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Treatment in the absence of disease reclassification among men on active surveillance for prostate cancer

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Abstract

BACKGROUND—Maintaining men on active surveillance (AS) 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. We sought to understand factors associated with treatment in a large, contemporary, prospective cohort.

METHODS—We identified 1,789 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 demographics data as well as information for patient-reported quality of life and urinary symptoms were used in multivariable Cox proportional hazards regression models to identify factors associated with time to treatment

RESULTS—Within 4 years of diagnosis, 33% (95% CI 30–35) of men underwent treatment, and 10% (95% CI: 9–12) were treated in the absence of reclassification. The most significant factor associated with any treatment was increasing Gleason grade group (GG) (adjusted HR (aHR) 14.5, 95% CI 11.7–17.9). Urinary quality of life scores were associated with treatment without reclassification (aHR 2.65, 95% CI 1.54–4.59, mostly dissatisfied-terrible versus pleased). In a subset analysis (N=692), married men, compared to singles, 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.

Lay Summary:

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

Precis:

Some men on active surveillance for prostate cancer will eventually choose to be treated even in the absence of clinical progression of their disease. These decisions may be driven in part by quality of life concerns or involvement of spouses.

Keywords

prostatic neoplasms; active surveillance; 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 risk of progression on active surveillance and subsequent decision to pursue definitive therapy.[4–14]

Less well characterized are the reasons why 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 comparing patients undergoing treatment in the presence versus absence of reclassification.

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.

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). Under the PASS protocol, prostate-specific antigen (PSA) is measured every 3 months, clinic visits occur every 6 months, and biopsies are performed 6 to 12 months and 24 months after diagnosis, and then every 2 years. Magnetic resonance imaging (MRI) is performed at the treating clinicians' discretion. The study population was 2,003 men enrolled in PASS as of April 2020. For this analysis, men enrolled more than 5 years after diagnosis (n=62), treated within 6 months after diagnosis or prior to the first surveillance biopsy (n=46) were excluded. In addition, men who reclassified to a higher biopsy Gleason Group (GG) prior to enrollment (n=90) or were diagnosed with GG 3 (n=8) or missing data (n=8) were also excluded, leaving 1,789 men in the analyses.

Statistical Methods

The primary endpoints examined include: 1) time from diagnosis to any prostate cancer treatment; and 2) time from diagnosis to prostate cancer treatment without grade reclassification at a surveillance biopsy. For both endpoints, participants without treatment were censored at the date of last study contact. Patients enrolled after diagnosis are treated as left truncated data and were only considered at risk after the time of enrollment. For models

examining 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 endpoints were estimated via Aalen-Johansen estimator. Time-varying covariate Cox proportional hazards (PH) regression models were used to examine the associations between the covariates of interest and time to any treatment and cause-specific Cox PH models were used for the time to treatment without reclassification endpoint to account for competing risk. Information on clinical, pathologic, urinary symptoms and demographics is considered for covariates, including GG at diagnosis, age at diagnosis, PSA at diagnosis (log transformed), race (Black, white or other). Additionally, increase in GG, percent of cores containing cancer, prostate size (log transformed) and difference in PSA from diagnosis (log transformed). AUA urinary QOL score (delighted, pleased/mostly satisfied/mixed, or mostly dissatisfied/unhappy/terrible), AUA symptom score, BMI and clinical T-stage were modeled as time-varying covariates, utilizing most recent information prior to event times. Sensitivity analyses were conducted restricting the cohort to men with GG 1 at diagnosis (n=1,618) 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), as well as in men who underwent MRI during enrollment. To explore whether marital status (married, single) was associated with treatment overall and in 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 two-sided p-value of <0.05 was considered statistically significant. Analyses were performed using R version 3.3.0.

