

Early results from South African men with low-risk, clinically localised prostate cancer managed with active surveillance

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Objective: To report the outcome of active surveillance (AS) offered to men with low-risk prostate cancer (PCa) at Universitas Academic Hospital in Bloemfontein, South Africa.

Methods: Men with PCa with a Gleason score of 6 (3+3) on ≤ 2 needle cores, $\leq$ cT2a, and prostate-specific antigen (PSA) lower than 10 ng/ml were offered AS. Age, self-reported ethnicity, clinical stage, PSA, PSA density (PSAD), number of positive cores and core percentage were recorded at baseline. Digital rectal examination (DRE), PSA, and PSA kinetics were recorded during follow-up and repeat prostate biopsy done routinely within 12 months of initial diagnosis or if there were unfavourable PSA kinetics. Patients older than 70 years with favourable-intermediate risk were included.

Results: Fifty-four men with median age of 64.8 years (range 43–73 years) were surveilled for low-risk PCa for a median of 31 months (range 7–126 months). Initial median PSA was 7 ng/ml (range 1.1–14.3 ng/ml). Self-reported ethnicity was 35 African (65%), 15 European (28%), one mixed race (2%) and three other (5%). Ethnicity was not associated with adverse reclassification (HR 0.5; $p = 0.366$). PSAD was the best predictor of reclassification (HR 1.5; $p = 0.09$). PSAD cut-off was determined with the receiver operating curves to be 0.13 ng/ml/ml which had a sensitivity of 92.9% and a specificity of 42.5% predicting favourable disease. Upgrade of Gleason score was noted in three (7%) and increased positive cores in 12 (27%) of the 44 men who had a repeat biopsy. Overall, 14 (26%) patients received definitive treatment for their PCa, while 40 (74%) remained on AS.

Conclusion: Based on early results, AS appears to be an appropriate management option for South African men with low-risk PCa and a PSAD ≤ 0.13 ng/ml/ml irrespective of ethnicity.

Keywords: active surveillance, prostate cancer, adverse reclassification, PSA density, repeat biopsy, South African men

List of abbreviations and acronyms

AS	Active surveillance
DRE	Digital rectal examination
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PCa	Prostate cancer
PSA	Prostate-specific antigen
PSAD	Prostate-specific antigen density
PSADT	Prostate-specific antigen doubling time
PSAV	Prostate-specific antigen velocity
ROC	Receiver operating characteristic
RP	Radical prostatectomy
SAPCS	South African Prostate Cancer Study
TRUS	Transrectal ultrasound

Introduction

Prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer death among men worldwide.¹ In South Africa, PCa is the most common histologically diagnosed cancer in men according to the National Cancer Registry.² PCa was the leading cause of cancer-related death in the Free State, North West, Mpumalanga and Limpopo provinces in 2014 and was second only to lung cancer in the other six provinces of South Africa.³ Widespread use of PSA screening has resulted in an increase in the overall

incidence of PCa worldwide, an increase in localised disease and a decrease in locally advanced and metastatic disease. This has not translated into improving cancer specific and overall survival as demonstrated by a recent meta-analysis.⁴ One possible reason for this is that screening has resulted in an increased incidence of predominantly low-risk disease. Low-risk PCa is defined as clinical stage T1–T2a, serum PSA level < 10 ng/ml and Gleason score ≤ 6 .⁵ It is well known that low-risk localised PCa may pursue a relatively indolent course as autopsy studies have demonstrated.⁶ Active surveillance (AS) involves the identification and close follow-up of men with low-risk disease with the intent to offer curative therapy should there be signs of progression to clinically significant disease. Even though several strategies have been described and a lack of standardisation exists, AS has become an established option for management of patients with low-risk PCa in the developed world.⁷

Treatment with curative intent is only administered when predefined thresholds indicative of potentially lifethreatening, but still curable disease in men with adequate life expectancy is present, or on patient request.⁸ Concerns, however, exist about the clinical course and progression of PCa in African men worldwide, and about 70% of the patients treated at our centre identify themselves as African.⁹

Determining the burden of PCa within the African continent has been problematic and compounded by a lack of unified systems of monitoring and reporting. A recent meta-analysis of literature on PCa in Africa over the last 35 years included only 40 studies.

