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QUALITY OF LIFE DURING CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

II. A longitudinal study of the EORTC Core Quality of Life Questionnaire and comparison with the Sickness Impact Profile

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Sixty-two patients with small cell lung cancer, 36–80 years of age, who were receiving chemotherapy during a maximum of one year, were consecutively included in a study of quality of life during treatment. An interim version (C-36) of the EORTC Core Quality of Life Questionnaire (QLQ) was applied for quality of life assessment prior to treatment and every third month during the treatment period. The assessments were related to clinical variables (performance status and tumour response), and compared with results from assessment with the Sickness Impact Profile (SIP). The QLQ was sensitive to differences in clinical status and responded to clinical change over time. In general, the pattern of correlations with SIP lends support to the construct validity of the QLQ. However, some questions arose from the comparison with SIP: QLQ emotional functioning did not change in concordance with SIP, and assessment of social functioning was not optimal prior to treatment. The questionnaire was well accepted by the patients. The EORTC QLQ C-36 constitutes a promising step in the development of a feasible standard instrument for quality of life assessment in cancer clinical trials.

Key words: Lung cancer, small cell type, chemotherapy, quality of life.

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Combination chemotherapy significantly improves short-term survival in small cell lung cancer (SCLC) but seldom cures the patient. Disease-free two-year survival in unselected patient materials is $<10\%$ (1). Since most effective treatment regimens cause substantial toxicity, studies on quality of life during treatment are warranted. During the 1980s, several patient self-rated questionnaires have been developed for evaluation of quality of life in clinical trials (2, 3), a majority of which are diagnosis- or study-specific and need to be sufficiently tested for general use. On the other hand, a number of well-documented generic health measures, such as the Sickness Impact Profile (SIP) (4), are available. They allow for comparison of results from studies across a wide range of chronic diseases but may be insensitive to some topics of interest in a specific diagnosis or research setting. We used the SIP for evaluation of the impact of disease and treatment on physical and psychosocial function in 62 SCLC patients who received chemotherapy (5). Functional limitations were well characterised, but the validity of SIP for assessment of depression has to be further evaluated among patients with advanced cancer. A major disadvantage of the SIP is the large number of items which makes it time-consuming and impractical for use in cancer clinical settings.

A few instruments, such as the Functional Living Index-

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Cancer (FLIC) (6) and the Toronto scale (7), were developed and psychometrically evaluated for general use in cancer trials. The FLIC, although well documented, has not yet been adopted as a standard quality of life measure in cancer trials, partly because of feasibility problems (8, 9), and partly due to problems with interpretation, as the instrument provides one summary index of all aspects of quality of life. The Toronto questionnaire, on the other hand, offers no summary measures of different aspects of quality of life, which makes the results difficult to incorporate into the medical decision-making process.

The Study Group on Quality of Life within the European Organization for Research and Treatment of Cancer (EORTC) has, during a number of years, been working on the development of a Core Questionnaire for general application in cancer trials. The goal of this work was to construct a cancer-specific, multidimensional and relatively short patient self-administered instrument with adequate levels of reliability, validity (cross-cultural as well as statistical) and responsiveness to clinical changes. An interim version (C-36) of the questionnaire has recently been evaluated in a field study with participating institutions from 15 countries (10). As one of the participating institutions in this research work, we adopted the C-36 version of the EORTC Core Quality of Life Questionnaire (QLQ) together with the SIP and the Hospital Anxiety and Depression scale (HAD) (11) for assessment of quality of life in a series of SCLC patients who received chemotherapy at the Renströmska Hospital. The results with SIP and HAD are discussed in detail elsewhere (5). In the present paper we will report on changes of quality of life during treatment for SCLC, as measured by the EORTC Core Quality of Life Questionnaire, and the results of statistical evaluation of the questionnaire and a comparison with the SIP.

Material and Methods

The study comprises 62 consecutive SCLC patients who received cytotoxic treatment at the Department of Pulmonary Medicine, Renströmska Hospital. Details on eligibility criteria, staging procedures, and treatment regimens are presented elsewhere (5). Briefly, in patients $\leqslant 70$ years, tumour staging was based on bone marrow investigation and liver sonography, and the treatment consisted of combination chemotherapy, while in patients >70 years the liver sonography was not routinely performed and treatment consisted of single-drug therapy with etoposide or teniposide, i.v. All treatment schedules extended over one year. Performance status (PS) was defined according to the World Health Organization (WHO) (12). The stage of disease was defined as extensive (ED) if distant metastases were detected, otherwise as limited (LD). Standard criteria were used for evaluation of response (12).

Quality of life assessment

Quality of life questionnaires were completed before start of treatment and then every third month until chemotherapy was discontinued. All questionnaires were completed in connection with scheduled visits at the outpatient clinic or on the ward. The patients had access to a research nurse for assistance if needed.

