Published in final edited form as:

Semin Radiat Oncol. 2008 January ; 18(1): 67–72. doi:10.1016/j.semradonc.2007.10.001.

Measuring Health-Related Quality of Life Consequences from Primary Treatment for Early Stage Prostate Cancer

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INTRODUCTION

Evidence in randomized trials that primary, definitive treatment for early stage prostate cancer increases survival,[1][2] has sharpened focus on the Health-Related Quality of Life (HRQOL) consequences of such treatment. Numerous questionnaires, or instruments, have been devised to measure these quality of life concerns. Some instruments (such as the FACT-P module of FACT-G) focus on general post-cancer treatment outcomes while others (such as the UCLA-PCI) target specific side-effects, or domains, associated with prostatectomy or radiotherapy. [3,4] Early studies in the development of these HRQOL instruments sought to identify various HRQOL domains impacted by common primary prostate cancer treatments, and to refine and adapt the questionnaires to be sensitive to a broad array of clinically significant side effects as measured from the patient's perspective. Such HRQOL instrument development and validation was followed by numerous single institution studies seeking to determine relationships of patient and treatment factors to HRQOL outcomes. However, single institution reports are especially susceptible to selection bias, and the generalizability of their findings is therefore limited. Multi-institutional studies have begun to evaluate prostate cancer HRQOL outcomes, but many aspects of prostate cancer HRQOL outcomes remain incompletely characterized in the generalizable, multi-center setting.

One goal of prostate cancer HRQOL research is to provide information that will enable setting individualized patient outcome expectations, so as to optimize treatment decisions for any individual prostate cancer patient. Although substantial progress has been made by early multi-center prostate cancer outcomes studies toward this goal, substantial knowledge gaps remain. From inspecting HRQOL domains identified as clinically relevant consequences of prostate cancer treatment, to summarizing existing, validate HRQOL instruments, and finally to evaluating findings from prospective, multi-institutional studies of prostate cancer patient-reported outcomes, this review will describe aspects of prostate cancer HRQOL outcomes and identify issues in need of further assessment for enabling optimal, evidence-based decision-making in treatment selection for individual patients.

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VALIDATED QUESTIONNAIRES: INSTRUMENTS TO MEASURE HRQOL

Validation of a questionnaire to substantiate its use as an instrument for measuring HRQOL has several components. First, the questionnaire should ideally be developed with input from patients (eg via focus groups or otherwise), practitioners, and survey experts. Next, questionnaires should be evaluated in target populations and the biometric basis for their measurement scales should be reported, with analyses of internal consistency and test-retest correlation that provide evidence supporting the validity. The final, and perhaps most important, component of a questionnaire's validity is the instrument's 'construct' validity, or simply put, evidence through use and results in HRQOL studies, that the instrument can elicit information that helps characterize outcomes and facilitates medical decision-making.

Historically, prostate cancer treatments were assessed primarily with general HRQOL instruments lacking direct assessment of treatment-specific side effects and outcomes. However, it became apparent that such general HRQOL instruments were not sensitive to pivotal HRQOL concerns – i.e., sexual, urinary, bowel issues that emerge following primary prostate cancer treatment. Litwin et al (1995) constructed and validated the first quantifiable instrument for measuring prostate specific HRQOL (UCLA-PCI: UCLA Prostate Cancer Index) with input from focus groups consisting of prostate cancer treatment patients as well as their spouses/partners along with expert opinions from clinical urologists and radiation oncologists (Table 1) [4]. Validation of the UCLA-PCI included response-based item reduction and evaluation of their measurement scale reliability via test-retest with a subset of their study sample. The eventual UCLA-PCI questionnaire consisted of 20 items with questions about both function and bother of urinary, bowel, and sexual function [4, 5]. Other multi-center studies have used the UCLA-PCI disease specific measurement scale in addition to a variety of general health scales to analyze the side effects of prostate cancer treatments [6-8]. The UCLA-PCI has been modified to address specific questions. Madalinska et al modified the UCLA-PCI to address more detailed questions about the nature of sexual dysfunction.[8] Potosky et al, used part of the UCLA-PCI together with ad-hoc, study-specific items, selected from unvalidated questionnaires, to conduct the Prostate Cancer Outcomes study (the first prospective, community-based evaluation of prostate cancer patient-reported and medical record-astracted outcomes).[7]

