ELSEVIER

European Journal of Cancer 41 (2005) 922–931

European Journal of Cancer

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Quality of life in prostate cancer

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Received 6 October 2004; accepted 2 December 2004
Available online 2 March 2005

Abstract

Little more than a decade ago, measurements of health-related quality of life (HRQOL) of prostate cancer patients began to enter the medical literature. Initially controversial and of little apparent relevance to clinical care, HRQOL has grown in importance in prostate cancer to the point that providing it in treatment discussions is now considered a core element of clinical care. The United States (US) Food and Drug Administration has used it to make approval decisions for prostate cancer drugs, and Europeans have endorsed its central role in prostate cancer as well [Altwein J, Ekman P, Barry M, *et al*. How is quality of life in prostate cancer patients influenced by modern treatment? The Wallenberg symposium. *Urology* 1997, **49**(Suppl 4A), 66–76.]. We propose to characterise the treatment dilemmas facing patients with prostate cancer, the clinical relevance of HRQOL research, its central conceptual elements, the characteristics of some available instruments to measure it, the use of HRQOL in clinical studies, and some of the remaining challenges we have identified during our 13 years in the field.

Keywords: Health-related quality of life; Prostate cancer; Treatment; Measurements

1. Introduction

Local surgery or radiation may cure clinically localised prostate cancer, while systemic therapy may palliate metastatic prostate cancer. The primary treatment for metastatic cancer is androgen deprivation treatment (ADT), although other options have been supported by recent investigations. Typically, a decade or more elapses before localised prostate cancer progresses to symptomatic or even detectable metastases [1]. During that long clinical course, the physician who performed the surgery or radiation treatment usually monitors patients afterwards, and initiates treatment when metastases appeared, referring to medical oncologists only when the tumour becomes refractory to androgen deprivation. This pattern became even more entrenched when long-acting luteinising hormone-releasing hormone (LHRH) agonists provided a convenient and more acceptable alternative to orchiectomy for ADT. As a result, while some large trials of systemic therapy have taken place [2–5], rigorous comparisons of alternative treatment strategies for ADT in patients with early evidence of metastasis have remained sparse compared with studies in patients with breast cancer, measurement of the increasingly apparent impact of ADT on HRQOL has not been incorporated into trials [6], and the most important changes in practice have resulted from physicians' evolving preferences in the form of "indication creep," as they initiated ADT in additional clinical scenarios unsupported by research results [7], perhaps in part influenced by commercial influences and financial incentives.

Quality of life enters into virtually all discussions of treatment for prostate cancer, but its integration into consultations is incomplete, even as its importance is

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doi:10.1016/j.ejca.2004.12.030

increasingly acknowledged. For patients with clinically localised disease, the potential for cure of alternative treatments has dominated treatment decision-making, although the urinary, bowel and sexual complications that localised treatments were known to cause are invariably discussed, if with variable accuracy. To make decisions, patients need to understand the unusually prolonged natural history of prostate cancer compared with other common tumours, make judgments about the efficacy of competing treatment alternatives in the absence of rigorous data, appreciate the potential toxicity of treatments and estimate how it might affect them over a time period of a decade or more. However, the complex issues involved in choosing treatment and the nature of doctor-patient consultations have not been well studied.

Patients seeking accurate information on both efficacy and quality of life outcomes of alternative treatments face important difficulties. Evidence indicates that consultations are strongly influenced by physicians' treatment preferences that in turn pivot on the physician's oncology specialty. Given the nearly complete absence of randomised data comparing the efficacy of radical prostatectomy, external beam radiation therapy and, more recently, brachytherapy with each other or with initial observation, physicians tend to recommend the treatment modality they provide [8,9]. Even physicians aware that research data do not indicate which modality is more efficacious and persuaded of the proper primacy of patient preferences in choosing treatment influence patient choices indirectly by signalling their preferred order of treatment. Active treatments are discussed first, with initial observation discussed afterwards, if at all [10,11]. If considering treatment efficacy does not produce a treatment decision, consultations widen to include the quality of life effects of treatment: which of the expected patterns of toxicity from the available local treatment modalities would be most tolerable to the patient? In some cases, particularly when comorbid medical conditions or very advanced patient age make prolonged survival unlikely, even in the absence of prostate cancer, treatment-related toxicity may be unacceptable: the risk of fatal progression during the patient's lifetime becomes so low it may not outweigh the expected impact of treatment-related toxicity. For many patients, in that setting only do physician and patient give close attention to initial observation, often called "watchful waiting" to the documented distress of some patients [12]. This process skews decision-making towards potentially curative treatments and although patients are five times more likely to be diagnosed with prostate cancer than to die from it and even successful treatment produces significant, long-term treatment-related dysfunction, fewer than one man in ten chooses initial observation. Further, the general presumption in favour of active treatment and the vagaries of monitoring treatment make ongoing observation difficult to continue. Only half of the patients, at most, who initially choose observation avoid crossing over to active treatment within 4 years [11,13].