The C-36 version of the EORTC Core Quality of Life Questionnaire (in the following referred to as QLQ) consists of 36 items concerned with different areas of disease and treatment consequences that are common to a wide range of cancer sites. Items that were hypothesized to measure aspects of the same quality of life domain were aggregated into scales (13). Thus, scales were constructed for physical functioning (PF), role functioning (RF), emotional functioning (EF), social functioning (SF), and overall health and quality of life (QL). In addition, two scales were constructed from cancer symptom items on fatigue and malaise (F) and nausea/vomiting (NV). Single items were included for assessment of financial impact, alertness behaviour and various common physical symptoms of cancer. Thirteen additional items, which specifically address disease symptoms in lung cancer and treatment side-effects, were adopted for a lung cancer module (LC) that was also used in the international field study. Three LC items on dyspnoea were aggregated into a dyspnoea scale.

The SIP was used as reference method for assessment of physical, psychosocial and overall dysfunction, while the HAD scale was applied for assessment of emotional distress. The properties of SIP and HAD are discussed elsewhere (5, 11, 14).

Statistics

Analyses were performed to establish the reliability and construct validity of the multi-item scales of the questionnaire. Scale scores were calculated according to Likert's method of summated ratings (15) by summation of the item scores and division by the number of items within each scale. A Likert-type scale was constructed from the dichotomous items of PF and RF respectively by summation of the item scores. Cronbach's alpha coefficient (16) was calculated for assessment of scale reliability (i.e. internal consistency). A matrix of item–scale correlations was created for testing of discriminant validity of items (17). Construct validity of the scales was examined by a correlation matrix of all EORTC scales, and by correlations between the EORTC scales and clinical variables. A correlation analysis was also made between the EORTC and SIP scales.

All correlations given in the text are Pearson's correlation coefficients. Correlations were tested for significance by Pitman's non-parametric permutation test (18). Significance testing of differences was performed by Fisher's two-tailed non-parametric permutation test (18). Stepwise regression was applied for multivariate analysis of dependent variables.

Table 1

Content of the EORTC Core Quality of Life Questionnaire (C-36 version) and results from pretreatment assessment in 62 SCLC patients. With the exception of the global quality of life scale, higher scores represent more pronounced dysfunction or symptoms

Quality of Life domain	No. of items	Score range	Mean score (n = 62)
Physical functioning	7	0–7	3.4
Role functioning	2	0–2	0.9
Emotional functioning	8	1–4	1.9
Social functioning	2	1–4	1.5
Financial impact	1	1–4	1.1
Disease symptoms			
Fatigue and malaise	5	1–4	2.4
Nausea/vomiting	2	1–4	1.3
Appetite	1	1–4	2.1
Diarrhoea	1	1–4	1.2
Constipation	1	1–4	1.7
Pain	1	1–4	2.1
Dyspnoea	1	1–4	2.5
Sleep disturbance	1	1–4	2.0
Alertness behaviour	1	1–4	1.5
Global health/quality of life	2	1–7	4.0

Table 2

Content of the EORTC Lung Cancer module and results from pretreatment assessment in 62 SCLC patients. Higher scores represent more pronounced symptoms

Symptoms	No. of items	Score range	Mean score (n = 62)
Disease symptoms			
Pain	4[a)]		
in chest	1	1–4	1.6
in arm/shoulder	1	1–4	1.5
elsewhere	1	1–4	1.7
Dyspnoea	3[b)]	1–4	2.1
Cough	1	1–4	2.4
Hemopthysis	1	1–4	1.2
Treatment side-effects			
Sore mouth	1	1–4	1.1
Dysphagia	1	1–4	1.2
Hair loss	1	1–4	1.1
Neuropathia	1	1–4	1.1

a) The pain items in LC were not aggregated into a scale. The 4th item on analgetics is excluded from the table.
b) In 3 patients, the scale score was calculated from 2 items due to missing data.

The significance level was set at 5% throughout. Analysis of response patterns according to assumptions of interrelationships minimized the risk of overestimation of the number of significant tests. In general, measures assumed to assess the same underlying construct (i.e. quality of life dimension) were hypothesized to be more highly intercorrelated than were measures assumed to assess different constructs, irrespective of the assessment method.

Results

Patient characteristics

Detailed information on patient characteristics are presented elsewhere (5). Briefly, 48% had ED, and 32% were mainly or totally confined to bed or chair (PS 3–4) by treatment start. Median age was 66 years (range 36–80), and 35% were >70 years of age. Nineteen patients were in gainful employments, but only 3 were working when chemotherapy was initiated. Twenty-seven per cent were living alone.

Pretreatment quality of life evaluation

The content of the QLQ is outlined in Table 1, and the mean scores of scales and single items, calculated from responses prior to treatment, are presented. Corresponding data concerning the LC are displayed in Table 2. The results are discussed in the following paragraphs.

a) Physical functioning (PF). The items of this scale have dichotomous response choices ('yes' or 'no'), reflecting a continuum of increasing level of dysfunction. Fifty-six patients (90%) were unable to do hard work (e.g. moving heavy furniture), while only two patients reported difficulties with self-care activities.

b) Role functioning (RF). The scale construction is equal to PF, although it contains only two items. Two-thirds of the patients reported limitations in performing their work or household jobs, while 20% were completely disabled.

