# Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

By

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## DECLARATION

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The author has no conflicts of interest to declare.

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## ABSTRACT

**Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.**

Authors: Willem Dahms, Josephus J Myburgh, Frederik M Claassen

**Introduction and 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.

**Materials and Methods:** Men with PCa with a Gleason score of 6 (3+3) on 2 needle cores or less, clinical stage cT2a and less, and prostate specific antigen (PSA) lower than 10 ng/ml were offered active surveillance. Variables such 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 was offered routinely within 12 months of initial diagnosis or in case of unfavourable PSA kinetics. Patients older than 70 years with low-intermediate risk were also included.

**Results:** A total of 54 men with median age 64.8 years (range 43 years to 73 years) were surveilled for low-risk PCa for a median of 31 months (range 7 months to 126 months). Their initial median PSA was 7 ng/ml (range 1.1 ng/ml to 14.3 ng/ml). Self-reported ethnicity was African 35 (65%), European 15 (28%) mixed race 1 (2%) and other 3 (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 = 009]. PSA density cut-off was determined with the receiver operating curves to be 0.13ng/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 3 (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 prostate cancer while 39 (85%) remained on active surveillance.

**Conclusions**: Based on early results, AS appears to be an appropriate management option for South African men with low risk-prostate cancer and a PSA density ≤0.13ng/ml/ml irrespective of ethnicity.

Key words: active surveillance, prostate cancer, adverse reclassification, PSA density, repeat biopsy, African men.

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| | |
|---|---|
| 3D | Three dimensional |
| ADC | Apparent diffusion coefficient |
| AS | Active surveillance |
| DRE | Digital rectal examination |
| DWI | Diffusion weighted imaging |
| EAU | European Association of Urology |
| JH | Johns Hopkins |
| mpMRI | Multiparametric Magnetic Resonance Imaging |
| MSKCC | Memorial Sloan Kettering Cancer Centre |
| NCCN | National Comprehensive Cancer Network |
| PCa | Prostate cancer |
| PIVOT | Prostate Intervention versus Observation trial |
| PRIAS | Prostate Cancer Research International Active Surveillance |
| PROTECT | Prostate Testing for Cancer and Treatment trial |
| 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 |
| SEER | Surveillance, Epidemiology, and End Result |
| SPCG-4 | Scandinavian Prostate Cancer Group Study Number 4 |
| TRUS | Transrectal ultrasound |
| UCSF | University of California San Francisco |
| UFS | University of the Free State |
| UM | University of Michigan |

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**Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.**

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# CHAPTER 1: LITERATURE REVIEW

## 1.1 INTRODUCTION

Prostate cancer is the second most incident cancer and the fifth leading cause of cancer death among men worldwide.[1] South African men have a lifetime risk of 1 in 19 of developing prostate cancer and represents the most common histologically diagnosed cancer in men according the South African National Cancer Registry.[2] Prostate cancer 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]

It is well known that localised prostate cancer may pursue a relatively indolent course as autopsy studies have demonstrated that prostate cancer may be found in up to 50% of men who died of non-prostate related causes.[4]

To date, no prospective randomized trial has shown an overall survival benefit to any of the therapeutic options for organ-confined prostate cancer - i.e., active surveillance, brachytherapy, external-beam radiation, or surgical radical prostatectomy. The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) during the pre-prostate specific antigen (PSA) screening era (1989 – 1999), demonstrated a 24% decrease in prostate-cancer-specific mortality in favour of radical prostatectomy, but only in patients with intermediate risk prostate cancer. The mean PSA at the time of RP was 13ng/ml and only 12% had clinical T1c disease, 10% clinical stage T1b and 77% clinical T2. (Differentiation between the different clinical T2 stages were not done). With a mean PSA of 13ng/ml, this underscores the low percentage of patients included with low risk prostate cancer.[5] During the PSA screening era from 1994-2002 the Radical Prostatectomy versus Observation for Localised Prostate Cancer Trial (PIVOT) demonstrated that the prostate-cancer-specific mortality was not significantly lowered. At 20 years follow-up the absolute difference in all-cause mortality was less than 6% and cancer specific mortality 4%. Once again only in intermediate risk patients with a 15 year or more follow-up. The trial however failed to accrue the initially attended number of participants and was criticized for the

abnormally low 10 year overall survival in both the intervention and observation groups, bringing into question whether the results are applicable to patients who have a good life expectancy. [6] The Prostate Testing for Cancer and Treatment trial (PROTECT) showed at a median of 10 years, prostate-cancer-specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring.[7] It should be noted that active monitoring is not the same as active surveillance described later. The only available randomized controlled trial comparing radical prostatectomy and brachytherapy as monotherapy was closed due to poor accrual.[8] These landmark trials (SPCG-4, PIVOT, PROTECT) showed that the long term prostate-cancer-specific mortality remains low with localized prostate cancer.

## 1.2 RATIONALE FOR ACTIVE SURVEILLANCE IN PROSTATE CANCER.

The widespread use of PSA-based screening programs in developed countries has resulted in an increased detection of early stage and less aggressive tumours. Thus, many men are potentially overtreated. This has been recognized as a growing concern due to patients who receive surgery or radiation therapy, but are unlikely to benefit due to the low cancer-specific mortality of low-risk disease or limited life expectancy.[9]

Approximately 45% of men with screening-detected localised prostate cancer are candidates for deferred treatment.[10] Treatment concerns are appropriately based on significant morbidity and functional impairment including urinary incontinence and erectile dysfunction that is associated with definitive treatment for prostate cancer.[11,12].

Low-risk prostate cancer has been defined as clinical stage T1-T2a, serum PSA level < 10ng/ml and Gleason score ≤ 6 by the National Comprehensive Cancer Network (NCCN) guidelines panel .[13] Previously Epstein *et al*. used a prostate cancer criteria associated with so called pathologically insignificant tumours (volume ≤ 0.5cm and Gleason sum ≤ 6) that would pose little threat to an individual's life and could refrain from significant morbidity that is associated with treatment of prostate cancer. These pre-treatment criteria were clinical stage T1c, Gleason sum ≤ 6, PSA < 10ng/ml, PSA density (PSAD) ≤ 0.15ng/ml/ml, ≤ 2 positive biopsy cores and ≤ 50% cancer involvement per core. [14] These latter criteria make up the NCCN very-low-risk group.

The observations from the landmark trials have led to the development of various strategies for conservative management, including active surveillance and watchful waiting. These

observations have led to a shift in the paradigm in the management of prostate cancer so that younger, healthier men with less aggressive prostate cancer can be encouraged to enrol in such a surveillance program. Patients that present with features of low or very-low risk prostate cancer often represent a dilemma for urologists and patients when deciding on definitive treatment options with non-negligible side effects.

Active surveillance of prostate cancer has emerged as one strategy to circumvent this. As a strategy it emphasizes close follow up of men who have been identified to have low risk disease with the intent to administer curative therapy should there be signs of progression to clinically significant disease which is defined as a lesion >0.5 $cm^3$, a combined Gleason score ≥ 7, and/or showing features of extraprostatic extension.[15] The close follow up regime commonly involves regular DRE, PSA, monitoring of PSA kinetics, repeat biopsies and in some centres prostate MRI. Treatment with curative intent is only administered when predefined thresholds indicative of potentially life threatening, but still curable disease in men with adequate life expectancy is present or on patient request (Table 1).

**Table 1.** Current active surveillance protocols for prostate cancer.

| Institution | Clinical stage | Gleason Score | Number of positive biopsy cores | Single core involvement (%) | PSA (ng/ml) | PSA-density (PSAD) |
|---|---|---|---|---|---|---|
| **JH** | T1c | ≤6 | ≤2 | <50 | - | ≤0.15 |
| **MSKCC** | T1c-T2a | ≤6 | ≤3 | ≤50 | <10 | - |
| **UCSF** | T1c-T2 | ≤6 | ≤33% (at least 6 cores) | ≤50 | <10 | - |
| **PRIAS** | T1c-T2 | ≤6 | ≤2 | - | <10 | ≤0.2 |
| **UM** | T1c-T2 | ≤6 | ≤2 | ≤20 | <15 | - |

JH – Johns Hopkins; MSKCC – Memorial Sloan Kettering Cancer Centre; UCSF – University of California San Francisco; PRIAS – Prostate Cancer Research International Active Surveillance; UM – University of Michigan.

