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Outcomes of Active Surveillance for Clinically Localized Prostate Cancer in the Prospective, Multi-Institutional Canary PASS Cohort

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Purpose: Active surveillance represents a strategy to address the overtreatment of prostate cancer, yet uncertainty regarding individual patient outcomes remains a concern. We evaluated outcomes in a prospective multicenter study of active surveillance.

Materials and Methods: We studied 905 men in the prospective Canary PASS enrolled between 2008 and 2013. We collected clinical data at study entry and at prespecified intervals, and determined associations with adverse reclassification, defined as increased Gleason grade or greater cancer volume on followup biopsy. We also evaluated the relationships of clinical parameters with pathology findings in participants who underwent surgery after a period of active surveillance.

Results: At a median followup of 28 months 24% of participants experienced adverse reclassification, of whom 53% underwent treatment while 31% continued on active surveillance. Overall 19% of participants received treatment, 68% with adverse reclassification, while 32% opted for treatment without disease reclassification. In multivariate Cox proportional hazards modeling the percent of biopsy cores with cancer, body mass index and prostate specific antigen density were associated with adverse reclassification (p=0.01, 0.04, 0.04,

Abbreviations and Acronyms

AS = active surveillance

BMI = body mass index

EPE = extraprostatic extension

NCCN® = National Comprehensive Cancer Network®

PASS = Prostate cancer Active Surveillance Study

PCa = prostate cancer

PSA = prostate specific antigen

SVI = seminal vesicle invasion

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respectively). Of 103 participants subsequently treated with radical prostatectomy 34% had adverse pathology, defined as primary pattern 4-5 or nonorgan confined disease, including 2 with positive lymph nodes, with no significant relationship between risk category at diagnosis and findings at surgery (p=0.76).

Conclusions: Most men remain on active surveillance at 5 years without adverse reclassification or adverse pathology at surgery. However, clinical factors had only a modest association with disease reclassification, supporting the need for approaches that improve the prediction of this outcome.

Key Words: prostatic neoplasms, prospective studies, watchful waiting

THE prostate specific antigen era has been associated with stage migration toward lower grade and stage prostate cancers such that the majority of newly diagnosed prostate neoplasms are apparently indolent.[1,2] The number of prostate cancers identified each year far exceeds the number of lethal cases and there is over diagnosis of those cancers that may never progress or cause harm if left untreated.[3] In the U.S. most men diagnosed with low risk PCa undergo curative therapy,[2,4,5] thereby resulting in substantial overtreatment.

Active surveillance is a management strategy for PCa that can mitigate overtreatment by delaying intervention in patients whose tumors initially have features consistent with a low risk cancer and treating only when a more clinically significant malignancy is identified. Patients treated with AS undergo serial monitoring with serum PSA measurements, clinical examinations and repeat biopsies. Intervention is only recommended with evidence of a more aggressive tumor, usually based on changes in biopsy characteristics or PSA values.

In 2008 we established a multi-institutional AS cohort in response to the increasing evidence of PCa overtreatment and the need for a prospective platform for the discovery and validation of biomarkers of PCa outcomes.[6] We present the first analysis to our knowledge of clinical factors associated with outcomes in 905 participants enrolled in the Canary PASS, and provide detailed pathological data for a subset of the cohort who underwent radical prostatectomy after initial AS.

METHODS

Canary PASS Cohort

Canary PASS opened for enrollment in 2008.[6] The protocol (clinicaltrials.gov NCT00756665) was approved by institutional review boards at each of 9 clinical sites and a coordinating center. All men provided written informed consent for entry into this prospective, observational, AS study.

To sample the full spectrum of men using AS broad eligibility criteria were used, including histologically confirmed adenocarcinoma of the prostate, cT1-2 disease, no previous treatment for PCa and willingness to undergo serial monitoring while providing biospecimens for subsequent analysis. Participants must have undergone 10-core or greater biopsy within 1 year before enrollment, or 2 or more biopsies, 1 of which was in the 2 years before study enrollment. Although there was no restriction to the time between diagnosis and enrollment, the median time was 8.4 months (IQR 14.4), with 67% of the participants enrolled after the diagnostic biopsy and 22% enrolled after the first surveillance biopsy.

Participants were followed with serum PSA measurements every 3 months, clinical and digital rectal examination every 6 months, and repeat prostate biopsy 6 to 12, 24, 48 and 72 months after diagnosis. At least 10-core regimens were required and 91% of study biopsy regimens were 12-core or more.