Clinically aggressive phenotypes have been reported within selected populations of West Africa, Eastern Africa and within ethnically admixed populations from Southern Africa.^{10,11} In the South African Prostate Cancer Study (SAPCS) the authors evaluated PCa in the most northern regions of South Africa and found that South African black men presented with a higher tumour grade and higher serum PSA at the time of diagnosis.¹²

At the Universitas Annex Department of Oncology in the Free State Province of South Africa, low-risk PCa patients were more likely to be lost to follow-up (39.1%) compared to other risk groups, possibly as their symptoms were not advanced enough for them to return for further treatment.⁹ This finding was reiterated by Heyns et al. in the Western Cape Province of South Africa where most patients were lost to follow-up with no reason available and only 12% of African men receiving potentially curative treatment.¹³ This is of concern when implementing an AS protocol due to the strict follow-up that is needed.

The question remains whether AS can be safely offered to African men of South Africa and, if so, what the appropriate selection and follow-up strategy should be. To our knowledge, this is the first attempt to describe a South African cohort of men with low-risk PCa, who have been managed with AS.

Methods

A retrospective cohort study was done from the medical records of patients managed with AS from 2014 to 2018 at the Universitas Academic Hospital in the Free State Province, South Africa. Our inclusion criteria for AS were low-risk PCa as defined by Epstein with a PSA lower than 10 ng/ml, clinical stage $\leq$ T2a, Gleason score of 6 (3+3) on 2 needle cores and less.⁵ Patients with favourable-intermediate risk PCa older than 70 years were also included if they had a Charlson comorbidity index $\leq$ 3.¹⁴ Data collected and recorded at baseline included self-reported race/ethnicity, age, clinical stage, initial PSA, PSA velocity (PSAV), PSA density (PSAD) and PSA doubling time (PSADT). The PSAD was calculated with transrectal ultrasound prostate volume determined with the ellipsoid method, length $\times$ height $\times$ width $\times \pi/6$.¹⁵ Follow-up prostate biopsy was routinely done at 12 months, change in DRE or for unfavourable PSA kinetics (PSADT $<$ 2 years or PSAV $>$ 0.75 ng/ml/year). Number of positive PCa biopsy cores and biopsy core percentage were documented. A PSAD cut-off value of 0.15 was used to determine its correlation with PSA kinetics, number of positive cores, Gleason score upgrade and number of patients remaining on AS. A sub-analysis was done to compare PSA, PSAD, PSAV, PSADT time, positive core percentage, and AS outcome between African and European men.

Reclassification was defined as an upgrade in Gleason grade or an increase in the number of positive prostate biopsy cores. Where available, the Gleason grade of the diagnostic prostate biopsies was compared with the Gleason grade of subsequent prostate biopsies and the radical prostatectomy (RP) histology.

Statistical analyses

A retrospective cohort study was done. Statistical analyses were performed by SPSS® version 25 (SPSS Inc. Chicago, IL, USA). The analysis included independent student's *t*-test and the Pearson's chi-square test for continuous and categorical variables. Receiver operating curves (ROC) were used to determine the cut-off value balancing sensitivity and specificity of PSAD predicting adverse outcome. A cut-off value for PSAD of 0.15 ng/ml/ml was used to correlate pathological outcome. Kaplan-Meier estimator was used to determine time to treatment or discontinuation of AS in months. The Mann-Whitney U test and Wilcoxon W were used as non-parametric tests to compare the medians of numerical variables.

Results

Fifty-four men with a median age of 64.5 years (range 43–73 years) with low-risk PCa underwent AS between 2014 to 2018. This included five men between 70 and 73 years with PSA level of 10.4–14.3 ng/ml, all with $<$ 2 cores positive Gleason score 6 (3+3). The clinical and pathological characteristics of the patient cohort are summarised in Tables I, II and III.

Self-reported ethnicity was mainly African (35; 65%), Caucasian/European (15; 28%), mixed race (1; 2%) and other (3; 5%). The median age of the African men was 62 years (43–73 years) compared to their European counterparts' age of 64 years (range 53–73 years) ($p = 0.147$). The median PSA of the cohort was 6.4 ng/ml (range 1.1–14.3 ng/ml) at time of diagnosis. The median follow-up was 31 months (7–126 months).

