The Relationship between Intolerance of Uncertainty and Anxiety in Men on Active Surveillance for Prostate Cancer

Hung-Jui Tan,* Leonard S. Marks, Michael A. Hoyt, Lorna Kwan, Christopher P. Filson, Malu Macairan, Patricia Lieu, Mark S. Litwin and Annette L. Stanton

From the Veterans Affairs/UCLA Robert Wood Johnson Clinical Scholars Program (HJT), Department of Urology, David Geffen School of Medicine (HJT, LSM, LK, CPF, MM, PL, MSL), Department of Health Policy and Management, Fielding School of Public Health (MSL), Departments of Psychology and Psychiatry/Biobehavioral Sciences (ALS) and Jonsson Comprehensive Cancer Center (ALS), University of California-Los Angeles, Los Angeles, California, and Department of Psychology, Hunter College, City University of New York (MAH), New York, New York

Purpose: Anxiety may serve as a major barrier to participation in active surveillance. Intolerance of uncertainty, that is the tendency to perceive the potential for negative events as threatening, has been linked to cancer related worry. Accordingly we explored prospectively the relationship of intolerance of uncertainty with anxiety along with other clinical factors among men treated with active surveillance for prostate cancer.

Materials and Methods: A total of 119 men with D'Amico low risk prostate cancer participating in active surveillance completed the HADS (Hospital Anxiety and Depression Scale), MAX-PC (Memorial Anxiety Scale for Prostate Cancer), IUS (Intolerance of Uncertainty Scale) and I-PSS (International Prostate Symptom Score) surveys from 2011 to 2014. We evaluated the relationship between anxiety and IUS score after adjusting for patient characteristics, cancer information and I-PSS using bivariable and multivariable analyses.

Results: Of the men 18 (15.1%) and 17 (14.3%) reported clinically significant anxiety on the generalized and prostate cancer specific scales, respectively. On bivariable analysis men with moderate/severe urinary symptoms and higher IUS scores reported more generalized and prostate cancer specific anxiety than men with mild urinary symptoms and lower IUS scores, respectively ($p \leq 0.008$). Men with depressive symptoms ($p = 0.024$) or a family history of prostate cancer ($p = 0.006$) experienced greater generalized anxiety. On multivariable analysis IUS score was significantly associated with generalized and prostate cancer specific anxiety (OR 1.22, 95% CI 1.09−1.38 and OR 1.29, 95% CI 1.13−1.49, respectively) while moderate/severe urinary symptoms were associated with prostate cancer specific anxiety (OR 6.89, 95% CI 1.33−35.68).

Conclusions: Intolerance of uncertainty and urinary symptoms may promote anxiety in men on active surveillance for prostate cancer. Patient education, management of lower urinary tract symptoms and behavioral interventions may lessen anxiety related to uncertainty intolerance and help maintain patient engagement in active surveillance.

Key Words: prostatic neoplasms, watchful waiting, anxiety, uncertainty, questionnaires

MOST men with prostate cancer are currently diagnosed with localized, low risk disease that is unlikely to be lethal.[1,2] Nevertheless, 70% to 80% of these men undergo surgery or radiation, which carry potential short-term and long-standing side effects.[3,4] As an alternative, AS offers acceptable cancer specific survival and minimal morbidity.[5,6] Accordingly, AS is now considered a valid management strategy with use reaching as many as half of the men with low risk prostate cancer in certain regions of the United States.[4,7,8]

Despite its potential benefits AS has been underused in men with localized prostate cancer.[4] An often mentioned reason is the toll of cancer related anxiety on expectantly treated patients.[9] Because the underlying threat of prostate cancer among patients on surveillance is small but ever present,[5] the severity of distress may vary with perceptions of health and overall psychological adjustment.[10] Intolerance of uncertainty, which is a predisposing trait for anxiety marked by the tendency to perceive uncertainty as threatening,[11] perpetuates anxiety symptoms in patients with a variety of health conditions, including prostate cancer.[12,13] Men on AS may be particularly vulnerable, given the monitoring based approach to care. Interval PSA testing and prostate biopsies integral to AS could exacerbate perceptions of threat and, therefore, worry. Physical symptoms and other patient attributes may also interact with uncertainty intolerance.[14] However, to our knowledge the impact of intolerance of uncertainty among men undergoing AS of prostate cancer has been unexplored to date.

