Aspects of health related quality of life in prostate cancer
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Chapter 12

Summary, conclusions and future perspectives
Summary
In the treatment of oncological patients, clinicians traditionally focused mainly on objective outcome parameters, such as survival, time until progression and control of symptoms. Little or no attention has been paid to the impact of the disease and its treatment on the patient’s health related quality of life (HRQOL). This attitude has changed over the last decades. Not only physicians, but patients also take more and more interest in the impact the disease and its treatment have on the HRQOL. This applies to patients with prostate cancer as well.

This dissertation aims to examine various aspects of the general and disease specific HRQOL in patients suffering from and treated for prostate cancer. In this chapter a summary of the thesis is given as well as the conclusions and future perspectives.

In chapter 1 the etiology, clinical aspects, therapeutic modalities and the prognosis of prostate cancer are discussed. To date, prostate cancer is, after lung cancer, the second most commonly diagnosed malignancy in men worldwide, and is recognized as one of the principal medical problems facing the male population. The precise cause or causes of prostate cancer are unknown. Risk factors are ageing, positive family history for prostate cancer, and race. Once diagnosed the choice of treatment generally is based on considerations about disease stage, prognosis, therapy results, complications, and the preferences of patients and practitioners. The best compromise between these considerations will finally decide which therapy is executed. However, in case of prostate cancer the facts about the mentioned factors playing a role in therapy decision making are not always that clear. Moreover, there are several treatment modalities for the same stage of the disease with more or less comparable objective response rates. It is for these reasons that there are no worldwide accepted strict guidelines for the treatment of prostate cancer. The European Association of Urology recently published her guidelines on the treatment of cancer of the prostate (see table 2, page 13). The indications and considerations of the several therapeutic options are listed in this table. Generally, it is stated that for clinically localized prostate cancer in men in good condition with a life expectancy of 10 years or more, the goal of treatment should be eradication of the disease. This can be achieved by radical surgery or radiation therapy (external or interstitial). In locally advanced disease there is evidence that the combination of radiation and hormonal therapy is the best choice. Patients with lymph node or distant metastasis can’t be cured anymore. Hormonal treatment is effective in most of these patients, but this effect is only temporary. The question whether hormonal treatment must be initiated immediately at the time of diagnosis or deferred to the time of the appearance of objective progression is still under debate. Once the disease is progressive under hormonal therapy, so called hormone resistant prostate cancer, there is no second-line treatment available demonstrating a consistent increase in overall survival. Despite all efforts and money put into research, there are still a lot of unresolved questions regarding all aspects of prostate cancer.

In chapter 2 a number of methodological HRQOL issues are considered. First, is identified what HRQOL research should involve. To date, most researchers agree that HRQOL is a multidimensional concept, grouped under the broad headings of physical, functional, psychological and social health. In this view physical health is related to symptoms, e.g. pain, fatigue, gastrointestinal problems, urinary problems, and so on. Functional health is related to mobility, role activities, self care and physical activities. Psychosocial health is related to cognitive function, psychological distress and psychiatric morbidity. Finally, social health is related to social activities and interpersonal relationships. However, until now relatively little attention has been paid to the relationship between these domains. How do they influence each other? For example, the individual judgement of the impact of the same symptom may vary widely and is most probably related to other personal factors (coping) as well as sociocultural factors and several resources (among others, economic resources, social support, and appropriate health care). This may hamper a good interpretation of HRQOL data, and may limit the usefulness of HRQOL data as an outcome measure in cancer treatment. Therefore, there’s a need for research programs which investigate the relationship between the different domains. If the outcome in one domain is influenced by the nature of another domain, the final HRQOL outcome should be corrected accordingly. As a result new models may be needed that can provide the proper corrections in these assumed relationships. On the other hand, this research may produce models that identify and link independent variables to patient-assessed individual patient’s factors.
with HRQOL assessment. Such models will facilitate the development of interventions that incorporate individual patient’s factors with HRQOL assessment. These models are more likely to give a sound view of the real impact of the disease and its treatment on HRQOL.