It is important to differentiate active surveillance from "watchful waiting" (Table 2), where emphasis is on the identification of symptomatic progression. Even low-grade, slow-growing, and clinically localised prostate cancer retains metastatic potential. The presumption of active surveillance compared with watchful waiting is that repeat evaluations will allow detection of progression of the prostate cancer with time to intervene. Watchful waiting is a strategy aimed at simply treating symptomatic manifestations of local or metastatic progression of a patient's prostate cancer. This strategy is usually reserved for patients with < 10 years life expectancy and severe debilitating comorbidities. [16]

**Table 2**. Comparison of active surveillance and watchful waiting for prostate cancer.

| | Active surveillance | Watchful waiting |
|---|---|---|
| **Treatment** | Curative | Palliative |
| **Markers** | Digital rectal examination (DRE), prostate specific antigen (PSA), prostate biopsy | Not defined |
| **Follow-up** | Schedule-based | Patient-dependant |
| **Life expectancy** | >10 years | <10 years |
| **Tumour stage** | Only low-risk patients | Patients at all stages |
| **Aim** | To reduce the side-effect of treatment without compromising the survival rate | To reduce the side-effects of treatment |

In 2001, only 6.2% of men with low-risk prostate cancer were managed with active surveillance or watchful waiting. By 2010, 40% of all low-risk prostate cancer patients had been offered surveillance, and this figure was up to 76% in men over 75 years with low-risk disease, as demonstrated in a large multi-centre clinical study.[17]

The most appropriate triggers for intervention remain controversial and currently there is a lack of standardized criteria for this. Most centres use histologic progression (either in tumour volume or tumour grade) or changes in PSA kinetics to indicate the need for treatment. While no standardized protocol exists, patients are usually followed up with a 3-6 monthly PSA and digital rectal examination.[18]

## 1.3 THE USE OF PSA IN ACTIVE SURVEILLANCE

Controversy remains over the use of PSA in active surveillance protocols with several authors finding little changes in PSA kinetics even with histological evidence of progression.[19] With this being said, a number of large institutions still use PSA and its derivatives as triggers for interventions. For example, the Memorial Sloan-Kettering Group uses a PSA > 10ng/ml,[20] University of Toronto uses a PSA doubling time <3 years[21] whilst the Royal Marsden Group uses a PSA velocity of > 1ng/ml/yr as a trigger for intervention.[22] A PSA velocity of 2ng/ml/yr was significantly associated with an increase in Gleason score.[23]

## 1.4 THE ROLE OF REPEAT PROSTATE BIOPSIES.

Because of this limitation with PSA kinetics, prostate biopsies are repeated every 1-3 years but may be done as early as 3 months. A significant proportion of men are under staged or under graded in active surveillance as demonstrated from post prostatectomy specimens. This risk may be as high as 20-30%. This likely demonstrates a limitation of systematic prostate biopsies.[18] Gleason grade "progression" may therefore actually be due to initial "under sampling" or under grading of disease present at baseline, but true progression due to tumour de-differentiation during the follow up period may also occur. It likely represents a combination of the two. At the Memorial Sloan-Kettering Cancer Centre, they demonstrated that early repeat biopsy of men on active surveillance within 3 months resulted in upgrading in 35%.[24] In the PRIAS group, 21% of men were no longer eligible for active surveillance following an early repeat biopsy.[25]

Different prostate biopsy strategies in active surveillance protocols are deployed. Confirmatory biopsies are done within the first year on AS to reduce the risk of under sampling of missed clinically significant prostate cancer. Routine follow-up biopsies are done every 1-3 years whereas triggered repeat prostate biopsies are performed once pre-defined clinical parameters are met.

Pathological progression on repeat biopsy includes, increase in the Gleason grade, number of positive cores or percentage of involvement of each core and constitutes grounds for discontinuation of surveillance.[18] Some authors suggest that this progression may in fact be "reclassification" as more of the prostate is sampled with surveillance biopsies. With progression or reclassification beyond the initial entry criteria, immediate curative treatment is offered.[18] Standard transrectal ultrasound-guided (TRUS) biopsies often underestimate disease volume and grade, especially for anterior tumours which are traditionally difficult to biopsy.[26]

## 1.5 THE ROLE OF MULTIPARAMETRIC MRI OF THE PROSTATE IN ACTIVE SURVEILLANCE.

Multiparametric MRI imaging of the prostate with subsequent biopsies could help in improving both the accuracy of Gleason grading at inclusion and during follow-up. If MRI with targeted biopsies improves Gleason grading, surrogate measures of Gleason progression could be omitted.

The establishment of the role of imaging for early prostate cancer and the timing of repeat imaging studies remain to be accepted in clinical practice. The heterogeneity of inclusion criteria for active surveillance of patients, the definition of clinically significant disease, and agreement about what should be understood as radiologic progression are the main issues that affect the potential impact of MRI on active surveillance protocols.[27]

Multiparametric MRI enables prostate cancer detection, its localization, and further characterization in terms of tumour size and stage.[28] Multiparametric MRI may be useful in two stages of the active surveillance protocol, as the baseline examination at patient enrolment, and an alternative to follow-up prostate biopsy during the active surveillance program.[27,28,29] MRI is still preferred in men where the balance between under-diagnosis and overdiagnosis favours the clinical priority of not missing significant cancer.[30] These patients include men with prior negative biopsies with unexplained raised PSA values, and those undergoing active surveillance who are being evaluated for an increased PSA levels or a change in clinicopathologic status.

The combined use of MRI findings, clinical data, and biopsy results in active surveillance enrolment has been previously proposed, as early as 2010.[21] According to previous studies, MRI-based models showed better results than clinical models ($P<0,05$).[21,31,32]. According to the current guidelines from the European Association of Urology (EAU) regarding men already on active surveillance and the treatment of patients with low-risk disease who qualified for active surveillance, there is a recommendation to perform multiparametric MRI before a confirmatory biopsy, if not done before the first biopsy.[33]

Most of the occurrences of reclassification of prostate tumours are caused by under-sampling at first biopsy rather than the progression of an indolent tumour as mentioned.[34] This finding indicates that the results of routine serial biopsies may be misleading. Therefore, there is a need for a method to reduce the risk of underestimation by targeting the biopsy needle to the most

significant area of the prostate tumour. Targeting the biopsy needle on the index lesion corresponding with the most significant area in the prostate cancer visualized by the initial anatomical and functional imaging reduces the risk of underestimation of the stage of the prostate cancer. The 95% negative predictive value of multiparametric prostate MRI highlights the opportunity to avoid repeat biopsies for active surveillance and monitoring.[35]

MRI shows a high degree of accuracy for the identification of significant prostate cancer.[15] Studies have shown that MRI-guided prostate biopsy detects a further 52% of tumours in patients with prior negative serial biopsies.[32,36]

Multiparametric MRI provides data on the tumour volume, location and on grade or behaviour according to the Gleason score. Studies have identified a correlation between the apparent diffusion coefficient (ADC) values, and the histological Gleason grade. Lower ADC values and a higher signal on diffusion weighted imaging (DWI) correspond with the denser structure of less differentiated cancers.[37] This inverse relationship between the Gleason score and the ADC value was found for prostate cancers in the peripheral zone. DWI imaging has resulted in the ability to distinguish between low-grade, intermediate-grade, and high-grade prostate cancer.[38] Also, the baseline ADC value is an independent predictor for unfavourable findings of control biopsy and time to radical prostatectomy.[39]

MRI is a useful tool for enrolling patients for active surveillance programs as well as a monitoring method for patients already under active surveillance. Patients under active surveillance who have a suspicion of malignancy on multiparametric MRI have an increased risk of the upgrading of the Gleason score when compared with patients who did not have imaging findings.[40] In 2012, Vargas *et al.* showed that the diagnosis of low-risk prostate cancer based on MRI had a negative predictive value of between 0.96 to 1.0 for upgrading, which means that these patients could have avoided repeat biopsy. For lesions deemed high risk for significant prostate cancer, the positive predictive value was between 0.87 and 0.98, which means that, in these cases, repeat biopsy was strongly recommended.[40]

Systematic errors in non-guided prostate biopsies are due to selective posterior zone sampling and inadequate transition and anterior zone biopsy.[41] Random errors occur because of the lack of awareness of the operator to the location of the tumour. The main strength of multiparametric MRI for active surveillance, regardless of the method of subsequent fusion of the images, is

the use of targeting biopsies.[42] Therefore, a concept of MRI-targeted biopsy is a method of choice in active surveillance qualification. MRI-targeted prostate biopsy in active surveillance is an alternative to repetitive biopsy sampling, and the use of three-dimensional (3D) transperineally mapping biopsy, which are invasive and expensive procedures, factors which limit their long-term use.[43]

Evidence-based clinical guidelines suggest that MRI will probably become the new triage test for men with suspicion of prostate cancer. Further large-scale prospective controlled studies are required to define the precise role of multiparametric MRI in active surveillance for prostate cancer.

## 1.6 ONCOLOGICAL OUTCOMES WITH ACTIVE SURVEILLANCE.

The oncological outcomes of active surveillance for men with very-low-risk prostate cancer are excellent. In a recent report of results from a large active surveillance cohort, 36% of patients demonstrated disease reclassification at a median of 2 years, the cumulative incidence of treatment was 57% after a median follow-up of 15 years and only 2 out of 1298 (0.15%) men died of prostate cancer. The median treatment-free survival was 8.5 years.[44] Five year survival approaches 100%, with 20-33% ultimately undergoing treatment.[45] In the literature, there have been six published reports (including more than 5,500 patients) that include at least 5-year follow-up data on patients placed on an active surveillance protocol.[46] Although in most studies there were differences in the threshold to intervene, most of the evidence in these studies support that active surveillance had comparable prostate-cancer-specific mortality to radical prostatectomy for treatment of low-risk prostate cancer.[7] Active surveillance has been included in the guidelines of all the major urological organizations including the European Association of Urology,[47] the American Urological Association[48] and the National Comprehensive Cancer Network.[15]

However, while the oncological outcomes of active surveillance are quite favourable, these outcomes are based largely on Caucasian patient cohorts, as black men are under-represented consisting of 7-10% of subjects in active surveillance series reported.[44,49] Despite the growing popularity of active surveillance for low-risk patients, increasing evidence has emerged questioning the safety of this approach in minority populations in American and European studies, particularly African Americans.[26]

## 1.7 CONCERNS AND LIMITATIONS OF SURVEILLANCE IN AFRICAN MEN.

There is concern over the implementation of an active surveillance protocol in our predominantly black population. This concern is justifiable as data emerges which suggests that patients of African ancestry may experience earlier disease progression while under active surveillance.[50]

Racial differences in prostate cancer incidence and mortality are well known. The incidence of prostate cancer is about 60% higher in African American men compared with Caucasian American men, and mortality rates for African American men are 2–3 times greater.[51] African American men both with and without prostate cancer have consistently demonstrated higher PSA values than their non-African American counterparts.[52] As a result, when using so called traditional PSA cut-off values for prostate biopsy, PSA becomes a less sensitive test for detecting prostate cancer. Although some have called for race-specific PSA thresholds, few clinicians utilize such measures in practice. Similarly, PSA density, when controlling for prostate volume, has been demonstrated to be higher in African American men.[53]

The following authors evaluated the outcomes based on pathological results of African American men who would have qualified for active surveillance but underwent radical prostatectomy.

