DOI:10.1093/jncimonographs/lgs026

Quality of Life in Men Undergoing Active Surveillance for Localized Prostate Cancer

Jonathan Bergman, Mark S. Litwin

Correspondence to: Jonathan Bergman, MD, UCLA Department of Urology, Box 951738, Los Angeles, CA 90095-1738 (e-mail: jbergman@mednet.ucla.edu).

Active surveillance is an important arrow in the quiver of physicians advising men with prostate cancer. Quality-of-life considerations are paramount for patient-centered decision making. Although the overall deleterious impact on health is less dramatic than for those who pursue curative treatment, men on active surveillance also suffer sexual dysfunction and distress. Five-year outcomes revealed more erectile dysfunction (80% vs 45%) and urinary leakage (49% vs 21%) but less urinary obstruction (28% vs 44%) in men undergoing prostatectomy. Bowel function, anxiety, depression, well-being, and overall health-related quality of life (HRQOL) were similar after 5 years, but at 6–8 years, other domains of HRQOL, such as anxiety and depression, deteriorated significantly for those who chose watchful waiting. Further research is needed to compare prospectively HRQOL outcomes in men choosing active surveillance and those never diagnosed with prostate cancer, in part to help weigh the potential benefits and harms of prostate cancer screening.

J Natl Cancer Inst Monogr 2012;45:242–249

Active surveillance is an important arrow in the quiver of physicians advising men with prostate cancer. Although the lifetime risk of developing prostate cancer is approximately 1 in 6, the lifetime risk of prostate cancer death is only 1 in 30 (1). Incidental prostate cancer is diagnosed in up to 45% of men undergoing cystoprostatectomy for a diagnosis of bladder cancer (2–4), and in 35% of American men at autopsy (5–6). Since the introduction of prostate-specific antigen (PSA) screening in the late 1980s, prostate cancer has been diagnosed at an early stage and grade with increased frequency (7). Low-risk prostate cancer often follows an indolent clinical trajectory (8), and the survival benefit of curative management is still debated (9–11).

Men diagnosed with low-risk prostate cancer are typically offered one of three treatment options: radical prostatectomy, radiation therapy, or active surveillance. Active surveillance entails repeating PSA testing, digital rectal examination, and prostate needle biopsy at predetermined intervals, although the ideal interval at which these three follow-up modalities should be used remains an unanswered question (12–20). Before the adoption of active surveillance protocols, men with localized disease who did not pursue curative treatment often underwent watchful waiting, which involved periodic visits and initiation of attempted curative or palliative treatment when symptoms progressed.

Intervention strategies for men choosing active surveillance differ more significantly than do follow-up protocols, and the dual questions of if and when to institute curative treatment are both actively debated (13–22). Some groups rely primarily on PSA kinetics (14,23), whereas others focus on progression in cancer grade or on the percentage of cancer in each biopsy core (15). Other treatment triggers include a change in digital rectal examination or worsening urinary symptoms (22). Patient preference is central to pursuing or not pursuing any treatment course (19,22). The role of imaging techniques, including magnetic resonance imaging and ultrasonography, is undefined. Approximately one-third of men choosing active surveillance eventually pursue curative treatment (13–22).

Despite the absence of demonstrated superiority of curative treatment compared with active surveillance for men with low-risk prostate cancer, population-based studies suggest that only one-tenth of men in that cohort undergo active surveillance (24). In an observational study of almost 2000 men with clinically localized prostate cancer, 16% were deemed candidates for active surveillance (25). Of those men, only 9% chose surveillance.

When individuals do choose active surveillance, they often divagate from predetermined follow-up protocols. In a recent population-based analysis, only 39% of men who underwent active surveillance had their PSA measured at least annually (26). A lower likelihood of annual PSA surveillance was associated with African American race, lower socioeconomic status, younger age, and lower comorbidity. Paradoxically, those in whom follow-up should be strictest receive the most capricious surveillance.

Because affected men are much more likely to die *with* their disease, rather than *of* it, the decision between curative treatment and active surveillance may hinge on factors other than expected cause-specific survival. As Harry Herr laconically noted in 1987, "The goal of any treatment strategy for cancer is to improve not only patient survival but also quality of that survival."(27) The art and science of systematically measuring quality of life (QOL) have been developed and refined for men with prostate cancer, and QOL considerations are paramount for patient-centered decision making.