c) Emotional functioning (EF). Each item has 4 response categories, ranging from 'not at all' to 'very much'. Eleven patients (18%) reported clinically significant levels ('quite a bit' or 'very much') of at least two anxiety symptoms, while 28 patients (45%) reported clinically significant levels of two or more depressive symptoms.

d) Social functioning (SF). Response categories were the same as in EF. Thirty-nine per cent of the patients reported that their health condition interfered 'quite a bit' or 'very much' with family or social life.

e) Disease symptoms. Fatigue and malaise (F) symptoms were substantial in 40% of the patients (average proportion, range 26 to 48%), while 48% reported feeling physically well. In 23 patients (37%), lack of appetite was substantial. Nineteen per cent were nauseated and 15% vomited more than 'a little'. Clinically significant sleep disturbances were reported by 16 patients (26%). One-third of all patients had substantial pain according to the single-pain item in QLQ. In the LC module, 8 patients (13%) reported substantial chest pain, 9 (15%) had pain in arm or shoulder, while 11 (18%) had pain at other sites. Of 28 patients who were taking analgetics, 6 reported none or little help from the medicine. Dyspnoea level was rated 'quite a bit' or 'very much' by 50% of all patients in the QLQ. According to the responses to the dyspnoea items in the LC module, 8% were short of breath at rest, 31% when walking, and 58% when climbing

stairs (3 patients though did not answer this item, being unable to climb stairs). Twenty-three patients (37%) were coughing more than 'a little', while only one patient reported hemopthysis. Fourteen patients (23%) were constipated and two had diarrhoea.

f) Financial impact. Only two patients reported substantial financial difficulties caused by the disease or treatment (which had not yet started).

g) Global health/quality of life (QL). Patients were asked to rate their overall physical condition and quality of life respectively. The response categories of the two items of this scale range from 1 ('very poor') to 7 ('excellent'), with category labels only at the extreme values. Eleven and 19% of the patients respectively rated their physical condition and quality of the life better than 5, while 15% rated both items worse than 3.

Follow-up data

Forty-one patients exited from the study prior to twelve months due to tumour progression (n = 28), death during chemotherapy (n = 11), or treatment toxicity (n = 2). The overall tumour response rate (partial and complete responses) was 82%. Overall performance status improved significantly during the first 3 treatment months ($p < 0.05$).

Subsequent quality of life assessments at 3, 6, 9 and 12 months were performed in 48, 34, 25 and 21 patients respectively. Mean scores of the functional QLQ scales at follow-up and changes from the pretreatment assessments are displayed in Table 3. Significant changes were seen only in social functioning which deteriorated at 6 months, and in emotional functioning which improved in the subpopulation of patients that were assessed after one year. A non-significant deterioration in mean physical functioning was observed after 3 months. Financial problems were reported by 0, 3 and 1 patients respectively at 3, 6 and 12 months.

Changes of symptoms and side-effects are shown in Table 4. The mean level of nausea increased at 6 months, while the nausea level at other points of measurement was unchanged in comparison with the pretreatment assessment. General physical well-being, as assessed by the fatigue and malaise scale, did not change substantially. A significant pain relief was recorded at 12 months. Cough and dyspnoea improved during the first 3 months and remained improved throughout the period of chemotherapy. Sleep disturbances were significantly reduced. Moderate or severe neuropathia was reported by approximately 30% of all patients throughout the treatment period. Fifty per cent of the patients were 'bothered' by hair loss after 3 months, but the proportion of bothered patients fell to 25% by 12 months, although the majority were apparently bald from 4 weeks and throughout the treatment period.

Correlations between quality of life data and clinical variables

The results from analysis of correlations and distribution of pretreatment QLQ function scales by tumour stage and performance status are displayed in Table 5. A high correlation was seen between physical functioning, as assessed by the patients, and physician-rated performance status. Of 23 patients with PS 0–1, 20 (87%) rated their physical functioning better (less) than 4, while 16 out of 20 patients with PS 3–4 (80%) rated their physical functioning 4 or worse. Significant correlations were seen also between the RF and QL scales and performance status, while neither of these scales correlated significantly with the stage of disease. Of QLQ symptom scales and items (not in table), only appetite was related to disease stage ($p < 0.05$), while performance status correlated with fatigue and malaise ($r = 0.55$, $p < 0.001$), appetite, dyspnoea ($r = 0.34$–0.39, $p < 0.01$) and sleep disturbances ($r = 0.31$, $p < 0.05$). Neither sex nor age correlated significantly with the quality of life variables.

