

Quality of life in patients suffering from prostate adenocarcinoma. A global approach

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Prostate cancer is a major health concern for Western men patients who are facing important decisions, alongside with the physicians, concerning their treatment. Additionally the physician has to take into account the potential side effects of the disease and the treatment itself. Treatment for advanced prostate cancer produces problematic physical and psychosocial side effects having subsequently a significant impact upon the patients' quality of life (QoL). The patient should be asked by the physician for information concerning daily life activities, overall satisfaction voiding ability and sexual activity in a standardized questionnaire assessing the QoL of the patient. The EORTC-GU has conducted multicenter, multinational and intercontinental trials, disseminating their results via workshops, congresses and symposia. Other questionnaires such as the SF-36, McGill and others assess the QoL of a patient sufficiently responding in parallel to the changing needs of a specific population, taking into account characteristics including poor performance status, difficulty with longitudinal study, rapidly deteriorating physical condition. Generally speaking many such questionnaires and studies have been evaluated or are still in progress regarding cancer patients and even less specifically for advanced prostate cancer. Modern QoL questionnaires are considered to be more than a necessity nowadays for the improvement of the treatment administered from the physician and the performance and functional status of the patient. *Hippokratia* 2005, 9 (1): 7-16

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Prostate cancer is at this moment in Europe the second most common site of cancer affecting males and has recently been reported to be the most common cancer among American men¹. The mortality rate due to prostate cancer has increased in most countries characterizing this cancer as the second leading cause of death in male and thus an important health care problem in many countries. Although the reason for the increase in incidence is unclear, factors such as improvement in screening techniques, greater incidence of the disease with advancing age and the increasing distribution of elderly men in Western cultures as well as the changes in social habits and in racial populations may play a role¹. Prostate cancer will be diagnosed in an estimated 230,110 men during 2004². There will also be approximately 29,900 men who will die from prostate cancer this year. While early detection and improved treatments have resulted in improved 5-year survival rates for individuals with early stage prostate cancer (recent data have put the 5-year survival rates at 100% for men diagnosed with local and regional prostate cancer), there remains a proportion of men (roughly 14%) who will be diagnosed with advanced prostate cancer. For these individuals, the 5-

year survival rate is much lower. Indeed only 34% of men diagnosed with distant disease will survive for 5 years³. Due to a greater awareness and better methods to diagnose prostate cancer at an early stage (PSA, sextant/octant transrectal ultrasound-guided biopsies) a stage shift has been observed in the past 3–5 years. In the 1980s approximately 70% of the patients presented with locally advanced or metastatic disease and this percentage has now decreased to 20%. This change will also have implications on the type of studies to be designed⁴.

Traditional evaluation end points frequently used in clinical cancer research or trials, (e.g. length of disease-free and overall survival, control of symptoms, frequency of loco-regional recurrence, time to disease progression or development of metastases) have not covered until recently, subjective parameters reflecting the patients own view of his condition except those related to clinical symptomatology and the performance status of the patient. Yet such parameters despite being of clearly subjective nature seem to be of utmost importance to the patients as representing their personal views regarding their condition. This overall perception of the patients as far as their condition is concerned has been termed

quality of life (QoL) assessment. In oncology research, quality of life (QoL) has been identified as the second most important outcome, with survival being the most important. The integration of QoL assessments into clinical practice and research presents some unique challenges. The life of patients with metastatic prostate cancer is compounded by the potentiality of development of a series of adverse effects due to the disease itself or the treatment administered. Unfortunately, such patients who have to face a life without the likelihood of a cure have to face also such uncertainties, which have a strong psychological impact upon the quality of their lives.

The evaluation of health status covers many domains such as physical and emotional status, intellectual and psychological status, social status as well as an overall sense of well being. Many rating scales have been developed (specific or non-specific to the disease involved) for the measurement of the health status in a variety of clinical situations. Providing sound QoL data to healthcare professionals and patients is essential to enable truly informed decision-making.

Quality of life

In general

Traditionally, clinicians have mainly focused their attention on the classical aspects of the evaluation of cancer treatment outcome, such as control of symptoms, response to treatment, relapse and survival. 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 and their participation in decision making, have increasingly been recognized⁵. This intriguing issue- the patients participation to the physicians decisions-should not be regarded as a paradox, since QoL is a multidimensional construct and its assessment covers much more than the simple estimation of treatment – and disease – related morbidity and is based upon the patients' personal experience and evaluation of his total life situation⁶. Certain studies have shown that patients' subjective morbidity is frequently overestimated or underestimated by treating physicians⁷⁻⁹. Regularly performed, patient completed, psychometrically oriented and tested questionnaires constitute a reliable, valid, practical and effective way of assessing patients' morbidity and the impact of symptomatology on their QoL. Advanced prostate cancer and its treatments have the potential to cause substantial morbidity in affected individuals thus prostate cancer has been the subject of great interest for quality of life researchers. Modern HR-QoL research should assess prevalence and severity of symptoms or functions, as well as the bother that symptoms or changes in functions inflict and whether this bother affects the overall well-being of the patient¹⁰. In the prostate cancer field, HR-QoL assessments have evolved rapidly during

the last decade. The importance of HR-QoL and associated research in prostate cancer is being more and more appreciated. Most published studies concern patients with early prostate cancer; studies in patients with late advanced stages are less frequent. Changes in functions, for example those associated with anxiety and treatment adverse effects such as changes in sexual, urinary and bowel functions often affect HR-QoL in patients with more advanced local stages of prostate cancer or metastatic disease¹⁰.

