Aspects of health related quality of life in prostate cancer

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Chapter 3

Health related quality of life in prostate cancer: a review of the literature

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Introduction

Traditionally, clinicians have mainly focused their attention on the more classical aspects of the evaluation of cancer treatment outcome, such as control of symptoms, response to treatment, relapse, and survival, while less attention has been paid to how the disease and its treatment affect health related quality of life (HRQOL). In the past decade the need to assess HRQOL in patients with malignancy has increasingly been recognised. This is also true for patients suffering from prostate cancer. As a result of this, a growing number of articles concerning HRQOL issues in prostate cancer patients was published. A PubMed research resulted in 854 articles after entering the keywords 'prostate cancer' and 'quality of life'. At this point it seems justified to ask: what did we learn from all this HRQOL research until now? Answering this question is the main objective of the present article. We present a systematic review of the published literature and finally the outcome will be discussed.

Methods

On 10-06-2002 a search of the MEDLINE database was performed over the period 1966 (start of MEDLINE) – 01-04-2002. This search was performed by using the PubMed service as offered by the US National Library of Medicine (NLM). MEDLINE is the NLM bibliographic database covering fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences. It provides access to abstracts of articles and citations from more than 4000 biomedical journals published world-wide. The search was performed using the subheadings MeSH ‘prostatic neoplasms’ and ‘quality of life’ and the keywords ‘prostate cancer’ and ‘quality of life’.

Articles were selected for review if they met the following inclusion criteria: publications and citations in English of which an abstract was available. All selected abstracts were judged and categorized. Eight categories were distinguished:

1. General aspects
   This category consists of articles concerning general aspects of HRQOL, such as methodological issues, questionnaire development, validation processes, personal views on HRQOL, and so on. Review articles and personal views of authors as well as editorial comments are also included in this category. Articles reporting the results of studies were not included in this category.

2. Radical prostatectomy
   Articles concerning HRQOL issues related to radical prostatectomy.

3. Radiation therapy
   Articles concerning HRQOL issues related to radiation therapy. These include external as well as interstitial radiation therapy.

4. Comparing radical prostatectomy with radiation therapy
   Articles in which the results of HRQOL assessment of patients treated with radical prostatectomy are compared with those of patients treated with radiation therapy.

5. Hormonal treatment
   Articles concerning HRQOL issues and hormonal treatment.

6. Hormone refractory disease
   Articles concerning HRQOL issues in hormone refractory disease.

7. Remaining HRQOL articles
   Articles resulting from the PubMed search that don’t fit in with one of the above formulated categories, but do deal with HRQOL.

8. Others
   Articles resulting from the PubMed search of which HRQOL is one of the keywords, but that in fact don’t deal with HRQOL issues.

The search resulted in a substantial number of articles in which quality of life (QOL) was indeed one of the keywords, but in which the authors didn’t report any structured research about the HRQOL. By structured research about HRQOL is meant all research that is performed with questionnaires, whether or not validated, to gain an insight in this quality. It is expressly not understood to mean research in which the researcher registers complications and side effects of treatments and
subsequently draws conclusions with regard to the HRQOL of patients, based on these data. This category of articles is placed in the group 'others' and will not be considered in this review. In addition, from a methodological point of view it is clear that prospective studies, in which baseline measures and the use of validated questionnaires are included, are scientifically the most valuable. Articles meeting these criteria will be considered extensiblly and are mentioned in the annexed tables. It is a well-known fact, however, that the sounder a study might look from a methodological point of view, the less remarkable the results often are. On the other hand, methodologically less sound studies, sometimes somehow show a remarkable trend. For this reason this type of studies will be considered here briefly, in the course of which it is attempted to formulate the detected trend in particular. Again, trials or studies using disease symptoms or adverse events as proxies but no HRQOL instruments, were not considered as studies in which HRQOL was evaluated and are therefore not discussed in this review.

Results
The primary search resulted in 854 citations. After selection according to the inclusion criteria 630 citations remained. As shown in figure 1 the number of articles produced with respect to HRQOL in prostate cancer has explosively grown in recent years. The oldest citation is from Baker. In 1975 he stated: 'Generally, recent reports on the side effects of oestrogen therapy for prostatic cancer have concerned mortality statistics, relatively little attention having been paid to the quality of life of individual patients.'[1] Although he argued in favour of more structured research about the quality of life in patients with prostate cancer, this wasn't implemented immediately. It was only in the beginning of the nineties of the last century, that this type of research in patients with prostate cancer began to receive more attention.

![Figure 1](image)

Figure 1: Presenting the year and the number of articles published in that year. Results of a Medline-Research on the keywords 'Prostate cancer' and 'Quality of Life', restricted to English citations including an abstract.

1. General aspects
This category contains 77 articles. Most of these articles deal with methodological issues like instrument or questionnaire development and validation processes [2-10]. A few articles report about patients preferences and the use of Quality Adjusted Life Years [11,12].
It is beyond the scope of this review to discuss them all. A lot of these methodological issues are described in chapter 2. Here we will highlight a few articles which we personally think are interesting or valuable.

To begin with, we mention two papers describing what an optimal questionnaire to measure HRQOL in prostate cancer should contain. The first one is the paper of Altweins report of the Wallenberg symposium. During this symposium the literature was screened for reports on the more common complications following various forms of therapy for prostate cancer. Frequencies were summarized. The scarce literature reporting on quality of life in prostate cancer was reviewed and conflicting data were discussed and reassessed. Among others, this resulted in the formulation of the optimal questionnaire for assessing HRQOL in prostate cancer patients; a Quality of Life Questionnaire should contain general domains relevant to cancer patients, cancer-specific questions, and prostate cancer-specific questions. The latter group includes: questions on worry about prostate cancer and its prognosis, bone/pelvic pain, lower urinary tract symptoms, urinary incontinence, urinary diversion, bowel function, sexual function, endocrine effects, and satisfaction with medical care for prostate cancer. The Wallenberg symposium finally concluded that a modern trial of prostate cancer treatment should be regarded as insufficient if it doesn't include a validated Quality of Life Questionnaire [13].

The second paper describing an optimal questionnaire concerned a questionnaire developed by Clark et al [14]. Based on focus groups with prostate cancer, patient's questionnaire items were constructed representing HRQOL issues that were important according to the patients. Psychometric analyses identified nine reliable and valid indicators of prostate cancer-related HRQOL: body image, sexual problems, spouse affection, spouse worry, masculinity, cancer-related self-image, cancer distress, cancer acceptance, and regret of treatment decision. Remarkably, the emotional status of spouses is identified as a factor influencing the HRQOL of the patient, which is also true for the regret of treatment decision. These issues are not incorporated in the HRQOL questionnaires developed so far. One other article worth mentioning is the one written by Cleary et al, describing the validation of a self-administered questionnaire to be used in hormonally treated advanced prostate cancer patients [15]. A brief self-administered 33 item questionnaire covering 10 domains was developed. Among others, these domains were general health perceptions, pain, vitality, sexual interest and sexual functioning. Cleary et al conclude that, with the exception of the measure of sexual interest and sexual functioning, the scales performed well with respect to the psychometric characteristics in each of the six study countries. So, the items sexual interest and sexual functioning are not validated in this study. Fayers explained the difficulties and the pitfalls by using the exploratory factor analysis (EFA) as one of the standard and most widely applied methods for demonstrating construct validity of new instruments. Factor analysis is irrelevant as a method of scale validation for those HRQOL instruments containing causal indicators, and should only be used for items which are effect indicators [16].

Knight et al examined the reliability and validity of spousal assessment by evaluating the collateral HRQOL ratings of patients with metastatic prostate cancer [17]. A comparison was made between spousal assessment of the patients HRQOL and the instruments filled in by the patients themselves. The collateral HRQOL assessments from spouses are potentially useful in assessing the functional status in patients of lower socioeconomic status with metastatic prostate cancer. For subjective domains, such as the social domain, direct patient assessments are needed. Sneeuw et al executed a comparable study, concluding that the spouses of men with metastatic prostate cancer evaluate with a fair degree of accuracy how patients experience physical and psychosocial functioning, symptoms and overall quality of life [18]. However, caution should be exercised when relying on proxy raters for assessing sexual functioning and satisfaction.

