this population group. The hypothesis that the black population may have a more aggressive disease course is given further credence by the crude analysis data suggesting a longer PFS for whites when compared to blacks.

Conclusions

This study invites further exploration of racial trends in PCa incidence, risk profile and outcomes amongst the diverse population groups of SA.

Based on the results of this study, the implementation of targeted study initiatives with end points designed to detect the disease earlier in the black population and begin appropriate management is justified. A commitment to address gross disparities in socio-economic status between the race groups is paramount to eradicate the racial bias that exists in terms of accessibility and affordability to healthcare and PCa screening programs.

Chapter 1: Introduction

PCa is the most commonly diagnosed male malignancy and the second leading cause of male cancer death in the Western world [1].

PCa incidence increased in Western countries during the late 1980s and 1990s largely owing to serum PSA testing [2]. The highest rates of PCa are in Scandinavia, where it is the leading cause of male cancer death. The lowest recorded rates are in Asia. In the United Stated of America (USA), incidence and mortality are higher among AAM. A 30- to 50-fold difference in risk between AAM at the highest end of the spectrum and native Japanese at its lowest end has been reported [1].

Although PCa is a major cause of cancer-related death, mortality rates have increased less than the incidence rates in many countries. Indeed, in the USA, Canada, and several European countries, recent declines in PCa mortality and metastatic disease have been reported. The decline in mortality may be partly due to PSA screening [2].

1.1 Prostate cancer screening initiatives

Screening for PCa is a controversial issue in health care in general and urological practice in particular. The merits of introducing national PCa screening programmes in Europe are currently being debated. At present, the evidence to support the implementation of national PCa screening programmes is inadequate. These programmes have therefore not been introduced in a systematic fashion outside randomised clinical trial settings [2]. Clinical practice patterns as well as proposed guidelines with regard to PSA screening or testing remains controversial and differs among countries.

In the USA, guidelines currently favour the principle of screening for PCa. The American Cancer Society recommends screening for all men aged at least 50 years, although it acknowledges that men should be educated about issues regarding early detection and PCa treatment, thereby aiding full participation in decision making. The American Urological Association recommends that healthy men over the age of 50 should consider PCa screening with a digital rectal examination (DRE) and a PSA test [2].

1.2 Prostate cancer screening in South Africa (SA): The pitfalls of a disjointed healthcare system

In SA, there is no national PCa screening program in existence. PCa screening is poorly co-ordinated and is often based on socio-economic factors, educational levels and health care access.

The healthcare system reflects and represents the broader fragmentation of society within SA. The health system is primarily split on racial grounds: the African population, and to a lesser extent the coloured population, use the public sector and the white population, and to a slightly lesser extent the Indian population, use the private sector. This racial fragmentation is, however, combined both with insurance status and income level (the uninsured poor use the public sector and the insured rich use the private sector), and with geography (the rural population uses the public sector and the (formal) urban population, the private sector) [3].

As a consequence, it is largely the insured rich, urban population groups with access to private healthcare that are better able to utilise PCa screening tools.

In a clinical study assessing the feasibility of detecting early-stage PCa in the primary healthcare setting in SA, it is of some concern that prostate biopsies were only obtained in 19% of black and 47% of coloured men with a serum PSA of > or = 4.0 ng/ml [4]. Further

research is required to ascertain the factors associated with patient reluctance to undergo prostate biopsies.

There is a dearth of literature exploring the incidence and treatment outcomes of this disease based on racial profiling in a South African population. This study was designed to provide some insight into this topic focusing on patients with PCa managed in the public health care sector in the province of KZN.

1.3 Kwazulu Natal: A melting pot of racial and socio-economic diversity

According to the National Census of 2001, KZN is home to about 21.0% of SA's population, making it SA's largest province.

Various absolute and relative poverty lines are used in SA. In recent years, the 40th percentile cut-off point of adult equivalent per capita income has become quite a popular poverty line. This was equal to R 5 057 per annum in 2000. These same national poverty lines are used for the provincial analysis as this allows for comparisons of poverty across provinces [5].

Measured by its total current income, KZN is the third richest province in SA. Although the people of KZN are in a relatively more secure financial standing, the province still experiences high poverty rates, inequalities in the distribution of income between various population subgroups, and unemployment [5].

Poverty rates vary significantly between racial groups. There is virtually no poverty among whites, and only 6.0% of the Asian population is poor. In sharp contrast, the poverty rates for coloured and black people are 17.2% and 64.4% respectively. Poverty is also clearly a rural

phenomenon, with the rural poverty rate estimated at 78.2% compared to 28.9% in urban areas. The poverty rate is also much higher among agricultural households (81.2%) than non-agricultural households (49.5%) [5].

The socio-economic disparities highlighted between the different racial groups should hypothetically impact on incidence and treatment outcomes in patients with PCa. Disadvantaged socio-economic groups are hampered by poor accessibility and affordability of specialised healthcare services.

Public healthcare oncology services are rendered exclusively in the Durban-Pietermaritzburg metropolitan areas. This may possibly impact on stage of disease at clinical presentation and compliance to treatment in patients with PCa that reside in outlying areas.

1.4 . Incidence of prostate cancer in SA

In Africa, the reported incidence of PCa in different countries correlates directly with the per capita gross national product (GNP) i.e. countries with the highest incidence rates have the highest per capita GNP. One explanation may be that the risk of PCa is related to industrialisation, environmental pollution or dietary factors in more affluent populations. However, a more likely explanation is that improved access to medical facilities, with increased diagnosis and reporting of PCa, is responsible for the higher incidence rates in more affluent countries [6].

The South African National Cancer Registry was a pathology-based registry that published its last report of cancer statistics in SA in 2001 [7].

Based on the South African National Cancer Registry figures from 1998 and 1999, PCa was the leading cancer reported in males, comprising 14% and 13% of all cancers reported in males in the respective years. The lifetime risk of developing PCa was 1 in 22 men in 1998 and 1 in 24 in 1999 [7].

Being a pathology-based registry, it has the limitation of possible under-reporting of cases which may confound the true incidence of malignancies in SA. The discontinuation of the National Cancer Registry has also created a void in terms of analysing more recent patterns of incidence of the various malignancies, including PCa.

1.5. Race based disparities in the incidence of prostate cancer in SA

Based on National Cancer Registry data, PCa was the leading cancer in all population groups over the two years, 1998 – 1999 (Table 1). White men comprised more than half of all PCa cases reported during this period and had the highest incidence rate. PCa comprised on average 14% of all cancers reported in white males. The second highest incidence rates were observed in coloured men. These comprised on average 10% of all PCa cases. PCa comprised on average 15% of all coloured male cancers. Black men constituted about one third of all prostate cancers in this period. Asian and black men had the lowest rates, and the risk of developing PCa in these two groups was four times lower than that in white men (Table 1) [7].