Ha *et al.* compared 124 African American men and 148 Caucasian American men. Disease upstaging (defined as ≥ pT3a) was observed in 19.4% of African American and 10.1% of Caucasian American men (p=0.037). They concluded that active surveillance in African American men with prostate cancer carries a higher risk of advanced stage cancer when compared to Caucasian American men and suggested a more stringent selection criteria for active surveillance.

Sundi *et al*. reported on a cohort of 256 African American and 1473 Caucasian American men. African American men were found to more frequently harbour adverse pathological features at surgery. African American men were more likely to experience pathological upgrading from Gleason sum 6 at biopsy to Gleason sum ≥ 7 at prostatectomy (27.3 vs 14.4%, P<0.001) and positive surgical margins (9.8 vs 5.9%l P=0.02) with African American race an independent predictor of adverse pathological features (odds ratio (OR): 3.23) and pathological upgrading (OR: 2.26). Dominant nodules in African American men were larger (median 0.28 vs 0.13 $cm^3$, P=0.002) and more often located in the anterior aspect of the prostate (51 vs 29%, P=0.003).[54]

As noted earlier, with the standard TRUS biopsy it is notoriously difficult to adequately sample the anterior prostate, which may partly explain the reported disparity.

Faisel *et al*. evaluated a large cohort with 15 993 Caucasian American and 1634 African American patients who underwent radical prostatectomy. The African American men were more likely to be upgraded in the very-low-risk prostate cancer (29.3 vs 15.4%; P<0.001) and low-risk prostate cancer (30.8 vs 24.9%; P=0.006) groups. Positive surgical margins rates were also found to be higher in African American men with very-low-risk (10.5 vs 5.8%; P=0.006), low risk (14.0 vs 10.5%; P=0.008) categories. African American race was also found to be an independent predictor of biochemical recurrence of the low-risk group (hazard ratio (HR): 2.16). The authors concluded that racial disparities in pathological and oncological outcomes were most pronounced in the very-low-risk and low risk prostate cancer groups and recommended that patients be counselled regarding their elevated risk for adverse outcomes when deciding on surveillance. [55]

A recent published database study of the Surveillance, Epidemiology, and End Results (SEER) program compared prostate specific mortality results of low-risk African American and Caucasian populations. This cohort consisted of 51 315 patients of whom 7523 were African American. Prostate cancer specific mortality rates were found to be higher in the African American population compared with Caucasian population, with 5-year prostate cancer-specific mortality rates of 1.0 vs 0.64% (P=0.019). African American race was also detected as an independent risk factor for prostate cancer-specific mortality (HR: 1.45 (1.03-2.05), P=0.032). When the results of patient who underwent curative treatment were considered in a subpopulation, again the African American population was found to have higher mortality rates and African American race was detected as an independent risk factor for prostate cancer-specific mortality.[56]

Weiner *et al.* aimed to determine the effect of time from biopsy to radical prostatectomy on development of adverse pathological outcomes (defined as pathological upgrading, nodal metastases, and positive surgical margins). African American race was shown to increase the risk of adverse pathological outcomes (OR: 1.16, P=0004).[57]

Yamoah *et al.* in their analysis determined whether disparities in adverse pathological features and biochemical recurrence-free survival outcomes exist between African American and Caucasian American men treated with radical prostatectomy. After radical prostatectomy, African American men were found to have higher rates of pathological Gleason sum ≥ 7 (52

vs 43%; P=0.01) and seminal vesicle invasion (6 vs 3%; P=0.02) The 7-year biochemical recurrence-free survival rates for Caucasian Americans and African Americans were 86% and 79% respectively (P=0.034).[51]

Overall these studies provide evidence for a higher likelihood of adverse pathological factors with respect to Gleason score, volume of disease, or positive surgical margins among African American men with apparent low-risk prostate cancer who underwent radical prostatectomy when compared with a similar Caucasian cohort.

There are relatively few studies investigating the results of active surveillance in black men. These studies have different inclusion criteria for active surveillance and different follow-up strategies and different end points. The following authors describe some of the characteristics and results of prospective studies on active surveillance involving the African American population.

At the University of Miami, Iremashvilli *et al.* reported on the results of 272 men (24 African American) enrolled in active surveillance. The primary endpoint was disease progression defined as high-grade cancer, more than two positive cores or greater than 20% involvement of any core on surveillance biopsy. They found that African American patients are more likely to experience disease progression on surveillance and that African American race was an independent predictor of progression on surveillance after controlling for number of positive biopsy cores, prostate volume and PSA density.[49]

Abern *et al.* reported on the active surveillance cohort at Duke University, which consisted of 145 patients (32 were African American), and noted that within 23 months of median follow-up, African Americans were almost three times as likely to receive treatment. The primary outcome was discontinuation of active surveillance for treatment due to prostate cancer progression. The demographic, clinical and follow-up characteristics did not differ by race. African American race was the sole predictor of discontinuation of active surveillance (HR: 3.08; P=0.01). This relationship persisted when adjusted for socioeconomic and clinical parameters. The authors suggest that this may be secondary to the increased prostate cancer growth rates in African American men.[58]

The John Hopkins active surveillance registry was reported on by *Sundi et al.* It included 615 Caucasian and 39 African American patients with NCCN very-low-risk prostate cancer. African American men were 1.8-fold more likely to experience disease progression on serial

biopsy. Progression by upgrading was the main driver of this disparity. African American men were also 3.02-fold more likely to demonstrate high-grade cancer on serial biopsy.[59]

Odom *et al.* stratified active surveillance outcomes by race in 139 patients (67 African American) with low-risk prostate cancer. Similarly with a median follow-up of 34 months, African American men were more likely to experience disease progression (HR 3.8; P=0.01).[60]

These studies are limited in that they utilise single-institution retrospective approaches with small sample sizes. There are no published reports of prospective studies of active surveillance in African American men, but the PIVOT trial is the single prospective randomized trial in the PSA screening era that has reported on the outcomes of radical prostatectomy compared to observation (rather than active surveillance). Although patients in the observation arm did not undergo repeat PSA testing, physical examination, or prostate biopsies as in the active surveillance cohorts, this trail provides insight into the natural history of PSA-detected prostate cancer. Inclusion criteria were men with newly diagnosed prostate cancer aged < 75 years, PSA < 50ng/ml and any Gleason score. Of note in this study that included 731 men, 232 (32%) were African American, the highest number of African American men in prospective observational studies. In a subgroup analysis of the African American population undergoing radical prostatectomy (as opposed to observation), no significant benefit on overall survival rate, disease-specific survival rate, or bone metastasis was observed with more than 10 years of follow-up. There was a significant advantage in terms of reduction in bone metastases with radical prostatectomy in the Caucasian American men. Even though observation and active surveillance both avoid immediate curative treatment, the safety of active surveillance irrespective of the prostate cancer risk cannot be argued. The limiting factors to generalise the PIVOT population to active surveillance cohorts is limited by the fact that 48% of patients were found to have Gleason Score 7 or higher and 66% of the patients had tumours in the intermediate or high-risk categories. They also did not report on oncological outcome and therefore its applicability to active surveillance cohorts is limited. Although given the high mortality among the PIVOT trail participants (48%) with no difference in mortality between those undergoing prostatectomy or observation, their data do provide evidence to support limiting aggressive therapy among men with significant comorbidities. [6]

Some of these differences can be attributed to socioeconomic factors. However, despite the availability of studies addressing specifically these biases, significant differences in outcomes remain. Powell *et al.* stratified patients into risk categories based on clinical tumour stage, PSA

at diagnosis, and Gleason grade. They could not account for the racial disparity in progression-free survival in patients with low-risk prostate cancer who underwent radical prostatectomy.[61] In another analysis that adjusted for socioeconomic factors, overall survival difference between African American and Caucasian American was non-significant, but prostate cancer-specific mortality was higher in African American men.[62]

African American men have a 45% increased risk for prostate cancer-specific mortality when compared to Caucasian men that cannot be explained by sociodemographic factors, stage or PSA. Of note, despite this increased risk, African American men with low-risk prostate cancer were 7% less likely to receive curative treatment than Caucasian men even after adjusting for sociodemographic and prostate cancer-specific characteristics.[63] These studies strongly suggest a biological difference that is partly responsible for more aggressive disease observed in African American men.[64]

Among 131 men Kim *et al*. looked at the expression of several biomarkers which are associated with prostate cancer progression (e.g. Ki67, androgen receptor, and alpha-methylacyl CoA racemase). All markers were expressed at higher levels among African Americans suggesting that their disease may be more biologically aggressive.[65] Epigenetic DNA alterations, chromosomal alterations, and gene expression profile alterations have been identified as factors with racial disparities.[66]

## 1.8 EVIDENCE FROM AFRICAN AND SOUTH-AFRICAN MEN.

Limited data are available pertaining to prostate cancer within Africa. Determining the burden of prostate cancer within the continent has been problematic and compounded by a lack of unified systems of monitoring and reporting. A recent meta-analysis of literature of prostate cancer 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.[67,68]

In the South African Prostate Cancer Study (SAPCS) the authors evaluated prostate cancer 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 time of diagnosis. In the aforementioned "gold standard" for treating localised prostate cancer with radical prostatectomy in the presence of negative surgical margins, less than 2% of patients within the SAPCS undergone curative surgery, with only 3% of men presenting as a result of a known elevated PSA.[69]

Sherriff *et al* at the Universitas Annex Department of Oncology in the Free State province of South Africa performed a cross sectional study and retrospective data collection from 497 patients with prostate cancer. Most of the patients (82.5%) had high-risk prostate cancer, 8.3% intermediate-risk group and only 9.3% in the low-risk prostate cancer group. From the low-risk group only a third (32.6%) of the patients were treated through active surveillance or watchful waiting. Almost half of the patients in this study (48.7%) presented with TNM stage IV prostate cancer. The authors argued that a possible cause for the advanced stage at presentation was a combination of insufficient screening of prostate cancer in the geographic locations referring to their institution as well that patients tend to wait for progression of local symptoms before they seek help. Noticeably a high number of patients (20.5%) was lost to follow up, possibly due a lack of transport, the patient was asymptomatic or did not understand the need for treatment, or the patient passed away and the family failed to inform the Department of Oncology. Low-risk patients were more likely to be lost to follow up (39.1%), possibly as their symptoms were not advanced enough for them to return for further treatment.[70].