One limitation of the UCLA-PCI that became apparent as primary prostate cancer treatments evolved, was that it lacked items for evaluating irritative urinary symptoms observed in patients post radiotherapy, (brachytherapy (BT) and external beam treatment (XRT)), [6] and lacked items regarding side effects of hormonal therapy (which has become a common therapy even in early stage prostate cancer). To address these concerns, the UCLA-PCI was revised and expanded to generate the EPIC (Expanded Prostate Cancer Index Composite) instrument. [9] In addition to querying sexual and bowel domains, EPIC divides the urinary domain into 2 subscales measuring incontinence versus irritative symptoms as discrete HRQOL domains (Table 1). The original version of EPIC had 50 items, and retained the ability to discern function versus bother. In order to facilitate efficient questionnaire administration and optimize patient participation, an item-reduction analysis subsequently led to construction of the EPIC-26 short form [10] that retain the ability to measure outcomes in 5 HRQOL domains: urinary incontinence, urinary irritative/obstructive, bowel/rectal, sexual, and vitality/hormonal. Although EPIC-26 does not have the capacity to distinguish function from bother in the urinary or bowel domains, three bother items from the original UCLA-PCI (global urinary bother, global bowel bother, and overall sexual bother) are retained in both the longer EPIC-50 as well as in the EPIC-26 short form.

Among several other comprehensive HRQOL instruments used to measure early stage prostate cancer outcomes, the symptom indexes constructed by Clark and Talcott, and the Prostate

Module appendix for the EORTC-QLQ C30, have also undergone validation and have been used to study early stage prostate cancer outcomes. [11-13] Instead of developing an instrument *de novo* based on input from prostate cancer survivors, Talcott and Clark constructed a questionnaire combining items adopted from various prior non-validated prostate cancer surveys with items constructed based on practitioner input. Their consequent “Symptom Index” has 29 items and was validated for quantifiable measurement of urinary, bowel, and sexual domains, with the ability to distinguish function and distress (Table 1). [12]

The EORTC Genito-urinary group developed a 12-item module for evaluating prostate cancer-related HRQOL in conjunction with the QLQ-C30 (Table 1). [13] This module included evaluation of urinary, bowel, and sexual domains; however, despite querying urinary irritative symptoms as well as urinary incontinence, the module was not designed to specifically measure the irritative and incontinence concerns as separate domains, and instead provides only a urinary summary score. A potential limitation of such a summary score is that discordant incontinence versus obstruction symptoms can be difficult to detect and evaluate. For this reason, more contemporary instruments, such as EPIC as well as the Symptom Index from Talcott and Clark, allow urinary outcomes to be measured both as distinct subscales that distinguish incontinence from irritation/obstruction, and as overall urinary summary scores that allow the impact of the combination of urinary concerns to be determined.

PROSPECTIVE, MULTI-CENTER COHORT STUDIES

The most commonly used treatments for early stage prostate cancer in the North America include prostatectomy, external beam radiotherapy, and brachytherapy. Unfortunately, efforts to compare these treatments directly via randomized clinical trials, such as the NCI SPIRIT trial (a NCI Intergroup Trial that randomized patients to brachytherapy versus prostatectomy), have not yet succeeded due to failure to meet accrual goals. Therefore, information regarding comparative outcome following early stage prostate cancer treatment relies largely on results from non-randomized observational cohorts. Because selection bias is pervasive when patients select treatment following physicians' recommendations, such outcomes data may serve as a basis for estimating outcomes among patients who have selected a particular treatment, rather than for comparing outcomes between different primary treatment types. Such observational studies can also be used to determine which HRQOL domains can be expected to be affected by specific primary treatment types, with an emphasis on whether or not a specific treatment type will impact a particular HRQOL domain, by comparing after treatment to baseline HRQOL status.