In this context we hypothesized that men on AS for prostate cancer who had greater intolerance of uncertainty would be more likely to experience anxiety. We examined this in a prospective cohort study. To understand this cognitive underpinning we may facilitate the development of strategies that decrease the psychological burden of expectant treatment approaches in men with prostate cancer.

MATERIALS AND METHODS

Patient Cohort
From February 2011 to June 2014 we enrolled 267 men in the UCLA AS program, an institutional review board approved, longitudinal registry with entry restricted to men with low or intermediate risk prostate cancer based on the D'Amico risk classification.[15] As part of this prospective cohort study 257 men (96.3%) completed questionnaires related to anxiety, depression, quality of life and urinary symptoms upon entry. Because the impact of prostate cancer on patient reported mental health tends to lessen with time,[16] we decreased the study population to 144 men enrolled within a year of initial diagnosis.

Finally, to limit heterogeneity we focused specifically on men with low risk disease (ie clinical stage T2 or less, Gleason 6 and PSA 10 ng/ml), resulting in a final cohort of 119.

As part of the study protocol participants underwent confirmatory magnetic resonance imaging-fusion guided biopsy, PSA/physical examination every 6 months and repeat biopsy within 1 year and annually or biannually thereafter. Participants completed surveys upon study entry and during subsequent followups in clinic or via a web based electronic platform. Initially participants completed questionnaires at 6-month intervals. To reduce the patient burden the protocol was amended to lengthen the interval to every 12 months midway through the study. At the time of analysis 69 of the 119 entrants (58.0%) had completed 2 or more surveys, yielding a subcohort of men with short-term followup data.

Primary Outcomes
Two validated, patient reported instruments were used to assess anxiety, including 1) the HADS anxiety subscale for generalized anxiety and 2) MAX-PC for prostate cancer specific anxiety. For each scale we used established cutoffs, including 8 or greater for HADS and 26 or greater for MAX-PC, to create binary measures of anxiety.[17,18]

Uncertainty Intolerance and Additional Covariates
To measure intolerance of uncertainty we used a modified version of IUS. We pared the original 27-item instrument to 8 items based on the highest item total correlations in the initial validation study.[19] Additionally, we collected information on patient demographics, comorbidities, family history, clinic visits and indicators of cancer severity by patient report and medical chart review. We assessed depressive symptoms using the depression subscale of the HADS instrument and urinary symptoms using I-PSS.

Statistical Analysis
First we examined the relationships at study entry between generalized and prostate cancer specific anxiety and intolerance of uncertainty as well as relevant demographic and clinical variables using the Student t-test or the chi-square test as appropriate. Next we performed multivariable logistic regression to assess the association of intolerance of uncertainty scores with anxiety at study entry, adjusting for patient age, race, marital status, education, comorbidities, urinary symptom score, family history of prostate cancer and depressive symptoms. From this we calculated the model adjusted probability of anxiety at the mean intolerance of uncertainty level and at half SDs above and below, which represent clinically significant changes in score.[20] We also compared the adjusted probability of anxiety according to mild vs moderate/severe urinary symptoms using an I-PSS cutoff of 7.

As an exploratory analysis we examined the relationship between intolerance of uncertainty and anxiety in the early surveillance period. First using the Student t-test or the chi-square test as appropriate we compared baseline characteristics between men who had yet to return for followup vs those who had completed at least 2 surveys. Next in the subcohort with followup we stratified

survey responses into 4 time based categories, including baseline, less than 9 months, 9 to 15 months and greater than 15 months, and examined the relationship with time using the chi-square test and ANOVA. Finally we constructed repeated measures, multivariable logistic regression models using all available data from study entry to last followup. We refitted our multivariable models, included time since study entry as an additional covariate and then again determined the model adjusted probability of generalized and prostate cancer specific anxiety. As sensitivity analyses we also examined models including men who had intermediate risk disease with further adjustment for PSA and Gleason score. We then incorporated select interaction terms between IUS score and other clinical variables.

All statistical testing was 2-sided and performed using SAS®, version 9.4 with significance considered at the 5% significance level. The registry and this study were approved by the UCLA institutional review board.