Measuring QOL in Men With and Without Prostate Cancer

Health-related QOL (HRQOL) encompasses a wide range of human experience, including the daily necessities of life, such as food and

shelter, intrapersonal and interpersonal responses to illness, and activities associated with professional fulfillment and personal happiness (28). Contemporary interpretations of HRQOL are based on the World Health Organization's longstanding definition of health as a "state of complete physical, mental, and social well-being and not merely the absence of disease" (29). Because illness may affect both quantity of life and QOL, all constituents of well-being must be addressed when treating patients with urologic diseases. Perhaps most importantly, HRQOL involves patients' own perceptions of their health and ability to function in life. Indeed, patient perceptions of physical function have prognostic value in predicting survival (30). In light of evidence that survival and clinical outcomes may be similar across treatments for many conditions, QOL considerations may be the critical factor in medical decision making in some instances.

Although quantity of life is relatively easy to assess in terms of survival, the measurement of QOL presents more challenges, primarily because it is less familiar to most clinicians (31–32). To quantify these qualitative phenomena, the principles of psychometric test theory are applied. This discipline provides the theoretical underpinnings for the science of survey research (33–38). Data are collected with HRQOL surveys, called instruments. Instruments typically contain questions, or items, which are organized into scales. Each scale measures a different aspect, or domain, of HRQOL. For example, items of a particular instrument may address a patient's ability to have an erection and his satisfaction with ejaculation, both of which might be included in a sexual domain.

Some scales comprise dozens of items, whereas others may include only one or two items. Each item contains a stem (which may be a question or a statement) and a response set. Most response sets are one of the following types: 1) Likert scale, in which the respondent selects from a list of degrees of agreement or disagreement with the stem; 2) Likert-type scale, in which the respondent chooses from a list of text responses; 3) visual analog scale, in which the respondent marks a point on a line that is anchored on both ends by descriptors; or 4) numerical rating scale, in which the respondent chooses a number, usually between 0 and 10. Other response sets and approaches have been developed for children, people of low literacy, and various other populations (39–41).

It is axiomatic that HRQOL assessments capture patients' own perceptions of their health and ability to function in life. Instruments are best when they are self-administered by the patient, but if interviewer assistance is required, it must be from a neutral third party in a standardized fashion. Some studies have demonstrated that physicians typically underestimate the symptom burden experienced by prostate cancer patients, perhaps because their queries are not sensitive enough or because patients tend to understate their problems when speaking directly with the primary caregiver (42–44). Other studies, however, suggest that physicians tend to overestimate the impact of the disease and its treatment on patients' psychosocial functioning and sense of well-being (45–47). Conversely, spouses may overstate some domains and understate others when compared with patient assessments (48). Kornblith et al. (49) presented results from a large sample of patients and spouses, both administered several validated HRQOL measures. Spouses reported greater psychological distress but fewer sexual problems than did patients themselves. In a study of perspectives on HRQOL during antihypertensive therapy, Testa (50) demonstrated that physicians were less sensitive to the impact of side effects, reporting less than 15% of the symptoms reported by patients. Spousal reports were more sensitive than patient self-assessments, particularly in the area of sexual functioning.

Rigorous methodology is vital to elucidating HRQOL outcomes. Randomized, prospective designs maximize internal validity. Propensity scoring, instrumental variable design, and multivariable analyses partly control for a variety of factors that affect HRQOL, but some endogeneity persists.

HRQOL Instruments

HRQOL instruments may be general or disease specific. General HRQOL domains address the components of overall well-being, whereas disease-specific domains focus on the impact of particular organic dysfunctions that may affect HRQOL. General HRQOL instruments typically address general health perceptions, sense of overall well-being, and function in the physical, emotional, and social domains. Disease-specific HRQOL instruments focus on special and/or more directly relevant domains, such as anxiety about cancer recurrence, dizziness from antihypertensive medications, or suicidal thoughts during depression therapy (51). Disease-specific and general HRQOL domains often affect each other, leading to important interactions that must be considered in the interpretation of HRQOL data (52). Further research is needed in urology to explore how much of the variation in overall HRQOL is explained by variation in the disease-specific domains.

