Original Article

Treatment in the Absence of Disease Reclassification Among Men on Active Surveillance for Prostate Cancer

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BACKGROUND: Maintaining men on active surveillance for prostate cancer can be challenging. Although most men who eventually undergo treatment have experienced clinical progression, a smaller subset elects treatment in the absence of disease reclassification. This study sought to understand factors associated with treatment in a large, contemporary, prospective cohort. **METHODS:** This study identified 1789 men in the Canary Prostate Cancer Active Surveillance Study cohort enrolled as of 2020 with a median follow-up of 5.6 years. Clinical and demographic data as well as information on patient-reported quality of life and urinary symptoms were used in multivariable Cox proportional hazards regression models to identify factors associated with the time to treatment **RESULTS:** Within 4 years of their diagnosis, 33% of men (95% confidence interval [CI], 30%-35%) underwent treatment, and 10% (95% CI, 9%-12%) were treated in the absence of reclassification. The most significant factor associated with any treatment was an increasing Gleason grade group (adjusted hazard ratio [aHR], 14.5; 95% CI, 11.7-17.9). Urinary quality-of-life scores were associated with treatment without reclassification (aHR comparing "mostly dissatisfied/terrible" with "pleased/mixed," 2.65; 95% CI, 1.54-4.59). In a subset analysis (n = 692), married men, compared with single men, were more likely to undergo treatment in the absence of reclassification (aHR, 2.63; 95% CI, 1.04-6.66). **CONCLUSIONS:** A substantial number of men with prostate cancer undergo treatment in the absence of clinical changes in their cancers, and quality-of-life changes and marital status may be important factors in these decisions. ***Cancer* 2022;128:269-274**.

LAY SUMMARY:

- This analysis of men on active surveillance for prostate cancer shows that approximately 1 in 10 men will decide to be treated within 4 years of their diagnosis even if their cancer is stable.
- These choices may be related in part to quality-or-life or spousal concerns.

KEYWORDS: active surveillance, prostatic neoplasms, quality of life.

INTRODUCTION

Active surveillance is well recognized as an essential management approach for men with newly diagnosed clinically localized prostate cancer.[1,2] However, despite increasing adoption of this strategy, enrolling and maintaining men on active surveillance can be challenging for a multitude of reasons.[3] A number of clinical factors have been found to be associated with the risk of progression on active surveillance and the subsequent decision to pursue definitive therapy.[4-14]

Less well characterized are the reasons that men elect to discontinue active surveillance and pursue therapy for prostate cancer in the absence of clinical progression of their disease. The role of anxiety as an obstacle to both enrollment and retention on active surveillance protocols has been recognized.[15-18] However, it is unclear whether other significant factors may drive some men on active surveillance to pursue treatment without important changes in their cancer staging or grading. We hypothesized that there would be measurable differences in men's self-reported symptomatology and quality of life (QOL) if we compared patients undergoing treatment in the presence or absence of reclassification.

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Specifically, we sought to identify factors associated with treatment in the absence of grade reclassification in a large, contemporary, prospective cohort of men on active surveillance for prostate cancer. Understanding the factors motivating these men to pursue treatment may inform the design of interventions to promote maintenance of active surveillance and thereby avoid or delay treatment and its associated side effects.

MATERIALS AND METHODS

Study Population

Data are from the Canary Prostate Active Surveillance Study (PASS), a prospective multicenter cohort initiated in 2008 of men diagnosed with clinically localized prostate cancer who choose active surveillance as their initial prostate cancer management strategy (clinicaltrials.gov NCT00756665), in which men are enrolled after providing informed consent under institutional review board supervision.[19] Under the PASS protocol, prostate-specific antigen (PSA) was measured every 3 months, clinic visits occurred every 6 months, and biopsies were performed 6 to 12 and 24 months after diagnosis and then every 2 years. Magnetic resonance imaging (MRI) was performed at the treating clinicians' discretion. The study population was 2003 men enrolled in PASS as of April 2020. For this analysis, men enrolled more than 5 years after their diagnosis (n = 62) or treated within the 6 months after their diagnosis or before the first surveillance biopsy (n = 46) were excluded. In addition, men who were reclassified to a higher biopsy Gleason grade group (GG) before enrollment (n = 90), were diagnosed with GG 3 (n = 8), or were missing data (n = 8) were also excluded; this left 1789 men in the analyses.

Statistical Methods

The primary end points examined included 1) the time from diagnosis to any prostate cancer treatment and 2) the time from diagnosis to prostate cancer treatment without grade reclassification at a surveillance biopsy. For both end points, participants without treatment were censored at the date of last study contact. Patients who enrolled after their diagnosis were treated as left-truncated data and were considered at risk only after the time of enrollment. For models examining the time to treatment without reclassification, grade reclassification was treated as a competing event, and men who experienced an increase in grade were censored at the date of that event.