Finally, we mention the existence of the CaPSURE database [19]. CaPSURE stands for Cancer of the Prostate Strategic Urologic Research Endeavor. The objective of this database is to document the impact of prostate cancer on resource utilization, clinical outcomes, HRQOL, and survival in typical practice setting. It was initiated in 1995 and from a methodological point of view it's very well constructed. The database includes approximately 1,000 clinical and patient reported variables. Over 30 clinical sites and thousands of patients participate. Analyses of data from the CaPSURE database have already delivered very valuable results, which are presented in several papers [20-27].
2. Radical prostatectomy

26 articles report about the results of HRQOL assessment in patients treated with radical prostatectomy. The 7 prospective, longitudinal studies, including baseline assessment, and using validated questionnaires, are listed in table 1. It must be noticed that Jonler and Sell report about the same study population. The other 19 studies are mostly retrospective and/or cross-sectional or they’re lacking baseline measures. Results are reported in a descriptive way [28]. Fowler et al showed in one such study that incontinence had a greater impact on HRQOL than loss of sexual capacity [29]. Grahnek et al studied the impact of nerve-sparing techniques. The results demonstrated that nerve-sparing surgery improved outcomes in physical function, role limitations, sexual function, and discomfort. Nerve-sparing techniques did not affect urinary or bowel function nor disease outcome [30]. However, this study has been criticised because of its methodological shortcomings. Litwin performed a cross-sectional study in 96 men treated with RRP. With respect to sexual, urinary and bowel function, men who had undergone nerve-sparing surgery, did not differ from those who hadn’t. However, he also stated that the ability to detect the difference was low. Finally, Talcott also performed a study to investigate the patient-reported outcome after radical prostatectomy [31]. He concluded that nerve-sparing prostatectomy, particularly when performed unilaterally, improves postoperative sexual function to a lesser extent than previously reported. Since men with preoperative impotence and more advanced cancers receive nerve-sparing surgery less often, some of the previously reported benefits of nerve preservation may be the result of patient selection and not necessarily of the technique.

In a study (n=868) of Kao et al, the incidence of patient’s self-reported incontinence, impotence, bladder neck contracture, or urethral stricture was 66%, 88% and 21%, respectively. The incidence of incontinence requiring protection was 33% [32]. In 1994 Leandri et al and Walsh et al reported different figures compared to Kao et al: incontinence 5%-8% respectively and preservation of sexual function in 71%-86% of the patients who were operated nerve-sparingly [33,34]. One must notice that in the last two studies no questionnaires were used to measure HRQOL. They are mentioned here because these studies are cited very often.

In a few assessments, patients retrospectively were asked about their situation before operation, which in several occasions had taken place more than 10 years earlier. Based on these results comparisons were made and conclusions were drawn of HRQOL parameters before and after operation and the impact of the operation on HRQOL [35,36]. In other studies two different groups of patients were compared. HRQOL assessment was performed in one group operated 12 months or longer before, and at the same time an assessment was performed in patients awaiting surgery. These two groups containing different patients were compared and, again, based on these results the impact of radical prostatectomy on HRQOL was reported [37-39]. Results of those studies demonstrate the negative impact of surgery on urinary and sexual functioning, which leads, however, to a none or only minimal decreased overall HRQOL. Two articles are not discussed because they meet a combination of the exclusion criteria as mentioned under Methods [40,41]. In several studies patients were asked after treatment if they would choose radical prostatectomy again [28,29,32,38,40,42-45]. The overall percentage of patients who would do so varies from 77.5%-92%

As one can imagine there was a sound relation between the seriousness of postoperative complications/side effects and the willing to choose surgery again. Patients experiencing a lot of problems as a result of surgery are less willing to choose prostatectomy again. Finally, Ruiz-Deya et al retrospectively evaluated the impact of standard perineal approach on patient outcome [46]. They concluded that the radical perineal prostatectomy is a low morbidity alternative for the treatment of localized prostate cancer. Outpatient radical perineal prostatectomy can be performed with good patient satisfaction and safety. There appears to be few bowel problems after long-term follow up.

3. Radiation Therapy

32 articles report about the results of HRQOL assessment in patients treated with radiation therapy. This includes external beam radiation (n=19) therapy as well as interstitial radiation therapy (brachytherapy) (n=13). The prospective, longitudinal studies, including baseline assessment, using validated questionnaires, are listed in table 2. Lee et al were the only ones who performed such a study in interstitial radiation therapy. They have written 3 articles about the same study population.
19 articles remained reporting HRQOL assessment in patients treated with radiation therapy only. Of these articles 11 did not fit in with the criteria as described under Methods. Of these remaining 11 articles with methodological shortcomings, the greater part is performed as a retrospective cross-sectional type of research [47-54]. These studies all report that the main problems in men after radiation therapy are related to urinary, bowel, and sexual functioning. These functions are disturbed. The degree of disturbance varies. Almost all these studies conclude that sexual dysfunction has the greatest impact on HRQOL, although this impact declines with rising age and for patients older than 74 years decreased sexual function was not perceived as such a significant problem, despite the loss of desire and erection. Roach stated that more research is needed to evaluate the true impact of radiation therapy on the HRQOL of patients and their partners to allow an adequate informed consent [54].

Changes in experienced HRQOL 4 and 8 years after radiation therapy compared with an age matched control group were studied by Fransson et al. The outcome did not change between 4 and 8 years after RT. The age-matched controls reported no change in urinary or sexual problems despite advanced age, but there was a reported decrease in intestinal problems [55]. Kupelian compared short course intensity modulated radiotherapy to conformal radiotherapy (SCIM-RT) [56]. After two years HRQOL reported by the patients using the EPIC questionnaire reveals no difference between patients treated with high-dose CRT at standard fractionation and patients treated with SCIM-RT.

A few studies asked patients after treatment if they would choose radiation therapy again [45,53,57,58]. The overall percentage of patients who would, varies from 81%-97%.

The search delivered 13 articles with respect to interstitial radiation therapy. Of these articles 10 didn’t fit with the defined methodological criteria. Among others, Arterbery et al and Merrick et al executed retrospective studies [59-66]. These studies demonstrate mild (<20%) urinary (frequency and urge, no incontinence) and bowel symptoms and about 50% of the treated patients has maintained potency. Joly et al compared patients (n=71) treated with combined external beam radiation therapy and interstitial radiation therapy with an aged- and residence-matched control group. Overall HRQOL didn’t differ between the two groups. Differences concerning sexual activity and interest and urinary function (incontinence and cystitis) were observed, all in favour of the control group [67]. In a few studies patients were asked after treatment if they would choose interstitial radiation therapy again [59,62]. The percentage of the patients who would want an implant again, varies from 98%-100%.

4. Comparing radical prostatectomy with radiation therapy

19 articles remained only reporting the results of HRQOL assessments in patients treated with radical prostatectomy compared with patients treated with radiation therapy. Four of these 19 studies show a prospective design, including baseline assessment and the use of validated questionnaires (see table 3). The other articles mostly report about retrospective analyses or analyses not including baseline assessment [26,27,68-73]. Results of all these studies are more or less comparable. Patients treated with radical prostatectomy or radiation therapy both experience urinary and sexual problems. These problems are, by and large, worse in surgically treated patients. Moreover, radiated patients show bowel problems. Nevertheless, the overall HRQOL was good or only slightly impaired in the majority of patients. Litwin demonstrated that patients undergoing radiation therapy or radical prostatectomy, whether or not nerve-sparing, all showed comparable rates of improvement in sexual function during the first year after treatment for early-stage prostate cancer. However, in the second year after treatment, patients treated with radiation therapy began to show declining sexual function; patients treated with radical prostatectomy did not. With respect to urinary incontinence, Litwin reported that urinary function improved with time during the first year after surgery but remained fairly constant during the second year [26,27]. Two studies were retrospectively executed in radiation therapy patients. The results were compared with a cohort of surgically treated patients. [74,75]. Again comparisons showed a higher rate of incontinence and impotence in the surgically treated patients and a higher rate of bowel dysfunction after radiation therapy. Krupinsky et al compared radical prostatectomy, external radiation therapy, interstitial radiation therapy and the combination of external and interstitial radiation therapy in a retrospective cross-sectional design [76]. The number of studied patients was small (n=138) and the group varied largely. They concluded that patients treated with the combination of external and interstitial radiation therapy had an overall lower quality of life compared with those treated with radical prostatectomy and external radiation therapy.
A study in which brachytherapy, whether or not combined with external radiation therapy, was compared with radical prostatectomy and an age-matched healthy control group was carried out by Brandeis [77]. His main conclusion was that general health related quality of life of patients undergoing brachytherapy with or without pre-treatment with external beam radiation, was similar to age matched controls, although urinary, bowel, and sexual problems were reported. Much of the impairment in disease specific health related quality of life among patients undergoing brachytherapy might be attributed to pre-treatment radiation.