Participants were considered to have adverse disease reclassification (referred to only as reclassification) on any increase in Gleason grade (primary or sum) on repeat biopsy and/or an increase in biopsy tumor volume, defined as an increase in the ratio of number of biopsy cores containing cancer-to-total number of cores, from less than 34% to 34% or more. Participants with disease reclassification were offered treatment. Those declining treatment were allowed to remain on study. Biopsies and radical prostatectomies were evaluated for Gleason score by genitourinary trained pathologists at each site using the 2005 WHO/International Society of Urological Pathology modified Gleason system.[7]

De-identified demographic, clinical and pathological data were maintained in a central data repository. A collaboration agreement governing study conduct and data use was executed at participating institutions.

Statistical Analysis

We used PASS data collected through May 2013 when 909 participants were enrolled in the study. Four participants enrolled more than 10 years after initial diagnosis were excluded from analysis. Age, race, Gleason score and tumor volume (ratio of number of cores containing cancer-to-total number of biopsy cores) were ascertained from the time of diagnosis. PSA was measured before PCa diagnosis. PSA density was calculated from the diagnostic PSA and the first available prostate volume. Clinical T-stage and BMI were from study enrollment.

Cases were stratified by NCCN risk criteria at diagnosis using the criteria of very low risk—cT1, PSA density less than 0.15, Gleason score 6 or less, 2 or fewer cores containing cancer, 50% or less of any core containing cancer; low risk—cT1/T2a, PSA less than 10 ng/ml, Gleason score 6 or less; intermediate risk—cT2b/T2c,

PSA 10 to 20 ng/ml, Gleason score 7; and high risk—meeting intermediate risk criteria except PSA greater than 20 ng/ml.[8] There were 462 participants with insufficient data to classify them as very low risk but who met the low risk criteria. Fisher's exact test was used to evaluate the relationship between risk classification and pathological outcome.

Continuous variables were categorized for meaningful clinical interpretation. Categorical variables were summarized using frequencies and percentages. Outcomes included time from diagnosis to grade reclassification, any pathological disease reclassification (grade and/or volume) or curative treatment. Participants without the event of interest were censored at the date of last study contact. A Kaplan-Meier curve was used to present the probability of disease reclassification or treatment over time. Median survival probabilities and confidence intervals were reported. Cox proportional hazards models were used to assess the association of clinical variables with reclassification or treatment. Univariate as well as multivariate models were applied to compare the unadjusted and adjusted hazards ratio for each variable. Statistical analysis was performed using SAS® version 9.3 and R studio version 0.98.501.

RESULTS

Demographics of the cohort are displayed in table 1. Median age was 63 (IQR 9). Although PASS uses broad eligibility criteria, most participants (87%) met NCCN criteria for very low risk or low risk cancer at diagnosis. More than 99% of the cohort had stage cT2a or less disease, 93% had PSA less

