reviews

Quality of Life in Patients With Lung Cancer*

A Review of Literature From 1970 to 1995

Ali Montazeri, MPH, PhD; Charles R. Gillis, MD; and James McEwen, MBChB

A review of the literature was carried out covering the last 25 years (1970 to 1995) by searching through the MEDLINE and manually. The review consists of two companion parts. The first includes studies of quality of life in lung cancer patients in general, while the second part is restricted to defined samples of small and non-small cell lung cancer patients. Excluding non-English and review articles, in total 151 citations were identified and all have been reviewed. Over 50 instruments were used to measure quality of life in lung cancer studies. Of these, the European Organisation for Research and Treatment of Cancer Quality of Life Lung Cancer Questionnaire (EORTC QLQ-LC13) in conjunction with the core cancer questionnaire (QLQ-C30) was found to be the best developed instrument, although there were two other lung cancer-specific measures with good reliability and validity. Several topics in this chapter have been highlighted, including the importance of regularly measuring quality of life in lung cancer patients. Progress and achievements in areas such as performance status as a proxy of quality of life measure, psychological morbidity and symptom distress as predictive factors of quality of survival, and communication problems in quality of life studies of lung cancer patients have been emphasized and their implications in lung cancer care discussed. It is argued that palliation of symptoms, psychosocial interventions, and understanding patients' feelings and concerns all contribute to improving quality of life in lung cancer patients. It is concluded that the future challenge in treatment of lung cancer lies not only in improving the survival, but mainly the patients' quality of life regardless of cell type. Clinical trial and epidemiologic population-based outcome studies are recommended to provide this and to allow a better understanding of the contribution of the socioeconomic characteristics of the patients to their pretreatment and posttreatment quality of life. ***(CHEST 1998; 113:467-81)***

Abbreviations: DDC=Daily Diary Card; ECOG=European Cooperative Oncology Group; EORTC-QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-L=Functional Assessment of Cancer Therapy-Lung; FLI-C=Functional Living Index-Cancer; HADS=Hospital Anxiety and Depression Scale; KPS=Karnofsky Performance Scale; LCSS=Lung Cancer Symptom Scale; PCI=prophylactic cranial irradiation; POMS=Profile of Mood States; RSCL=Rotterdam Symptom Checklist; SIP=Sickness Impact Profile

Lung cancer is the most common cancer in the world, accounting for 17.6% of cancers of men worldwide, and 22% of cancers in men in the developed countries.[1] More importantly, in some parts of the world such as Glasgow (Scotland), the age-standardized incidence of lung caner has overtaken that of breast cancer in women.[2] Since >80% of lung cancer patients die within a year,[3] the issue of quality of life in this group of patients is paramount.

There are several articles on the subject (22 papers and 2 books). Of these, most are commentaries,[4-12] one is a symposium agenda,[13] one is a report,[14] one is an article that examines different ways of analyzing the quality of life data,[15] and three are presentation abstracts.[16-18] The books consist of a number of published articles (already included in this review),[19] and articles about quality of life instruments for use in studies of lung cancer.[20] The remaining articles

---

*From the Department of Public Health (Dr. Montazeri and Prof McEwen), University of Glasgow, and the West of Scotland Cancer Surveillance Unit (Prof Gillis), Ruchill Hospital, Glasgow, Scotland.

Manuscript received August 20, 1996; revision accepted July 17, 1997.

Reprint requests and questionnaire correspondence: Dr. Ali Montazeri, Director, Iranian Center for Breast Cancer, PO Box 13185-1488, Tehran, Iran

are reviews.[21-29] These review articles mainly focus on two issues: review of instruments used, and the effect of disease and its treatment on quality of life of lung cancer patients. All articles suggest that assessment of quality of life should be included in evaluating treatment outcomes. Of these, only two articles include a summary of quality of life studies in lung cancer patients.[26,28] Some of these review articles have a narrow focus on clinical trials, and none were carried out in a systematic way. The method of review and the criteria for including articles are not identified. In addition, these reviews did not include all published articles at the time they were carried out.

This article reviews the literature on quality of life studies in lung cancer patients and gives an insight into the improvement achieved. The review has been carried out in conjunction with a population-based epidemiologic study on quality of life in lung cancer patients in Glasgow, Scotland. The review consists of three sections. Section 1 includes studies on quality of life in patients with lung cancer coving more general aspects, while sections 2 and 3 include studies of small and non-small cell lung cancer and discuss more specific issues. This distinction was made due to the fact that in the former studies, either the cell type was not identified or different histologic types were included in the studies, whereas in the latter studies, only small or non-small cell lung cancer patients were included in the studies.

MATERIALS AND METHODS

Two methods of investigations were carried out: a MEDLINE search and a manual search through published articles from 1970 to 1995. The year 1970 was chosen because the first study (to our knowledge) of quality of life in patients with lung cancer was published in 1970. For the MEDLINE search, the key words "quality of life" and "lung cancer" were used. This provided the initial database for the review. The initial search was carried out in 1994 and updated twice in 1995 and once at the end of January 1996.

