Published in final edited form as:

BJU Int. 2016 March ; 117(3): 469–477. doi:10.1111/bju.13099.

The Relationship Between Illness Uncertainty, Anxiety, Fear of Progression, and Quality of Life in Men With Favorable Risk Prostate Cancer Undergoing Active Surveillance

Patricia A. Parker,

University of Texas MD Anderson Cancer Center, Houston, TX

John W. Davis,

University of Texas MD Anderson Cancer Center, Houston, TX

David M. Latini,

Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX

George Baum,

University of Texas MD Anderson Cancer Center, Houston, TX

Xuemei Wang,

University of Texas MD Anderson Cancer Center, Houston, TX

John F. Ward,

University of Texas MD Anderson Cancer Center, Houston, TX

Deborah Kuban,

University of Texas MD Anderson Cancer Center, Houston, TX

Steven J. Frank,

University of Texas MD Anderson Cancer Center, Houston, TX

Andrew K. Lee,

University of Texas MD Anderson Cancer Center, Houston, TX

Christopher J. Logothetis, and

University of Texas MD Anderson Cancer Center, Houston, TX

Jeri Kim

Corresponding author: Jeri Kim, MD, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1374, Houston, TX 77030. Tel: (713) 792-2830; Fax: (713) 745-1625; jekim@mdanderson.org.

Presented in part at the 2014 Genitourinary Cancers Symposium, San Francisco, CA, January 30 to February 1, 2014.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: John W. Davis, Jeri Kim, Patricia A. Parker

Collection and assembly of data: Jeri Kim, Patricia A. Parker

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

Objectives—To evaluate prospectively the associations between illness uncertainty, anxiety, fear of progression, and general and disease-specific quality of life (QOL) in men with favorable risk prostate cancer undergoing active surveillance (AS).

Patients and Methods—After meeting stringent enrollment criteria for an AS cohort study at a single tertiary care cancer center, 180 men with favorable-risk prostate cancer completed questionnaires at enrollment and every 6 months for up to 30 months. Questionnaires assessed illness uncertainty, anxiety, prostate-specific (Expanded Prostate Cancer Index Composite; EPIC) and general QOL (Short Form 12; SF-12) and fear of progression. We used linear mixed model analyses and multilevel mediation analyses.

Results—EPIC sexual scores significantly declined over time ($P < 0.05$). Illness uncertainty was a significant predictor of all EPIC summary, SF12 physical component summary (PCS), mental component summary (MCS), and fear of progression scores (all P values, < 0.05), despite controlling for demographic and clinicopathologic factors. Anxiety predicted all EPIC summary, MCS, and fear of progression scores (all P values, < 0.05) but not PCS scores ($P = 0.08$). Scores on PCS, MCS, EPIC summary scales (except sexual scale), and fear of progression did not change significantly over the study period (all P values, > 0.10).

Conclusion—Over the 2.5-year follow-up, QOL remained stable; only sexual function scores significantly declined. Illness uncertainty and anxiety were significant predictors of general and prostate-specific QOL and fear of progression. Interventions to reduce uncertainty and anxiety may enhance QOL for men with prostate cancer on AS.

Keywords

Active surveillance; anxiety; fear; prostate cancer; quality of life; watchful waiting

INTRODUCTION

Prostate cancer is being diagnosed early in the disease process because of the increased use of prostate-specific antigen (PSA) testing, resulting in detection in many men unlikely to die from the disease [1]. Active surveillance (AS) is a viable option for many men with low-volume/low-grade (LV/LG) prostate cancer of indolent nature [2–4].

AS involves regular monitoring with PSA screening, digital rectal examination, and biopsy, though the optimal criteria and schedule for monitoring remain under investigation. Managing prostate cancer with AS using stringent selection criteria may delay or avoid potentially debilitating long-term side effects of such aggressive treatments as surgery or radiation [5–8]. Men on AS who show early signs of disease progression can receive early intervention and do not have poorer pathological outcomes than men receiving immediate treatment [4, 9, 10]. The Prostate Cancer Intervention versus Observation Trial demonstrated that men on AS do not have poorer all-cause or prostate cancer-specific mortality than men having surgery through at least 12 years of follow-up [11]. A recent analysis found that

observation slightly improved quality-adjusted life expectancy and is less expensive than treatment for men age 65–75 with localized prostate cancer [12].

Despite these potential benefits, being on AS may create uncertainty and distress for men. Many patients have difficulty with the emotional burden of living with an untreated cancer [13,14], and anxiety may be one reason men choose immediate treatment instead of AS [15–17]. However, empirical results are mixed. A recent meta-analysis suggests that the prevalence of anxiety is highest (27%) among men with early stage prostate cancer before undergoing active treatment and declines during treatment (15.9%) with a slight rise after treatment (18.5%) [18]. There are limited data on the trajectory of anxiety among men on AS. A recent review indicated that anxiety and uncertainty were two prevalent responses that men on AS report [19]. It has been proposed that when individuals experience uncertainty, it leads to increased anxiety [20,21]. Although the direction of the association between uncertainty and anxiety is suggestive, it has not been examined in large prospective studies. Although anxiety may be higher for some men on AS, results suggest that urinary, bowel, and sexual functioning may be higher among men on AS than among those who receive active treatment. For example, in a study that compared men on AS with those who received radiation therapy, men on AS had better bowel function, less bother with bowel function, and fewer problems getting an erection than men who had radiotherapy but had similar general quality of life (QOL) [22].