Correlations between changes (Δ) of variables within the EORTC questionnaire and clinical changes are shown in

Table 3

*Mean scores of quality of life scales and items at follow-up assessments during chemotherapy. Numbers in brackets are mean changes from the initial (pretreatment) assessments in the corresponding patient subpopulations. With the exception of global health/quality of life, which has a reversed scaling, changes > 0 indicate deterioration, while changes < 0 indicate improvement. Levels of statistical significance are indicated with * (p < 0.05) or ** (p < 0.01); Fisher's test*

Quality of Life domain	Months from treatment start		
	3 (n = 48)	6 (n = 34)	12 (n = 21)
Physical functioning	3.3 (0.3)	2.9 (0)	2.6 (−0.4)
Role functioning	1.0 (−0.1)	0.9 (0.1)	0.7 (−0.1)
Emotional functioning	1.7 (−0.1)	1.7 (0.2)	1.7 (−0.3)*
Social functioning	1.6 (0.1)	2.1 (0.5)**	1.5 (0.1)
Financial impact	1.1 (−0.1)	1.3 (0.1)	1.1 (0.1)
Global health/quality of life	4.4 (0.3)	4.4 (0.2)	4.6 (0.4)

Table 4

*Mean scores of symptom scales and items at follow up during chemotherapy. Numbers in brackets are mean changes from the initial (pretreatment) assessments in the corresponding patient subpopulations. Changes > 0 indicate deterioration, while changes < 0 indicate improvement. Levels of statistical significance are indicated with * ($p < 0.05$) or ** ($p < 0.01$); Fisher's test*

Symptoms	Months from treatment start		
	3 (n = 48)	6 (n = 34)	12 (n = 21)
Disease symptoms			
Fatigue and malaise	2.2 (−0.1)	2.3 (0)	2.0 (−0.3)
Nausea/vomiting[a)]	1.3 (0)	1.6 (0.4)*	1.2 (−0.2)
Appetite	1.7 (−0.3)	2.0 (0)	1.1 (−0.4)
Pain	1.8 (−0.1)	2.1 (0.1)	1.6 (−0.4)*
Dyspnoea			
single item (QLQ)	2.0 (−0.5)**	2.4 (−0.2)	2.0 (−0.6)*
3-item scale (LC)	1.8 (−0.2)	2.0 (0)	1.9 (0)
Sleep disturbance	1.5 (−0.3)	1.6 (−0.3)	1.4 (−0.5)*
Cough	1.7 (−0.5)**	1.9 (−0.4)**	1.5 (−0.6)**
Treatment side effects			
Neuropathia	2.0 (0.9)**	2.0 (0.9)**	2.1 (1.0)**
Hair loss	2.5 (1.4)**	2.0 (0.9)**	1.8 (0.8)*

a) Symptoms likely also to reflect treatment side effects

Table 5

*Distribution of quality of life scales by pretreatment clinical variables. Numbers in brackets are correlations. Only correlations > 0.20 are given. Levels of statistical significance are indicated with * ($p < 0.05$) or ** ($p < 0.01$); Pitman's test*

Quality of Life domain	Clinical variables					
	PS				Stage	
	0–1	2	3–4		LD	ED
Physical functioning	2.3	3.1	5.0	(0.65)**	3.2	3.6
Role functioning	0.4	1.1	1.2	(0.46)**	0.9	0.8
Emotional functioning	1.8	1.8	2.1	(0.24)	1.9	1.9
Social functioning	1.3	1.6	1.6		1.6	1.3
Global health/quality of life	4.4	4.3	3.3	(−0.33)**	4.0	4.0

Table 6. While ΔPS correlated with changes of both physical and emotional variables, tumour response related mainly to changes of emotional functioning and pain. The correlation between ΔQL and ΔPS was explained by the first QL item, which measures overall physical health, that is closely related to fatigue, while the second item, which measures overall quality of life, did not correlate at all with ΔPS. The responsiveness to improvement of PS was better for the fatigue scale than for the PF scale, while the reverse was true for deterioration. Of 24 patients who were improved with respect to PS, 17 (71%) reported less fatigue at follow-up than before treatment start, as compared to 13 (54%) who reported less physical dysfunction. Of 11 patients with deterioration of performance status, 7 and 9 deteriorated with regard to fatigue and physical functioning respectively.

Correlations between the EORTC questionnaire and the Sickness Impact Profile

Correlations between EORTC QLQ scales and SIP categories from the pretreatment assessment are displayed in Table 7. The QLQ scales of physical and role functioning correlated well with categories within the physical dimension of SIP, while emotional functioning correlated best, although moderately, with categories within the psychosocial dimension of SIP and with the sleep/rest scale. The QLQ scale of global quality of life was related to both SIP dimensions. The QLQ scale of social functioning did not correlate well with any of the SIP categories prior to treatment. However, at 3 months' evaluation, the SF scale correlated significantly with the SIP scales of social inter-

Table 6

*Correlations between changes (Δ) of quality of life scales 0–3 months and clinical variables in 48 SCLC patients. Only correlations > 20 are given. Levels of statistical significance are indicated with * ($p < 0.05$) or ** ($p < 0.01$); Pitman's test*

	Clinical variables	
	ΔPS	Tumour response
Quality of life domains		
Physical functioning	0.58**	
Role functioning	0.47**	
Emotional functioning	0.40**	0.39**
Social functioning		
Global health/quality of life[a)]	−0.29*	
Symptom scales and items		
Fatigue and malaise	0.48**	0.29*
Nausea/vomiting		
Appetite	0.43**	
Dyspnoea[b)]	0.24	
Pain	0.29	0.35*

a) Negative correlations due to reversed scaling
b) Single item in QLQ

action ($r = 0.41$, $p < 0.01$) and communication ($r = 0.39$, $p < 0.05$). In general, correlations between the EORTC and SIP scales were significantly stronger at 3 months' follow-up (not in table) compared with the pretreatment assessment. The correlation pattern of the fatigue and malaise scale was similar to that of the global health/quality of life scale, though fatigue/malaise did not correlate significantly with SIP emotional behaviour.