In the second procedure, using the initial database, the articles cited in the literature were examined for possible additional existing articles. There were no specific criteria for inclusion of articles in the review, but they were excluded if the language was not English. A similar method of investigation in reviewing quality of life in patients with ovarian cancer was used.[30]

RESULTS

A total of 151 citations were identified and reviewed. Of these, 48 citations were in abstract form and there were studies that appeared both in an abstract form and in a complete publication form. This means that some studies were counted twice (once in an abstract form and once in form of a complete publication). In addition, there were identical studies from the same author(s) that have been published in different stages of the studies or with different findings. These were also counted as many times as they appeared in the literature.

Of 151 citations, 68 were not restricted to specific cell type of lung cancer (47 citations on quality of life in lung cancer patients in general, and 21 citations on quality of life in cancer patients including that of lung). The remaining 83 citations were restricted to define samples of small or non-small cell lung cancer patients (41 citations on quality of life in patients with small cell lung cancer and 42 studies of non-small cell lung cancer).

However, of 151 citations, 30 were validation studies and 3 were feasibility studies. The rest were studies with different objectives, including clinical trials with survival time and quality of life as end points, and descriptive studies measuring clinical outcomes.

INSTRUMENTS

Over 50 instruments were used to measure quality of life or some dimensions of life quality in patients with lung cancer (Table 1). Some of these instruments were used rarely, some were used only for validation purposes, and some were not true quality of life measures. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-36 or C-30), the Rotterdam Symptom Checklist (RSCL), the Hospital Anxiety and Depression Scale (HADS), the Functional Living Index-Cancer (FLI-C), and the Daily Diary Card (DDC) were among the most popular instruments used, and their applications in studies of quality of life are well documented.

The DDC is one of the widely used instruments in the UK context. The instrument was developed by the Medical Research Council Lung Cancer Working Party and has been used in many randomized trials. Although its sensitivity is well documented, it has been criticized because compliance with DDC is low, and it has a limited focus on treatment-related side effects.

There were three site-specific (lung cancer) measures: the Lung Cancer Symptom Scale (LCSS), the Functional Assessment of Cancer Therapy-Lung (FACT-L), and the EORTC QLQ LC-13.

The LCSS focuses on the physical and functional dimensions of quality of life, measuring major lung cancer symptoms and their effect on activity status. It consists of two instruments: one for patients and one for health professionals as observers. The patient

Table 1—*Selected Quality of Life Measures Used in Lung Cancer Studies**

Instruments	Items	Dimensions
1. Performance status		
KPS	11	Performance status
ECOG performance status scale	5	Performance status
2. Generic measures		
SIP	136	Physical and psychological status, sleep and rest, work, home management, recreation and pasttimes
3. Psychological		
Profile of Mood States (POMS)	65	Tension, depression, anger, vigor, fatigue, confusion
HADS	14	Anxiety, depression
Symptom Checklist-90	90	Nine subscales: depression, anxiety, somatization, obsessive-compulsive, interpersonal sensitivity, hostility, phobic anxiety, paranoid ideation, and psychotics
4. Cancer specific		
DDC	5	Overall condition, physical activity, vomiting, mood, anxiety
FLI-C	22	Physical symptoms, mood, physical activity, work, social interaction; it is a VAS
RSCL	38	Physical, psychological, and functional status
Symptom Distress Scale	13	Cancer symptoms (appetite, nausea, sleep, elimination, pain, fatigue, breathing, cough, outlook, appearance, concentration)
EORTC QOL-C36 or QOL-C30	36 (30)	Functioning (physical, role, emotional, social), cancer symptoms, financial impact, physical symptoms, overall health, and quality of life
5. Site specific		
EORTC QOL-LC13	44 (13)	EORTC core questionnaire plus lung cancer-related symptoms and treatment side-effects (30 core items+13-item lung cancer specific)
LCSS	15	Lung cancer-related symptoms (patient and observer rated)
FACT-L	44 (10)	Physical well-being, social/family well-being, relationship with physician, emotional well-being, functional well-being, lung cancer symptoms (34 items general and 10 specific)

*Note: the entire list is available from the corresponding author. VAS=visual analog scale.

scale consist of nine items: six measuring major symptoms for lung cancer (loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain) and three summation items related to total symptomatic distress, activity status, and overall quality of life all using visual analog scale. The observer scale is a five-point ordinal level scale similar in content to the patient scale measuring the intensity of six major lung cancer symptoms.

The LCSS is a very limited measure of quality of life because it does not contain many of the important components of the quality of life and in addition, its introductory statement contains the word "lung cancer," which might be seen as a limiting factor.

The FACT-L (version 3) is a 44-item self-reported instrument and consists of two parts. Part 1 is a 34-item measure of general health-related quality of life covering five dimensions; physical, social and family, emotional, and functional well-being, and relationship with physician. Part 2 (Lung Cancer Subscale) is a 10-item measure of quality of life with emphasis on lung cancer symptoms.

The problem with the FACT-L is that it mostly covers lung cancer-related symptoms and not the treatment-related symptoms. The most important feature of the FACT-L is that it measures the relative weight of importance attached to the components of quality of life.