RESULTS

Table 1 summarizes demographic and clinical characteristics of the study sample. The cohort was predominantly white men with GG 1, clinical stage T1 disease. Median (Interquartile range, IQR) AUA symptom score at enrollment was 7 (3–12) (and the most common AUA QOL scores were “pleased” or “mostly satisfied”. With a median (IQR) follow-up of 5.6 (2.5 – 8.6) years, 401 were treated after GG reclassification at biopsy, and 181 were treated without GG reclassification. Within 4 years of diagnosis, the estimated cumulative incidence (95% confidence interval, CI) of being treated was 33% (95% CI: 30–35), and 10% (95% CI: 9–12) for being treated with and without grade reclassification, respectively. The subset of 692 men enrolled since 2015 when data about marital status were collected had similar characteristics (Supplementary Table 1).

Table 2 highlights the univariable and multivariable associations of individual factors with risk of any treatment during follow-up. The strongest factor independently associated with receiving treatment over time was GG upstaging, with an 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 BMI. AUA QOL score was associated with time to treatment (HR 1.72 comparing “mostly dissatisfied/terrible” with “pleased/mixed”, 95% CI 1.25 – 2.36; HR 1.31 comparing “delighted” with “pleased/mixed”, 95% CI 1.09

– 1.58; p <0.001); however, the effects were attenuated and not significant after adjusting for other factors (p = 0.3). AUA symptom score was not significantly associated with any treatment.

Table 3 displays the univariable and multivariable associations of individual factors with time to treatment in the absence of GG reclassification. Similar to associations for any treatment, GG at diagnosis, PSA, and percent of positive cores were all strongly associated with treatment without reclassification. AUA QOL score was significantly associated with treatment without reclassification (aHR 2.65 comparing "mostly dissatisfied/terrible" with "pleased/mixed", 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 2.63 for married men compared with single men, 95% CI 1.04–6.66), though it was not associated with any treatment (Supplementary Tables 2 and 3). Associations of AUA QOL with treatment in the absence of reclassification were similar when restricted to men with GG 1 at diagnosis (aHR=3.45, 95% CI 1.9–6.38) and when the endpoint excluded volume reclassification (aHR=2.41, 95% CI 1.28–4.53). Overall, 593 men (33%) had MRI imaging performed at some point during their enrollment in PASS. Inclusion of MRI as a covariate did not appreciably alter the other associations, and while MRI results were significant in the model for any treatment (aHR 1.52 PIRADS ≥ 4 versus no MRI, 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 utilizing PSA density rather than PSA and prostate volume in the models did not show any appreciable differences in the other reported associations.

DISCUSSION

We found that within this large, contemporary cohort of men on active surveillance for prostate cancer, approximately one-third underwent treatment within four years of diagnosis, and one-in-ten 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—independent of clinical factors—appears to be an important factor. Exploratory analyses also suggest that married men were 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 lower threshold to pursue treatment in patients with more aggressive baseline characteristics (GG2 disease, more positive cores, and/or higher PSA at diagnosis) as well as changes such as rising PSA which prompt treatment before these changes are manifested in the form grade reclassification.

The results of this study are consistent with prior work examining the decision to pursue treatment rather than continue active surveillance.[13,20] Longitudinal population-based data have suggested that as many as 20% of men electing to discontinue active surveillance did so due to personal preference rather than biopsy or PSA progression.[20] Prior results from the PASS cohort have found that within the first two 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 motivations and factors involved in the decision-making for those men.

Interestingly, although QOL was significantly associated with treatment without reclassification in this study, symptom score was not, which 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 symptom score is associated with treatment without reclassification, this relationship is not independent of QOL. Further, the lack of an attenuation of the association between QOL and treatment without reclassification between univariable and multivariable models further implies additional unmeasured factors impacting 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 pursuit of treatment in the absence of reclassification. This could be from the anxiety of the partner themselves influencing decision-making. Alternatively, spouses may affect the way that 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 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 which 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 community urology patients. However, if there were a difference, we would expect that it would favor even larger differences than those measured here, as resources and support to help manage the stress of active surveillance are likely more available to study participants than to general prostate cancer patients in the community. Lastly, this data source does not include detailed information regarding treating physician, and it is likely that treating physician preferences and biases may play some role in the decision making regarding discontinuation of active surveillance.

