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ORIGINAL PAPER

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Quality of life in patients with prostatic carcinoma: a review and results of a study in N⁺ disease

Prostate-specific antigen as predictor of quality of life

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Abstract Clinical evaluation in oncology has typically focused on outcome indicators, while less attention has been paid to how treatment affects quality of life (QOL) of the patient. In this article some general aspects of quality of life are discussed, a short review of published data on QOL in patients with prostate cancer is given and results of a QOL study executed by the authors on patients with lymph node positive prostatic cancer are presented. The purpose of the study was to examine the impact of immediate or delayed treatment (after objective progression) in patients with prostatic carcinoma (T1-3 N1-3 M0) on quality of life parameters. To this end an extended questionnaire was constructed. Fifty-five patients participated. Assessment was performed twice, in 1994 and 1995. The comparison between patients with and patients without treatment showed in 1994 as well as in 1995 significant differences for hormonal treatment side effects such as sexual functioning and hot flushes, all of which were experienced more frequently by treated patients. In 1994 the treated patients experienced more psychological distress while in 1995 they showed worse physical function, less energy and more fatigue when compared to patients under surveillance. The premise that active treatment would improve the psychological quality of life was not sustained. In addition global health status and quality of life were identified as independent factors for progression in untreated patients with lymph node positive prostate cancer. Finally, an increase in prostate-specific antigen (PSA) in hormonally treated patients not only indicated hormonal escape but also a decrease in QOL.

In the past decade the need to assess quality of life (QOL) in patients with malignancy has become increasingly recognized. 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 treatment affects QOL. In this article some general aspects of QOL assessment are discussed, a short review of published urological QOL data is given, and finally the results of a QOL study in patients with lymph node positive prostatic carcinoma are presented.

Quality of life assessment

Interest in QOL assessment in clinical research has been growing rapidly. That this aspect has not been seen as more important previously is surprising as, from the days of Hippocrates, the primary goal of a doctor has been to improve the well-being of patients, and not only to attempt to control the disease. Treatments given in an effort to control disease sometimes conflict with this primary goal. Therefore knowledge of a patient's well-being, or in other words assessment of a patient's QOL, and insight into how this is influenced by treatment, is an indisputable need in good clinical practice.

What should QOL assessment involve?

Most researchers agree that QOL involves a number of relatively independent domains, including, at a minimum, physical, functional, psychosocial and social well-being. Some also emphasize other areas, such as symptoms, sexuality, spiritual concerns and satisfaction with health care [14]. Nevertheless most investigators restrict their QOL assessment to health-related QOL (HRQOL). Aspects of QOL that are important in an individual's subjective evaluation of life as a whole are excluded in this approach [12]. So, most of the models presented

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consist of identifying different dimensions that may influence QOL, while relatively little attention has been paid to specifying among other things the relationship between symptoms and functioning, performance and satisfaction, occurrence of a symptom and experience of the symptom as a problem. The individual judgement of the impact of the same symptom may vary widely and is strongly related to other personal factors as well as sociocultural factors and several resources (including economic resources, social support and appropriate health care). This fact interferes with the good interpretation of QOL data, and limits the usefulness of QOL data as an outcome measure in cancer treatment. It is for this reason that models are needed to identify and link independent variables to patient-assessed QOL. Such models will facilitate the development of interventions that incorporate individual patient factors with QOL assessment. Thus QOL assessment, however difficult, should involve more than simply an inventory of symptoms and functioning.

When should QOL be assessed and for what purpose?

Cella and Tulsky [10] formulated three purposes for measuring QOL: (a) to identify the full range of side effects and impacts of the treatments in order to assess rehabilitation needs; (b) to compare treatments in a trial; and (c) to use QOL ratings as a predictor of response to future treatment. Others emphasize that knowledge of the QOL may be important when the impact of a different treatment on the length of life is expected to be small. Beitz [4] stated, based on the recommendations from the Oncologic Drugs Advisory Committee, that beneficial effects on QOL and/or survival should be the basis for approval of new anticancer drugs, and that from a regulatory standpoint, for drugs that do not have an impact on survival, demonstration of a favourable effect on QOL is more important than most other traditional measures used to assess efficacy, such as objective tumor response.

The European Organization for Research and Treatment of Cancer (EORTC) has finally defined criteria for the inclusion of QOL issues in their phase III cancer clinical trials [21]. They stated that theoretically QOL assessment can be a relevant end-point if:

1. No improvement in overall, recurrence-free, or systemic disease-free survival is expected, but when significant changes or differences in (at least) one aspect of quality of life are expected.
2. One treatment results in a better survival but has more toxic effects.
3. The patients have an extremely poor prognosis with or without treatment.
4. Treatment is known to be very burdensome to patients.
5. A new (invasive) treatment is to be evaluated.

In conclusion, generally, QOL assessment might be important in evaluating new treatment modalities, when

the treatment itself has side effects (positive or negative) or when a new or different treatment has little or no impact on survival.

Which instruments for measuring QOL are available at this moment?

