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Original Paper

The Quality of Life of Patients with Newly Diagnosed M1 Prostate Cancer: Experience with EORTC Clinical Trial 30853

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This study was undertaken to evaluate the quality of life (QoL) of previously untreated patients with M1 prostate cancer before and during androgen-suppressive treatment. Assessment of QoL was included as an optimal component of EORTC protocol 30853, a phase III trial comparing LH-RH (luteinising hormone-releasing hormone) analogue combined with a non-steroidal anti-androgen versus orchiectomy in patients with M1 prostate cancer. At pretreatment and during the follow-up period, patients were asked to complete a questionnaire assessing their physical and psychosocial functioning, and their symptom levels. Physicians rated the patients' performance status, pain, urological symptoms and erectile function. Due to its optional nature, only a minority of the patients in the trial were recruited for the QoL investigation. 63 patients completed a pretreatment questionnaire, of whom 49 completed a second questionnaire at least once during the initial 15 month follow-up period. While statistically significant correlations were observed between patients' and physicians' ratings of physical functioning and pain, these were of only a moderate magnitude (r = 0.43 and 0.30, respectively). No significant association was observed between physicians' and patients' ratings of micturation problems or of erectile function. Before treatment, fatigue, pain and decreased social role and sexual functioning were the problems most frequently reported by patients. With an average of approximately 1 year follow-up, statistically significant improvements were observed in patients' self-reported urological symptoms and metastatic pain. No significant changes were noted for the other QoL domains assessed. The results of this study confirm earlier findings that physicians' ratings may not reflect accurately the functional health and symptom experience of their patients. Patient-based QoL questionnaires offer the most direct means of evaluating the subjective morbidity associated with prostate cancer and its treatment. To increase participation and compliance rates in future studies, it is recommended that QoL assessment be made mandatory in those clinical trials in which QoL is considered to be an important study endpoint.

Key words: M1 prostate cancer, quality of life, hormonal treatment
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INTRODUCTION

THE TRADITIONAL endpoints employed in clinical cancer research include the frequency of local recurrence, development of metastases, duration of disease free and overall survival, and the control of major physical symptoms. Additionally, the inclusion of physicians' assessments of their patients' performance status and of significant somatic morbidity has become the rule in clinical trials in oncology [1–3].

In recent years, however, there has been a growing recognition of the potential value of incorporating the patients' perspective

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in clinical trials. Using self-administered questionnaires or interviews, patients can be asked to describe their symptoms, to report their current level of physical, pyschological and social functioning, and to provide an overall rating of their "quality of life" (QoL) [2]. Importantly, the available evidence suggests that such patient-based assessments may yield results and may lead to conclusions that are quite different from those based on physicians' symptom and toxicity ratings [4, 5].

In clinical prostate cancer research, QoL assessments may be of particular importance in that: (1) this malignancy is one of the most common forms of cancer in men above the age of 50 years: (2) there is little evidence of major improvement in survival rates from current therapies; and (3) the symptoms of the disease and the side-effects of available therapies often result in considerable impairment of physical and psychosocial functioning.

In earlier overviews, information regarding the principal morbidity associated with prostate cancer and the major side-effects of treatment was derived from case record forms (CRFs) completed by the responsible physican [6]. More recent studies have included patient-based evaluations to establish the prevalence of symptoms and of functional impairment in this patient population [7, 8]. In addition to such descriptive studies, QoL assessments have been included in prospective studies of prostate cancer patients undergoing androgen-suppressive treatment [9–11], and of patients with hormone-resistant prostate cancer receiving secondary treatment [12–16].

In 1985, the EORTC Genitourinary Tract Cancer Cooperative Group, in cooperation with the EORTC Quality of Life Study Group, designed a questionnaire to assess the QoL of patients participating in the EORTC protocol 30853 on metastatic prostate cancer. The study was closed to patient entry in 1988, and the results of the first analysis of the principal endpoints have been published [17]. In the present report, the experience with QoL assessment in this trial is reviewed. Topics to be addressed include: (1) levels of compliance with the QoL component of the trial; (2) levels of concordance between physicians' and patients' assessments; and (3) the patients' evaluation of their QoL before and during androgen-suppressive treatment.