Though several studies of the QOL of men on active treatment have been published [23–25], relatively few on AS have comprehensively described the psychosocial impact; therefore, our goal was to examine prospectively the psychosocial adjustment and QOL of men on AS. We also examined the associations over time between illness uncertainty, anxiety, and QOL and fear of progression and whether anxiety mediated the association between uncertainty and QOL.

PATIENTS AND METHODS

Participants

Participants were 180 men with low-risk prostate cancer who were enrolled 2006–2012 in the AS protocol at The University of Texas MD Anderson Cancer Center (MDACC). Diagnosis of prostate cancer was within 6 months of enrollment and low-risk as defined by either a 3 + 3 Gleason score (GS) in one core (tumor focus, <3 mm) or a 3 + 4 GS in one core (tumor focus, <2 mm) and PSA <4 ng/mL (adjustable for volume) [26]. Men were 18 years or older and able to speak and read English. Patients were evaluated every 6 months by clinical exam, including digital rectal examination, and measures of serum PSA and testosterone levels. Concomitant medications, including 5 α -reductase inhibitors, were recorded at each follow-up. Median follow-up time on AS for the patients was 3 years. Eligible patients had prostate cancer histopathologically confirmed by internal biopsy or repeated review of outside biopsy results. In June 2007, the protocol was amended to mandate an onsite entry biopsy at study enrollment or within 6 months of diagnosis. Prostate biopsies were repeated every 1–2 years using the 11-core multisite-directed biopsy scheme [27]. If the biopsy was negative, then the biopsy was skipped the next year, unless the patient requested it. Disease was reclassified when a significant change was detected in

tumor volume or upgrading of tumor to a dominant Gleason grade 4 or any Gleason grade 5 component; or a significant change in PSA level of a >30% increase, confirmed within a month of laboratory results or three months after biopsy.

Procedure

The decision to undergo surveillance was based on patient and disease characteristics and was at the discretion of the physicians in the context of the physician-patient interaction. Participants completed a baseline questionnaire immediately after enrollment (within 6 months of initial prostate cancer diagnosis) and additional questionnaires every 6 months thereafter. The current paper reports on results from baseline to up to 2.5 years later (44% of patients were followed for 2 or more years; 71% of patients were followed for 1 year or more); others had not yet reached those time points for their assessments. Seventeen percent of men had their disease reclassified during the course of the study, and, of these, 10 men went off AS and had active treatment. Patients who went off AS protocol did not complete additional questionnaires after they went off study. This study was approved by the Surveillance Committee for the Protection of Human Subjects at MDACC. Written informed consent was obtained before study enrollment. No compensation was offered to participants.

Demographic, Clinical, and Quality-of-Life Measures

Demographic factors (age, ethnicity) and clinicopathologic variables were abstracted from patients' charts. These included GS, cancer stage, baseline PSA level, testosterone, body mass index (BMI), number of surveillance biopsies, family history of cancer, whether patient was taking a 5-alpha-reductase inhibitor (5ARI), and whether tumor reclassification occurred. PSA kinetic variables were not included because these are calculated over time, and therefore there would have been significant missing data points in the main analyses.

Measures included the following:

1. Illness uncertainty was assessed with the Mishel Uncertainty in Illness Scale (MUIS) [28]. The MUIS assesses patients' perceptions of uncertainty about their disease. The MUIS has four subscales—ambiguity, complexity, lack of information, and unpredictability—which can be combined into a single total score (used in these analyses) that has demonstrated reliability and validity [28–30].
2. State anxiety was assessed using the Spielberger State and Trait Anxiety Inventory for Adults-State (STAI) [31]. It has established reliability and validity and has been widely used in clinical and medical populations [32–35].
3. Prostate-specific QOL was assessed with the Expanded Prostate Index Composite (EPIC) [36]. The EPIC assesses prostate-specific symptoms in four domains: urinary, bowel, sexual, and hormonal [37]. Each domain evaluates symptom severity and impairment, which can be summarized into domain summary scales. The EPIC has good reliability and validity [36,38,39].
4. General QOL was assessed with the Medical Outcomes Study (MOS) 12-item Short-Form Health Survey (SF-12) [40]. The SF-12 is a shorter version of the

SF-36. Two summary scores can be derived from the SF-12—physical and mental health component summary scores (PCS and MCS).

5. Fear of disease progression or recurrence was assessed using the 4-item fear of recurrence subscale of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC) [41]. It has high internal consistency and concurrent and discriminant validity [41,42].

Statistical Methods

Descriptive statistics were computed. We then examined whether prostate-specific and general QOL and fear of progression changed over time as well as whether illness uncertainty and anxiety predicted prostate-specific (EPIC summary scales) and general (SF-12 PCS and MCS) QOL and fear of progression. We included demographic and clinicopathologic variables (i.e., age, ethnicity, GS, cancer stage, PSA, testosterone, BMI, number of biopsies, family history of cancer, whether patients were taking a 5ARI, and whether tumor was reclassified) in all models. We did this using linear mixed models with *proc mixed* in the the SASTM software package (version 9.4; SAS Institute, Cary, NC). Mixed models control for both the between and within-person variation and also allow for missing data and improves the precision of effect estimates by using all observed data. We used the compound symmetry (CS) covariance structure, but, we also tested various other covariance structures and found that the best fitting models based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) fit criteria was the CS structure. To examine whether anxiety mediated the association between uncertainty and QOL, we conducted a series of multilevel mediation analyses [43].