Secondly, the question how HRQOL should be measured is addressed. There is enough evidence in the literature that HRQOL should be assessed in a prospective manner, including pre-treatment measurements, using validated questionnaires, self-administered by the patients, and analysed anonymously. It is discussed how questionnaires meant to measure HRQOL should be developed in order to get them well validated. An overview of the existing instruments is presented. The question if HRQOL assessment might be, theoretically, a relevant endpoint in clinical studies is explored. It is concluded that HRQOL assessment in general might be important in evaluating (relatively) new treatment modalities, when treatment itself has side effects (positive or negative), or when a new or different treatment has little or no impact on survival. Methodological problems such as missing items and compliance are addressed. Moreover, the issue of statistically versus clinically relevance in HRQOL research outcome is discussed. What is the clinical meaning of a statistically significant difference of 6 points on a scale running from 0 till 100. In the literature are only a few articles addressing this issue. In fact the interpretation of results remains essentially quantitative. Clinical significance is subjective and a matter of opinion. Based on the present data and the variety of personal opinions, it is unlikely that a single threshold value will be universally accepted as a cut-off point that separates clinically important changes from trivial and unimportant ones. However, many investigators agree that a change of 5–10 points on the 1 to 100 scale may be interpreted as clinical significant. Finally, the question how to incorporate HRQOL outcome in therapeutic decision making for the individual patient is discussed. There are two models developed trying to combine objective clinical data with HRQOL outcome; the multi-attribute utility theory (MAUT) and the Quality Adjusted Life Years (QUALY). Notwithstanding the existence of these models, and in absence of a widely accepted golden standard, the incorporation HRQOL results in clinical decision making still remains difficult and will mostly depend on the personal view of the physician.

Chapter 3 contains an extensive review of the literature. The objective of this review was to answer the question, what have we learned from the research on HRQOL in prostate cancer so far? A PubMed research was performed using the keywords ‘prostate cancer’ and ‘quality of life’. Of the 854 citations only abstracts in English dealing with structured HRQOL research were selected (630). Only 54 of these report about longitudinal studies, including pre-treatment measures and using validated questionnaires. The results of these studies can be summarised as follows;

Radical treatment: Radical prostatectomy (RP) has only a minor effect on the overall HRQOL. There are fluctuating reports on continence and erectile disorder, varying from 7%-39% for incontinence and 14%-69% for erectile dysfunction. The loss of erection can cause permanent distress, especially in younger preoperative sexual active patients. Overall 85% of the patients would choose RP again. External radiation therapy (ERT) hardly has any significant impact on the HRQOL in the long term. In time it leads to limited gastrointestinal and urinary problems and decreased sexual function; 90% would choose ERT again. The few studies comparing RP with ERT show that surgically treated patients suffer more incontinence and erectile dysfunction and ERT patients more bowel irritation, while no differences were demonstrated regarding general HRQOL domains. Adequate data about the impact of interstitial radiation therapy on HRQOL are not available yet

Hormonal treatment. The impact of an LHRH agonist and orchietomy on HRQOL are comparable. Patients treated with maximal androgen blockade (orchietomy + flutamide) report a worse overall HRQOL, more diarrhea, and a more deteriorated emotional function compared with patients only treated with orchietomy. Comparative studies of hormonal monotherapy versus castration (medical or surgical) showed no differences, except for sexual interest and physical capacity in favour of the monotherapy. A few groups have studied the effect of immediate versus delayed hormonal treatment. It turned out that in comparison with patients receiving no treatment, hormonally treated patients report more hot flushes, more fatigue, more loss of energy, more emotional distress, a worse sexual function, and a worse overall HRQOL.

Treatment for hormone resistant disease. Only two therapeutic strategies have a positive impact on HRQOL. First the combination of ERT and Strontium, while to date the combination of Prednisone
and Mitoxantrone is considered as the golden standard because it showed the best (temporarily) improvement in disease-specific and general HRQOL domains.