However, both the LCSS and the FACT-L have been validated and show a high level of reliability and validity, including good internal consistency, content validity, and responsiveness.[31,32]

The EORTC QLQ-LC13 is a tumor-specific questionnaire supplementary to the EORTC quality of life cancer questionnaire (QLQ-C30). It is a 13-item measure of lung cancer-related symptoms and treatment side effects, including the following: coughing (1 item), hemoptysis (1 item), dyspnea (3 items), sour mouth or tongue (1 item), trouble swallowing (1 item), tingling hands and feet (1 item), hair loss (1 item), experience of pain (3 items), and pain medication (1 item).

A recent publication by the EORTC Study Group on Quality of Life concluded that the results from international field testing, yielding a database with >700 lung cancer patients, lent support to the EORTC QLQ-LC13 as a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients, when combined with the EORTC core quality of life questionnaire. All symptom and toxicity scores changed significantly over time, with disease symptoms declining and treatment toxic reactions increasing during the treatment period. In a few cases, however, the questionnaire module could benefit from further refinements. In addition, its performance over a longer period still needs to be investigated.[33]

However, these are the most useful instruments[34] and can provide information additional to the clinical data. With such a relatively good number of measures, it appears that there is no excuse for not measuring quality of life in lung cancer patients. Such information has an important role in clinical decision-making and ensuring effective care for lung cancer patients.

General Findings

Performance Status

The frequent use of performance status as a proxy of quality of life is not uncommon (Table 2). In lung cancer patients, it is an important prognostic factor and predictor of survival.[35] The history of quality of life studies in lung cancer patients goes back to 1970 when the first article (to our knowledge) was published by Carlens et al[36] using the "vitagram index." It consisted of two dimensions: x-axis (survival) and y-axis (every month of survival as judged on a scale of performance status ranging from -20 to 20). They found that patients undergoing radical operations had a substantially better survival and performance status. Subsequent studies confirmed that performance status is a good predictor of quality of life or that there is a significant correlation between performance status and psychological, physical, and symptomatic distress.[37-40] Although the use of performance status has been controversial, correlation between performance status and global quality of life is well established.[41] It has also been shown that the number and severity of symptoms increase with worsening performance status.[42] In addition, it has been suggested that psychiatric disorder in lung cancer patients is significantly associated with poorer performance status.[43] Schag et al[44] studied 57 disease-free lung cancer survivors and reported that the Karnofsky Performance Scale (KPS) was the best predictor of quality of life. In contrast, in studying 139 lung cancer patients receiving palliative treatment, quality of life was found to be a much broader concept than was reflected by the KPS, and there was a weak association between the KPS and the quality of life as measured by the EORTC QLQ-C30.[45] Contradictory to these findings, Osoba et al[41] found that performance status as measured by the Eastern Cooperative Oncology Group (ECOG) strongly correlated with several domains of quality of life as measured by the EORTC QLQ-C30.

However, although performance status is not a true measure for quality of life and there is inconsistency in findings, it should be seen as an important predictor of survival and quality of life. This implies that physicians, especially oncologists, should record the performance status of the lung cancer patients in the case notes. They can use either the KPS or the ECOG performance status. Although the ECOG is superior to the KPS, both are valid, easy to score, and take a few seconds to rate.[46]

Quality of Life as a Prognostic Factor

One of the most interesting findings in quality of life studies of lung cancer patients is that initial quality of life was found to be the strongest prognostic factor for survival. This was confirmed by studies carried out by Ruckdeschel and Piantadosi[47] and by Ganz et al.[48] Using the Functional Living Index-Cancer (FLI-C), it was found that FLI-C score was an independent predictor of survival even after correcting for initial performance status, weight loss, stage of disease, number of metastatic sites, and type of treatment.

These findings have shown that nonmedical factors such as quality of life assessment play an important role in predicting survival and that they should be evaluated. For example, Buccheri et al,[40] in a study of 128 lung cancer patients using the Therapy Impact Questionnaire, found that in addition to the stage of disease, some aspects of quality of life such as difficulty at work and doing household jobs are prognostic factors of improved survival.

Communication

The contribution of communication problems between patients and their physicians to the quality of life in lung cancer patients has been investigated by several researchers. Early studies on the subject showed that psychological adjustment in lung cancer patients might be improved if patients were given opportunities to ask questions about their disease and participate in decisions about treatment.[50] Berglund and Sjoden[51] noticed that communication problems with medical staff were strongly associated with anxiety and with anticipatory nausea and vomiting. Of 94 lung cancer patients, 74% wanted to be told about their diagnosis. However, in those who did not want to know about the disease, their quality of life was found to have deteriorated as measured by psychological, social, and financial factors.[52]

However, these indicate firstly the importance of the communication issues, and secondly that studying quality of life requires a straightforward communication with patients themselves. Relying on other sources of information such as relatives or physicians may not reflect the exact nature of the patients' feelings and concerns. Interviewing 40 lung cancer patients and their relatives showed that relatives

Table 2—*Summary of Selected Quality of Life Studies in Patients with Lung Cancer**