RESULTS

Participants in this study averaged 67.2 years old (SD, 8.9 years; range, 40.0–87.0 years) and were mostly non-Hispanic white men (86%) (Table 1). Baseline PSA level was 3.3 ng/mL (SD, 1.6; range, 0.2–8.1) and baseline GS was 6 (98%). About 38% of men reported having a first-degree relative, a second-degree relative, or first- and second-degree relatives who had prostate cancer. Thirty-one of 180 (17%) men had disease reclassification during the study period and of these 10 went on to have treatment.

We examined the means and SDs of scores at each assessment point (Table 2). Mean baseline EPIC Summary Scores were similar or slightly higher than those reported in other studies of men with prostate cancer [36]. Mean baseline MUIS scores were similar to scores reported in other cancer populations [44]. Mean PCS and MCS scores at baseline were similar to mean scores of men in similar age range in the general population [38,45]. Average baseline STAI scores compared with a normative sample of males was at the 40th percentile. We examined whether there were changes over time in uncertainty, anxiety, cancer-specific (EPIC summary) and general (PCS and MCS) QOL, and fear of progression. Time was a significant predictor of MUIS scores ($P < 0.0001$) with scores significantly lower than baseline starting from 12 months until 2.5 years. Time was a significant predictor of STAI scores ($P = 0.009$), with scores at 18 months and 2.5 years significantly different from baseline value. Time was a significant predictor of EPIC sexual summary scores ($P =$

0.0467); scores decreased at every time point after baseline to 30 months (see Fig 1). Although statistically significant, these results may not be clinically significant [46]. There were no changes over time in any other summary scores—EPIC, PCS, or MCS—or fear of progression scores (all P values, >0.10).

Examining patient characteristics (Table 3), we found that age was significantly associated with PCS scores and a number of the EPIC subscale scores, including, sexual ($P < 0.0001$) and satisfaction ($P = 0.031$), and the SF-12 PCS ($P < 0.0001$). In each case, an increase in age was associated with poorer QOL scores. BMI was significantly associated with EPIC Hormonal ($P = 0.012$) and Satisfaction measures ($P = 0.002$) and with SF-12 PCS ($P = 0.003$) and MCS ($P = 0.022$) values. Just as increasing age was associated with lower QOL, higher BMI measures were associated with lower QOL scores. Overall, 5ARI therapy was significantly associated with EPIC Urinary QOL ($P = 0.021$), with subjects who had used 5ARI having lower scores for EPIC Urinary QOL. Baseline PSA was significantly associated with EPIC Hormonal ($P = 0.003$), Urinary ($P < 0.0001$), and Bowel scores ($P = 0.0001$), with those who had higher PSA values having higher EPIC Hormonal scores and those with higher PSA scores having lower Urinary and Bowel QOL scores. The number of prostate biopsies men underwent had no bearing on sexual function scores.

Illness uncertainty was significantly associated with all of the EPIC summary scores (Urinary, $P = 0.0002$; Bowel, $P = 0.02$; Sexual, $P = 0.004$; Hormonal, $P < 0.0001$; Satisfaction, $P < 0.0001$), PCS ($P < 0.0002$), MCS ($P < 0.0001$), and fear of progression ($P < 0.0001$) (Table 4). The direction of the relationship was as expected, with an inverse relationship between the MUIS uncertainty score and the EPIC summary scores, indicating that as uncertainty increased, EPIC QOL measures decreased (Urinary, $\beta = -0.115$; Bowel, $\beta = -0.063$; Sexual, $\beta = -0.177$; Hormonal, $\beta = -0.142$; Satisfaction, $\beta = -0.529$). The association between the uncertainty and the MCS and PCS values was also in the expected negative direction (PCS, $\beta = -0.099$; MCS, $\beta = -0.128$). Uncertainty was positively related to fear of progression, with higher uncertainty scores associated with higher fear of progression ($\beta = 0.072$).

Anxiety was significantly associated with all of the EPIC summary scores (Urinary, $P = 0.02$; Bowel, $P = 0.007$; Sexual, $P < 0.0001$; Hormonal, $P < 0.0001$; Satisfaction, $P < 0.0001$), fear of progression ($P < 0.0001$), and MCS score ($P < 0.0001$). However, anxiety was not associated with PCS score ($P > 0.10$). As was the case with MUIS uncertainty, the direction of the association of anxiety to the different QOL outcomes was as expected. An inverse relationship between anxiety and the EPIC and MCS QOL indicated that higher anxiety predicted lower QOL (Urinary, $\beta = -0.098$; Bowel, $\beta = -0.094$; Sexual, $\beta = -0.379$; Hormonal, $\beta = -0.282$; Satisfaction, $\beta = -0.481$; MCS = -0.365). A positive association between fear of progression and anxiety indicated that higher anxiety was associated with greater fear of progression ($\beta = 0.109$). Finally, we examined whether anxiety mediates the associations between illness uncertainty and QOL summary scores, and the mediation analysis was negative for all variables.