Pop / Sex	N(Obs)	N(Adj)	Percent	Crude	ASR	95%LCL	95%UCL	Cumrisk	LR
				Males, 1998					
Asian	61	64	1.54	11.95	20.41	15.41	25.42	2.2	46
Black	1360	1432	34.36	8.72	20.64	19.57	21.71	2.39	42
Coloured	375	396	9.47	21.58	47.14	42.53	51.76	6.17	17
White	2162	2277	54.62	92.31	78.51	75.28	81.73	10.35	10
Total	**3958**	**4169**	**100.00**	**19.61**	**37.59**	**36.45**	**38.73**	**4.59**	**22**
				Males, 1999					
Asian	55	59	1.52	10.89	18.34	13.65	23.03	2.6	39
Black	1143	1220	31.59	7.26	17.17	16.21	18.13	2.01	50
Coloured	386	410	10.67	22.04	47.98	43.33	52.62	5.43	19
White	2034	2169	56.22	87.86	74.38	71.25	77.52	10.05	10
Total	**3618**	**3858**	**100.00**	**17.81**	**34.12**	**33.05**	**35.20**	**4.18**	**24**

N (Obs)	Number of cases observed
N (Adj)	Observed cases adjusted for unknown population group
Percent	Percentage of all site cancers
Crude	Number of cases per 100 000 of population
ASR	Age standardised incidence rate per 100 000 (World standard population)
95% LCL	95% Lower confidence limit for ASR
95% UCL	95% Upper confidence limit for ASR
Cumrisk	Cumulative lifetime incidence risk (0-74 years)
LR	Lifetime risk (0-74 years) of developing a cancer expressed as 1 in X number of people

Table 1: Summary statistics for prostate cancer in SA, 1998-1999 [7]

The lifetime risk of PCa amongst the different race groups based on the South African National Cancer Registry data from 1999 is as follows: Asian 1:39, Black 1:50, Coloured 1:19, White 1: 10, with a combined risk of 1:24 amongst all race groups [7].

The apparent lower incidence among black men in SA is most probably due to lower rates of diagnosis or reporting due to socio-economic reasons [6].

1.6. International race based comparisons of incidence

PCa rates for white South African men rank among the highest rates in the world (Table 2). South African incidence rates for PCa are higher than rates reported in many developing countries, particularly those in sub-Saharan Africa [7].

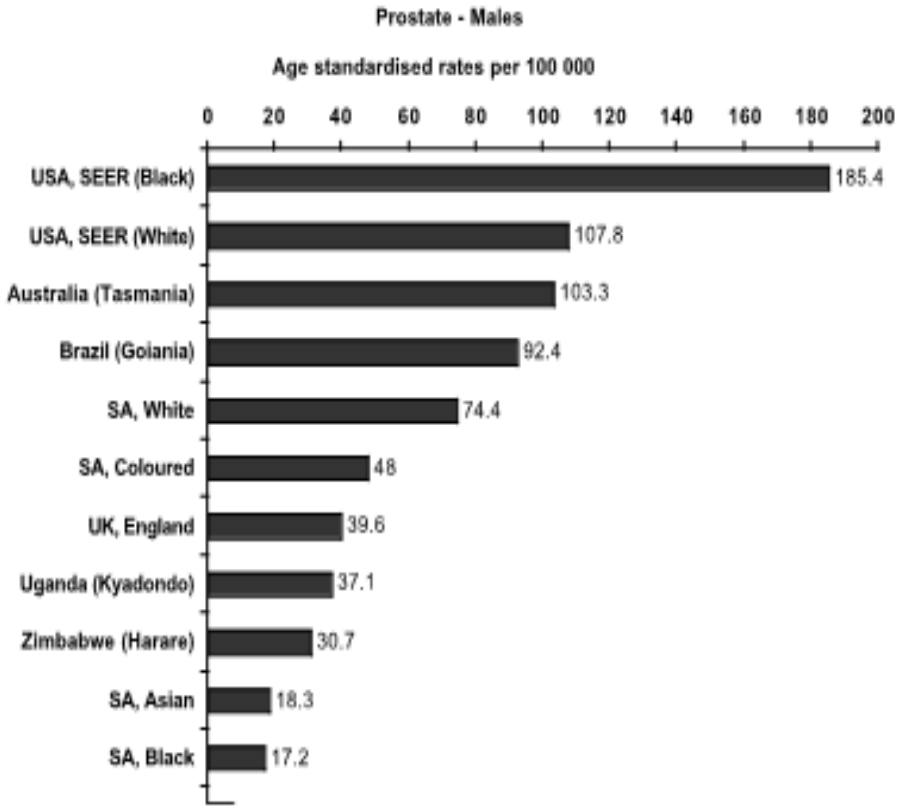

Table 2: Prostate cancer age standardised rates (ASR) per 100 000 for selected populations [7]

In the USA, the converse holds true, with AAM having the highest rates of PCa in the world. They develop the disease 1.5 times more frequently than EAM of the same age. The reasons for the higher incidence rates in AAM remain unclear but are likely multifactorial, combining environmental and genetic factors [8].

Several studies have shown a higher average or mean total PSA and PSA density in AAM compared with EAM, even after controlling for tumour stage [6].

The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program currently collects and publishes cancer incidence and survival data from population-based cancer registries, covering approximately 26 percent of the USA population. Table 3 illustrates high incidence rates of PCa in blacks when compared to other race groups diagnosed in **2000-2004** in 17 SEER geographic areas [9].

Incidence Rates by Race	
Race/Ethnicity	**Male**
All Races	168.0 per 100,000 men
White	161.4 per 100,000 men
Black	255.5 per 100,000 men
Asian/Pacific Islander	96.5 per 100,000 men
American Indian/Alaska Native	68.2 per 100,000 men
Hispanic	140.8 per 100,000 men

Table 3: Incidence rates by race, SEER Cancer Statistics Review, 2000-2004 [9]

1.7. Race-based mortality rates

The mortality rate is approximately two to three times higher for AAM compared to EAM, indicating that PCa is a major public health problem in this population [6].

There are no reliable age-adjusted PCa mortality rates available for African countries [6] and this poses a challenge in our understanding of the clinical course of this disease in the African population.

Table 4 illustrates mortality rates for men with PCa during the period 2000-2004 in the USA.