The availability of the prostate-specific antigen (PSA) test, a blood test that identifies both undiagnosed patients at higher risk of a prostate biopsy positive for cancer and diagnosed patients at greater risk of eventual symptomatic metastases, further complicates treatment decisions. Rising PSA indicates the possibility of an adverse outcome that may eventually merit an intervention, but the importance of this signal is blurred by both the possibility that the rise could be artifactual and uncertainty with regard to the time frame when the rise is tumour-related: i.e., it may be a false alarm or it may signal true tumour progression that is too slow to cause symptoms during the patient's lifetime. Length-biased sampling causes any screening test to preferentially diagnose slower-growing tumours, since they are more likely to be detected before symptoms arise than rapidly progressing tumours are. This property coupled with the extraordinary prevalence of prostate cancer in older men – perhaps half of men over 60 years of age harbour cancers in their prostates that can be found at autopsy – may result in stunning prostate cancer detection rates when physicians biopsy more often. The Prostate Cancer Prevention Trial of finasteride, which performed an "exit biopsy" on men not previously biopsied for an elevated PSA, diagnosed cancer in nearly a fourth of placebo patients after 7 years [14]. As a result of the PSA test, prostate cancer is diagnosed in many more men, the tumours are diagnosed in men at progressively lower risk of eventual symptomatic disease, and the prostate cancer and any treatment-related dysfunction begins years earlier in their lives, making the trade-off of between potential cure for treatment complications more expensive. Using PSA to monitor for prostate cancer recurrence moves up the treatment decisions made later in the course of disease. An increasing PSA forces patients who have undergone potentially curative local therapy to consider toxic treatments for metastases that may appear years later or may not appear at all, and later on signals that the prostate cancer may have become hormone-refractory, or is no longer responsive to ADT. In each case, men face accelerated decisions about potentially toxic treatments for prostate cancer. As a result, measuring and conveying the likely impact of treatment on their quality of life becomes increasingly important.

Physicians have long known and told their patients that potentially curative local treatments may cause urinary, bowel and sexual dysfunction. What HRQOL research added were the mechanics of valid measurement, the instruments with which to measure them, and the desire to determine their broader impact on patients' lives. The increased attention of quality of life

researchers to these questions helped describe other treatment-related dysfunction that had largely escaped clinicians, such as fatigue and the impact of ADT. Less toxic than the cytotoxic agents used by medical oncologists in other cancers, ADT causes short- and long-term vasomotor instability (''hot flashes''), bone mineral loss, decreased muscle mass and increased adipose tissue, and fatigue [15,16]. When tumours no longer respond to ADT, oncologists try additional hormonal manipulations, with side-effects similar to ADT and often additional systemic effects, and more recently have tried cytotoxic drugs, that were long thought to be ineffective in prostate cancer [17]. Finally, patients with advanced androgen-insensitive metastatic prostate cancer require palliation that reduces symptoms, primarily pain [18,19]. Reducing pain without a survival benefit justified FDA approval for one regimen, mitoxantrone and prednisone [19]. As new agents are evaluated, quality-of-life measurement will be relevent for both regulatory and clinical decision-making.

HRQOL measurement occurs separately from traditional measures of treatment efficacy such as survival and tumour responses, but it also reinforces them. Cancer progression wreaks damage of many varieties as it pushes patients towards death, and quality of life measurements detect much of the damage. Efficacious treatment reverses or arrests the damage. It is not surprising that, in most cases, treatments that prolong survival and shrink or eliminate tumour masses also improve measured HRQOL. However, interventions that affect HRQOL do not always affect survival or measurably shrink tumours. Interventions without a detectable effect on survival or tumor size reduce pain in patients with hormone-refractory prostate cancer. Primary treatments can cause substantial dysfunction that may affect quality of life cumulatively in patients with early prostate cancer long before their impact on mortality can be ascertained. While local treatments likely prolong survival for some patients, most die of other causes, and the most aggressive tumours are probably metastatic at diagnosis. For many men with early prostate cancer, quality of life is therefore the most relevant outcome.

Asymptomatic patients with evidence of initial progression after primary treatment, presumed to have hormone-sensitive disease, have treatment options with substantially different effects on quality of life. ADT causes erectile dysfunction, fatigue, changes in body composition, and bone mineral loss, while continued observation has no physical effects, but may make patients anxious if their PSA level continues to rise. The choice of chemical or surgical castration does not affect survival, but the latter may affect quality of life through its impact on body image. The marginal impact on survival from adding an anti-androgen, or combined androgen blockade (CAB) may potentially be outweighed by the toxicity associated with this treatment, but this has not been measured in trials [6]. Treatment alternatives for advanced hormone-refractory prostate cancer vary little with regard to their impact on survival, although some recently presented studies document that chemotherapy is efficacious in some settings. However, marginally efficacious agents can reduce pain in patients with metastatic prostate cancer, providing important palliation that measurably improves quality of life.

In summary, measuring HRQOL has provided provide information helpful for men with prostate cancer in a variety of clinical circumstances and to investigators comparing treatments, and will continue to do so. While large differences in efficacy would make quality of life moot for many men, the modest survival benefits that appear likely from current opinions makes it likely that quality of life information will continue to influence treatment choices for the foreseeable future.

2. Measuring HRQOL

Measuring quality of life would appear to be an enterprise of hubris. However, armed with the pragmatic demands of clinical care, investigators have defined their research sphere as the narrower yet still daunting objective to measure the impact of changes in health on physical, mental and social well-being.