Overall cumulative incidences of both end points were estimated via the Aalen-Johansen estimator. Time-varying covariate Cox proportional hazards regression models were used to examine the associations between the covariates of interest and the time to any treatment, and cause-specific Cox proportional hazards models were used for the time to treatment without a reclassification end point to account for competing risk. Information on clinical characteristics, pathologic characteristics, urinary symptoms, and demographics was considered for covariates, including GG at diagnosis, age at diagnosis, PSA at diagnosis (log-transformed), and race (Black, White, or other). Additionally, we considered increases in GG, the percentage of cores containing cancer, the prostate size (log-transformed), and differences in PSA from the diagnosis (log-transformed). The American Urological Association (AUA) urinary QOL score (delighted, pleased/mostly satisfied/mixed, or mostly dissatisfied/unhappy/terrible), the AUA symptom score, the body mass index, and the clinical T stage were modeled as time-varying covariates, with the most recent information before event times being used. Sensitivity analyses were conducted restricting the cohort to men with GG 1 at diagnosis (n = 1618) and altering the endpoint to time to treatment in the absence of grade or volume reclassification, where volume reclassification was defined as an increase in cancer volume from <34% to ≥34% cores containing cancer (n = 131 events). An additional analysis was conducted with inclusion of available MRI results as a covariate. To explore whether marital status (married vs single) was associated with treatment overall and in the absence of reclassification, univariable and multivariable models were also evaluated among the subset of men enrolled after June 2015 (n = 692), when PASS started collecting these data. A 2-sided P value < .05 was considered statistically significant. Analyses were performed with R version 3.3.0.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the study sample. The cohort was predominantly White men with GG 1, clinical stage T1 disease. The median AUA symptom score at enrollment was 7 (interquartile range, 3-12), and the most common AUA QOL scores were "pleased" and "mostly satisfied." With a median follow-up of 5.6 years (interquartile range, 2.5-8.6 years), 401 were treated after GG reclassification at biopsy, and 181 were treated without GG reclassification. Within 4 years of the diagnosis, the estimated cumulative incidence of being treated was 33% (95% confidence interval [CI], 30%-35%) and 10% (95% CI, 9%-12%)

TABLE 1. Demographics and Clinical Data

	Not Treated (n = 1207)	Treated After Reclassification (n = 401)	Treated Without Reclassification (n = 181)	Total (n = 1789)
Age, y	63 (58-67)	63 (58-67)	63 (58-67)	63 (58-67)
Race				
White	1056 (87)	346 (86)	164 (91)	1566 (88)
Black	91 (8)	34 (8)	11 (6)	136 (8)
Other	60 (5)	21 (5)	6 (3)	87 (5)
BMI, kg/m^2 [a]	27.6 (25.2-30.7)	27.7 (25.2-30.7)	26.6 (24.4-29.4)	27.5 (25.1-30.6)
Gleason group				
1	1107 (92)	370 (92)	141 (78)	1618 (90)
2	100 (8)	31 (8)	40 (22)	171 (10)
PSA, ng/mL	5.1 (3.9-6.6)	5.1 (4.2-6.6)	5.0 (4.1-6.5)	5.1 (4-6.6)
Prostate size, cm^3	46.5 (34.5-62.8)	35.5 (27.1-50.9)	39.6 (33.1-50.4)	43.4 (32.1-58.6)
% positive cores	8.3 (8.3-16.7)	16.7 (8.3-25)	16.7 (8.3-25)	10 (8.3-16.7)
Clinical T stage[a]				
T1	1083 (90)	352 (88)	160 (88)	1595 (89)
T2a	115 (10)	46 (11)	20 (11)	181 (10)
T2b/c	9 (1)	3 (1)	1 (1)	13 (1)
AUA symptom score[a]	7 (4-12)	7 (3-11)	6 (3-11)	7 (3-12)
AUA QOL[a]				
Delighted	266 (22)	107 (27)	56 (31)	429 (24)
Pleased	317 (26)	122 (30)	48 (27)	487 (27)
Mostly satisfied	347 (29)	97 (24)	43 (24)	487 (27)
Mixed	187 (15)	47 (12)	22 (12)	256 (14)
Mostly dissatisfied	56 (5)	19 (5)	7 (4)	82 (5)
Unhappy	25 (2)	4 (1)	4 (2)	33 (2)
Terrible	9 (1)	5 (1)	1 (1)	15 (1)
Years between diagnosis and enrollment	0.6 (0.3-1.2)	0.6 (0.3-0.9)	0.6 (0.3-1.3)	0.6 (0.3-1.1)
Marital status[a,b]				
Married	429 (79)	81 (77)	38 (86)	548 (79)
Single	114 (21)	24 (23)	6 (14)	144 (21)

