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Prostate Cancer

Review

Active surveillance for prostate cancer: Is it ready for primetime in the Caribbean?



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Abstract

Objective: In this paper we discuss the strategy of active surveillance (AS) as a whole followed by the implications of its use in the Caribbean.

Methods: The literature was reviewed with a view to establishing the merits of AS and to identify potential pitfalls in the application of AS among a primarily black population.

Results: Active surveillance (AS) has emerged as a viable treatment strategy aimed at reducing overtreatment of indolent disease. However, there have been concerns raised over the applicability of AS among men of African descent. Black men are at higher risk of aggressive disease and data are emerging which suggest outcomes may not parallel those of their white counterparts. Recent advances such as multiparametric MRI and genetic testing have the potential to guide decision making in these men.

Conclusion: Active surveillance should not be universally rejected in black men and perhaps further study is needed to determine race-specific recommendations. Until then, discussion with the patient should reflect the potential pitfalls for black men on active surveillance.

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It is well known that localized prostate cancer may pursue a relatively indolent course as autopsy studies have revealed that prostate cancer may be found in up to 50% of men who died of non-prostate related causes [1]. In the era of PSA screening, there has been an

increased detection of early stage and less aggressive tumors and as a result, many low risk malignancies are therefore over treated. Active surveillance has emerged as one strategy to circumvent this. It involves the identification and close followup of men with low risk disease – treatment with curative intent is only administered upon clinical progression or patient request. Active surveillance has now been included in the guidelines of several major organizations including the American Urological Association [2], European Association of Urology [3] and the National Comprehensive Cancer Network [4].

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Table 1 Active surveillance inclusion criteria. The Royal Marsden Group (Van As et al.) has less stringent criteria than the others.

Author	Clinical stage	PSA	Gleason grade	Positive cores	Other
Carter et al., 2007 [7]	≤T2a	–	≤6	≤2	PSAD ≤0.15
Dall’Era et al., 2008 [8]	≤T2a	≤10	≤6	≤33%	
Berglund et al., 2008 [9]	≤T2a	≤10	≤6	≤3	–
van As et al., 2008 [10]	≤T2a	≤15	≤7	≤50%	
Soloway et al., 2008 [11]	≤T2a	≤10	≤6	≤2	
Klotz et al., 2010 [12]	–	≤10	≤6	–	

First described in 1994, and updated in 2004, The Epstein criteria are used to identify low risk cancers [5,6]. Features of insignificant disease according to the criteria include – Gleason sum ≤6, PSA density <0.15, no more than 2 cores positive with ≤50% involvement of any one core and stage ≤T1c. While various selection protocols are described, criteria from most large centers, with the odd exception, have a few common features—Gleason score ≤6, Stage ≤T2a and PSA ≤10 [7–12] (Table 1). While not a part of surveillance protocols at the moment, volume of tumor has been proposed as another tool in calculating risk. Data from the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial suggest that total volume of ≤1.3 cm³ is predictive of low risk disease [13]. However, it has been noted that active surveillance criteria perform poorly in men of African descent compared to whites [14].

Most centers use either changes in PSA kinetics or adverse pathological features on biopsy as triggers for intervention. Patient request is also an indication for intervention. While no standardized protocol exists, patients are usually followed with 3–6 monthly PSA measurements and digital rectal examinations [15]. The role of PSA in active surveillance protocols is controversial with several authors, among large cohorts, finding little change in PSA kinetics even with histological evidence of progression [16,17]. Nonetheless, a number of large institutions still list various derivatives of PSA among their primary triggers for intervention. For example, Klotz et al. at the University of Toronto use a PSA doubling time of <3 yrs while the Memorial Sloan Kettering group uses a PSA >10 ng/ml [9,12]. The Royal Marsden Group uses a PSA velocity of >1 ng/ml/yr as a trigger for intervention [10]. Ng et al. demonstrated a PSA velocity of 2 ng/ml/yr was significantly associated with an increase in Gleason score [18].

Bearing in mind the potential limitations with PSA kinetics, biopsies are repeated every 1–3 years but may be done as early as 3 months [15]. Data garnered from post prostatectomy specimens in active surveillance patients have confirmed that a significant proportion of men are understaged or undergraded and it is estimated that this risk may be in the order of 20–30% [15]. Progression of Gleason grade may be ascribed either to tumor de-differentiation or to undersampling of the gland and may likely represent a combination

of the two. Adamy and colleagues at Memorial Sloan-Kettering Cancer Center demonstrated that early rebiopsy of men on active surveillance within 3 months, resulted in upstaging of 35% [19]. In the PRIAS group the authors also found that 21.5% of men were no longer eligible for active surveillance following early repeat biopsy [20]. Therefore, one strategy employed by some centers such as MSKCC to combat understaging is the use of early confirmatory biopsies, usually within 3 months [9]. Pathological progression on repeat biopsy, that is, increase in Gleason grade, number of positive cores or percentage of involvement of each core, constitute grounds for discontinuation of surveillance [15]. It is our practice to rebiopsy patients at 12 months and we have not adopted the strategy of early rebiopsy.

