

Three-year Active Surveillance Outcomes in a Contemporary Community Urology Cohort in the United States



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OBJECTIVES

To determine the 3-year outcomes of men with prostate cancer managed with active surveillance (AS) in a cohort of geographically diverse community-based urology practices. AS is the management of choice for a majority of men with lower risk prostate cancer.^{1,2,3} Little is known about the contemporary “real-world” follow-up and adherence rates in the most common setting of urologic care, community (private) practice.⁴

METHODS

We retrospectively evaluated outcomes for men diagnosed between January 1, 2013 and May 31, 2014 with National Comprehensive Cancer Network (NCCN) very low, low and intermediate risk prostate cancer who selected AS in 9 large community urology practices. We used univariate and multivariate analyses to describe associations between race, age, insurance status, family history, comorbidity, clinical stage, Gleason score, NCCN risk-group, and PSA density with discontinuation of AS.

RESULTS

Five hundred and forty-eight men on AS were followed for a median of 3.35 years. 89% (492) continued to follow-up with diagnosing practice. 32% (171) discontinued AS. On multivariate analysis, increasing NCCN risk classification (Hazard ratio [HR] 1.65, $P = 0.02$ and HR 2.09, $P < 0.01$ for low and intermediate risk vs very low risk) was significantly associated with discontinuation. Among those who discontinued AS, surgery and radiation were utilized equally (47% and 53%, respectively, $P = 0.48$).

CONCLUSION

In this community-based cohort of men on AS, a minority was lost to follow-up and adherence to AS was similar to other reports. Disease characteristics more than sociodemographic characteristics correlated with adherence to AS, while surgery and radiotherapy were utilized equally among those discontinuing AS, both suggesting guideline concordant practice of medicine. UROLOGY 130: 72–78, 2019. Published by Elsevier Inc.

The management of lower risk prostate cancer with active surveillance (AS) is now the evidence-based preference reflected in multiple clinical guidelines.¹⁻³ Utilization of active surveillance has increased rapidly in the last decade such that a majority of men with very low-risk disease are managed initially with

AS.^{4,5,6} Less is known, however about the “real-world” follow-up and adherence rates of men on AS in the most common setting of urologic care, community-based (“private”) practice, estimated to account for 59.5% of urologic care in the 2017 AUA Annual Census.⁷ It is further estimated that 33% of all urologic care and 30% of urologic cancer care in the US was delivered by practices with 10 or more physicians (hereafter referred to “large urology practices”).^{7,8} Understanding delivery trends in this growing segment of urological care delivery in the US is of heightened importance in this period of intense debate about healthcare in the US and in a disease management process that relies on careful follow-up for its value to quality of life and safety.⁹

We describe contemporary disease progression and adherence rates after 3 years of follow-up among men with prostate cancer who were initially managed with AS

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in a cohort of men from large, geographically diverse, community-based urology practices.

MATERIALS AND METHODS

We performed a retrospective chart review in 9 large community-based urology practices in eight states to examine the 3-year clinical course and management of men diagnosed between January 1, 2013 and May 30, 2014 and followed until September 30, 2017 with National Comprehensive Cancer Network (NCCN) very low, low and intermediate risk prostate cancer (PCa) who selected active surveillance as the initial management option. AS was defined by documentation of AS in the medical record, or by continual follow-up of at least 6 months with no curative therapy. Only men diagnosed by prostate biopsy at the participating practices were included. We excluded men who did not stay on AS for at least 6 months, men with high risk disease, and, using age as a proxy for life expectancy, men over the age of 75. Participating practices had a median of 30 urologists (range, 12-50) and 8 midlevel providers (range, 3-9). Eight of 9 practices provided radiation oncology services and had an average of 1.33 radiation oncologists (range, 0.5-2). Chart review was performed by an independent professional chart abstraction firm (CIOX[®]), which employs multiple, industry standard quality assurance methods to ensure data accuracy.