These findings were reiterated by Heyns *et al* from the Western Cape province of South Africa with only 12% of African men receiving potentially curative treatment. Patients were most often lost to follow-up with no reason available. The mean duration of follow-up was significantly shorter in the African group compared to their European counterparts.[68] This is of great concern when active surveillance is considered where strict follow-up dictates the success of the management strategy.

## 1.9 RESEARCH QUESTION AND AIM.

The racial discrepancies in prostate cancer presentation and disease progression in American men have thus been well described and a paucity of data from native African men exists. Very little is known about the reason for the racial discrepancy in American men and although several theories exist, we have to be careful of assuming a biologic cause and ignoring potential inequality both socioeconomically and with regards to access to healthcare and potentially inadvertently further reinforcing this racial discrepancy by our own research and practice. This discussion is however relevant as approximately 70% of the patients we serve at our centre in the Free State identifies themselves as African. Active surveillance is the standard of care for low risk prostate cancer according to all international guidelines and we believe that this

research is important as the assumption that African men should not be offered the opportunity to avoid treatment related side effects by undergoing active surveillance for low risk prostate cancer, could potentially strengthen the racial divide that has existed before. At the same time and for the same reasons, the safety of such a strategy needs to be carefully considered and urgent research is needed in this area. The evidence demonstrates that African American men have a greater incidence of prostate cancer and are more likely to die from it, PSA is less accurate and are at greater risk of failure from local treatment when compared with Caucasian American counterparts. It is also clear that active surveillance is a legitimate treatment option in the management of localised prostate cancer which can prevent "overtreatment" in many men.

The aim of the study is to describe our early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance at the Universitas Academic Hospital in the Free State Province, South Africa.

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## CHAPTER 2: ARTICLE SUBMITTED TO THE CANCER CONTROL JOURNAL.

# Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

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## ABSTRACT

**Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.**

**Introduction and 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.

**Materials and Methods:** Men with PCa with a Gleason score of 6 (3+3) on ≤ 2 needle cores, ≤ cT2a, and prostate specific antigen (PSA) lower than 10ng/ml were offered active surveillance. 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 unfavourable PSA kinetics. Patients older than 70 years with low-intermediate risk were included.

**Results:** 54 men with median age 64.8 years (range 43 years to 73 years) were surveilled for low-risk PCa for a median of 31 months (range 7 months to 126 months). Initial median PSA was 7 ng/ml (range 1.1 ng/ml to 14.3 ng/ml). Self-reported ethnicity was African 35 (65%), European 15 (28%) mixed race 1 (2%) and other 3 (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 = 009]. PSA density cut-off was determined with the receiver operating curves to be 0.13ng/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 3 (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 prostate cancer while 39 (85%) remained on active surveillance.

**Conclusions**: Based on early results, AS appears to be an appropriate management option for South African men with low-risk prostate cancer and a PSA density ≤0.13ng/ml/ml irrespective of ethnicity.

**Key words:** active surveillance, prostate cancer, adverse reclassification, PSA density, repeat biopsy, 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] Prostate cancer 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 prostate cancer, an increase in localized disease and a decrease in locally advanced and metastatic disease but the cancer specific and overall survival benefit has not been 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 prostate cancer is defined as clinical stage T1-T2a, serum PSA level < 10ng/ml and Gleason score ≤ 6.[5] It is well known that low- risk localized prostate cancer 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 standardization exists, AS has become an established option for management of patients with low risk prostate cancer in the developed world.[7]

Treatment with curative intent is only administered when predefined thresholds indicative of potentially life threatening, but still curable disease in men with adequate life expectancy is present or on patient request.[8] Concerns however exists 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 prostate cancer 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 of prostate cancer 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 prostate cancer 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 time of diagnosis. [12]

At the Universitas Annex Department of Oncology in the Free State Province of South Africa, low-risk prostate cancer 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 great concern when active surveillance is considered were strict follow-up dictates the success of the management strategy.

The question remains whether AS can be safely offered to African men 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 prostate cancer, who have been managed with active surveillance.

**Methods**

A retrospective cohort study was done from the medical records of patients managed with active surveillance from 2014 to 2018 at the Universitas Academic Hospital in the Free State Province, South Africa. Our inclusion criteria for active surveillance were low-risk prostate cancer as defined by Epstein with a PSA lower than 10 ng/ml, clinical stage ≤ T2a, Gleason score of 6 (3+3) on 2 needle cores and less.[5] Patients with low-intermediate risk prostate cancer older than 70 years were also included if they had a Charlson comorbidity index ≤ 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 the trans rectal ultrasound prostate volume determined with the ellipsoid method, length x height x width x $\pi/6$.[15] Follow up prostate biopsy was routinely done at 12 months or for unfavourable PSA kinetics (PSADT < 2 years or PSAV > 0.75ng/ml/year). Number of positive prostate cancer 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 either an increase in PSA above inclusion criteria, upgrade in Gleason grade, an increase in the number of positive prostate biopsy cores or patient choice.

Where available the Gleason grade of the diagnostic prostate biopsies was compared with the Gleason grade of subsequent prostate biopsies and the radical prostatectomy 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 *t* test and the Parson'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 PSA density (PSAD) predicting adverse outcome. A cut-off value for PSAD of 0.15ng/ml/ml was used to correlate pathological outcome. Kaplan – Meier estimator was used to determine time to treatment or discontinuation of AS in months. Mann-Whitney U test and Wilcoxon W was used to compare nonparametric test comparing the medians of numerical variables.

**Results**

A total of 54 men with median age of 64.5 years (range 43 years to 73 years) with low-risk prostate cancer underwent active surveillance between 2014 to 2018. This included 5 men between 70 and 74 years with PSA level of 10.4 – 14.3ng/ml, all with <2 cores positive Gleason score 6 (3+3). The clinical and pathological characteristics of the patient cohort is summarized in Table 1, 2 and 3.

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 were 61.8 years (43 years to 73 years) comparable to their European counterparts age 64 years (range 53 years to 73 years) (p=0.147). The median PSA of the cohort was 6.4 ng/ml (range 1.1 ng/ml to 14.3 ng/ml) at time of diagnosis. The median follow-up was 31 months (7 – 126 months).

Table 1. 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 2. Median age.

| Self-reported ethnicity | Median age in years |
|---|---|
| African | 61.8 (43 – 73) |
| European | 64 (53 – 73) |
| Mixed | 69 |
| Other | 69 (43 – 73) |
| 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 discontinuation rate or rate of progression to treatment between African and European men, 9 (26%) vs. 3 (20%) (p=0.274). Progress to treatment occurred in 13 (33%) men.

Table 3. 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%) | |
| **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%) | |
| **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 |

European men had a lower median PSA density of 0.10 ng/ml/ml compared with their African counterparts of 0.17 ng/ml/ml. African men had higher positive core percentage 19.5% compared to European men (9.3% p=0.037) (Table 4).

Table 4. Sub analysis comparing African with European men. *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.

| 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.

A multivariate Cox regression analysis showed that PSAD [HR 1.5; p = 009] 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 PSA density of 0.15ng/ml/ml as cut-off value to select patients for AS. A sub analysis was done with PSAD cut-off of 0.15ng/ml/ml (Table 5.)

PSAD cut-off value of 0.15ng/ml/ml showed no correlation with PSA kinetics and subsequent repeat biopsy Gleason upgrade and positive cores (Table 5). The median PSAD was 0.13ng/ml/ml in the patients who remained on active surveillance and differed from the 0.2ng/ml/ml in the patients who progressed to treatment (p = 0.035) (Table 3). Considering the coordinates on the ROC, a PSA density cut-off at 0.13ng/ml/ml had the best balance between sensitivity and specificity. PSAD cut-off of 0.13ng/ml/ml had a sensitivity of 92.9% and a specificity of 42.5% predicting favourable disease. (Figure 1).