The spectrum of prospective observational studies that have used validated HRQOL instruments to measure early stage prostate cancer HRQOL outcomes across surgical, as well as radiation, treatment is probably best represented by three multi-center, community-based cohorts and a fourth cohort that evaluated outcomes in several hospital affiliates of a single university (Table 2). The Prostate Cancer Outcomes Study (PCOS), the CaPSURE cohort, and one community-based cohort from the Netherlands are the principal community-based, multicenter studies that reported concurrent, prospective evaluation of surgical and radiotherapy treated patients. However, none of the community-based cohorts was well-sampled with patients who had received brachytherapy, so information about brachytherapy outcomes, evaluated in the same context as surgical and external beam radiotherapy treatment, is largely limited to single-institution studies that may be prone to institutional practice bias as well as selection bias.

The Prostate Cancer Outcomes Study (PCOS) laid important groundwork as the first reported prospective study of patient-reported outcomes among prostate cancer survivors. To measure the two and five year side-effects of XRT or radical prostatectomy (RP) in PCOS, Potosky and

colleagues used both the general SF-36 and disease-specific (PCOS modification of the UCLA-PCI) questionnaires to measure patient-reported outcome [7]. The PCOS cohort was genuinely multi-regional, representing six geographic regions in the United States, and was primarily community - based, conducted at SEER sites. Limitations of this study included lack of brachytherapy subjects, and lack of information regarding contemporary treatment refinements such as 3-D conformal or intensity-modulated radiotherapy. These limitations could not have been anticipated when the PCOS study was initiated, because the emergence of these treatments occurred after PCOS was underway.

Madalinska and colleagues reported a Dutch community-based cohort that evaluated the side effects of RP and XRT, over a shorter time scale (6 months to 1 year) [8]. Patients in this study were from the European Randomized Trial of Screening for Prostate Cancer with participation from seven different European cancer centers. The measurement scales used were the SF-36 and an expanded version of the UCLA-PCI. Although smaller in total number of participants than PCOS, there were a similar number of patients receiving RP and XRT.

The third prospective, community-based cohort wherein patient-reported outcomes were evaluated following early stage prostate cancer treatment was a small subset of patients participating in the CaPSURE (Cancer of the Prostate Strategic Urological Research Endeavor) database (Table 2). CaPSURE is a prospective cohort which consists of community based practices from over 30 urology practices predominantly in the Western United States. The measurement scales included both the general health assessment SF-36 as well as the disease-specific UCLA-PCI. Limitations of the CaPSURE cohort included that HRQOL participants represented only a minor subset of the entire CaPSURE cohort, and that the cohort was enrolled and followed principally by urology practices. Therefore, this cohort evolved from the focal point of a single clinical discipline (Urology). This selection bias of CaPSURE participants toward those undergoing prostatectomy led to limitations regarding available details regarding radiotherapy. Moreover, in many cases, CaPSURE follow-up questionnaires were administered by the participating practitioners, allowing the possibility for 'passive coercion' bias (patients responding more favorably when questionnaires are administered by their treating physician, in an effort to please their doctor). Perhaps the most limiting aspect of the CaPSURE data is that less than half of patients completed informative patient-report survey beyond one year, which is well below the accepted threshold of 70% response rates for survey studies to be considered informative. Nevertheless, this cohort represents one of the few available datasets characterizing brachytherapy outcomes based on data collected by the same instruments used for concurrently evaluating external radiotherapy and surgery.