Madalinska et al studied the baseline HRQOL in patients with screen-detected versus clinically diagnosed prostate cancer treated with radical prostatectomy or radiation therapy [78]. Screen-detected prostate cancer patients presented with more favourable cancer stage and grade. HRQOL was related to both the tumour stage and the detection method. Pre-treatment HRQOL differences between prostatectomy and radiotherapy patients were associated neither with tumour characteristics nor with the detection method. Baseline differences in HRQOL should be taken into account when evaluating post-treatment HRQOL.

Finally, Tefilli et al reported about salvage procedures for locally recurrent prostate cancer [79]. They compared salvage prostatectomy after primary radiation therapy with salvage radiation therapy after primary surgery. They demonstrated that patients receiving salvage radiation therapy have better urinary incontinence rates and a better overall HRQOL.

5. Hormonal treatment

41 articles are left only reporting the results of HRQOL assessments in patients treated with androgen deprivation. Again we distinguish prospective studies, including baseline measures, using validated questionnaires, from other designed studies. The former are listed in table 4. For easy reference we classified the remaining articles in several categories. These are studies reporting outcome in:

- a. partial androgen blockade (PAB);
- b. maximal (or combined) androgen blockade (MAB);
- c. intermittent androgen deprivation;
- d. bicalutamide;
- e. remaining.

a. Partial androgen blockade

In a small study (n=15) in patients with stage D disease treated with orchiectomy, Lucas et al found that orchiectomy did not appear to affect quality of life, or sex-role identity. However, loss of sexual function did turn out to be an area of concern. It was noted that 55% of premorbidly sexually active patients found this loss disturbing. These patients, premorbidly, appeared to have higher sex-role stereotype [80]. Nygard et al executed a HRQOL and cost effectiveness study, comparing patients treated with orchiectomy or LHRH analogue (Goseraline) [31]. After three years, the overall HRQOL was comparable in both groups whereas the costs for the treatment with LHRH were significantly higher. They conclude that orchiectomy is the treatment of choice in case of a life expectancy of more than two years. Also Potosky et al concluded, based on the results of their study that the HRQOL results of both treatment modalities (LHRH versus orchiectomy) were comparable [82].

Except for the studies with bicalutamide, the search delivered no other studies with respect to HRQOL in PAB.

b. Maximal androgen blockade

A systematic review is performed by Schmitt et al [83]. Their main objective was to assess the effect of MAB on survival when compared with castration (medical or surgical) only for patients suffering from advanced prostate cancer. Moreover, they addressed adverse events and HRQOL aspects. Finally, they concluded that MAB produces a modest overall and cancer-specific survival at 5 years but it is also associated with increased adverse events and reduced quality of life. The conclusion with respect to the HRQOL aspects, however, is based on one single trial studying orchiectomy plus placebo versus orchiectomy plus Flutamide [84].
Albertsen et al compared hormonal treatment (MAB) in patients with metastatic prostate cancer in remission (n=60) and patients who are in progression (n=53). Men with hormone-sensitive cancer had significantly less bodily pain, more vitality, more social interactions, and better mental health than patients with hormone-resistant disease. No differences were observed between the two groups concerning treatment-related problems such as diarrhea, constipation, urinary symptoms, sexual function, sexual satisfaction, or hot flashes, although men in remission tended to rate each of these items more favourably than men with disease progression. Patients in remission receiving an LHRH agonist and flutamide have a quality of life that is indistinguishable from a matched male population without prostate cancer, and which is significantly better than that of men with androgen-resistant disease [85].

c. Intermittent androgen deprivation
Bouchot et al executed a study in patients with M1b prostate cancer. They concluded that intermittent androgen deprivation or suppression could be associated with a significant period off-therapy in the first cycle (55.8%), and with a chance of second hormone response. But in the second cycle, the off-therapy period was short and required a careful follow-up. No difference was observed in the EORTC QLQ-C30 between therapy and off-therapy periods, only a rapid decrease in adverse events due to the hormonal deprivation was reported in all cases during the off-therapy period [86]. This was the only article reporting about intermittent androgen deprivation using questionnaires to measure HRQOL. Several articles concerning intermittent androgen deprivation made statements about HRQOL but didn’t use questionnaires for investigation [87-90].

d. Bicalutamide
11 studies dealt with bicalutamide, and, with respect to the HRQOL assessment, had methodological shortcomings as formulated before [91-101]. One of the problems is the validation of the questionnaire used in several trials [94,95,97-99]. This questionnaire was not validated for the items sexual interest and sexual functioning (see also page 34). Therefore the results of the trials using this questionnaire in relation to these items, should be interpreted with some reserve.

The results of a controlled trial of bicalutamide (50mg) versus orchiectomy in advanced prostate cancer were reported by Bales et al [91]. No baseline QOL assessment was available. Although sexual functioning and sexual relations were higher in the bicalutamide group during the first months of assessment, this therapy appears inferior to castration in overall objective and subjective response rates. These results were similar to those reported by Chodack et al [93], Kaisary et al [96], and Iversen et al [102] who also studied the impact of bicalutamide (50 mg) versus orchiectomy.

Boccardo et al report about a study comparing bicalutamide (150 mg) monotherapy versus flutamide plus Goseraline in newly diagnosed advanced prostate cancer patients [92]. They stated that HRQOL analysis might be biased by the low compliance (20%-60%) and methodological shortcomings. With this in mind, they conclude that fewer patients in the bicalutamide group complained of loss of libido ($p<0.01$) and of erectile dysfunction ($p=.002$). Significant trends favoured bicalutamide-treated patients also with respect to their HRQOL, especially in relation to social functioning, vitality, emotional wellbeing, and physical capacity.

Iversen et al showed the results of a study comparing bicalutamide monotherapy (150mg) versus castration (medical or surgical). A total of 480 patients was randomized. It is unclear how many patients filled out the QOL questionnaires. Surely only 183 patients (compliance 38%) responded to the questions related to sexual issues. The authors concluded that there were statistically significant benefits in the bicalutamide monotherapy group in the 2 quality of life parameters of sexual interest ($p=0.029$) and physical capacity ($p=0.046$) [94].

There are a few articles of the casodex study group, reporting a trial comparing LHRH plus flutamide versus LHRH plus bicalutamide (50 mg) [97-99]. These articles don’t show a proper explanation about the used HRQOL questionnaire. It is unclear whether it is validated or not. As far as we are able to judge, they used the same questionnaire as in other trials with bicalutamide (see above). With respect to the HRQOL data, they concluded that there were no differences between the two study arms.
c. Remaining

Herr investigated the impact of hormonal treatment on HRQOL in newly diagnosed metastatic prostate cancer. He compared immediate versus delayed therapy. Baseline HRQOL was not assessed. The results of the assessment after 6 months are reported: the premise that active therapy, despite its side effects, would improve or maintain the psychosocial quality of life was not substantiated, and the no-therapy group had better physical and sexual functioning [103]. Van Andel et al studied also delayed versus immediate hormonal treatment. HRQOL was assessed in a group of 55 men suffering from lymphnode positive prostate cancer. Immediate hormonal treatment proved to have a negative impact on several HRQOL parameters (energy, fatigue, emotional, physical and sexual function, and hot flushes) when compared with patients who are under surveillance [104]. These results are in line which those reported by Potosky et al and Seftelet al [105,106].

Addressing deferred treatment, Jonler et al studied a population of 73 patients with localized prostate cancer whose initial therapeutic modality was ‘wait and see’. Of the 53 patients responding to the questionnaire, 44% received hormonal treatment during follow-up. Although they found a high frequency of incontinence and impotence, 52% of the patients rated their health as excellent or good and 61% would be happy to spend the rest of their lives feeling the way they did at the time of administering the questionnaire. Moreover, 96% would choose deferred treatment again if faced with the decision [107].