Table I: Self-reported ethnicity

Self-reported ethnicity	Sample (n)	Remain under AS	Progressed to treatment
African	35	26 (74%)	9 (26%)
European	15	12 (80%)	3 (20%)
Mixed	1	1 (100%)	NA
Other	3	2 (67%)	1 (33%)
Total	54	41 (76%)	13 (24%)

Table II: Median age

Self-reported ethnicity	Median age in years
African	62 (43–73)
European	64 (53–73)
Mixed	69
Other	69 (66–71)
Total	64.5 (43–73)

The clinical stages of the men were T1a (20%), T1b (4%), T1c (74%) and T2a (2%). There was no statistically significant difference of median age and median PSA at the time of diagnosis between patients who remained under surveillance and those who progressed to treatment ($p = 0.676$ for age and $p = 0.838$ for PSA). There was no difference in the rate of progression to treatment between African and European men, nine (26%) vs three (20%) ($p = 0.274$). Progress to treatment occurred in 13 (33%) men.

European men had a lower median PSAD of 0.10 ng/ml/ml compared with their African counterparts of 0.17 ng/ml/ml. African

Table III: Clinical and pathological variables between patients remaining under AS and those progressed to treatment

Characteristic	Total	Remain under AS	Progressed to treatment	p-value
Median initial PSA ng/ml	6.4 (1.1–14.3)	6.1 (1.10–14.3)	7.2 (4.7–10.9)	0.225
Median PSAD ng/ml/ml	0.15 (0.03–0.62)	0.13 (0.03–0.62)	0.20 (0.10–0.33)	0.003
Clinical stage				
T1a	11 (20%)	11 (100%)	0 (0%)	0.040
T1b	2 (4%)	2 (100%)	0 (0%)	
T1c	40 (74%)	27 (68%)	13 (33%)	
T2a	1 (2%)	0	1 (100%)	
Positive cores				
1 core	41 (76%)	32 (78%)	9 (22%)	0.301
2 cores	14 (24%)	9 (64%)	5 (36%)	
Follow up in months	31 (7–126)	35.8 (10–126)	17.3 (7–31)	0.019

Table IV: Sub-analysis comparing African with European men

Characteristic (medians)	African men	European men	p-value
Sample size	35	15	
Initial PSA ng/ml	7.3	7.4	0.321
PSA density ng/ml/ml	0.17	0.10	0.037
PSA velocity ng/ml/year	0.38*	0.01	Not done
PSA doubling time in months	-2.2*	43.5	Not done
Core percentage	19.5%	9.3%	0.03
Remain under AS	26 (74%)	12 (80%)	0.482

*Significant inter-visit fluctuation in follow-up PSA levels occurred in many patients and this made the interpretation of PSADT and PSAV of questionable value. For this reason, we decided to omit this from statistical analysis. (18/35 African men had negative PSADT therefore the overall negative value. All these men had a higher initial PSA than their follow-up PSA.)

Table V: PSA density cut-off of 0.15 ng/ml/ml at diagnosis correlation with PSA kinetics and repeat biopsy over time

	PSAD ≤ 0.15 ng/ml/ml n = 33	PSAD > 0.15 ng/ml/ml n = 21	p-value
PSA velocity ng/ml/year	0.7 (-4.21–15.0)	-0.5 (-5.5–4.3)	0.11
PSA doubling time (median) in months	15.0	10.03	0.268
Positive cores			
1 core	24 (73%)	17 (81%)	0.363
> 1core	9 (27%)	4 (19%)	
Repeat biopsy histology (n)			
Negative (9)	8 (24%)	1 (5%)	0.249
Unchanged (20)	13 (39%)	7 (33%)	
Increased cores (12)	7 (21%)	5 (24%)	
Gleason 7 (3+4) (2)	1	1	
Gleason 8 (4+4) (1)	0	1	0.249
Repeat biopsy not done (10)	4	6	
Remain under AS	27 (82%)	13 (62%)	0.096

men had a higher positive core percentage (19.5%) compared to European men (9.3% $p = 0.037$) (Table IV).

Significant inter-visit fluctuation in follow-up PSA levels occurred in many patients and this made the interpretation of PSADT and PSAV of questionable value. For this reason, we decided to omit this from statistical analysis.

A multivariate Cox regression analysis showed that PSAD (HR 1.5; $p = 0.09$) is an important predictor of progression to treatment over time. The number of cores did not influence treatment progression over time ($p = 0.548$). Various protocols recommend PSAD of 0.15 ng/ml/ml as cut-off value to select patients for AS. A sub-analysis was done with PSAD cut-off of 0.15 ng/ml/ml (Table V).