A spectrum of QOL instruments have been developed, ranging from global to disease-specific, to ad hoc instruments that are specific to a single study [1]. Of course instruments used have to be proven valid and reliable. Table 1 lists several general QOL instruments, while Table 2 shows some cancer-specific QOL instruments. Global instruments are most applicable to health policy research and their advantage lies in examining a wide range of potential impacts of disease on mental and social functioning, while cancer-specific instruments have the advantage of addressing problems specific to a given cancer patient population, and may permit cross-study comparison. Cancer-specific core instruments (a more focused type of global measurement) are supplemented with disease-specific or treatment-specific modules, aimed to provide a compact and useful instrument, combining the advantages of the global and cancer-specific instruments. Examples include the European Organization for Research and Treatment Core QOL Questionnaire (QLQ-C30), supplemented by a lung cancer-specific module (QLQ-LC13) or the general Functional Assessment of Cancer Therapy Scale

Table 1 General quality of life instruments (*MOS* Medical Outcome Studies)

Instrument	No. items	Reliability
RAND 36-Item Health Survey	36	Coefficient > 0.78
Quality of Well-being Scale	18	Test-retest 0.93–0.96
Sickness Impact Profile	136	Test-retest 0.88–0.92
Nottingham Health Profile	38	Test-retest 0.57–0.88
Part 1		
General Health Index	–	Test-retest 0.85–0.90
Mental Health Index MOS	5	–

Table 2 Cancer-specific quality of life instruments. All instruments were constructed for self-assessment (*CARES* Cancer Rehabilitation Evaluation System, *CIPS* Cancer Inventory problem Scale, *FACT-G* Functional Assessment of Cancer Therapy – General Form, *FLIC* Functional Living Index: Cancer, *EORTC-QLQ-C30* European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core 30, *RSCL* Rotterdam Symptoms Check List)

Instrument	No. items	Reliability
CARES	59 (short) 139 (long)	Test-retest 0.81–0.86
CIPS	145	Test-retest 0.84–0.91
FACT-G	28	Test-retest 0.82–0.92
FLIC	22	–
EORTC-QLQ-C30	30	Coefficient > 0.70
RSCL Symptoms	34 (42)	Test-retest 0.88–0.94

(FACT-G), supplemented by the ovarian cancer-specific module (FACT-Ovarian).

The choice of QOL instrument is directly related to the trial structure and the questions to be answered. A broad and comprehensive approach is likely to be particularly useful for treatments for which little is known about potential effects on patient well-being, whereas assessment in order to distinguish between treatments needs to be specific and sufficiently sensitive.

As stated by Varricchio [32], the results of QOL assessment in clinical oncology should focus on interventions to lessen the negative impact of cancer and its treatment on QOL, while the translation of QOL findings into valid, effective clinical applications is the most important concern of researchers and clinicians at this time. After all it is important that QOL research con-

tinues to develop and to address cancer research questions of clinical importance to patients.

Quality of Life assessment in prostate cancer

Over the period 1980–1996, research by means of the CD-ROM Medline on the combination of the key words “prostate”, “prostatic”, “neoplasm”, “cancer”, “malignancy”, “radical prostatectomy”, “radiation”, “hormonal”, “hormonally” and “quality of life” produced only 27 articles, which could be subdivided into articles concerning QOL after radical prostatectomy, QOL after radiation therapy and QOL in patients with metastatic prostate cancer. Results are summarized in Tables 3–6. The instruments used to measure QOL in the different

Table 3 Published studies concerning quality of life after retropubic radical prostatectomy (*FLIC* Functional Living Index: Cancer, *POMS* Profile of Moods States, *CARES-SF* Cancer Rehabilitation Evaluation System – Short Form, *FACT-G* Functional Assessment of Cancer Therapy – General Form, *GHI* General Health Index, *MHI-5* Mental Health Index)

Author (ref.)	Instrument	No. patients	Outcome
Walsh et al. [35]	Questionnaire on sexual functioning	955	Good correlation between survey and case record
Pedersen et al. [28]	The Qualy (modified for disease-specific use)	131	Loss of potency caused severe distress
Lim et al. [25]	FLIC POMS Disease-specific questionnaire (sexual, urinary and bowel items)	136	Urinary incontinence and loss of sexual function associated with depression, tension and fatigue
Braslis et al. [6]	FLIC POMS Disease-specific questionnaire	79	Compared with presurgery assessment, decreased tension, family interaction and sexual functioning and increased incontinence
Frohmüller et al. [18]	No psychometric instruments used	139	N+ disease: androgen deprivation with/without radical prostatectomy. More micturition problems in patients without prostatectomy
Litwin et al. [26]	RAND 36 CARES-SF FACT-G Disease-specific questionnaire (sexual, urinary and bowel items)	98	Compared to age-matched control worse sexual and urinary function, sexual function not significantly different after nerve sparing – or standard prostatectomy
Fowler et al. [17]	GHI/MHI-5	1072	Decrement in QOL when incontinence was present

Table 4 Published studies concerning quality of life after radiation therapy (*FLIC* Functional Living Index: Cancer, *POMS* Profile of Moods States, *CARES-SF* Cancer Rehabilitation Evaluation System – Short Form, *FACT-G* Functional Assessment of Cancer Therapy – General Form, *FACT-BL* Functional Assessment of Cancer Therapy – Bladder, *CUF* Changes in Urinary Function, *SAQ* Sexual Adjustment Questionnaire)

Author (ref.)	Instrument	No. patients	Outcome
Lim et al. [25]	FLIC POMS Disease-specific questionnaire	60	Compared to radical prostatectomy; less incontinence, better sexual function, worse bowel function
Litwin et al. [26]	RAND-36 CARES-SF FACT-G Disease-specific questionnaire	56	Compared to radical prostatectomy or observation; more troublesome bowel function
Watkins-Bruner et al. [36]	FACT-BL CUF SAQ	24	Serious disagreement between self-reports of symptoms and medical professional rating
Helgason et al. [19]	Scale of sexual functioning	53	Half of the patients active prior to therapy lost erectile capacity

Table 5 Published studies concerning quality of life in patients with metastatic prostatic carcinoma who received primary therapy (*FLIC* Functional Living Index: Cancer, *POMS* Profile of Moods States, *CIPS* Cancer Inventory Problem Scale)