Correlations between ΔPF, ΔEF and ΔQL and changes of SIP physical, psychosocial and total index respectively, are displayed as scatter-grams in the Figure. The overall concordance of the physical variables was 52%, while 9 patients (19%) changed their SIP and EORTC ratings in opposite directions, although no major discordance was seen. The concordance of the emotional/psychosocial variables was 54%. However, the concordance of the emotional function and behaviour scales of QLQ and SIP (not in figure) was only 29%. Changes of the anxiety items of the QLQ emotional functioning scale were best related to the changes of SIP emotional behaviour ($r = 0.35$), while no relationship was found between changes of EF depression items and SIP ($r = 0.12$). Changes of overall health measures were concordant in 58% and discordant in 23% of the patients (Figure). ΔF was closely related to the change of SIP total index ($r = 0.61$, $p < 0.001$, not in figure), and correlated significantly with changes of all SIP subscales with the exception of emotional behaviour, alertness behaviour, work, and eating.

Correlation between EORTC scales and HAD

As the eight items of the QLQ emotional functioning scale were derived from the HAD, corrections for overlap

Table 7

*Correlations between EORTC QLQ quality of life scales and SIP categories at pretreatment administration. Only correlations > 20 are given. Levels of statistical significance are indicated with * ($p < 0.05$) or ** ($p < 0.01$); Pitman's test*

SIP categories	QLQ scales					
	PF	RF	EF	SF	QL[a)]	F
Mobility	0.61**	0.54**	0.28*		−0.52**	0.62**
Ambulation	0.59**	0.46**			−0.34**	0.47**
Body care/movement	0.62**	0.46**			−0.32**	0.34**
Emotional behaviour	0.26*	0.32*	0.37**		−0.32**	
Alertness behaviour		0.28*				
Communication	0.41**	0.31*	0.33*		−0.48**	0.36**
Social interaction	0.44**	0.43**	0.36**		−0.53**	0.50**
Sleep/rest	0.50**	0.48**	0.33*		−0.44**	0.56**
Home management	0.59**	0.57**	0.32*		−0.47**	0.58**
Work		0.29*				
Recreation/pastimes	0.35**				−0.28*	0.32*
Eating	0.35**		0.26		−0.29*	0.24
SIP physical index	0.67**	0.53**			−0.42**	0.49**
SIP psychosoc. index	0.39**	0.46**	0.36**		−0.51**	0.40**
SIP total index	0.63**	0.60**	0.28*		−0.49**	0.55**

a) Negative correlations due to reversed scaling
Abbreviations: PF = physical functioning; RF = role functioning; EF = emotional functioning; SF = social functioning; QL = global health/quality of life; F = fatigue/malaise

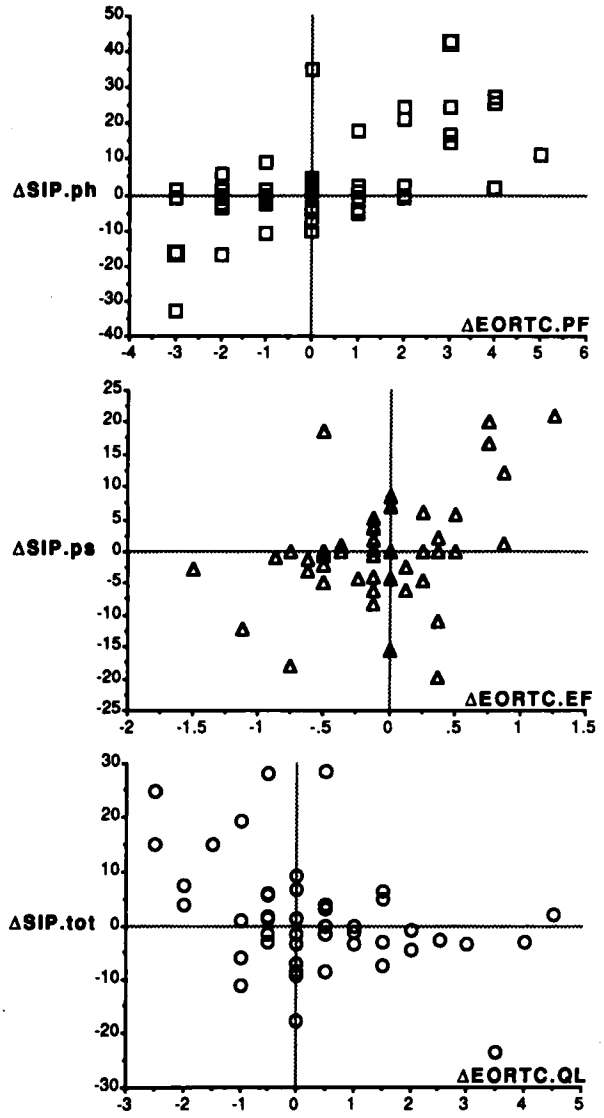

Figure. Correlations between scales of physical, emotional and overall functioning within the EORTC questionnaire and corresponding SIP indices. With the exception of ΔEORTC.QL, all changes towards higher scores indicate impairment, while changes towards lower scores indicate improvement. The correlation between changes of QLQ physical functioning and SIP physical index was 0.62 ($p < 0.001$), between changes of QLQ emotional functioning and SIP psychosocial index 0.40 ($p < 0.01$), and between changes of QLQ global health/quality of life and SIP total index −0.43 (reversed scaling of the QLQ scale, $p < 0.01$); Pitman's test.