Table 1. *Participant demographics at diagnosis*

	PASS Cohort		Reclassification		No Reclassification + Repeat Biopsy		Treatment		Treated with Surgery	
No.	905		216		560		170		103	
No. race (%):										
Caucasian	816	(91)	194	(90)	507	(91)	152	(89)	94	(91)
African-American	52	(6)	12	(5)	29	(5)	10	(6)	3	(3)
Asian	24	(3)	8	(4)	15	(3)	7	(4)	6	(6)
Other	7	(less than 1)	2	(1)	4	(1)	1	(less than 1)	0	
Unknown	6		0		5		0		0	
No. age (%):										
Less than 50	42	(5)	5	(2)	30	(6)	8	(5)	8	(8)
50–60	291	(32)	66	(31)	193	(34)	51	(30)	35	(34)
61–70	471	(52)	113	(52)	284	(51)	88	(52)	50	(49)
Greater than 70	101	(11)	32	(15)	53	(9)	23	(13)	10	(10)
No. ng/ml PSA (%):										
0–3.99	268	(29)	47	(22)	179	(32)	34	(20)	22	(21)
4.0–10.0	576	(64)	154	(71)	344	(61)	123	(72)	73	(71)
Greater than 10.0	61	(7)	15	(7)	37	(7)	13	(8)	8	(8)
No. clinical T-stage (%):*										
T1	804	(89)	188	(87)	492	(88)	146	(86)	92	(89)
T2a	96	(10)	26	(12)	65	(12)	21	(12)	11	(11)
T2b/c	5	(less than 1)	2	(less than 1)	3	(less than 1)	3	(2)	0	
No. Gleason score (%):										
6 or Less	846	(94)	205	(95)	528	(94)	162	(95)	101	(98)
7 (3+4)	56	(6)	11	(5)	29	(5)	8	(5)	2	(2)
7 (4+3)	3	(less than 1)	0		3	(1)	0		0	
No. % cores containing Ca (%):										
1–10	414	(53)	60	(33)	283	(58)	45	(33)	29	(35)
11–33	340	(43)	109	(59)	189	(39)	86	(62)	51	(61)
34 or Greater	34	(4)	14	(8)	16	(3)	7	(5)	3	(4)
Unknown	117		33		72		32		20	
No. PSA density (%):										
0–0.15	508	(70)	97	(56)	348	(74)	69	(52)	41	(51)
0.151–0.30	176	(24)	63	(36)	97	(21)	48	(36)	29	(36)
Greater than 0.30	43	(6)	14	(8)	25	(5)	16	(12)	10	(13)
Unknown	178		42		90		37		23	
No. kg/m^2 BMI (%):*										
Less than 25	230	(25)	57	(26)	154	(27)	43	(25)	29	(28)
25–29.9	457	(50)	96	(44)	283	(50)	84	(49)	50	(49)
30–34.9	154	(18)	42	(20)	92	(17)	27	(16)	16	(16)
35 or Greater	64	(7)	21	(10)	31	(6)	16	(9)	8	(8)
No. family history (%):										
Yes	229	(27)	55	(27)	140	(26)	45	(28)	28	(29)
No	634	(73)	147	(73)	393	(74)	115	(72)	70	(71)
Unknown	42		14		27		10		5	
No. NCCN PCa classification (%):										
Very low risk	284	(31)	41	(19)	208	(37)	31	(18)	24	(23)
Low risk	503	(56)	150	(69)	284	(51)	115	(68)	69	(67)
Intermediate risk	115	(13)	25	(12)	66	(12)	23	(14)	9	(9)
High risk	3	(less than 1)	0		2	(less than 1)	1	(less than 1)	1	(1)

* From study entry.

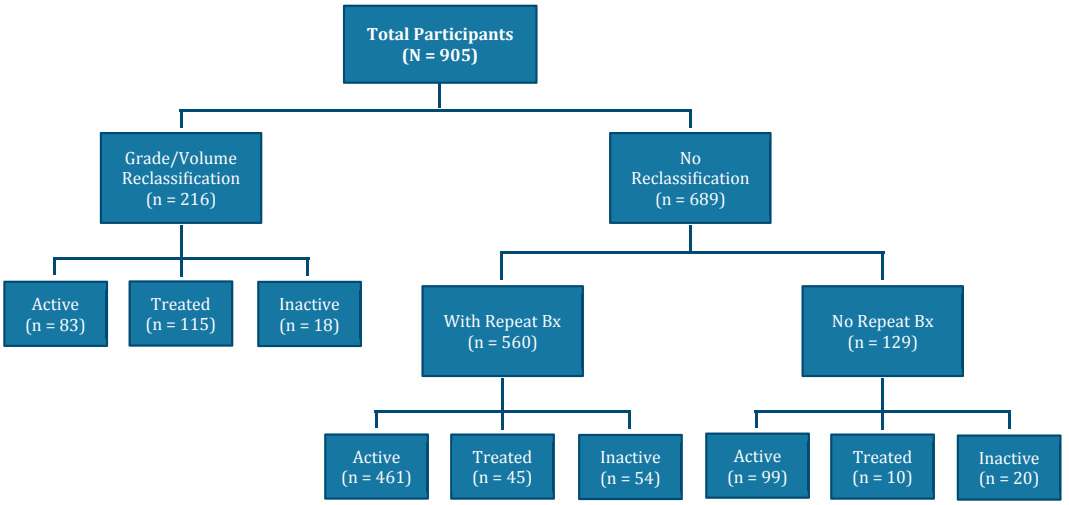


Figure 1. Status of PASS participants. Participants are grouped according to whether they experienced adverse reclassification (increase in biopsy Gleason grade and/or ratio of number of cores containing cancer-to-total number of cores from less than 34% to 34% or greater) or had no reclassification. Participants with no reclassification are further divided into those who had at least 1 repeat biopsy (Bx) and, thus, are able to have disease reclassified, and those who had not yet undergone repeat biopsy and, thus, are not able to have disease reclassified. Participants are further divided into those who are active (continuing on AS), had documented treatment or are inactive (left study with no documentation of treatment).

than 10 ng/ml and 94% had a Gleason score of 6 or less.