Measuring health-related quality of life, in addition to survival outcomes, enriches clinical research and may be decisive at treatment decision-making points during prostate cancer's long natural history when effects on survival are similar or minimal. The patient's HRQOL may be affected on various levels, and the instruments designed to measure it vary correspondingly, differing in their intended breadth and specificity. General (or generic) measures evaluate aspects of the patient's experience affected by many illnesses and facilitate broad comparisons between populations with different diseases and with the general population [20,21]. Cancer-specific measures evaluate effects common to many cancers, especially when they are advanced or under treatment, and can thus assess and compare the effect of tumours of different tissues of origin and histology and their treatments [22–25]. Cancer-specific instruments, in this case prostate cancer-specific, focus on the most salient effects of a single tumour and its treatment [26–29]. Generic HRQOL instruments are also useful in measuring the pretreatment status of distinct research populations or subpopulations, calibrating their HRQOL starting points. Disease-targeted scales focus on cancer- and prostate cancer-specific issues that may not be relevant to other populations [30]. It may be useful to narrow the focus of these instruments even further. For example, for many patients with advanced metastatic prostate cancer, painful bone

lesions are a dominating factor. In this setting, measuring HRQOL and assessing pain are almost equivalent [17].

Investigators characterise the HRQOL impact of treatment for localised prostate cancer by contrasting patient's outcomes with those of patients who have undergone alternative primary treatments [31,32], with patients with other cancer diagnoses [33], and with patients who do not have cancer. While each of these comparisons provides perspective on the HRQOL costs of prostate cancer and its treatment to patients considering treatment options, the last two are obviously less relevant to the choices a patient faces.

As for other issues in early, or clinically localised, prostate cancer clinical care, the quality of HRQOL information available has been deeply compromised because few randomised trials, which alone can provide unbiased data, have compared alternate treatments, although some interim results have recently emerged assessing primary modalities [34–37] and psychosocial or supportive care interventions [38,39]. Observational trials are subject to bias, and unique clinical features of early prostate cancer compound the problem. Unlike most other malignancies, competing treatment modalities offer potential cure. Further, for many patients, initial observation may produce better physical outcomes than active treatment, although choosing not to undergo a potentially curative treatment creates psychological stress, and most patients cross-over to active treatment within 4 years [11]. All active treatments often cause long-term treatment-related dysfunction to intimate organ systems (urinary, bowel and sexual), and survivors typically live a decade or more. The course of early prostate cancer is unusually indolent, and because it occurs late in men's lives, patients are at least 5-fold more likely to die from another cause than prostate cancer, particularly since mass PSA screening has dramatically increased the number of cancers observed and selectively identifies slower-growing tumours. Finally, the efficacy of active treatment has not been rigorously demonstrated.

Further, patients receive biased recommendations, and patients receiving alternative treatments differ systematically. Physicians tend to prefer the treatment they provide, leading to strong, opposing recommendations by urologists and radiation oncologists [8,9]. In addition, surgery is preferentially offered to patients who are younger and thus more likely to benefit if surgery is more efficacious, have less medical comorbidity and thus more easily tolerate the rigors of surgery, and have less advanced cancers more likely to be successfully excised. These biases have largely blocked the development of and recruitment of patients to randomised trials. However, observational trials are plentiful, as they are far easier to accrue patients to and produce both larger study populations and more generalisable results. Because of their size, large uncontrolled observational studies provide precise estimates of treatment-related complications in their populations. When large differences exist, pretreatment differences in status and prognosis cannot entirely obscure differences in treatment-related complications. Multiple regression models adjusting for age, comorbidity, race, socioeconomic status, education, insurance coverage, and other variables that may indicate varying vulnerability to the effects of treatment may reduce confounding by treatment choice, but can never eliminate it. As a result, non-randomised comparisons of treatment-related outcomes are always suspect, particularly when outcomes differ only a little and if, as in cross-sectional surveys, patients' baseline functional status, usually the most powerful predictor of post-treatment outcomes, is unknown.

Generic HRQOL instruments were designed to document the physical and mental health status of patient populations, and population-based norms exist for several of them [21,40,41]. Therefore, they have been used as surrogates for comorbidity to characterise early prostate cancer patient populations. In patients with metastatic prostate cancer, systemic and local cancer symptoms characteristic of other advanced malignancies are more common, and HRQOL assessment is more clinically relevant to the disease course than in early prostate cancer, where cancer symptoms are infrequent and treatment-related dysfunction predominates. Therefore, cancer-specific instruments have been used more extensively in trials involving metastatic prostate cancer [17,34,42–47].

Other than obstructive uropathy from age-related benign prostatic hyperplasia, most men with early prostate cancer do not have symptoms associated with prostate cancer. In contrast, prostate cancer treatment may affect sexual, urinary, and bowel function directly, and most disease-specific quality-of-life instruments contain scales measuring them. Thus, prostate cancer-specific instruments primarily measure treatment-related symptoms. Because the distress, or bother, men experience may vary independently from dysfunction, most instruments include separate items to measure it [48]. For example, men vary in their reaction to sexual dysfunction, which all treatments produce in most men. Particularly if they have had erectile difficulties before the diagnosis of prostate cancer, men may accept treatment-related dysfunction as age-related, unavoidable, and thus acceptable after treatment. However, function and bother cannot be separated cleanly. Patients are likely to report the symptoms they are most bothered by as the most intense. Therefore, patient reports of the severity of and bother from their symptoms are not entirely independent [49]. Attempts to identify the disparate impacts of sexual dysfunction [50] and other treatment-related dysfunction on men's lives have appeared [51]. Even when both dysfunction and bother are distinguishable, their relationship may evolve over time as men accommodate

to dysfunction or their other, more compelling health problems arise.

