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Long term cancer-specific anxiety in men undergoing active surveillance for prostate cancer: findings from a large prospective cohort

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Abstract

Purpose—Active surveillance is the preferred management of men with low-risk prostate cancer. Cancer-specific anxiety during active surveillance remains understudied. We sought to report long-term anxiety for men on active surveillance to determine if interventions need to be tailored to improve adherence.

Materials and Methods—Four hundred and thirteen men enrolled in active surveillance at a single tertiary care center completed quality of life surveys as part of routine care. A modified version of the Memorial Anxiety Scale for Prostate Cancer was used to determine cancer-specific anxiety. Generalized estimating equations evaluated the association between anxiety and length of time on surveillance. Additionally, we examined associations between anxiety and patient age, marital status, Gleason score, number of positive cores, family history, and overall health.

Results—The median age of men was 61 years with a median PSA at diagnosis 4.4 ng/ml; 95% of patients had Gleason 6 disease. The median time from initiation of active surveillance to last survey was 3.7 years. There was a 29% risk of reporting cancer-specific anxiety within the first year. Anxiety significantly decreased over time (OR=0.87; 95% CI: 0.79, 0.95; p=0.003). Pathologic and demographic characteristics were not associated with anxiety after adjusting for time on surveillance.

Conclusion—In men undergoing active surveillance, we observed a moderate risk of cancer-specific anxiety that significantly decreases over time. Those considering conservative management can be informed that, although it is common experience some anxiety initially, most patients rapidly adjust and report low levels of anxiety within 2 years.

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Keywords

Prostate cancer; anxiety; active surveillance

Introduction

The era of prostate specific antigen (PSA) screening has led to the widespread over diagnosis of non-lethal low-grade prostate cancer.¹ Subsequently, active surveillance has emerged as the preferred management strategy for appropriately selected patients with low-risk disease. By avoiding or postponing definitive intervention, the morbidity and impairments associated with radical treatment are reduced without compromising oncologic safety, or cancer specific survival.^{2,3,4,5} The use of active surveillance has dramatically increased in the United States over the last decade.^{6,7,8} However, despite its growing acceptance, studies have documented that up to one third of men may discontinue active surveillance for reasons other than disease reclassification, and that an estimated 5 to 13% of men may pursue treatment due to cancer-related anxiety.^{9,10,11,12}

Although recent studies have demonstrated no differences in health-related quality of life (HRQoL) and mental health between men undergoing active surveillance and those receiving treatment,⁵ evaluations of anxiety were conducted using generic instruments such as the Hospital Anxiety and Depression Scale (HADS). It is unclear if these tools are best suited to measure the sort of disease-specific anxiety that might be caused by living with untreated prostate cancer. For example, assessments of anxiety may yield different results if men are asked if they “feel butterflies in their stomach” – a question found in general anxiety instruments - versus being asked if they have “distressing worries or thoughts due to their cancer”, a typical item for disease-specific anxiety instruments.

Although a small number of studies have appropriately used cancer-specific questionnaires such as the Memorial Anxiety Scale for Prostate Cancer amongst men with active surveillance,^{12,13, 14} these are limited by small sample sizes, such as 32 patients, and short-term follow up, such as 9 months. At our institution, we have integrated the use of patient-reported outcomes for prostate cancer into routine clinical practice. For men followed on active surveillance, our routine questionnaires include assessment of cancer-related anxiety. This provides data on large numbers of patients with follow-up over many years.

The objective of this study was to estimate the risk of cancer-specific anxiety over time in men on active surveillance. Specifically, we sought to determine if prostate cancer-related anxiety for an individual patient changed over time, and if any clinical variables were associated with anxiety.

Materials and Methods

Patient Cohort

Following Institutional Review Board approval, we identified 463 patients from a longitudinal registry that were enrolled in active surveillance at Memorial Sloan Kettering Cancer Center from 2000 until 2016. Men were eligible for inclusion in the cohort if they

were diagnosed with D'Amico low or intermediate risk prostate cancer and underwent a repeat biopsy within 6 months of the initial diagnosis. Patients were followed with routine PSA and digital rectal examination every 6 months. Repeat biopsy was recommended within 12 after initiating active surveillance and then every 3 years thereafter. In patients with a MRI lesion, a targeted biopsy was performed. Starting in 2013, our institution implemented the collection of patient-reported outcomes in men undergoing active surveillance via a web-based platform. Of the eligible patients, 413 had completed surveys assessing their current quality of life status. Surveys were administered to patients as part of routine clinical care for all prostate cancer related visits (i.e., follow-up/counseling, prostate biopsy, or MRI).