Author (ref.)	Instrument	No. patients	Therapy	Outcome
Cassileth et al. [9]	FLIC, POMS, disease-specific questions	115	Gosereline vs orchiectomy	Compared to baseline improvement of QOL at 6 months in Gosereline group, no change in orchiectomy group
		32		
Calais da Silva [8]	EORTC Quality of Life Questionnaire	76	Orchiectomy vs LHRH with flutamide	Disagreement between patients and investigators evaluation of QOL. Patient evaluation: 70% psychological distress at entry, 41% decreased performance at 12 months
Tyrell [31]	Specifically designed questionnaire (30 items)	422	Castration vs Casodex (150 mg/day)	Results not conclusive
		851		
Herr et al. [20]	EORTC-C30 Prostate Module, Event Scale, Selby Uniscale, CIPS, sexual functioning	20	No therapy versus hormonal	No therapy group had better sexual and physical functioning therapy
		15		

Table 6 Published studies concerning quality of life in patients with hormonal escaped metastatic prostatic cancer (*VAS-PPI* Visual Analogue Scale – Present Pain Intensity, *MIT* mitoxantrone, *LASA* Linear Analog Self Assessment)

Author (ref.)	Instrument	No. patients	Therapy	Outcome
Fossa [15]	EORTC Questionnaire	31	89-Strontium or extended radiation therapy	Patients' perception of physical function is an independent prognostic factor of survival
		106		
Cresswell et al. [11]	WHO pain score specific QOL/activity score	27	Sodium clodronate; intravenous followed by oral	Pain relief in 37% after intravenous therapy; similar results for activity and performance
Fossa et al. [16]	EORTC Questionnaire	34	Estramustine vs mitomycin	Decreased functional status, fatigue and pain, major morbidities before study entry
		38		
Moore et al. [27]	EORTC-C30 Prostate-Specific Module VAS-PPI	27	MIT + prednisone	Improvement in social and emotional function, pain and anorexia after MIT and prednisone
Tannock et al. [30]	LASA pain score	37	Prednisone	19% maintained pain improvement for 3–30 months after 7.5 mg prednisone. Pain relief associated with improvement of quality of life

studies are mentioned. Globally QOL data after radical prostatectomy show that patients experience a worse sexual and urinary function than age-matched controls, leading to a lessening of emotional functioning. The shortcoming of most studies is that no comparisons were made with baseline values within the reported population. Interesting is the finding reported by Litwin et al. [26] that sexual functioning does not significantly differ after nerve sparing or standard radical prostatectomy. Compared with radical prostatectomy, patients after radiation therapy have a better sexual and urinary function but a worse bowel function.

Due to the methodology applied, straight conclusions are difficult to draw from most studies reported so far. Prospective studies using adequate instruments con-

cerning QOL in patients with prostatic carcinoma are badly needed.

Lymph node positive prostatic cancer

QOL as a parameter for studying the treatment modalities is especially useful when the therapies in question show many side effects or when the time chosen to start treatment will possibly not influence the duration of survival. The latter may be the case in patients having prostatic cancer metastasized only to the lymph nodes. Cure is no longer possible, hormonal treatment having only a temporary effect on the course of the disease. When hormonal treatment should be best initiated has not yet

been defined. Options are: (1) immediate treatment when metastases to the lymph nodes are identified, or (2) in the event of biochemical or clinical progression. Several uncontrolled studies addressing this issue show that immediate hormonal treatment in patients with lymph node positive prostate cancer prolonged the time to progression when compared with delayed hormonal treatment [24, 33]. In 1984, the European Organization for Research and Treatment of Cancer (EORTC) started a prospective randomized study (protocol 30846), which aimed to evaluate immediate versus delayed hormonal treatment in patients with a prostatic carcinoma category T1-3 N1-4 M0. When this study was activated by the EORTC, a QOL assessment was still not an obligatory part as it became in later studies. In 1993, Van den Ouden et al. [34] analysed a subgroup of patients and reported a median time to progression of 20 months for immediate hormonal treatment compared to 72 months after delayed hormonal treatment. Analysis of duration of survival was still not possible. Arguing that hormonal treatment in patients with metastases only to the lymph nodes may either positively or negatively influence a patient's life, we investigated this issue in this group of patients. Baseline QOL values were available only for patients diagnosed with lymph node metastases in the year of starting this investigation or diagnosed at a later date.

Material and methods

In January 1994 our database contained 55 patients alive with a T2-3 G1-3 N1-3 M0 prostatic cancer, given immediate hormonal treatment or deferred treatment when objective progression was documented. Of these patients, 39 participated in the EORTC trial no. 30846. The 16 patients who did not participate in this trial mostly preferred a particular therapy and therefore did not fit the inclusion criteria.

At the time of their diagnosis all patients were asymptomatic, with the exception of several patients with minimal micturition disorder. Lymph node metastasis was diagnosed in 3 patients by means of puncture, and in 12 by means of laparoscopic lymph node dissection. In 32 patients it was diagnosed by means of frozen section examination during open lymph node dissection, previous to planned radical prostatectomy, which consequently was not executed. In eight patients a frozen section of the lymph nodes was negative; they underwent radical prostatectomy, and lymph node metastases were diagnosed only in the paraffin-embedded material.

In February 1994 and in February 1995 an extended questionnaire was sent to the 55 patients in question, who also received a personal explanation and a self-addressed envelope. If requested, all patients were welcome to have a personal talk, if they felt they were in need of a more extended explanation. In 1994 all patients returned their completed questionnaires, and in 1995 all patients but two did so.