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: worry for prostate cancer and its prognosis, bone/pelvic pain, lower urinary tract symptoms, urinary incontinence, urinary diversion, bowel function, sexual function, endocrine effects (hot flushes and gynaecomastia), and satisfaction with medical care for prostate cancer^{11,12}. Previous studies of cancer patients have identified major concerns about obtaining accurate information, maintaining a sense of control, disclosing feelings, and searching for meaning. Gaining information is a way in which some patients regain a sense of control over their cancer and the circumstances surrounding it. Providing sound information has been shown to have several positive effects, including pain reduction, speedier recovery, increased participation in decision making, greater satisfaction with the consultation, and improved mental health and better coping skills. In addition, most patients do not wish to take a completely passive role in the doctor-patient relationship; they want some input into the decision making process. Enhanced patient participation may produce better outcomes, such as improved patient self-esteem and satisfaction; however, older, married, and less educated^{13,14} cancer patients may choose to delegate all decisions to their physicians. Studies of health-care providers have found that clinicians frequently underestimate their patients' wish for information and discussion, while overestimating patients' desire to make decisions^{15,14}.

Health related quality of life data are collected with survey instruments, which may be self-administered or require a trained interviewer. Some are completed at a medical facility, while others are completed independently at home or by telephone. To yield useful information, such instruments must undergo extensive pilot testing and be shown to have sound psychometric properties. This testing determines whether an instrument can produce data that are reliable or reproducible, and valid or meaningful. Health related quality of life instruments typically contain several collections of items, called scales, which apply to particular dimensions of quality of life. These scales contribute to a qualitative profile of the health-related components of the daily life of a subject. General health related quality of life measures include broad issues that concern many types of patients concerning their level of general QoL, while disease-

targeted measures address issues that are specific to the condition under study. Both are necessary to create a full and rich picture of patient quality of life^{16,17}. It is important to note that while conducting a QoL assessment study methodological problems and limitations should be considered. Firstly, because the sociodemographic characteristics differ between cohorts in various QoL studies the results are not always comparable¹⁸. Moreover low literacy considerations affect predominantly the study procedures and their interpretation. Self-administered QoL questionnaires are more vulnerable than those conducted in person with the participants in a clinic or by phone. Additionally, using a questionnaire that is easy to complete will minimize deficit values, and raise the accuracy data. Use of sample questionnaires will be useful in preliminary surveys¹⁷. Table 1 demonstrates some of the methodological problems that physicians face during a QoL evaluation in the elderly.

Forms of questionnaires

Several instruments are used for QoL assessment in prostate cancer, some of which have been specifically developed for, or adapted to, patients with this disease, such as the Functional Assessment Cancer Therapy (FACT) tool, Prostate Cancer Treatment Outcome Questionnaire (PCTO-Q), Prostate Cancer Specific Quality of Life Instrument (PROSQoLI)¹⁹, and the EORT QLQ¹⁷. EORTC QLQ and FACT are most often used in clinical research. The European Organization for the Research and Treatment of Cancer (EORTC) has chosen to base QoL evaluations on the implementation of a general core questionnaire in combination with disease specific and treatment specific modules. The QLQ-C30 (EORTC)²⁰ the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C30 consists of 30 items that list the functioning and symptoms of cancer patients²¹. Six multi-item function scales are scored: physical function, role function, emotional function, cognitive functioning, social function, and global health-related quality of life. Furthermore, nine single-item

symptom scales are scored: fatigue, pain, dyspnoea and gastro-intestinal problems. The scales are linearly transformed according to the EORTC guidelines—all scales range from 0 to 100, in which a higher scale score represents a higher level of functioning. With respect to the single-item scales, a higher score indicates more symptoms or problems⁵. Moreover, the Rotterdam Symptom Check List²² and the SF-36 (MOS Short Form 36 General Health Survey) questionnaires are well established to determine quality of life in cancer patients generally. For prostate cancer many disease-specific questionnaires are available. One is the prostate cancer module QLQ-PR25 with 25 questions highlighting side effects (voiding, bowel function, and sexual function) from prostatectomy, radiotherapy or antihormonal therapy²⁰. In the last decade, quality-of-life (QoL) assessment measures such as the McGill, McMaster, Global Visual Analogue Scale, Assessment of QoL at the End of Life, Life Evaluation Questionnaire, and Hospice QoL Index have been devised specifically for patients with advanced cancer²³. The developers of these instruments have tried to respond to the changing needs of this specific population, taking into account characteristics including poor performance status, difficulty with longitudinal study, rapidly deteriorating physical condition, and change in relevant issues. Emphasis has been placed on patient report, ease and speed of completion, and the existential domain or meaning of life²³. Novel techniques in QoL measurement have also been adapted for palliative care, such as judgment analysis in the Schedule for the Evaluation of Individual Quality of Life.

The RAND 36-Item Health Survey 1.0 (SF 36) HRQoL instrument is a self-administered, 36-item questionnaire that quantifies the general HRQoL using eight different multi-item scales: physical function, social function, bodily pain, emotional well-being, energy/fatigue, general health perceptions, role limitations due to physical health problems, and role limitations due to emotional problems²⁴. In addition, two summary scales, the physical (PCS) and mental (MCS) health composites, may be calculated to provide more global assessments of the HRQoL in those domains. The domains are scored separately from 0 to 100, with higher scores representing better outcomes. The SF-36 has been extensively tested and validated and has been shown to be both reliable and valid (test-retest reliability coefficients of 78% or more and internal consistency Cronbach's alpha coefficient²⁵ of 0.78 to 0.93 in various populations)²⁶. Additionally, sociodemographic and comorbidity data should be collected at the time of the baseline survey with a separate instrument that includes relevant questions and a medical history checklist based on an established comorbidity rating scale²⁷.