DISCUSSION

This study is one of the largest prospective studies to examine QOL, the influence of important psychosocial factors (illness uncertainty and anxiety) on QOL, and fear of disease progression in men with prostate cancer on AS. What is important is that the sample was homogeneous in terms of criteria for participating in AS. We had applied the most stringent criteria to identify men with LV/LG prostate cancer. Another strength of these results is that we statistically controlled for several important demographic, clinical, and cancer-related variables including age, ethnicity, GS, cancer stage, PSA, testosterone, BMI, number of biopsies, family history of cancer, whether patients were taking a 5ARI, and whether tumor was reclassified) that have been found in other prostate cancer studies to influence QOL; thus, the observed associations are independent of these characteristics. Interestingly, both general and cancer-specific QOL remained fairly stable over the 2.5-year study period.

Illness uncertainty decreased over time beginning at 12 months after study entry. Anxiety was also significantly lower at 18 and 30 months after study entry. It may be that anxiety at 12 and 24 months was higher because men were undergoing annual biopsies around the time the questionnaires were completed and may have been more anxious about the status of their prostate cancer [47].

Overall, our results suggest that men on AS maintain high QOL following their prostate cancer diagnosis. One important exception was sexual function, which decreased significantly over time (even when controlling for age and disease characteristics). However, using a recommended half standard deviation difference in scores, we found that the decline in sexual functioning may not be clinically significant [46]. We did examine whether the number of prostate biopsies men had was associated with sexual function scores and found that number of biopsies did not affect sexual functioning scores. It should be noted, however, that men had on average 2 biopsies, so it is not known if there would be an association between number of biopsies and decline in sexual functioning with additional biopsies. Past research has been mixed about whether the number of biopsies is associated with declines in sexual functioning. For example, Fujita et al. [48] found that serial prostate biopsies were associated with an increased risk of erectile dysfunction in men with prostate cancer on AS; however, this study was done cross-sectionally with baseline data on erectile dysfunction collected from medical charts. Our results are consistent with a recent study by Hilton et al. [49], who found that the effect of biopsies on erectile functioning was negligible. As increasing numbers of men are on AS for longer periods of time, the potential impact of serial biopsies on sexual functioning increases, and it should be examined in future studies.

Our results, which indicated minimal declines in QOL across the study period, are consistent with previous findings that being on AS may prevent or delay the multiple decrements in QOL seen following immediate active treatment [8]. For example, when comparing QOL outcomes of men receiving prostatectomy, external beam radiation therapy, or brachytherapy, Litwin et al. [50] found that each of these treatments differentially affected QOL outcomes. Urinary control and sexual function were better after external beam radiation, although bilateral nerve-sparing surgery diminished the differences among men

who had surgery. In addition, men who had brachytherapy had more obstructive and irritative urinary symptoms, and both radiation treatments caused more bowel dysfunction. In the Prostate Cancer Outcomes Study (PCOS) [7], men undergoing radical prostatectomy were more likely to have urinary incontinence and erectile dysfunction than those undergoing radiation therapy 2 years and 5 years post-treatment; however, men undergoing radiation therapy experienced more bowel urgency at 2 years and 5 years post-treatment. At 15 years post-treatment, there were no differences between treatment types; however, both groups had significant declines in urinary, sexual, and bowel functioning. From this study, it is not known if the declines seen after 15 years were related to prostate cancer, its treatment, the normal aging process, a combination of these factors, or other factors. Longer follow-up of men on AS is needed to determine whether AS protects against some of these decrements over time.

Controlling for several key demographic and medical characteristics, we found that both illness uncertainty and anxiety predicted both general QOL and cancer-specific QOL. This is consistent with the findings from studies by Bailey [13] and Oliffe [51] that found uncertainty to be important for men with prostate cancer on AS. These results highlight the importance of conducting longitudinal studies so that the direction of effects can be determined. These variables are particularly important as they may affect men's decisions about whether to continue on AS or receive active treatment [17]. Future studies may incorporate aspects of managing anxiety and uncertainty inasmuch as these may be two key reasons that patients go off AS without any changes in their tumor status, which may lead to potentially unnecessary interventions and side effects [17,52]. Possible interventions could incorporate cognitive behavioral strategies for managing both uncertainty and anxiety such as relaxation training, stress management, enhancing coping skills, and cognitive restructuring. In addition, psycho-educational programs that provide information to patients about prostate cancer, its management, and treatment options may also be beneficial, as well as symptoms management education, as needed. Finally, the impact of the physicians' recommendations and the discussion between the patient and physicians on patients' psychosocial outcomes was not examined in this study; this is an important area for future research.

Some limitations of our current study should be noted. First, this study was conducted at a specialized cancer center, and our cohort may differ from those cohorts treated in community hospitals or other settings. It is also important to note that our criteria for going on AS was quite conservative compared to other AS trials [53,54]. Decisions about AS were made jointly between physicians and patients, considering both disease characteristics and personal preferences. The sample was mostly non-Hispanic white men (86%), so the results may not generalize to other racial or ethnic groups. However, because the sample size was quite large, there were a fair number of men from a variety of racial and ethnic groups, but it is important to note that it is not known how these results would generalize to other AS cohorts such as those with more comorbidities or those with more diverse racial/ethnic samples. Other studies should address these issues as well as the potential impact of characteristics such as the influence of socioeconomic status and education that were not included in this study. Additionally, future studies should include PSA kinetics and their association with anxiety and illness uncertainty as they have been shown to be important

triggers for discontinuing AS [17]. It is unknown whether differences in QOL would emerge more than 30 months after AS is begun or if there were other factors not assessed in this study (such as other comorbidities (e.g., hypertension, diabetes) or sexual functioning prior to prostate cancer diagnosis) that may have affected men's QOL. Another factor that may impact QOL is the stress associated with the diagnosis of prostate cancer, regardless of treatment or management strategy; this could be evaluated further in future studies. Another limitation is that we did not assess psychosocial and QOL outcomes of men who went off AS; this is important to pursue in future studies. An important aspect of our study is that we assessed both general and cancer-specific QOL as well as measured two psychosocial factors that can be modified through established interventions. We are currently building on these findings by designing a patient-centered educational intervention focused on reducing uncertainty and anxiety in this group of men with prostate cancer for whom interventions are limited.