The questionnaire consisted of the EORTC Core Quality of Life questionnaire (EORTC QLQ-C30) [2], a global measurement of quality of life (Selby Uniscale) [29], the International Prostate Symptom Score (IPSS) [3], the Sexual Behaviour questionnaire as described by Derogatis and Kourlesis [13], and some questions about the side effects of hormonal treatment (including hot flushes), as well as questions about sexual activity before prostatic cancer was diagnosed. In total, the questionnaire contained 59 items, which were all translated into Dutch.

The EORTC QLQ-C30 consists of 30 questions which list the functioning and the symptoms of cancer patients. Six multi-item

function scales are scored: physical functioning (PF), role functioning (RF), emotional functioning (EM), cognitive functioning (CF), social functioning (SF) and global health status/quality of life (QL). Furthermore, nine single-item symptom scales/items are scored, including fatigue, sickness and vomiting, and diarrhoea. The first seven questions relate to physical activities. They are dichotomic (yes/no). The other questions can be answered with not at all, a little, rather and very much (four-point Likert scale), except for the last two. These two questions concern the general physical condition and the overall quality of life. They are scored on a visual analogue scale from 1 to 7, 1 meaning very bad and 7 excellent. The results of each function scale are added up for each individual patient and divided by the number of items within the scale. Subsequently, these scale scores are linearly transformed such that all scales range from 0 to 100, in which a higher scale score represents a higher level of functioning.

The results of the single-item symptom/item scale were also linearly transformed to a 0–100 scale; a higher score indicating more symptoms or problems. The EORTC-QLQ-C30 has proven to be a reliable and valid questionnaire for measurement of the quality of life parameters in cancer patients.

The Selby uniscale was scored on a visual analogue 0–10 scale. This was transformed to a 0–100 scale, 0 meaning less energy than contemporaries and 100 meaning just as much. The IPSS is an internationally used questionnaire concerning micturition disorders. It consists of seven questions, and the results are scored on a five-point scale, in which 0 indicates no and 5 severe disorders. The results of the seven questions are added up, which means that the total score can vary from 0 to 35; a higher result indicates more disorders.

The sexual behaviour questionnaire as described by Derogatis and Kourlesis [13] contains six questions concerning relationships and sexuality. Among other things, the patients are asked about sexual interest, frequency and pleasure. The questions can be answered on a four-point Likert scale, 0–3, in which a higher score correlates with a worse function.

The 55 patients participating in the present study were diagnosed between January 1988 and November 1993. Eighteen patients were given primary immediate hormonal treatment, all medicinal. A wait-and-see policy was pursued with 37 patients, of whom 9 showed progression (bone metastases) in the interval between diagnosis and completion of the first questionnaire. All these nine patients received hormonal therapy. At the time of the completion of the questionnaire they had already been treated for 3 months or more. We therefore ranked these patients in the immediate hormonal treatment group when we analysed the data. As a result, this group consisted of patients who actually received immediate treatment as well as patients who received delayed hormonal treatment, but more than 3 months before the completion of the questionnaire. As a result, in February 1994 the delayed treatment group consisted of 27 patients and the immediate treatment group 28 (Table 7).

The second questionnaire was completed by the same patients in February 1995. Meanwhile, seven patients from the delayed treatment group had shown progression. They were hormonally treated. When the second questionnaire was completed all seven patients had been treated for 3 months or more. Of the 28 patients from the immediate treatment group, 3 died in the intervening year and 2 did not return their questionnaires. Consequently, in February 1995 the delayed treatment group consisted of 20 patients and 30 patients were hormonally treated. The last group included patients treated hormonally only after objective progression was observed.

In February 1995, the period between the diagnosis of prostatic cancer and the last follow-up of the 55 patients averaged 40 months, the median follow-up being 33 months. All patients, including those who do not participate in the EORTC study (30846), were followed up according to protocol, and the acquired information was stored in our own database. Thus the prostate-specific antigen (PSA) of all patients could be checked at regular intervals. In this way, it was possible to examine the relation between the PSA level on one hand and the results of the questionnaires on the

Table 7 Treatment modality and numbers of patients (*n*): development over time (*QNR* questionnaire not returned)

Period	Treatment modality				
1988–1993	T1-3 G1-3 N1-3 M0 prostatic carcinoma (<i>n</i> = 55, incl. radical prostatectomies)				
		No therapy (<i>n</i> = 37)	Hormonal therapy (<i>n</i> = 18)		
	No therapy (<i>n</i> = 27)	Progressive (<i>n</i> = 10)			
February 1994		No therapy (<i>n</i> = 27)	Hormonal therapy (<i>n</i> = 28)		
	No therapy (<i>n</i> = 20)	Progressive (<i>n</i> = 7)	Died (<i>n</i> = 3)	<i>QNR</i> (<i>n</i> = 2)	Hormonal therapy (<i>n</i> = 23)
February 1995 ^a		No therapy (<i>n</i> = 20)	Hormonal therapy (<i>n</i> = 30)		

^a Mean follow-up February 1995, 40 months; median follow-up February 1995, 33 months

other. Statistical analyses were performed by Student's *t*-test, always using the average of the scores per item in order to determine the differences between the groups under comparison. In Table 8 all analyses performed between the subgroups are listed.