Another important QoL questionnaire is the Quality of Life Questionnaire designed by the European Organization for Research and Treatment of Cancer (EORTC QLQ C33)^{28,29}. This questionnaire has been

Table 1. *Methodological problems of Quality of Life (QoL) evaluation in the elderly*

- Higher proportion of illiteracy as compared to younger patients
- Presence of cognitive disorders with difficulty to understand QoL questionnaires
- Presence of comorbidities potentially confusing the real impact of cancer and treatment on QoL
- Use of QoL instruments needs validation in elderly patients
- Analysis of QoL data from subgroups of elderly patients enrolled in clinical trials without upper age limit suffer from selection bias.

developed for patient self-assessment of QL. It is a prior version of the current EORTC QLQ C30, and evaluates symptoms (e.g. pain, P: two items or fatigue, F: three items), physical function (PF: five items), psychosocial dimensions, social functioning (SF: two items), global health status and QL (two items). Originally, the EORTC QLQ C30 has been designed for prospective randomized trials in cancer patients but is today also used as a screening instrument in cross-sectional studies. There are, however, no generally accepted criteria for caseness. Recently, this questionnaire has been applied to describe QL in a "normal population" demonstrating the relationship between QL and age or gender³⁰.

Furthermore we should mention that sometimes measuring QoL using a single instrument implies a significant risk of underdiagnosis of significant side effects. We find many examples in the literature that show the use of more than one instrument for the evaluation of QoL components. In one study the authors assessed general and prostate-targeted HRQoL with two self-administered, validated instruments (the RAND 36-Item Health Survey and the UCLA Prostate Cancer Index) in a longitudinal, observational study of 63 men newly diagnosed with metastatic prostate cancer and treated with bilateral orchiectomy or combined androgen blockade with leuprolide and flutamide³¹. During recent years increasing attention has been paid to mental health among cancer patient. Due to the life-threatening illness and the other severe side effects of treatment, depression and anxiety represent common mental symptoms in oncological patients. Both symptoms were assessed in a study by using comparable results of two QoL instruments while in the meantime the relation between these two instruments, by comparing patients' responses, was evaluated. This study used the emotional functioning (EF) dimension of EORTC QLQ C33 and the Hospital Anxiety and Depression Scale (HADS), HADS-D (depression) and HADS-A (anxiety) to evaluate anxiety and depression³².

QoL and advanced prostate cancer side effects

Prostate cancer is a major health concern for Western men, but little is known about its consequent impact on sexual function for men and their partners. The effect of the diagnosis and treatment of prostate cancer on sexual function as it affects men and their partners should be a subject of discussion³³. For men with advanced prostate cancer, the side effects of hormone treatments, such as hot flushes, impotence and loss of libido may also be accompanied by symptoms of disease progression, such as bodily pain and decreased vitality^{34,35}. Also such men report difficulties in domains of self-image and masculinity, relationships with their spouses, fears about cancer and treatment decisions³⁶. Thus there is a range of both physical and psychosocial difficulties that may be experienced by men with advanced prostate cancer and there is evidence that these concerns continue over time³⁷. Additionally some study findings, after

comparison of patient and spouse assessment of HRQoL suggest that the spouses of men with advanced prostate cancer evaluate with a fair degree of accuracy how patients experience physical and psychosocial functioning, symptoms and overall quality of life. However the same study advises caution to be exercised when relying on spouses for assessing sexual functioning and satisfaction³⁸.

The EORTC Genitourinary Tract Cancer Cooperative Group, in close cooperation with the EORTC Study Group on Quality of Life, designed a study in order to assess, among others, the QoL of patients with metastatic prostate cancer treated according to the EORTC Protocol 30853. In this randomised phase III trial the efficacy of orchiectomy was compared to that of the combination of an LHRH depot analogue with flutamide (a pure non-steroidal antiandrogen) in patients with metastatic prostate cancer. Primary end points of this trial were the incidence and duration of response, time to progression and overall survival. As an optional assessment in the overall study, QoL evaluation was undertaken, so that the impact of these two treatment modalities on the daily lives and function of the patients could be estimated³⁹.

Thus, a 30-item questionnaire was developed in order to assess: i) personal functioning, ii) social role functioning, iii) symptomatology, iv) fatigue and malaise, v) psychological disturbances, vi) psychological distress, vii) sexual dysfunction, viii) disruption of family or social life. Most of the above items and scales of the questionnaire had established levels of reliability and validity since they had been previously used within the context of several EORTC trials. Questions regarding prostate cancer specific symptoms were developed specifically for this trial. The whole questionnaire was designed to be totally self-administered (i.e. not requiring any outside assistance except clarifications and provision of help for its completion, due to the advanced age of many of the participating patients). The incorporation of a QoL component in this trial would indicate whether psychosocial research parameters could be integrated within the structure of a clinical trial, a hypothesis which if proved successful, would lead to a much better understanding of the sequelae of metastatic prostate cancer on human/psychosocial level and would contribute greatly to the identification and implementation of therapeutic approaches, that would suit best the well being of these patients and also improve their clinical outcome. Moreover, the answers obtained show that clinically significant and therapeutically relevant valid information can be obtained by the completion of QoL questionnaires. For example, one important conclusion is that large variations exist between the physicians and the patients' evaluation regarding the performance status and the potency (sexual) status of the patient and that these parameters can better assessed by patients themselves³⁹.