Acknowledgments

Supported in part by Cancer Center Core Grant P30CA 16672 from The University of Texas MD Anderson Cancer Center.

We thank all of the men who participated in this study.

References

1. Dall'Era MA, Cooperberg MR, Chan JM, et al. Active surveillance for early-stage prostate cancer: Review of the current literature. *Cancer*. 2008; 112:1650–9. [PubMed: 18306379]
2. Zerbib M, Zelefsky MJ, Higano CS, et al. Conventional treatments of localized prostate cancer. *Urology*. 2008; 72:S25–35. [PubMed: 19095125]
3. Singer EA, Kaushal A, Turkbey B, et al. Active surveillance for prostate cancer: Past, present and future. *Curr Opin Oncol*. 2012; 24:243–50. [PubMed: 22450149]
4. Venderbos LD, Bokhorst LP, Bangma CH, et al. Active surveillance: Oncologic outcome. *Curr Opin Urol*. 2013; 23:268–72. [PubMed: 23425994]
5. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008; 358:1250–61. [PubMed: 18354103]
6. Soloway MS, Soloway CT, Eldefrawy A, et al. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol*. 2010; 58:831–5. [PubMed: 20800964]
7. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med*. 2013; 368:436–45. [PubMed: 23363497]
8. Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. *J Natl Cancer Inst Monogr*. 2012; 2012:242–9. [PubMed: 23271780]
9. van den Bergh RC, Roemeling S, Roobol MJ, et al. Outcomes of men with screen-detected prostate cancer eligible for active surveillance who were managed expectantly. *Eur Urol*. 2009; 55:1–8. [PubMed: 18805628]
10. Warlick C, Trock BJ, Landis P, et al. Delayed versus immediate surgical intervention and prostate cancer outcome. *J Natl Cancer Inst*. 2006; 98:355–7. [PubMed: 16507832]
11. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012; 367:203–13. [PubMed: 22808955]
12. Hayes JH, Ollendorf DA, Pearson SD, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: A cost-effectiveness analysis. *Ann Intern Med*. 2013; 158:853–60. [PubMed: 23778902]

13. Bailey DE Jr, Wallace M, Mishel MH. Watching, waiting and uncertainty in prostate cancer. *J Clin Nurs*. 2007; 16:734–41. [PubMed: 17402955]
14. Wallace M. Uncertainty and quality of life of older men who undergo watchful waiting for prostate cancer. *Oncol Nurs Forum*. 2003; 30:303–9. [PubMed: 12692664]
15. Xu J, Dailey RK, Eggly S, et al. Men's perspectives on selecting their prostate cancer treatment. *J Natl Med Assoc*. 2011; 103:468–78. [PubMed: 21830629]
16. van den Bergh RC, Essink-Bot ML, Roobol MJ, et al. Anxiety and distress during active surveillance for early prostate cancer. *Cancer*. 2009; 115:3868–78. [PubMed: 19637245]
17. Latini DM, Hart SL, Knight SJ, et al. The relationship between anxiety and time to treatment for patients with prostate cancer on surveillance. *J Urol*. 2007; 178:826–31. [PubMed: 17632144]
18. Watts S, Leydon G, Birch B, et al. Depression and anxiety in prostate cancer: A systematic review and meta-analysis of prevalence rates. *BMJ Open*. 2014; 4:e003901.
19. Kazer MW, Psutka SP, Latini DM, et al. Psychosocial aspects of active surveillance. *Curr Opin Urol*. 2013; 23:273–7. [PubMed: 23422588]
20. Bailey DE, Mishel MH, Belyea M, et al. Uncertainty intervention for watchful waiting in prostate cancer. *Cancer Nurs*. 2004; 27:339–46. [PubMed: 15525860]
21. Kazer MW, Bailey DE Jr, Whittemore R. Out of the black box: Expansion of a theory-based intervention to self-manage the uncertainty associated with active surveillance (AS) for prostate cancer. *Res Theory Nurs Pract*. 2010; 24:101–12. [PubMed: 20549916]
22. Thong MS, Mols F, Kil PJ, et al. Prostate cancer survivors who would be eligible for active surveillance but were either treated with radiotherapy or managed expectantly: Comparisons on long-term quality of life and symptom burden. *BJU Int*. 2010; 105:652–8. [PubMed: 19747357]
23. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008; 358(12): 1250–61. Epub 2008/03/21. [PubMed: 18354103]
24. Bacon CG, Giovannucci E, Testa M, Kawachi I. The impact of cancer treatment on quality of life outcomes for patients with localized prostate cancer. *J Urol*. 2001; 166(5):1804–10. [PubMed: 11586228]
25. Eton DT, Lepore SJ, Helgeson VS. Early quality of life in patients with localized prostate carcinoma: an examination of treatment-related, demographic, and psychosocial factors. *Cancer*. 2001; 92(6):1451–9. [PubMed: 11745222]
26. Babaian RJ, Miyashita H, Evans RB, et al. The distribution of prostate specific antigen in men without clinical or pathological evidence of prostate cancer: Relationship to gland volume and age. *J Urol*. 1992; 147:837–40. [PubMed: 1371558]
27. Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol*. 2000; 163(1):152–7. [PubMed: 10604335]
28. Mishel MH. The measurement of uncertainty in illness. *Nurs Res*. 1981; 30:258–63. [PubMed: 6912987]
29. Mishel MH, Hostetter T, King B, et al. Predictors of psychosocial adjustment in patients newly diagnosed with gynecological cancer. *Cancer Nurs*. 1984; 7:291–9. [PubMed: 6564913]
30. Bailey DE Jr, Wallace M, Latini DM, et al. Measuring illness uncertainty in men undergoing active surveillance for prostate cancer. *Appl Nurs Res*. 2011; 24:193–9. [PubMed: 20974073]
31. Spielberger, C.; Gorsuch, R.; Lushene, R. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press; 1970.
32. Cassileth BR, Knuiman MW, Abeloff MD, et al. Anxiety levels in patients randomized to adjuvant therapy versus observation for early breast cancer. *J Clin Oncol*. 1986; 4:972–4. [PubMed: 3711963]
33. Dropkin MJ. Body image and quality of life after head and neck cancer surgery. *Cancer Pract*. 1999; 7:309–13. [PubMed: 10732529]
34. Wellisch DK, Hoffman A, Goldman S, et al. Depression and anxiety symptoms in women at high risk for breast cancer: Pilot study of a group intervention. *Am J Psychiatry*. 1999; 156:1644–5. [PubMed: 10518180]