Study (yr)	Design	Treatment	Sample	Quality of Life Measure	Results/Conclusions
Ganz et al[48] (1991)	Descriptive	Palliative RT+SC, CT+SC	40	FLI-C	Initial QL was found as an independent predictor of survival
Eguchi et al[38] (1992)	Descriptive	CT	64 cases, 50 control subjects	FLI-C (modified version), designed questionnaire (derived from EORTC)	Significant correlation between PS and psychological, physical, and symptomatic scores, but not for social aspects
Buccheri et al[54] (1993)	Descriptive	None, surgery, RT, CT	71 pts and their relatives and phyns	Italian translation of EORTC+3 items for three groups: tolerance, physical feeling, depression, KPS, ECOG	Significant difference among pts, phyns, and relatives; phyns were more optimistic, relatives were more pessimistic; phyns were most reliable raters of treatment tolerance
Aaronson et al[39] (1993)	Descriptive	CT or RT	354 (305)	EORTC QLQ-C30, ECOG	Validation study; strong correlation between physical and role functioning and fatigue; pts with a better PS and less weight loss, showed significant higher level of physical, role, and cognitive functioning, overall QL, and lower symptoms; no significant change over time.
Hollen et al[31] (1993)	Descriptive	CT or RT or surgery or no treatment	121 cases, 52 observer	LCSS	Validation study; LCSS demonstrated good reliability and content validity
Bergman et al[33] (1994)	Descriptive	CT or RT	346 (305)	ECOG, EORTC QLQ-C30, QLQ-LC13	EORTC QLQ-LC13 was found to be valid and useful tool for measuring disease and treatment-specific symptoms in LC pts receiving CT or RT when combined with EORTC core QL questionnaire
Ruckdeschel and Piantadosi[47] (1994)	Randomized	Preoperative therapy +surgery or Surgery +postoperative therapy	437	FLI-C, KPS	Baseline QL was the strongest prognostic factor for survival; FLI-C sensitive to clinical status and predictor of survival even after correcting for initial PS, stage, and treatment
Schaafsma and Osoba[45] (1994)	Descriptive	PT	162 (139)	EORTC QLQ-C30, KPS	Cross validation study; the QL found to be much broader concept than the KPS; weak association between KPS and EORTC QLQ-C30; difficulty in breathing has strongest negative impact on QL, and the fatigue the least
Buccheri and Ferrigno[46] (1994)	Descriptive	Various	471	KPS, ECOG	Validation study; KPS and ECOG are both valid, but the ECOG is superior
Cella et al[49] (1994)	Descriptive	Various	58	FACT-L, ECOG	Validation study; good internal consistency and sensitive to change in PS
Stephens[55] (1994), Hopwood and Stephens[42] (1995)	Descriptive (main studies randomized)	(a) Two CT policies (b) Two RT policies	(a) 310 SCLS (232); (b) 509 NSCL (423)	Phyns: physical symptoms Pts: RSCL+(3 LC specific questions)	Phyns underestimating the level of severity of the patients' symptoms; overall pattern of symptom prevalence very similar for two disease; NSCLC patients reported higher levels of chest pain, coughing up blood; SCLC pts reported on average 17.4 symptoms, but NSCLC pts reported 14.3; in both, disease number and severity of symptoms increases with worsening PS

*Pt(s)=patient(s); Phyns=physicians; LC=lung cancer; QL=quality of life; CT=chemotherapy; RT=radiotherapy; PT=palliative treatment; SC=supportive care; NSCL=non-small cell lung cancer; SCLC=small cell lung cancer. The entire list of studies is available to the reader on request from the corresponding author; numbers in parentheses are actual sample sizes in quality of life assessments; other abbreviations as in Table 1.

rated symptoms higher and mood lower than patients.[53] Significant differences were found between 71 lung cancer patients and their relatives or physicians. Physicians were more optimistic, relatives were more pessimistic. Physicians were most reliable at rating treatment tolerance by patients.[54] Two British randomized clinical trials revealed high levels of agreement between clinicians and patients in reporting symptoms, but increasing disagreement with increasing severity of symptoms. They found that physicians underestimated the level of severity of the patient's symptoms.[55]

QUALITY OF LIFE IN PATIENTS WITH SMALL CELL LUNG CANCER

Combination chemotherapy with or without radiotherapy is the treatment of choice in small cell lung cancer. Thus, most studies, both randomized trials and descriptive ones, evaluated chemotherapy and its effects on quality of life (Table 3). In reviewing quality of life studies in patients with small cell lung cancer, the following results could be identified.