In some conditions, such as chronic renal failure, cirrhosis with ascites, and stroke, general HRQOL may be so profoundly affected that disease-specific HRQOL assessment is unnecessary. In many indolent conditions, however, the treatments may alter bodily functions that cannot be fully appreciated by assessing only the broader domains of general HRQOL. Conversely, in patients with advanced cancer, HRQOL may be affected predominantly by pain, fatigue, and other constitutional symptoms that are well captured by general HRQOL instruments.

There are numerous HRQOL instruments validated for use in urologic and other conditions. Many psychologists, sociologists, and statisticians devote their entire professional careers to the activity of developing and validating these instruments. Most medical research collaboratives devote substantial efforts to the development and standardization of HRQOL instruments (53–54). An abundance of literature exists on general HRQOL, and a significant body of work has been published on HRQOL in patients with various conditions (28,55). In urology, HRQOL research has been broad, but much has focused on individuals with prostate cancer, urinary incontinence, benign prostatic hyperplasia, end-stage renal disease, and bladder cancer (56–61). A comprehensive resource for validated HRQOL instruments is available at www.proqolid.org. The National Cancer Institute has been particularly active in establishing interest in outcomes measurement for patients with malignant disease (www.outcomes.cancer.gov).

QOL in Men Choosing Watchful Waiting or Active Surveillance

Watchful waiting and active surveillance do not leave men at their baseline state of health. What remains unclear is whether deterioration in HRQOL is caused by distress over disease, by physiological

symptoms caused by the cancer, by the inexorable burden of age, or by a combination of the three.

Although the overall deleterious impact on health is less dramatic than for those who pursue curative treatment, men on watchful waiting or active surveillance may also suffer significant sexual dysfunction and distress. In the only large, prospective, randomized, controlled trial published to date in which HRQOL has been compared between men receiving curative treatment and those on watchful waiting, 5-year outcomes revealed more erectile dysfunction (80% vs 45%) and urinary leakage (49% vs 21%), but less urinary obstruction (28% vs 44%), in men undergoing prostatectomy (62). Bowel function, anxiety, depression, well-being, and overall HRQOL were similar in the two groups after 5 years, but at 6–8 years, other domains of HRQOL, such as anxiety and depression, deteriorated significantly for those who chose watchful waiting (63).

At a median follow-up of 12 years, HRQOL was then compared among men receiving radical prostatectomy, those on watchful waiting, and in population-based controls (64). Self-assessment revealed high HRQOL in 35% of men after radical prostatectomy, 34% of men on watchful waiting, and 45% of those in the population. Anxiety was higher in the prostatectomy (43%) and watchful waiting (43%) groups than in the control group (33%). Erectile dysfunction was similar between the group receiving radical prostatectomy (84%) and men on watchful waiting (80%), but both levels were significantly higher than that in the population control (46%). Urinary leakage was reported in 41% of those receiving prostatectomy, 11% of men on watchful waiting, and 3% of those in the population. The relative contribution of the physiological effects of cancer and the psychosocial impact of a cancer diagnosis to deterioration in HRQOL in men on watchful waiting has yet to be appropriately attributed.

Short-term mental health differs significantly from long-term mental health in men on active surveillance. One-year analyses of the Finnish arm of the prospective, observational, longitudinal Prostate Cancer Research International: Active Surveillance (PRIAS) study compared general HRQOL, erectile function, urinary function, and mental health before and one year after pursuing active surveillance for low-risk prostate cancer (65). No significant changes were seen in urinary or erectile function, and neither mental nor physical HRQOL declined over time. In fact, both physical and mental health were slightly better than the same in an age-stratified group from the general Finnish male population.

In the long term, however, mental health differs significantly among men choosing radical prostatectomy, radiation therapy, or watchful waiting. Patient-reported outcomes from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE)—a national, longitudinal registry of men with prostate cancer in community and academic settings across the United States (66–68)—suggest significant variation in HRQOL over time. Although short-term outcomes were similar among the groups, over time, those treated with radical prostatectomy had the best mental health, followed by men who chose watchful waiting and those treated with radiation therapy (69). Disparities increased over time.