35. Wells ME, McQuellon RP, Hinkle JS, et al. Reducing anxiety in newly diagnosed cancer patients: A pilot program. *Cancer Pract.* 1995; 3:100–4. [PubMed: 7704066]
36. Wei JT, Dunn RL, Sandler HM, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. *J Clin Oncol.* 2002; 20:557–66. [PubMed: 11786586]
37. Litwin MS, Hays RD, Fink A, et al. The UCLA Prostate Cancer Index: Development, reliability, and validity of a health-related quality of life measure. *Med Care.* 1998; 36:1002–12. [PubMed: 9674618]
38. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology.* 2000; 56:899–905. [PubMed: 11113727]
39. Link RE, Su LM, Sullivan W, et al. Health related quality of life before and after laparoscopic radical prostatectomy. *J Urol.* 2005; 173:175–9. [PubMed: 15592069]
40. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Med Care.* 1996; 34:220–33. [PubMed: 8628042]
41. Roth AJ, Rosenfeld B, Kornblith AB, et al. The memorial anxiety scale for prostate cancer: Validation of a new scale to measure anxiety in men with with prostate cancer. *Cancer.* 2003; 97:2910–8. [PubMed: 12767107]
42. Roth A, Nelson CJ, Rosenfeld B, et al. Assessing anxiety in men with prostate cancer: Further data on the reliability and validity of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). *Psychosomatics.* 2006; 47:340–7. [PubMed: 16844894]
43. Bauer DJ, Preacher KJ, Gil KM. Conceptualizing and testing random indirect effects and moderated mediation in multilevel models: New procedures and recommendations. *Psychol Methods.* 2006; 11:142–63. [PubMed: 16784335]
44. Mishel, M. *Uncertainty in Illness Scales Manual.* Chapel Hill, NC: University of North Carolina; 1997.
45. Ware, JE.; Kosinski, M.; Keller, SD. *SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales.* 3. Lincoln, RI: Quality Metric Incorporated; 1998.
46. Chipman JJ, Sanda MG, Dunn RL, et al. Measuring and predicting prostate cancer related quality of life changes using EPIC for clinical practice. *J Urol.* 2014; 191:638–45. [PubMed: 24076307]
47. Dale W, Bilir P, Han M, et al. The role of anxiety in prostate carcinoma: A structured review of the literature. *Cancer.* 2005; 104:467–78. [PubMed: 15959911]
48. Fujita K, Landis P, McNeil BK, et al. Serial prostate biopsies are associated with an increased risk of erectile dysfunction in men with prostate cancer on active surveillance. *J Urol.* 2009; 182:2664–9. [PubMed: 19836757]
49. Hilton JF, Blaschko SD, Whitson JM, et al. The impact of serial prostate biopsies on sexual function in men on active surveillance for prostate cancer. *J Urol.* 2012; 188:1252–8. [PubMed: 22902015]
50. Litwin MS, Gore JL, Kwan L, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. *Cancer.* 2007; 109:2239–47. [PubMed: 17455209]
51. Oliffe JL, Davison BJ, Pickles T, et al. The self-management of uncertainty among men undertaking active surveillance for low-risk prostate cancer. *Qual Health Res.* 2009; 19:432–43. [PubMed: 19229061]
52. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: Progression patterns of early stage kidney cancer. *Eur Urol.* 2011; 60:39–44. [PubMed: 21477920]
53. Dall-Era MA, Konety BR, Cowan JE, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. *Cancer.* 2008; 112:2664–70. [PubMed: 18433013]
54. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol.* 2010; 28:126–31. [PubMed: 19917860]

Sexual Summary Score

Fig. 1. Expanded Prostate Index Composite Sexual quality of life summary scores from baseline to 30 months in 6-month intervals.