Patients were followed until the start of secondary treatment, transfer of care from the diagnosing urology practice, death or end of the abstraction period, whichever came first. Men on AS were managed at the discretion of the patient and his provider. There was no standard AS protocol across practices. We defined discontinuation of AS as receipt of curative therapy, and this was the primary outcome. Secondary outcomes included the rate of disease progression among men who were rebiopsied and choice of curative therapy among men discontinuing AS. Reasons for discontinuation that were documented in the medical record were abstracted. The use of commercially available genomic tests was abstracted and the results were categorized into summary interpretations to show whether the results suggested that in comparison to the initial stage and risk categorization the disease was either less aggressive, confirmatory, or more aggressive. The following socioeconomic and disease-specific covariates were analyzed: age, race/ethnicity, insurance status, comorbidities and NCCN risk group, including its individual components, Gleason score, T stage, PSA, and PSA density.

Descriptive statistics, using Chi-squared and log-rank tests, were conducted to compare patient groups for race, age, insurance type, comorbidity measured with the Adult Comorbidity Evaluation 27 (ACE-27), NCCN risk group (very low, low, intermediate), family history of prostate cancer, Gleason score, clinical stage of disease, and PSA density.¹⁰ Disease progression was defined as any increase in Gleason score or an increase in disease volume to ≥ 3 cores based on repeat biopsy. Overall comorbidity scores were based on the highest ranked single item and then dichotomized to low vs moderate/severe as is commonly done in many reports. PSA density was categorized into <0.15 , 0.152 - 0.303 , and >0.30 ng/ml/cc³ based on previously published reports.¹¹ Insurance status was dichotomized to government (Medicare and Medicaid) and private (all others) as further subgroups were too small for analysis.

We used a Cox shared frailty model to estimate hazard ratios (HR) for discontinuing AS and censored patients who were lost to follow-up. Among those who discontinued AS and sought

curative therapy (surgery or radiotherapy), we conducted a multilevel, multivariate logistic regression to test associations of disease, and patient characteristics with type of curative therapy received. In both models, we included the urology practice as a level 2 variable to account for unmeasured within-practice correlations. Only de-identified data were analyzed, and Institutional Review Board approval was obtained. Partial funding was provided by an unrestricted grant from Genomic Health, Inc which had no involvement in any phase of this study.

RESULTS

We identified 548 men who started on AS after diagnosis from January 1, 2013 to May 31, 2014, 521 (95%) had specific documentation of AS and 27 (5%) did not have specific documentation but continued to be followed without evidence of curative therapy. The median time to event or censorship was 3.35 years (range, 0.53-4.83 years). 40% (218) of men had very low-risk disease, 47% (259) had low-risk disease, and 13% (70) had intermediate risk disease. Of these 70, intermediate risk was determined by PSA 10-20 in 34, Gleason 3+4 in 29, Gleason 4+3 in 4 and clinical T stage in 3. 78% (427) were White, 14% (75) African-American (AA), 21% (113) had a positive family history of PCa and the median PSA at diagnosis was 5.2. 12% (65) of patients were lost to follow-up. 57% (313/548) elected to undergo repeat biopsy and 44% (138/313) had disease progression, or 25% of the total cohort (138/548). 31% (171) elected to proceed to curative therapy from active surveillance (Table 1). Among those who did, the mean, minimum and maximum time to receipt of curative therapy was 1.79, 0.53, and 3.98 years, respectively.

On multivariate analysis of predictors of discontinuation of AS, increasing NCCN risk classification, low and intermediate vs very low risk (HR 1.65, 95% confidence interval [CI] 1.07-2.53; HR 2.09 95% CI 1.22-3.56, respectively) was significantly associated with conversion to curative therapy, while men of race classified as other (non-White and non-African American) were more likely to adhere to AS (HR 0.35, 95%CI 0.15-0.82) (Table 2). Age, family history of prostate cancer, insurance type and comorbidity were not significantly associated with adherence to AS. Figure 1 displays Kaplan-Meier plots showing the association of disease and patient characteristics with discontinuation of AS. Reasons cited in the medical record for discontinuation of AS include an increase in Gleason score (56%, 98), rising PSA (15%, 27), increase in disease volume (14%, 24), concerning findings on genomic testing (0.5%, 1), stress of living with cancer diagnosis (0.5%, 1), and other/unknown (14%, 24).