Primary Outcome

Patient reported outcomes for prostate cancer-related anxiety were determined through the use of a modified version of the Memorial Anxiety Scale for Prostate Cancer.¹⁵ Men currently enrolled on active surveillance were asked three questions related to their current level of prostate cancer-specific anxiety: (1) if prostate cancer impaired their ability to plan for the future, (2) if prostate cancer resulted in distressing worries or thoughts, and (3) if these thoughts have affected their mood. Responses for each of the questions were measured on a 5-item Likert scale with responses ranging from “strongly agree” to “strongly disagree”. A liberal definition of anxiety was used: responses indicating agreement or strong agreement with any of the statements resulted in a label of cancer-related anxiety. Men were also asked to rank their current overall state of health on a 10-point Likert scale, with lower scores indicating poorer overall health.

Statistical Analysis

Generalized estimating equations (GEE) were used to estimate the risk of prostate cancer anxiety throughout the duration of active surveillance and ascertain whether length of time on active surveillance influenced the risk of anxiety. Additionally, we wished to assess predictors of anxiety levels. We tested the association between anxiety and age, marital status, Gleason score on diagnostic biopsy, number of positive cores on biopsy, family history, visit type (biopsy related vs non-biopsy related), and overall state of health after adjusting for the length of time on active surveillance using separate multivariable GEE regression models. We investigated whether nonlinear terms for time on active surveillance would improve model fit, but they were not significant and therefore not included in any models. All statistical analyses were completed with Stata version 13.0 (StataCorp, College Station, TX).

Results

Patient characteristics are described in Table 1. The median age was 61 years (IQR 56, 67) with a median PSA at diagnosis of 4.4 ng/ml (IQR 3.3, 6.3). Upon initiation of surveillance, approximately 95% of patients had grade group 1 disease (Gleason 6) and the remainder had grade groups 2 & 3 disease (Gleason 7), with the exception of one patient who elected to be observed with grade group 4 (Gleason 8) after initially refusing radical treatment. Overall, 40 men discontinued active surveillance and were subject to radical treatment: 33 underwent radical prostatectomy after a median 3.5 years (IQR 1.8, 4.8), 5 men received external beam

radiotherapy after a median 2.1 years (IQR 1.8, 2.5), and 2 men underwent brachytherapy after 1.7 and 2.5 years.

Participants completed a median of 2 surveys (IQR 1, 3) while on active surveillance. The median time from the start of surveillance to the first and last survey was 2.8 (IQR 1.7, 4.5) and 3.7 (IQR 2.3, 5.4) years respectively. Due to the relatively recent implementation of the surveys, we do not have more than three years of responses for any patient. The data are therefore predominately cross-sectional. To determine the validity of drawing longitudinal inferences from cross-sectional data, we tested for an association between the date of enrollment on AS and the risk of elevated anxiety after adjusting for the time on AS and found no significant association with the direction of the central estimate corresponding to a decrease in the risk of elevated anxiety in more recent years (OR corresponding a year increase in enrollment date=0.89; 95% CI 0.74, 1.07; $p=0.2$).

Figure 1 illustrates the univariable predicted risk of prostate cancer-related anxiety with time on surveillance (OR=0.87 per year; 95% CI: 0.79, 0.95; $p=0.003$). After 1 year on active surveillance, the estimated risk of anxiety was 29%. This decreased by half, 14%, after 7.5 years.

One possible explanation for these findings would be if anxious patients gradually quit active surveillance due to anxiety, then anxiety levels would appear to fall with increasing duration of time on surveillance. To evaluate this hypothesis, we analyzed data on the reason for discontinuation of surveillance. Only 8% of those who switched to treatment – constituting about 2 – 3% of the total cohort, did so for personal reasons. Selective withdrawal of anxious patients would therefore not explain a 15% or greater absolute decrease in the risk of anxiety over time.

The multivariable GEE models adjusting for time on active surveillance are shown in Table 2. We did not find evidence to suggest that age, Gleason score on diagnostic biopsy, number of positive cores on biopsy, relationship status, family history or visit type were associated with the risk of reporting prostate cancer anxiety after adjusting for time on surveillance (Table 2, p -values 0.14). There was a significant association between overall health scores and cancer-related anxiety with men, reporting a better overall state of health having a lower risk of anxiety (OR=0.83; 95% CI: 0.74, 0.93; $p=0.001$).