As mentioned above progression may be defined as changes in PSA with time or increases in the volume or grade of cancer on surveillance biopsy. Dall’Era suggests that “progression” may in fact be “reclassification” as more of the prostate is sampled with surveillance biopsies. Nonetheless, with progression or reclassification beyond the initial entry criteria, immediate curative treatment is offered. Some men may elect treatment even with no change to their status [15].

Outcome data are available from several large institutional studies and are very encouraging for the strategy as a whole. Five-year survival approaches 100%, with 20–33% ultimately undergoing treatment. These results are perhaps best summarized in a tabular format (Table 2). With the exception of the groups from Miami and Johns Hopkins, an analysis of outcomes as a function of race is not forthcoming in most series.

There is concern over the applicability of active surveillance protocols to our predominantly black population. This concern is justifiable as data are emerging which suggest that patients of African ancestry may experience earlier disease progression while under surveillance [14]. What is more worrisome is that these patients have been noted to have more aggressive disease at prostatectomy which may compromise long-term cancer related outcomes. This propensity to progress and progress with aggressive disease may make curative treatment challenging and seems to go against the whole premise of active surveillance.

Table 2 Outcome data from various active surveillance cohorts.

Institution/author	No. treated (%)	Median time to Rx (yrs)	10-year cancer specific survival
Johns Hopkins/Tosoian et al., 2011 [21]	255 (33)	2.2	100
USCF/Cooperberg et al., 2011 [22]	113 (30)	3.5	100
University of Toronto/ Klotz et al., 2010 [12]	135 (30)	N/R	97
University of Miami/Soloway et al., 2010 [23]	67 (20)	2.6	100
Royal Marsden/van As et al. [10]	65 (20)	1.3	100

The burden of prostate cancer mortality is high within the Caribbean territories. In Jamaica the annual incidence rate has been reported to be as high as 304 per 100,000 [24]. In Barbados the incidence rate has been estimated at 160.4 per 100,000 [25] while in Tobago the prevalence of prostate cancer among men who were screened was 10% [26]. In Trinidad and Tobago prostate cancer is the leading cause of cancer mortality, accounting for 38% of cancer related deaths among men (Data, Trinidad and Tobago Cancer Registry). The Caribbean collectively has the highest prostate cancer mortality in the world [27].

Correspondingly, the Caribbean has a large black population. In Jamaica 91% of the population are of African descent [28] while in Tobago this number is 94% [26]. The increased risk of prostate cancer among black men in the Caribbean, likely, reflects an increased genetic susceptibility of the race as similarly high incidence rates have been noted in black populations in the United States of America and the United Kingdom [26,28,29]. In a recent study at our institution, it was noted that blacks were more likely to present with higher PSA values – 27.5% of blacks had a PSA greater than 100 ng/ml compared to 10.6% of Indians ($p < 0.001$). Blacks were also more likely to have higher Gleason scores [30].

The biology of prostate cancers in the black male may place him at increased risk of progression while on active surveillance. Among 131 men Kim looked at the expression of several biomarkers which were associated with progression (e.g. Ki67, androgen receptor, and alpha-methylacyl CoA racemase) and compared them as a function of race. All markers were expressed at higher levels among blacks suggesting that their disease may be more biologically aggressive [31]. In a study of 1056 men, Powell and colleagues reported on clinicopathological characteristics of subclinical prostate cancer at autopsy, comparing them to post prostatectomy specimens. These authors noted that while pathologic findings were similar between blacks and whites at autopsy, blacks were more likely to have higher Gleason scores and tumor volume at prostatectomy [32]. These findings led the authors to conclude that prostate cancer may become aggressive earlier in the black male.

Sanchez-Ortiz and colleagues looked at the post-radical prostatectomy specimens of 37 African-American and 35 white men, matching them for age, PSA, clinical stage and prostate weight with all having cT1c disease. The authors demonstrated that that Gleason score and tumor volume were significantly higher in black males [33]. Similarly, in a recent multi-institutional study Ha et al. compared clinicopathological characteristics of black vs. white males who underwent radical prostatectomy while in an active surveillance program. Black men were more likely to be upstaged at prostatectomy ($\geq pT3$) than their white counterparts (19.4% vs. 10.1%). These findings point to the fact that black men may easily be misclassified as low risk using current active surveillance protocols [34].