Genomic testing of prostate biopsies (either OncotypeDx[®] or Prolaris[®]) was utilized to facilitate risk stratification in 119 (22%) men. Twenty-eight percent (33) of testing suggested the disease was less aggressive, 60% (71) confirmed disease staging, and 13% (15) of testing suggested more aggressive disease. Univariate analysis showed similar rates of discontinuation of AS in men with less aggressive or confirmatory results on genomic testing (33.3% [11/33] and 33.8% [24/71], respectively) vs a rate of discontinuation of 66.7% (10/15) among men with testing suggesting higher risk disease ($P = 0.05$). The limited subgroup size precluded a multivariate analysis.

Of those men who discontinued AS, 161 men sought standard of care curative therapy, surgery (76, 47%) or radiotherapy (85, 53%) and 10 underwent other therapies including cryotherapy. On bivariate analysis, there is a significant association between age and insurance and choice of curative therapy.

Table 1. Demographic and clinical characteristics of men on active surveillance, with disease progression on repeat biopsy, and who discontinued active surveillance (white background), with a median follow-up of 3.35 years.

	Total Cohort N (%)	Repeat Biopsy n (%)	Disease Progression ^a n (%)	Continued on AS n (%)	Curative Therapy n (%)	P Value ^b
Total	548	313 (57.1)	138 (25.2)	377 (68.8)	171 (31.2)	
Age						
≤55	60 (11.0)	35 (11.2)	13 (9.4)	38 (10.1)	22 (12.9)	0.6052
56-65	238 (43.4)	148 (47.3)	63 (45.7)	164 (43.5)	74 (43.3)	
>65	250 (45.6)	130 (41.5)	62 (44.9)	175 (46.4)	75 (43.9)	
Race						
White	427 (78.2)	259 (83.0)	113 (82.5)	289 (77.1)	138 (80.7)	0.0252
African-American	75 (13.7)	32 (10.3)	15 (11.0)	48 (12.8)	27 (15.8)	
Other	44 (8.1)	21 (6.7)	9 (6.6)	38 (10.1)	6 (3.5)	
Insurance						
Private	291 (53.1)	174 (55.6)	77 (55.8)	201 (53.3)	90 (52.6)	0.8818
Government	257 (46.9)	139 (44.4)	61 (44.2)	176 (46.7)	81 (47.4)	
Comorbidity score						
None/Mild/Unknown	431 (78.6)	244 (78.0)	104 (75.4)	293 (77.7)	138 (80.7)	0.4298
Moderate/Severe	117 (21.4)	69 (22.0)	34 (24.6)	84 (22.3)	33 (19.3)	
Family history						
No	435 (79.4)	240 (76.7)	103 (74.6)	304 (80.6)	131 (76.6)	0.2802
Yes	113 (20.6)	73 (23.3)	35 (25.4)	73 (19.4)	40 (23.4)	
Risk group						
Very Low	218 (39.8)	119 (38.0)	44 (31.9)	168 (44.6)	50 (29.2)	0.0022
Low	259 (47.3)	159 (50.8)	79 (57.2)	167 (44.3)	92 (53.8)	
Intermediate	71 (13.0)	35 (11.2)	15 (10.9)	42 (11.1)	29 (17.0)	
Stage						
TX	29 (5.3)	13 (4.2)	3 (2.2)	23 (6.1)	6 (3.5)	0.5277
T1	433 (79.3)	256 (82.3)	114 (82.6)	292 (77.9)	141 (82.5)	
T2a	81 (14.8)	41 (13.2)	20 (14.5)	58 (15.5)	23 (13.4)	
T2b/c	3 (0.6)	1 (0.3)	1 (0.7)	2 (0.5)	1 (0.6)	
Diagnostic Gleason						
3 + 3	515 (94.0)	294 (93.9)	134 (97.1)	362 (96.0)	153 (89.5)	0.0066
3 + 4	29 (5.3)	16 (5.1)	3 (2.2)	14 (3.7)	15 (8.8)	
4 + 3	4 (0.7)	3 (1.0)	1 (0.7)	1 (0.3)	3 (1.7)	
PSA, median (IQR)	5.2 (4.3-6.8)	5.2 (4.3-6.5)	5.4 (4.6-6.8)	5.2 (4.1-6.8)	5.3 (4.6-6.8)	0.5191 ^c
PSA density						
<0.15	347 (65.6)	193 (64.8)	76 (57.1)	254 (69.8)	93 (56.4)	0.0088
0.15-0.30	160 (30.2)	95 (31.9)	53 (39.9)	98 (26.9)	62 (37.6)	
>0.30	22 (4.2)	10 (3.4)	4 (3.0)	12 (3.3)	10 (6.1)	