Both cancer growth, primarily causing obstructive symptoms, and treatment may cause urinary dysfunction, which may include obstruction, irritation, or incontinence; in practice, despite distinctive pathophysiology, these are difficult to distinguish. Obstructive symptoms are common in older men and may be dramatically increased after brachytherapy. Treatment-related urinary incontinence after treatment may be long-lasting, usually not improving significantly beyond a year after treatment. It may be measured by patient reports of the circumstances, frequency, and quantity of leaked urine, or by the frequency of pad use. However, these measures may be inexact. As for sexual dysfunction, the organic dysfunction and the distress caused by incontinence may diverge, both *ab initio* or over time [52,53]. For some men with significant dysfunction, distress may be mitigated because of satisfactory control of constant dripping with a pad or device or because of the expectation of improved function. For others with even mild dysfunction, an occasional unexpected squirt may cause social embarrassment and humiliation that is psychologically damaging.

Assessment of bowel symptoms, including diarrhoea, rectal urgency, tenesmus, rectal bleeding, and others is also essential, especially for patients who undergo radiation therapy. Like urinary symptoms, bowel dysfunction may be highly disruptive in some men's lives, and the time-course and severity of specific bowel symptoms may diverge.

The focus of prostate cancer-specific HRQOL measurement has been expanded by both changes in the treatment practice, such as the expansion of ADT into primary treatment of early prostate cancer, and by awareness of previously underappreciated effects of treatment, such as fatigue associated with ADT [54]. This evolution is expected to continue.

3. Commonly used HRQOL measures in prostate cancer

Instruments used to assess quality of life in prostate cancer include global, or generic measures, cancer-specific measures, prostate cancer-specific measures, and symptom-specific scales, although the domains measured by instruments in one category may overlap with those of another. Generic HRQOL measures assess physical and mental health broadly. General cancer domains assess symptoms commonly arising from cancer and its treatment, including systemic effects such as fatigue and disrupted sleep patterns and local or system-specific effects, such as pain, hair loss and shortness of breath. Prostate cancer-specific measures also assess cancer- and treatment-related effects, but focus on effects that are unique to prostate cancer. Symptom-specific scales amplify important symptoms that are relevant for many cancers and diseases, such as pain, fatigue or depression. The researcher has many well-validated instruments available to measure clinically relevant domains, depending on the most salient features of the clinical manipulations being studied.

Investigators have borrowed cancer-specific HRQOL instruments used elsewhere in oncology to investigate prostate cancer patients and have come to appreciate their strengths and limitations in this setting. For example, widely used generic instruments, such as the SF-36, document the difference between progression and remission in patients with metastatic prostate cancer [55], that HRQOL declines as metastatic prostate cancer progresses [56,57], and that insurance status and HRQOL are correlated [58]. However, they have weak and erratic associations with both the onset and improvement of treatment-related organ dysfunction [59–61]. Similarly, while cancer-specific instruments, such as the EORTC QLQC30 or the FACT-G, can document differences between clinically distinct prostate cancer patient groups [62] and distinguish patients who received different palliative or salvage treatments [45,63], they also correlate erratically with specific treatment-related dysfunction [64–67]. This equivocal relationship between more broadly focused HRQOL instruments and the organ dysfunction most commonly encountered clinically has led investigators to develop prostate cancer-specific measures, including supplements to the cancer-specific instruments [28,68–70]. In addition, the increasingly apparent need to use more than one instrument to meet all investigators' objectives provided an additional incentive to develop shorter forms of widely used instruments. The SF-12 [71] provides much of the global physical and mental summaries of the SF-36, and the Brief POMS [72] greatly shortens the Profile of Mood States (POMS) [21], a commonly used measure of emotional distress.

The major cancer-specific instruments, the EORTC Quality of Life Core Questionnaire (QLQ-C30) [22] and the Functional Assessment of Cancer Therapy-General (FACT-G) [23] diverge in both the areas or domains they measure [73] and the geographical areas in which they are primarily used. Both instruments have been used in a modular fashion, in which the core instrument is combined with supplemental items addressing specific issues of particular cancers. The 30-item QLQ-C30 assesses physical, role, cognitive, emotional, and social function, three symptoms (fatigue, pain, and nausea and vomiting), patient assessments of both their overall health and their quality of life. It overlaps substantially, but not completely, with the FACT, although its social and cognitive domains are distinctive. It is primarily used in Europe and Canada, while the FACT-G predominates in the United States. It has been used to distinguish patients with hormone-responsive and

hormone-refractory prostate cancer [55] and patients with symptomatic metastases who underwent ADT from those who deferred treatment [74]. A 19-item prostate cancer-specific module measures urinary, bowel, and sexual symptoms, with an item assessing effects of androgen deprivation.

The 27-item FACT-G [23] measures social/family well-being and the patient's relationship with the doctor, as well as their physical, emotional and functional well-being. A 12-item prostate cancer-specific module (FACT-P) adds prostate cancer-specific content to the FACT-G. The FACT-P items assess urinary, bowel, and sexual function, three specific symptoms (weight, appetite and pain), and emotional role [70]. Its use of single items for some domains and a single summary score emphasises brevity over robustness and richness of the data-set. The FACT-P has documented transient post-treatment dysfunction in early prostate cancer [75,76] and distinguished surgical and radiation salvage therapy in patients with local recurrence [63].

Other commonly used cancer-specific instruments include the Functional Living Index-Cancer (FLIC) [25], the Quality of Life Index (QL-Index) [24] and the Rotterdam Symptom Checklist (RSCL) [77].