One multicenter study that compared all three treatments (RP, XRT, BP) in a longitudinal prospective cohort was conducted by Talcott and colleagues (Table 2). [11] The study consisted of patients from teaching hospitals associated with Harvard Medical School, and was well balanced with regard to participation by surgery and brachytherapy patients. Patients were questioned prospectively over three years post-treatment using both the general SF-36 and a prostate cancer treatment symptom index.[12] The principal limitation of the study was its setting at the local hospital affiliates of a single university; hence, though technically enrolling patients from four hospitals, these hospitals were adjacent, shared faculty, and lacked the heterogeneity of practice pattern that would be encountered in a truly multi-center, multi-regional setting. As with CaPSURE, this cohort also was susceptible to passive coercion bias (as questionnaires were administered by the participating practitioners), and encountered difficulties in subject retention, and questionnaire completion rates dropped substantially in the later follow-up time points.

Despite limitations that may be apparent in hindsight, these four prospective cohort studies (Table 2) established a fundamental foundation of basic principles in prostate cancer HRQOL

for investigators, practitioners, and patients alike. Ongoing and future studies may build upon this foundation to address knowledge gaps, such as the impact of hormone therapy and refinements in radiotherapy or surgery techniques, while implementing improved methodology, such as the emphasis of third-party survey and use of survey strategies to improve follow-up completion.

IMPACT OF PRIMARY PROSTATE CANCER TREATMENT ON SPECIFIC HRQOL DOMAINS

While anticipating forthcoming advances in our understanding of prostate cancer HRQOL, some conclusions can be drawn, based on the multicenter studies described above, regarding the impact of well established treatments on specific HRQOL domains (Table 3). Informative data from these studies includes an understanding of how radical prostatectomy and external radiotherapy impact urinary, sexual, and bowel HRQOL early and late after treatment, as compared to pre-treatment baseline status. Valid, conclusive data regarding impact of brachytherapy on these HRQOL domains is limited to early follow-up (1 year or less). [6,11] The hormonal and vitality HRQOL domain, that has emerged as a significant component of HRQOL status among prostate cancer patients (due to increasing utilization of neoadjuvant hormonal therapy) has not been characterized in multicenter studies as of yet, though ongoing cohorts aim to address this knowledge gap.

Urinary incontinence is well recognized as being impacted by prostatectomy in early and late (>1 year) follow-up after radical prostatectomy. [6-8,11] External beam radiotherapy has not been found to cause incontinence in these studies, whereas evidence suggests that brachytherapy may impact urinary incontinence at low levels, whose clinical significance is uncertain. Brachytherapy and external beam radiotherapy have both been found to impact overall urinary functioning, with the principal impacted subdomain being urinary irritative/obstructive symptoms, that are common during early follow-up after brachytherapy, and less common, but also detected, after external radiotherapy. [6,11] The urinary irritative symptoms most commonly reported by patients after brachytherapy or radiotherapy include dysuria and frequency. [10] Changes in long-term urinary outcomes more than 1 year after brachytherapy are not well characterized as of yet, because sample size for later follow-up in these studies was low due to loss of follow-up. It should be noted that dysuria is not measured by the AUA-SI instrument, which has been used by some investigators to evaluate post-brachytherapy changes in urinary HRQOL. The AUA-SI (also called the IPSS) was developed for evaluating symptoms of benign prostatic hyperplasia in the absence of cancer or radiation, and hence is not valid for detecting the full range of post-radiotherapy urinary HRQOL outcomes.

Sexual dysfunction is the most commonly impacted HRQOL domain following prostatectomy, external radiotherapy, or brachytherapy (Table 3). Each of these treatments has been shown to impact sexual HRQOL beyond one year after treatment. [6-8,11] Analyses from PCOS cohort and the Dutch screening cohort each attempted to compare the prevalence of sexual dysfunction between patients treated by prostatectomy compared to those treated by external beam radiotherapy, using multivariable modeling to adjust for baseline differences (in the absence of randomization). These analyses found that the sexual outcome was more adversely impacted by prostatectomy than by radiotherapy, despite the latter showing diminishing functioning in later follow-up. [8,9] Brachytherapy has also shown significant adverse effects on sexual HRQOL in early, and later, follow-up. [6,11] The impact of these treatments on utilization of medications or devices for ED by patients, and their effectiveness, has not yet been reported in the multi-center setting.