An important fact that emerges is the need for

development of a better scoring system for the evaluation of pain by the physician. The current system of pain evaluation that is based on the use of analgesics, their type and their doses, seems inadequate because it does not indicate whether effective pain relief has actually been achieved. A current study evaluated the analgesic activity and impact on quality of life (QoL) of a new chemotherapy regimen of calcitriol and docetaxel in men with androgen-independent prostate carcinoma. Analgesic response was defined as a 2-point reduction on the Present Pain Intensity (PPI) scale (or complete relief if baseline PPI was 1) without an increase in analgesic use or a 50% decrease in analgesic medication use without an increase in pain, maintained for = 4 weeks. Pain, pain medication consumption, and QoL (measured by the European Organization for Research and Treatment of Cancer QLQ-C30) were evaluated every 4 weeks. Treatment resulted in an analgesic response in 14 of 29 evaluable patients. Worsening in physical and role functioning, fatigue, appetite, and global health status and improvement in constipation were detected using the QLQ-C30 QoL questionnaire. Significant analgesic activity was demonstrated, although worsening in several QoL domains was observed in a patient population with relatively low pain intensity (median PPI, 2)⁴⁰. In one study patients were asked to identify three troublesome symptoms on the McGill QoL and on the Palliative Care Outcome Scale (POS) two main problems. They use a group of day care patients and a comparison group. The symptoms and problems identified by both patient groups on the two QoL questionnaires were similar. In both patient groups, pain was the main problem at baseline interview and the most frequent other symptoms were tiredness and weakness at follow-up interviews. In the comparison group, breathlessness was also identified as a problem. More day care patients appeared to identify financial, social, or family problems at each interview than the comparison group. This difference was not significant. The problems identified ranged from filling in forms, thinking about the future and waiting for social services⁴¹.

Another study investigated the support and psychological care needs of men with prostate cancer. Patients were approached during urological oncology clinics and asked to complete the: Support Care Needs Survey (SCNS), Support Care Preferences Questionnaire, EORTC QLQ-C30 (Version 3) Measure plus Prostate Module, and the Hospital Anxiety and Depression Scale (HADS). There were 210 patients that met the entry criteria for the study. The data showed that significant unmet need exists across a number of domains in the areas of psychological and health system/information. The more commonly reported needs were "fears about cancer spreading (44%)", "concerns about the worries of those close to you (43%)", and "changes in sexual feelings (41%)". Half of all patients reported some need in the domain of sexuality, especially men younger than 65 years. Needs were being well met in the

domain of patient care and support. A significant number of patients reported having used or desiring support services, such as information about their illness, brochures about services and benefits for patients with cancer (55%), a series of talks by staff members about aspects of prostate cancer (44%), and one-on-one counselling (48%). Quality of life (QoL) was most negatively impacted in those who: were = 65 years old, and had metastatic disease. Men = 65 had decreased social functioning, greater pain, increased sleep disturbance, and were more likely to be uncomfortable about being sexually intimate. Patients recently diagnosed had increased fatigue, more frequent urination, greater disturbance of sleep, and were more likely to have hot flushes. Those with advanced disease scored lower on 12 out of 15 QoL categories. Men with advanced disease had greater levels of depression and those = 65 years old were more likely to be anxious⁴².

Additionally, anaemia is a frequent finding in patients with prostate cancer. Reduction of erythropoiesis caused by androgenic blockade is among its aetiologies. Therefore, quality of life of these patients' results decreased, being origin of significant morbidity and mortality. Recombinant forms of human erythropoietin have demonstrated their effectiveness improving quality of life of patients with various solid tumours, but specific studies in prostate cancer are a few. Evaluating the efficacy of human recombinant erythropoietin (EPO) in correction of anaemia and improving the quality of life of patients with prostate cancer, led to the conclusion that the administration of EPO increases significantly the levels of haemoglobin and the quality of life of patients with prostate adenocarcinoma, being the response worse in patients with low levels of baseline haemoglobin⁴³.

The importance of a correct diagnosis and treatment of depression in advanced cancer is underlined by the strong relation between depression and global health status and the other QoL dimensions. Several investigators have also pointed out a strong association between depression and fatigue in cancer patients^{44, 45}. Studies observed that depressed patients often display a poor cognitive function. In daily oncological practice only limited attention is paid to the relation between cognitive function and depression. This is strange, because the psychological literature about cognitive function in depressed patients is substantial. Though statistically significant, the relation between anxiety and the different QoL issues is much weaker or absent (fatigue) than the association with depression⁴⁶. If we consider mental distress of major interest in screening studies among cancer patients, a more suitable questionnaire, than those that already exist, for assessment of depression should be used.

The experience from EORTC trials 30853(8,) and the 30865^{47, 48} as well as from current medical literature and clinical experience indicate that a general QoL Questionnaire can be combined successfully with a

prostate cancer specific module. Within such an extended QoL questionnaire a variety of issues such as micturition, sexuality, vitality, fatigue, hot flashes, gynaecomastia, bone pain and physical, emotional and social function can be assessed and their impact evaluated. Questions addressing the above mentioned issues are currently being used in the prostate specific modules in ongoing EORTC prostate cancer trials. However, more extensive psychometric testing and psychosocial data collection is considered necessary for the development and the final refinement of a valid, reliable and clinically meaningful (both objectively and subjectively) prostate cancer questionnaire. The implementation of such measuring instruments is feasible only if there is sufficient interest and motivation among the medical and paramedical personnel and adequate resources are available.