Other HRQOL analyses from CaPSURE revealed modest decreases in HRQOL over time for men pursuing watchful waiting, with more meaningful declines in physical than mental HRQOL. After controlling for confounders, bowel bother, sexual function, and sexual bother declined significantly over time, but bowel function, urinary bother, and urinary function did not (70).

Men who choose active surveillance can improve their HRQOL by making lifestyle changes (71). In the proof-of-principle Prostate Cancer Lifestyle Trial, 93 men with low-risk prostate cancer on active surveillance were randomized to regular care versus an intervention strategy that included dietary changes, exercise, and stress management. Participants who significantly improved their lifestyle over a 12-month period reported improved physical HRQOL and reduced stress. A healthier lifestyle at baseline was associated with better mental HRQOL, physical HRQOL, and sexual function.

The effect of active surveillance on QOL among US veterans has also been studied, although with more limited power. A prospective, observational, multicenter trial from five Veterans Affairs Medical Centers found that for men with localized prostate cancer, urinary control, dysuria, and sleep patterns all deteriorated within the first 12 months after diagnosis (72). The declines in HRQOL were statistically significant, whereas the magnitude of decline was less dramatic than the decline for men who opted for curative treatment.

Further research is needed to compare prospectively HRQOL outcomes in men choosing watchful waiting or active surveillance and those never diagnosed with prostate cancer, in part to help weigh the potential benefits and harms of prostate cancer screening. The detriment of receiving a prostate cancer diagnosis, if one chooses not to pursue curative treatment, can then more accurately be compared with the potential harm of not diagnosing a conceivably curable malignancy. Avenues to mitigate HRQOL declines in men on active surveillance must also be defined.

QOL in Men Treated for Prostate Cancer

Prospective, National, Observational Trials

The two largest prospective, national, nonrandomized, multicenter cohort studies in prostate cancer are CaPSURE (described above) and the Prostate Cancer Outcomes and Satisfaction with Treatment: Quality Assessment (PROST-QA). PROST-QA is a consortium of nine academic centers, which has tracked more than 1800 men and spouses for several years with a specific focus on QOL outcomes after surgery, external beam radiation, or interstitial brachytherapy (73).

CaPSURE has enriched our understanding of temporal HRQOL changes in men treated for prostate cancer (74). Enrollees undergoing radical prostatectomy have immediate postoperative declines in disease-specific and general HRQOL, with significant improvements in all domains during the first year after treatment. Sexual function continues to improve in year 2. Compared with men treated with external beam radiation therapy, primary androgen deprivation, or surveillance, sexual function declines most precipitously for those treated with radical prostatectomy, but the prostatectomy group enjoys the greatest degree of recovery, as well. After all treatments, recovery of urinary and sexual function generally occurs within 2 years, with a smaller magnitude of change in year 3 (75). For men treated with radical prostatectomy, urinary

function improved over the first year and remained stable during year 2. For men treated with radiation therapy, urinary function was stable over time, but urinary bother was worse throughout the 2 years, with improvement observed relative to year 1 (76).

Men who received multimodal therapy appeared to have greater declines in urinary and sexual functions than those who were treated with monotherapy (77). Older patients treated with radiation therapy had the most substantial decline in sexual function over a 2-year period, whereas older men treated with radical prostatectomy returned to their relatively low baseline sexual function (78).

Short- and long-term CaPSURE analyses of patient–physician concordance in assessing HRQOL revealed significant discord within the dyad (79). Urologists were sensitive to urinary and sexual declines in HRQOL but less aware of changes in fatigue and pain. Dyadic discordance did not improve from short- to long-term or from earlier to later cohorts. The findings highlight the need to improve patient–clinician communication, allowing health-care providers 1) to better understand men's motivations and understanding as the latter are counseled about prostate cancer treatment options and 2) to address posttreatment deficiencies as they occur.

Analyses from PROST-QA have confirmed and externally validated those reported in CaPSURE. Compared with men undergoing radical prostatectomy or external beam radiotherapy, those who pursue brachytherapy have longer-lasting urinary storage symptoms, bowel difficulty, sexual symptoms, and problems with vitality or hormonal function (73). Immediate postoperative sexual function declines were noted in those undergoing radical prostatectomy, but anatomic nerve-sparing procedures mitigated sexual decline (73,80). Although reliable urinary storage was compromised after radical prostatectomy, voiding and storage symptoms improved after surgery, especially for men with large prostates. Serious adverse events were scarce, no deaths occurred, and symptoms were most severe in those who were obese, older, or who had a large prostate or high PSA levels. African American men reported lower overall satisfaction with treatment, and changes in HRQOL were associated with satisfaction among patients and partners.