Tumor Response

In a study of 321 patients with small cell lung cancer (of those, 195 patients were entered into the quality of life study), quality of life was found to be dependent on tumor stage and tumor response.[56] Using the Sickness Impact Profile (SIP) in measuring quality of life in 62 patients, Bergman et al[57] found that tumor response correlated with SIP summary scores and anxiety. The same authors with the same patients using the EORTC QLQ-C36 reported that there was good correlation between changes of the QLQ-C36 scores over a given time period and clinical variables as measured by tumor response and performance status.[58]

These findings, however, indicate that early detection of lung cancer is an important issue. Detection of disease at an early stage would allow better management and thus increase the chance of cure. Benefit achievable by screening is limited.[59] Early detection mainly depends on referrals by general practitioners. Figures from the Yorkshire Cancer Registry (England) 1988 to 1991 showed that the median delay was 12 days (range, 6 to 20 days) between referral and first hospital visit and 22 days (range, 11 to 40 days) between this hospital visit and the start of treatment.[60]

Intensive vs Less Intensive Therapy

The challenge to improve survival and quality of life led some investigators to study different ways of managing small cell lung cancer. Most studies have shown that conventional (scheduled, planned) policies, although intensive, are providing a better quality of life (less nausea and pain, better sleep, mood, and general well-being) than less intensive (experimental, as required, unplanned) regimens.[61-63] Comparing standard chemotherapy with a palliative regimen, Wolf et al[64] studied 221 patients and found no significant difference in survival between these two regimens. However, patients receiving the standard regimen had a better tumor response and improvement of quality of life than patients receiving palliative treatment, but the former group had more severe side effects.

In a similar study (standard vs palliative chemotherapy), a significantly better survival was observed in patients receiving standard treatment, despite its greater toxicity. Assessment of quality of life using the EORTC 42-item QLQ demonstrated no significant difference in most areas measured. Less mucositis and alopecia were reported by the patients receiving palliative treatment, while patients in the standard group had better values for sleep disturbance, fatigue, and psychological distress.[65] It is argued that regular chemotherapy, although producing unpleasant side effects, also could be palliative and may control the effects of the progression of cancer.[12] Several studies have shown that different management policies resulted in no major survival benefit. Studying early vs late alternating chemotherapy in a group of 127 patients showed that there was no significant survival difference between treatment groups, but patients receiving early alternating chemotherapy had a better quality of life as measured by the EORTC QLQ questionnaire.[66]

However, some studies suggested that the less intensive the treatment, the better the quality of life. The result of a recent randomized trial comparing conventional vs intensive chemotherapy showed a better quality of life in favor of conventional chemotherapy.[67] In a randomized trial of 12 (maintenance) vs six (no maintenance) courses of chemotherapy with addition of radiotherapy in both regimens, it was shown that there were no significant differences in survival. Both assessments of the quality of life as measured by patients using the DDC and as measured by physicians indicated a better quality of life in favor of 6 courses of treatment.[68] However, it was reported that no patients receiving maintenance chemotherapy experienced a gradually deteriorating quality of life as compared to the more severe effects in the maintenance group.[69] Using the same method of measurement, Geddes et al,[70] in a study of eight vs four courses of chemotherapy, reported that there was no significant survival difference between these two regimens. The study results indicated that each

Table 3—*Summary of Selected Quality of Life Studies in Patients With Small Cell Lung Cancer**

Study (yr)	Design	Treatment	Sample	Quality of Life Measure	Results/Conclusions
Bernhard et al[73] (1988)	Randomized	Two combination CT	279	EORTC QLQ (41 items)	Physical functioning, treatment side effects, disease-related symptoms, psychological distress, fatigue, and malaise are most relevant aspects of QL
Geddes et al[61] (1988)	Randomized	CT (scheduled vs as required)	220 (80)	DDC	A better QL (less nausea and pain, better sleep, mood and general well-being) in scheduled CT
Bleehen et al[68] (1989)	Randomized	CT (12 vs 6 courses), RT in limited disease	497 (109)	(a) Pts: DDC (b)Phyns: overall condition, physical activity, dyspnea	No significant difference in survival; both assessments showed a better QL in favor of 6-course CT regimen; mood similar in both groups
Fayers et al[69] (1991)	Randomized	CT+RT (maintenance vs no maintenance)	369 (61)	(a) Pts: DDC, adverse reaction to treatment (b) Phyns: overall condition, activity	No significant difference in survival; worse mood and better overall condition in no maintenance group, while those in maintenance group showed more severe adverse effects of chemotherapy; anxiety similar in both groups
Earl et al[63] (1991)	Randomized	CT (planned vs as required)	300 (62)	DDC	No significant difference in survival; more severe symptoms in as required group and less palliative effect seen
Wolf et al[56] (1991)	Randomized	CT (continuous vs alternating)	321 (195)	EORTC QLQ-C36	No significant difference in survival; continuous CT slightly superior; QL depended on tumor stage and tumor response; overall, improvement in QL
Hurny et al[74] (1993)	Randomized	CT (early vs late alternation)	415 (188)	EORTC QLQ-C30, QLQ-LC13	Fatigue and malaise found to be as a global indicator of QL
Flechtner et al[71] (1993)	Randomized	(a) CT (alternating vs response dependent); (b) (carbo- vs cis-platinum), (c) (treatment for extensive vs limited disease)	600	EORTC quality of life questionnaire	No significant difference between treatment arms in trial (a), but in trail (b) and (c) different; intensive treatment more than 4 cycles results in overall marked negative effect on pts' QL
Cull et al[80] (1994)	Descriptive (retrospective)	PCI	64 (52)	HADS, RSCL	Anxiety and depression lower than pts recently receiving active treatment; high proportion of pts still experiencing treatment-related symptoms, but not functional impairment
Gower et al[67] (1995)	Randomized	CT (intensive vs conventional)	75	DDC, ECOG	No significant difference in survival; better QL in favor of conventional CT
Joss et al[66] (1995)	Randomized	CT (early vs late alternating), RT (in those with remission)	406 (127)	Study specific (derived from EORTC 42-item QLQ)	No significant difference in survival; better QL in pts receiving early alternating CT