Results

Table 9 shows the results of the 1994 questionnaires, comparing the patients without therapy with the patients treated hormonally (Table 8, analysis 1). Of the function scales, only the emotional scale shows a statistically significant difference, the patients without therapy function scoring emotionally better than the hormonally treated patients. There were also significant differences regarding items related directly to the hormonal treatment, such as obtaining an erection, sexual parameters and hot flushes. Logically, the hormonally treated patients complained more often about erectile dysfunction and decreased sexual activity. They had less sexual interest and pleasure and more hot flushes. The 1995 questionnaire was analysed similarly (Table 8, analysis 2). Apart from the above-mentioned items relating to the hormonal treatment, significant differences

were found with respect to physical function, fatigue and energy. Patients who received no therapy experienced a better physical function, less fatigue and more energy. Emotional function, which gave a *P* value of 0.270 in 1995, remarkably no longer showed a significant difference (Table 10).

If the patients who received delayed hormonal treatment are excluded from the above-mentioned analyses – in other words, if we analyse only the patients who are given primary treatment or otherwise (1994: no therapy *n* = 27 vs therapy *n* = 18, and 1995: 20 vs 15, respectively), the results do not change essentially, and there are still significant differences concerning identical items in both groups (data not shown).

We also compared the results of the 1994 and 1995 questionnaires of patients who did not receive treatment in any of these years (Table 8, analysis 3). Analysis of these data showed no significant difference for any of the items. The same goes for the comparison of the 1994 and 1995 questionnaires of patients who were treated hormonally in both years (Table 8, analysis 4). Compared to the results of the 1994 questionnaire, it should be noted that the results of the 1995 questionnaire for both

Table 8 Analyses performed including the crude results (*COV* cutoff value, *Delayed* patients who received no therapy, *Immediate* patients who received hormonal therapy, *NS* analysis showed no statistical significant differences for any of the parameters measured, *Progressive* patients who initially received no therapy and became progressive in 1994, *PSA* prostate-specific antigen, *Significant difference* analysis showed statistical significant differences for several parameters)

Number of analysis	Group	Comparison	Result
1.	Questionnaire 1994	Delayed vs immediate	Significant difference
2.	Questionnaire 1995	Delayed vs immediate	Significant difference
3.	Delayed	Questionnaire 1994 vs questionnaire 1995	NS
4.	Immediate	Questionnaire 1994 vs questionnaire 1995	NS
5.	Delayed/questionnaire 1994	Progressive vs not progressive	significant difference
6.	Progressive	Questionnaire 1994 vs questionnaire 1995	NS
7.	Delayed/questionnaire 1994	PSA < COV vs PSA ≥ COV	
8.	Delayed/questionnaire 1995	PSA < COV vs PSA ≥ COV	
9.	Immediate/questionnaire 1994	PSA < COV vs PSA ≥ COV	
10.	Immediate/questionnaire 1995	PSA < COV vs PSA ≥ COV	

Table 9 Quality of life in patients receiving no therapy vs hormone therapy: questionnaire 1994 (*IPSS* International Prostate Symptom Score, *NS* not significant)

Quality of life scale	No therapy (<i>n</i> = 27)	Hormone therapy (<i>n</i> = 28)	<i>P</i> value
Physical function	93.0	86.7	NS
Role function	89.5	92.6	NS
Emotional function	93.8	88.4	0.043
Cognitive function	94.1	93.2	NS
Social function	96.7	91.4	NS
Overall quality of life	81.3	79.0	NS
Fatigue	11.7	16.9	NS
Pain	5.8	9.9	NS
Energy	83.9	71.5	NS
Erections	1.2	1.8	0.000
Sexual interest	0.8	2.0	0.000
Sexual activity	0.9	2.7	0.000
Sexual enjoyment	0.8	2.1	0.001
IPSS	8.1	7.0	NS
Hot flushes	2.0	38.5	0.000

Table 10 Quality of life in patients receiving no therapy vs hormone therapy: questionnaire 1995 (*IPSS* International Prostate Symptom Score, *NS* not significant)

Quality of life scale	No therapy (<i>n</i> = 20)	Hormone therapy (<i>n</i> = 30)	<i>P</i> value
Physical function	93.7	83.4	0.027
Role function	87.5	84.4	NS
Emotional function	90.4	87.2	NS
Cognitive function	93.3	90.8	NS
Social function	94.7	87.5	NS
Overall quality of life	80.4	72.7	NS
Fatigue	8.2	24.9	0.004
Pain	11.4	6.3	NS
Energy	84.0	64.4	0.018
Erections	1.3	1.8	0.000
Sexual interest	1.0	2.2	0.000
Sexual activity	1.2	2.5	0.001
Sexual enjoyment	0.3	2.3	0.000
IPSS	8.9	7.1	NS
Hot flushes	4.0	41.5	0.000

groups generally show a lower level of functioning and more symptoms. However, the differences are not significant. When the patients who received hormonal treatment during 1994 were excluded from the hormonally treated group of 1995, the analysis results remain unchanged. Furthermore, a restricted analysis of the seven patients who became progressive in the course of 1994 was performed (Table 8, analysis 5). Comparison of the results of the 1994 questionnaire of these 7 patients with the 20 patients who did not become progressive the year after shows significant differences for two items, global health status and quality of life. Patients who became progressive the year after the assessment judged their own global health status and quality of life on a visual analogue scale of 1–7 (EORTC-QL Q-C30) to be worse than that of patients who did not become progressive. Furthermore, differences were found for emotional function, physical

function, fatigue and energy, but, although a trend was seen, these differences were not significant, probably due to the small numbers of patients (Table 11).