PSAD cut-off value of 0.15 ng/ml/ml showed no correlation with PSA kinetics and subsequent repeat biopsy Gleason upgrade and/or positive cores (Table V). The median PSAD was 0.13 ng/ml/ml in the patients who remained on AS and differed from the 0.2 ng/ml/ml in the patients who progressed to treatment ($p = 0.035$) (Table III). Considering the coordinates on the ROC, a PSAD cut-off at 0.13 ng/ml/ml had the best balance between sensitivity and specificity. PSAD cut-off of 0.13 ng/ml/ml had a sensitivity of 92.9% and a specificity of 42.5% predicting favourable disease (Figure 1).

A total of 44 patients had a repeat prostate biopsy within the first 12 months after initial biopsy. Reclassification of PCa occurred in 15 (34%) patients. Increased positive cores were found in 12 (22%) and Gleason score upgrade in three (6%) patients, respectively. Negative repeat biopsy for cancer was found in nine (17%), and

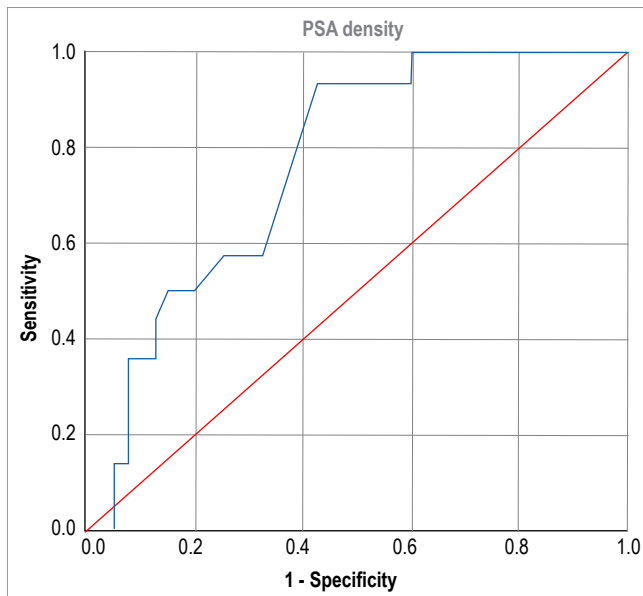


Figure 1: The ROC curve for PSA density. AUC = 0.766

in 20 (37%) patients, the Gleason score, positive core numbers and percentage remained unchanged (Table VI). A confirmatory or routine prostate biopsy was not done in ten (18%) of the patients.

Table VI: Repeat biopsy pathology

Repeat biopsy finding	Sample = 54	Percentage
Negative	9	17%
Histology unchanged	20	37%
Increase in positive cores	12	22%
Gleason upgrade to 3+4	2	4%
Gleason upgrade to 4+4	1	2%
Second biopsy not done	10	18%

Progression to treatment or discontinuation of AS occurred mostly in the first 30 months. After this period, 73% continued AS.

There was no difference between European and African men after a median follow-up of 24 months (range 7–126 months) who remained on AS (80% and 74%, $p = 0.482$). In sub-analysis overall, there was no difference in reclassification-free survival between European and African men (Log Rank $p = 0.377$, CI [95] 75.27–108.5) (Figure 2).

The management strategy was changed from AS to watchful waiting in seven patients due to advancing age (> 75 years), after a median follow-up of 88 months. All patients were of African descent and their median age was 68 years (range 65–73 years) at time of diagnosis. Their median PSA was 5.7 ng/ml (range 1.6–9.8 ng/ml). All patients had a Gleason score of 6 (3+3). The median PSAD was 0.09 ng/ml/ml (range 0.05–0.22 ng/ml/ml).

Progression to definitive treatment for PCa occurred in 14/54 (26%) patients. Four patients received external beam radiation therapy, and ten patients had an RP for increased Gleason grade or increased positive cores on repeat prostate biopsy after a median follow-up of 24 months (range 7–126 months). One patient that was

reclassified (increased number of cores [3], Gleason 3+3) opted for watchful waiting rather than active treatment.

The ten patients who had an RP had a median PSAD of 0.2 ng/ml/ml. Their baseline median PSA was 7.1 ng/ml (range 5.0–10.9 ng/ml). An increase in the Gleason score of the RP specimen occurred in seven (70%) of the patients compared with the initial prostate biopsy Gleason score. The Gleason score increased to 7 (3+4) in six, and 8 (4+4) in one patient. Upstaging occurred after RP in two patients who had extracapsular disease with seminal vesicle involvement. The PSAD of these two patients was 0.2 and 0.27 ng/ml/ml, respectively. The indication to treat these two patients was an increase in positive cores after confirmatory prostate biopsy. In these two patients with seminal vesicle infiltration, PSA nadir was 0.1 ng/ml and 0.2 ng/ml respectively and increased to 0.7 ng/ml and 0.4 ng/ml at 12 months after RP. The other eight patients treated with RP still had undetectable PSA levels at a median of 36 months follow-up.