The bowel and rectal HRQOL domain has been found to be influenced significantly after either external radiotherapy or brachytherapy. [6-8,11] The range of symptoms reported by patients

ranges from rectal pain or urgency to chronic diarrhea to fecal incontinence. The bowel/rectal problems are not as prevalent as is sexual dysfunction after prostate cancer treatment, but appear to have an overall impact (in terms of severity of bother) closer to that of the urinary HRQOL domain. [8,10] The onset of these symptoms occurs during or early after treatment, and can linger into later follow-up. A multivariable analysis of the HMS cohort suggested that bowel and rectal symptoms were less profound after brachytherapy than after external beam radiotherapy. [11] Whether intensity-modulated techniques can reduce the impact of external radiotherapy on bowel/rectal concerns has not been determined in a multi-center setting.

One domain that has received limited evaluation from the patient-report perspective is that of HRQOL concerns related to androgen manipulation, or the vitality and hormonal HRQOL domain. Symptoms in this category include gynecomastia, lack of energy, weight gain, hot flashes, and mood changes (eg feeling depressed). These concerns are increasingly relevant in the measurement of consequences from primary prostate cancer treatment as the use of neoadjuvant hormonal therapy (NHT) has become more common. NHT has also been used in attempts to reduce the size of prostates that are too large for brachytherapy, so as to render these men eligible for brachytherapy. The HRQOL impact of these and other strategies that employ hormonal therapy in early stage disease are not well characterized and await characterization in ongoing multicenter observational cohort studies.

For clinically localized prostate cancer, there does not seem to be one superior single treatment that is without any side effects. Instead, HRQOL measurement scales will help physicians have informed discussions with patients about potential likelihood of a given set of side effects with the various prostate cancer treatment options. Early, groundbreaking prospective cohort studies (Table 2) established a fundamental foundation of basic principles in prostate cancer HRQOL (Table 3). Limitations of these early studies that are apparent in hindsight, include under-sampling of contemporary radiotherapy and surgery techniques, passive coercion due to survey administration by practitioners, and substantial loss of patients to follow-up after one year. These limitations indicate a continued need for further investigation of prostate cancer HRQOL outcomes. Ongoing and future studies may build upon this foundation by using improved methodology, such as third-party surveys to reduce passive coercion, and phone or web-based survey to improve follow-up. Moreover, knowledge gaps including the impact of hormone therapy and of refinements in radiotherapy or surgery techniques, warrant evaluation by validated HRQOL measures. The emerging understanding of prostate cancer HRQOL will allow practitioners and patients to set realistic expectations regarding outcomes, and thereby facilitate individualized decision making regarding treatment.

REFERENCES

1. Bolla M, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337(5):295–300. [PubMed: 9233866]
2. Bill-Axelson A, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352(19):1977–84. [PubMed: 15888698]
3. Esper P, et al. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997;50(6):920–8. [PubMed: 9426724]
4. Litwin MS, et al. Quality-of-life outcomes in men treated for localized prostate cancer. *Jama* 1995;273(2):129–35. [PubMed: 7799493]
5. Litwin MS, et al. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. *Med Care* 1998;36(7):1002–12. [PubMed: 9674618]
6. Downs TM, et al. Health related quality of life patterns in patients treated with interstitial prostate brachytherapy for localized prostate cancer--data from CaPSURE. *J Urol* 2003;170(5):1822–7. [PubMed: 14532784]

7. Potosky AL, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. *J Natl Cancer Inst* 2004;96(18):1358–67. [PubMed: 15367568]
8. Madalinska JB, et al. Health-related quality-of-life effects of radical prostatectomy and primary radiotherapy for screen-detected or clinically diagnosed localized prostate cancer. *J Clin Oncol* 2001;19(6):1619–28. [PubMed: 11250990]
9. Wei JT, 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]
10. Miller DC, et al. Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005;23(12):2772–80. [PubMed: 15837992]
11. Talcott JA, et al. Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol* 2003;21(21):3979–86. [PubMed: 14581420]
12. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. *Med Care* 2001;39(10):1118–30. [PubMed: 11567174]
13. Joly F, Brune D, Couette JE, et al. Health-related quality of life and sequelae in patients treated with brachytherapy and external beam irradiation for localized prostate cancer. *Ann Oncol* 1998;9:751–7. [PubMed: 9739442]

Domains evaluated by instruments that have been validated to measure HRQOL effects of primary, definitive treatment for early stage prostate cancer.