RESULTS

Baseline Analysis
Of 119 men 18 (15.1%) and 17 (14.3%) reported generalized and/or prostate cancer specific anxiety, respectively. Table 1 lists several factors associated significantly with anxiety. Intolerance of uncertainty related directly to generalized and prostate cancer specific anxiety ($p \leq 0.001$). Additionally, men with increased depressive symptoms ($p = 0.024$), moderate/severe urinary symptoms ($p = 0.008$) or a family history of prostate cancer ($p = 0.006$) were more likely to have generalized anxiety whereas men with moderate/severe urinary symptoms were more like to have anxiety related to prostate cancer ($p = 0.003$). We did not observe an association of PSA

with generalized anxiety ($p = 0.438$), prostate cancer specific anxiety ($p = 0.760$) or PSA specific anxiety as measured by the PSA subscale of the MAX-PC instrument ($p = 0.916$). We found no difference in the number of previous biopsies ($p = 0.251$) or the performance of biopsy at the time of survey administration ($p = 0.433$) between patients with and without anxiety.

Five men (5.0%) without and 1 (5.6%) with generalized anxiety elected to withdraw from AS without evidence of disease progression as of June 2014 ($p = 0.918$). Seven men proceeded to treatment due to disease progression.

On multivariable analyses intolerance of uncertainty remained significantly associated with generalized and prostate cancer specific anxiety (OR 1.22, 95% CI 1.09–1.38 and OR 1.29, 95% CI 1.13–1.49, respectively, supplementary table 1, http://jurology.com/). Although it was not significantly associated with generalized anxiety (OR 2.88, 95% CI 0.76–10.99), moderate/severe urinary symptoms were more common among men with prostate cancer specific anxiety (OR 6.89, 95% CI 1.33–35.68). Men with a family history of prostate cancer also had an increased likelihood of generalized anxiety (OR 4.26, 95% 1.11–16.42). Figure 1 shows the change in the probability of generalized and prostate cancer specific anxiety in response to meaningful changes in intolerance of uncertainty and in men with moderate/severe vs mild urinary symptoms.

Longitudinal Analysis
A total of 69 men completed 2 or more surveys at a median followup of 12 months (IQR 7–18). Patient

Table 1. *Patient and clinical factors according to generalized and prostate cancer specific anxiety*

	HADS Anxiety Subscale*			MAX-PC Prostate Ca†		
	Generalized	None	p Value	Anxiety	No Anxiety	p Value
No. pts	18	101		17	102	
Mean ± SD age	62.5 ± 6.0	63.8 ± 7.5	0.503	62.8 ± 5.9	63.7 ± 7.5	0.636
% Nonwhite race/ethnicity	16.7	14.9	0.735	11.8	15.7	0.999
% Married	83.3	81.2	1.000	76.5	82.4	0.517
% College graduate	61.1	77.0	0.237	70.6	75.2	0.765
Mean ± SD body mass index (kg/m^2)	26.9 ± 3.5	26.6 ± 3.9	0.760	26.3 ± 3.4	26.7 ± 3.9	0.760
Mean ± SD baseline PSA (ng/ml)	3.9 ± 2.2	4.4 ± 2.5	0.438	4.5 ± 2.5	4.3 ± 2.4	0.701
% Biopsy at time of survey	44.4	54.5	0.433	47.1	53.9	0.600
% Any comorbidity	44.4	41.6	0.821	29.4	44.1	0.255
% BPH	33.3	32.7	0.956	41.2	31.4	0.425
% Prostate Ca family history	55.6	20.8	0.006	47.1	22.5	0.069
% HADS depression subscale*	16.7	2.0	0.024	11.8	2.9	0.148
% I-PSS:						
0—7	27.8	61.4	0.008	23.5	61.8	0.003
8+	72.2	38.3		76.5	38.2	
% I-PSS bother:						
0—2	61.1	81.2	0.069	58.8	81.4	0.055
3—6	38.9	18.8		41.2	18.6	
Mean ± SD IUS total score	17.2 ± 6.5	10.9 ± 4.2	<0.001	18.2 ± 7.9	10.8 ± 3.6	0.001