Abbreviations: AUA, American Urological Association; BMI, body mass index; PSA, prostate-specific antigen; QOL, quality of life.
Numbers and percentages (in parentheses) are displayed for categorical variables, and medians and interquartile ranges (in parentheses) are displayed for continuous variables.
[a]At enrollment.
[b]Percentages are based on participants with a known marital status. Before 2015, marital status was not collected.

with and without grade reclassification, respectively. The subset of 692 men who were enrolled since 2015 when data about marital status were collected had similar characteristics (Supporting Table 1).

Table 2 highlights the univariable and multivariable associations of individual factors with the risk of any treatment during follow-up. The strongest factor independently associated with receiving treatment over time was GG upstaging, with an adjusted hazard ratio (aHR) of 14.5 for a 1-unit GG increase (95% CI, 11.7-17.9). Additional significant factors included GG at diagnosis, PSA, age, prostate size, volume of positive cores, and body mass index. The AUA QOL score was associated with the time to treatment (hazard ratio comparing "mostly dissatisfied/terrible" with "pleased/mixed," 1.72; 95% CI, 1.25-2.36; hazard ratio comparing "delighted" with "pleased/mixed," 1.31; 95% CI, 1.09-1.58; $P < .001$); however, the effects were attenuated and not significant after adjustments for other factors ($P = .3$). The AUA symptom score was not significantly associated with any treatment.

Table 3 displays the univariable and multivariable associations of individual factors with the time to treatment in the absence of GG reclassification. Similarly to the associations for any treatment, GG at diagnosis, PSA, and the percentage of positive cores were all strongly associated with treatment without reclassification. The AUA QOL score was significantly associated with treatment without reclassification (aHR comparing "mostly dissatisfied/terrible" with "pleased/mixed," 2.65; 95% CI, 1.54-4.59). Among the subset of 692 men with marital status data, marital status was also independently associated with treatment in the absence of reclassification (aHR for married men vs single men, 2.63; 95% CI, 1.04-6.66), although it was not associated with any treatment (Supporting Tables 2 and 3). Associations of AUA QOL with treatment in the absence of reclassification were similar when the analysis was restricted to men with GG 1 at diagnosis (aHR, 3.45; 95% CI, 1.9-6.38) and when the end point excluded volume reclassification (aHR, 2.41; 95% CI, 1.28-4.53). Overall, 593 men (33%) had MRI imaging performed at some point

TABLE 2. Univariable and Multivariable Results of a Cox Proportional Hazards Model of Any Treatment Among PASS Participants

	Univariate Hazard Ratio	*P*	Multivariate Hazard Ratio	*P*
Gleason grade group[a]		<.001		<.001
1 (referent)	1.00		1.00	
2	1.83 (1.42-2.34)		1.73 (1.33-2.26)	
Increase in Gleason grade group		<.001		<.001
1	25.5 (21.1-30.8)		14.5 (11.7-17.9)	
2	64.67 (49.6-84.4)		36.6 (27.4-49.0)	
3	84.1 (54.2-130.7)		31.1 (19.2-50.2)	
4	140.0 (69.8-280.9)		52.3 (25.3-108.4)	
PSA[a,b]	1.31 (1.14-1.51)	<.001	1.68 (1.39-2.02)	<.001
Difference in PSA[b]	2.63 (2.23-3.1)	<.001	1.7 (1.44-2.01)	<.001
Age[a]	1.00 (0.99-1.01)	.7	0.98 (0.97-0.99)	.003
Prostate size[b]	0.46 (0.39-0.56)	<.001	0.70 (0.56-0.89)	.003
% positive cores[c]	1.83 (1.77-1.89)	<.001	1.31 (1.24-1.37)	<.001
Clinical T stage		<.001		.13
T1c (referent)	1.00		1.00	
T2a	1.96 (1.55-2.49)		1.2 (0.93-1.55)	
T2b+	2.07 (1.19-3.6)		0.68 (0.38-1.2)	
AUA symptom score[d]	0.95 (0.89-1.02)	.17	1.07 (0.99-1.16)	.11
AUA QOL score		<.001		.3
Delighted	1.31 (1.09-1.58)		1.12 (0.9-1.38)	
Pleased/ mixed (referent)	1.00		1.00	
Mostly dissatisfied/ terrible	1.72 (1.25-2.36)		1.21 (0.85-1.72)	
Race		.2		.4
White (referent)	1.00		1.00	
Black	1.36 (1-1.84)		1.20 (0.88-1.65)	
Other	1.03 (0.70-1.52)		0.86 (0.58-1.28)	
BMI	1.00 (0.98-1.02)	>.9	0.98 (0.96-1)	.029