Retrospective National, Observational Trials

Building on Fowler's early cross-sectional work in Medicare patients (81), Carroll's national CaPSURE registry (76–68), Talcott's early prospective single-institution series (82–83), and the availability of validated instruments (84–86), Potosky and colleagues at the National Cancer Institute undertook the Prostate Cancer Outcomes Study (PCOS). Drawing subjects from SEER (Surveillance, Epidemiology, and End Results) registries across the United States, PCOS was the first nationally representative, population-based, longitudinal cohort examining outcomes and HRQOL from the patient perspective in men who had undergone active treatment for prostate cancer.

Initial PCOS results indicated that 2 years after radical prostatectomy, more than 90% of men were continent, and about half were (by some definition) potent (87). This represented a dramatic improvement compared with the era before Walsh and Donker reported their now-classic description of the cavernous erectile nerves (88).

Subsequent PCOS results revealed that 5 years after treatment, men who had undergone surgery reported stable urinary function, whereas those who had undergone radiation experienced progressive urinary impairment. Just as striking was the finding that 3–5 years after treatment, those irradiated saw a much sharper decline in sexual function than did those operated (89), thus providing empiric evidence for the leitmotif that time homogenizes sexual outcomes after surgery or radiation. This may be due to the effects of aging, cumulative radiation injury, postoperative nerve recovery, or all three.

Follow-up 5-year PCOS data featured several important observations for men undergoing radical prostatectomy (90). First, significant urinary leakage, uncommon though not trivial, remains fairly constant—between 11% at 2 years and 14% at 5 years—postoperatively. Associated urinary distress is commensurate with leakage, occurring in only 13% of surgical cases. Second, our understanding of how vastly different are the sexual outcomes between urologists in general and those in referral centers with high-volume subspecialty practices was reiterated (91). Third, sildenafil appears to aid in the postoperative return of erections for men who are potent at baseline and who undergo bilateral nerve sparing. Fourth, for the majority of men, functional outcomes remain fairly stable between 2 and 5 years after surgery. Finally, even though only 28% of respondents overall report erections firm enough for intercourse, almost twice as many (54%) state that they are sexually active at least once a month. This clarifies that the nature of sexual function in prostate cancer survivors includes activities beyond coitus alone, an observation that has clinical relevance for men whose sexual partner is unable or unwilling to have intercourse.

Single-Institution Series

A prospective, longitudinal, nonrandomized study of recovery profiles in 475 men before and through 4 years after prostatectomy, external beam radiation, or interstitial brachytherapy compared short- and long-term outcomes after each treatment modality. For 2 years, general HRQOL was not dramatically affected by treatment (92). Storage and voiding urinary symptoms were most common after brachytherapy, whereas urinary control and sexual function were best after external beam radiation, followed by brachytherapy and radical prostatectomy; nerve-sparing techniques mitigated urinary and sexual disparities for the radical prostatectomy group. Sexual bother was more common than urinary or bowel bother in all treatment groups. Bowel function was best after radical prostatectomy.

After 4 years, urinary incontinence was more common after prostatectomy, whereas voiding and storage urinary symptoms were more prevalent after brachytherapy (93). Sexual dysfunction profoundly affected all treatment groups, with a relatively low likelihood of regaining baseline function among prostatectomy subjects. Bowel dysfunction was more common after radiation. Capturing baseline function before treatment permitted comparison of mean scores of an interval with pretreatment function. In a separate analysis of prostatectomy survivors in this longitudinal cohort, mean recovery time was approximately 11 months for sexual function, 9 months for sexual bother, 7 months for urinary domains, and 5 months in bowel domains, with significant variability (94). This highlights the need to inspirit patients with the knowledge that

recovery after radical prostatectomy is a marathon rather than a sprint, with significant improvements possible even years after surgery.

Further data from the same cohort showed that continence and potency vary by the terms used to describe them (95). Variation in potency was most pronounced, elucidating the importance of clearly defining HRQOL goals and outcomes in delivering patient-centered care.