In Chapter 4 the quality of the HRQOL research in randomized controlled clinical trials (RTC) is reviewed. 25 RCT’s were identified, involving 8015 patients primarily with metastatic cancer. Bicalutamide was the medical treatment against which most treatment comparisons were made. Limitations identified included, only 44% of the studies gave a rationale for selecting a specific HRQOL measure, 64% of the studies failed to report information about the administration of the HRQOL measure, and 56% failed to report compliance at baseline. Only 13% stated a ‘a priori’ hypothesis. The measure most often used was the EORTC QLQ-C30, although some studies used non-validated HRQOL tools. This review revealed the lack of a uniform approach to HRQOL assessment, even in RCTs, as well as several methodological limitations. It is conceivable that such methodological limitations have influenced trial findings as for HRQOL outcomes. Again the results of the HRQOL research were disappointing, which emphasises the plea for the worldwide standardisation of HRQOL research.

Chapter 5, 6 and 7 all deal with the results of a study we conducted in the Amsterdam region in men suffering from localized prostate cancer treated with radical prostatectomy or external radiation therapy. Finally, 138 men participated in this study. All relevant clinical characteristics were administered. Moreover, before treatment and after 12 months all men filled in an extended questionnaire in order to assess HRQOL and psychosocial factors (PF). This extended measure was constructed of existing questionnaires which were almost all validated. It consists of the following instruments;

Sociodemographic characteristics: We examined the patients’ age, level of education, marital, ethnicity (open question), and employment status.
Social desirability: This refers to the tendency that subjects are guided by what they consider socially desirable in responding to test questions, and do not give the same answers as they would when they tried to be as honest as possible.
Health Related Quality of Life: The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ C30) consists of 30 items that list the functioning and symptoms of cancer patients.
Micturation symptoms: The International Prostate Symptom Score (IPSS) was used in order to measure micturition symptoms.
Incontinence: To measure the severity of urinary incontinence, an instrument developed by Van Vierhouten has been used.
Sexual functioning: Sexual functioning was measured by a newly developed scale, consisting of items from the Sexual Behavior Questionnaire as described by Derogates, as well as items adopted from a questionnaire developed by the Dutch Social Sexuological Research Institute (NISSO).
Gastrointestinal symptoms: A self constructed Dutch questionnaire based on the EORTC colorectal module (CR38) was used for measuring gastrointestinal symptoms.
Coping style: The coping style was measured by the standardized Utrecht Coping List (UCL). The dimensions are: active coping palliation, distraction, seeking social support, denial, expression of emotions, and cognitive adjustment.
Psychological distress: To measure the psychological distress, the Profile of Mood States (POMS) has been used, including the following dimensions: depression, anger, fatigue, vigour, tension, and a total mood disturbance score.
Impact of having prostate cancer: A Dutch version of the Impact of Event Scale (IES) has been used to measure the emotional impact of having prostate cancer.
Expression and non expression of emotions: The expression and non-expression of emotions were measured by a Dutch validated questionnaire. The dimensions includes rationality, emotions-in, emotions-out, and emotional control.
Social support: The level of social support was measured by the Dutch version of the shortened Social Support Questionnaire (SSQ) developed by Sarason.
Life Events (LES): The Dutch version of the Life Experience Survey (LES) has been used, developed by Sarason. The LES score concerned 40 potential life events during the last 12 months.
In Chapter 5 the possible correlation between the measured HRQOL and PF is explored. Important psychosocial factors representing the psychological and social health status in oncological patients are stress, social support, emotional expression, and coping strategies. Stress concerns the level and number of experienced stressful life events, such as the loss of a partner. Social support means the level and quality of support of relatives, friends, and formal caregivers. By emotional expression is understood the ability to acknowledge and express emotions, while coping style involves the efforts to appraise and manage a situation (e.g., distraction from it, active coping, denial, and cognitive adjustment).

Studies concerning other areas than prostate cancer showed evidence that the experienced HRQOL is influenced by PF. The objective was to explore whether the assessed baseline HRQOL of patients with localized prostate cancer scheduled for radical prostatectomy or external radiation therapy was also correlated with psychosocial factors. First, the results showed that the assessed HRQOL is strongly correlated to age and socioeconomic status. Moreover, there turned out to be several significant correlations between HRQOL and PF. Denial as coping style, fatigue as mood state, and the number of experienced negative life events (stress), among other things, were negatively correlated to almost all general HRQOL function scales. Avoiding was positively correlated with sexual dissatisfaction. It was concluded that the experienced general and disease specific HRQOL in prostate cancer patients scheduled for primary treatment were correlated with several psychosocial factors. Further research, among larger, heterogeneous groups of patients in a longitudinal design, has to establish the precise features of this correlation as well as the extent to which they influence the measured HRQOL. The results of these studies may prove that, in non-randomized studies, it is necessary to take the influence of psychosocial factors into account, in order to measure the real impact of a therapy on the HRQOL.