*Abbreviations and notes as in Tables 1 and 2.

successive cycle of chemotherapy had a negative impact on the patient's quality of life, especially in patients receiving eight courses of chemotherapy. In a series of randomized trials comparing alternating vs response-dependent chemotherapy, carbo- vs cisplatinum, and treatment for extensive vs limited disease, it was noticed that intensive treatment of more than four cycles resulted in an overall marked negative effect on a patient's quality of life.[71]

Although these findings are not consistent, the results suggest that when there is no clinical benefit, for example in survival time or tumor response, perceptions and attitudes of patients toward different treatment policies could provide additional information. Therefore, measuring quality of life becomes essential, and it seems that it is the most reasonable way of judging the clinical outcomes. As Hopwood and Cull[72] remind us, there is no guarantee that adding quality of life measures makes the choice of treatment policy easier, but it does serve to clarify the potential trade-offs that need to be discussed with patients. There is evidence that physical functioning, treatment side effects, disease-related symptoms, psychological distress, fatigue, and malaise are the most relevant aspect of quality of life in patients receiving chemotherapy.[73] Furthermore, fatigue and malaise were found to be global indicators of quality of life.[74] Using such findings may provide a better understanding of clinical achievements. It is argued that it is important to ascertain what patients feel about the trade-offs between improved quality of life and toxicity where there is a significant potential for long-term side effects that may result in less than an optimum quality of life.[75]

Radiotherapy

Little is known about the effect of radiotherapy on a patient's quality of life. The International Association for the Study of Lung Cancer workshop on quality of life reported that local radiation in addition to chemotherapy in small cell lung cancer showed a significant advantage in median and long-term survival. Randomized trials of prophylactic cranial irradiation (PCI) have failed to demonstrate survival advantage.[76] Recent meta-analysis of thoracic radiotherapy for small cell lung cancer has also confirmed the view that radiotherapy can have survival benefits.[77]

Studying 53 patients receiving therapeutic or elective brain irradiation, it was found that patients receiving elective irradiation had both better survival and quality of life as measured by the KPS.[78] The role of chemotherapy in addition to radiotherapy has been studied, and it was shown that patients receiving immediate chemotherapy plus radiotherapy had better survival, as compared to groups of patients who received palliative treatment. In terms of quality of life, physicians reported a better "condition" in favor of immediate chemotherapy plus radiotherapy, but patients reported a better quality of life in favor of palliative treatment. Both groups reported the same "overall condition" and anxiety.[79] Recently Cull et al[80] have reported the results of a retrospective study on 52 patients who had received PCI. They observed that anxiety and depression in these patients were lower than patients recently receiving active treatment. However, it was found that a high proportion of patients still experienced treatment-related symptoms, but not functional impairment.

These studies highlight the palliative effect of the radiotherapy in the management of small cell lung cancer. Radiotherapy is a common treatment, but there are few studies that investigate the quality of life in patients receiving radiation treatment. The need to conduct such studies is essential.

QUALITY OF LIFE IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

There are various policies in the management of non-small cell lung cancer and aspects of the treatment related to quality of life outcome are discussed (Table 4).

Chemotherapy

As Thatcher et al[81] pointed out, non-small cell lung cancer can no longer be regarded as resistant to chemotherapy. Early studies of quality of life in patients receiving chemotherapy suggested that treatment-related toxicity reactions and the deterioration of patient's well-being offset any potential survival advantage for most patients.[82] In a more systematic assessment of quality of life, change in quality of life scores, as measured by FLI-C, correlated with performance status change and weight loss, but not with treatment regimen, side effects of treatment, or change of pain.[83] Consequent studies pointed out that after chemotherapy, patients had marked relief of symptoms.[84,85] Recent studies, however, have shown that improved or stable quality of life mainly depends on tumor response. For example, Pujot et al,[86] in a study of 54 patients, found a stable quality of life in responders as compared to those who had not responded to treatment. Another explanation is that baseline quality of life not only predicts the likelihood of response and survival, but also has greater impact than most known prognostic factors (treatment types, performance status, gender, and age). Gralla et al,[87] in a multicenter, randomized trial of a combination chemotherapy regimen, stud-

Table 4—*Summary of Selected Quality of Life Studies in Patients With Non-small Cell Lung Cancer**