Table 5. PSA density cut-off of 0.15ng/ml/ml at diagnosis correlation with PSA kinetics and repeat biopsy over time.

| | **PSAD ≤ 0.15ng/ml/ml n = 33** | **PSAD > 0.15ng/ml/ml n = 21** |
|---|---|---|
| **PSA Velocity ng/ml/year** | 0.7 ( -4.21 – 15.0) | -0.5 (-5.5 – 4.3) |
| **PSA doubling time (Median) in months** | 15.0 | 10.03 |
| **Positive cores** | | |
| **1 core** | 24 (73%) | 17 (81%) |
| **> 1core** | 9 (27%) | 4 (19%) |
| **Repeat biopsy histology (n)** | | |
| **Negative (9)** | 8 (24%) | 1 (5%) |
| **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 |
| **Repeat biopsy not done (10)** | 4 | 6 |
| **Remain under AS** | 27 (82%) | 13 (62%) |

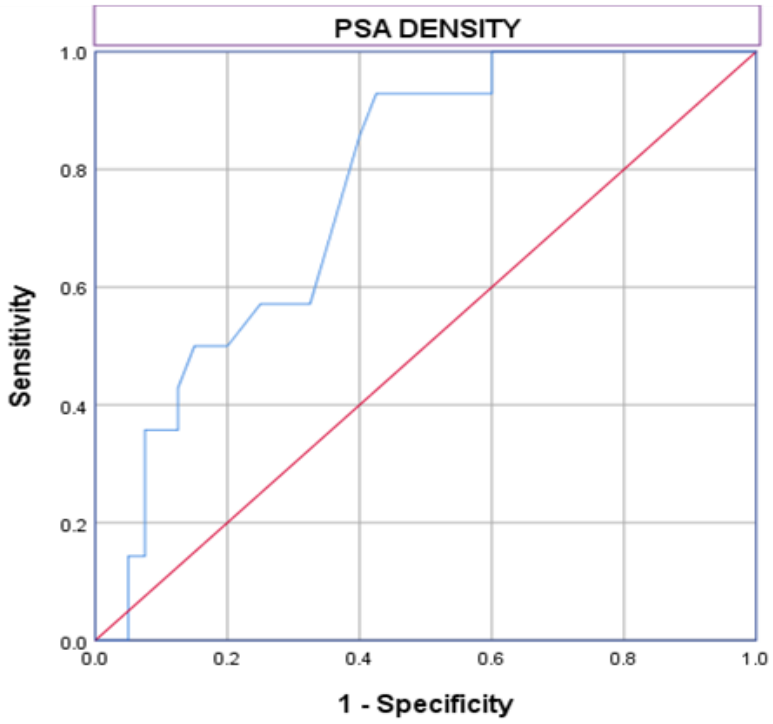



**Figure 1:** The ROC curve for PSA density. AUC = 0.766

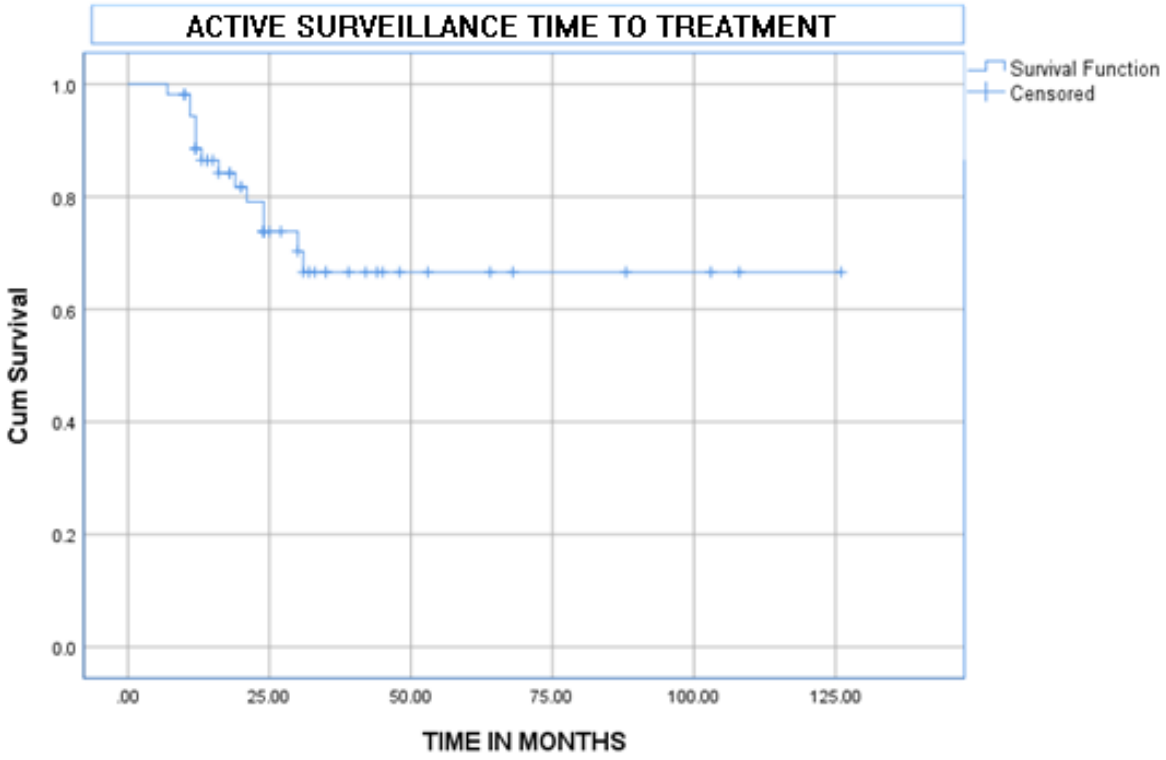
A total of 44 patients had a repeat prostate biopsy within the first 12 months after initial biopsy. Reclassification of PCa occurred in 15 (28%) patients. Increased positive cores were found in 12 (22%) and Gleason score upgrade in 3 (6%) patients, respectively. Negative repeat biopsy for cancer was found in 9 (17%) and in 20 (37%) of patients the Gleason score, positive core numbers and percentage remained unchanged (Table 6). A confirmatory or routine prostate biopsy was not done in 10 (18%) of patients.

Table: 6. Repeat biopsy and pathological outcomes.

| **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 active surveillance.

There was no difference between European and African men after a median follow up of 24 months (range 7 months to 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 to 108.5) (Figure 2.)




| Time in Months | 6 | 12 | 18 | 24 | 30 |
|---|---|---|---|---|---|
| Remained on Active surveillance (%) | 98 | 94 | 84 | 79 | 73 |

**Figure 2:** Overall treatment free rates of men on AS.

The management strategy was changed from AS to watchful waiting in 7 patients due to advancing age (>75 years), after a median follow up of 88 months. All patients were from African descent and their median age were 68 years (range 65 years to 73 years) at time of diagnosis. Their median PSA was 5.7 ng/ml (range 1.6 ng/ml to 9.8 ng/ml). All patients had a Gleason score of 6 (3+3). The median PSA density was 0.09 ng/ml/ml (range 0.05 to 0.22ng/ml/ml).

Progression to definitive treatment for prostate cancer occurred in 14/54 (26%) patients. Four patients received external beam radiation therapy and 10 patients had a radical prostatectomy

for increased Gleason grade or increased positive cores on repeat prostate biopsy and DOof 24 months (range 7 months to 126 months).

The 10 patients who had a radical prostatectomy had a median PSA density of 0.2 ng/ml/ml. Their baseline median PSA was 7.1 ng/ml (range 5.0 to 10.9ng/ml). An increase in the Gleason score of the radical prostatectomy specimen occurred in 7 (70%) of patients compared with the initial prostate biopsy Gleason score. The Gleason score increased to 7 (3+4) in 6 and 8 (4+4) in one patient. Upstaging occurred after radical prostatectomy in two patients who had extracapsular disease with seminal vesicle involvement. The PSAD of these 2 patients were 0.2 and 0.27ng/ml/ml, respectively. The indication to treat these two patients were an increase in positive cores after confirmatory prostate biopsy and not PSA kinetics. 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 radical prostatectomy. The other 8 patients treated with RP still had undetectable PSA levels at a median of 36 months follow up.

At the end of the study period 6 (9%) patients (5 African, 1 Other) were lost to follow up for unknown reasons.

**Discussion**

Considering the racial disparities in presentation, progression and outcomes of prostate cancer described in the literature, the question remains whether AS is a safe management strategy to adopt in our patient population – of which at least 70% self-identifies as African. While considering this, it is important to recognize that most studies describing prostate cancer 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 currently no evidence to suggest that AS should not be offered to African men and AS remains the accepted standard of care for men with low-risk prostate cancer according to international guidelines. African American race was 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) who evaluated 1 315 men with 89 (7%) African American and 1 226 (93%) Caucasian American men.[16]

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.[16]

Different AS protocols have been described and we decided to use the strict criteria originally described by Epstein for low-risk prostate cancer.[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 prostate cancer.[17] PSAD is higher in African American men and may influence the decision making.[18] This was also found in our study where the European men had a significant lower PSAD of 0.10ng/ml/ml compared with the 0.17ng/ml/ml of their African counterparts. Pre-treatment PSAD ≤ 0.15ng/ml/ml is recommended by different protocols. The PSAD of > 0.15ng/ml/ml is associated with a 31% upgrading of the tumour.[19]

Our study showed that a cut-off value of 0.15ng/ml/ml had less an effect on the AS outcome, histology, and PSA kinetics. PSA density was higher in men with adverse pathological outcomes. Progression to treatment was seen in this cohort who had a PSAD of 0.2ng/ml/ml, whereas men with a lower PSAD of 0.13ng/ml/ml remained on AS. PSAD cut-off value of 0.13ng/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 0.13ng/ml/ml, which is much lower than 0.19ng/ml/ml found by a much larger study.[20]

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 pathologic upstaging/upgrading rate in men with low-risk disease who undergo radical prostatectomy.[8] Pathologic progression can occur over time due to tumour de-differentiation.[21] An early confirmatory biopsy has been used to try and circumvent the initial under sampling that may occur.[22]

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 prostate cancer, 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".[23,24]

While the oncological outcomes of active surveillance are quite favourable, these outcomes are based largely on Caucasian patient cohorts, as African patients are under-represented consisting 7-10% of subjects in active surveillance series reported.[19,25] In our cohort, although small, African patients represents 65% of subjects and is one of the main strengths of this study.