Given the fact that there is evidence that the assessed HRQOL is influenced by PF as stated in chapter 5, knowledge of the baseline HRQOL and PF profile of two groups of patients under comparative study might be interesting. Because if pre-treatment (baseline) HRQOL and PF measures of two treatment modalities vary, this should be taken into account when evaluating the impact of the therapy on the post-treatment HRQOL in non-randomized studies. In Chapter 6 we investigated whether baseline HRQOL and psychosocial profile differ in prostate cancer patients scheduled for radical prostatectomy (RP) or external radiation therapy (ERT). The results showed that patients scheduled for ERT were 7.9 years older (p<0.001), had a lower socioeconomic status (p<0.001), showed more frequently stages T3 and T4 (p<0.01), poorer histopathological differentiation (p<0.01) and higher levels of PSA (p<0.01). Moreover, they reported a worse physical, role, cognitive and social function, more fatigue, more pain, a lower overall HRQOL and a worse sexual function, compared with patients scheduled for RP. No differences were found for urinary and bowel function, nor for the assessed psychosocial factors. Based on the results of the present study, it is concluded that the baseline HRQOL profile of patients scheduled for RP is better than that of patients scheduled for ERT. These results are in line with the results of the few other studies about this subject. Knowledge about the real impact of RP and ERT on the HRQOL, therefore, should be based mainly on longitudinal studies including baseline measures, the analyses of which should be adjusted for age and socioeconomic status. In the small present study, baseline PF did not differ between both treatment modalities. However, this could be due to the small sample size in which a statistically significance was not reached.

In Chapter 7 we compared the impact on the general and disease specific HRQOL of external radiation therapy with radical prostatectomy in patients with localized prostate cancer, and we explored which factors, and to what extent, contribute to the assessed changes in HRQOL 12 months after therapy was executed compared with pre-treatment assessments. To this end among other things, multiple regression analyses including all baseline characteristics, HRQOL and PF, were executed. The RP patients demonstrated significantly more improvement in their emotional function, while they report more incontinence, and a worse sexual function. Improvement in the overall HRQOL was significantly better in ERT patients, while the changes in the gastrointestinal function of these patients were significantly worse. Only the differences with respect to incontinence can be attributed to the treatment itself. Almost all HRQOL change scores are influenced the most by there
Patients with lymph node positive prostate carcinoma can't be cured. The first line palliative treatment is hormonal therapy. The best time to start this hormonal treatment is as yet unknown. Knowledge about the impact of this treatment on the HRQOL is therefore essential. In Chapter 8 the impact of androgen deprivation on HRQOL in patients with asymptomatic lymph node positive prostatic carcinoma (LPPC) is examined. HRQOL domains were measured, using standard instruments in 91 patients with histologically proven LPPC. Most patients were randomized for immediate or deferred hormonal treatment until progression was observed. For analyses concerning the time to progression and survival, the Kaplan-Meier method was used. Patients treated with androgen deprivation showed a significantly worse sexual, emotional, and physical function, experienced more hot flushes and a worse overall HRQOL, compared with patients receiving no therapy. Time to progression was significantly shorter in the deferred treated patients in comparison with the immediately treated patients (33 vs 62 months, p<0.001). No significant differences were found with respect to the duration of survival. We concluded that hormonally treated patients with asymptomatic LPPC have a worse HRQOL compared with patients receiving no therapy. The duration of survival was similar, whether patients received immediate or deferred hormonal treatment. Nowadays, with patients' preferences playing an increasingly important role in therapeutic decision making, physicians should be aware of this negative impact and ought to inform the patients on this.