Nonetheless this study has important implications for patients undergoing active surveillance for prostate cancer and providers caring for these men. Attempts to retain men on active surveillance in the absence of disease progression will need to find ways to target and improve QOL, whether through direct management of lower urinary tract symptoms

medically or surgically or 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 avoid 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographics and clinical data.

	Not treated (n =1,207)	Treated following reclassification (n =401)	Treated without reclassification (n =181)	Total (n =1,789)
Age, years	63 (58–67)	63 (58–67)	63 (58–67)	63 (58–67)
Race				
White	1,056 (87)	346 (86)	164 (91)	1,566 (88)
Black	91 (8)	34 (8)	11 (6)	136 (8)
Other	60 (5)	21 (5)	6 (3)	87 (5)
BMI *, kg/m^2	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				
Group 1	1,107 (92)	370 (92)	141 (78)	1,618 (90)
Group 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 *				
T1	1,083 (90)	352 (88)	160 (88)	1,595 (89)
T2a	115 (10)	46 (11)	20 (11)	181 (10)
T2b/c	9 (1)	3 (1)	1 (1)	13 (1)
AUA symptom score *	7 (4–12)	7 (3–11)	6 (3–11)	7 (3–12)
AUA QOL *				
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 *^				
Married	429 (79)	81 (77)	38 (86)	548 (79)
Single	114 (21)	24 (23)	6 (14)	144 (21)

N (%) are displayed for categorical variables, median (interquartile range) for continuous.

*At enrollment.

^% are out of participants with known marital status. Prior to 2015, marital status was not collected.

Table 2.

Univariable and multivariable results of Cox proportional hazards model of any treatment among PASS participants.

	Univariate Hazard Ratio	P value	Multivariate Hazard Ratio	P value
Gleason grade group *		<0.001		<0.001
1 (referent)	1.00		1.00	
2	1.83 (1.42–2.34)		1.73 (1.33–2.26)	
Increase in Gleason grade group		<0.001		<0.001
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]	1.31 (1.14–1.51)	<0.001	1.68 (1.39–2.02)	<0.001
Difference in PSA[a]	2.63 (2.23–3.1)	<0.001	1.7 (1.44–2.01)	<0.001
Age *	1.00 (0.99–1.01)	0.7	0.98 (0.97–0.99)	0.003
Prostate size[a]	0.46 (0.39–0.56)	<0.001	0.70 (0.56–0.89)	0.003
% positive cores[b]	1.83 (1.77–1.89)	<0.001	1.31 (1.24–1.37)	<0.001
Clinical T-stage		<0.001		0.13
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[c]	0.95 (0.89–1.02)	0.17	1.07 (0.99–1.16)	0.11
AUA Quality of life score		<0.001		0.3
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		0.2		0.4
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)	>0.9	0.98 (0.96–1)	0.029

*At diagnosis

[a]log.

[b]per 10% increase.

[c]per 5 unit increase.

Table 3.

Univariable and multivariable results of Cox proportional hazards model predicting treatment in the absence of grade reclassification.

	Univariate Hazard Ratio	P value	Multivariate Hazard Ratio	P value
Gleason grade group *		<0.001		0.011
1 (referent)	1.00		1.00	
2	3.62 (2.54–5.16)		1.69 (1.14–2.51)	
PSA *a	1.32 (1.02–1.7)	0.029	1.79 (1.28–2.52)	<0.001
Difference in PSA a	2.48 (1.84–3.34)	<0.001	2.31 (1.67–3.18)	<0.001
Age *a	0.99 (0.97–1.02)	0.6	0.98 (0.96–1)	0.093
Prostate size a	0.59 (0.43–0.81)	0.001	0.69 (0.46–1.04)	0.076
% positive cores b	1.84 (1.71–1.97)	<0.001	1.7 (1.57–1.84)	<0.001
Clinical T-stage		0.043		0.9
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 c	1.00 (0.89–1.12)	>0.9	1.05 (0.91–1.21)	0.5
AUA Quality of life score		<0.001		0.002
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		0.7		0.5
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)	0.093	0.98 (0.95–1.01)	0.3

*At diagnosis

*a*log.

*b*per 10% increase.

*c*per 5 unit increase.