In our study, 14 patients received treatment for progression upgrading on repeat biopsy (either increase in affected core number or increase in Gleason score).

These patients were managed with external beam radiation therapy and radical prostatectomy in 4 and 10 men, respectively. Six patients upgraded from Gleason 6 (3+3) to Gleason 7 (3+4) and one patient to Gleason 8 (4+4) after radical prostatectomy.

African men had higher positive core percentage 19.5% compared to 9.3% of the European men which was not found in a much larger study.[16]

Upstaging occurred in 2 men who had extracapsular disease with seminal vesical infiltration. Their PSAD at entry to AS were 0.2ng/ml/ml and 0.27ng/ml/ml respectively, reinforcing that a lower PSAD for entry into our AS program should be used.

The delayed treatment of prostate cancer in this cohort of patients had no negative effect on biochemical recurrence after RP. In 8 men who had a RP, the PSA remained undetectable after 36 months of follow up. Studies have shown that delayed RP in men with low-risk prostate cancer does not increase the risk of adverse pathology.[25,26] The two cases who 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 6 (9%) patients (5 African, 1 Other) were lost to follow up for unknown reasons. Much less 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. PSA density 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 0.13ng/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 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 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 prostate cancer and a PSA density ≤0.13ng/ml/ml irrespective of ethnicity.

**Ethical approval**

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

**Statement of Human Rights**

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.

**Statement of informed consent**

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

## Conflict of interest

The authors have no conflict of interest to declare.

## Funding

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

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# APPENDICES

## APPENDIX A: DEPARTMENT OF HEALTH APPROVAL

health
Department of Health
FREE STATE PROVINCE

04 October 2019

Dr W Dahms
Dept. of Urology
UFS

Dear Dr W Dahms

**Subject: Early results of men with low-risk, clinically localized prostate cancer on active surveillance**

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **Universitas Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** scheelatsz@fshealth.gov.za / koekoeelz@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day.**

Trust you find the above in order.

Kind Regards

**Dr D Motau**
**HEAD: HEALTH**
**Date:** 9/10/19

Head : Health
PO Box 227, Bloemfontein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfontein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemi@fshealth.gov.za/@fshealth.gov.za/chikobvup@fshealth.gov.za
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## APPENDIX B: LETTER OF CLEARANCE FROM ETHICAL COMMITTEE UFS

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

**Health Sciences Research Ethics Committee**

15-Oct-2019

Dear **Dr Willem Dahms**

Ethics Clearance: **Early results of men with low-risk, clinically localized prostate cancer on active surveillance**

Principal Investigator: **Dr Willem Dahms**

Department: **Urology Department (Bloemfontein Campus)**

**APPLICATION APPROVED**

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/0636/2910**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

**Health Sciences Research Ethics Committee**
**Office of the Dean: Health Sciences**
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
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## APPENDIX C: LETTER OF PERMISSION FROM HEAD OF DEPARTMENT

UNIVERSITY OF THE
FREE STATE
UNIVERSITEIT VAN DIE
VRYSTAAT
YUNIVESITHI YA
FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Departement Urologie

Department of Urology

PO Box 339 (G35), Bloemfontein 9300, SA
E mail: gnurvvn@ufs.ac.za and/or claassen@ufs.ac.za

Tel: (051) 4053542 Fax: (051) 444 0875

Head of Department: Prof FM Claassen

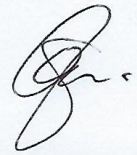
27/03/2019

**To Whom it may concern**

Dr Dahms is given permission to do research in the Department Urology in order to obtain his M.Med degree. I hereby grand permission for Dr Dahms to conduct his research in the Department and use the prostate cancer database on the department's computer.

The title: **Early results of men with low-risk, clinically localized prostate cancer on active surveillance.**

Regards



FM Claassen

## APPENDIX D: EXCEL® SPREADSHEET USED TO CAPTURE DATA

| Hospital number | Race | Age | PSA | Local stage | Number cores | Core percentage | Bx Gleason | PSA density | PSA velocity (at last visit) | PSA-DT (at last visit) | Months F/U | Repeat Bx? (number) | Repeat bx findings | Progress to Rx? | Reason for Rx | Changed to WW? | RRP pGleason | RRP pECE | RRP +SM | RRP Seminal Vesicles | RRP Lymphnodes | RRP upstaged? | Kattan post op | LOST TO FOLLOW UP? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | White = 1 | at enrolmen | initial | T1a = 1 | | 6 (3+3) = 1 | | ng/ml/year | months | | | | | | | | | | | | | | | |
| | Black = 2 | | | T1b = 2 | | 7 (3+4) = 2 | | | | | | | negative = 0 | No = 0 | Patient wish = 1 | No = 0 | 6 (3+3) = 1 | No = 0 | No = 0 | No = 0 | No = 0 | No = 0 | 7yr progr | 0= No |
| | Coloured = 3 | | | T1c = 3 | | 7 (4+3) = 3 | | | | | | | unchanged = 1 | RRP = 1 | Unfavourable PSA kinetics = | Yes = 1 | 7 (3+4) = 2 | Yes = 1 | Yes = 1 | Yes = 1 | Yes = 1 | Yes = 1 | free probabili | 1 = Yes |
| | Other = 4 | | | T2a = 4 | | | | | | | | | increase cores = 2 | EBRT = 2 | Advancing local stage = 3 | | 7 (4+3) = 3 | Not specified = 3 | | | | | % | |
| | | | | T2b = 5 | | | | | | | | | GI increase 3+4 = 3 | ADT = 3 | Bx increase cores = 4 | | 8(4+4) = 4 | | | | | | | |
| | | | | | | | | | | | | | GI increase 4+3 = 4 | | Bx increased grade = 5 | | 9(4+5) = 5 | | | | | | | |
| | | | | | | | | | | | | | GI increase 4+4 = 5 | | Metastases = 6 | | 9(5+4) = 6 | | | | | | | |
| | | | | | | | | | | | | | GI increase 9 or 10 = 6 | | | | 10 (5+5) = 7 | | | | | | | |

## APPENDIX E: HSREC APPROVED PROTOCOL

**Title:**

**Early results of men with low-risk, clinically localized prostate cancer on active surveillance.**

**Researchers**

W Dahms, JJ Myburgh, FM Claassen. Department of Urology, University of the Free State.

**Introduction**

Prostate cancer is the second most incident cancer and is the fifth leading cause of cancer death among men worldwide.[1] South African men have a lifetime risk of 1 in 19 of developing prostate cancer and this cancer is the most common histologically diagnosed cancer in men according the National Cancer Registry.[2] In the era of widespread prostate cancer screening with prostate specific antigen (PSA), the incidence has increased markedly over time. The negative outcome of prostate cancer screening was an increased diagnosis of low-risk prostate cancer particularly among young men. Low-risk prostate cancer is defined as clinical stage T1-T2a, serum PSA level < 10ng/ml and Gleason score ≤ 6.[3] It is well known that low- risk localized prostate cancer may pursue a relatively indolent course as autopsy studies have demonstrated. These autopsies found prostate cancer in up to 50% of men who died of non-prostate related causes.[4] The earlier detection of prostate cancer as a result of screening resulted in the over treatment of earlier stage, less aggressive tumors which otherwise would have had an indolent course. Overtreatment of prostate cancer has been recognized as a growing concern due to patients who receive surgery or radiation therapy, but are unlikely to benefit due to low risk disease or limited life expectancy.[5] Treatment concerns are appropriately based on significant morbidity and functional impairment including urinary incontinence and erectile dysfunction that is associated with definitive treatment for prostate cancer.[7,8]

To date, no prospective randomized trial has shown an overall survival benefit to any of the therapeutic options for organ-confined disease—i.e., active surveillance, brachytherapy, external-beam radiation, or surgical radical prostatectomy. Approximately 45% of men with screening-detected localized prostate cancer are candidates for deferred treatment or active surveilance.[6] Previously Epstein *et al*. used a prostate cancer criteria associated with so called pathologically insignificant tumors (volume ≤ 0.5cm and Gleason sum ≤ 6) that would pose little threat to an individual's life and could refrain from significant morbidity that is associated

with treatment of prostate cancer. Evidence from prospective observational series and randomized controlled trials have all demonstrated that conservative management of low-risk prostate cancer does not significantly impact mortality when compared to active intervention.[9] These observations have led to a shift in the paradigm in the management of prostate cancer so that younger, healthier men with less aggressive prostate cancer can be encouraged to enroll in such a surveillance program.