QoL and treatment of advanced Prostate cancer

Prostate adenocarcinoma is still often detected at an advanced stage, despite efforts for earlier diagnosis. Treatment depends especially on the stage of the disease at the time of diagnosis, on potential development, which varies among types of tumours, on the presence of symptoms related to local-regional or general dissemination, and on age, which may be advanced in these patients. In the presence of metastases hormonal control is the best means of slowing disease progression. The various means of hormonal treatment (surgical castration, LH-RH agonists, anti-androgens) should be considered with regard to the status of the patient, the manifestations of cancer and potential side effects of treatment^{49,50}. In some cases, for the same stage of disease different treatment strategies do not impact differently on overall survival (OS). This makes the choice between treatments offering similar survival but different toxicity patterns, body and behavioural consequences more difficult. Quality of Life (QoL) is considered a reasonable end point when differences in OS do not seem to be striking. Men with advanced prostate carcinoma are faced with important treatment decisions and quality of life (QoL) information has become a crucial element of decision making⁵¹.

In patients with advanced disease, research has recently focused on using chemotherapy for symptom management and palliation. Several chemotherapeutic agents reduce pain and fatigue, although the development of fatigue is often the dose-limiting factor of some agents. Chemotherapy is also being explored as adjuvant therapy in men with early stage disease where length of survival may be lengthened by its administration. In both cases, but particularly among men receiving chemotherapy as treatment for advanced cancer, the effect that chemotherapy may have on quality of life is extremely important. This QoL includes not only the individual's physical well-being, but their mental well-being, role functioning and levels of emotional distress as well⁵². It is remarkable the fact that in the literature there is little concern regarding issues such as

emotional distress, depression and anxiety that an advanced prostate cancer patient may experience during or after treatment. There is an overwhelming lack of information concerning for example the emotional functioning of chemotherapy treated patients. It is hard to believe that such patients who are receiving a palliative care, are frequently androgen deprived and have a short life expectancy are not experiencing some emotional distress. Additionally regarding other post-treatment symptoms several studies exist. In the literature we find some that assess the impact of chemotherapy on pain. One study randomized 161 hormone-resistant prostate cancer patients either to prednisolone or prednisolone plus mitoxantrone. The goal was to determine the impact on pain reduction as a palliative endpoint. Also included was the overall assessment of QoL using the EORTC QLQ-30 and a specific prostate cancer QoL measure composed of nine analog scales. The results demonstrated that the addition of mitoxantrone to prednisolone reduced pain in 29% of patients compared to 10% for those who only received prednisolone. Improvements in pain, mood, and physical activity were also observed on the QoL measures for the individuals who received mitoxantrone. Additional analyses from this study revealed that after six weeks of treatment, pain and physical functioning remained improved in the mitoxantrone plus prednisone group. Moreover, after 12 weeks of treatment, overall quality of life in this group was improved, as was quality of life in four functional domains and nine specific symptoms⁵³. Pain was also assessed in several other studies utilizing different chemotherapeutic agents alone or in combination to each other such as mitoxantrone^{53,54}, docetaxel⁵⁵, and docetaxel+estramustine^{56,57}. In all the abovementioned studies the utilization of chemotherapy improved the overall QoL. Mean pain scores on quality of life scales were reduced over the course of treatment. The overall point, of the evaluation of the treatments according to patients' QoL, is that for prostate cancer patients with advanced disease, exists a variety of chemotherapeutic agents that have beneficial palliative effects and specifically a reduction of pain (Table 2).

Prostate carcinoma and its treatment have been associated with adverse effects on health-related quality of life (HRQoL). Individual differences in appraisal and coping have been suggested to mediate these HRQoL outcomes⁵⁸. Metastatic prostate cancer is an incurable disease with a median survival of patients is 3 years. Prostate cancer is a hormone-dependent cancer and androgen blockade is the most active treatment. However, hormone resistance occurs after a median interval of 2 years. The major symptom is pain; others are urinary obstruction, neurological complications of bone metastases and haematological disorders. Other treatments are radiotherapy radio-pharmaceutics and chemotherapy as we have already mentioned⁵⁹. Nevertheless the most important treatment issue still always remains quality of life. Respecting this demand a

Table 2. Review articles

Authors	chemotherapeutic agent	QoL measure	Direction of effect
Fuse et al, 1996 ⁶⁶	Cisplatin/carboplatin	Rating scale	Improved Pain
Tannock et al, 1996 ⁶⁷	Mitoxantrone	EORT QLQ-30, Pain rating	Improved Pain, mood and physical activity
Sinibaldi et al, 1999 ⁵⁶	Docetaxel	Brief Pain Inventory	Improved Pain
Small et al, 2000 ⁶⁸	Suramin	Brief Pain Inventory	Improved Pain
Copur et al, 2001 ⁵⁷	Docetaxel	Numeric rating scale	Improved Pain
Beer et al, 2001 ⁵⁵	Docetaxel	Present Pain Intensity scale	Improved Pain

study assessed and compared the quality of life of men with advanced prostate cancer who are in remission receiving treatment with a luteinizing hormone-releasing hormone (LHRH) agonist and flutamide or who are in progression. A cohort of 113 patients with metastatic prostate cancer, 60 in remission and 53 with disease progression where used, following a battery of questionnaires, including the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, the Medical Outcomes Study Short Form Health Survey SF-36, and a prostate cancer-specific module. 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. Men in remission have a health-related quality of life that is similar to an equivalent norm for men in the United States general population as compared with men with disease progression, who demonstrate significant compromise in all domains measured. Concluding, 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 a quality of life significantly better than that of men with androgen-resistant disease⁶⁰. In the controversy, side effects of the hormonal therapy deserve greater attention. Side effects such as hot flashes, decreased libido, decreased sexual function, and fatigue primarily affect the patients' quality of life. Other side effects such as osteoporosis and changes in lipid profiles may also affect the patients overall health. Patients and physicians should be well aware of the potential side effects of hormonal (e.g. androgen-deprivation) therapy as well as the preventive and treatment strategies for these side effects in order to improve patients' quality of life and health⁶¹.