^a Disease progression could only be assessed in the 57% of men who had a repeat biopsy.

^b Chi-square test (or Fisher's exact) between "Continued on AS" vs "Curative Therapy".

^c Median test. P values are for bivariate comparisons between men who stayed on active surveillance vs men who discontinued active surveillance (grey background). Asterix (*) indicate $P < 0.05$.

Multivariate logistic regression revealed significantly less likely use of surgery for age >65 (odds ratio [OR] 0.23, $P = 0.035$), while race, comorbidity, insurance status, and NCCN risk group were not associated with treatment choice (Table 3). Of the 161 men who underwent standard curative therapies, there was no difference between the use of surgery vs radiotherapy, 47% vs 53% respectively ($P = 0.48$).

DISCUSSION

With 3 years of follow-up in this contemporary cohort of 548 patients receiving care in large community based urology practices, we found similar rates of disease progression and curative therapy as reported in other studies.^{9,12,13} Established markers of disease severity such as NCCN risk group and Gleason score at diagnosis were also predictive of adherence to AS in this real-world community cohort. Additionally, these disease parameters

were most predictive of outcome rather than socioeconomic factors like age and insurance type, but there was a small difference in AS adherence seen between "other" racial/ethnic groups and White men.

We found the rate at which men sought curative therapy was similar to the range of reported adherence rates from study and community cohorts in the US and elsewhere. For example, 3 reports from prominent early studies of AS found 5-year adherence rates of 76%, 63%, and 60%.¹⁴⁻¹⁶ Newcomb also found a relatively high rate of adherence to AS of 81% at 28 months.¹¹ In addition, in a report from a national Swedish database, the reported 5-year adherence rate was 64%.¹³ The adherence rate in this cohort of 66% at 3.3 years appears to be similar, but on the lower side of other reported series, suggesting that adherence in US community practices may be more challenging than in the setting of clinical trial or nationally administered health system. The rate of reclassification in

Table 2. Multivariate analysis with Cox shared frailty model for the association between clinical characteristics at initial diagnosis with discontinuation of active surveillance.

	Hazard Ratio	95% CI	P Value
Age group (ref ≤ 55)			
56-65	0.75	[0.45, 1.24]	0.2661
>65	0.59	[0.32, 1.09]	0.0901
Race (ref White)			
Black	1.22	[0.79, 1.89]	0.3792
Other	0.35*	[0.15, 0.82]	0.0148
Insurance (ref Private)			
Government	1.37	[0.90, 2.09]	0.1458
Comorbidity (ref None/Mild)			
Moderate/Severe	0.74	[0.50, 1.09]	0.1299
Family history (ref No)			
Yes	1.26	[0.87, 1.82]	0.2209
Risk group (ref Very Low)			
Low	1.65*	[1.07, 2.53]	0.0232
Intermediate	2.09*	[1.22, 3.56]	0.0072
PSA density group (ref <0.15)			
0.15-0.30	1.20	[0.80, 1.78]	0.3802
>0.30	1.63	[0.80, 3.30]	0.1783

Asterix (*) indicate $P < 0.05$. (n = 548).
CI, confidence interval.

this analysis (21% at 3.35 years) is lower than the rate of reclassification reported by Newcomb et al, and referenced above, (25% at 2 years), potentially supporting the role for increased use of at least one repeat biopsy for men on AS, as suggested by expert opinion in several clinical guidelines.