Predicted risks of prostate cancer anxiety by overall health score and time on active surveillance based on the multivariable GEE model are presented in Table 3. After 5 years, those who reported a poor overall health score (4 out of 10) had an estimated risk of anxiety more than twice as great than those reporting excellent overall health (10 out of 10); (Figure 2).

Discussion

Using a liberal definition for cancer-specific anxiety, we identified that a moderate proportion of men initially report some form of anxiety related to their disease, but risk of anxiety decreased over time. With the exception of how patients ranked their overall health,

there were no demographic or clinical variables associated with cancer-specific anxiety during active surveillance.

Only a limited number of studies have investigated how levels of prostate cancer anxiety change over the course of active surveillance. The current published literature is lacking in terms of sample size and duration of follow up. For example, van den Bergh *et al.* report anxiety scores for 108 men until only 9 months after diagnosis.¹² Punnen *et al.* report estimates out to 3 years but their sample size is very small, with only 32 patients recording scores after 1 year.¹³ Anderson *et al.* report anxiety levels in 86 participants but do not present longitudinal data.¹⁴ Our study represents the largest sample size with the longest follow up investigating prostate cancer-specific anxiety during active surveillance.

Other assessments of HRQoL in men managed conservatively have suggested that overall anxiety and distress levels in this population are generally very low.^{14,13} Tan *et al.* report much lower rate of prostate cancer-specific anxiety (Memorial Anxiety Scale for Prostate Cancer = 26) at 14% among men diagnosed up to 1 year prior.¹⁶ The predicted risk of prostate cancer-specific anxiety within the first year in our study was twice as high (29%). This is likely because we use a much more liberal definition of anxiety. We believe it is important to note if a patient is declaring any form of cancer-related anxiety as opposed to using a sum score and cut point as has been done in many other studies. Our findings suggest that the degree of cancer-specific anxiety is not insignificant and maybe underestimated in the existing literature.

Despite moderate reports of anxiety within the initial survey period, Figure 1 demonstrates a clear trend of decreasing anxiety over time. This finding echoes results from a Dutch cohort that suggested decreasing anxiety among men in as little as 9 months after initiating active surveillance.¹² Reduced disease related anxiety over time may indicate the importance of maintaining structured and routine follow-up in the care of men on surveillance. Furthermore, the clear relationship between how patients perceive their overall health and reports of disease specific anxiety (Figure 2) also mirror the findings of the Dutch study.¹² Although poor overall health should not preclude men from participating in active surveillance, this should alert members of the health care team for the possibility of a higher likelihood of experiencing prostate cancer anxiety; that said, we cannot exclude reverse causation, that is, that the anxiety is leading to reduced health rather than the other way around.

A unique aspect of this study was the ability to track survey responses according to the type of hospital visit for each patient. By utilizing the unique web-based platform available at our institution¹⁷, we were able to ascertain survey data related to each patient's hospital visit separately by type of visit: routine follow-up, imaging-related visit, or prostate biopsy. To our knowledge, this is the first study that has attempted to do so. Although it was expected that biopsy visits would likely trigger disease related concerns, and that this may translate to heightened levels of prostate cancer-specific anxiety, we found no significant association between anxiety levels and the type of clinical visit after adjusting for the patients' length of time on active surveillance. Findings from other studies evaluating the psychological impact of prostate biopsy remain variable. In a prospective study investigating the effect of biopsy

on general anxiety in men undergoing PSA screening, investigators identified that the overall level of general anxiety is low.¹⁸ However, in men diagnosed with prostate cancer or those experiencing post-biopsy adverse events, the level of anxiety is significantly higher.^{18,19}

Our study only assessed HRQoL in relation to clinical encounters. It is plausible that in some men, hospital visits may trigger a heightened awareness of their disease and translate into greater cancer-related anxiety. Future studies may benefit from routine HRQoL assessments of men on active surveillance in settings unrelated to hospital or clinic visits.