It becomes more and more clear that health related quality of life (HRQoL) is increasingly reported as an important endpoint in cancer clinical trials. However, evidence suggests that HRQoL reporting is often

inadequate suffering several methodological problems and limitations. A comprehensive search of the literature from 1980 to 2001, revealed twenty-five randomized controlled clinical trials (RCTs) involving 8015 patients primarily with metastatic cancer. Bicalutamide was the medical treatment against which most treatment comparisons were made. Limitations identified, included the fact that 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. The measure most often used was (EORTC QLQ-C30). The conclusions revealed a lack of a uniform approach to HRQoL assessment and several methodological limitations possible to have influenced trial findings for HRQoL outcome⁶². A randomised trial of 65 men with non-localized prostate cancer compared several treatments and tested associations between appraisal, coping, and HRQoL. Compared with baseline assessments, men on hormonal treatments reported impaired sexual function. Groups did not differ on emotional distress, existential satisfaction, subjective cognitive function, physical symptoms, or social and role functioning. For individuals, hormonal treatments were more frequently associated with decreased sexual, social and role functioning, but were also associated with improved physical symptoms. These results showed that pharmacological hormonal ablation for prostate cancer can improve or decrease HRQoL in different domains⁶³.

The QoL questionnaire should be regarded as a useful tool regarding the evaluation of a treatment or its success to the patient and the disease. Subjective quality-of-life assessments obtained from investigators and patients were compared in a subset of 76 patients from an EORTC study (protocol 30853) on metastatic prostate carcinoma. In this study the therapeutic effect of orchiectomy was compared with a luteinizing hormone-releasing hormone analogue depot preparation and flutamide in 327 patients in total. Pre-

treatment, 6- and 12-month quality-of-life assessments revealed large variations between the patients' and the investigators' evaluation of performance status and sexual status (potency). Correlation analysis showed that reduced social life, impaired sexual potency and fatigue played important roles in overall psychological well being. It was concluded that quality-of-life assessments obtained by self-administration questionnaires are a feasible approach and provide a tool to evaluate the benefits of treatment in advanced prostate cancer⁶⁴.

The majority of the recent studies align with the fact that the information obtained by the physician from the patient performing the QoL issues in routine clinical practice is insufficient. These conclusions have important therapeutic implications because whenever patients' complaints are underestimated; they are not treated adequately, which has as a consequence an increase of their subjective morbidity and their rightful dissatisfaction with the therapeutic results.

QoL and financial considerations

The "holistic" evaluation of a prostate cancer patient should incorporate into the overall evaluation of a treatment QoL survival results, and financial considerations. Based on epidemiological data of incidence, the estimated prevalence of advanced prostate carcinoma in Germany and the cost of androgen deprivation of different regimens were determined in correlation to surgical treatment in a study model by Rochde et al⁶⁵. The authors analysed data, which indicate that from 3,838 patients with carcinomas of the prostate, 38% has been treated exclusively with hormone suppression therapy, 14% of patients had undergone a combined radiation therapy and hormone suppression therapy and 9% underwent combined surgical therapy and hormone suppression therapy. The mean survival time of patients treated with medical therapy alone, for patients treated with combined radiation therapy and medical therapy were 60, 24, and 120 months, respectively. The cost for orchiectomy was estimated as \$1,072 and for LH-RH therapy as \$224/month. This study estimated an incidence of 17,700 (per year) and a prevalence of 115,000 patients with advanced prostate cancer for Germany. Provided all patients received LH-RH treatment, a total cost of approximately 20fold greater emerged than the patients who underwent surgery. If all patients received LH-RH agonists, the treatment would amount to \$16,944 per patient, independently of the prognostic group and for surgery \$1,072 per patient would arise. Limited health care budgets mandate critical determination and evaluation of costs to provide a component for the complex decision making process. However, they must be complimented by validated data of quality of life, which can then be a basis for new guidelines of decision making⁶⁵.

In conclusion prostate cancer can cause multiple impairments, activity limitations and participation restrictions. According to individual case findings and

needs, rehabilitation treatment is varied. Because of functional deficits cancer patients suffer from persistent emotional and social distress and a reduced QoL. QoL encompasses at least the four dimensions of physical, emotional, social and cognitive function. The management of sexuality dysfunction has to begin with a thorough history taking and a consequent sexuality counselling. The physician should focus to the significant patient-reported side effects-complications regarding the disease itself or the treatment administered. The utility of the already existed and the development of more sophisticated questionnaires would lead to improvements of treatments and performance status of the patient combined with a reasonable functional status.