A separate cross-sectional HRQOL survey included 902 men who underwent radical prostatectomy, external beam radiation, or brachytherapy at an academic medical center and 112 age-matched controls (96). Sexual function was worse in all treatment groups than in controls, and urinary HRQOL was worst in those undergoing radical prostatectomy. External beam radiotherapy was associated with decreased bowel HRQOL, whereas men treated with brachytherapy had significant impairment in all domains. Twelve months after therapy, HRQOL after brachytherapy was worse in all domains compared with that after external beam radiation or radical prostatectomy. Biochemical recurrence was associated with worse sexual and hormonal HRQOL.

Special Populations

Results from low-income, underserved populations with prostate cancer have been reported primarily in men enrolled in a large, state-funded program, Improving Access, Treatment and Counseling for Californians with Prostate Cancer (IMPACT), details of which may be found at www.california-impact.org. IMPACT enrollees' HRQOL scores are significantly worse at baseline in all domains of the SF-12 than men in the general population. Subsequently, sexual bother worsens significantly, whereas bowel domains improve (97–98). Nurse case management appears to improve patients' HRQOL (99). Enrollees with low self-efficacy fare worse over a range of psychosocial outcomes and both general and disease-specific HRQOL (100).

Conclusion

The dual goals of prostate cancer treatment that guide clinical practice and drive research involve maximizing the quantity of life and QOL. That so few men with low-risk disease choose active surveillance raises concern about how well men and their partners understand the different treatment modalities and the natural prostate cancer trajectory. Men with prostate cancer should be advised of the dramatic and disparate impact of radical prostatectomy, radiation therapy, and active surveillance on physical and emotional health. With improved counseling and a more layered understanding of HRQOL, men could more knowledgeably navigate prostate cancer treatment options.

Physicians interacting with men who have prostate cancer should advise them that treatment is unlikely to affect general HRQOL but may be associated with clinically significant changes in sexual, urinary, or bowel function. Treatment decisions should continue to be individualized. Any survival gains from surgery or radiation must be balanced with expected decrements in some areas of function and bother. With richer information on HRQOL, in addition to duration of survival, patients will be able to make more informed decisions and feel more comfortable proceeding with therapy or observation for localized prostate cancer.

Several randomized, controlled trials are currently investigating active surveillance as a treatment option for men with low-risk prostate cancer. The Canadian-centered Standard Treatment Against Restricted Treatment (START) trial is expected to enroll 2130 men from Canada, the United States, and the United Kingdom. The trial will compare early active prostate cancer treatment (in the form of radical prostatectomy or radiation therapy) with active surveillance (with delayed intervention when indicated). The aforementioned Dutch-based Prostate Cancer Research International Active Surveillance (PRIAS) study is enrolling European and North American men with low-risk prostate cancer who pursue an active surveillance protocol that includes repeat prostate needle biopsies for up to 10 years after enrolment; preliminary results have been released and are summarized above (101). In longer-term analyses, changes in PSA and PSA kinetics will also be described. In the United Kingdom, the Prostate Testing for Cancer and Treatment (ProtecT) trial recruited patients until 2008 and intends to compare active surveillance with up-front curative treatment with a follow-up period of 10–15 years (102).

If more men are to embark on the active surveillance journey, we must further elucidate anxiety and fear of recurrence if prostate cancer is diagnosed but not actively treated. Although little is known about the psychosocial impact of active surveillance, one study found that patient uncertainty over treatment outcomes, support from physicians, and concerns about side effects often influence men to choose surveillance (103). Yet many men perceive active surveillance as "doing nothing," which they consider inherently unacceptable (104–111). Barriers to choosing active surveillance are anxiety, uncertainty, and lack of education (18,112–116). Understanding HRQOL in men on active surveillance may lead more men down that path, or, alternatively, dissuade them from prostate cancer screening in the first place.

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Affiliations of authors: Department of Urology (JB, MSL), Robert Wood Johnson Clinical Scholars Program (JB), Health Services (MSL), and Jonsson Comprehensive Cancer Center (MSL), University of California Los Angeles, Los Angeles, CA; Veterans Administration Greater Los Angeles Healthcare System, Los Angeles, CA (JB).