*Cutoff 8 points.
†Cutoff 26 points.
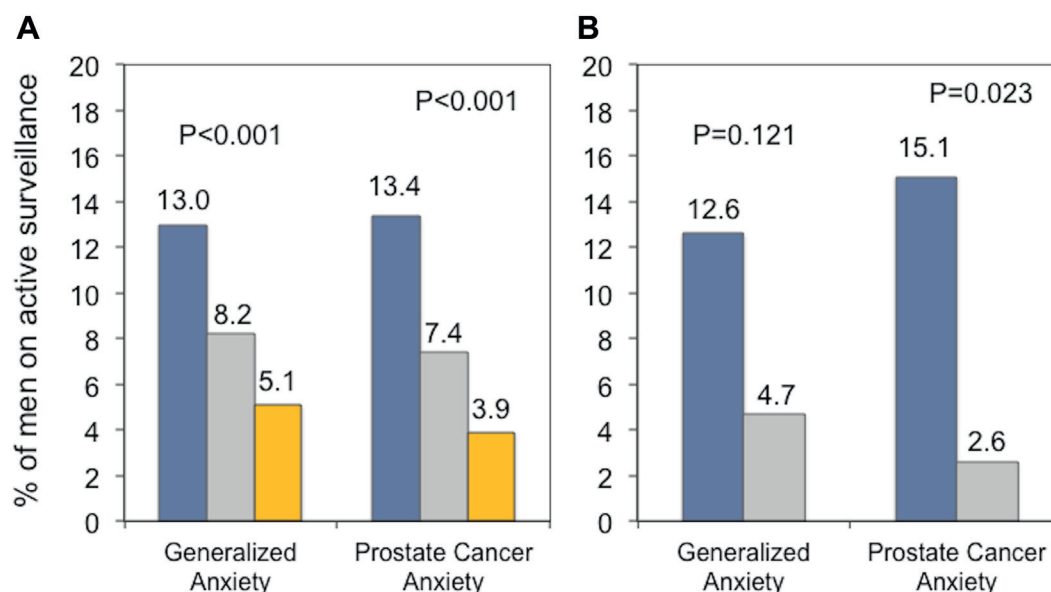
Figure 1. Adjusted multivariable regression model shows predicted probability and p values of generalized and prostate cancer specific anxiety at baseline. *A,* according to IUS score. Blue bars represent mean score + 0.5 SD. Gray bars represent mean score. Yellow bars represent mean score − 0.5 SD. *B,* according to intolerance of urinary symptoms based on I-PSS. Blue bars represent moderate to severe symptoms. Gray bars represent mild symptoms.

demographics, cancer specific covariates and the proportion with anxiety did not differ significantly between the 69 patients with followup data and the 50 with only baseline data (p >0.05). Patient reported outcomes did not vary significantly with time (table 2).

During the initial surveillance period greater intolerance of uncertainty (OR 1.15, 95% CI 1.07−1.23) and moderate/severe urinary symptoms (OR 3.44, 95% CI 1.13−10.50) were associated with greater odds of generalized anxiety compared to lower intolerance of uncertainty and mild urinary symptoms, respectively, in the repeated measures, multivariable regression models (supplementary table 1, http://jurology.com/). We noted similar findings with respect to prostate cancer specific anxiety for intolerance of uncertainty and moderate/severe urinary symptoms (OR 1.28, 95% CI 1.17−1.40 and OR 6.18, 95% CI 2.36−16.20, respectively). Figure 2 shows predicted probabilities. Months on surveillance did not predict generalized or prostate cancer specific anxiety (OR 0.95, 95% CI 0.89−1.01 and OR 0.92, 95% CI 0.85−1.01,

respectively). Otherwise only nonwhite race/ethnicity was associated with prostate cancer specific anxiety (OR 3.82, 95% CI 1.05−13.82). Study findings remained consistent across the specified sensitivity analyses (supplementary table 2, http://jurology.com/).