Table 1

Baseline demographic and medical characteristics of study participants

Characteristic	No.	%
No. of patients	180	100.0%
Age, mean, years	67.2 (SD, 8.9; range, 40–87)	
Ethnicity		
White	155	86.1
African American	12	6.7
Hispanic	11	6.1
Asian	2	1.1
Body mass index, mean (SD and range)	29.1 (SD, 3.9; range, 20.4–39.9)	
Initial prostate-specific antigen level, mean, ng/mL	3.3 (SD, 1.6; range, 0.2–8.1)	
Testosterone, mean, ng/dL (SD)	406.8 (152.8)	
Transrectal ultrasound, total, mean, mL (SD)	47.7 (25.3)	
Number of biopsies	1.90 (SD, 1.1; range, 1–6)	
Gleason score		
5	2	1.1
6	176	97.7
7	2	1.1
Clinical stage		
cT1a	5	2.7
cT1c	153	85.0
cT2a	18	10.0
cT2b	2	1.1
cT2c	2	1.1
Family history of prostate cancer		
None	112	62.2
First-degree relative only	40	22.2
Second-degree relative only	23	12.7
First- and second-degree relatives	5	2.8

Table 2

Mean Scores on Study Variables at Each Observation

Study variable	Mean values over time						<i>P</i>
	T1	T2	T3	T4	T5	T6	
MUIS	73.7	72.5	71.2	67.0	66.2	62.4	<0.0001
STAI	30.9	30.4	29.3	28.6	29.1	26.8	0.0091
EPIC							
Urinary	86.8	86.8	87.7	88.1	86.9	86.9	0.9429
Bowel	93.9	93.4	93.9	93.7	93.2	92.9	0.5397
Sexual	59.5	58.5	56.7	54.6	52.7	52.4	0.0467
Hormonal	90.4	91.6	91.7	92.6	93.0	91.8	0.5966
Satisfaction	80.5	75.9	79.9	78.3	83.9	85.4	0.1246
SF-12 PCS	50.8	50.0	51.2	51.1	51.2	51.9	0.3534
SF-12 MCS	53.2	53.8	53.1	53.9	53.6	54.0	0.9406
Fear of progression	4.3	3.7	3.3	3.0	2.6	2.6	0.3252

Abbreviations: T, time; MUIS, Mishel Uncertainty in Illness Scale; STAI, State Trait Anxiety Inventory; EPIC, Expanded Prostate Index Composite; SF-12 PCS, Short-form Health Survey, Physical Component Summary; SF-12 MCS, Short-form Health Survey, Mental Health Component Summary.

Note: Values were calculated while controlling for age, ethnicity, Gleason score, cancer stage, prostate-specific antigen level, prostate-specific antigen density, testosterone, body mass index, number of biopsies, family history of cancer, whether patient was taking a 5-alpha-reductase inhibitor, and whether tumor was reclassified.

Table 3

Associations between demographic and clinical characteristics and EPIC, SF-12 PCS and MCS and Fear of Disease Progression Scores