The status of participants in the cohort is shown in figure 1. Median followup from diagnosis was 28 months (IQR 33.5). Of the 905 participants enrolled 216 (24%) experienced tumor grade and/or volume reclassification. Increased grade was the most common type of disease reclassification, seen in 188 of 216 (87%) men with reclassification (table 2). Of 216 participants with disease reclassification 83 remained on AS or were considering treatment, 115 received curative treatment and 18 dropped out of PASS without confirmed treatment.

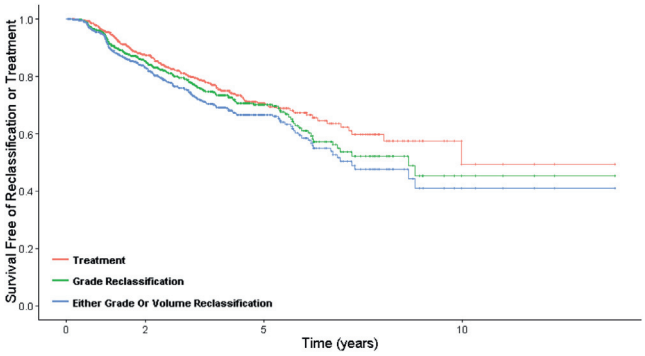
Reclassification type did not differ in those treated/not treated. Of 689 participants without reclassification 560 underwent repeat biopsy while 129 had not yet undergone repeat biopsy. Of these 689 participants who did not experience disease reclassification 560 remained on AS, 55 received treatment and 74 dropped out of study followup. Overall 170 (19%) participants received treatment, including 115 (68%) who had associated disease reclassification and 55 (32%) who opted for treatment without study defined reclassification. Of these participants approximately 40% had increasing tumor volume yet did not meet the definition for volume reclassification, while the remainder had no identifiable reason for treatment. Of the 92 participants who were inactive 32 moved, 41 were lost to followup, 13 refused future contact and 6 died of causes other than PCa. There were no distant metastases or PCa deaths.

Kaplan-Meier estimates of time to disease reclassification or treatment are shown in figure 2. The probability of a patient remaining on AS at 2, 5 and 10 years after diagnosis was 88%, 71% and 50%, respectively. Median time free of treatment, grade reclassification or any biopsy reclassification (grade and/or volume) was 10.0 years (95% CI 8.0, -), 8.6 years (95% CI 6.7, -) and 7.2 years (95% CI 6.2, -), respectively.

Table 2. *Participants by reclassification type and treatment status*

	No. Reclassified (%)	No. Reclassified, Treated	No. Reclassified, Scheduling Treatment or Inactive	No. Reclassified, Continuing on AS	No. No Reclassification, Treated
Grade	138 (64)	69	21	48	—
Vol	28 (13)	13	6	9	—
Grade + vol	50 (23)	33	7	10	—
None	—	—	—	—	55
Totals	216	115	34	67	55

Of the 216 cases that were reclassified by biopsy Gleason grade or tumor volume, 115 (53%) had documented treatment, 34 (16%) were in the process of scheduling treatment (16) or inactive (18, 7 of which likely received treatment, 1 died of causes other than prostate cancer, 10 are lost to followup) and 67 (31%) remained on active surveillance. A total of 170 participants had been treated, including 115 (68%) with associated reclassification and 55 (32%) without study defined reclassification.



No. at risk	0 (Dx)	2 yr	5 yr	10 yr
Treatment	905	514	130	5
Grade Reclassification	905	481	118	5
Grade/volume Reclassification	905	476	116	5

Figure 2. Kaplan-Meier estimates of survival free of outcome. Outcomes are any increase in biopsy Gleason score (grade reclassification), increase in biopsy Gleason score or volume to 34% or more with cancer (grade/volume reclassification), or treatment. Time zero was defined as time of diagnosis (Dx). Participants without event were censored at date of last study contact.