Death Rates by Race	
Race/Ethnicity	**Male**
All Races	27.9 per 100,000 men
White	25.6 per 100,000 men
Black	62.3 per 100,000 men
Asian/Pacific Islander	11.3 per 100,000 men
American Indian/Alaska Native	21.5 per 100,000 men
Hispanic	21.2 per 100,000 men

Table 4: Death rates by race, SEER Cancer Statistics Review, 2000-2004 [9]

1.8. Exploring possible aetiological factors to account for racial differences in incidence and mortality

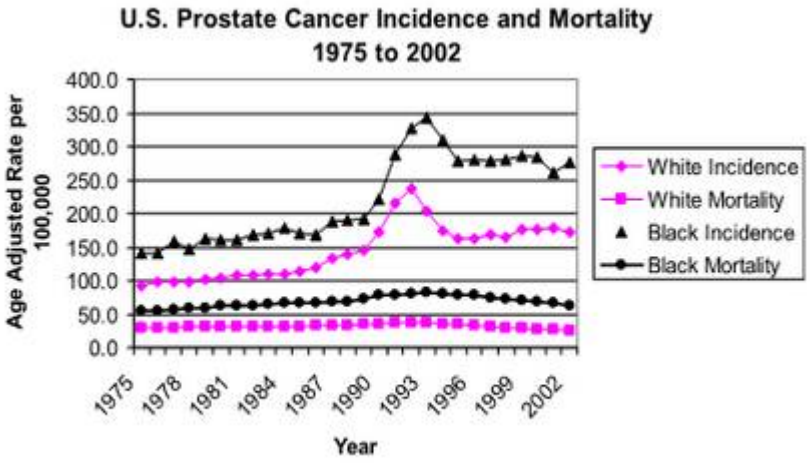

Table 5: USA Prostate cancer incidence and mortality, SEER Cancer Statistics Review, 1975 to 2002 [9]

There are many postulated factors to account for the racial differences in the clinical profile of patients with PCa. Some of the implicated factors include hormonal, nutritional, genetic, behavioural, and environmental influences [6].

1.8.1 Possible factors accounting for racial differences in prostate cancer incidence

Genetic factors

The higher incidence of PCa among AAM may be explained by alterations in genes that control the androgen receptor, the 5-alphareductase (SRD5A2) or poly ADP-ribose polymerase (PADPRP) enzymes [6].

Dietary factors may also account for the higher PCa incidence in AAM. Diets containing a high fat content and large consumption of red meat may increase the risk, while a high intake of dietary phyto-oestrogens, tomato based products containing lycopene, selenium, vitamins E and D are thought to decrease the risk of developing PCa [6].

Raised serum testosterone and dihydrotestosterone levels have not been convincingly associated with an increased risk of PCa. While some groups have reported that serum levels of these androgens are higher in patients with PCa than in age matched controls, others were not able to detect any differences. There are, however, reports documenting that mean serum testosterone levels are about 15% higher in young AAM compared with EAM, a difference that may be relevant to the increased PCa risk in AAM in later years [10].

1.8.2 Possible factors accounting for racial differences in prostate cancer mortality

The greater PCa mortality in AAM may be attributable to the higher incidence, as well as higher tumour stage and grade at presentation in this demographic group [6].

Differences in treatment may also account for the disparity in mortality rates between the racial groups. Several studies show that AAM tend to receive aggressive therapy more infrequently than EAM or they go untreated more often [10].

There have been reports that the tumour stage at diagnosis was inversely correlated with health insurance, income status, PCa awareness and previous participation in PSA screening among AAM but not EAM. Studies have also demonstrated that socio-economic factors and limited access to healthcare contribute to the poorer outcomes in AAM even after adjusting for differences in pre-treatment disease characteristics [6].

The role of socio-economic factors was evaluated in a retrospective cohort study which compared the survival rates of black and white American men with PCa using a multivariate model including socio-economic status and treatment method. This study reported that

household income explained half of the difference in survival rates between the two groups, while lower surgical treatment rate in AAM accounted for 34% of the difference in survival [11].

Delayed diagnosis resulting from cultural differences, such as the fear of PCa diagnosis and rectal examination has also been hypothesised as a factor accounting for racial disparities in mortality rates [8].

However, the question of biologic differences remains, as stratification for socio-economic and educational level does not negate disparities in incidence and mortality. There is a suggestion that PCa among AAM is biologically more aggressive than among EAM based on data showing a younger age at presentation and greater risk of mortality in the former group. However, the majority of reports indicate that, when controlled for major prognostic factors, the outcome for clinically localised as well as advanced PCa is independent of race [6].

One of the few studies that explored the disease from a South African context analysed the incidence and stage at presentation of PCa in black patients from Soweto, Johannesburg, and compared mortality to that of white patients [12]. Of the 101 black men recruited between1982-1984, 90 patients had stage D (metastatic) disease. An indirect analysis of mortality rates in comparison with studies done on white patients was inconclusive.

Chapter 2: Patients and methods

2.1 Aim

The aim of this study was to examine racial differences in disease stage and risk profile at presentation in patients with PCa and to correlate this with treatment outcome.

Compliance was also assessed as a secondary endpoint to ascertain whether this may also contribute to outcome in different race groups.

2.2 Specific objectives

This study was designed to analyse whether patients with PCa in KZN, SA would demonstrate racial differences in incidence and mortality similar to that demonstrated between AAM and EAM with PCa in the USA. This would enable to us implement greater awareness campaigns and screening programmes in racial groups demonstrating higher incidence, more aggressive risk profile, higher disease stage at presentation and poorer treatment outcomes.

2.3 Method

The study design was in the form of a retrospective analysis of patients with PCa treated at Inkosi Albert Luthuli Central Hospital and Addington Hospital which are both based in the Durban Metropolitan area in the province of KZN. Data extracted from the folders of patients with PCa who presented between March 2003 and December 2007 were collated onto a data capture form (Appendix) and analysed.

This study was granted approval by the Faculty of Medical Ethics Committee and the postgraduate education committee of the University of KwaZulu-Natal.

Patient data were analysed in the following categories:

- Patient demographics;
- Patient follow-up period;
- Disease risk profile;
- Response to treatment;
- Compliance on treatment.

2.4 Analysis of patient demography

Patient demography was analysed in terms of**:**

- Age and
- Race (race was assigned based on documentation from administrative staff).

2.5 Analysis of follow-up period

The follow-up period in the different racial groups was defined as the time from first consultation to the date of data analysis. Follow-up period is highly skewed, with the median therefore representing the most appropriate measure of central tendency.

2.6 Analysis of disease risk profile

Disease profile was based on the following parameters:

- Total Serum Prostatic Specific Antigen (PSA)
- Bone scan
- Pathological findings (Gleason score, Perineural invasion, High-grade prostatic intraepithelial neoplasia)
- Clinical stage/Pathological stage

2.7 Analysis of treatment response

The assessment of treatment response was first based on establishing defined disease categories and then using the varying study endpoints within each disease category to assess treatment response in the different race groups.