Finally the relation between the PSA level and the results of the questionnaires in the various patient groups was examined (no therapy/therapy and 1994/1995). To this end, within all groups to be analysed a comparison was made between the results of the questionnaires of patients with a PSA lower than a certain value and those of patients with a PSA higher than this value. The analyses were done for PSA values < or ≥ 10, 20, 50 and 100 ng/ml. Table 12 shows the analysis outcome of the 1995 questionnaires results of the hormonally treated patients, comparing the patients with a PSA < 10 ng/ml to those with a PSA ≥ 10 ng/ml. There are significant differences concerning physical function,

Table 11 Quality of life in patients receiving no therapy; questionnaire 1994. Progressive patients vs patients without progression in the year following assessment (*IPSS* International Prostate Symptom Score, *NS* not significant)

Quality of life scale	Progressive (<i>n</i> = 7)	Not progressive (<i>n</i> = 20)	<i>P</i> value
Physical function	80.0	97.0	0.066
Role function	83.3	95.0	NS
Emotional function	84.5	97.0	0.055
Cognitive function	83.3	96.7	NS
Social function	92.9	97.5	NS
Global health status	4.7	6.2	0.001
Quality of life	5.1	6.1	0.013
Overall quality of life	65.4	85.8	0.001
Fatigue	30.1	8.3	0.092
Pain	4.7	5.0	NS
Energy	28.7	11.8	NS
Erections	1.7	1.7	NS
Sexual interest	0.9	1.0	NS
Sexual activity	1.3	1.2	NS
Sexual enjoyment	1.0	0.8	NS
IPSS	9.1	7.9	NS
Hot flushes	1.6	2.1	NS

Table 12 Quality of life in patients receiving hormonal treatment PSA < 10 ng/ml vs PSA ≥ 10 ng/ml; questionnaire 1995 (*IPSS* International Prostate Symptom Score, *NS* not significant)

Quality of life scale	PSA < 10 (<i>n</i> = 16)	PSA ≥ 10 (<i>n</i> = 11)	<i>P</i> value
Physical function	91.3	76.3	0.042
Role function	90.6	72.8	NS
Emotional function	93.2	78.3	0.014
Cognitive function	94.8	89.4	NS
Social function	93.8	80.3	NS
Overall quality of life	83.3	59.8	0.002
Fatigue	16.0	32.3	NS
Pain	3.1	10.6	NS
Energy	56.0	54.4	NS
Erections	1.8	1.8	NS
Sexual interest	2.1	2.4	NS
Sexual activity	2.4	2.6	NS
Sexual enjoyment	2.2	2.2	NS
IPSS	7.4	7.7	NS
Hot flushes	45.6	44.0	NS

Table 13 Quality of life in patients receiving hormonal treatment PSA < 20 ng/ml vs PSA ≥ 20 ng/ml: questionnaire 1995 (IPSS International Prostate Symptom Score, NS not significant)

Quality of life scale	PSA < 20 (n = 21)	PSA ≥ 20 (n = 6)	P value
Physical function	90.5	66.7	0.004
Role function	90.5	58.3	0.009
Emotional function	92.9	65.0	0.000
Cognitive function	95.2	83.3	0.024
Social function	95.3	63.9	0.044
Overall quality of life	79.4	54.2	0.005
Fatigue	15.8	46.3	0.004
Pain	2.4	19.4	NS
Energy	74.0	43.3	0.025
Erections	1.8	1.9	NS
Sexual interest	2.2	2.3	NS
Sexual activity	2.5	2.5	NS
Sexual enjoyment	2.2	3.0	0.020
IPSS	6.7	10.1	NS
Hot flushes	42.2	55.0	NS

emotional function and overall quality of life. The patients with a PSA ≥ 10 ng/ml show worse physical and emotional function and also have a worse overall quality of life. The outcome of the analysis of the same group, this time at a PSA value < or ≥ 20 ng/ml, is shown in Table 13. Differences are significant in physical, role, emotional, cognitive and social function, as well as in the overall quality of life, fatigue, energy and sexual pleasure; the patients with a PSA ≥ 20 ng/ml always perform worse than the patients with a PSA < 20 ng/ml. Analyses of the remaining groups, with respect to the various PSA cut-off values, did not show significant differences in one of the items.

Discussion

Relatively little is known about the quality of life of men suffering from prostatic cancer in various stages of the disease and after different treatments. Quality of life in patients with prostatic cancer metastasized only to the lymph nodes has not yet been evaluated. This could be an interesting patient group, since beside micturition problems this group is asymptomatic and it is unclear whether immediate hormonal treatment has a favourable impact on duration of survival. When early hormonal treatment does not increase QOL, but may cause morbidity due to side effects, and at the same time duration of survival is not negatively influenced by delaying treatment until progression is observed, the treatment strategy could be influenced. The purpose of the present study was to examine the impact of immediate or delayed treatment on quality of life parameters. The reliability and validity of all components of the questionnaire used in this study have already been proven in former studies [2, 13, 29]. Consequently we may assume that the quality of life parameters can be appropriately assessed with the instruments used.

Comparative analyses of hormonally and not hormonally treated patients in 1994 as well as 1995 showed significant differences with regard to the items related to the treatment. Hormonally treated patients had significantly less frequent erections, they experienced less sexual interest, activity and pleasure and they had hot flushes more often. Logically, the results correspond to those of other studies, and can be regarded as side effects of the therapy. Furthermore, in 1994 there was a significant difference regarding the emotional function in favour of the non-treated patients (no therapy 93.8 vs therapy 88.4, $P = 0.04$). Although in 1995 a difference in emotional function was observed (no therapy 90.4 vs therapy 87.2), this difference is no longer significant, for which we do not have a sound explanation. When emotional function and the stage of the disease are related, the decrease in the emotional function in the non-treated patients in 1995 compared to 1994 could possibly be explained by a clinically unrecognized progression of the disease in some patients. Another explanation could be that hormonally treated patients become used to the side effects of the hormonal treatment while these initially affected their emotional function. However, the premise that immediate hormonal treatment improves the overall psychological quality of life is not sustained.