	Urinary	Bowel	Sexual	Hormonal	Satisfaction	PCS	MCS	Fear of Progression
Race	$F_{3,148} = 0.54$ $p = 0.6580$	$F_{3,150} = 0.26$ $p = 0.8535$	$F_{3,147} = 0.34$ $p = 0.7967$	$F_{3,146} = 1.90$ $p = 0.1327$	$F_{3,149} = 0.98$ $p = 0.4041$	$F_{3,150} = 0.41$ $p = 0.7459$	$F_{3,150} = 0.19$ $p = 0.9056$	$F_{3,116} = 1.48$ $p = 0.2223$
Age	$F_{1,148} = 3.08$ $p = 0.0814$	$F_{1,150} = 0.61$ $p = 0.4369$	$F_{1,147} = 69.95$ $p < .0001$	$F_{1,146} = 0.93$ $p = 0.3359$	$F_{1,149} = 2.07$ $p = 0.1519$	$F_{1,150} = 16.18$ $p < .0001$	$F_{1,150} = 6.43$ $p = 0.0123$	$F_{1,116} = 3.71$ $p = 0.0566$
Cancer Stage	$F_{4,148} = 2.61$ $p = 0.0378$	$F_{4,150} = 0.83$ $p = 0.5056$	$F_{4,147} = 0.96$ $p = 0.4303$	$F_{4,146} = 1.21$ $p = 0.3071$	$F_{4,149} = 0.50$ $p = 0.7391$	$F_{4,150} = 1.31$ $p = 0.2705$	$F_{4,150} = 0.22$ $p = 0.9257$	$F_{4,116} = 1.17$ $p = 0.3270$
Reclassified	$F_{1,148} = 0.01$ $p = 0.9367$	$F_{1,150} = 0.06$ $p = 0.8130$	$F_{1,147} = 0.59$ $p = 0.4433$	$F_{1,146} = 0.17$ $p = 0.6852$	$F_{1,149} = 2.94$ $p = 0.0883$	$F_{1,150} = 0.94$ $p = 0.3346$	$F_{1,150} = 0.05$ $p = 0.8287$	$F_{1,116} = 0.79$ $p = 0.3770$
Gleason Score	$F_{2,148} = 0.13$ $p = 0.8755$	$F_{2,150} = 0.06$ $p = 0.9450$	$F_{2,147} = 0.08$ $p = 0.9245$	$F_{2,146} = 0.01$ $p = 0.9928$	$F_{2,149} = 0.47$ $p = 0.6255$	$F_{2,150} = 0.87$ $p = 0.4216$	$F_{2,150} = 0.22$ $p = 0.8007$	$F_{2,116} = 0.60$ $p = 0.5500$
Family History	$F_{1,148} = 0.18$ $p = 0.6754$	$F_{1,150} = 0.54$ $p = 0.4630$	$F_{1,147} = 1.69$ $p = 0.1963$	$F_{1,146} = 0.41$ $p = 0.5231$	$F_{1,149} = 0.26$ $p = 0.6132$	$F_{1,150} = 1.98$ $p = 0.1618$	$F_{1,150} = 0.00$ $p = 0.9671$	$F_{1,116} = 1.98$ $p = 0.1618$
Number of Biopsies	$F_{5,148} = 0.18$ $p = .8797$	$F_{5,150} = 0.86$ $p = 0.5114$	$F_{5,147} = 1.04$ $p = 0.3950$	$F_{5,146} = 1.16$ $p = 0.3333$	$F_{5,149} = 0.51$ $p = 0.7691$	$F_{5,150} = 1.33$ $p = 0.2547$	$F_{5,150} = 1.58$ $p = 0.1687$	$F_{4,116} = 0.48$ $p = 0.7507$
Testosterone	$F_{1,415} = 0.08$ $p = 0.7759$	$F_{1,415} = 0.26$ $p = 0.6071$	$F_{1,401} = 0.43$ $p = 0.5105$	$F_{1,407} = 2.64$ $p = 0.1052$	$F_{1,408} = 0.00$ $p = 0.9657$	$F_{1,400} = 0.81$ $p = 0.3675$	$F_{1,400} = 1.55$ $p = 0.2140$	$F_{1,228} = 0.01$ $p = 0.9266$
BMI	$F_{1,415} = 0.77$ $p = 0.3796$	$F_{1,415} = 0.41$ $p = 0.5239$	$F_{1,401} = 1.72$ $p = 0.1901$	$F_{1,407} = 3.09$ $p = 0.0793$	$F_{1,408} = 6.43$ $p = 0.0116$	$F_{1,400} = 5.22$ $p = 0.0229$	$F_{1,400} = 5.90$ $p = 0.0156$	$F_{1,229} = 0.55$ $p = 0.4611$
ARI 5	$F_{1,148} = 5.44$ $p = 0.0210$	$F_{1,150} = 0.53$ $p = 0.4676$	$F_{1,147} = 1.03$ $p = 0.3109$	$F_{1,146} = 0.47$ $p = 0.4924$	$F_{1,149} = 0.24$ $p = 0.6271$	$F_{1,150} = 0.39$ $p = 0.5346$	$F_{1,150} = 0.53$ $p = 0.4684$	$F_{1,116} = 0.73$ $p = 0.3950$
PSA	$F_{1,415} = 18.02$ $p < .0001$	$F_{1,415} = 12.60$ $p = 0.0004$	$F_{1,401} = 1.55$ $p = 0.2134$	$F_{1,407} = 7.70$ $p = 0.0058$	$F_{1,408} = 1.32$ $p = 0.2518$	$F_{1,400} = 0.99$ $p = 0.3213$	$F_{1,400} = 0.15$ $p = 0.7018$	$F_{1,228} = 0.03$ $p = 0.8709$
PSA Density Total	$F_{1,148} = 2.80$ $p = 0.0961$	$F_{1,150} = 0.07$ $p = 0.7910$	$F_{1,147} = 0.73$ $p = 0.3935$	$F_{1,146} = 0.02$ $p = 0.9010$	$F_{1,149} = 1.71$ $p = 0.1933$	$F_{1,150} = 0.15$ $p = 0.7010$	$F_{1,150} = 0.64$ $p = 0.4244$	$F_{1,116} = 3.28$ $p = 0.0729$

Table 4

Uncertainty Score and Anxiety Predicting Quality of Life and Fear of Disease Progression

Outcome variable	MUIS score			Anxiety		
	F	Estimate	P	F	Estimate	P
EPIC						
Urinary	14.31	-0.1149	0.0002	5.51	-0.09834	0.0193
Bowel	6.03	-0.06285	0.0145	7.39	-0.09424	0.0068
Sexual	8.18	-0.1768	0.0045	18.96	-0.3792	<0.0001
Hormonal	23.12	-0.1423	<0.0001	54.81	-0.2822	<0.0001
Satisfaction	47.53	-0.5287	<0.0001	21.73	-0.4813	<0.0001
SF-12 PCS	14.38	-0.0989	0.0002	1.97	-0.04341	0.1612
SF-12 MCS	25.78	-0.1278	<0.0001	149.30	-0.3646	<0.0001
Fear of progression	56.31	0.07181	<0.0001	71.59	0.1085	<0.0001

Abbreviations: T, time; MUIS, Mishel Uncertainty in Illness Scale; STAI, State Trait Anxiety Inventory; EPIC, Expanded Prostate Index Composite; SF-12 PCS, Short-form Health Survey, Physical Component Summary; SF-12 MCS, Short-form Health Survey, Mental Health Component Summary.

Note: Values were calculated while controlling for age, ethnicity, Gleason score, cancer stage, prostate-specific antigen level, prostate-specific antigen density, testosterone, body mass index, number of biopsies, family history of cancer, whether patient was taking a 5-alpha-reductase inhibitor, and whether tumor was reclassified.