At the end of the study period, six (9%) patients (five African, one other) were lost to follow-up for unknown reasons.

Discussion

Considering the racial disparities in presentation, progression and outcomes of PCa described in the literature, the question remains whether AS is a safe management strategy to adopt in our South African patient population – given that at least 70% self-identify as African.⁹ While considering this, it is important to recognise that most studies describing PCa epidemiology in African men are retrospective and descriptive in nature and that assumptions of causation remain mostly theoretical at this stage. Although there is a paucity of literature evaluating AS in African men, there is some evidence to suggest that AS should not be offered to African men due to the risk of initial under-grading or under-staging and subsequent disease progression.¹⁶ AS remains the accepted standard of care for men with low-risk PCa according to international

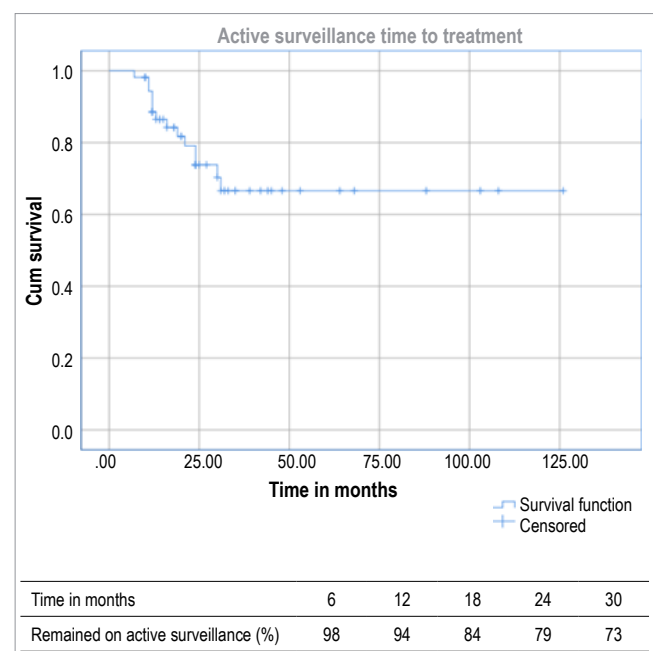


Figure 2: Overall treatment free rates of men on AS

guidelines. African American men were not associated with the risk of reclassification (HR = 1.16, 95% CI 0.78–1.72) in the Canary Prostate Cancer Active Surveillance Study (PASS) which evaluated 1 315 men, with 89 (7%) African American and 1 226 (93%) Caucasian American men.¹⁷

Our objective was to describe the early outcomes of our cohort of patients managed with AS.

This study showed no difference in the outcome of AS where progression to treatment was the same for African and European men, where 74% and 80% of men remained on AS after 35 months of follow-up. This finding is supported by the PASS study.¹⁷

Different AS protocols have been described and we decided to use the strict criteria originally described by Epstein for low-risk PCa.⁵ Our rationale for this was due to concerns about initial under-staging and/or -grading at the time of diagnosis in this potentially high-risk population.

PSAD has been demonstrated to have good predictability for clinically significant PCa.¹⁸ PSAD is higher in African American men and may influence the decision making.¹⁹ This was also found in our study where the European men had a significantly lower PSAD of 0.10 ng/ml/ml compared with the 0.17 ng/ml/ml of their African counterparts. Pre-treatment PSAD $\leq$ 0.15 ng/ml/ml is recommended by different protocols. The PSAD of $>$ 0.15 ng/ml/ml is associated with a 31% upgrading of the tumour.²⁰

Our study showed that a cut-off value of 0.15 ng/ml/ml had little effect on the AS outcome, histology, and PSA kinetics. PSAD was higher in men with adverse pathological outcomes. Progression to treatment was seen in this cohort who had a PSAD of 0.2 ng/ml/ml, whereas men with a lower PSAD of 0.13 ng/ml/ml remained on AS. PSAD cut-off value of 0.13 ng/ml/ml had the best balance between sensitivity and specificity predicting adverse pathological outcome in this study. Our data suggests a PSAD cut-off value of 0.13 ng/ml/ml, which is much lower than 0.19 ng/ml/ml found by a much larger study.²¹