were made before analysis of correlation between these scales was performed. This was done by calculating the HAD scale scores only from items that were not included in the QLQ. The EF scale of the QLQ correlated well with both HAD anxiety and depression, corrected for overlap ($r = 0.56$ and 0.65 respectively, $p < 0.001$). High correlations were also seen between QL and HAD anxiety and depression ($r = -0.44$ and -0.65 respectively, $p < 0.001$). Furthermore, NV and appetite correlated moderately with HAD anxiety ($r = 0.29$–0.31, $p < 0.05$), while PF and F related to HAD depression ($r = 0.50$–0.52, $p < 0.001$), as did appetite ($r = 0.44$, $p < 0.01$).

Score ranges of the EF scale for detection of clinically significant emotional distress were defined by the HAD scales, using the recommended cut-off score levels for borderline and probable psychiatric morbidity (11). Of 34 patients who were psychologically well according to HAD, 30 (88%) had EF scores <2. Of 15 patients who were emotionally distressed by means of HAD, 14 (93%) had EF scores ⩾2.

Changes of emotional functioning 0–3 months correlated significantly with changes of HAD anxiety and depression, corrected for overlap ($r = 0.42$ and 0.47 respectively, $p < 0.01$). Change of HAD depression also correlated with changes of fatigue and global quality of life ($r = 0.47$ and -0.39 respectively, $p < 0.01$).

Statistical evaluation of the QLQ scales

Internal consistency and correlation matrix of the QLQ scales are shown in Table 8 (pretreatment assessment). The internal consistency of a scale was considered acceptable for group comparisons if Cronbach's alpha coefficient was >0.50. With the exception of social functioning, all scales met this criterion. The internal consistency of the SF scale was substantially higher (0.76) at 3 months' follow-up. The pattern of correlations supports both discriminant and convergent validity of the scales, since categories within the same dimension of quality of life correlated better with each other than with conceptually different scales. The global quality of life scale correlated significantly with all other scales, however best with emotional functioning and fatigue.

A matrix of item–scales correlations was created for analysis of discriminant validity (not in table). In pretreatment analysis, 9 items correlated higher with another scale than with its own (corrected for overlap). However, the criteria by Campbell & Fiske (17) were not applicable for definitions of definite and probable scaling errors, as the correlation standard errors, due to the relatively small number of patients, were too big for this analysis to be conclusive.

Five of the seven PF items correlated less than 0.40 with their own scale, corrected for overlap, at the initial assessment, but the correlations were substantially higher at 3 months' follow-up. The correlation between the RF items was 0.37 on both occasions.

The correlation between the SF items was only 0.31 prior to treatment but 0.61 at follow-up. All items in the F, EF and QL scales correlated substantially with their respective scales.

Multivariate analysis of global quality of life

Stepwise regression analysis was performed to study the extent to which the variance of the global health/quality of

Table 8

*Correlations between EORTC QLQ scales[a] at pretreatment administration. Levels of statistical significance are indicated with * ($p < 0.05$) or ** ($p < 0.01$); Pitman's test. Cursive figures in diagonal are coefficients of internal consistency*

QLQ scales	PF	RF	EF	SF	QL	F	NV
PF	*0.66*						
RF	0.51**	*0.54*					
EF	0.30*	0.21	*0.81*				
SF	0.24	0.29*	0.29*	*0.47*			
QL[b]	−0.48**	−0.34**	−0.67**	−0.33**	*0.83*		
F	0.56**	0.41**	0.42**	0.17	−0.60**	*0.85*	
NV	0.07	0.07	0.42**	0.01	−0.28*	0.32*	*0.79*

a) In this table including the nausea/vomiting scale
b) Negative correlations due to reversed scaling
Abbreviations: PF = physical functioning; RF = role functioning; EF = emotional functioning; SF = social functioning; QL = global health/quality of life; F = fatigue/malaise; NV = nausea/vomiting

life scale could be accounted for by the other QLQ scales prior to treatment. Emotional functioning and fatigue/malaise entered the multivariate model, explaining 57% of the total variance of the QL scale. As one of the items in the QL scale was conceptually measuring the fatigue level, the analysis was repeated with the single global quality of life item as dependent variable. Again, the EF and F scales entered the model, explaining 56% of the variance of the global quality of life item. The relation of other cancer symptoms to global quality of life was separately analysed. Only appetite correlated significantly with global quality of life but did not enter the stepwise regression model when emotional functioning and fatigue were included.