Active surveillance involves the identification and close follow up of men with low risk disease. Treatment with curative intent is only administered when predefined thresholds indicative of potentially life threatening, but still curable disease in men with adequate life expectancy is present or on patient request. Active surveillance is becoming a popular modality in treatment centers.[10] In a study done in the United States of America 2001, only 6.2% of men with low-risk prostate cancer were initiated on active surveillance or watchful waiting. By 2010, 40% of all low-risk prostate cancer have been placed on surveillance, and this figure was up to 76% in men over 75, with low-risk disease, as demonstrated in a large multi-center clinical study.[10]

Most centers use either changes in PSA kinetics (the rate PSA increase over time) or adverse pathological findings on biopsy as triggers for intervention. While no standardized protocol exists, patients are usually followed up with a 3-6 monthly PSA and digital rectal examination.[11] Because of this limitation with PSA kinetics, prostate biopsies are repeated every 1-3 years. A significant proportion of men up to 30%, are under staged or under graded in active surveillance demonstrated from post prostatectomy specimens. [14] The oncological outcomes of active surveillance for men with very-low-risk prostate cancer are overall excellent. Five year survival approaches 100%, with 20-33% ultimately undergoing treatment.[12] Active surveillance has been included in the guidelines of all the major urological organizations including the European Association of Urology, the American Urological Association and the National Comprehensive Cancer Network.[13,14,15]

However, while the oncological outcomes of active surveillance are quite favorable, these outcomes are based largely on Caucasian patient cohorts, as black men are under-represented consisting of 7-10% of subjects in active surveillance series reported.[16,17] Despite the growing popularity of active surveillance for low-risk patients, increasing evidence has emerged questioning the safety of this approach in minority populations in American and European studies, particularly African Americans.[18] There is concern over the implementation of an

active surveillance protocol in our predominantly black population. This concern is justifiable as data emerges which suggests that patients of African ancestry may experience earlier disease progression while under active surveillance.[19]

There are relatively few studies investigating the results of active surveillance in African American men. These studies have different inclusion criteria for active surveillance and different follow-up strategies and different end points. These studies strongly suggest a biological difference that is partly responsible for more aggressive disease observed in African American men.[20, 21]

Limited data are available pertaining to prostate cancer within Africa. Determining the burden of prostate cancer within the continent has been problematic and compounded by a lack of unified systems of monitoring and reporting.[21] Because of the extensive literature on racial differences in prostate cancer among men in America and Europe and the lack of such studies in African countries, the essential question can be asked: if prostate cancer is generally more aggressive and deadlier for African American men, is it safe to consider active surveillance for these "higher" risk patients in South Africa? We set out to describe our patient population in the Free State Province, South Africa, that is enrolled in active surveillance for prostate cancer at Universitas Academic Hospital.

**Question and Aim**

The question remains if it is safe to consider active surveillance for low-risk prostate cancer in men from the Free State. The aim of this study is to describe the patient profiles as well as the results obtained of men who are on active surveillance for low grade prostate cancer at Universitas Academic Hospital in Bloemfontein.

**Methodology**

**Study design**

A retrospective descriptive study will be done using the active surveillance database in the Department of Urology from 2010 to 31 July 2019. The files of the patients on the active surveillance database will be retrospectively reviewed. No patients will be seen or prospectively followed up.

**Study population and Sample size**

The population studied will consist of all the men who were offered active surveillance for their low risk prostate cancer from 2010 to 31 July 2019.

**Inclusion criteria**

Men with the following prostate criteria were offered active surveillance on the active surveillance database:

1. PSA lower than 10 ng/ml.
2. PSA density of less than 0.15ng/ml.
3. Gleason score of 6 (3+3) on 2 needle cores or less.
4. All the men had a follow-up prostate biopsy within 12 months of initial diagnosis.

**Exclusion criteria**

1. Patients who refused active surveillance as an option for low risk prostate cancer.
2. Patients on active surveillance lost during their follow-up.
3. Incomplete patient folders.

The expected number of participants will be 50 men on the prostate cancer data base.

**Measurement**

The patient profile which will include race, age, clinical stage, PSA, PSA kinetics, PSA density, Gleason Grade, doubling times, positive biopsy cores will be determined and documented. The histology (Gleason Grade) of the diagnostic prostate biopsies will be compared with the Gleason Grade of subsequent prostate biopsies. If a radical prostatectomy was done the histology will be compared to that of the biopsy. The data of the men who opted for active surveillance will be collected by the principal investigator Dr W Dahms. The information captured will be patient age, clinical stage, initial PSA, PSA velocity, PSA density and Gleason Grade.

**Data analysis**

The principal investigator Dr Dahms will enter the data into Excel (appendix 1). Once data is captured it will be analyzed by the help of Department Biostatistics UFS. Results will be summarized by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables).

**Methodological and Measurement errors.**

The data interpretation will not be biased as the data of the men on active surveillance for their low risk prostate cancer will be collected and interpreted by the principal investigator Dr Dahms.

**Pilot study**

A pilot study of the first 10 men on active surveillance, from the database from 2010, will be performed in order to determine the feasibility of the study and to determine if the data collection is appropriate. These cases will be included in the main study.

**Implementation of findings**

The information from this study will be valuable and may answer the question if active surveillance is a safe option for men in central South Africa and be offered safely.

**Time Schedule**

The plan is to submit the protocol to the ethics committee in May 2019. When written approvals is received from the ethics committee and the Free State Department of Health the collection of data will begin. The data collection will commence in October 2019 after HSREC approval obtained. Analysis of data to be done by Department of Biostatistics at the end of November 2019. The plan is to complete this study by January 2020.

**Budget**

The estimated cost will be R1950 which will be covered by the department of Urology. These costs will be the printing of the prostate cancer data-base information from Meditech.

**Ethical aspect**

Ethical approval for this study will be obtained from the Health Sciences Research Ethics Committee of the University of the Free State before commencing the study.

Permission will be obtained from the Free State Department of Health.

Confidentiality of data will be ensured, and no patients names or hospital numbers used during the study.

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CHAPTER 2: ARTICLE SUBMITTED TO THE SOUTH AFRICAN JOURNAL OF MEDICINE

Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

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ABSTRACT

Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

Authors: Willem Dahms, Josephus J Myburgh, Frederik M Claassen

**Introduction and objective:** To report the outcome of active surveillance (AS) offered to men with low grade prostate cancer (PCa) at Universitas Academic Hospital in Bloemfontein, South Africa.

**Materials and Methods:** Men with PCa with a Gleason score of 6 (3+3) on 2 needle cores or less, clinical stage cT2a and less, and prostate specific antigen (PSA) lower than 10 ng/ml were offered active surveillance. Variables such as age, 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 was offered routinely within 12 months of initial diagnosis or in case of unfavourable PSA kinetics. Patients older than 70 years with low-intermediate risk were also included.

Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

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3. Your work meets all Research Ethics and Reporting Standards**.** Many study types require a workflow as a figure and/or a completed checklist uploaded as a supplementary file for peer review. Visit here to see if your study type requires a workflow and/or checklist.
4. Your figures are of acceptable quality and uploaded as separate files. **Line art should be 900-1200 DPI, images 300 DPI.** Images should be minimally processed to uphold their original integrity. More figure information here.
5. Your references are formatted correctly and numbered as they appear in the text. Please visit here for reference style.
6. Data and complete methods should be made available so that others may replicate your study. If applicable, please see here for more information and data repositories.
7. Authors must have an understanding and agreement to pay any applicable article processing charges (APCs).
8. Only manuscripts of sufficient quality that meet the aims & scope of the journal will be reviewed.
9. Full guidelines are below**. Submissions that don't adhere to these instructions will be returned prior to peer review.**

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## 3. What do we publish?

### 3.1 Aims & scope

Before submitting your manuscript to *Cancer Control*, please ensure you have read the Aims & Scope.

### 3.2 Article types

At the time of submission, authors are required to answer three questions, which will be
incorporated into a "highlights" section at the beginning of the published article.

- What do we already know about this topic?
- How does your research contribute to the *Cancer Control* field?
- What are your research's implications towards theory, practice, or policy

**Original Research Papers**

While there are no strict formatting requirements all manuscripts must still contain abstract,
introduction, materials and methods, results, and discussion/conclusion sections.

Please make sure the abstract is a paragraph of fewer than 250 words. The primary goal of the
abstract should be to make the general significance and conceptual advance of the work clearly
accessible to a broad readership. References should not be cited in the abstract.

We also ask that you provide 5-10 keywords for indexing purposes.

In the Materials & Methods section, describe the selection of patients or experimental animals,
including controls. Do not use patient's names or hospital numbers. Identify methods, apparatus
(manufacturer's name and address), and procedures in sufficient detail to allow other workers
to reproduce the results. Provide references and brief descriptions of methods that have been
published. When using new methods, evaluate their advantages and limitations. Identify drugs
and chemicals, including generic name, dosage, and route(s) of administration.
Results should be presented in a logical sequence in tables and illustrations. In the text,

explain,
emphasize or summarize the most important observations. Units of measurement should be
expressed in accordance with Systeme International Unites (SI Units).
In the discussion do not repeat in detail data given in the Results section. Emphasize the new
and important aspects of the study. Relate observations to other relevant studies. On the basis
of your findings (and others), discuss possible implications/conclusions. When stating a new
hypothesis, clearly label it as such.

There is no limit for references.

Tables should be numbered consecutively with Arabic numerals and include descriptive titles
and legends

Figure legends should be concise, yet descriptive so that the reader can clearly interpret the
results being presented.

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These are short experimental papers that may present as little as a single experiment or observation. Brief Reports should constitute unusually interesting data combined with a discussion of what the data might mean, or an explanation of why the data contradicts current
paradigms.

The abstract includes a single paragraph of fewer than 150 words. The primary goal of the abstract
should be to make the general significance and conceptual advance of the work clearly accessible to a broad readership. Please include 5-10 keywords for indexing purposes.

**Reviews**

Reviews should be recognized as scholarly by specialists in the covered field, but should
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and should be presented using simple prose. Please avoid excessive jargon and technical detail. Reviews should capture the broad developments and implications of recent
work. The opening paragraph should make clear the general thrust of the review and provide a
clear sense of why the review is now particularly appropriate. The concluding paragraph should
provide the reader with an idea of how the field may develop or future problems to be overcome, but should not summarize the article. To ensure that a review is likely to be

accessible to as many readers as possible, it may be useful to ask a colleague from another discipline to read the review before submitting it. Submitted reviews are subject to the same charges as original papers -- whether APCs will apply for commissioned reviews will be made clear when each review is commissioned. Reviews should include an abstract of 150 words and should cite no more than 150 references. Please include 5-10 keywords for indexing purposes.

**Auto-commentaries**

The Editor or Editorial Board will solicit authors of the most significant recent and forthcoming papers, published elsewhere, to provide a short summary with additional insights, new interpretations or speculation on the relevant topic. These manuscripts may include data or models, which due to space limitations were not included or discussed in the original paper. In other words, the authors may provide biased and uncensored points of views, complementing their article.