PATIENTS AND METHODS

In EORTC protocol 30853, 327 patients with newly diagnosed M1 prostate cancer from 22 institutions were randomised to undergo either orchiectomy or to receive monthly injections with LH-RH (luteinising hormone-releasing hormone) analogues (Zoladex^{R}, Zeneca, U.K.) combined with a non-steroidal antiandrogen (Flutamide 250 mg × 3 daily). Patients were to be evaluated at 1, 3 and 6 months following study entry, and every 6 months thereafter. Patients went off-study at the time of disease progression.

The QoL component of this trial was optional, as were a number of other "side-studies". For those patients enrolled in the QoL study, self-report questionnaires were to be completed at study entry and at each follow-up visit, until disease progression.

Physician-based assessments

Physicians completed a CRF before start of treatment and at each follow-up visit. These forms included the history of the disease and the significant clinical, biochemical and radiological findings. In addition, the physicians were asked to evaluate the patients' performance status (World Health Organisation (WHO) criteria: 0–4); pain level (0 = no analgesics required; 1 = non-narcotic analgesics used irregularly; 2 = non-narcotic analgesics used regularly; 3 = narcotic analgesics used irregularly; or 4 = narcotic analgesics used regularly); urological symptoms (0 = no problems; 1 = mild, not requiring treatment; 2 = moderate, requiring medical treatment; or 3 = severe, requiring surgical treatment or catheterisation); and erectile function (1 = potent; 2 = impotent).

Patient-based assessments

Based on previous QoL studies of the EORTC and clinical experience with prostate cancer patients, a questionnaire* was constructed, comprising a series of multi-item scales assessing the following QoL domains: physical functioning (PhysF; six items), social role functioning (RF; two items), urological symptoms (UrS; four items), fatigue (Ftg; six items), sexual functioning (SexF; three items), emotional functioning (EmF; five items), and social functioning (SocF; two items). The degree of pain (not related to the primary tumour) was evaluated by a single question. For the PhysF and RF scales, dichotomous (i.e. yes/no) response categories were available. For the remaining scales and items, the patients were asked to respond on a four-point categorical scale ranging from "not at all" to "very much." All scores were linearly transformed to a 0 to 100 scale, with higher scores representing a higher level of functioning or fewer symptoms. Some of the scales were subsequently collapsed into three levels (scores of 0–33, 34–67 and 68–100) to facilitate comparisons with the physicians' ratings of comparable QoL domains.

The reliability (internal consistency) of the multi-item scales, as assessed by Cronbach's alpha coefficient, ranged from 0.65 (RF) to 0.84 (EmF) (see Table 1). With the exception of the RF scale, all scales met the 0.70 reliability criterion recommended for group comparisons [18].

RESULTS

Level of participation

As noted above, participation in the QoL component of the trial was optional. In total, only 63 patients (from seven institutions) of the 327 (from 22 institutions) patients enrolled in the medical trial completed a pretreatment QoL questionnaire. As shown in Table 1, these 63 patients did not differ significantly from the 264 patients who did not complete a pretreatment QoL assessment on any important clinical parameters. Thus, despite the low level of participation, there was no evidence of a systematic bias in the recruitment of patients for the QoL substudy.

For 49 of the 63 patients with pretreatment QoL questionnaires, at least one follow-up QoL questionnaire was available between 6 and 15 months following the start of treatment (on-treatment QoL). Patients lost to QoL follow-up tended to report more impairment in physical and psychosocial functioning, and higher symptom levels at the pretreatment assessment than did those for whom QoL follow-up data were available (data not presented).

If, within the first 15 months of follow-up, multiple on-treatment QoL questionnaires were available for a given patient, the questionnaire completed last was used in the current analysis. For the 49 patients with follow-up QoL data, a median of 11 months (range 6–15 months) had elapsed between the pretreatment and the on-treatment QoL assessment. Due to the limited number of patients with QoL data, no attempt was made to

* This questionnaire was similar, but not identical to the QLQ-C30, the current EORTC core quality-of-life questionnaire [19].