In multivariate analysis of global health/quality of life at 3 months, the same explanatory variables (EF and F) entered the model for the QL scale, while EF and PF were included in the model with the single quality of life item as dependent variable. The determination (r^2) was 0.51–0.58. Change of global health/quality of life (QL scale) and global quality of life (QL item) was predicted only by ΔF in the multivariate analysis ($r^2 = 0.36$ and 0.26 respectively).

Discussion

The C-36 version of the EORTC Core Quality of Life Questionnaire has been thoroughly validated with respect to psychometric properties and cross-cultural applicability in a baseline and short-term follow-up study of lung cancer patients (10). The present study was undertaken to further investigate its responsiveness to changes over a longer period of time in lung cancer patients who are likely to respond to chemotherapy, and to compare the results with those obtained by the Sickness Impact Profile (5).

The psychometric properties of the QLQ were satisfactory and, in general, confirmed the results from the EORTC field study. The low reliability of the social functioning scale prior to treatment was due to the second item, which was concerned with interference from treatment with family or social life, thus yielding only a small score variance among untreated patients. Consequently, the scale reliability was substantially better at follow-up assessment. Some of the problems with the emotional functioning scale that arose in the field study were less obvious in our study. These problems were a number of inconsistent score patterns, suggesting that the mixture of positively and negatively worded questions in the scale, a technique that was chosen to avoid response patterns of general agreement ('yes-saying'), may instead have caused confusion and mistakes in filling in the questionnaire.

The inclusion of an independent global health/quality of life scale or item in a multidimensional questionnaire has been recommended (19) to capture aspects of quality of life that are not defined by the other dimensions. Another advantage of such a scale is the possibility to quantify the relations of different components to global quality of life. In this study, emotional functioning and fatigue/malaise were the best predictors of global quality of life. However, only half of the total variance of global quality of life was explained by these components, which further implies the multidimensional nature of the quality of life concept.

A main purpose was to compare the EORTC questionnaire with the SIP. The pattern of correlations between the SIP scales and physical functioning, role functioning and emotional functioning confirms the construct validity of these QLQ scales. The deficient performance of the social functioning scale prior to treatment was demonstrated also by low correlations with the corresponding SIP scales (Table 7). However, follow-up assessment at 3 months revealed a correlation pattern with SIP scales that supports the construct validity of the SF scale during treatment. Interestingly, the EORTC QL scale correlated best with the SIP scales of social interaction and mobility, which are

conceptually related scales concerned with the ability to maintain external relations. This is in agreement with clinical experience and empirical data, which emphasize the importance of social functioning and social support in the lives of cancer patients (20).

Changes of QLQ emotional functioning correlated poorly with changes of SIP emotional behaviour. With reference to our previous finding of a low correlation between changes of SIP emotional behaviour and the HAD depression scale, the results with the QLQ emotional functioning scale were less surprising, as the items of this scale were derived from the HAD. The disparate changes of emotional functioning, as measured by EORTC and SIP, were mainly confined to the depression items. The disparity may in part be explained by different approaches and time reference periods of the questionnaires. While the SIP emotional behaviour scale is concerned with functional aspects of depression and refers to 'today', the EORTC/HAD items rely on anhedonic aspects of depression, referring to 'the last week'. A comparison of HAD and SIP revealed that they, in part, identified different cases with psychological distress, although they pinpointed the same level of psychiatric morbidity (5).

The scales of physical and role functioning, fatigue and global quality of life were shown to distinguish between patient groups varying in performance status, which lends support to the construct validity of these scales. However, neither of the functional scales correlated with the stage of disease, which would have been expected, considering that performance status was significantly worse in ED than in LD. Responsiveness to clinical change over time was shown for all functional scales, with the exception of social functioning, and both improvement and deterioration of functional status were detected.

Nausea and vomiting, as assessed by the patients, did not change significantly over time, with the exception of one assessment at 6 months. This finding highlights the importance of timing in quality of life assessment. While several of the regimens obviously caused substantial acute nausea and vomiting, persistent nausea was less common, however not rare. As quality of life assessment was performed immediately before treatment administrations, only persistent and conditioned nausea were captured, according to the intentions of the study. Although quality of life may have been temporarily affected by nausea during treatment administrations, this could not be demonstrated during the rest periods. Low correlations between nausea and psychosocial or general well-being were also found in previous studies of lung cancer patients receiving chemotherapy or radiotherapy (21, 22). These findings must not lead to the conclusion that nausea and vomiting from chemotherapy can be ignored, but suggest that these side-effects are reasonably well tolerated over longer periods.

The social functioning scale did not perform very well in pretreatment assessment. One reason has already been discussed. Another factor of importance is the lack of distinction between family relations and external social relations. The results from assessment with SIP clearly demonstrated that the variance of social interaction in this patient group was explained mainly by disruption of external social relations and less by interference with family relations (5). As these two aspects were mixed in the QLQ items of social functioning, interference from disease or treatment with external social relations may have been underreported.

Most patients did not experience financial impact of the disease or treatment. At the time of the study, the Swedish social security system ensured the patients 90% compensation for loss of income if they were unable to work, and medical costs were heavily subsidized.