Definition of disease categories

Disease Categories were defined as follows:

- **Localised Disease**
  - Clinical Stage T1/T2
- **Locally Advanced Disease**
  - Clinical Stage T3/T4
- **Biochemical Failure**
  - Based on the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of 3 consecutive rises in serum PSA levels
- **Metastatic Disease**
  - Presence of bone metastases as confirmed on radiographic evaluation
- **Hormone Refractory Disease**
  - Progression of metastatic disease based on radiographic, clinical and/or biochemical parameters along with a serum testosterone < 50ng/ml

Response to treatment was analysed using the following endpoints in the respective disease categories:

- **Localised Disease – Clinical Stage T1/T2**
    i. Progression Free Survival (PFS)

- **Locally Advanced Disease – Clinical Stage T3/T4**
    i. Progression Free Survival (PFS)

- **Biochemical Failure**
    i. Progression Free Survival (PFS)

- **Metastatic Disease – M1**
    i. Progression Free Survival (PFS)

- **Hormone Refractory Disease**
    i. Time to Hormone Refractory disease (TTHRD)
    ii. Progression Free Survival (PFS)
    iii. Time to Biochemical Response on chemotherapy (TTBR)

Definitions of endpoints used:

The above-mentioned endpoints used for the disease categories to evaluate treatment response were defined as follows:

Progression free survival (PFS) in months

Progression is defined in terms of biochemical and/or radiographic and/or clinical parameters:

1. **Biochemical:**

   Biochemical progression differs for different disease categories:

   - **Localised/Locally Advanced Disease :**

     Any rise in PSA after achieving PSA values <0.1 ng/ml post curative surgery or PSA <0.1 ng/ml post radical radiotherapy

   - **Biochemical Failure :**

     Any subsequent rise in PSA after diagnosis of biochemical failure

   - **Metastatic Disease :**

     Any further rise in PSA after diagnosis of metastatic disease

   - **Hormone Refractory Disease :**

     Any further rise in PSA after diagnosis of hormone refractory disease

2. **Radiographic:**

   Defined as:

   - Any new focus of skeletal or other metastases or
   - Progression of previously documented metastases based on RECIST Criteria: **PD (progressive disease)** = 20% increase in the sum of the longest diameter of target lesions.

3. **Clinical:**

   Defined as*:*

   - Progression of clinical stage noted on digital rectal examination (DRE) or
   - Worsening of European Cooperative Oncology Group (ECOG) performance status or
   - Progression of pain.

Time to hormone refractory disease (TTHRD)

Defined as the time from diagnosis of PCa to the development of hormone refractory disease.

Time to biochemical response on chemotherapy (TTBR)

Defined as time from initiation of chemotherapy to any subsequent decrease in PSA levels.

2.8 Analysis of compliance to treatment and follow-up

Assessment of compliance was based on the following factors:

- History of missed appointments and
- Documented non-compliance on treatment.

Each of the above factors scored a solitary point for a tally of 2. Scores were tabulated and assessed to derive a scoring system reflecting patient compliance.

Score	Compliance
0	Good
1	Average
2	Poor

Table 6: Compliance index

Statistical Analysis

SPSS version 15.0 was used to analyse the data. Within each disease category, the response variables defined previously were analysed by race group using non-parametric Kruskal-Wallis tests. Multiple comparisons were made using pairwise Mann-Whitney tests and Bonferroni adjusted significance levels according to the number of multiple comparisons made. In order to control for other confounding factors such as age, serum PSA levels and compliance, Cox proportional hazards models were used. Hazard ratios and 95% confidence intervals were also reported.

Chapter 3: Results

3.1 Demographic profile of target population

Demographic Profile of Target Population	Blacks	Whites	Indians	Coloureds	Total
No.(%) of patients per demographic group	86 (57.7%)	41 (27.5%)	17 (11.4%)	5 (3.4%)	149
Mean age (SD)	70.0 (8.4)	69.1 (7.4)	71.0 (9.2)	69.0 (7.4)	p value = 0.856
Age range	51-88	53-79	51-86	57-76	

Table 7: Age and racial composition of study population

3.1.1 Racial composition

The mean age, age range and racial composition of the study groups are shown in Table 7.

3.1.2 Age at presentation in the different racial groups

The mean age at presentation was not significantly different among the different race groups (Table 7).

3.2 Analysis of follow-up period in the different racial groups

	Race			Statistic	Std. Error
Follow-up (months)	**Black**	Mean		20.02	2.067
		95% Confidence Interval for Mean	Lower Bound	15.91	
			Upper Bound	24.13	
		Median		20.00	
		Variance		367.388	
		Std. Deviation		19.167	
		Minimum		0	
		Maximum		58	
		Range		58	
		Interquartile Range		36	
	White	Mean		27.15	2.716
		95% Confidence Interval for Mean	Lower Bound	21.66	
			Upper Bound	32.64	
		Median		29.00	
		Variance		302.528	
		Std. Deviation		17.393	
		Minimum		0	
		Maximum		58	
		Range		58	
		Interquartile Range		28	
	Indian	Mean		34.06	4.693
		95% Confidence Interval for Mean	Lower Bound	24.11	
			Upper Bound	44.01	
		Median		36.00	
		Variance		374.434	
		Std. Deviation		19.350	
		Minimum		0	
		Maximum		58	
		Range		58	
		Interquartile Range		30	

	Race			Statistic	Std. Error
Follow-up (months)	**Coloured**	Mean		21.20	9.494
		95% Confidence Interval for Mean	Lower Bound	-5.16	
			Upper Bound	47.56	
		Median		20.00	
		Variance		450.700	
		Std. Deviation		21.230	
		Minimum		0	
		Maximum		55	
		Range		55	
		Interquartile Range		36	

Table 8: Descriptives of mean, median, interquartile range and range for each race group