Table 1. Sociodemographic and clinical characteristics for patients with and without pretreatment quality-of-life (QoL) data

	Pretreatment QoL data	
	Present	Absent
n	63	264
Mean age in years (range)	70 (56–80)	70 (42–82)
Mean interval in months from diagnosis to trial entry (range)	4 (10–83)	6 (0–84)
T category		
0/1/2	28%	25%
3	50%	48%
4	22%	28%
Hotspots on bone scan	100%	96%
Concurrent chronic disease	52%	54%
Weight loss		
≤5%	81%	80%
>5%	18%	20%
Mean haemoglobin (g/100 ml) (range)	12.8 (8.5–16.1)	13.2 (6.3–17.5)
Elevated serum creatinine	8%	11%
Elevated alkaline phosphatase	58%	57%
Randomisation		
Orchiectomy	50%	54%
Medical castration	50%	46%
WHO performance status		
0/1	90%	85%
2	8%	12%
3/4	2%	3%
Physician-rated pain		
No/mild	71%	71%
Moderate	22%	18%
Severe/intolerable	7%	11%
Physician-rated sexual status		
Potent	35%	44%
Impotent	65%	56%

compare the QoL of patients in the two treatment arms of the trial.

Physicians' versus patients' evaluation of pretreatment QoL

A comparison of the physicians' and patients' pretreatment assessments of physical functioning, pain, urological symptoms and erectile function are presented in Tables 2 to 5. Statistically significant, but only moderate correlations were observed between physicians' and patients' assessments of daily physical functioning ($r = 0.43$; $P < 0.001$) and pain ($r = 0.30$; $P = 0.02$). Importantly, with increasing impairment in physical functioning or increasing pain (as reported by the patients), the level of disagreement between the physicians' and patients' assessments was more pronounced.

No statistically significant correlations were observed between the urologists' and the patients' evaluations of micturation problems or of erectile function. Only half of the patients reporting moderate or severe urological symptoms were so recognised by their physician. Conversely, of the 15 patients who reported no or only slight problems in getting or maintaining an erection, 8 were reported to be impotent by their urologist.

Similar results were obtained when comparing physicians' versus patients' on-treatment assessments of daily physical functioning, pain and erectile function. However, the correlation between the physicians' and patients' ratings of urological symptoms was substantially higher at the on-treatment assessment point ($r = 0.51, P < 0.001$).

Table 2. Patients' (QoL) and physicians' (CRF) assessment of pretreatment functioning and symptoms (n = 63)

A. Physical functioning ($r = 0.43$; $P < 0.001$)

	Physicians' WHO performance status		
Patients' PhysF*	0/1	2	Total
Very good/good	35	3	38
Moderately reduced	9	3	12
Severely reduced	6	7	13
Total	50	13	63

*Scores on the physical functioning (PhyS) scale ranged from 0 to 100, with higher scores representing better functioning. Scale scores were trichomised into 68–100 (very good/good), 34–67 (moderately reduced) and 0–33 (severely reduced).

Table 3. Pain (r = 30; P = 0.02)

	Physicians			
Patients*	1†	2†	3†	Total
None/slight	17	3	0	20
Moderate	25	14	1	40
Severe	2	0	0	2
Total	44	17	1	62

*Scores ranged from 0 to 100, with higher scores representing less pain. Scale scores were trichomised into 68–100 (none/slight), 34–67 (moderate) and 0–33 (severe); †Pain scored in terms of required analgesics: 1 = none or non-narcotics irregularly; 2 = non-narcotics regularly or narcotics irregularly; 3 = narcotics regularly.

Table 4. Urological symptoms (r = 0.18; P > 0.05)

	Physicians			
Patients' UrS*	None/minor†	Moderate†	Severe†	Total
None/slight	30	4	8	42
Moderate	10	4	6	20
Severe	0	0	1	1
Total	40	8	15	63

*Scores ranged from 0 to 100, with higher scores representing fewer urological symptoms. Scale scores were trichomised into 68–100 (none/slight), 34–67 (moderate) and 0–33 (severe); †Rated as 1 = no urological symptoms or minor problems not requiring treatment; 2 = moderate symptoms requiring treatment; 3 = severe symptoms requiring surgical treatment or catheterisation.