Buchholz studied the incidence and impact of post-orchiectomy hot flushes in 82 patients. From 32 patients (39%) HRQOL questionnaires were available for analyses. Between 30%-50% of the patients experience hot flushes which cause significant discomfort and inconvenience affecting both sleep and social activities, and which are considered severe enough to seek palliation [108].

The results of EORTC trial 30891 concerning sexual function are reported by Schroeder et al [109]. This was an open, prospective, randomized study of 310 patients with previously untreated metastatic prostate cancer with favourable prognostic factors, who were treated with either flutamide (FLU) or cyproterone acetate (CPA) monotherapy. For evaluation of sexual functions, a non-validated 5-item questionnaire was used. The analyses showed that maintenance of potency under treatment with FLU as reported in the literature is not confirmed in this study. Loss of sexual functions under monotherapy with both antiandrogens is slow and 10-20% of the men retain sexual activity after 2-6 years of treatment. The advantage of FLU in time, and total preservation of sexual functions is statistically not significant and must be balanced against the side effects of FLU and other pure antiandrogens, which may exceed those of CPA especially with respect to gynaecomastia. Hepatic toxicity may limit the long-term use of both drugs.

Lubeck studied the impact of androgen deprivation therapy (ADT) on the HRQOL, using the data from the CaPSURE database [110]. Patients who received ADT had reduced energy, poorer sexual and urinary function, and were more bothered by their urine and sexual function than patients undergoing other treatments, except surveillance.

6. Hormone refractory disease

23 articles have been published addressing HRQOL assessment in hormone refractory prostate cancer. The objective of all these studies was to test new treatment modalities. It is well known that hormone refractory prostate cancer can’t be cured. So far, none of the therapeutic regimens examined in this particular patient group demonstrated a consistent increase in overall survival. When objective response is unlikely, the main goal should be to reduce symptoms and also to improve the quality of life. For this reason it is not surprising that most studies (n=17) correctly executed HRQOL assessment from a methodological point of view. Articles using validated questionnaires, and showing a prospective, longitudinal design, including baseline measures, are listed in table 5. The remaining articles are mentioned briefly.

Radiation therapy. HRQOL was assessed in 137 patients of whom 31 received SR89 and 106 external beam radiation therapy. The patients’ perception of physical function represents an independent prognostic factor of overall survival, combined with alkaline phosphatase and performance status. After 3 months, palliative radiotherapy was effective in only 25% of the investigated patients, two-thirds of whom had 20 hot spots or more on bone scan. Fossa suggested that palliative radiotherapy should probably be offered during an earlier phase of the disease [111].

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Kraeber et al evaluated retrospectively the toxicity and efficacy of strontium-89 chloride (Metastron, Amersham) in 94 patients with painful bone metastases of prostate cancer and compared the efficacy of treatment in patients with moderate and extensive bone involvement. An improvement in quality of life was obtained in 65% of the cases, a decrease in pain in 78% (31% complete response) and a reduction of analgesics in 60%. Efficacy was significantly better for pain decrease ($p=0.005$) and reduction of analgesics ($p=0.018$), and response was significantly longer ($p<0.0035$) in patients with moderate bone involvement than in patients with extensive bone involvement. These results confirm the benefit of 89Sr chloride for the treatment of metastatic bone pain and suggest that internal radiotherapy should be started earlier [112].

Kalkner et al aimed in their study (n=23) to compare bone scintigraphy with pain extension and other HRQOL factors in order to evaluate HRQOL and the appropriateness of using pain figures and a subjective pain description as the basis for palliative radiotherapy (RT) portals. Restriction of mobility caused by pain in weight bearing regions highly correlates with impaired overall HRQOL. However, they determined that there existed hardly any correlation when comparing location of pain with location of uptake on bone scintigraphy. They suggest to irradiate painful weight bearing regions of the skeleton in order to increase HRQOL, and not only to irradiate locations with uptake on bone scintigraphy [113].

Intravenous clodronate followed by maintenance oral clodronate. Cresswell investigated the effect of intravenous clodronate therapy. In 10 of 27 (37%) patients it was effective in relieving the pain resulting from prostate cancer bone metastases, but the benefit was shortlived. A HRQOL/activity questionnaire, which assesses aspects of everyday life that are important to the patient, was used. Results showed that 8 of 27 patients reported an improvement in activity score at completion of intravenous clodronate, but again this was shortlived. After 12 weeks only 3 patients experienced the initial advantage of the treatment [114].

Prednisone. Tannock et al reported in 1989 about a prospective study treating HRPC patients with Prednisone 5 mg tid. They concluded that a low dose Prednisone may cause relief of pain in some patients. This was also associated with improved HRQOL parameters [115].

7. Remaining QOL articles
There remained 26 articles that dealt with HRQOL assessment in prostate cancer but did not fit into one of the 6 categories mentioned above. None of these articles met the methodological criteria as described above.

In a cross-sectional study, Fossa et al found LUTS and fatigue to be independent predictive factors for global HRQOL after initial treatment in patients with prostate cancer. Radiotherapy of the prostate leads to higher morbidity than was generally anticipated by physicians. The incongruity between physicians’ and patients’ assessments of HRQOL following treatment indicates the necessity for further systematic HRQOL evaluation in these patients [116].

Clark et al [117] executed a study to explore the effects of urinary, bowel, and sexual symptoms following treatment for early (non-metastatic) prostate cancer on health related quality of life through an examination of the responsiveness of the Medical Outcomes Study Short Form Health Survey (SF-36). They concluded that the SF-36 is associated with the presence of physical symptoms but demonstrates a complicated pattern of change following treatment and the development of new urinary, bowel, and sexual problems.

Fulmer et al conducted a prospective assessment comparing voiding and sexual function in patients treated with radical prostatectomy to hormonobrachytherapy with or without external beam radiotherapy [118]. They only used disease-specific and no general HRQOL instruments. The impact on the sexual and urinary function was significantly higher in surgically treated patients.

Only one study investigates, next to the adaptation of prostate cancer patients, the HRQOL of the spouses of these patients. Patients experiencing problems in adaptation were significantly more likely to suffer advanced stage disease, and to receive surgical or medical hormonal therapy. They were reporting greater pain, fatigue, urinary problems, and deteriorating physical functioning compared with lower stage disease patients who received curative or deferred treatment. Spouses reported significantly greater psychological distress than did patients (EORTC Psychological Distress subscale, $p<0.001$; LS, $p<0.001$) [119].
Analysis from the CaPSURE database of 692 patients treated with radical prostatectomy, radiation or hormonal therapy, or observation, are reported by Lubeck et al. Baseline assessments were not available. Patients undergoing radical prostatectomy have low HRQOL scores just after treatment in almost all general and disease-specific areas, but after 1 year there is a sharp improvement. Patients undergoing observation, radiotherapy, or hormonal therapy remain stable over time. All treatment groups continue to have decrements in sexual function [22]. The same analysis was performed by Litwin in 1995 and Davis in 2002 [70,120]. A comparable cross-sectional study was done by Bacon et al, delivering the same results. They conclude that important differences in quality of life go beyond known physical symptoms associated with various prostate cancer treatment options, many of which involve making a trade-off [121].

Another HRQOL analysis from the CaPSURE database of patients before they die, was performed by Litwin [21]. It turned out that HRQOL begins a steady and inexorable decline in the final 12 months of life in men with prostate cancer. He concluded that increased attention to quality of life changes may provide new clinical opportunities to enhance quality of care in these men’s final year. The findings of Melmed et al are in line with those of Litwin [122].

Lubeck studied HRQOL differences between black and white men, again using the data from the CaPSURE database [23]. Significant differences exist in clinical presentation, sociodemographic characteristics, and health related quality of life between black and white men with prostate cancer. These health related quality of life differences remain after treatment. Physicians should not assume that outcomes in black men are similar to other patients.

Combined hormonal and radical (surgery/radiation) treatment was studied by Akakura et al [124]. The mode of hormonal therapy was diverse. The rate of incontinence was higher in the surgery group, impotence rates in both groups were high (radiation: surgery – 85%: 95%), the overall QOL was less disturbed in the radiation group.

Combined brachytherapy and additional external radiation therapy was investigated by Egawa et al [125]. Morbidity associated with combined radiation therapy was greatest during the first month of treatment and affected quality of life significantly. Most measures recovered to baseline levels 12 months after radiation therapy.