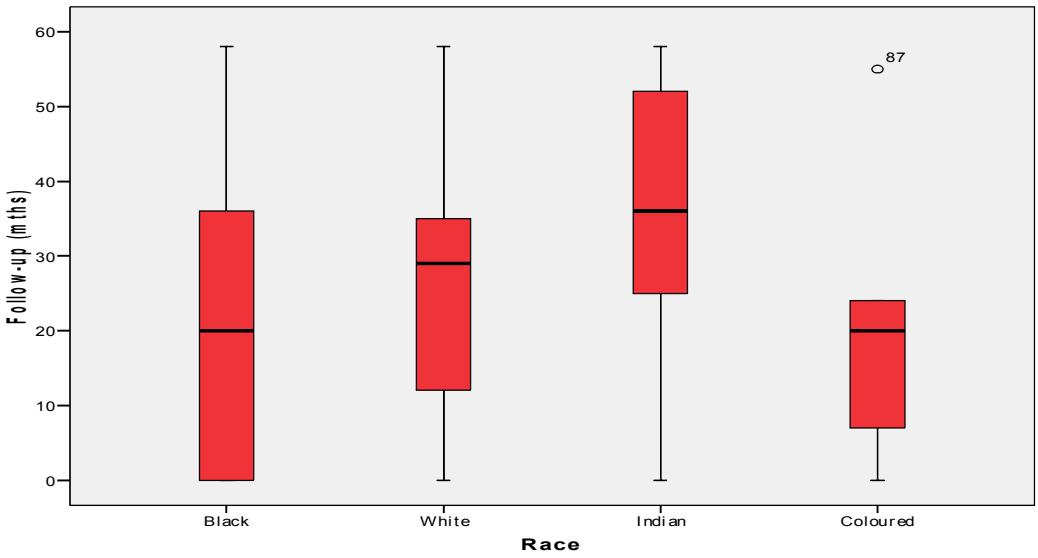

Table 9: Median follow-up duration in the racial groups

There was a statistically significant difference in median follow-up in the various racial groups (p=0.023). Mann-Whitney tests were performed to analyse if the difference noted among all race groups translated into differences between individual race groups. This did not reveal any statistically significant findings.

3.3 Evaluation of race and disease risk profile (Gleason score, PNI, PSA)

Evaluation of race and disease risk profile	Blacks	Whites	Indians	Coloureds	p value
Median (inter-quartile range) total PSA (ng/ml) in all evaluable patients	197 (50-651) n=86	20 (10-143) n= 41	73 (19-169) n= 17	106 (34-2947) n=5	<0.001
Median (IQR) total PSA (ng/ml) level for patients with localised and locally advanced disease	33 (18-123) n=24	16 (8-22) n=27	31 (19-130) n=9	106 (66-147) n=2	0.008
Median (IQR) total PSA (ng/ml) for patients with metastatic disease	417 (130-1264) n=62	259 (107-790) n=14	161 (73-720) n=8	2875 (3-5747) n=3	0.645
Incidence of perineural invasion (%)	16.3	14.6	17.6	0	0.791
Mean (SD) Gleason score in evaluable patients	7.0 (1.2) n=63	6.9 (1.2) n=29	7.0 (1.3) n=15	7.7 (1.2) n=3	0.775
Incidence of evaluable GS score readings in each racial group (%)	73.3	70.7	88.2	60	0.468

Table 10: Evaluation of race and risk profile (PSA, Gleason score, PNI)

3.3.1 Race and total serum PSA level on presentation

Median total serum PSA at presentation in the whole study cohort ($p<0.001$) and in the group with localised or locally advanced PCa ($p=0.008$) displayed significant differences among the four race groups (Table 10). Bonferroni adjusted multiple comparison tests showed that there were only significant differences in the serum PSA levels when comparing the black and white groups in the overall population ($p<0.001$) and in the non-metastatic disease group ($p=0.003$). No statistically significant disparities were noted in the group of men with metastatic disease (Table 10).

3.3.2 Race and incidence of perineural invasion

The incidence of perineural invasion was not found to be statistically significant between the different racial groups.

3.3.3 Race and Gleason score

As demonstrated in Table 10, the mean Gleason score did not differ significantly among the race groups ($p=0.775$), and there were also no significant differences noted in the incidence of evaluable GS readings in each racial group ($p=0.468$).

3.4 Evaluation of race and clinical stage of disease

Evaluation of race and stage of disease	Blacks	Whites	Indians	Coloureds	p value
No (%). of patients with localised and locally advanced disease	24 (27.9%)	27 (65.8%)	9 (52.9%)	2 (40%)	0.001
No (%). of patients with metastatic Disease	62 (72.1%)	14 (34.2%)	8 (47.1%)	3 (60%)	
No. of patients with biochemical failure	5	4	2	0	
No. of patients with hormone refractory disease	13	4	1	1	

Table 11: Evaluation of race and clinical stage of disease

Looking specifically at comparisons between the black and white populations of patients, it is demonstrated that in the black group, 27.9% had localised or locally advanced disease and 72.1% had metastatic disease, whereas in the white group 65.8% had localised or locally advanced disease and 34.2% had metastatic disease.

There was a significant association between stage of disease and race (Pearson's chi-square test = 17.47, p = 0.001). In the black group, a greater proportion had metastatic rather than

localised or locally advanced disease, and in the white group the converse was seen, whereas in the Indian and coloured groups an almost equal proportion had localised or locally advanced disease versus metastatic disease.

3.5. Comparison of race and treatment outcomes

3.5.1. Crude analysis of the impact of race on treatment outcomes

Crude analysis entailed non-parametric Kruskal-Wallis tests to compare study endpoints for treatment outcomes (PFS) between the races in different groups of cases.

Comparison of race and treatment outcomes	**Blacks (months)**	**Whites (months)**	**Indians (months)**	**Coloureds (months)**	**Kruskal Wallis p value**
PFS for localised and locally advanced disease in evaluable patients (median, IQR)	31 (17.5-54.5)	27 (9-46)	30 (25-52.0)	10 (0-20)	0.146
PFS for biochemical failure in evaluable patients (median, IQR)	28 (23-34)	30 (15-49)	2 (1-3)	NE	0.097

Comparison of race and treatment outcomes	Blacks (months)	Whites (months)	Indians (months)	Coloureds (months)	Kruskal Wallis p value
PFS for metastatic disease in evaluable patients (median, IQR)	8 (0-24)	27 (17-33)	39 (9-50.5)	24 (7-55)	0.003
Time to hormone refractory disease in evaluable patients (median, IQR)	22 (21-27)	33 (32-40)	7 (7-7)	7 (7-7)	0.025
Time to biochemical response in evaluable patients (median, IQR)	4 (2-5)	NE	2 (2-2)	NE	0.445
PFS for hormone refractory disease	NE	NE	NE	NE	

NE: Not evaluable

Table 12: Crude analysis of race and treatment outcome endpoints

Localised and locally advanced disease:

The lack of statistically significant data when comparing PFS across racial groups is probably due to low patient numbers and large variation (Table 12).

Metastatic disease:

When evaluating PFS data in patients with metastatic disease, an important distinction was that PFS was significantly (p = 0.003) longer for whites when compared to blacks (Table 12).

Hormone refractory disease:

Whites demonstrated the longest time to development of hormone refractory disease (TTHRD) when compared to the other race groups (p= 0.025). Due to the small number of patients (n=19) with hormone refractory disease, these results must be treated with reserve. The small number of patients in this disease category also negatively impacted on analysis of PFS and TTBR. Longer follow-up is necessary to better evaluate treatment outcomes in patients with hormone refractory disease.

3.5.2 Cox regression analysis of the impact of race on PFS

Adjusted analysis involved Cox regression analysis to evaluate the role of race while adjusting for confounders such as age, PSA and PNI. Gleason score could not be added to the models as there were too many missing values.