This study supports the utility in “real-world” community-based practices of NCCN risk grouping and Gleason score, as determined at initial biopsy, as significant predictors of adherence to active surveillance. There was no association with comorbidity and PSA density with adherence to AS, although there was a trend toward lower use of curative intervention among men with higher comorbidity, suggesting consideration of comorbidity in the decision to undergo curative therapy, and suggesting a grey-zone in the distinction between AS and watchful waiting as men on AS age. There was a significant association with insurance status and treatment decisions on univariate analyses, although this disappeared on multivariate analysis suggesting this trend was driven by the increased use of radiotherapy among older men and the increased prevalence of government insurance (Medicare) among older men. We found similar adherence rates among White and African-American (AA) men, though increased adherence among other races, a mix of predominantly Asian and Hispanic backgrounds. Krishna et al reported that AA’s are significantly less likely to be on AS strategies vs watchful waiting.¹⁷ While this study was not designed to assess this question, it is encouraging that race did not seem to play a role in management of AA and White men, although the difference in adherence to AS among “other” racial/ethnic groups, while limited by the relatively small sample size, does raise the question that there may be either cultural or disease specific differences in less studied racial/ethnic groups that contribute to different outcomes among men on AS.

AS is a management strategy whose safety relies on continuous management. It is particularly reassuring to see that a majority of men (89%) continued care with their diagnosing practice at an average follow-up of 3.3 years. On the other hand, the fact that 12% of men stopped care with the practice that diagnosed them and the chart abstractors involved in this study were not able to determine what happened to them, illustrates the risks in the real world of long-term surveillance particularly given the increasing role for AS in men with intermediate-risk disease.^{18,19} While multiple studies have shown the safety of AS in intermediate-risk disease, the higher curative treatment rate underscores the need for close follow-up in this subset of men.¹⁹⁻²¹ Improving long-term follow-up is something the developing field of cancer survivorship has focused on, in part, through use of care plans to help ensure patients, and other providers, have a clear understanding of the long-term care goals and plan.^{22,23}

Given its recent introduction, a surprisingly high number of men in this study underwent genomic testing to further clarify their prostate cancer risk grouping (22%, 119/548). While this study cannot assess the utility of these tests, it is interesting that the 15 men in whom results suggested more aggressive disease discontinued AS at double the rate of men with confirmatory or favorable scores on genomic testing (66.7% vs 33.3% and 33.8%). This suggests that patients and/or their physicians appear to have put credence in these results, which is in part supported by the increasing body of evidence in the scientific literature.^{24,25} Interestingly, genomic testing was not in the NCCN or American Urological Association guidelines at the time of diagnosis in this cohort (2013/2014), but by 2018 was recommended in the NCCN as an optional component of the risk stratification in men with low and favorable intermediate-risk disease with >10 years life