Several validated prostate cancer-specific instruments are now available. All, like the first and most widely used instrument, the UCLA Prostate Cancer Index (UCLA PCI) [26,78] developed by Litwin and colleagues, measure sexual, urinary, and bowel dysfunction and attempt to distinguish dysfunction from the distress or bother that dysfunction causes. Some instruments distinguish between urinary incontinence, obstruction and irritation, although there is overlap between them [27,29,49,69,79]. The widely used American Urological Association's International Prostate Symptom Score (IPSS), developed to assess obstructive urinary symptoms due to benign prostatic hyperplasia (BPH), has been used to assess the effects of radiation treatments, which transiently increases urinary obstruction in prostate cancer, especially brachytherapy. Sexual dysfunction, particularly erectile dysfunction, the most frequent treatment-related dysfunction in prostate cancer, has received intense interest in other medical settings, particularly since oral drug treatments such as sildenifil (Viagra) have become available. Instruments focused on erectile dysfunction include Sexual Problems scale of the Medical Outcomes Study [80], the Brief Male Sexual Function Inventory [81] and the International Index of Erectile Function (IIEF) [82]. Other symptom specific-measures have been used in prostate cancer, such as pain scales in advanced, hormone-refractory disease, where pain is the major target of palliative treatments [17,42–47,83].

Recent developments in the measurement of prostate cancer-related quality of life have begun to define additional psychosocial domains beyond problematic urinary, bowel, and sexual dysfunction. The physical side-effects of treatment entail behavioural, emotional, and interpersonal adjustments. In addition, the realisation that one has prostate cancer and the challenge of participating in treatment decisions amid ambiguous data and conflicting physician recommendations may have long-term psychosocial effects. A few studies have sought to develop scales that capture these aspects of prostate cancer-related quality of life. Giesler and colleagues added ratings of the disability men attribute to urinary, bowel, and sexual dysfunction, as well as a multi-item scale of cancer distress. In studies of patients treated for metastatic disease and then of patients with early prostate cancer, Clark and his coworkers conducted extensive series of focus groups to collect qualitative data on men's perceptions of the bodily and psychosocial changes of their lives following diagnosis. Their findings led to the development of psychometric scales that address the behavioural effects of impaired urinary and bowel function, changes in sexual intimacy, sexual self-confidence, and masculine self-esteem, health worry, and heightened concern with one's PSA level. Attributes of the chronic uncertainty men expressed in focus groups were incorporated into measures of perceived cancer control, confidence in treatment decisions, and regret of one's treatment decisions [51,84].

4. Summary and future directions

Quality of life measurement will continue to be central to both clinical research and treatment decision-making for the foreseeable future. For clinically localised prostate cancer, both observational data and the limited randomised trial data [36] available indicate that efficacy differences between treatments are modest enough that for some men adverse quality of life impacts would outweigh their likely benefit, particularly since initial observation, which trades treatment-related dysfunction for the anxiety that bypassing potentially curative treatments (even if they are unlikely to be necessary) often provokes, is a plausible option. In metastatic prostate cancer, cure is currently not possible, and the overall treatment goal is palliation, making quality of life a key outcome.

For patients with early prostate cancer, the patient must understand the potential impact on their quality of life of the alternative treatment modalities so they can select treatment options that are appropriate and best fit with their priorities and preferences. Further, they needs reliable information to anticipate and adapt to the treatment he chooses and to satisfy the innate need to monitor one's course against typical outcomes. The specific organ systems affected by alternative treatments and the time-course in which various symptoms emerge, improve or worsen and become stable long-term

vary according to the treatment given. For example, several studies have documented that sexual function declines early after radical prostatectomy, but improves subsequently, while radiation therapy results in slower, but ongoing declines [31,85,86]. Documenting these changes may influence the patient's treatment choices and facilitate their adaptation to complications.

Physicians must understand the patient's functional status of the urinary, bowel and sexual organ systems at presentation to help identify those most vulnerable to treatment-related toxicity, and the contraindicated modalities. Empirical evidence suggests that sufficient information may not be obtained from the patient by the physician to ensure that the most vulnerable patients avoid contraindicated treatment modalities (data not shown).

Given the key importance of HRQOL, it must be incorporated consistently into studies assessing treatment efficacy. To ensure that the HRQOL measurement is adequate to meet the scientific need for such data, investigators must use existing measurement tools appropriately, acknowledging their limitations and strengths in particular clinical and research settings, expand these tools to include additional HRQOL domains that require investigation, as well as clarifying their interpretation of the results. Measuring patient dysfunction, symptoms, and health-related functioning must be complemented by investigation of how it affects patient's daily lives. Other factors affecting HRQOL, such as trust of the physician, social support, understanding of the natural history and patients' health expectations may contribute importantly to their situation. Physicians' understanding of these additional aspects may allow them to provide additional support and identify helpful resources for their patients. Valid measures of prostate cancer-specific outcomes also provide a metric to assess the success of technical changes in treatment modalities intended to reduce treatment-related toxicity [87].

However, optimal use of HRQOL data in patients with prostate cancer requires that investigators not only use existing tools appropriately and consistently, but also address additional challenges. Unresolved problems central to its use remain. As we indicated above, generic measures of physical and mental HRQOL often remain stable or improve despite significant new morbidity documented by prostate cancer-specific instruments, particularly if it arises from treatment, not disease progression. Additional research is required to understand this apparent discrepancy between significant functional losses in intimate bodily functioning and stable generic HRQOL scores. Alternate explanations exist. Significant treatment-related toxicity may simply not affect HRQOL, existing measures of generic HRQOL may not be sensitive to the magnitude of the effect, or we may not be measuring the relevant HRQOL domains. Studies addressing these unexpected results could demonstrate a preferred measurement approach for patients with early prostate cancer, from designing generic measures with greater responsiveness or from a more complete understanding of how treatment-related morbidity affects these men's lives. Some of the studies we mentioned above that directly address newly appreciated domains indicate potentially fruitful research directions.