The objective of a study performed by Pummer et al was to evaluate whether patients (n=145) with previously untreated advanced prostate cancer benefit from combining total androgen blockade (TAB) with weekly Epirubicin chemotherapy (E-TAB) [126]. They concluded that the combination of TAB and Epirubicin was tolerated well by patients with advanced prostate cancer and that it resulted in a significant extension of progression-free survival. This effect of E-TAB on objective treatment outcome was accompanied by prolonged time without treatment-induced adverse effects and tumor progression, i.e. time with good quality of life. Therefore, further studies with E-TAB seem justified in patients with advanced prostate cancer [127].

The possible relationship between HRQOL and quantity of live (survival) was investigated by Kongrad et al [128]. They evaluated the association of marital status and survival in patients with prostate cancer. Using the 146,979 prostate cancer patients of the 1973 to 1990 public use tape of the Surveillance, Epidemiology and End Results, program a survival analysis and multivariate proportional hazards modeling to estimate the relative risk of mortality was performed. It turned out that married patients had significantly longer median survival than those who were divorced, single, separated, or widowed. They discuss several hypothetical models that can explain the association of marital status and mortality in men with prostate cancer. In their opinion the most attractive model relies on the putative salutary effects of being married on social support and/or mood. A social support and depressed mood model of mortality raises the possibility that in prostate cancer quality of life determines quantity of life. Understanding the relationships among marital status, social support, mood, and mortality, could open the way to rational strategies for postponing death in men with prostate cancer.

The study of Singer et al is interesting. He concluded that some men may choose treatment with lower long-term survival to increase their chance of remaining sexually potent. Because these men may be difficult to identify in clinical practice, physicians should thoroughly discuss both surgery and radiotherapy options with patients who have localized prostate cancer [130]. Clark et al examined the variation in men's long-term regret of treatment decisions, i.e. surgical versus chemical castration, for
metastatic prostate cancer and its associations with quality of life [131]. They found that regret was substantial in the whole group (23%) and was associated with treatment choice and HRQOL. Eton et al investigated the relation between HRQOL, treatment, demographic and psychosocial factors in patients treated for localised prostate cancer [132]. Shortly after undergoing treatment men who underwent radical prostatectomy, older men, and Afro-American men are suffer a greater risk for experiencing prostate-specific and general deficits in HRQOL. Having psychosocial resources from which to draw, may enhance HRQOL. Penson et al investigated the association between socioeconomic status, health insurance coverage, and HRQOL in men with prostate cancer [133]. The study confirms the commonly held belief that patients of lower SES tend to have worse quality of life at baseline and following treatment of their disease.

The HRQOL in patients with PSA recurrence after radical prostatectomy was retrospectively studied by Pietrow et al [134]. Their study demonstrates small health related quality of life differences in patients with biochemical PSA recurrence versus those without. In a prospective survey, Fowler et al evaluated the impact of the Viadur 12 months implant on the HRQOL [135]. Patients found the Viadur 12-month leuprolide implant convenient, and the implant did not affect their health-related quality of life. Predictors of utilities for health states in early stage prostate cancer were analysed by Saigal et al [136]. They conclude that men who perceived that general health was better, appear to place higher value on quantity of life, while those who already are suffering from poor general health place higher value on quality of life. Ethnicity appears to modify some effects of other variables on patient preference. Utility assessment provides a quantitative tool to aid physicians in counselling patients when making treatment decisions for localised prostate cancer. The influence of pain on the HRQOL was investigated in a cross-sectional study executed by Sandblom et al [137]. Of 1243 patients, 42% had perceived pain during the previous week and 26% stated their quality of life to be 50% or lower on a visual analogue scale. A high rating of health care availability and short time since diagnosis were found to significantly predict lower ratings of pain (P < 0.05). Pain was found to be a significant predictive factor for decreased quality of life together with high age, low rating of health care availability, and palliative treatment (P < 0.05). They concluded that the assessment and treatment of pain is essential for a good quality of life in men with prostate cancer. Finally there are four articles published concerning HRQOL and screening studies for prostate cancer [78,138-140]. Carvahal et al evaluated correlates of patient-reported dissatisfaction with treatment of prostate cancer detected by screening [138]. They concluded that patients in whom prostate cancer was detected by screening 11% were dissatisfied with treatment. Urinary function and bothersomeness were the only important correlates of dissatisfaction. Essing-Bot et al evaluated the impact of screening itself on the HRQOL in the framework of the European Screening Study for Prostate Cancer [139]. At the group level, no evidence was found that prostate cancer screening induced important short-term health-status effects, despite the short-lasting side effects related to the biopsy procedure. However, subgroups may experience high levels of anxiety. The implication is that unfavourable health-status effects of prostate cancer screening occur mainly in the treatment phase. Madalinska et al described the baseline profile of patients entered in a screening program compared with those clinically detected [78]. Screen-detected prostate cancer patients presented with more favourable cancer stage and grade. HRQOL was related to both the tumor stage and the detection method. Pre-treatment HRQOL differences between prostatectomy and radiotherapy patients were associated neither with tumor characteristics nor with the detection method. Baseline differences in HRQOL should be taken into account when evaluating post-treatment HRQOL. Their article about the same study population reporting on the impact of radical prostatectomy versus external radiation therapy is listed in table 3 [140].

8. Others

These category contains 386 articles. In most of these articles the term HRQOL is mentioned just once or twice. These articles don’t expressly deal with HRQOL issues. Examples of such articles are papers published by Paul [141]. He reports about the pathophysiology of the antiandrogen withdrawal syndrome. It is a rather technical article in which he states that ‘patients who respond to antiandrogen withdrawal experience approximately 6 months with improved quality of life’. Sallgales discusses the possibilities of gene therapy in advanced prostate cancer. He argues that ‘immune cells, for example, T-
lymphocytes and dendritic cells, have already demonstrated treatment benefit, as well as the ability to maintain an excellent quality of life for participants' [142]. On top of that, there are a lot of articles concerning cost-effectiveness issues. Again the term HRQOL is used a few times, but the subject itself is not a substantial issue in these articles[143]. Finally, there are papers about pure technical aspects of prostate cancer treatment, mostly suggesting that the new modality theoretically will improve HRQOL [144].

**Discussion**

The research on Quality of Life has definitely found its place in urology. A PubMed search on this subject, using the keywords 'prostate cancer' and 'Quality of Life', produced 854 articles. Still, the structural research on Quality of Life falls far behind by the extent to which the subject is discussed. Of the 854 articles mentioned above, 630 remained after selecting publications and citations in English of which an abstract was available. Of these, 77 deal with general aspects of Quality of Life. They particularly address methodological aspects, such as the development of questionnaires. 167 articles report on studies in which Quality of Life is researched by means of questionnaires. The remaining 386 articles do mention Quality of Life, but don't report any structured research on the subject.

The findings of the Wallenberg symposium, as reported by Altwein et al and Clark et al, are, from a methodological point of view, very significant. Altwein and Clark conclude that, next to the known HRQOL-influencing factors, there are other relevant factors. These are the emotional status of the spouse and the extent to which the decision on the type of treatment is regretted. These issues are not incorporated in the HRQOL questionnaires developed so far. The fact that spouses do have worries about their partners' prostate cancer is demonstrated by Kornblitt [119]. He assessed HRQOL in 172 patients and 83 spouses/partners. It turned out that spouses reported significantly greater psychological distress than patients did. One can imagine that worries of the spouses affect the emotional well-being of patients and are therefore a factor related to HRQOL. Looking at the questionnaire developed by Cleary et al, it becomes all the more clear that also in HRQOL-research it is very useful to survey the methodological aspects very critically. Cleary et al developed a 33 item-questionnaire covering 10 domains of HRQOL. This questionnaire has frequently been used in later studies. Each time it was reported that this was a fully validated questionnaire. The article, however, which describes the validation of this questionnaire, states frankly that although 8 of the domains are valid, this does not go for the items sexual interest and sexual function. Exactly these two items often produce significant differences in studies in which this questionnaire has been used. It would take things too far to say that the conclusions of these studies are therefore useless, but the interpretation of the results should at least be performed with some reserve.