Patient Characteristics

Disease Characteristics

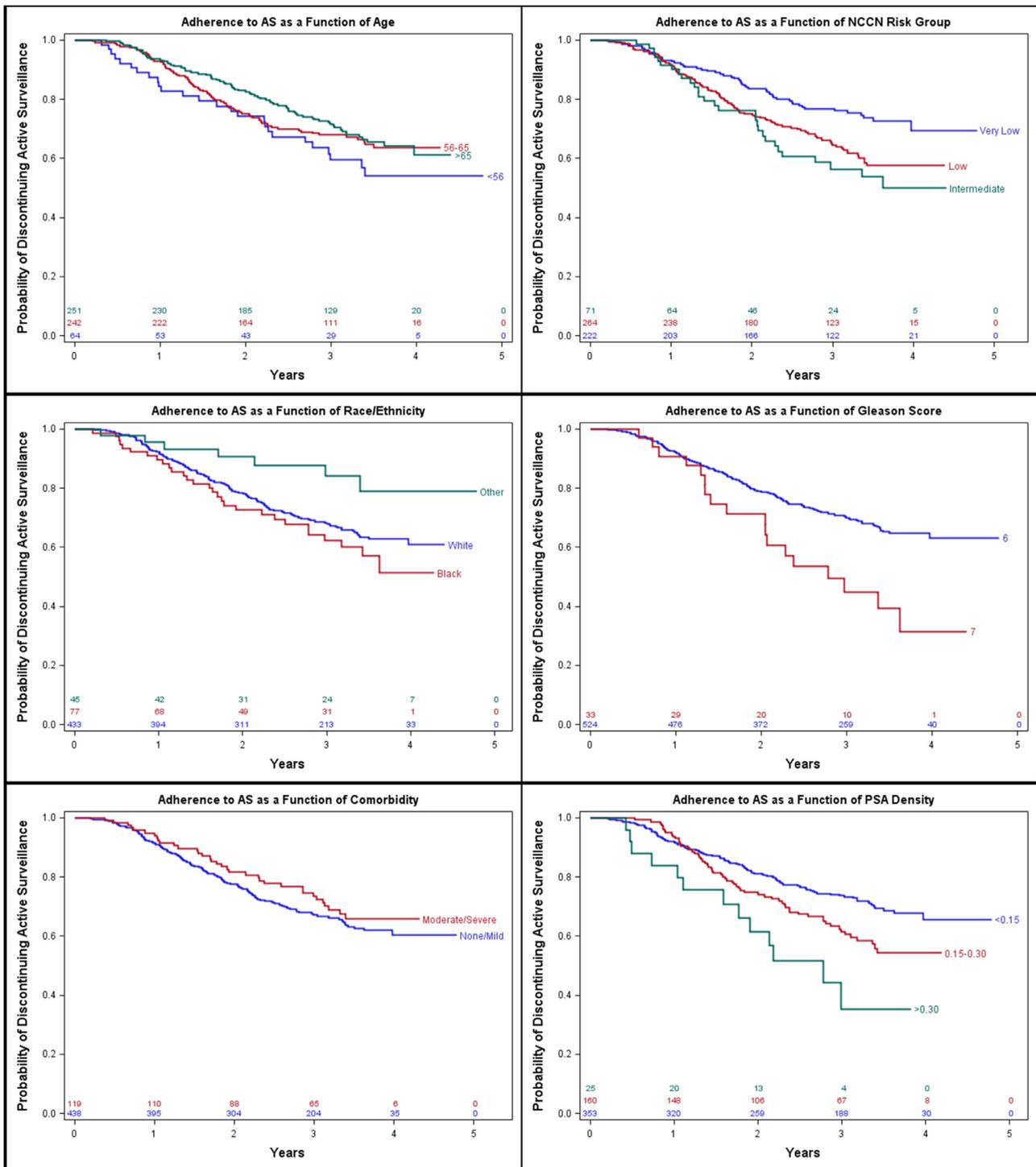


Figure 1. Kaplan-Meier curves showing adherence to active surveillance by patient (age, race/ethnicity, comorbidity) and disease (NCCN risk group, Gleason score, PSA density) characteristics at a median follow-up of 3.35 years. (Color version available online.)

expectancy and who are considering AS, which are the groups that received genomic testing in this study.³

Of the 161 men who underwent standard curative therapies, there was no difference between use of surgery vs radiotherapy 47% vs 53%, respectively ($P = 0.48$), which seems to match the reported equivalence of both modalities.²⁶ While this finding can only be considered

hypothesis generating due to the small number of cases, it does mirror the equivalent use of primary curative therapy modalities that we previously reported among incident disease.²⁷ This distribution of secondary curative therapies described here differs from other reports. In one, for example, 69% of men seeking secondary curative therapy after AS underwent surgery, although that study was conducted

Table 3. Use of surgery vs radiotherapy among men who discontinued active surveillance.