A question of importance to the clinician is at what levels the scale scores indicate functional limitations that are clinically relevant. Physical functioning may be related to measures that are familiar to the clinicians, such as the performance status. In this study, the distribution of patient ratings of physical functioning implied that score levels at 4 or higher represented clinically significant dysfunction. Emotional functioning has to be validated against standardised psychiatric interviews or previously validated psychological scales with established cut-off score levels for psychiatric illness. Such levels have been defined for the HAD scales (11). In our study, a comparison of the QLQ emotional functioning scores with corresponding scores of the HAD scales pointed at 2 as the cut-off level for psychological distress. However, such levels need to be evaluated for each of the scales and for all cancer sites, preferably in larger study samples.

The EORTC questionnaire was well accepted by the patients. Most patients completed the 50 items (QLQ plus LC module) in 10 min. Some of the older patients needed repeated or extended instructions to understand the categories of answers. In most cases, however, the questionnaire was patient self-administered after a brief instruction from the research nurse.

In conclusion, the C-36 version of the EORTC Core Quality of Life Questionnaire in this comparative study proved to be a valid instrument for assessment of physical and emotional dysfunction in SCLC patients during chemotherapy, although the performance of the social functioning scale was not optimal. The instrument was sensitive to differences in clinical status and responded to clinical change, and score levels of clinical significance were possible to define. It provided sufficient information on cancer symptoms and treatment side-effects. Our experience from use with physically very ill patients supports its feasibility in cancer clinical trials. A refined version of the QLQ has recently been developed on the basis of the findings in the EORTC study previously referred to (10) and is currently undergoing field testing.

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REFERENCES

1. Johnson DH, Greco FA. Small cell lung cancer; Current perspective. Am J Med Sci 1987; 293: 377–89.
2. de Haes JCJM, van Knippenberg FCE. The quality of life of cancer patients: a review of the literature. Soc Sci Med 1985; 20: 809–17.
3. Cella DF, Tulsky DS. Measuring quality of life today: methodological aspects. Oncology 1990; 4: 29–38.
4. Bergner M, Bobbit RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. Med Care 1981; 19: 787–805.
5. Bergman B, Sullivan M, Sörenson S. Quality of life during chemotherapy for small cell lung cancer. I. An evaluation with generic health measures. Acta Oncol 1991; 30: 947–57.
6. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life in cancer patients: the Functional Living Index-Cancer. J Clin Oncol 1984; 2: 472-83.
7. Selby PJ, Chapman J-AW, Etazadi-Amoli J, Dalley D, Boyd NF. The development of a method for assessing the quality of life for cancer patients. Br J Cancer 1984; 50: 13–22.
8. Ganz PA, Haskell CM, Figlin RA, la Soto N, Siau J. Estimating the quality of life in a clinical trial of patients with metastatic lung cancer using the Karnofsky performance status and the Functional Living Index-Cancer. Cancer 1988; 61: 849–56.
9. Finkelstein DM, Cassileth BR, Bonomi PD, Ruckdeschel JC, Ezdinli EZ, Wolter JM. A pilot study of the Functional Living Index-Cancer (FLIC) scale for the assessment of quality of life for metastic lung cancer patients. Am J Clin Oncol 1988; 11: 630–3.
10. Aaronson NK, Ahmedzai S, Bullinger M, et al. The EORTC Core Quality of Life Questionnaire: interim results of an international field study. In: Osoba D, ed. Effect of cancer on quality of life. Boca Raton: CRC Press, 1991: 185–203.
11. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. Acta Psychiatr Scand 1983; 67: 361–70.
12. WHO handbook for reporting results of cancer treatment. Geneva: WHO, 1979.
13. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality of life assessment in cancer clinical trials. In: Recent results in cancer research. Berlin-Heidelberg: Springer-Verlag, 1988: 231–49.
14. Sullivan M. The Sickness Impact Profile (SIP): an instrument for overall health assessment, a basic evaluation. J Drugther Res 1988; 13: 167–9.
15. Likert R. A technique for the measurement of attitudes. Arch Psychol 1932; 140: 1–55.
16. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrica 1951; 16: 297–334.
17. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull 1959; 56: 81–105.
18. Bradley JW. Distribution-free statistical tests. London: Prentice-Hall, 1968: 68–86.
19. McMillen Moinpour C, Feigl P, Metch B, Hayden KA, Meyskens FLJ, Crowley J. Quality of life end points in cancer clinical trials: review and recommendations. J Natl Cancer Inst 1989; 81: 485–95.
20. Wortman CB. Social support and the cancer patient: conceptual and methodological issues. Cancer 1984; 53: 2339–62.
21. Coates A, Fischer Dillenbeck C, McNeil DR, et al. On the receiving end—II. Linear Analogue Self-assessment (LASA) in evaluation of the quality of life of cancer patients receiving therapy. Eur J Cancer Clin Oncol 1983; 19: 1633–7.
22. Kaasa S, Mastekaasa A. Psychosocial well-being of patients with inoperable non-small cell lung cancer. The importance of treatment- and disease-related factors. Acta Oncol 1988; 27: 829–35.