The univariate and multivariate association of clinical variables at diagnosis with time to grade reclassification are presented in table 3 and supplementary table 1 (http://jurology.com/). On multivariate Cox proportional hazards modeling (605), percentage of cores containing cancer at diagnosis, BMI and PSA density were significantly associated with grade reclassification (p=0.01, 0.04 and 0.04, respectively). Analysis excluding individuals who used 5α-reductase inhibitors did not alter the conclusion and the rate of reclassification was the same in the participants excluded from multivariable analysis due to missing variables as in the full cohort. Modeling for the outcomes of grade or volume reclassification or of treatment was similar (supplementary tables 2 and 3, http://jurology.com/).

Surgery was the most common form of treatment, with 105 men undergoing radical prostatectomy, 59 receiving radiation, 3 receiving hormones and 1 treated with cryotherapy. Data were available for 103 participants who underwent radical prostatectomy (table 4 and supplementary table 4, http://jurology.com/). Before surgery these men had undergone a mean of 2.5 biopsies (range 1 to 7). The biopsy most proximal to surgery had the highest Gleason score in all but 3 participants who had a negative biopsy and then underwent surgery.

Table 3. *Cox proportional hazards models for time to grade reclassification*

	Time to Grade Reclassification					
	No.	Univariate Adjusted HR (95% CI)	p Value	No.	Multivariate Adjusted HR (95% CI)	p Value
Age:						
Less than 55	137	Reference		93	Reference	
55—65	464	1.03 (0.66, 1.62)	0.45	310	1.08 (0.59, 1.97)	0.82
Greater than 65	304	1.24 (0.78, 1.98)		202	1.19 (0.64, 2.23)	
Clinical T-stage:						
T1	804	Reference		541	Reference	
T2a	96	1.06 (0.68, 1.64)	0.29	60	0.91 (0.50, 1.65)	0.26
T2b/c	5	3.05 (0.76, 12.32)		4	3.31 (0.77, 14.16)	
PSA (ng/ml):						
0—3.99	266	Reference		166	Reference	
4.0—10.0	578	1.78 (1.25, 2.52)	<0.01	387	0.96 (0.58, 1.59)	0.98
Greater than 10.0	61	1.56 (0.83, 2.91)		52	0.91 (0.38, 2.17)	
% Cores containing Ca:						
1—10	414	Reference		314	Reference	
11—30	315	1.87 (1.32, 2.64)	<0.01	243	1.81 (1.21, 2.73)	0.01
Greater than 30	59	2.57 (1.52, 4.35)		48	2.13 (1.14, 3.95)	
Family history:						
No	634	Reference		446	Reference	
Yes	229	0.95 (0.68, 1.34)	0.78	159	0.98 (0.65, 1.49)	0.92
Race:						
Caucasian	816	Reference		545	Reference	
African-American	52	1.31 (0.73, 2.36)	0.19	38	1.39 (0.70, 2.76)	0.50
Other	31	1.70 (0.89, 3.22)		22	1.43 (0.57, 3.61)	
BMI (kg/m^2):						
Less than 25	230	Reference		155	Reference	
25—29.9	457	0.97 (0.68, 1.39)		318	1.15 (0.72, 1.83)	
30—34.9	154	1.29 (0.84, 1.97)	0.03	92	1.71 (0.96, 3.03)	0.04
35 or Greater	64	1.93 (1.15, 3.24)		40	2.38 (1.2, 4.70)	
PSA density:						
0—0.10	296	Reference		235	Reference	
0.101—0.15	212	1.19 (0.78, 1.80)		181	0.97 (0.57, 1.62)	
0.151—0.30	176	2.12 (1.44, 3.11)	<0.01	153	1.85 (1.09, 3.13)	0.04
Greater than 0.30	43	1.28 (0.63, 2.61)		36	1.08 (0.41, 2.80)	

Modeling for the outcomes of time to grade or volume reclassification or time to treatment are similar, and are shown in supplementary tables 2 and 3 (http://jurology.com/).