n (row %)	Bivariate			Multivariate Logistic		
	Surgery n (%)	Radiotherapy n (%)	P Value	OR	(95% CI)	P Value
Total	76 (47)	85 (53)	0.48			
Age						
≤55	14 (67)	7 (33)	<0.001*	referent		
56-65	42 (60)	28 (40)		0.72	(0.25, 2.09)	0.543
66-75	20 (29)	50 (71)		0.24*	(0.06, 0.91)	0.035*
Race						
White	63 (48)	67 (52)	0.760	Referent		
Black	10 (40)	15 (60)		0.52	(0.19, 1.38)	0.187
Other	3 (50)	3 (50)		1.06	(0.18, 6.44)	0.946
Insurance						
Private	52 (60)	34 (40)	<0.001*	Referent		
Government	24 (32)	51 (68)		0.62	(0.25, 1.57)	0.317
Comorbidity						
None/Mild	65 (49)	67 (51)	0.269	referent		
Moderate/Severe	11 (38)	18 (62)		0.81	(0.31, 2.07)	0.655
Risk group at diagnosis						
Very low	25 (51)	24 (49)	0.701	referent		
Low	37 (44)	47 (56)		0.70	(0.31, 1.55)	0.378
Intermediate	14 (50)	14 (50)		1.44	(0.50, 4.16)	0.504
Practice level variance	-	-		0.02	(0.00, 2463)	0.428

Bivariate comparisons between surgery and radiotherapy patients, and odds ratio from a multivariate logistic regression comparing likelihood of receiving surgery vs radiotherapy (referent). Asterix (*) indicate $P < 0.05$. (n = 161).

over a time period during which the evidence supporting curative therapies shifted substantially (1990-2013).¹⁶ In another more contemporary (2008-2013) and multicenter study, 64% of men discontinuing AS received surgery.¹¹ Viewed in the context of the literature assessing appropriate utilization of curative therapies for prostate cancer, which often suggests a negative influence of nonclinical factors in decision making, this finding suggests that a closer examination may be warranted of how specific characteristics of community-based practices, like size, structure, use of multidisciplinary care, and other factors influence quality of care.²⁸⁻³¹

There are several limitations to this study, the largest of which is that the study cohort was not randomly selected. Participating practices were all LUGPA (formerly the Large Urology Group Practice Association) members and self-selected out of an interest to better understand their own practice patterns. This is offset in part by the large sample size, and by the value in understanding real-world care delivery. Use of self-selecting practices may bias the results toward more organized practices that have the infrastructure to focus on quality. By relying on documentation of AS in the medical record as opposed to measurement of components of AS, it is possible that there was variation within the cohort as to the exact definition of AS, however the benefit of this is generation of real-world evidence. The small subset of patients we included in the AS cohort who did not have documentation of AS, but continued to follow-up like they were on AS, could have included some men on watchful waiting, however all men over 75 were excluded and this group did not appear notably different from those with documentation of AS. To limit the possibility of AS being conflated with indecision, although we

are not aware of a formal method to evaluate this, we required men to be on AS for 6 months to be included. This may have excluded some men who discontinued AS early due to changes in disease characteristics or other unmeasured factors. Only 9 men we excluded by this criteria and sensitivity analyses demonstrated little impact on the results. We use the validated ACE-27 to assess comorbidities; however, in many cases abstractors only had access to the comorbidities as documented in the urologic record. We assessed insurance status at the time of diagnosis only, introducing the possibility of an unmeasured change over the 3-year follow-up. The progression rate we report here may not reflect the true progression rate for the entire cohort, as repeat biopsy was not mandated, but was performed at the prerogative of the provider and patient.

CONCLUSION

The application of AS in this contemporary community-based cohort yielded results at 3.35 years similar to those reported from clinical trials, providing real-world validation of a common clinical risk stratification parameter, NCCN risk group, while also demonstrating that only a small minority of men were lost to follow-up. Furthermore, disease characteristics, more than sociodemographic characteristics correlated with adherence to AS, while surgery and radiotherapy were utilized equally among those discontinuing AS, suggesting guideline concordant practice of medicine.

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