The optimal, palliative treatment of patients with metastatic hormone resistant prostate cancer (HRPC) is still investigational. In Chapter 9 we studied the effect of Epirubicin combined or not combined with Medroxy Progesterone Acetate (MPA), in this particular patient group. The aim of the study was to investigate the feasibility of the HRQOL measurement and to ascertain whether MPA added to Epirubicin produces a better HRQOL than Epirubicin alone. Of the 28 randomised patients with symptomatic metastatic HRPC, 26 were eligible. Fourteen of them received Epirubicin intravenously 100mg/m² every three weeks in combination with MPA orally 500 mg twice a day. Twelve patients received only Epirubicin. For the HRQOL assessment the Rotterdam Symptom Checklist (RSCL) was used. Toxic side effects of chemotherapy were assessed by the 'WHO' criteria. Subjective response includes performance status and pain score. Compliance to complete HRQOL questionnaires was high (87.5%). Of the HRQOL domains studied, none of the patients, irrespective of their treatment, experienced an improvement in their HRQOL. Moreover, after 12 and 24 weeks patients in both treatment arms experienced significant worsening of physical symptom distress when compared with study entry. Toxicity was moderate to severe. Biochemical response (drop of PSA by more than 50%) was observed in 5 out of 26 patients (19.1%) and subjective response in 7 out of 26 patients (26.9%). The median survival for all patients was 30 weeks. There was no statistically significant difference between the two treatment arms. Performance status and the global quality of life as judged by the patients themselves are associated with duration of survival. No relation was found between initial observed subjective response and survival. In conclusion, the feasibility to measure HRQOL in patients with symptomatic AHRPC is demonstrated in the present study. Subjective and biochemical response was observed in both treatment arms, but this was not translatable to improved measured HRQOL domains.

The primary objective of the study presented in Chapter 10 was to compare the effect on the HRQOL of Epirubicin 100mg/m² (Epi100) administered in a 4 weekly intravenous regimen to that of Epirubicin 25 mg/m² (Epi25) administered in a weekly intravenous regimen in patients with hormone resistant prostatic cancer. Moreover, subjective, and objective responses, as well as the disease-specific survival were studied. 87 patients took part in this randomized study of which finally 79 patients (38 Epi25 and 41 Epi100 patients) were evaluable. For the assessment of the HRQOL, the EORTC-QLQ-C30 was used. Subjective, biochemical and bonescan responses were monitored. Toxic side effects of chemotherapy were assessed by WHO criteria. HRQOL assessment and monitoring
were performed before treatment and every four weeks after the start of treatment. None of the patients in the Epi25 group nor in the Epi100 group experienced a change in the overall HRQOL or in any of the HRQOL function scales. Statistically significant changes were found in the HRQOL symptom scales only. Compared with baseline, patients treated with Epi25 reported less pain during the first 3 months. Patients treated with Epi100 reported more dyspnoea after 4 weeks, whereas after 8 weeks they experienced less pain, less insomnia but more loss of appetite compared with the assessment at baseline. In both arms the toxicity was similar, except for a statistically significant difference in WHO grade II-III alopecia in 82% in the Epi100 group versus 31% in the Epi25 group.

There were no significant differences between the two treatment arms with respect to response rates and disease specific survival. In conclusion, both therapeutic regimens showed comparable response rates. However, the observed responses did not result in an improved HRQOL. This observation is in line with other studies using single agent Epirubicin. Therefore, Epirubicin, as single agent therapy, should not be used in future treatment of patients with advanced hormone resistant prostate cancer anymore.