In this discussion we will only address the results of prospective and longitudinal studies using validated questionnaires and providing baseline measurements. The central question of most studies concerns the side effects of a given treatment; the chances of getting those side effects; and the effects of the disease and the treatment on the overall HRQOL. For a number of reasons a biased answer to those questions seems almost impossible. Such a judgment should be based on the results of a great number of well comparable studies. Even then, it's still difficult to reach a biased conclusion as we well know from the analysis of the use of the maximal androgen blockade. Concerning the methodology, the number of sound studies of the HRQOL of patients treated for prostate cancer is small. Moreover, these studies are often not comparable because of substantial methodological differences. For instance, different instruments are used for measuring HRQOL. One also uses varying definitions, and reports are based on different measuring points. Therefore, the results of the studies of HRQOL of patients treated for prostate cancer reach hardly any further than the collection of single institution experiences. One should keep this in mind while interpreting the results of HRQOL research.

There are seven methodologically sound studies which report on the impact of a radical prostatectomy on the HRQOL. Twelve months after radical prostatectomy, incontinence varies from 7% to 39%, erection disorder from 14% to 69% (table 1). Especially the loss of erection can cause permanent distress. Pre-operative urinary problems, whether mild or severe, improve after surgery. A year after surgery, 86% to 97% of the patients is back on the pre-operative level on all the measured domains of HRQOL, apart from urinary and sexual functioning. But, just as was reported in
methodologically less sound studies, the general feeling is that after radical prostatectomy especially the percentage of erection disorder is substantially higher than 14% to 60%. In my opinion, the results as described by Walsh are only practicable for a very experienced and zealous surgeon. The greater part of the urologists will yet fail to achieve those results. Every urologist should in fact make a standardized assessment of his own results to be able to inform his patients properly. 77.5% to 92% of the patients would choose a radical prostatectomy again, if given the choice.

Concerning the HRQOL after radical prostatectomy, one could conclude in general that radical prostatectomy has a minor effect on the overall HRQOL, that there are fluctuating reports on continence and erection disorder, and that 85% of the patients would choose radical prostatectomy again. A year after treatment, external radiation therapy leads to gastrointestinal problems in 20% of the patients [145]. Directly after radiation therapy, about 75% of the patients experience urinary problems and perianal pain. A year after treatment, those problems have largely disappeared, whereas erection disorders will increase in time. External radiation therapy has hardly any impact on the overall HRQOL. It’s remarkable though, that none of the articles mention adequate percentages of the above mentioned effects of radiation therapy (table 2). 81% to 97% would choose the same treatment again.

In conclusion one could state that radiation therapy for prostate cancer does hardly have any significant impact on the HRQOL in the long term, whereas in time it leads to limited gastro-intestinal and urinary problems and decreased sexual functioning. 90% would choose radiation therapy again.

The only study on treatment with interstitial radiation therapy has been performed by Lee et al. Using the Fact-P and IPSS questionnaires, he found that after one year 46 patients did not show any differences compared with the baseline measures. 99% of the patients would choose treatment with interstitial radiation therapy again.

There are only four methodologically optimal performed studies which draw a comparison between radical prostatectomy and external radiation therapy. In the study performed by Talcott et al, 260 patients participated, 135 of whom were treated with radiation therapy and 125 with radical prostatectomy (table 3). 3% of both groups suffered pre-operative incontinence. 35% of the operated patients reported the use of pads after 12 months. Of this group, 11% reported to lose lots of urine and 5% used a penile clamp to control urination. 5% of the patients in the radiation therapy group used absorbent pads, 2% reported urinary loss and none of the patients used a penile clamp. As for the sexual function, one should notice in advance that the compliance (68%) on the sexual items fell far behind, compared to the other items. 11% of the patients due to surgery and 18% of the patients due for radiation therapy reported a total loss of erection. After applying the definition ‘inadequate erection resulting in the disability to sexual intercourse’, these percentages were respectively 32% and 45%. From the group of patients who had a sound erection before treatment, 69% of the surgically treated patients and 24% of the patients treated with radiation therapy reported a total loss of erection after 12 months. Insufficient erections obstructing intercourse were reported by respectively 91% and 61%. Bowel irritation was reported by respectively 4% and 13%. This article doesn’t describe the impact of these problems on the overall HRQOL. Lee et al found that one year after treatment there were both in the surgically treated group and the radiated patients no significantly differences regarding general HRQOL domains compared with pre-treatment assessment [146]. All researchers found a greater impact on urinary and sexual function in radical prostatectomy patients compared to patients treated with external radiation therapy. Bowel function was only affected by external radiation therapy.

In conclusion, there are only a few studies comparing between patients treated with radical prostatectomy and radiation therapy. These studies emphasize the bowel, urinary, and sexual function, while partly describing the impact on the overall HRQOL. Surgically treated patients suffer more incontinence and erection disorders, whereas radiated patients suffer more bowel irritation.

Remarkably more studies are performed on hormonally treated patients (n=41) (table 4). Cassileth compared 115 patients who were treated with a LHRH analogue with 32 patients who underwent orchietomy. Stratification was based on patients selection, not on randomization. Besides, the number of patients in the orchietomy group is relatively small. Furthermore, the 6 months follow-up of the study is relatively short. Nevertheless, the researchers conclude that a LHRH analogue after 3 and 6 months procures a better overall HRQOL and psychosocial status in relation to baseline, while no changes were detected in the orchietomy group. Litwin et al compared orchietomy to maximal
...androgen blockade in 63 patients No changes were found in any of the HRQOL domains. All patients reported a better HRQOL in most of the domains during the first year.

Of great importance is the study of Moinpour et al. In 739 patients they studied the effects of orchiectomy + placebo versus the effects of orchiectomy and flutamide. All analyses were in favour of orchiectomy + placebo. Patients treated with maximal androgen blockade reported more diarrhea and a deteriorated emotional function after 3 and 6 months. Also of great importance is the study of Herr et al of lymphnode positive or advanced prostate cancer. Patients suffering from this type of cancer can't be cured anymore. Several research groups have studied the effects of immediate versus delayed hormonal treatment on objective parameters, like time to progression and survival. Herr is the only one who has made a prospective study of the impact of hormonal therapy on the HRQOL parameters. He compared immediate (monotherapy or maximal androgen blockade) to delayed hormonal treatment. It turned out that hormonally treated men felt more fatigued, suffered more loss of energy, experienced more emotional distress and reported a lower overall HRQOL than men who had been treated with maximal androgen blockade. The effects of hormonal treatment are also described by Stone et al, who treated 62 patients with maximal androgen blockade. They particularly reported an increased fatigue in the first months after treatment. They also reported decreased virility and potency. Twenty three articles have been published on the subject of HRQOL assessment in hormone refractory disease. Seventeen of them showed a sound methodology (table 5). Especially this group of patients is of the utmost interest for studying the HRQOL, since none of the treatments have shown any survival benefits so far. Although everyone knows that radiation therapy of painful bone metastasis is effective, hardly any structured HRQOL research has been conducted on this subject. Nielsen et al proved that radiation therapy of painful bone metastasis showed an obvious reduction of pain and therefore an improvement of HRQOL. There proved to be no difference between a single radiation with 8 gray versus four times radiation with 5 gray. Porter et al proved that a combination of external radiation with a Strontium 89 injection is superior to a treatment of only external radiation therapy. Prednison as well as the combination Prednison + Mitoxantrone prove to be effective in the treatment of the hormone resistant prostate carcinoma. This effectiveness is only temporary (lasting about 10 to 12 weeks). Osoba and Tannock proved that the combination of Mitoxantrone and Prednison takes a longer and better effect than single Prednison. In small patient groups a slight improvement of the HRQOL of 13 out of the 27 patients was reached after treatment with Carboplatin. Gemcitabine procured a reduction of the pain in 14 out of the 21 patients during 8 weeks. In other HRQOL domains no differences were detected. Idarubicin has no effects on the HRQOL parameters. Epirubicin showed, also in combination with Medroxy Progesteron Acetate, a subjective and biochemical response, though this couldn't be translated to an improved HRQOL.