3.5.2.1 Race as a risk factor for disease progression in patients with localised and locally advanced disease:

		N	Percent
Cases available in analysis	**Event(a)**	10	16.1%
	Censored	41	66.1%
	Total	51	82.3%

		N	Percent
Cases dropped	**Cases with missing values**	3	4.8%
	Cases with negative time	0	.0%
	Censored cases before the earliest event in a stratum	8	12.9%
	Total	11	17.7%
Total		62	100.0%

a Dependent variable: Total PFS

Table 13: Case processing summary for Cox regression in localised and locally advanced disease

The number of cases evaluated using Cox regression statistical tests was 45 of the total presenting number of 62 patients with localised and locally advanced disease. 27.4% of patients presenting in these stage groupings were excluded for reasons including missing values and censored cases.

Variables in the equation

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
Race			.351	3	.950			
Black vs. White	.236	.828	.081	1	.776	1.266	.250	6.417

Coloured vs. White	-11.365	1087.367	.000	1	.992	.000	.000	.
Indian vs. White	-.366	.983	.138	1	.710	.694	.101	4.767
PSA	.003	.002	2.769	1	.096	1.003	.999	1.007
Age	-.063	.048	1.747	1	.186	.939	.854	1.031
PNI (yes vs. no)	.273	.819	.111	1	.739	1.314	.264	6.540

B: Beta (coefficient)
SE: standard error
Wald: Wald's test statistic
df: degrees of freedom
Sig: p value
HR: Hazard ratio
95% CI for HR: 95% confidence intervals for the hazard ratio

Table 14: Cox regression with all covariates in the model for disease progression in localised and locally advanced disease

Overall, race was not a significant predictor of PFS in those with localised or locally advanced disease (p = 0.950). Blacks were slightly more at risk than whites (HR = 1.266) but this was not statistically significant, and Indians were slightly less at risk than whites (HR = 0.694, p = 0.710). PSA and the presence of PNI were not significant risk factors with p-values of 0.096 and 0.739 respectively. An increase in age did not confer a significant protective effect (p = 0.186).

Therefore none of the co-variates explored to ascertain their impact on the risk of progression in non-metastatic prostate cancer, including race, demonstrated any statistically significant difference.

3.5.2.2 Race as a risk factor for disease progression in patients with metastatic disease

		N	Percent
Cases available in analysis	**Event (a)**	20	23.0%
	Censored	28	32.2%
	Total	48	55.2%
Cases dropped	**Cases with missing values**	11	12.6%
	Cases with negative time	0	.0%
	Censored cases before the earliest event in a stratum	28	32.2%
	Total	39	44.8%
Total		87	100.0%

a Dependent variable: Total PFS

Table 15: Case processing summary for Cox regression in metastatic disease

Only 48 of 87 patients presenting with metastatic disease were evaluated. 44.8% of cases were dropped with the predominant reason being censored data or missing data values.

Variables in the equation

	B	SE	Wald	df	Sig.	HR	95.0% CI for HR	
							Lower	Upper
Race			.279	3	.964			
Black vs. White	.277	.697	.158	1	.691	1.319	.337	5.169
Coloured vs. White	.650	1.368	.226	1	.635	1.916	.131	27.977
Indian vs. White	.042	.966	.002	1	.965	1.043	.157	6.925
PSA	.000	.000	7.133	1	.008	1.000	1.000	1.001
Age	-.041	.030	1.935	1	.164	.959	.905	1.017
PNI	-1.138	1.036	1.206	1	.272	.320	.042	2.444

B: Beta (coefficient)
SE: standard error
Wald: Wald's test statistic
df: degrees of freedom
Sig: p value
HR: Hazard ratio
95% CI for HR: 95% confidence intervals for the hazard ratio

Table 16: Cox regression with all covariates in the model for disease progression in metastatic disease

As seen in Table 16, race was not a significant predictor of disease progression in patients with metastatic disease (p = 0.964). The above data suggest that blacks and coloureds have a higher predisposition towards progression in metastatic disease than whites; however, these data must be treated with reserve due to large number of excluded cases and the non-significant p values. A one year increase in age was non-significantly protective for progression (4.1% protective, p = 0.164). An increase in PSA significantly increased the risk

of progression (p = 0.008). A 10 ng/ml increase in PSA equated to a HR of 1.005 (95% CI 1.001 – 1.008) while a 20 ng/ml increase in PSA increased the risk by 1.009 times (95 % CI 1.002 -1.016). Presence of PNI was not significantly related to time to progression (p = 0.272).

There were discordant racial differences in treatment outcomes noted when using crude analytic techniques and Cox regression techniques. While the crude analytic techniques reflected that PFS data for patients with metastatic disease were significantly superior for whites compared to blacks, this was not borne out with Cox regression techniques. This may be explained by the high proportion of cases dropped (44.8%) when using Cox regression and by the influence of confounding factors which were adjusted for in the Cox regression analysis.

3.5.2.3 Race as a risk factor for disease progression in all stages (non-metastatic and metastatic) of prostate cancer

		N	Percent
Cases available in analysis	**Event(a)**	30	20.1%
	Censored	69	46.3%
	Total	99	66.4%

		N	Percent
Cases dropped	**Cases with missing values**	14	9.4%
	Cases with negative time	0	.0%
	Censored cases before the earliest event in a stratum	36	24.2%
	Total	50	33.6%
Total		149	100.0%

a Dependent variable: Total PFS

Table 17: Case processing summary for Cox regression in all disease stages

The limitations posed by missing data are again in evidence with only 66.4% of the study population being evaluated.

Variables in the equation

	B	SE	Wald	df	Sig.	HR	95.0% CI for Exp(B)	
							Lower	Upper
Race			.430	3	.934			
Black vs. White	.290	.493	.347	1	.556	1.337	.509	3.511
Coloured vs. White	.495	1.212	.167	1	.683	1.641	.153	17.650
Indian vs. White	.084	.663	.016	1	.899	1.088	.297	3.988
PNI	-.487	.619	.619	1	.431	.615	.183	2.066

Age	-.046	.022	4.516	1	.034	.955	.915	.996
PSA	.000	.000	6.144	1	.013	1.000	1.000	1.001

B: Beta (coefficient)
SE: standard error
Wald: Wald's test statistic
df: degrees of freedom
Sig: p value
HR: Hazard ratio
95% CI for HR: 95% confidence intervals for the hazard ratio

Table 18: Cox regression with all co-variates in the model for disease progression in all disease stages

Overall, race was not a significant risk factor for disease progression (p = 0.934). Blacks and coloureds showed a trend towards an increased risk for disease progression when compared to whites but this was not found to be statistically significant. Age was significantly protective (p = 0.034) by 4.5% with every one year increase in age. As PSA increased, so did the risk of disease progression (p = 0.013). A 10 ng/ml increase in PSA increased the risk by 1.005 times (95% CI 1.002 – 1.008) and a 20 ng/ml increase in PSA increased the risk by 1.010 times (95% CI 1.004 – 1.016).