The results of the 1995 questionnaire of non-treated patients generally showed lower values for the function scales and higher values for the symptom items in comparison to the 1994 questionnaire, suggesting that with the duration of the disease functioning is slightly (not significantly) decreasing whereas symptoms increase.

Analyses of the 1995 questionnaire comparing patients who received no therapy with hormonally treated patients showed, apart from the items related to the hormonal therapy, better physical function, less fatigue and more energy for the not treated patients. Yet it is unclear whether this is due to the long-term hormonal treatment or to disease progression in the hormonal treated group (hormonal escape). Future analyses with data available after a longer follow-up will hopefully provide an answer to this question. In an effort to find independent factors for progression, we compared within the untreated group in 1994 ($n = 27$) the results of the questionnaire of the 7 patients who showed clinical evidence of progression the year after the assessment with those of the 20 patients who did not become progressive. It turned out that the seven progressive patients judged their own global health status and quality of life on a visual analogue scale to be significantly worse than the not progressive patients. Therefore, as a result of these analyses, global health status and quality of life can be seen as independent factors for progression in untreated patients with lymph node positive prostate cancer. In view of the small number of analysed patients, these results obviously lack any statistical strength. Therefore, to confirm these results a study with a greater number of patients is necessary; such a study is presently ongoing in our clinic.

Finally, we have examined the relation between the biochemical marker of progression, PSA, and the quality of life parameters. Currently, PSA is the most important, accurate and clinically useful biochemical marker of prostate cancer [5]. Many studies have demonstrated the relationship between PSA value, clinical stage, histological grade and the presence of extracapsular extension or invasion in the vesiculae seminales [22]. PSA is valuable for the prediction of the presence of lymph nodes or bone metastases and survival after hormonal therapy. It is also a good marker for the demonstration of progression (biochemical progression precedes objective progression for several months) or relapse after surgical or radiotherapeutic treatment [7]. The present study also shows a positive relation between PSA and several quality of life parameters. Hormonally treated patients with a PSA > 20 ng/ml have a significantly lower level of functioning for all examined function scales, and they have a lower overall quality of life, less energy and less sexual pleasure, and they are more tired compared to hormonally treated patients with a PSA < 20 ng/ml. In view of these results, the PSA seems valuable as predictor of the quality of life in hormonally treated patients as well.

Only a few reports have been published with an objective of assessing quality of life in prostate cancer patients. Herr et al. [20] investigated QOL in 35 newly diagnosed patients with distant metastases hormonally treated or not. Sixteen patients were hormonally treated and 19 did not receive therapy. Patients were assessed after 1, 2 and 6 months. Analysis showed that the non-treated patients had fewer sexual problems and more physical energy than the hormonally treated patients. It also turned out that the psychological distress in the non-treated patients had diminished after 6 months, while it had increased in the treated patients. In our group of examined patients, we can confirm the significant differences with regard to fatigue and physical symptoms after 6 months in favour of non-treated patients as reported by Herr et al. [20], taking into account that the patients we examined were all asymptomatic, had prostatic cancer metastasized only to the lymph nodes, were assessed only at annual intervals, had a longer follow-up and with no comparison with baseline assessment.

Kornblith et al. [23] assessed QOL after treatment for localized or metastatic disease in 172 patients. Treatment given was radical prostatectomy or radiation therapy in 28% and hormonal therapy in 55%, and 18% patients were on a surveillance protocol. Hormonally treated patients with metastasized disease reported more pain, fatigue, micturition trouble and diminished physical function. In addition, a specially designed questionnaire was prepared for patient's spouses. Interestingly, spouses experienced more psychological distress than their treated or monitored husbands. This illustrates the impact of treated or monitored malignant disease on the well-being of the patients' relatives.

In conclusion the present study also shows the negative effects of hormonal treatment on several quality of

life parameters. This fact should be kept in mind when discussing therapeutic options with a patient. Furthermore, the increased PSA in hormonally treated patients not only heralds hormonal escape, but – as shown in the present study – also a decrease in several QOL parameters. Studies of larger groups of patients to confirm the reported results are vital and currently in progress in our institution.