Table 4. *Pathology results from participants undergoing surgery*

		No. Prostatectomy Gleason (%)							Adverse Pathology	
Highest Gleason Biopsy	No.	3+3	3+4	3+5	4+3	4+4	4+5	5+4	No. (%)	Description
NCCN very low risk at diagnosis:										
3+3	13	5 (38)	6 (46)	—	1 (8)	1 (8)	—	—	3 (20)	2 Primary pattern 4, 1 EPE + N1
3+4	6	—	5 (83)	—	1 (17)	—	—	—	1 (17)	1 Primary pattern 4
4+3	4	—	—	—	2 (50)	—	1 (25)	1 (25)	4 (100)	2 Primary 4 or 5, 1 primary 4 + EPE, 1 primary 4 + EPE + SVI
4+4	1	—	—	—	1 (100)	—	—	—	1 (100)	1 Primary pattern 4
Totals	24								9 (37)	
NCCN low risk at diagnosis:										
3+3	24	9 (37)	15 (63)	—	—	—	—	—	2 (9)	2 EPE
3+4	29	4 (14)	22 (76)	1 (3)	1 (3)	1 (3)	—	—	9 (31)	2 Primary pattern 4, 7 EPE
3+5	2	—	—	—	2 (100)			—	2 (100)	2 Primary pattern 4
4+3	11	—	5 (45)	—	5 (45)	—	1 (9)	—	7 (64)	3 Primary pattern 4, 1 EPE, 2 primary 4 + EPE, 1 primary 4 + N1
4+4	2	—	1 (50)	—	1 (50)	—	—	—	1 (50)	1 Primary 4 + EPE + SVI
4+5	1	—	1 (100)	—	—	—	—	—	1 (100)	1 EPE + SVI
Totals	69								22 (32)	
NCCN intermediate or high risk at diagnosis:										
3+3	4	3 (75)	1 (25)	—	—	—	—	—	0	
3+4	2	—	1 (50)	—	1 (50)	—	—	—	1 (50)	1 Primary pattern 4
4+3	2	—	1 (50)	—	1 (50)	—	—	—	1 (50)	1 Primary 4 + EPE
4+4	1	—	—	—	1 (100)	—	—	—	1 (100)	1 Primary 4 + EPE + SVI
4+5	1	—	—	—	—	—	1 (100)	—	1 (100)	1 Primary 4
Totals	10								4 (40)	
Overall	103	21 (20)	58 (57)	1 (1)	17 (16)	2 (2)	3 (3)	1 (1)	35 (34)	

The biopsy with the highest Gleason score before surgery is shown (the biopsy immediately preceding surgery in all but 3 participants), along with Gleason score at the time of surgery. All but 2 participants were diagnosed with Gleason 3+3 disease. Adverse pathology was defined as primary pattern 4 or 5, EPE, positive lymph nodes (N1) and/or SVI at the time of surgery.

Table 4 shows the distribution of participants according to the highest biopsy Gleason score and corresponding Gleason score at prostatectomy. Participants are stratified by NCCN risk category at diagnosis. Overall there were 34 cases (33%) that were pathologically upgraded at prostatectomy and 14 (14%) that were downgraded. A total of 35 (34%) had adverse pathological features at surgery including primary Gleason pattern 4-5, EPE, SVI or lymph node metastasis. Importantly there was no significant relationship between risk classification at diagnosis and adverse pathology at surgery. Overall 9 of 24 (37%) very low risk cases had adverse pathology, 22 of 69 (32%) low risk cases had adverse pathology and 4 of 10 (40%) intermediate or high risk cases had adverse pathology at surgery ($p=0.76$).

DISCUSSION

Overtreatment for low risk prostate cancer is one of the most important issues in PCa management and was a large factor in the U.S. Preventive Services Task Force recommendation against PSA screening.[9] Due to the relatively indolent natural history of low risk disease, active surveillance is an effective strategy to mitigate overtreatment by delaying or avoiding primary therapy. Multiple series have demonstrated no or very low PCa specific mortality. Nonetheless, current monitoring tools lack the specificity and sensitivity needed for many clinicians and patients to more broadly embrace AS for localized PCa, resulting in persistently high curative treatment rates in the U.S.[2]

In our prospective, multicenter cohort with participants from 9 sites throughout North America, we demonstrated that in a diverse clinical setting AS delays or avoids active treatment with a median time free from treatment of more than 5 years, consistent with results from single center studies.[10–13] Interestingly a substantial proportion of patients who experience disease reclassification on AS do not opt for primary treatment, while many without reclassification opt for curative treatment during a relatively short followup.