Patients with metastatic hormone refractory prostate cancer (HRPC) are often viewed as an homogeneous group with median overall survival lasting about ten months. The identified prognostic factors in metastatic HRPC patients are biochemical (baseline Prostate Specific Antigen [PSA], Lactate Dehydrogenase, Alkaline phosphates, Haemoglobin, Creatinine), objective (number of bone metastases, duration of response to primary hormonal treatment, age), or subjective (performance status [PS], disease related symptoms). HRQOL measurements have rarely been considered as potential prognostic factors in this disease. Objective of the study presented in chapter 11 was twofold. First, to explore whether it was possible to identify HRQOL domains with independent prognostic value for the survival. Second, to perform a prognostic factor analysis in order to develop risk groups that could distinguish patients with a relatively good prognosis from patients with a particularly bad or particularly favourable prognosis. The data from 391 metastatic HRPC patients randomized in three EORTC trials (30903, 30921, 30944), were used. The 15 scales from the EORTC QLQ-C 30 (version 1.0) and ten baseline clinical and biochemical variables were considered. Univariate and multivariate Cox proportional hazard models stratified for trial and treatment were used. It turned out that insomnia, dyspnoea and appetite loss, bone scan result, performance status (WHO PS) and haemoglobin level were independent predictors of survival in the multivariate analysis. Based on these 6 factors, a prognostic index (PI) was computed. The patients could be classified into three groups: good prognosis (PI 0-2: 29,8%) with 17,8 months median survival, intermediate prognosis (PI 3-4: 43,8%) with 11,1 months median survival, and poor prognosis (PI≥5: 26,4%) with a median survival of 5,4 months. In conclusion, HRQOL domains (dyspnoea, appetite loss, insomnia), as measured with the EORTC QLQ C30, turn out to be of independent predictive value with regard to the survival of patients with metastatic HRPC. It was possible to construct a clinically easy to use model containing the number of bone metastases, Haemoglobin, WHO performance status, dyspnoea, insomnia and appetite loss, which can distinguish between patients with a good, an intermediate, and a poor prognosis. This model remains to be validated on an independent dataset and a comparison to other prognostic models not including HRQOL factors is needed to determine which model is best. Prognostic models and risk groups, however, should be used in order to treat and inform patients efficiently and to select patients with homogeneous (good) prognosis for inclusion in future clinical trials aiming to improve survival in HRPC.

Final conclusions and future perspectives
Nowadays, it is clear that the research into HRQOL has definitively found its place within the field of research on patients with prostate cancer. Yet, we should be aware that this research is still very young. This is shown by, among other things, the results of the reviews as presented in the chapters 3 and 4. Actually, we have to conclude that these 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 available results show every sign of a collection of single institution experiences. There is a lot of work to be done, especially concerning the unambiguous use of HRQOL questionnaires. An international questionnaire, available in many languages and cross-culturally validated, should be
developed, addressing all the specific problems a prostate cancer patient can encounter. Moreover, one will also have to establish which statistical differences in the assessed HRQOL will be widely accepted as clinically significant.

Finally, further research is needed into the relationship between several psychosocial factors and the assessed HRQOL. Apart from a study of Eton and the study described in this thesis, there has hardly been any research into this subject among patients with prostate cancer. While there is proof of a correlation between the two in cross-sectional studies, in the literature, no longitudinal studies has been executed about the influence of psychosocial factors on the changes in the measured HRQOL. The results of the research described in this thesis show that the influence of psychosocial factors on the measured HRQOL in a multiple regression analysis is limited. We should realise, though, that this research only concerns a small group of patients. It's very well possible that this influence does become clear when studied among larger groups of patients. Therefore, this research should be conducted, since knowledge concerning the influence of the psychosocial factors on the measured HRQOL is vital for a sound interpretation of the results of a HRQOL assessment.

Given the methodological problems, it isn't surprising that the results of HRQOL research aren't considered as a solid clinical endpoint yet. For instance, these results never have been included in the formulation of (inter)national guidelines on prostate carcinoma. It's neither surprising that, among clinics, there's a certain scepticism about the clinical applicability of HRQOL research, despite the fact that the additional value is endorsed widely, in theory. It's clear that this scepticism should be overcome, not only in the interest of the patient, but also in that of the clinicians themselves. Hence my plea in favour of the implementation of a worldwide standardisation of HRQOL research in prostate cancer. This standardisation particularly involves the instruments used for measuring HRQOL, the study design and power, the timing of data collection, compliance, the statistical analysis, and the presentation of the results. Only then, we can really put HRQOL on the map as a valuable tool for use in daily clinical practice, as well as a solid endpoint of clinical trials. An instrument comparable to, for example, PSA response, time to progression, and survival. Yet, there's a long way to go until this goal will be achieved.