Resuming, in patients suffering of hormone resistant prostate carcinoma, only radiation therapy seems to be of any effect, the combination of radiation therapy and Strontium-injection giving the optimal response in relation to the HRQOL parameters. Prednison and Mitoxantrone are effective as well, the combination of those two giving better results than single Prednison. All the other treatments show no improvement in the HRQOL domains. It's a known fact that treatment in this group of patients is always temporary. Hence we do want to emphasize again that reporting the duration of the response is of the utmost importance in order to be able to rate the finally reported response at its true value. However, to date treatment with the combination of Prednisone and Mitoxantrone can be considered as the standard therapy in this category of patients.

Finally, we return to our question, 'what have we learned from the research on HRQOL so far?' Actually, we have to conclude that the results are rather disappointing. This is primarily caused by the relatively small number of studies that has been conducted and the current methodological chaos. Consequently, study results are not comparable, and therefore the limited number of currently available results shows every sign of a collection of single institution experiences.

Hence my plea in favour of the implementation of a worldwide standardization of HRQOL assessment in prostate cancer. Standardization particularly involves the instruments used for measuring HRQOL, the timing of data collection, the study design and power, compliance, the statistic analysis, and the presentation of the results. One also has to establish which differences in the assessed HRQOL will be widely accepted as clinically significant. There is a lot of work to be done, especially concerning the unambiguous use of HRQOL questionnaires. One should develop an international questionnaire, available in many languages and cross-cultural validated, addressing all the specific problems a
prostate cancer patient can encounter. Only then we can really put HRQOL on the map as solid endpoint of clinical trials. An endpoint comparable with, for example, PSA response, time to progression, and survival.
<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>No. Patients</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Jonler et al [147]</td>
<td>24</td>
<td>91% of patients reported incontinence 1 month after surgery and 67% after 6 months.</td>
</tr>
<tr>
<td>Litwin et al [148]</td>
<td>90</td>
<td>1 year after surgery 86-97% of the patients returned to baseline levels in each domain of HRQOL. For urinary and sexual functioning this was respectively 61% and 31%.</td>
</tr>
<tr>
<td>Litwin et al [149]</td>
<td>247</td>
<td>Most quality of life recovery occurs early after radical prostatectomy, except in several domains, including urinary and sexual, which continue to improve even beyond 2 years postoperatively.</td>
</tr>
<tr>
<td>Pedersen et al [150]</td>
<td>131</td>
<td>Patients' feelings of distress in several QOL domains are measured. Patients experience post-operative distressful short-term side-effects such as anxiety, voiding disorders and impotence. After 18 months patients feel better than before operation, except for distress due to failure of erection.</td>
</tr>
<tr>
<td>Sall et al [151]</td>
<td>24</td>
<td>Many patients experience pain after RRP. There is a strong relationship between pain and cancer worry as well as pain and incontinence. Severe chronic pain after RRP is unlikely.</td>
</tr>
<tr>
<td>Schwartz et al [152]</td>
<td>104</td>
<td>Moderate and severe urinary symptoms as well as QOL due to urinary problems improved after RRP.</td>
</tr>
<tr>
<td>Walsh et al [153]</td>
<td>64</td>
<td>Patient-reported rates of continence and potency after RPP performed by an experienced surgeon are high. After 12 months 93% were dry and 86% were potent defined as the ability to have unassisted intercourse with or without the use of Sildenafil.</td>
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Table 2: Prospective, longitudinal HRQOL studies, including baseline assessments, using validated questionnaires in patients treated with radiation therapy (external beam n=8 and interstitial brachytherapy n=1) for prostate cancer.

<table>
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<tr>
<th>Author (ref.)</th>
<th>No. Patients</th>
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<tr>
<td>Beard et al [145]</td>
<td>121</td>
<td>Irritative gastrointestinal and genitourinary side effects were frequent 3 months after treatment, but were substantially improved at 12 months. Sexual dysfunction increased steadily over the study period. The POMS and the SF-36 did not demonstrate significant changes over time.</td>
</tr>
<tr>
<td>Beckendorf et al [154]</td>
<td>164</td>
<td>No significant difference was observed between conventional dose levels and high dose levels in terms of toxicity or quality of life.</td>
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<tr>
<td>Duncan et al [155]</td>
<td>215</td>
<td>Comparison of pion versus photon radiotherapy: global QOL, toxicity and physical scores were found to be worse in pion-treated patients at the end of treatment. There are no long-term differences in the QOL of pion-versus photon-treated patients. There was a progressive loss of sexual interest and erectile function in both groups.</td>
</tr>
<tr>
<td>Franklin et al [156]</td>
<td>169</td>
<td>50% of patients experienced dysuria, 75% perianal discomfort and 87% frequency at the end of the treatment. Most factors recovered.</td>
</tr>
<tr>
<td>Janda et al [157]</td>
<td>43</td>
<td>After treatment patients experience a temporary deterioration of fatigue and role functioning. Despite physical deterioration, an improvement in emotional functioning was observed.</td>
</tr>
<tr>
<td>Hamilton et al [158]</td>
<td>497</td>
<td>Sexual function was the most adversely affected quality-of-life domain, with problems continuing to increase between 12 and 24 months. Bowel function problems increased at 6 months, with partial resolution observed by 24 months. Urinary function unchanged. Despite the side effects, satisfaction with therapy was high.</td>
</tr>
<tr>
<td>Monga et al [159]</td>
<td>36</td>
<td>Significant improvement of fatigue after radiotherapy. Higher levels of fatigue are associated with worse physical well being scores.</td>
</tr>
<tr>
<td>Lee et al [161,162] [163]</td>
<td>46</td>
<td>Clinically meaningful decreases in quality of life, as measured by the FACT-P instrument, were evident within weeks after permanent source interstitial brachytherapy. After 3 months FACT-P scores returned to near baseline levels. The I-PSS demonstrated that moderate to severe urinary symptoms persisted for at least 6 months. One year following brachytherapy, the scores on the FACT-P and IPSS questionnaires had returned to baseline.</td>
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</table>
Table 3: Comparative, prospective, longitudinal HRQOL studies, including baseline assessment, using validated questionnaires in patients treated with radical prostatectomy or radiation therapy (external or interstitial) for prostate cancer.

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<tr>
<th>Author (ref.)</th>
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<tr>
<td>Lee et al [146]</td>
<td>90</td>
<td>Comparing radical prostatectomy (RP), external radiation therapy (ER) and brachytherapy (BT). Significant decreases in HRQOL, as measured by the FACT-P instrument, are evident in the first month after BT or RP, but not after ER. One year after treatment, however, the FACT-P scores were not statistically different from the baseline measures for any group. For all treatment groups, most of the HRQOL decreases were observed in the physical, functional, and prostate cancer-specific domains.</td>
</tr>
<tr>
<td>Madalinska et al [140]</td>
<td>278</td>
<td>Prostatectomy and radiotherapy differed in the type of HRQOL impairment. Because the HRQOL effects may be valued differently at the individual level, patients should be made fully aware of the potential benefits and adverse consequences of therapies for early prostate cancer.</td>
</tr>
<tr>
<td>Schapira [164]</td>
<td>361</td>
<td>Radical prostatectomy (RP), external radiation therapy (ER) and expectant management (EM). RP substantial decline in sexual and urinary function. ER no change in urinary function but also a decline in sexual function. HRQOL in the EM stable over one year.</td>
</tr>
<tr>
<td>Talcaott et al [165]</td>
<td>260</td>
<td>External beam radiotherapy of early prostate cancer is followed by bowel and bladder irritability, by increasingly severe sexual dysfunction and, in men of 65 and older, occasional urinary incontinence. Greater sexual dysfunction and urinary incontinence occur in the year following radical prostatectomy. These post surgical complication rates from patient questionnaires are greater than have been reported in other treatment series and confirm the results of two retrospective studies of patient-reported complications</td>
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<tr>
<td>Author (ref.)</td>
<td>No. Patients</td>
<td>Therapy</td>
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<tr>
<td>Cassileth et al [166]</td>
<td>115</td>
<td>Goseraldine vs Orchietomy</td>
</tr>
</tbody>
</table>
| da Silva et al  
*EORTC 30853* | 327 | Orchietomy vs LHRRH + Flutamide | Poor compliance, QOL assessment (22%) incongruity between patients’ and physicians’ evaluation. |
| de Reijke et al  
*EORTC 30893* | 90 | Orchietomy vs Orchietomy + Mitomycin C | Orchietomy plus Mitomycin C for metastatic prostate cancer in patients with poor prognostic factors cannot be recommended due to failure of improvement in survival and reduced quality of life parameters. |
| Herr et al [173] | 144 | Immediate (monotherapy and MAB) vs Deferred | Men who received androgen suppression had more fatigue, loss of energy, emotional distress and a lower overall quality of life than men who received deferred hormone therapy. Combined androgen blockade had a greater adverse effect on quality of life than monotherapy. |
| Litwin et al [174] | 63 | Orchietomy vs Leuprolide + Flutamide | No differences in any of the QOL domains between both groups. In all patients improvement in most QOL domains during the first year. |
| Moinpour et al [84] | 739 | Orchietomy + placebo vs orchietomy + Flutamide | Analyses in favour of orchietomy + placebo. patients receiving Flutamide reported more diarrhea at 3 months ($P = .001$) and worse emotional functioning at 3 and 6 months (both $P < .003$). |
| Sarosdy et al [175] | 59 | Goseraldine 12wks vs Goseraldine 13 wks | Except for a significant ($P=0.014$) decrease in overall sexual interest, QOL was unchanged during therapy. The most common side-effects, regardless of causality, were hot flushes (67%), pain (31%) and pelvic pain (22%). |
Table 4 (2): Prospective, longitudinal HRQOL studies, including baseline assessment, using validated questionnaires in patients receiving **hormonal treatment** for prostate cancer