Study (yr)	Design	Treatment	Sample	Quality of Life Measure	Results/Conclusions
Minet[103] (1987)	Randomized	RT vs RT+CT	81	KPS	No significant difference between arms in survival and QL as measured by KPS
Finkelstein et al[83] (1988)	Descriptive	CT	46	FLI-C	Change of FLI-C correlated with PS change and weight loss, but not with treatment regimen, side effects of treatment, or change of pain
Kaasa et al[96] (1988)	Randomized	RT vs CT	95	Purposed questionnaire (assessing psychosocial well-being, physical functioning, treatment related symptoms, daily activity, global QL)	Significant difference in psychosocial well-being and global QL in favor of RT; no significant group differences in physical functioning and daily activity. Significant difference in treatment-related symptoms in favor of RT
Ganz et al[90] (1989)	Randomized	SC vs SC+CT	48	FLI-C+KPS	Positive correlation between FLI-C and KPS; due to poor compliance, studying difference between treatment arms was impossible
Buccheri et al[89] (1989)	Randomized	CT vs SC alone	74	Ad hoc (3 items on treatment tolerance, physical well-being, depression)+KPS	No significance difference in depression and PS between treatment arms; better tolerance in favor of SC, but better physical status in favor of CT
Bleehen et al[97] (1991)	Randomized	RT (experimental vs conventional)	365	DDC	No survival difference; dysphagia rose during treatment and fell after 2 wk; reduction in physical activity rose during treatment and fell after 5 wk; similar results for mood and overall condition; findings similar in two groups
Bleehen et al[99] (1992)	Randomized	Palliative RT (2 fractions vs single)	235 (145)	Pts: DDC Phyns: overall condition, PS, symptoms	No survival difference; no significant differences in most areas that have been assessed, except less dysphagia in favor of single fraction arm
Hopwood and Stephens[100] (1994)	Randomized	RT (shot vs aggressive regimen)	500	RSCL, HADS	Survival slightly improved in favor of aggressive regimen, but in other respects (palliation of main symptoms, adverse effects, response, appearance of metastases), the two regimens were very similar
Hollen et al[88] (1994)	Descriptive	CT	(a) 207 pts (b) 21 observer	LCSS, KPS, SCL-90, POMS	Validation study; LCSS pts and observer scales were found to be reliable, valid, and responsive to change
Gralla et al[87] (1995)	Randomized	CT (with vs without edatrexate)	673	LCSS	QL at baseline not only predicts for the likelihood of response and for survival, but also has greater impact than most known prognostic factors.

*Abbreviations and notes as in Table 1 and 2. SCL-90=symptom checklist-90.

ied 673 patients using the LCSS and found that baseline quality of life was the best predictor of both response to the treatment and survival. Using the same instrument (LCSS), Hollen et al[88] found that physical and functional dimensions were the most important predictors of quality of life in patients receiving chemotherapy.

Chemotherapy and Best Supportive Care

Comparing chemotherapy vs supportive care alone, Buccheri et al[89] studied 74 patients and found that there was no significant difference in depression and performance status between treatment arms. As expected, while a better treatment tolerance was reported in favor of supportive care, a better physical status has been found in favor of the chemotherapy group. In another study, by Ganz et al,[90] due to poor compliance with quality of life assessment, it was impossible to examine differences between treatment arms (supportive care vs supportive care plus chemotherapy). However, they found that there was a positive correlation between quality of life scores as measured by the FLI-C and performance status as measured by the KPS. In a retrospective study in which patients had received chemotherapy or supportive care, it was found that chemotherapy produced a temporary benefit in quality of life as measured by improvement in performance status.[91]

In terms of quality of life, there is no single answer to the question as to whether the best supportive care or chemotherapy could produce a better quality of life, but there is evidence that chemotherapy is less expensive than supportive care. This is because chemotherapy produces tumor control, requires shorter hospital stay, and thus is less expensive.[92]

As Manegold and Schwarz[93] argue, since supportive care is relevant to all patients with non-small cell lung cancer, more education, research, and financial support are needed to optimize quality of life and supportive care of patients.

Radiotherapy

The value of radiotherapy in controlling specific cancer-related symptoms is undisputed and can be achieved with unsophisticated and undemanding schedules.[94] Yet, more research is needed to answer the critical issues of the role of radiotherapy in the treatment of non-small cell lung cancer.[95] As far as quality of life studies are concerned, there are several studies to help answer some of these issues. Kaasa et al[96] randomised 95 patients to receive either radiotherapy or chemotherapy. They found significant differences in psychosocial well-being and global quality of life in favor of radiotherapy. There were no significant group differences in physical functioning and daily activities. A British study has shown that conventional and experimental radiotherapy policies are the same both in survival time and quality of life. The study suggested that dysphagia and reduction in physical activities were the most important side effects of the radiotherapy.[97] Considering these side effects that affect a patient's quality of life, consequent studies indicated that there were no survival benefits with multiple or even two fractions as compared with single-fraction radiotherapy. The quality of life assessment as measured by the DDC, the HADS, and the RSCL showed that disease-related symptoms improved, anxiety improved, depression was unchanged, and there was less dysphagia in favor of single fraction.[98,99] In their recent study comparing short vs aggressive radiotherapy, they found that survival improved slightly in favor of the aggressive regimen, but in other respects (palliation of main symptoms, adverse effects, response, appearance of metastases), the two regimens were very similar.[100]