A final area of research that has been little explored is the impact of HRQOL research on patient's decisions. Researchers have devoted much of their energy towards measuring it, with increasing methodological sophistication. Methodological standards have risen. Outcome data now is almost always patient- not physician-reported, measures and adjusts for pretreatment patient functional status and uses validated measures [88]. However, while these methods produce valid and reliable results, their format may constitute a major obstacle for patients trying to understand them. The most useful and robust measures for research – multi-item scale or index scores – are expressed as purely numerical results that are resistant to patients' attempts to translate them into their experience so that they can understand the likely effects of the treatments they are evaluating and use them in their decision-making. Methodological progress has produced more valid data, but patients choosing treatment and the physicians they consult understand them less. More effort must be put into bringing this information back to the clinic, understanding how patients use it in their thinking, revising the information to make it more useful, and documenting that patient care is improved as a result. Measuring HRQOL in prostate cancer patients has come a long way in little more than a decade, but the result has been to identify still greater challenges ahead.

Conflict of interest statement

None declared.

References

1. Pound CR, Partin AW, Eisenberger MA, *et al*. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999, **281**, 1591–1597.
2. Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. *Cancer* 1973, **32**, 1126–1130.
3. Crawford ED, Eisenberger MA, McLeod DG, *et al*. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma [published erratum appears in N Engl J Med 1989 Nov 16;321(20):1420]. *N Engl J Med* 1989, **321**, 419–424.
4. Eisenberger MA, Blumenstein BA, Crawford ED, *et al*. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998, **339**, 1036–1042.

5. Pilepich MV, Caplan R, Byhardt RW, *et al*. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85–31. *J Clin Oncol* 1997, **15**, 1013–1021.
6. Loblaw DA, Mendelson DS, Talcott JA, *et al*. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. *J Clin Oncol* 2004, **22**, 2927–2941.
7. Talcott JA. Androgen deprivation as primary treatment for early prostate cancer: should we ''Just Do Something''. *J Natl Cancer Inst* 2002, **94**, 407–409.
8. Moore MJ, O'Sullivan B, Tannock IF. How expert physicians would wish to be treated if they had genitourinary cancer. *J Clin Oncol* 1988, **6**, 1736–1745.
9. Fowler FJ, McNaughton Collins M, Albertsen PC, *et al*. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer [see comments]. *JAMA* 2000, **283**, 3217–3222.
10. Mills N, Donovan JL, Smith M, *et al*. Perceptions of equipoise are crucial to trial participation: a qualitative study of men in the ProtecT study. *Control Clin Trials* 2003, **24**, 272–282.
11. Zietman AL, Thakral H, Wilson L, *et al*. Conservative management of prostate cancer in the prostate specific antigen era: the incidence and time course of subsequent therapy. *J Urol* 2001, **166**, 1702–1706.
12. Donovan J, Mills N, Smith M, *et al*. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002, **325**, 766–770.
13. Carter CA, Donahue T, Sun L, *et al*. Temporarily deferred therapy (watchful waiting) for men younger than 70 years and with low-risk localized prostate cancer in the prostate-specific antigen era. *J Clin Oncol* 2003, **21**, 4001–4008.
14. Thompson IM, Goodman PJ, Tangen CM, *et al*. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003, **349**, 215–224.
15. Michaelson MD, Talcott JA, Smith MR. Prostate cancer: metastatic. *Clin Evid*, 881–890.
16. Pietrow PK, Parekh DJ, Smith JA, *et al*. Health related quality of life assessment after radical prostatectomy in men with prostate specific antigen only recurrence. *J Urol* 2001, **166**, 2286–2290.
17. Tannock IF, Osoba D, Stockler MR, *et al*. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996, **14**, 1756–1764.
18. Tannock I, Gospodarowicz M, Meakin W, *et al*. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 1989, **7**, 590–597.
19. Tannock IF. False-positive results in clinical trials: multiple significance tests and the problem of unreported comparisons. *J Natl Cancer Inst* 1996, **88**, 206–207.
20. McHorney CA, Ware JE, Raczek AE. The MOS36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 1993, **31**, 247–263.
21. McNair DM, Lorr M, Droppleman LF. *Profile of Mood States*. 2nd ed. San Diego, Educational and Industrial Testing Service, 1981.
22. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993, **85**, 365–376.
23. Cella DF, Tulsky DS, Gray G, *et al*. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol* 1993, **11**, 570–579.
24. Spitzer WO, Dobson AJ, Hall J, *et al*. Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. *J Chronic Dis* 1981, **34**, 585–597.
25. Schipper H, Clinch J, McMurray A, *et al*. Measuring the quality of life of cancer patients: the Functional Living Index-Cancer: development and validation. *J Clin Oncol* 1984, **2**, 472–483.
26. 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**, 1002–1012.
27. 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.
28. Stockler MR, Osoba D, Corey P, *et al*. Convergent discriminitive, and predictive validity of the Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) assessment and comparison with analogous scales from the EORTC QLQ-C30 and a trial-specific module. European Organisation for Research and Treatment of Cancer. Core Quality of Life Questionnaire. *J Clin Epidemiol* 1999, **52**, 653–666.
29. Dale W, Campbell T, Ignacio L, *et al*. Self-assessed health-related quality of life in men being treated for prostate cancer with radiotherapy: instrument validation and its relation to patient-assessed bother of symptoms. *Urology* 1999, **53**, 359–366.
30. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 1989, **27**, S217–S232.
31. Talcott JA, Manola J, Clark JA, *et al*. Time course and predictors of symptoms after primary prostate cancer therapy. *J Clin Oncol* 2003, **21**, 3979–3986.
32. Clark JA, Inui TS, Silliman RA, *et al*. Patients' perceptions of quality of life after treatment for early prostate cancer. *J Clin Oncol* 2003, **21**, 3777–3784.
33. Ganz PA, Schag CA, Lee JJ, *et al*. The CARES: a generic measure of health-related quality of life for patients with cancer. *Qual Life Res* 1992, **1**, 19–29.
34. Akakura K, Isaka S, Akimoto S, *et al*. Long-term results of a randomized trial for the treatment of Stages B2 and C prostate cancer: radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities. *Urology* 1999, **54**, 313–318.
35. Fransson P, Damber JE, Tomic R, *et al*. Quality of life and symptoms in a randomized trial of radiotherapy versus deferred treatment of localized prostate carcinoma. *Cancer* 2001, **92**, 3111–3119.
36. Holmberg L, Bill-Axelson A, Helgesen F, *et al*. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. *N Engl J Med* 2002, **347**, 781–789.
37. Steineck G, Helgesen F, Adolfsson J, *et al*. Quality of life after radical prostatectomy or watchful waiting. *N Engl J Med* 2002, **347**, 790–796.
38. Auvinen A, Vornanen T, Tammela TL, *et al*. A randomized trial of the choice of treatment in prostate cancer: design and baseline characteristics. *BJU Int* 2001, **88**, 708–715.
39. Rosenberg HJ, Rosenberg SD, Ernstoff MS, *et al*. Expressive disclosure and health outcomes in a prostate cancer population. *Int J Psychiatry Med* 2002, **32**, 37–53.
40. McHorney CA, Ware JE, Lu JF, *et al*. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994, **32**, 40–66.