Table 1

HRQOL Instrument	Evaluated HRQOL Domains					
	Function vs Bother	Urinary Incontinence	Urinary Irritation	Bowel / Rectal	Sexual	Vitality/ Hormonal
UCLA-PCI	X	X		X	X	
EORTC-QL Q30 Prostate Module	X	X ¹	X ¹	X	X	
EPIC-50	X	X	X	X	X	X
Symptom Index	X	X	X	X	X	
EPIC-26 ²	X ²	X	X	X	X	X

¹ Urinary assessment in the EORTC Prostate module includes items about incontinence and irritation/obstruction but subscale scores are not used to discern these 2 domains, instead only a urinary summary score is provided.

² Bother items that comprise the UCLA-PCI bother subscales are retained as part of EPIC-26, enabling calculation of bother scores for overall urinary bother that can be measured distinctly from urinary incontinence or irritative/obstructive subscale; the sexual domain can be parsed into the sexual bother score as distinct from the sexual function questions. Overall bowel bother can also be calculated with the UCLA-PCI bother item within EPIC-26. However, hormonal function versus bother distinction is not possible with EPIC-26 and the hormonal domain is limited to the hormonal summary score in EPIC-26.

Table 2
Prospective, multi-center studies of HRQOL after primary treatment for early stage prostate cancer

Cohort	Treatment Groups ¹			Study Limitations ²		
	RP	XRT	BT	All Three Treatment Groups not Represented	Passive Coercion: survey administered by practitioners	Validity > 1 Year after Rx Limited: Follow-up <70%
PCOS	Yes	Yes	No	X		
Dutch Screening	Yes	Yes	No	X		X
CaPSURE ³	Yes	Few ³	Yes		X	X
HMS ⁴	Yes	Yes	Yes		X	X

¹ RP = radical prostatectomy; XRT = external beam radiotherapy; BT = brachytherapy

² X indicates that the cohort was impacted by the indicated limitation

³ Although CaPSURE enrolled patients treated by external beam radiotherapy, details regarding their treatment and outcome are too sparse to enable conclusive analyses. In addition, radiotherapy practitioners were not fully engaged in patient enrollment or data collection, and hence the setting was not as multidisciplinary as that of the other cohorts

⁴ Each of the participating HMS hospitals was affiliated with a single medical school (Harvard Medical School); therefore the HMS cohort was not multi-regional or multi-centric to the same extent as the other studies tabulated

Table 3

Impact of Primary Prostate Treatment on Clinically Relevant HRQOL Domains¹

HRQOL Domain	Treatment Group					
	Radical Prostatectomy		External Radiotherapy		Brachytherapy	
	early	late	early	late	early	late
Time after treatment; ²						
Sexual	++	++	+	+	+	+
Urinary Incontinence	++	+			+	NA
Urinary Irritative/Obstructive	+		+		++	NA
Bowel/Rectal			++	+	++	NA
Vitality/Hormonal	NA	NA	NA	NA	NA	NA

¹ ++ symbols designate an HRQOL domain impacted *commonly* at the indicated timepoint following the corresponding treatment; + symbols designate an HRQOL domain impacted *occasionally*; NA designates that informative, valid data with adequate sample size for conclusive analyses at the indicated timepoint is not available for the corresponding domain and treatment

² *Early* time after treatment designates the first 6 months after the indicated treatment; *Late* time after treatment indicates one year and beyond after treatment