References

1. Curran D, Fossa S, Aaronson N, Kielbert G, Keuppens E, Hall R. Baseline quality of life of patients with advanced prostate cancer. *Eur J Cancer* 1997; 33:1809-1814
2. American Cancer Society. *Cancer Facts and Figures-2004*. American Cancer Society, 2004
3. Trask P C. Quality of life and emotional distress in advanced prostate cancer survivors undergoing chemotherapy. *Health Qual Life Outcomes* 2004; 2:37
4. De Reijke T, Laurence C. EORTC prostate cancer trials: what have we learnt? *Critical Reviews in Oncology/Haematology* 2002; 43:159-165
5. Visser A, van Andel G, Willems P, et al. Changes in health-related quality of life of men with prostate cancer 3 months after diagnosis: the role of psychosocial factors and comparison with benign prostate hyperplasia patients. *Pat Edu Couns* 2003; 49:225-232
6. Osoba D. Lesson learned from measuring health - related quality of life in oncology. *J Clin Oncol* 1994; 12:608-616
7. Calais de Silva F, Reis E, Costa T, Denis L and the members of the quality of life committee of the EORTC Genitourinary Group. Quality of life in patients with prostate cancer. A feasibility study. *Cancer* 1993; 73:1138-1142
8. Fossa SD, Aaronson NK, Newling D, et al. Quality of life and treatment of hormone resistant metastatic prostate cancer. The EORTC Genito-Urinary Group. *Eur J Cancer* 1990; 26:1133-1136
9. Slevin ML, Plant H, Lynch D. Who should measure quality of life the doctor or the patient? *Br J Cancer* 1988; 57:107-112
10. Adolfsson J. Health-related quality-of-life assessments in patients with advanced cancer of the prostate. *Pharmacoeconomics* 2003; 21:241-247
11. Altwein J, Ekman P, Barry M, et al. How is quality of life in prostate cancer patients influenced by modern treatment? The Wallenberg Symposium. *Urology* 1997; 49:66-76
12. Fossa SD. Quality of life in prostate cancer: what are the issues and how are they measured? *Eur Urol* 1996; 29:121-123
13. Degner LF, Sloan JA. Decision making during serious illness: what role do patients really want to play? *J Clin Epidemiol* 1992; 45:941-950
14. Wong F, Stewart D, Dancy J, et al. Men with prostate cancer influence of psychological factors on informational needs and decision-making. *J Psych Res* 2000; 49:13-19
15. Strull WM, Lo B, Charles G. Do patients want to participate in medical decision-making? *JAMA* 1984; 252:2990-2994
16. Litwin MS. Measuring health related quality of life in men with prostate cancer. *J Urol* 1994; 152:1882-1887
17. Hinotsu A, Miyanaga N, Akaza H. The significance of assessment of quality of life as a cancer treatment. *Gan to Kagaku Ryoho* 2002; 29:1319-1324

18. Siston A, Knight S, Slimack N, et al. Quality of life after a diagnosis of prostate cancer among men of lower socioeconomic status: results from the Veterans Affairs Cancer of the Prostate Outcomes Study. *Urology* 2003; 5:172-178
19. Turini M, Redaelli A, Gramegna P, Radice D. Quality of life and economic considerations in the management of prostate cancer. *Pharmacoeconomics* 2003; 21:527-541
20. Doehn C, Jocham D. Quality of life in urologic oncology: new aspects. *Onkologie* 2003; 26:30-34
21. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-376
22. De Haes JCJM, van Knippenberg FCE, Neijt JP. Measuring psychological and physical distress in cancer patients: Structure and application of the Rotterdam symptom checklist. *Br J Cancer* 1990; 62:1034-1038
23. Rosenfeld B, Roth AJ, Gandhi S, Penson D. Differences in health-related quality of life of prostate cancer patients based on stage of cancer. *Psychooncology* 2004; 13:800-807
24. Melmed G, Kwan L, Reid K, Litwin M. Quality of life at the end of life: trends in patients with metastatic prostate cancer. *Urology* 2002; 59:103-109
25. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika* 1951; 16:297-334
26. Ware JE, Sherbourne JR, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30:473-483
27. Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement: comorbidity and outcomes after hip replacement. *Med Care* 1993; 31:141-154
28. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a Quality-of-Life Instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-376
29. Osoba D, Zee B, Warr D, Kaizer L, Latreille J. Psychometric properties and responsiveness of the EORTC Quality-of-Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Qual Life* 1994; 3:353-364
30. Hjerstad MJ, Fayes PM, Bjordal K, Kaasa S. Health-Related Quality-of-Life in general Norwegian population assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire: the QLQ-C30 (+3). *J Clin Oncol* 1998; 3:1188-1196
31. Litwin MS, Shpall AI, Dorey F, Nguyen TH. Quality-of-life outcomes in long-term survivors of advanced prostate cancer. *Am J Clin Oncol* 1998; 21:327-332
32. Skarstein J, Aass N, Fosse S, Skovlund E, Dahl A. Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire 2000; 49:27-34
33. Crowe H, Costello AJ. Prostate cancer: perspectives on quality of life and impact of treatment on patients and their partners. *Roll Nurs* 2003; 23:279-285
34. Albertsen PC, Aaronson NK, Muller MJ, Keller SD, Ware Jr JE. Health related quality of life among patients with metastatic prostate cancer. *Adult Urol* 1997; 49:207-217
35. Moinpour CM, Savage MJ, Troxel A, et al. Quality of life in advanced prostate cancer: results of a randomized therapeutic trial. *J Nat Cancer Inst* 1998; 90: 1537-1544
36. Clark JA, Wray N, Brody B, Ashton C, Giesler B, Watkins H. Dimensions of quality of life expressed by men treated for metastatic prostate cancer. *Soc Sci Med* 1997; 45:1299-1309
37. Shrader-Bogen CL, Kjellberg JL, Mc Pherson CP, Murray CL. Quality of life and treatment outcomes: prostate carcinoma patients' perspectives after prostatectomy or radiation therapy. *Cancer* 1997; 79:1977-1986
38. Sneu W, Kommer C, Albertsen A., Peter C., Aaronson NK. Comparison of patient and spouse assessments of health related quality of life in men with metastatic prostate cancer. *Urology* 2001; 165:478-482
39. Aaronson NK. EORTC protocol 15861: Development of core quality of life questionnaire for use in cancer trial. Brussels: EORTC Data Center; 1987
40. Beer TM, Eilers KM, Garzotto M, Hsieh YC, Mori M. Quality of life and pain relief during treatment with calcitriol and docetaxel in symptomatic metastatic androgen-independent prostate carcinoma. *Cancer* 2004; 100:758-763
41. Goodwin D, Higginson BM, Myers BM, Douglas HR, Normand C. Effectiveness of Palliative Day Care in Improving Pain, Symptom Control, and Quality of Life. *J Pain Symp Manag* 2003; 25:202-212
42. Lintz K, Moynihan C, Steginga S, et al. Prostate cancer patients' support and psychological care needs: Survey from a non-surgical oncology clinic. *Psychooncology* 2003; 12:769-83
43. Queipo K, Zaragoza JA, Chicote PF, et al. Improvement of anaemia and quality of life of patients with prostate cancer by treatment with human recombinant erythropoietin. *Arch Esp Urol* 2004; 57:35-40
44. Kaasa S, Malt U, Hagen S, Wist E, Moum T, Kvikstad A. Psychological distress in cancer patients with advanced disease. *Radiother Oncol* 1993; 27:193-197
45. Loge LH, Abrahamsen AF, Ekeberg O, Hannisdal E, Kaasa S. Psychological distress after cancer cure: a survey of 459 Hodgkin's survivors. *Br J Cancer* 1997; 76:791-796
46. Skarstein J, Aass N, Fosse S, Skovlund E, Dahl A. Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *J Psych Res* 2000; 49:27-34
47. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLC-C30: A quality of life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-376
48. Fossa SD, Aaronson NK, Newling D. Quality of life treatment of hormone resistant metastatic prostate cancer. *Eur J Cancer* 1989; 26:1133-1136
49. Fournier G. Management of advanced prostate cancer. *Rev Prat* 1994; 44:595-600
50. Baltogiannis D, Giannakopoulos X, Charalabopoulos K, Sofikitis N. Monotherapy in advanced prostate cancer: an overview. *Exp Oncol* 2004; 26:185-191
51. Bertetto O, Bracarda S, Tamburini M, Cortesi E. Quality of life studies and genito-urinary tumors. *Ann Oncol* 2001; 12:43-48
52. Trask P. Quality of life and emotional distress in advanced prostate cancer survivors undergoing chemotherapy. *Health and Quality of Life Outcomes* 2004; 2:37
53. Osoba D, Tannock IF, Ernst DS, Neville AJ. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone. *J Clin Oncol* 1999; 17:1654-1663
54. Autorino R, Di Lorenzo G, Damiano R, De Placido S, D'Armiento M. Role of chemotherapy in hormone-refractory prostate cancer: Old issues, recent advances and new perspectives. *Urol Int* 2003;70:1-14
55. Beer TM, Pierce WC, Loew BA, Henner WD. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. *Ann Oncol* 2001; 12:1273-1279
56. Sinibaldi VJ, Carducci M, Laufer M, Eisenberger M. Preliminary evaluation of a short course of estramustine phosphate and docetaxel (Taxotere) in the treatment of