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<th>Author (ref.)</th>
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<th>Therapy</th>
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<tbody>
<tr>
<td>Stone et al [176]</td>
<td>62</td>
<td>MAB (longitudinal)</td>
<td>Fatigue increased significantly after 3 months treatment. Treatment was associated with a reduction in voluntary muscle function, loss of muscle bulk, a decline in virility and potency, an improvement in pain and a reduction in nausea/vomiting.</td>
</tr>
</tbody>
</table>
Table 5 (1): Prospective, longitudinal HRQOL studies, including baseline assessment, using validated questionnaires in patients treated for hormone refractory prostate cancer

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<th>Outcome</th>
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<tr>
<td>Dawson et al [177]</td>
<td>149</td>
<td>Megestrol Acetate (MA) 160 mg/day vs 640 mg/day</td>
<td>There were no differences in the toxicity or quality-of-life outcomes between the two arms. poorer performance status (2 vs. 0-1), greater than 5% weight loss, higher baseline PSA, and measurable disease all predicted shorter survival. MA has limited activity in hormone-refractory prostate carcinoma, and there is no apparent dose–response correlation.</td>
</tr>
<tr>
<td>Debruyne et al [178]</td>
<td>321</td>
<td>RAMBA (a) vs CPA(b)</td>
<td>Liarozole is superior to CPA in terms of PSA response, PSA progression, and survival, and is capable of maintaining patients' quality of life. The observed adverse events were mild to moderate in nature.</td>
</tr>
<tr>
<td>Fossa et al [179]</td>
<td>201</td>
<td>Flutamide vs Prednisone</td>
<td>In symptomatic HRPC, treatment with prednisone or flutamide leads to similar rates of TTP and overall survival and no difference in subjective or biochemical response. The QL results favor the use of low-cost prednisone in patients with HRPC.</td>
</tr>
<tr>
<td>Johansson et al [180]</td>
<td>180</td>
<td>Epoetin β 1000 IU vs Epoetin β 5000 IU</td>
<td>There were no differences between the groups. The treatment was well tolerated in both groups. Epoetin beta is shown to be safe and effective, it improves QOL and physical functioning, and relieve fatigue symptoms in many of these critically ill patients.</td>
</tr>
<tr>
<td>Jungi et al [181]</td>
<td>27</td>
<td>Carboplatin 400 mg/m2 i.v. every 28 days</td>
<td>Carboplatin had only limited objective activity in advanced prostate cancer, but induced palliation and an improvement in QOL in 13 out of 27 patients for at least two months.</td>
</tr>
<tr>
<td>Kantoff et al [42]</td>
<td>142</td>
<td>Hydrocortisone (H) vs H + Mitoxantrone(M)</td>
<td>Modest advantage for H + M with respect to pain, emotional state and family disruption.</td>
</tr>
<tr>
<td>Kornblith et al [182]</td>
<td>44</td>
<td>Docetaxel Estramustine Hydrocortisone (feasibility study)</td>
<td>Despite feeling worse from side effects, patients' prostate cancer-specific problems and emotional state significantly improved in the first four months of treatment.</td>
</tr>
</tbody>
</table>

(a) RAMBA = retinoic acid metabolism-blocking agent (in this study Liarozole was used)  
(b) CPA = cyproterone acetate
Table 5 (2): Prospective, longitudinal HRQOL studies, including baseline assessment, using validated questionnaires in patients treated for hormone refractory prostate cancer

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>No. Patients</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moore et al [183]</td>
<td>27</td>
<td>Mitoxantrone 12 mg/m2 i.v every 3 weeks + Prednisone 10 mg dd orally</td>
<td>Well-tolerated treatment regimen that has some beneficial effects on disease related symptoms and quality of life; improvements in social and emotional functioning, and in pain and anorexia.</td>
</tr>
<tr>
<td>Morant et al [184]</td>
<td>43</td>
<td>Gemcitabine 1,200 mg/m2 over 2 hours</td>
<td>Significant beneficial impact on pain, 14 out of 41 patients for at least 8 weeks, despite its limited activity in terms of PSA response and considerable, especially haematological, toxicity.</td>
</tr>
<tr>
<td>Nielsen et al [185]</td>
<td>82</td>
<td>1 x 8 Gy vs 4 x 5 Gy</td>
<td>Both treatment modalities effective no significant differences.</td>
</tr>
<tr>
<td>Porter et al [186,187]</td>
<td>126</td>
<td>external beam radiation therapy +/- Strontium-89</td>
<td>The addition of Strontium-89 is an effective adjuvant therapy to local field radiotherapy, improving quality-of-life and reducing the need for analgesics compared to radiation therapy alone.</td>
</tr>
<tr>
<td>Osoba et al [188]</td>
<td>161</td>
<td>Mitoxantrone 12 mg/m2 i.v every 3 weeks + Prednisone 10 mg dd orally</td>
<td>Treatment with Mitoxantrone plus Prednisone is associated with greater and longer lasting improvement in several QOL domains and symptoms than treatment with Prednisone alone.</td>
</tr>
<tr>
<td>Tannock et al [189]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmid et al [190]</td>
<td>26</td>
<td>oral Idarubicin 35 mg day 1 and day 8 every 3 weeks</td>
<td>None of the evaluable patients achieved a response. QOL did not change significantly during therapy.</td>
</tr>
<tr>
<td>Small et al [191]</td>
<td>460</td>
<td>Suramin (S) + Hydrocortisone (H) vs Placebo (P) + Hydrocortisone</td>
<td>Although S+H achieved a significant better pain response, there were no differences in QOL outcome in both groups.</td>
</tr>
<tr>
<td>Smith et al [192]</td>
<td>24</td>
<td>oral Estramustine 280 mg tid + oral Etoposide 100 mg/d for 7 days + Paclitaxel 135 mg/m(2) i.v. over 1 hour on day 2 of each 21-day treatment cycle</td>
<td>The regimen is active, tolerable and does not have a significant impact on QOL.</td>
</tr>
</tbody>
</table>
Table 5 (3): Prospective, longitudinal HRQOL studies, including baseline assessment, using validated questionnaires in patients treated for hormone refractory prostate cancer

<table>
<thead>
<tr>
<th>Author (ref.)</th>
<th>No. Patients</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner et al [193]</td>
<td>93</td>
<td>Strontium 89</td>
<td>62% pain reduction and overall 70% increase in HRQOL. Significant correlation between pain response and HRQOL improvement. No relation between PSA and HRQOL response</td>
</tr>
<tr>
<td>Van Andel et al [194]</td>
<td>26</td>
<td>Epirubicin (100 mg/m(2) i.v.) every 3 weeks +/- oral dose of 500 mg of Medroxy Progesterone Acetate</td>
<td>Subjective and biochemical responses were observed in both treatment arms, but these were not translatable as improved measured QOL domains</td>
</tr>
</tbody>
</table>
References


Seffel A. Quality of life following localized prostate cancer treated initially with androgen deprivation therapy or no therapy. J Urol 2002;168:2316-2317.