Abbreviations: AUA, American Urological Association; BMI, body mass index; PASS, Prostate Active Surveillance Study; PSA, prostate-specific antigen; QOL, quality of life.
[a]At diagnosis.
[b]Log.
[c]Per 10% increase.
[d]Per 5-unit increase.

during their enrollment in PASS. The inclusion of MRI as a covariate did not appreciably alter the other associations, and although the MRI results were significant in the model for any treatment (aHR for Prostate Imaging–Reporting and Data System score ≥ 4 vs no MRI, 1.52; 95% CI, 1.20-1.91) they were not significant in the model of treatment without reclassification (aHR, 1.59; 95% CI, 0.99-2.56). Sensitivity analyses using PSA density rather than PSA and prostate volume in the models did not show any appreciable differences in the other reported associations.

TABLE 3. Univariable and Multivariable Results of a Cox Proportional Hazards Model Predicting Treatment in the Absence of Grade Reclassification

	Univariate Hazard Ratio	*P*	Multivariate Hazard Ratio	*P*
Gleason grade group[a]		<.001		.011
1 (referent)	1.00		1.00	
2	3.62 (2.54-5.16)		1.69 (1.14-2.51)	
PSA[a,b]	1.32 (1.02-1.7)	.029	1.79 (1.28-2.52)	<.001
Difference in PSA[b]	2.48 (1.84-3.34)	<.001	2.31 (1.67-3.18)	<.001
Age[a,b]	0.99 (0.97-1.02)	.6	0.98 (0.96-1)	.093
Prostate size[b]	0.59 (0.43-0.81)	.001	0.69 (0.46-1.04)	.076
% positive cores[c]	1.84 (1.71-1.97)	<.001	1.7 (1.57-1.84)	<.001
Clinical T stage		.043		.9
T1c (referent)	1.00		1.00	
T2a	1.79 (1.15-2.8)		1.15 (0.71-1.85)	
T2b+	1.76 (0.56-5.51)		1.05 (0.33-3.36)	
AUA symptom score[d]	1.00 (0.89-1.12)	>.9	1.05 (0.91-1.21)	.5
AUA QOL score		<.001		.002
Delighted	1.47 (1.06-2.05)		1.26 (0.87-1.84)	
Pleased/ mixed (referent)	1.00		1.00	
Mostly dissatisfied/ terrible	2.78 (1.71-4.54)		2.65 (1.54-4.59)	
Race		.7		.5
White (referent)	1.00		1.00	
Black	1.01 (0.55-1.85)		1.02 (0.55-1.89)	
Other	0.73 (0.32-1.64)		0.62 (0.27-1.42)	
BMI	0.97 (0.94-1.01)	.093	0.98 (0.95-1.01)	.3

Abbreviations: AUA, American Urological Association; BMI, body mass index; PSA, prostate-specific antigen; QOL, quality of life.
[a]At diagnosis.
[b]Log.
[c]Per 10% increase.
[d]Per 5-unit increase.

DISCUSSION

We found that within this large, contemporary cohort of men on active surveillance for prostate cancer, approximately one-third underwent treatment within 4 years of their diagnosis, and 1 in 10 pursued treatment in the absence of grade reclassification. For most patients, GG upgrading is the strongest predictor of prostate cancer treatment. However, for men who end up being treated without GG reclassification, urinary QOL, independently of clinical factors, appears to be an important factor. Exploratory analyses also suggest that married men are more likely to undergo treatment without reclassification. Our findings suggest that factors other than cancer characteristics play an important

role in men on active surveillance electing to pursue treatment for their prostate cancer. It should be noted, however, that disease characteristics remain important predictors of treatment even in the absence of grade reclassification. This may reflect both a lower threshold to pursue treatment in patients with more aggressive baseline characteristics (GG 2 disease, more positive cores, and/or higher PSA levels at diagnosis) and changes such as rising PSA levels that prompt treatment before these changes are manifested in the form of grade reclassification.

The results of this study are consistent with prior work examining the decision to pursue treatment rather than continuing active surveillance.[13,20] Longitudinal, population-based data have suggested that as many as 20% of men electing to discontinue active surveillance do so because of personal preference rather than biopsy or PSA progression.[21] Prior results from the PASS cohort showed that within the first 2 years of follow-up on active surveillance, nearly one-third of men who decided to pursue treatment did so in the absence of adverse disease reclassification.[22] This work helps to clarify the motivations and factors involved in the decision-making for those men.