- hormone-refractory prostate cancer. *Semin Oncol* 1999; 26:45-48
57. Copur MS, Ledakis P, Lynch J, et al. Weekly docetaxel and estramustine in patients with hormone-refractory prostate cancer. *Semin Oncol* 2001; 28:16-21
58. Green HJ, Pakenham KI, Headley BC, Gardiner RA. Coping and health-related quality of life in men with prostate cancer randomly assigned to hormonal medication or close monitoring. *Psychooncology* 2002; 11:401-414
59. Droz JP, Flechon A, Terret C. Metastatic prostate cancer. *Rev Prat* 2003; 53:2258-2262
60. Albertsen PC, Aaronson NK, Muller MJ, Keller SD, Ware JE Jr. Health-related quality of life among patients with metastatic prostate cancer. *Urology* 1997; 49:207-216
61. Holzbeierlein JM, Castle EP, Thrasher JB. Complications of androgen-deprivation therapy for prostate cancer. *Clin Prostate Cancer* 2003; 2:147-152
62. Efficace F, Bottomley A, van Andel G. Health related quality of life in prostate carcinoma patients: a systematic review of randomized controlled trials. *Cancer* 2003; 97:377-388
63. Scalliet PG, Remouchamps V, Curran D, et al. Retrospective analysis of results of p (65) +Be neutron therapy for treatment of prostate adenocarcinoma at the cyclotron of Louvain-la-Neuve. Part II: Side effects and their influence on quality of life measured with QLQ-C30 of EORTC. *Int J Radiat Oncol Biol Phys* 2004; 58:1549-1561
64. Denis L, Robinson M, Mahler C. Protocol for a randomized prospective study of the treatment of patients with metastatic prostatic cancer to compare the therapeutic effect of orchiectomy versus LHRH- analog depot (Zoladex) preparation supplemented by an anti-androgen: protocol no. 30853.Brussels: EORTC Genitourinary Group, 1986
65. Rohde V, Wellmann A, Fogt F. Economical data and advanced prostate carcinoma: do we need new guidelines for decision-making? *Oncol Rep* 2002; 9:1185-1188
66. Fuse H, Nuraishi Y, Fujishiro Y, Katayama T. Etoposide, epirubicin and carboplatin in hormone refractory prostate cancer. *Int Urol Nephrol* 1996; 28:79-85
67. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone resistant prostate cancer. A Canadian randomised trial with palliative end points. *J Clin Oncol* 1996; 14:1756-1764
68. Small EJ, Meyer M, Marshall ME, et al. Suramin therapy for patients with symptomatic hormone refractory prostate cancer: results of a randomised phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. *J Clin Oncol* 2000; 18:1440-1450