DISCUSSION

Given the indolent nature of low risk prostate cancer and the probability of death from other causes, AS has been endorsed as a management strategy by several organizations, including the AUA (American Urological Association).[2,7] While utilization trends indicate increasing application of AS,[4,8] many men continue to elect surgery or radiation despite the small margin of benefit.[2] Among a host of considerations mental and emotional health have been found to vary with treatment, and likely factor into the individual treatment decision.[16]

In this health domain anxiety and management of uncertainty arise as potential barriers to the adoption of and adherence to AS by patients and

Table 2. *Patient reported urinary symptoms and psychosocial measures with time*

Measure	Cutoff	Baseline	Period 1	Period 2	Period 3	p Value
No. pts		69	40	43	40	—
% Moderate/severe I-PSS	8	43.5	55.0	51.2	55.0	0.573
Mean ± SD IUS score	—	12.0 ± 5.8	12.5 ± 6.3	12.3 ± 6.7	13.4 ± 7.0	0.723
% Anxiety:						
HADS generalized subscale	8	15.9	20.0	11.9	12.5	0.595
MAX-PC prostate Ca	26	14.5	15.0	14.6	12.5	0.988
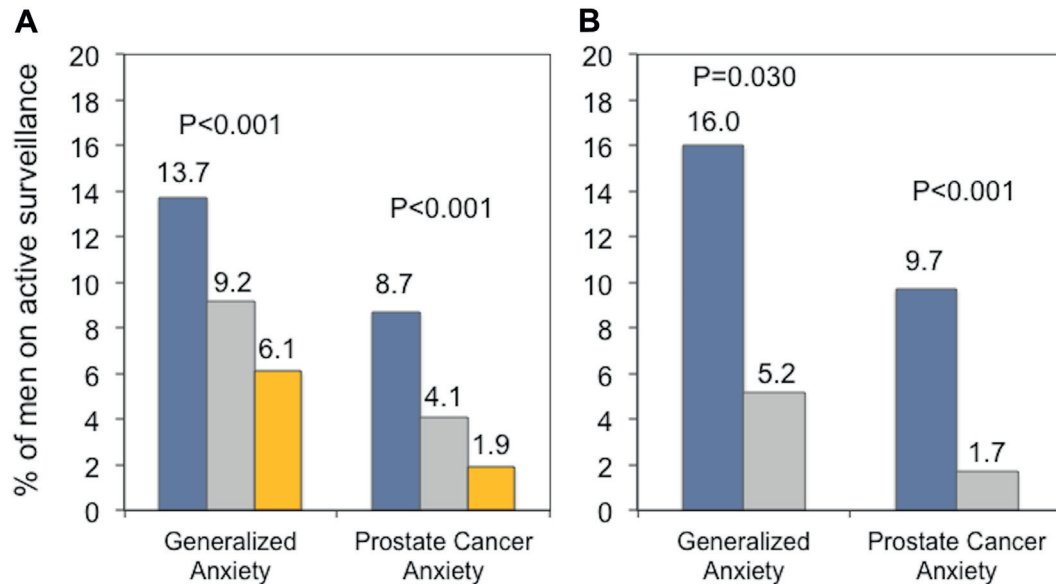
Figure 2. Repeated measures multivariable model shows probability and p values of generalized and prostate cancer specific anxiety during initial surveillance period. *A*, according to IUS score. Blue bars represent mean score + 0.5 SD. Gray bars represent mean score. Yellow bars represent mean score − 0.5 SD. *B*, urinary symptoms. Blue bars represent moderate to severe symptoms. Gray bars represent mild symptoms.

providers.[9,21] Consistent with previous studies,[22] approximately 1 of 5 men in our surveillance protocol reported clinically significant anxiety. Additionally, the proportion of men who experienced anxiety did not decrease, at least in the short term. Although it was not assessed in this study, registry data have suggested similar or higher levels of anxiety among men treated with AS compared with men treated with radical prostatectomy.[16,23] Overall these findings confirm that pervasive worry and psychological distress occur with some regularity in the expectantly managed population.