3.6 Exploring racial differences in compliance to follow-up and treatment

Compliance score by race is shown in Table 19. Compliance was used as an ordinal score ranging from 0 (good compliance) to 2 (poor compliance). The median score was compared between the race groups using the Kruskal-Wallis test.

			Compliance score			Total
			Good	Average	Poor	
Race	Black	Count	30	52	4	86
		% within Race	34.9%	60.5%	4.7%	100.0%
	Coloured	Count	1	4	0	5
		% within Race	20.0%	80.0%	.0%	100.0%
	Indian	Count	13	3	1	17
		% within Race	76.5%	17.6%	5.9%	100.0%
	White	Count	17	23	1	41
		% within Race	41.5%	56.1%	2.4%	100.0%
Total		Count	61	82	6	149
		% within Race	40.9%	55.0%	4.0%	100.0%

Kruskal-Wallis p = 0.027

Table 19: Evaluating race and compliance to treatment and follow-up

There was a significant association between race and compliance score (p = 0.027). The table shows that Indians were more inclined to have good compliance than the other race groups. The other race groups tended to have average compliance. On account of the limited number of Indians included in the total study population, it is difficult to establish any definitive conclusions from the evaluation of compliance scores.

These results do, however, underline the fact that despite the high poverty rates in black Africans (64.4%) compared to almost negligible poverty rates in whites [5], this did not translate into significant differences in compliance between these racial groups.

Chapter 4: Discussion

The concepts of incidence and prevalence offer different information. Incidence shows the number of new cases diagnosed in a population during a specific period, while the study of prevalence will yield information about the number or proportion of people who have that disease in a specified period [8].

Unfortunately, the major differences in screening policies and health care systems between African countries, Europe, and the United States make the comparison in terms of PCa incidence unreliable. Furthermore, the calculated incidence of diagnosed PCa cases does not reflect accurately the disease's true prevalence. Denominators, which include population counts, are confounded by census difficulties in many African countries. PCa-specific mortality rates would probably lead to a better understanding of the natural history of the disease as it is less sensitive to screening practices. Unfortunately, these data are difficult to obtain [8].

AAM have been shown to have a higher susceptibility to the disease. While several factors have been hypothesised to account for this susceptibility, the reasons remain largely unknown. As compared with African Americans, sub-Saharan populations previously showed very low PCa rates, suggesting more the importance of environmental over genetic factors. However, PCa incidence trend in sub-Saharan African countries is now showing a marked increase, suggesting a changing disease pattern in PCa among these populations [8]. There still remains a dearth of literature exploring the racial trend of PCa incidence and prognosis in SA.

Chapter 4: Discussion

This study, despite a relatively small study population and an evaluation of patients treated in the public health sector alone, does offer some insight into the incidence and course of PCa in the diverse population groups of KZN.

4.1 Evaluation of racial incidence of prostate cancer in study population

AAM have some of the highest incidence and mortality rates of PCa in the world. Only multiple myeloma has greater black–white disparity than PCa [13].

In KZN, the majority of the population is classified as blacks (82.9%). The Indian population group makes up 9.0% of the provincial population, white and coloured people make up 6.1% and 2.0% of the provincial population, respectively [5].

In our study population, blacks formed the predominant race group in the study population, making up 57.7% of the total number of patients. Whites made up 27.5% of the study population, followed by 11.4% Indians and 3.4% coloureds. Based on these figures, there is a suggestion that whites have a relatively higher incidence of PCa when analysing their demographic profile in the province.

This may reflect socio-economic disparities between whites and blacks with the former having improved educational levels and better access to medical facilities, and consequently increased diagnosis of PCa. Black men are usually diagnosed because of long-standing symptoms or complications due to advanced disease e.g. paraparesis or paraplegia [6].

4.2 Evaluation of age at presentation

Epidemiological data from the USA indicate that AAM present with PCa at a younger age than EAM (difference of about 3 years).

The peak age for the occurrence of PCa is about a decade earlier in African countries than that reported in most developed countries. However, because the incidence of PCa increases with age, the peak age at presentation depends on the life expectancy of the population, which is substantially lower in African countries as compared to developed nations. [6]

The mean age in the different race groups in our study population ranged from 69.0 – 70.0 with no statistically significant differences noted.

4.3 Evaluation of race and risk profile

The most pertinent observation when exploring factors conferring a higher risk was the significantly higher median total PSA levels in blacks on presentation when compared to the other race groups, which is consistent with findings observed in AAM.

4.4 Evaluation of race and clinical stage at presentation

An interesting observation was that white males tended to present more commonly with localised or locally advanced (non-metastatic) PCa in this study population, while blacks tended to present more often with advanced disease.

Extrapolating from studies performed in AAM, we may speculate whether this is a biological phenomenon reflecting a more aggressive disease course or whether it reflects differences in socioeconomic factors, health seeking behaviour, literacy, cultural beliefs or

environmental/life-style factors. A body of evidence also indicates that PCa has a genetic basis [10].

Evidence of an influence of socioeconomic status on stage at diagnosis and survival demonstrates that the cohort with advanced disease at initial diagnosis tends to be disproportionately poorer and less educated. The reasons why the poor present with more advanced stages are unclear. They may relate to diet and other environmental influences, or it may relate to less attention to health on the part of the poor. Lack of health insurance, a more specific factor than low socio-economic status, has been associated with an increased risk of a diagnosis of metastatic PCa [13].

These trends noted in the influence of socio-economic status on stage at diagnosis and survival may assume greater importance in SA on account of the significant racial disparities in socio-economic status. The average household incomes of white, and to lesser extent Asian households, are much higher than those of black and coloured households [5] and this may impact on the greater predisposition of blacks presenting with a more advanced disease stage as demonstrated in this study population.

4.5 Evaluation of race and treatment outcomes

Crude analysis using non-parametric Kruskal-Wallis tests to analyse treatment outcomes for blacks using the endpoint of PFS demonstrated that blacks with metastatic disease had a significantly shorter PFS ($p = 0.003$) than whites with equivalent disease stage.

Cox regression analysis to assess the impact of race on PFS in the different stages of disease did not demonstrate any significant predictive value of race on PFS. This was confounded by only 55.2% of patients with metastatic disease and 66.4% of patients with all stages of disease (metastatic and non-metastatic) being evaluated due to missing values and censored

cases. Greater diligence in record-keeping to allow for a more comprehensive analysis of data is necessary to address the predictive value of race on treatment outcome in sub-Saharan Africa.