In a retrospective study, Sundi et al. reported on pathological characteristics among a cohort of 256 African-American and 1473 white men who underwent radical prostatectomy and also satisfied the National Comprehensive Cancer Network (NCCN) criteria for active surveillance. The authors found that African-American men were more likely to have disease upgrading (27.3% vs. 14.4%) as well as a higher rate of positive margins (9.8% vs. 5.9%). African-Americans also had higher Cancer of the Prostate Risk Assessment (CAPRA) scores (14.8% vs. 6.9%). On multivariate

analysis African-American race was independently associated with adverse pathological features [35].

What are the implications of this data for black men on active surveillance? Of 272 men enrolled in an active surveillance program in Miami 64 progressed. Twenty-four African American men were enrolled in the study of whom 14 progressed (58.3%) compared to 50 of 225 (22.2%) white males. The rate of progression was almost 3 times as great among African American men [36].

Recently, Abern and colleagues at Duke University reported on their review of 145 patients in which they investigated the impact on race on the outcome of patients on active surveillance particularly as it related to discontinuation of surveillance for treatment. The cohort comprised 32 (22%) black men. When adjusted for socioeconomic status and clinical parameters, black race was associated with a higher rate of discontinuation of active surveillance for treatment, with a hazard ratio of 3.08 [37].

It is clear from the body of evidence so far that active surveillance is a legitimate treatment option in the management of prostate cancer which can prevent “over treatment” in many men. However, the data as it relates to the black race point to significant clinical considerations for the black Caribbean man on active surveillance. For starters, the increased risk of progression while on observation should be fully discussed with the patient. He should be counseled that outcomes in his race may not parallel those published from large active surveillance cohorts. In addition, Ha suggested that criteria for entry in to active surveillance should be amended to reflect the fact that black patients are at higher risk of being upgraded and upstaged at prostatectomy, that is, they are at higher risk of having either their disease characteristics underestimated at the time of entry into active surveillance programs or of truly developing aggressive disease. The authors suggest more stringent criteria utilizing a maximum of one core or using a lower PSA cutoff [34]. Given that misclassification of risk seems to be greater in this group, Iremashvili and colleagues urge more extensive biopsy protocols along with intensified followup for earlier detection of progression [36]. Following the publication of Dr Sundi’s paper cited above, the team at Johns Hopkins also called for the development of race-specific entry criteria.

Recently, magnetic resonance imaging has emerged as a potential adjunct to improve accuracy in classifying men for active surveillance. Park and colleagues recently reviewed 298 men who underwent radical prostatectomy and who fit the PRIAS active surveillance criteria. Approximately 7% of patients were upstaged and 46% were upgraded at surgery; patients with visible disease were more likely to have their disease upgraded [38]. Similarly, in a cohort of 388 men with low risk prostate cancer, Vargas and colleagues noted that MRI imaging scores, indicative of tumor visibility, correlated significantly with the risk of upgrading on confirmatory biopsy while on active surveillance. That is to say, highly visible tumors were much more likely to be upgraded on subsequent biopsy [39]. Margel also found that risk of reclassification was much less when no tumor was visualized on MRI [40]. In a small study which requires further validation, Stamatakis and colleagues using morphological and functional characteristics of the lesion on MRI, derived a nomogram which may predict disease reclassification. Number of lesions, lesion density and lesion suspicion were associated with disease reclassification [41]. This was a small study of 85 men and the authors readily acknowledge the need for validation

of the study. The use of MRI as part of active surveillance selection criteria is an evolving field which holds much potential, particularly so among a population such as ours. The application of MRI in the Caribbean poses a challenge for a region with high disease burden and limited access to MRI facilities.

Genetic testing as well as serum and urinary biomarkers may in the future assist with more accurate stratification of these men. Urinary PCA-3 and the TMPRSS-ERG fusion gene have been studied for this purpose. Li recently demonstrated that both of these markers were associated with higher volume disease [42]. Klein and colleagues have also recently validated a multigene test called the Genomic Prostate Score (GPS) for its ability to more accurately predict men with high grade and high stage disease. 17 genes were identified and combined to form the GPS algorithm [43]. This is indeed exciting but, as with MRI, its application in an often resource poor setting such as ours will be a challenge.

Although active surveillance should not be universally rejected in Black men, further study is needed to determine race-specific recommendations. Until then, discussion with the patient should reflect the potential pitfalls for Black men on active surveillance.

Authors' contributions

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Conflicts of interest

We have no conflicts of interest.

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