Despite the many strengths of this study, there are some notable limitations. Our data lacked information regarding the patient's history of anxiety, depression, or mental health issues prior to a cancer diagnosis. Although our assessments of disease-specific anxiety throughout the duration of active surveillance may have adjusted for possible discrepancies in baseline anxiety levels, we were unable to specifically evaluate if patients with a history of depression or mental health illnesses differed in any way with regards to their HRQoL. Additionally, although our analysis revealed that marital and partner status was not associated with the risk of reporting anxiety, we lacked formal assessments of anxiety in the partners themselves. Overall, we are unable to discern the exact influence of partners on cancer-specific anxiety levels of men in this study, however the high acceptance rate of active surveillance in our institution (81%)²⁰ mitigates the impact of selection bias. Whether partners induce a positive or negative impact on psychological HRQoL in active surveillance patients is an area that warrants further study as the literature remains equivocal.^{21,22} Furthermore, this study did not assess HRQoL following crossover to active treatment in order to determine if prostate cancer-specific anxiety resolves following definitive intervention.

This study identified moderate anxiety at the beginning of active surveillance. Physicians counselling men with prostate cancer should inform patients that these feelings are normal. By using a systematic approach and by normalizing cancer specific anxiety, barriers to acceptance of active surveillance can be overcome.²⁰ Since anxiety levels decrease over time, interventions specifically aimed at reducing anxiety routinely will have less impact. In our cohort, we did not identify risk factors associated with cancer specific anxiety during active surveillance; therefore, strategies to reduce anxiety for select men should be targeted during the initial diagnosis of prostate cancer, since this is likely the critical time point to improve adherence to active surveillance.

Conclusion

Men with prostate cancer followed on active surveillance initially demonstrate moderate levels of disease specific anxiety, but these decrease over time. Although there are no clinical or demographic variables that are associated with reports of prostate cancer anxiety, men that perceive themselves to have poor overall health report significantly higher cancer-specific anxiety. Patients considering active surveillance can be informed that, although it is expected to experience a certain degree of anxiety at first, most men adjust rapidly and report low levels of anxiety within 2 years. These results should be taken into consideration when counseling patients and justify the need for systematic follow up during the expectant management of prostate cancer.

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List of abbreviations

HRQoL	Health Related Quality of Life
PSA	Prostate Specific Antigen
GEE	Generalized Estimating Equations

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Figure 1: Univariable predicted risk and 95% confidence interval of prostate cancer anxiety by time from active surveillance to survey date (n=413). The shaded region represents the distribution of the times from active surveillance to survey response.

Table 1.

Patient Characteristics. Estimates are given as median (interquartile range) or frequency (percentage).

Characteristic	N=413
Age	61 (56, 67)
PSA at diagnosis in ng/ml (N=386)	4.4 (3.3, 6.3)
Family history of prostate cancer	121 (29%)
Relationship Status	
Single	79 (19%)
Married	333 (81%)
Unknown	1 (0.2%)
Biopsy Grade Group (Gleason score)	
Grade Group 1 (3+3)	391 (94.7%)
Grade Group 2 (3+4)	17 (4.1%)
Grade Group 3 (4+3)	4 (1.0 %)
Grade Group 4 (4+4)	1 (0.2%)

Table 2.

Multivariable GEE models adjusting for time on active surveillance.

Variable	OR	95% CI	p-value
Age (n=413)	0.98	0.96, 1.01	0.3
Overall Health Score (n=413)	0.83	0.74, 0.93	0.002
Number of Positive Cores on Diagnostic Biopsy (n=399)	1.00	0.83, 1.19	1
Relationship Status (n=412)			
Single	Ref.	.	.
Married	0.69	0.42, 1.13	0.14
Gleason Score on diagnostic biopsy (n=412)			
6	Ref.	.	.
7–8	0.43	0.12, 1.49	0.2
Family History of prostate cancer (n=413)	1.03	0.66, 1.61	0.9
Visit Type (n=372)			
Non-Biopsy	Ref.	.	.
Biopsy	1.26	0.83, 1.92	0.3

Table 3:

Predicted risk of anxiety by overall health score and time on active surveillance (n=413).

Overall Health Score	2.5 Years	5 Years	7.5 Years
4	39% (28%, 49%)	31% (21%, 41%)	25% (13%, 36%)
6	30% (24%, 36%)	24% (18%, 29%)	18% (11%, 25%)
8	23% (19%, 27%)	18% (14%, 21%)	13% (8%, 18%)
10	17% (11%, 22%)	13% (8%, 17%)	10% (5%, 14%)