The primary end point in our analysis was detection of higher grade or volume cancer on repeat prostate biopsy. This finding during AS may be due to actual disease evolution or, most often, to the presence of a higher grade or volume tumor that was missed due to undersampling of the prostate during biopsy. We use the term adverse reclassification

rather than progression to describe our end point. Higher grade tumors are a more aggressive phenotype and generally have worse outcomes.[14–16] Similarly, a higher proportion of biopsy cores involved with cancer is correlated with disease stage and worse outcomes after primary treatment.[17,18] While many series use 2 cores with cancer to define higher volume cancer, we chose a conservative threshold for reclassification of 34% of total biopsy cores containing cancer.[19] The use of PSA kinetics to define disease progression while on AS is controversial,[20] and although PSA kinetics are not currently used to define disease progression in PASS, PSA data are collected for evaluation as the cohort matures.

Our study shows that while clinical factors are related to disease reclassification, such associations are modest. We found significant but modest associations between adverse disease reclassification and PSA density, tumor volume and BMI. PSA density has been associated with time to treatment, progression and adverse pathological features in other AS cohorts,[10,13,21,22] and is an eligibility criterion in some series.[12] In our experience prostate volume was inconsistently collected, suggesting that it is generally not used to influence AS decisions. Volume of cancer, defined by the proportion of total cores involved with cancer, is a surrogate measure for overall disease volume, which is correlated with worse disease specific outcomes.[23] Likewise, obesity has been associated with less favorable outcomes in a variety of cancers including PCa.[24]

The PASS cohort included 103 participants who underwent radical prostatectomy after initial surveillance. Of these 103 patients 101 (98%) were initially diagnosed with Gleason 3+3 disease. There were 61 (59%) men who experienced upgrading on biopsy before surgery, presumably leading to the decision to treat the cancer, while 41 men were treated with 3+3 disease. Interestingly 24 of 41 (58%) participants who underwent prostatectomy for 3+3 disease were found to have higher grade disease at surgery. Some of this upgrading is likely due to the previously described rates of intraobserver and interobserver variability.[25]

Our pathological data demonstrate a poor correlation of initial risk group with adverse surgical pathology. Using a definition of adverse pathology of primary Gleason pattern 4-5 and/or nonorgan confined disease, participants who fulfilled the NCCN definition of very low risk, low risk or intermediate/high risk disease at diagnosis had adverse pathology at surgery at 37%, 32% and 40%, respectively, after a period of AS. In our cohort 2 participants had positive lymph nodes, both of whom underwent surgery less than 1 year after cancer diagnosis. One met NCCN criteria for very low risk disease at initial diagnosis (2 of 12 cores of 3+3, less than 50% tumor per core), had pattern 3+3 carcinoma in 3 of 12 cores with greater than 50% tumor in 1 core on repeat biopsy, and at surgery had pT3a, 3+4 disease with 1 positive node. The other participant was diagnosed with low risk Gleason 3+3 disease, had 4+3 disease in 4 of 14 cores on repeat biopsy, and at surgery had pT2c, 4+3 disease with a single positive node. While the interpretation of these observations is limited by small numbers, primarily of patients who experienced reclassification on followup, these data suggest that clinical characteristics alone are not sufficient to accurately distinguish indolent cancers from those that may be more aggressive. There is a clear need to move beyond PSA, stage and biopsy characteristics to a more biologically based assessment of risk at diagnosis as well as during periodic re-evaluation. The serial biospecimens collected in PASS will allow us to evaluate genomic and molecular diagnostic tests designed to distinguish aggressive cancers from those that will not cause harm if left untreated.[26]

There are limitations of this study. Evaluation of the impact of AS on the more established disease specific end points, such as PCa metastasis or mortality, is not possible with our short followup. However, previous studies, including randomized clinical trials,[27] have shown that low risk disease is associated with low long-term disease mortality.[11] Similarly cancer reclassification in AS to higher grade or volume disease often represents undersampling at original prostate biopsy. However, the detection of intermediate risk disease in a man on AS would then permit therapeutic interventions that are more likely beneficial to the patient.[14,19] Finally, central pathological review was not performed for the primary end point of biopsy reclassification. A benefit of this approach is that pathological evaluation in our multicenter study better reflects community practice.

CONCLUSIONS

At the time of diagnosis clinical characteristics alone do not completely distinguish indolent prostate cancers from those cancers that may benefit from early intervention, as evidenced by equal rates of adverse prostatectomy pathology among very low, low and intermediate risk disease at diagnosis. Better tools are needed to improve risk stratification. The PASS biorepository will allow for the validation of biomarkers to identify cases that may be better managed with treatment, vs those with a long-term prognosis allowing a less intensive followup schedule, and provide greater confidence in the appropriateness of a nontreatment management strategy.

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