Interestingly, although QOL was significantly associated with treatment without reclassification in this study, the symptom score was not, and this could imply that other unmeasured factors may be driving the lower observed QOL. One possible explanation is that patients with worsened anxiety surrounding their diagnosis and active surveillance interpret their symptoms differently and with more severe detriment to their QOL even in the absence of measurable differences in their urinary symptoms. Cancer-related anxiety was previously associated with worsened urinary symptoms.[23] The results of our sensitivity analyses suggest that although the symptom score is associated with treatment without reclassification, this relationship is not independent of QOL. Furthermore, the lack of an attenuation of the association between QOL and treatment without reclassification between univariable and multivariable models further implies additional unmeasured factors affecting QOL. Work assessing factors influencing QOL scores has found that additional psychological factors such as anxiety and depression are independent factors influencing urinary QOL score results.[24]

We also found in an exploratory subset analysis that marital status is an independent factor associated with the pursuit of treatment in the absence of reclassification. This could be from the anxiety of the partner influencing decision-making. Alternatively, spouses may affect the way in which patients perceive their symptoms and QOL and help to define what is tolerable versus intolerable. Either way, this result suggests that any intervention to help to optimize the retention of men enrolled in active surveillance will need to incorporate partners in the decision-making process.

This study has several important limitations. Although this work includes data from surveys of urinary symptoms and QOL, it will be important for future work in this area to include comprehensive measures of anxiety that we did not have available for these analyses. There has been significant study of anxiety as a driving factor in the decision of men not to pursue active surveillance.[15,16] Our study is further limited by the intrinsic selection of the men included in this study. They opted to enroll in a prospective cohort study, and their motivations for pursuing treatment could theoretically differ from those of community urology patients. However, if there were a difference, we would expect that it would favor even larger differences than those measured here because resources and support to help to manage the stress of active surveillance are likely more available to study participants than general patients with prostate cancer in the community. Lastly, this data source does not include detailed information regarding the treating physicians, and it is likely that treating physicians' preferences and biases may play some role in the decision-making regarding the discontinuation of active surveillance.

Nonetheless, this study has important implications for patients undergoing active surveillance for prostate cancer and for the providers caring for these men. Those attempting to retain men on active surveillance in the absence of disease progression will need to find ways to target and improve QOL, whether by directly managing lower urinary tract symptoms medically or surgically or by better controlling cancer-related and general anxiety. These approaches will also need to incorporate the partners and caregivers of patients to fully address this issue.

In summary, we demonstrate that an important subgroup of men on active surveillance pursue treatment in the absence of clinically important changes in their cancers and that lower reported urinary QOL and marital status appear to be important factors related to these decisions in addition to prostate cancer characteristics. These insights could be used to design focused interventions to help to prevent premature treatment and potentially avoidable side effects. Similarly, spouses and caregivers should be incorporated as key stakeholders in shared decision-making and decision aid–based discussions. Doing so could enable

increased, longer term participation of more men on active surveillance for prostate cancer.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Peter S. Kirk: Conceptualization, visualization, and writing–original draft. **Kehao Zhu:** Conceptualization, data curation, formal analysis, software, visualization, and writing–original draft. **Yingye Zheng:** Formal analysis, methodology, and writing–review and editing. **Lisa F. Newcomb:** Conceptualization, methodology, project administration, supervision, and writing–review and editing. **Jeanette M. Schenk:** Methodology and writing–review and editing. **James D. Brooks:** Conceptualization and writing–review and editing. **Peter R. Carroll:** Conceptualization and writing–review and editing. **Atreya Dash:** Conceptualization and writing–review and editing. **William J. Ellis:** Conceptualization and writing–review and editing. **Christopher P. Filson:** Conceptualization and writing–review and editing. **Martin E. Gleave:** Conceptualization and writing–review and editing. **Michael Liss:** Conceptualization and writing–review and editing. **Frances Martin:** Conceptualization and writing–review and editing. **Jesse K. McKenney:** Conceptualization and writing–review and editing. **Todd M. Morgan:** Conceptualization and writing–review and editing. **Peter S. Nelson:** Conceptualization and writing–review and editing. **Ian M. Thompson:** Conceptualization and writing–review and editing. **Andrew A. Wagner:** Conceptualization and writing–review and editing. **Daniel W. Lin:** Conceptualization, funding acquisition, methodology, supervision, and writing–review and editing. **John L. Gore:** Conceptualization, methodology, supervision, and writing–original draft.

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