41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983, **67**, 361–370.
42. Johansson JE, Wersall P, Brandberg Y, *et al*. Efficacy of epoetin beta on hemoglobin, quality of life, and transfusion needs in patients with anemia due to hormone-refractory prostate cancer – a randomized study. *Scand J Urol Nephrol* 2001, **35**, 288–294.
43. Boccardo F, Rubagotti A, Barichello M, *et al*. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer patients: results of an Italian Prostate Cancer Project study. *J Clin Oncol* 1999, **17**, 2027–2038.
44. Fossa SD, Slee PH, Brausi M, *et al*. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European organization for research and treatment of cancer genitourinary group. *J Clin Oncol* 2001, **19**, 62–71.
45. Fossa SD, Curran D, Aaronson NK, *et al*. Quality of life of patients with newly diagnosed poor prognosis M1 prostate cancer undergoing orchiectomy without or with mitomycin C. Results from the EORTC Phase-III trial 30893. *Eur Urol* 2000, **37**, 541–551.
46. Moinpour CM, Savage MJ, Troxel A, *et al*. Quality of life in advanced prostate cancer: results of a randomized therapeutic trial. *J Natl Cancer Inst* 1998, **90**, 1537–1544.
47. Sharp LK, Knight SJ, Nadler R, *et al*. Quality of life in low-income patients with metastatic prostate cancer: divergent and convergent validity of three instruments. *Qual Life Res* 1999, **8**, 461–470.
48. Oesterling JE, Jacobsen SJ, Chute CG, *et al*. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. *JAMA* 1993, **270**, 860–864.
49. Clark JA, Talcott JA. Symptom indexes to assess outcomes of treatment for early prostate cancer. *Med Care* 2001, **39**, 1118–1130.
50. Bokhour BG, Clark JA, Inui TS, *et al*. Sexuality after treatment for early prostate cancer: exploring the meanings of erectile dysfunction. *J Gen Intern Med* 2001, **16**, 649–655.
51. Clark JA, Wray N, Brody B, *et al*. Dimensions of quality of life expressed by men treated for metastatic prostate cancer. *Soc Sci Med* 1997, **45**, 1299–1309.
52. Litwin MS, Pasta DJ, Yu J, *et al*. Urinary function and bother after radical prostatectomy or radiation for prostate cancer: a longitudinal, multivariate quality of life analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor. *J Urol* 2000, **164**, 1973–1977.
53. Litwin MS, Flanders SC, Pasta DJ, *et al*. Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. Cancer of the Prostate Strategic Urologic Research Endeavor. *Urology* 1999, **54**, 503–508.
54. Beard CJ, Propert KJ, Rieker PP, *et al*. Complications after treatment with external-beam irradiation in early stage prostate cancer patients: a prospective multiinstitutional outcomes study. *J Clin Oncol* 1997, **15**, 223–229.
55. Albertsen PC, Aaronson NK, Muller MJ, *et al*. Health-related quality of life among patients with metastatic prostate cancer. *Urology* 1997, **49**, 207–216., discussion 216–217.
56. Litwin MS, Shpall AI, Dorey F, *et al*. Quality-of-life outcomes in long-term survivors of advanced prostate cancer. *Am J Clin Oncol* 1998, **21**, 327–332.
57. Kim SP, Bennett CL, Chan C, *et al*. QOL and outcomes research in prostate cancer patients with low socioeconomic status. *Oncology (Huntingt)* 1999, **13**, 823–832.
58. Penson DF, Stoddard ML, Pasta DJ, *et al*. The association between socioeconomic status, health insurance coverage, and quality of life in men with prostate cancer. *J Clin Epidemiol* 2001, **54**, 350–358.
59. Clark JA, Rieker P, Propert KJ, *et al*. Changes in quality of life following treatment for early prostate cancer. *Urology* 1999, **53**, 161–168.
60. Bacon CG, Giovannucci E, Testa M, *et al*. The association of treatment-related symptoms with quality-of-life outcomes for localized prostate carcinoma patients. *Cancer* 2002, **94**, 862–871.
61. Davis JW, Kuban DA, Lynch DF, *et al*. Quality of life after treatment for localized prostate cancer: differences based on treatment modality. *J Urol* 2001, **166**, 947–952.
62. Curran D, Fossa S, Aaronson N, *et al*. Baseline quality of life of patients with advanced prostate cancer. European Organization for Research and Treatment of Cancer (EORTC), genito-urinary tract cancer cooperative group (GUT-CCG). *Eur J Cancer* 1997, **33**, 1809–1814., E[corrected to Keuppens F].
63. Tefilli MV, Gheiler EL, Tiguert R, *et al*. Quality of life in patients undergoing salvage procedures for locally recurrent prostate cancer. *J Surg Oncol* 1998, **69**, 156–161.
64. 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**, 751–757.
65. Shrader-Bogen CL, Kjellberg JL, McPherson CP, *et al*. Quality of life and treatment outcomes: prostate carcinoma patients' perspectives after prostatectomy or radiation therapy. *Cancer* 1997, **79**, 1977–1986.
66. Fossa SD, Woehre H, Kurth KH, *et al*. Influence of urological morbidity on quality of life in patients with prostate cancer. *Eur Urol* 1997, **31**(Suppl 3), 3–8.
67. Krupski T, Petroni GR, Bissonette EA, *et al*. Quality-of-life comparison of radical prostatectomy and interstitial brachytherapy in the treatment of clinically localized prostate cancer. *Urology* 2000, **55**, 736–742.
68. Sprangers MA, Cull A, Groenvold M, *et al*. The European Organization for Research and Treatment of Cancer approach to developing questionnaire modules: an update and overview. EORTC quality of life study group. *Qual Life Res* 1998, **7**, 291–300.
69. Borghede G, Sullivan M. Measurement of quality of life in localized prostatic cancer patients treated with radiotherapy. Development of a prostate cancer-specific module supplementing the EORTC QLQ-C30. *Qual Life Res* 1996, **5**, 212–222.
70. Esper P, Mo F, Chodak G, *et al*. Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997, **50**, 920–928.
71. Ware Jr J, 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**, 220–233.
72. Cella DF, Jacobsen PB, Orav EJ, *et al*. A brief POMS measure of distress for cancer patients. *J Chronic Dis* 1987, **40**, 939–942.
73. Kemmler G, Holzner B, Kopp M, *et al*. Comparison of two quality-of-life instruments for cancer patients: the functional assessment of cancer therapy-general and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. *J Clin Oncol* 1999, **17**, 2932–2940.
74. Herr HW, O'Sullivan M. Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol* 2000, **163**, 1743–1746.
75. Stone P, Hardy J, Huddart R, *et al*. Fatigue in patients with prostate cancer receiving hormone therapy. *Eur J Cancer* 2000, **36**, 1134–1141.
76. Monga U, Kerrigan AJ, Thornby J, *et al*. Prospective study of fatigue in localized prostate cancer patients undergoing radiotherapy. *Radiat Oncol Investig* 1999, **7**, 178–185.
77. de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990, **62**, 1034–1038.