QoL before and during androgen-suppressive therapy

Before treatment, fatigue, pain and decreased social role and sexual functioning were the problems most frequently reported by the patients (Table 6). At this pretreatment assessment, moderate to high correlations were observed between physical

Table 5. Erectile dysfunction (r = 0.21; P > 0.05)

Patients' erectile problems*	Doctors Potent	Impotent	Total
None/slight	7	8	15
Moderate	2	5	7
Severe	13	24	37
Total	22	37	59

*Scores ranged from 0 to 100, with higher scores representing fewer problems, with getting or maintaining an erection. Scale scores were trichomised into 68–100 (none/slight), 34–67 (moderate) and 0–33 (severe).

functioning and social role functioning ($r = 0.73$), physical functioning and pain ($r = 0.51$), emotional functioning and fatigue ($r = 0.53$), and between fatigue and sexual functioning ($r = 0.56$).

Table 7 presents the pretreatment versus on-treatment mean QoL scores for the 49 patients for whom both assessments were available. With an average of approximately 1 year follow-up after start of treatment, statistically significant improvements were observed in patients' self-reported urological symptoms and metastatic pain. No significant changes over time were found for the remaining functioning or symptom scales.

When analysed at the level of individual urological symptoms (Table 8), a significant reduction over time was noted for dysuria, urgency and urinary incontinence. Haematuria was rarely reported at either baseline or follow-up. Within the period of follow-up evaluation (i.e. between 6 and 15 months), a significant association was found between the severity of self-reported urological symptoms and the time elapsed since start of treatment ($r = 0.39$; $P < 0.01$).

Although no statistically significant changes over time were observed in the mean scores on the sexual functioning scale, an examination of the individual items (Table 8) suggests that patients experienced some decline in sexual enjoyment, while libido and erectile function remained unchanged.

DISCUSSION

The present study represents the EORTC GU Group's first attempt to assess the QoL of patients with urological cancer. At the time that this trial was initiated, most of the urologists in the group were unfamiliar with the methods of QoL assessment, and many were sceptical as to whether the additional effort required to collect QoL data from their patients would yield useful information beyond that reported on the CRFs (e.g. clinician's ratings of performance status, morbidity and toxicity data, biochemical and radiological data).

Given this relatively high level of scepticism on the part of the participating clinicians, it was decided that QoL assessment should be an optional component of the clinical trial. This proved to be a crucial decision, with serious adverse consequences for participation rates. Only seven of the 22 institutions which

Table 7. Pretreatment versus on-treatment QoL questionnaire scores (n = 49)*

QoL domain	Pretreatment mean (S.D.)	On-treatment mean (S.D.)
PhysF	72 (33)	73 (33)
RF	66 (41)	66 (44)
UrS†	81 (17)	91 (12)
Ftg	51 (23)	51 (26)
SexF	52 (29)	54 (30)
EmF	76 (18)	79 (23)
SocF	78 (26)	80 (28)
Pain‡	66 (29)	75 (29)

*Student's *t*-test for correlated data. †$P < 0.05$; ‡$P < 0.01$.
For abbreviations see Table 6.

Table 8. Pretreatment versus on-treatment urological symptoms and sexual functioning scores (n = 49)*

	Pretreatment mean (S.D.)	On-treatment mean (S.D.)
Urological symptoms		
Dysuria†	89 (16)	97 (9)
Urgency‡	60 (29)	80 (25)
Urinary incontinence§	77 (30)	88 (25)
Haematuria	93 (20)	98 (8)
Sexual functioning		
Interest	74 (28)	73 (30)
Enjoyment	31 (39)	22 (34)
Erection	45 (40)	44 (46)

*Student's *t*-test for correlated data; †$P < 0.01$; ‡$P < 0.001$; §$P < 0.05$.

Table 6. Scale score distributions and reliability for the pretreatment QoL questionnaire (n = 63)

QoL domain	Number of items	Mean	Standard deviation	Cronbach's alpha
Physical function (PhysF)	6	71	32	0.86
Role function (RF)	2	60	42	0.65
Urological symptoms (UrS)	4	78	18	0.72
Fatigue (Ftg)	5	52	22	0.77
Sexual function (SexF)	3	49	29	0.77
Emotional function (EmF)	5	72	21	0.84
Social function (SocF)	2	77	25	0.76
Pain	1	64	30	—

participated in the medical trial included patients in the QoL substudy. Further, within these seven institutions, not all patients entered into the medical trial were included in the QoL investigation.