References

1. Aaronson NK (1991) Methodologic issues in assessing the quality of life of cancer patients. *Cancer* 67(Suppl):844
2. Aaronson NK, Ahmedzai S, Bergman, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, Haes de JCJM, Kaasa S, Klee M, Osaba D, Razavi D, Rofo PB, Schraub S, Sneeuw K, Sullivan M, Takeda F for the European Organization for Research and Treatment of Cancer Study Group on Quality of Life (1993) 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 Nat Cancer Institute* 85:365
3. Barry MJ, Fowler JR, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Meibust WK, Cockett ATK and the Measurement Committee of the American Urological Association (1992) The American Urological Association Symptom Index for Benign Prostatic Hyperplasia. *J Urol* 148:1549
4. Beitz J, Gnecco C, Justice R (1996) Quality-of-life end points in cancer clinical trials: The U.S. Food and Drug Administration Perspective. *J Natl Cancer Inst Monogr* 20:7
5. Bostwick DG (1995) Prostate-specific antigen and pathology of the prostate. *Eur Urol* 27(Suppl 2):5
6. Braslis KG, Santa-Cruz C, Brickman AL, Soloway MS (1995) Quality of life 12 months after radical prostatectomy. *Br J Urol* 75:48
7. Brawer MK (1994) Prostate-specific antigen: critical issues. *Urology* 44(6S):9
8. Calais da Silva F (1993) Quality of life in prostatic carcinoma. *Eur Urol* 24(Suppl 2):113
9. Cassileth BR, Soloway MS, Vogelzang NJ, Chou JM, Schellhammer PD, Seidmon EJ, Kennealy GT and members of the Zoladex Prostate Cancer Study Group (1992) Quality of life and psychosocial status in stage D prostate cancer. *Qual Life Res* 1:323
10. Cella DF, Tulsky DS (1993) Quality of life in cancer: definition, purpose, and method of measurement. *Cancer Invest* 11:327
11. Cresswell SM, English PJ, Hall RR, Roberts JT, Marsh MM (1995) Pain relief and quality of life assessment following intravenous and oral clodronate in hormone-escaped metastatic prostate cancer. *Br J Urol* 76:360
12. De Haes JC (1988) Quality of life: conceptual and theoretical considerations. In: Watson M, Greer S, Thomas C (eds) *Psychosocial oncology*. Oxford University Press, Oxford, p 61
13. Derogatis LR, Kourlesis SM (1981) An approach to evaluation of sexual problems in the cancer patients. *CA Cancer J Clin* 31:46
14. Donovan K, Sanson-Fisher RW, Redman S (1989) Measuring quality of life in cancer patients. *J Clin Oncol* 7:959
15. Fosså SD (1994) Quality of life after palliative radiotherapy in patients with hormone-resistant prostate cancer: single institution experience. *Br J Urol* 74:345
16. Fosså SD, Aaronson NK, Newling D, Van Cangh PJ, Denis L, Kurth KH, de Pauw M and members of the EORTC Genito-Urinary Group (1990) Quality of life and treatment of hormone resistant metastatic prostate cancer. *Eur J Cancer* 26:1133
17. Fowler FJ Jr, Barry MJ, Lu-Yoa G, Wasson J, Roman A, Wennberg J (1995) Effect of radical prostatectomy for prostate cancer on patient quality of life: results from a medicare survey. *Urology* 45(6):1007

18. Frohmüller HGW, Theiss M, Manseck A, Wirth MP (1995) Survival and quality of life of patients with stage D1 (T1-3 pN1-2 M0) prostate cancer. *Eur Urol* 27:202
19. Helgason AR, Fredrikson M, Adolfsson J, Steineck G (1995) Decreased sexual capacity after external radiation therapy for prostate cancer impairs quality of life. *Int J Radiat Oncol Biol Phys* 32:33
20. Herr HW, Kornblith AB, Ofman U (1993) A comparison of the quality of life of patients with metastatic prostate cancer who received or did not receive hormonal therapy. *Cancer Suppl* 71:1143
21. Kiebert GM, Kaasa S (1996) Quality of life in clinical cancer trials: experience and perspective of the european organization for research and treatment of cancer. *J Natl Cancer Inst Monogr* 20:91
22. Kleer E, Oesterling JE (1993) PSA and staging of localized prostate cancer. *Urol Clin North Am* 20:695
23. Kornblith AB, Herr HW, Ofman U (1994) Quality of life of patients with prostate cancer and their spouses. *Cancer* 73:2791
24. Kramalowsky EV (1988) The value of testosterone deprivation in stage D1 adenocarcinoma of the prostate. *J Urol* 139:1242
25. Lim AJ, Brandon AH, Fiedler J, Brickman AL, Boyer CI, Raub WA, Soloway MS (1995) Quality of life: radical prostatectomy versus radiation therapy for prostate cancer. *J Urol* 154:1420
26. Litwin MS, Hays RD, Fink A, Ganz PA, Leak B, Leach GE, Brook RH (1995) Quality of life outcomes in men treated for localized prostate cancer. *JAMA* 273:129
27. Moore MJ, Osoba D, Murphy K, Tannock IF, Armitage A, Findlay B, Coppin C, Neville A, Venner P, Wilson J (1994) Use of palliative end points to evaluate the effects of mitoxantrone and low-dose prednisone in patients with hormonally resistant prostate cancer. *J Clin Oncology* 12:689
28. Pedersen KV, Carlsson P, Rahmquist M, Varenhorst E (1993) Quality of life after radical retropubic prostatectomy for carcinoma of the prostate. *Eur Urol* 24:7
29. Selby PJ, Chapman JAW, Etazadi-Amoli J (1984) The development of a method for assessing quality of life cancer patients. *Br J Cancer* 50:13
30. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W (1989) Treatment of metastatic prostate cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. *J Clin Oncol* 7:590
31. Tyrell CJ (1994) Tolerability and quality of life aspects with the anti-androgen Casodex (ICI 176,334) as monotherapy for prostate cancer. *Eur Urol* 26(Suppl 1):15
32. Varricchio CG, McCabe MS, Trimble E, Korn EL (1996) Introduction. *J Natl Cancer Inst Monogr* 20:vii-viii
33. Van Aubel OGJM, Hoekstra WJ, Schröder FH (1985) Early orchiectomy for patients with stage D1 prostatic carcinoma. *J Urol* 134:292
34. Van de Ouden D, Tribukait B, Blom JHM, Fossa SD, Kurth KH, Ten Kate FJW, Heiden TH, Wang H, Schröder FH, and members of the EORTC GU group (1993) Deoxyribonucleic acid ploidy of core biopsies and metastatic lymph nodes of prostate cancer patients: impact on time to progression. *J Urol* 150:400
35. Walsh PC, Partin AW, Epstein JI (1994) Cancer control and quality of life following anatomical radical retropubic prostatectomy: results at 10 years. *J Urol* 152:1831
36. Watkins-Bruner D, Scott C, Lawton C, DelRowe J, Rotman M, Buswell L, Beard C, Cella D (1995) RTOG's first quality of life study- RTOG 90-20: a phase II trial of external beam radiation with etanidazole for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 33:901