78. Litwin MS, Hays RD, Fink A, *et al*. Quality-of-life outcomes in men treated for localized prostate cancer. *JAMA* 1995, **273**, 129–135.
79. Barry MJ, Fowler Jr FJ, O'Leary MP, *et al*. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992, **148**, 1549–1557.
80. Stewart A, Ware JEJ. *Measuring functioning and well-being: The Medical Outcomes Study approach*. Durham, NC, Duke University Press, 1992.
81. O'Leary MP, Fowler FJ, Lenderking WR, *et al*. A brief male sexual function inventory for urology. *Urology* 1995, **46**, 697–706.
82. Rosen RC, Riley A, Wagner G, *et al*. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997, **49**, 822–830.
83. Small EJ, Meyer M, Marshall ME, *et al*. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000, **18**, 1440–1450.
84. Clark JA, Bokhour BG, Inui TS, *et al*. Measuring patients' perceptions of the outcomes of treatment for early prostate cancer. *Med Care* 2003, **41**, 923–936.
85. Talcott JA, Rieker P, Clark JA, *et al*. Patient-reported symptoms after primary therapy for early prostate cancer results of a prospective cohort study. *J Clin Oncol* 1998, **16**, 275–283.
86. Lubeck DP, Litwin MS, Henning JM, *et al*. Changes in health-related quality of life in the first year after treatment for prostate cancer: results from CaPSURE. *Urology* 1999, **53**, 180–186.
87. Seo PH, D'Amico AV, Clark JA, *et al*. Assessing a prostate cancer brachytherapy technique using early patient-reported symptoms: a potential early indicator for technology assessment. *Clin Prostate Cancer* 2004, **3**, 38–42.
88. Litwin MS, Talcott JA. Quality of life in prostate cancer: past, present, future. In: Lipscomb J, Gotay CC, Snyder C, editors. *Outcomes assessment in cancer*. Cambridge: Cambridge University Press; 2003 (in press).