Nonetheless, these findings are consistent with the predominance of clinical evidence which suggests that equal treatment yields equal outcome and race need not have an impact on patient survival. Most clinical studies conclude that race is not an independent predictor of treatment failure. Specifically after evaluating other prognostic factors such as stage, grade, and co-morbid disease, race is not predictive of poor outcomes after treatment with radiation, radical prostatectomy, hormone therapy, or chemotherapy [13-14].

Higher PCa mortality rates in black compared to white patients may be explained by their presentation at later stages with higher grade tumours and due to differences in their age and treatment. More advanced disease stage at diagnosis had the largest impact on explaining the greater likelihood for black patients to die of their disease [14].

Population-based patterns of care studies demonstrate racial differences in the treatment and care administered. The proportion of black men obtaining optimal high-quality care is lower than the proportion of whites getting optimal high-quality care. Blacks are less likely to benefit from aggressive therapy for localised disease and they are less likely to receive intense observation while on “watch and wait” therapy [13].

4.6 Compliance to treatment and follow-up

It was hypothesised that economically disadvantaged race groups would display poorer levels of compliance to treatment and follow-up. While the Indian population group demonstrated a tendency towards better compliance, the numbers in this race group were insufficient. There was no evidence of disparity in compliance between whites and blacks.

4.7 Study limitations

The following limitations were noted in the study:

1. Missing values due to inadequate record keeping.
2. No routine record of presence or absence of perineural invasion on histology.
3. Sample population drawn exclusively from the state sector not reflecting the demographic findings of patients in the private sector, where it must be presumed that there is a higher incidence of patients presenting with organ-confined disease due to benefits of screening.
4. Short follow-up period may have confounded interpretation of treatment outcomes, especially in patients with biochemical failure and hormone refractory disease.
5. Data on clinical presentation (symptoms, signs and complications) and treatment modalities employed in the different race groups were not analysed.

Chapter 5: Conclusion

There appears to be a disproportionately higher incidence of PCa in the white population but the evidence is presumptive rather than conclusive. Socio-economic differences across racial lines certainly deserve greater mention when analysing data in a uniquely South African context. This may mask the higher incidence of PCa one would expect in blacks when compared to whites extrapolating from the disparities noted in AAM and EAM.

This study noted interesting correlates between the sub-Saharan black population and that of AAM. This is reflected in the higher median PSA levels on disease presentation and more advanced disease presentation when compared to white population groups. The impact of race on treatment outcomes revealed contradictory results between the crude analysis and Cox regression analysis and further research is warranted to explore this aspect in greater detail.

The results of this study necessitate the implementation of targeted study initiatives with end points designed to detect the disease early in the black population and begin appropriate management. A commitment to address gross disparities in socio-economic status between the race groups is paramount to eradicate the racial bias that exists in terms of accessibility and affordability to healthcare and PCa screening programs.

In addition, there must be more education about PCa and its consequences in the black population group along with improved support initiatives for patients and their families.

Chapter 5: Conclusion

The WHO estimates that up to 80% of the population in Africa makes use of traditional medicine. In Sub-Saharan Africa, the ratio of traditional healers to the population is approximately 1:500, while medical doctors have a 1:40 000 ratio to the rest of the population. It is apparent that traditional healers play a significant role in the lives of African people and have the potential to serve as crucial components of a comprehensive health care strategy [15]. This highlights the need for cultural sensitivity and also dictates collaboration with traditional healers in our context to raise awareness about PCa and the available treatment options.

With this plan of action a decrease in the racial/ethnic outcome disparity may be accomplished.

Chapter 6: References

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Appendix

Data Collation Sheet

Patient Profile	
Name	
Hospital Number	
Age	
Family history of prostate cancer	
Date of first consultation	

Tumour Risk Profile	
Stage(TNM)	a. Clinical stage: b. Pathological stage: _____
Gleason Score	
Perineural Invasion	
High Grade Prostatic Intraepithelial Neoplasia (HGPIN)	
Associated prostatitis	
Initial PSA	

Appendix

Localised Disease (T1/T2)	Yes / No
Treatment modality	1. Neoadjuvant Hormonal Treatment 2. External Beam Radiotherapy with Concurrent Hormonal Treatment 3. Adjuvant Hormonal Treatment i. Drug/s: _____ ii. Duration:_____ 4. Radical Prostatectomy 5. Adjuvant External Beam Radiotherapy post prostatectomy 6. Other (specify)
Treatment start date	
Progression Free Survival(PFS)	

PSA											
Date											

Appendix

Locally Advanced Disease (T3/T4)						Yes / No					
Treatment modality						1. Neoadjuvant Hormonal Treatment 2. External Beam Radiotherapy with Concurrent Hormonal Treatment 3. Adjuvant Hormonal Treatment i. Drug/s: _____ ii. Duration: _____ 4. Radical Prostatectomy 5. Adjuvant External Beam Radiotherapy post prostatectomy 6. Other (specify)					
Treatment start date											
Progression Free Survival(PFS)											
PSA											
Date											

Appendix

Biochemical Failure	Yes/No
PSA reading post curative treatment modality	Date: PSA:
3 consecutive PSA rises	Date: PSA: Date: PSA: Date: PSA:
Treatment modality on diagnosis of biochemical failure	1. External Beam Radiotherapy 2. Chemotherapy i. Drug: _____ 3. Medical Castration i. Drug/s: _____ 4. Surgical Castration (BSO) 5. Other(specify)
Progression free survival (PFS)	
PSA readings on diagnosis of biochemical failure :	

PSA											
Date											

Appendix

Metastatic Disease (M1)						Yes / No					
Treatment modality						1. Medical Castration i. Drug/s: _____ 2. Surgical Castration (BSO) 3. Palliative External Beam Radiotherapy 4. Bisphosphonates i. Drug: _____ 5. Chemotherapy i. Drug: _____ 6. Other (specify)					
Treatment start date											
Progression free survival (PFS)											
PSA											
Date											

Appendix

Hormone Refractory Disease	Yes / No
Number of hormonal manipulations (including BSO) prior to diagnosis of hormone refractory disease	
Time to hormone refractory disease	
Serum testosterone level at time of diagnosis	
Treatment Modality	1. Anti-androgen withdrawal 2. Chemotherapy alone i. Drug _____ 3. Chemotherapy and Hormonal Therapy i. Drug/s_____ 4. Best supportive care 5. Other (specify)
Time to biochemical response on chemotherapy (TTBR)	
Progression Free Survival (PFS)	
PSA readings on diagnosis of Hormone Refractory disease :	

PSA											
Date											

Appendix

Compliance Assessment	
History of missed appointments	/1
Documented non-compliance on treatment	/1
Compliance Score	/2