Importantly, the low recruitment rate for the QoL substudy did not reflect a lack of willingness on the part of the patients to complete the requisite questionnaires. To our knowledge, no patients asked to participate in the QoL substudy declined to do so. There was also no evidence of any systematic bias in the selection of patients for the QoL substudy. This is reflected in the fact that no significant differences in sociodemographic or clinical characteristics were observed between those patients who were or were not initially recruited for the QoL substudy. Rather, the inconsistent recruitment of patients for the QoL study appeared to result from both inadequate motivation on the part of some clinicians, and practical constraints operating within the local institutions (e.g. busy outpatient clinic schedules, lack of research personnel, etc.).

A related problem encountered in the QoL substudy concerned the loss of patients to follow-up. Of the 63 patients who completed a pretreatment QoL questionnaire, only 49 (78%) completed at least one additional questionnaire during the first 15 months of follow-up. The completion rates beyond this initial follow-up period were so low as to prohibit serial analysis of the QoL data. This loss to follow-up could, at least in part, be attributed to the same factors affecting the initial recruitment rates (i.e. lack of salience, logistical problems). At the same time, there is some evidence to suggest that a systematic bias may have been operating during the follow-up period. That is, patients for whom follow-up QoL were unavailable tended to report more functional impairment and higher symptom levels at the pretreatment assessment than did those patients for whom follow-up data were collected. Unfortunately, no information was available to determine whether patients were unwilling or unable to complete the follow-up questionnaires as they became more ill, or whether the clinicians were simply reluctant to ask them to do so.

Despite the administrative and logistical problems encountered, a number of useful substantive findings emerged from the QoL component of protocol 30853. A comparison of physicians' and patients' ratings on similar QoL measures indicated clear discrepancies. Although the physicians' ratings on measures of physical functioning and metastatic pain correlated significantly with those of the patients, the magnitude of the correlations was only moderate. Importantly, concordance levels declined with increasing levels of dysfunction and symptoms. No significant association was found between physicians' and patients' ratings of micturation problems or erectile function. These findings confirm the results of other studies indicating that observers' ratings (whether they be physicians, nurses or spouses) may not reflect the health experience of the patients themselves [4].

Data from the pretreatment QoL questionnaire indicated that the principal subjective morbidity associated with newly diagnosed metastatic prostate cancer includes pain, fatigue, micturation problems, impaired sexual life and reduced social role functioning. The high level of sexual dysfunction observed at pretreatment confirms clinical impressions that many patients with newly diagnosed M1 prostate cancer already experience such problems before any androgen-suppressive treatment has been initiated. Not only the prostate cancer itself, but also advanced age and concurrent chronic health conditions may all contribute to sexual dysfunction. Importantly, although erectile dysfunction and comprised sexual enjoyment are characteristic of this patient population, libido remains relatively strong. This suggests that clinicians should not assume that, because of the advanced age of many of these patients, sexuality and sexual function are of little importance.

After the start of hormonal treatment, the patients' urological symptoms and pain improved significantly, whereas fatigue, sexual functioning and social role functioning remained relatively unchanged. Contrary to the findings of Cassileth and colleagues [9], no improvement was observed in the patients' emotional functioning during therapy.

As a result of the experience gained in this and other EORTC clinical trials, several steps have been taken to facilitate the successful implementation of future QoL investigations. First, substantial efforts have been devoted to increasing clinicians' awareness of the availability of robust methods for assessing patients' QoL. In particular, the adoption within the EORTC of a standard 'core' QoL questionnaire with demonstrated reliability and validity [19], combined with a programme to generate supplementary, tumour-specific questionnaire modules [20] has helped to allay concerns about the scientific basis and potential clinical relevance of QoL investigations.

Second, a quality of life unit has been established at the EORTC Data Centre in order to better coordinate QoL research activities, and to provide timely advice and feedback to clinicians and data managers responsible for carrying out such investigations. The membership of the EORTC protocol review committee has also been expanded to include an expert in QoL research in order to assure that QoL data collection procedures are appropriate and realistic.

Finally, and perhaps most importantly, the EORTC GU Group has adopted a policy which makes participation in QoL investigations mandatory for those clinical trials in which QoL is considered to be an important study endpoint. It is expected that these changes in QoL policy and practice will result in accrual and compliance rates sufficiently high to allow for the comparative analyses central to phase III trials, as well as the more descriptive analyses of the type reported here for the 30853 protocol. Early results from those phase III clinical trials which have been initiated following the introduction of these policies suggest that this will be the case.

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