Repeat biopsy forms an important part of AS protocols. The goal is to either detect initial under-staging/grading or to detect tumour progression over time. Initial “under sampling” of standard TRUS-guided prostate biopsy has been well described as demonstrated by a significant pathological upstaging/upgrading rate in men with low-risk disease who undergo RP.⁸ Pathological progression can occur over time due to tumour de-differentiation.²² An early confirmatory biopsy has been used to try and circumvent the initial under-sampling that may occur.²³

All the patients that progressed to treatment in our study, did so within the first 30 months under AS. Considering the tumour biology of low-risk PCa, these cases most likely represent tumour reclassification rather than true progression. The implication of this is that our short-term outcomes can probably be improved by improving the accuracy of our initial staging and grading. One such strategy is the use of early confirmatory repeat targeted biopsy by incorporating multiparametric MRI prior to this, thereby decreasing early “under sampling”.^{24,25}

While the oncological outcomes of AS are quite favourable, these outcomes are based largely on Caucasian patient cohorts, as African patients are under-represented, consisting of 7–10% of subjects in AS series reported.^{20,26} In our cohort, although small, African patients represent 65% of subjects and this is one of the main strengths of this study.

In our study, 14 patients received treatment for progression due to upgrading or an increase in the affected number of prostate biopsy cores.

These patients were managed with external beam radiation therapy and RP in four and ten men, respectively. Six patients upgraded from Gleason 6 (3+3) to Gleason 7 (3+4) and one patient to Gleason 8 (4+4).

African men had higher positive core percentages, 19.5% compared to 9.3% of the European men which was not found in a much larger study.¹⁷

Upstaging occurred in two men who had extracapsular disease with seminal vesical infiltration. Their PSAD at entry to AS were 0.2 ng/ml/ml and 0.27 ng/ml/ml respectively, reinforcing that a lower PSAD for entry into our AS programme should be used.

The delayed treatment of PCa in this cohort of patients had no negative effect on biochemical recurrence after RP. In eight men who had an RP, the PSA remained undetectable after 36 months of follow-up. Studies have shown that delayed RP in men with low-risk PCa does not increase the risk of adverse pathology.^{26,27} In the two cases which had seminal vesicle invasion, the PSA did not nadir at undetectable levels and they were offered adjuvant radiotherapy.

At the end of the study period, six (9%) patients (five African, one Other) were lost to follow-up for unknown reasons. This was far fewer than previously reported in similar clinical settings.^{9,13}

Overall, our findings demonstrate that most patients in our cohort have continued with AS at a median time to follow-up of 35.8 months (range 10–126 months). Progression to treatment occurred within the first 30 months in our cohort and likely indicates that a strategy to improve baseline risk stratification would further improve patient selection and the safety for this management strategy. PSAD has emerged as an important and readily available marker to predict successful surveillance, and early data from our cohort suggests that a slightly lower cut-off value of 0.13 ng/ml/ml may be more appropriate in our population.

The limitations of our study include the small sample size, relatively short median follow-up period as well as the retrospective study design. Selection bias may have occurred, as it is likely that treating physicians might be less inclined to select AS as a management strategy for African men. We believe this should, however, not play a major role in our centre, as all management decisions are taken within the context of a multidisciplinary team with well-defined and relatively strict selection criteria. Although a specific protocol for follow-up intervals exists in our department, strict adherence to this protocol is difficult to enforce due to challenges related to our referral and clinic system. Our outcomes may therefore be more

representative of a “real-world” context, instead of the context of a controlled prospective study design.

At this early stage, there appears to be no difference in outcome between African and Caucasian South African men in our study population, but we recognise that we need a significantly larger cohort with longer follow-up before definite conclusions can be made.

Conclusion

Based on early results, AS appears to be an appropriate management option for South African men with low-risk PCa and a PSAD ≤ 0.13 ng/ml/ml irrespective of ethnicity.

Conflict of interest

The authors have no conflict of interest to declare.

Funding source

No financial remuneration was involved in executing this study. All costs involved were covered by the Department of Urology, University of the Free State, Bloemfontein, South Africa.

Ethical approval

Ethical approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State before commencing this study (UFS – HSD2019/0636/2910).

All procedures in this study were conducted in accordance with the Health Sciences Research Ethics Committee of the University of the Free State, South Africa.

Patient confidentiality was maintained where the principal investigator alone had access to patient folders and during the analysis a research number was allocated to the patients to maintain privacy.

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