Please include an abstract of 150-200 words and 5-10 keywords for indexing purposes. The citation for the original article including the full author list, title of article and journal information should be included on the title page. The typical length of an auto-commentary will be approximately 500-1,000 words and may include up to 30 references.

**Commentaries and Views**

Commentaries and/or views may be short and focused opinion articles, commentaries on papers recently published in JOURNAL TITLE or elsewhere, or commentaries on significant conceptual changes, important trends or new directions in the field. These may include figures and up to 30 references. Please include an abstract of 150-200 words and 5-10 keywords for indexing purposes.

**Journal Club**

Journal Club articles to include descriptions and critiques of major advances published in other leading journals. This will be modeled after and driven by journal club presentations held in most institutions around the country.

**Technical Papers**

Technical papers contain original research, however, they differ from Research Papers in that
they describe new approaches, methods, or reagents rather than new understanding of a natural molecule or biological process. Papers may be submitted as either Technical or Research Papers, but the assignment to either category is the discretion of the Editors. All
submissions will be peer reviewed.

**Letters to the Editor**

Letters to the Editor should consist of one or two paragraphs totalling no more than 500 words,
no abstract, no subheadings and fewer than 8 references (one author, et al., no titles). If an
abstract is included, it will automatically be made the first paragraph. Letters should not include
figures or research material. Letters to the editor are not charged an APC.

A letter to the editor is a brief communication that addresses the contents of a published article.
Its purpose is to make corrections, provide alternative viewpoints, or offer counter-arguments. Avoid
logical fallacies and ad hominem attacks. Letters to the editor must be written in a professional tone
and include references to support all claims if appropriate.

**Validation Studies**

Validation or Replication studies can be submitted to the journal. These should be carried out to validate that a scientific finding is accurate, reliable and reproducible. These may be written in the style of a Brief Communication or a Research Paper with a brief introduction.

**3.3 Writing your paper**

The SAGE Author Gateway has some general advice and on how to get published, plus links to further resources.

**3.3.1 Making your article discoverable**

When writing up your paper, think about how you can make it discoverable. The title, keywords and abstract are key to ensuring readers find your article through search engines such as Google. For information and guidance on how best to title your article, write your abstract and select your keywords, have a look at this page on the Gateway: How to Help Readers Find Your Article Online.

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## 4. Editorial policies

### 4.1 Peer review policy

Following a preliminary triage to eliminate submissions unsuitable for *Cancer Control* all papers
are sent out for review. The covering letter is important. To help the Editor in his preliminary evaluation, please indicate why you think the paper suitable for publication.

The journal's policy is to have manuscripts reviewed by two expert reviewers. *Cancer Control*
utilizes a double-blind peer review process in which the reviewer and authors' names and information are withheld from the other. All manuscripts are reviewed as rapidly as possible while maintaining rigor. Reviewers make comments to the author and recommendations to the
Section Editor and Editor-in-Chief who then makes the final decision.

The Editor or members of the Editorial Board may occasionally submit their own manuscripts for
possible publication in the journal. In these cases, the peer review process will be managed by
alternative members of the Board and the submitting Editor / Board member will have no involvement in the decision-making process.

### 4.2 Authorship

Papers should only be submitted for consideration once consent is given by all contributing authors. Those submitting papers should carefully check that all those whose work contributed
to the paper are acknowledged as contributing authors.
The list of authors should include all those who can legitimately claim authorship. This is all those who:

(i) Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,
(ii) Drafted the article or revised it critically for important intellectual content,
(iii) Approved the version to be published,
(iv) Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the
content.

When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully
meet the criteria for authorship.

Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship, although all contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section. Please refer to the International Committee of Medical Journal Editors (ICMJE) authorship guidelines for more information on
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All contributors who do not meet the criteria for authorship should be listed in an Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, or a department chair who provided only general support.

#### *4.3.1 Third party submissions*

Where an individual who is not listed as an author submits a manuscript on behalf of the author(s), a statement must be included in the Acknowledgements section of the manuscript and in the accompanying cover letter. The statements must:

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It is the policy of *Cancer Control* to require a declaration of conflicting interests from all authors enabling a statement to be carried within the paginated pages of all published articles. Please ensure that a 'Declaration of Conflicting Interests' statement is included at the end of your manuscript, after any acknowledgments and prior to the references. If no conflict exists, please state that 'The Author(s) declare(s) that there is no conflict of interest'.

For guidance on conflict of interest statements, please see the ICMJE recommendations.

**4.6 Research ethics and patient consent**

IMPORTANT: If you are reporting on animal and/or human studies, please ensure that you include a section on research ethics and, where applicable, patient consent, at the end of your manuscript.

Medical research involving human subjects must be conducted according to the World Medical Association Declaration of Helsinki.

Submitted manuscripts should conform to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, and all papers reporting animal and/or human studies must state the relevant Ethics Committee or Institutional Review Board provided (or waived) approval. Please ensure that you have provided the full name and institution of the review committee, in addition to the approval number.

For research articles, authors are also required to state whether participants provided informed consent and whether the consent was written or verbal.

Information on informed consent to report individual cases or case series should be included in the manuscript text. A statement is required regarding whether written informed consent for patient information and images to be published was provided by the patient(s) or a legally authorized representative. Please do not submit the patient's actual written informed consent with your article, as this in itself breaches the patient's confidentiality. The Journal requests that you confirm to us, in writing, that you have obtained written informed consent but the written consent itself should be held by the authors/investigators themselves, for example in a patient's hospital record. The confirmatory letter may be uploaded with your submission as a separate file.

Please also refer to the ICMJE Recommendations for the Protection of Research Participants

All research involving animals submitted for publication must be approved by an ethics committee with oversight of the facility in which the studies were conducted. The journal has adopted the Consensus Author Guidelines on Animal Ethics and Welfare for Veterinary

Journals
published by the International Association of Veterinary Editors.

### 4.7 Clinical trials

*Cancer Control* conforms to the ICMJE requirement that clinical trials are registered in a WHO-approved public trials registry at or before the time of first patient enrolment as a condition of consideration for publication. The trial registry name and URL, and registration number must be included at the end of the abstract.

### 4.8 Reporting guidelines

The relevant EQUATOR Network reporting guidelines should be followed depending on the type
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a completed CONSORT flow chart as a cited figure and the completed CONSORT checklist should
be uploaded with your submission as a supplementary file. Systematic reviews and meta-analyses
should include the completed PRISMA flow chart as a cited figure and the completed PRISMA checklist should be uploaded with your submission as a supplementary file. For observational studies in epidemiology (cohort, case-control, cross-sectional studies) the completed STROBE checklist should be uploaded with your submission as a supplementary file. The
EQUATOR wizard can help you identify the appropriate guideline.

Other resources can be found at NLM's Research Reporting Guidelines and Initiatives.

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Where relevant, *Cancer Control* encourages authors to share their research data in a suitable public
repository subject to ethical considerations and to include a data accessibility statement in their manuscript
file. Authors should also follow data citation principles. For more information please visit the SAGE Author
Gateway, which includes information about SAGE's partnership with the data repository Figshare.

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## 5. Publishing policies

### 5.1 Publication ethics

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refer to the Committee on Publication Ethics' International Standards for Authors and view the
Publication Ethics page on the SAGE Author Gateway.

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## 6. Preparing your manuscript

### 6.1 Word processing formats

The preferred format for your manuscript is Word. LaTeX files are also accepted. Word and (La)Tex templates are available on the Manuscript Submission Guidelines page of our Author Gateway.

### 6.1.1 Title and Authors (On a separate title page)

- The title should be in upper and lower case (Do not use all UPPERcase)
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- and degree(s)
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### 6.1.2 Manuscript preparation

**Abstract**
The abstract should be 250-300 words and should reflect the results. Describe the purpose of the study and briefly explain how the study was performed. Summarize the most important observations and their significance. Do not use abbreviations in the abstract.

**Keywords**
Following the abstract, please list 5-6 keywords for indexing the article. Keywords, along
with the abstract and title, are central to ensuring that readers can search for and find your article online. For this reason, to aid in search-ability, words in the title should not be used as keywords. For keyword suggestions, please visit the National Library of Medicine's Medical Subject Headings (MeSH®) website.

**Abbreviations**
Please include a list of all abbreviations used in the manuscript. These should be listed in alphabetical order. (Example: MRI, Magnetic Resonance Imaging; RT, Radiation Therapy)

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Provide background that allows readers outside the discipline to understand the significance
of the study. Include a brief review of important literature in the relevant field. References cited should be in parentheses ( ).

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Please do not use numbering or subheadings. Describe in detail any new methods or protocols used, in order that other investigators can replicate the study. Older, better known
methods may be cited in references but should be described enough that the reader may understand the method.

**Specific Reporting Guidelines**
Medical research involving human subjects must be conducted according to the World Medical Association Declaration of Helsinki. Submitted manuscripts should conform to
the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, and all papers reporting animal and/or human studies must state in the methods section that the relevant Ethics Committee or

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Explain how the results relate to the premise of the study especially in relation to previous related studies and how the present study results might have potential in directing future research.

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Describe the interpretation of the data.

**Conclusion (Optional)**
Avoid overemphasizing the conclusion.

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List the names of the individuals along with the contributors who have participated in some capacity but cannot be qualified as authors.

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Disclose if any funds were received to conduct the research.

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## 7. Submitting your manuscript

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## 8. On acceptance and publication

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## 9. Further information

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# Submission Confirmation

Print

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CCX-20-0504

**Title**
Early results of South African men with low-risk, clinically localized prostate cancer managed with active surveillance.

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