Anxiety during AS appears to be linked to psychological and clinical factors that may be modifiable. In men with prostate cancer uncertainty concerns appear crucial and often stem from questions about the risks of mortality, disease progression and migration, treatment outcomes and/or treatment related side effects.[21] Although uncertainty itself can be distressing, the patient attitude toward uncertainty may be particularly important. The tendency to consider uncertainty threatening, unacceptable or unmanageable may be a principal precursor to pervasive worry and anxiety. As explored in this study, the probability of anxiety increased substantially with meaningful increases in intolerance of uncertainty. Similar findings have been reported for patients with lung cancer as well as men treated for prostate cancer.[13,24]

In addition to intolerance of uncertainty, urinary symptoms also had a significant relationship with anxiety. Interestingly the interpretation of bodily

cues has been linked to patient reported psychological stress throughout the spectrum of prostate cancer care. Urinary symptoms in particular have been associated with heightened levels of cancer fear and mood disturbances in men treated with radical prostatectomy.[25] Previous research also suggests that uncertainty intolerance perpetuates misinterpretation of bodily sensations during an anxiety or panic episode in patients with anxiety disorders.[14] Consistent with the common sense model of illness representations,[26] somatic signals, especially when arising from the urinary system, might facilitate catastrophic thinking and cycles of worry in men with high intolerance for uncertainty. Taken together intolerance of uncertainty, urinary symptoms and their interplay may serve as a potent catalyst for anxiety in men pursuing AS.

Our findings should be considered in the context of several limitations. 1) Because this prospective cohort study focuses on AS participants, we were unable to ascertain whether a relationship also exists between intolerance of uncertainty and the initial treatment decision. Similarly we could not assess whether the influence of uncertainty intolerance on anxiety varies with the selected management modality. Future empirical work is needed to understand the role of intolerance of uncertainty on decision making and management specific anxiety, particularly in men who elect definitive treatment despite being suitable candidates for AS.

2) Our study may miss subtle changes in anxiety associated with surveillance related testing.

However, it is worth noting that patient reported anxiety did not differ according to receipt of biopsy or PSA level.

3) Because of the limited cohort size and followup, we were unable to assess whether intolerance of uncertainty and urinary symptoms affect anxiety and discontinuation of AS in the long term, and whether this changes substantively with time. As part of this cohort study, a planned future analysis with more mature longitudinal data may clarify the time varying interplay among determinants of anxiety, biochemical and/or pathological changes and surveillance attrition, providing additional information that may aid patient selection and intersurveillance management. Similarly additional determinants of anxiety may become identifiable as the study population grows.

4) Given our study design, we were unable to determine causality, especially as it relates to the observed relationship between urinary symptoms and anxiety. Notably treatment of intolerance of uncertainty reduces anxiety symptoms, supporting the concept of intolerance of uncertainty as a cause of anxiety.[27]

5) Finally, as our study describes findings from a single institution, they may not be broadly generalizable. For example, illness related uncertainty, which was not measured in the current series, has been shown to differ based on patient race/ethnicity and education level. Intolerance of uncertainty and its relationship with anxiety may also vary across practice settings depending on the patient mix.[28]

These limitations notwithstanding, our findings have potential implications for professionals who care for men with prostate cancer on AS, given the modifiable nature of intolerance of uncertainty and urinary symptoms. In the case of the former, cognitive behavioral therapy that helps patients manage or accept uncertainty has been shown to reduce anxiety in a randomized, controlled trial.[27] Previous qualitative work also suggests that men on AS use several coping mechanisms to deal with uncertainty, such as framing prostate cancer as a benign process or augmenting surveillance with adjuncts (eg dietary modification and exercise).[21] While future research will be pivotal, cognitive and self-management interventions tailored toward these coping mechanisms along with effective patient education may help decrease uncertainty related distress.[29] Multidisciplinary prostate cancer survivorship programs that include social workers, psychologists and psychiatrists may be well positioned to offer such services to men at risk.

Urological management of urinary symptoms may further help lower anxiety in men on AS. Some data suggest that decreasing lower urinary tract symptoms medically or surgically may lessen anxiety in men with benign prostatic hyperplasia.[30] Although additional studies are needed, treatment of urinary symptoms may provide similar relief to men on AS with the added potential benefit of removing body cues that trigger and amplify intolerance of uncertainty. Identifying and addressing these determinants may minimize anxiety during AS, making this management approach more acceptable to men with low risk prostate cancer.

CONCLUSIONS

Intolerance of uncertainty may function as a potent determinant of anxiety among men pursuing AS for low risk prostate cancer. Lower urinary tract symptoms also are associated with patient reported anxiety. Risk assessment, patient education, management of lower urinary tract symptoms and behavioral interventions to increase uncertainty tolerance may lessen anxiety and help maintain patient engagement in AS.

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