Adjuvant Chemotherapy With Radiotherapy

A recent meta-analysis of randomized trials of combined chemotherapy and radiotherapy in non-small cell lung cancer concluded that cisplatin-based chemotherapy and radiotherapy are superior to the other regimens, but these results must be considered in the light of the balance among quality of life, toxicity, and costs of chemotherapy.[101] There are a few studies that examine the quality of life. Early studies used the KPS as the proxy of quality of life and had shown different results. Arcangeli et al[102] reported that chemotherapy plus radiotherapy improved a patient's performance status markedly, while Minet et al,[103] in a randomized trial comparing radiotherapy alone vs radiotherapy along with chemotherapy found that there was no significant difference between treatment arms in both survival and quality of life. In a study in which patients were randomized to receive radiotherapy alone, radiotherapy plus chemotherapy, or palliative treatment, the results suggested that the patients who received radiotherapy or radiotherapy plus chemotherapy had fewer physical and psychological problems as compared with those who received palliative treatment.[104]

Surgery

Surgery is the treatment of choice for stage I and II non-small cell lung cancer. To our knowledge, the only study that has been reported so far is the one that was carried out by Dales et al.[105,106] They studied 117 patients, 92 patients with and 25 patients without a confirmed postoperative diagnosis of lung cancer. They found that preoperatively, the prevalence of dyspnea was four times higher in the cancer group, but other global quality of life indicators were similar. Dyspnea worsened in both groups at 1 and 3 months postoperatively. Quality of life deteriorated postoperatively in those with cancer and returned to preoperative levels at 6 to 9 months, but showed no deterioration postoperatively in those without cancer even at 1 and 3 months. They concluded that surgery resulted in deterioration in the quality of life during the first 3 months postoperatively in those with final diagnosis of cancer, but improvement back to baseline can be expected thereafter.

Discussion and Conclusions

Survival in lung cancer patients is poor and has improved little over time. Despite the increasing research, there remains among many physicians a high degree of pessimism about the gains made in clinical care,[107] especially when one considers the side effects of treatments and the costs involved. However, there are those who believe that using both traditional outcomes (survival and tumor response) and patient-based quality of life assessment may offer a more comprehensive approach to evaluating the relative risks and benefits associated with treatment.[28] It is argued that if there is no gain in survival time from clinical investigations, there are several other ways to improve health-care delivery for lung cancer patients and add quality to their lives. Strategies for supportive care or inclusion of quality of life measures as an end point in clinical practice are a few examples of such proposals.[108]

The review highlights both the progress and the shortcomings of the research activities on the subject. Despite 25 years of investigations and existence of nearly 150 articles and reviews, discrepancies are obvious. Many studies are built on common-sense conclusions. For example, in a study of 455 patients, it was found that performance status and extent of disease had a significant association with reported distress as measured by Profile of Mood States (POMS). The study concluded that the extent of disease can be seen as a risk factor for distress.[109] When there is no insight into the patients' daily experiences or to their living conditions, little is gained from studying such limited aspects of quality of life. In addition, many researchers included a restricted sample of patients in their studies. In these studies, mostly, there is generally no explanation of why the other patients were not included. It is not possible to be sure that these investigations are unbiased. Again, as these tables show, studies have used *ad hoc* instruments to measure quality of life, and the findings in such assessments should be interpreted with caution. However, the achievements of researchers in this field should not be underestimated, especially the efforts of the clinicians and the oncologists who enthusiastically conducted the research.

Although clinical findings in these studies are important and have been discussed, the emphasis of this review was on general aspects of the findings concerning the quality of life. These findings constitute a crucial role in the treatment of lung cancer patients and reflect a wide spectrum of issues that should be integrated into clinical practice.

Several topics in this article have been highlighted: first, that quality of life assessment can be a prognostic factor and predictor of survival; second, that the need for inclusion of quality of life as a valid end point in evaluation of the treatment of lung cancer patients has been emphasized. Since most lung cancer patients live for a short time, the need for palliation of symptoms is the first priority. Data from clinical studies of lung cancer clearly indicate that, for example, of 100 lung cancer patients, 86 suffer from pain, 70 have dyspnea, and 68 have anorexia.[110] These findings suggest that to improve the quality of life in lung cancer patients, resources should be directed to palliative care, and this has implications for lung cancer care purchasers.

As discussed earlier, several recent meta-analyses have shown promising clinical achievements in the management of small and non-small cell lung cancer.[95,101,111] These findings suggest that for patients with advanced and metastatic small and non-small cell lung cancer, survival alone should not be considered as the only outcome, rather the best way forward is through further clinical trials looking at new drug schedules and using as end points cost effectiveness and validated quality of life measures.[112]

The problem is that in these meta-analyses, it is not possible to study quality of life. Thus, individual clinical trials need to address quality of life in an agreed manner and find out whether the progress in survival could lead to better quality of life or not. In addition to the clinical trials, it is worthwhile to conduct population-based outcome studies to have a better understanding of patients' pretreatment and posttreatment quality of life. In such evaluations, patients' socioeconomic characteristics may play an important role. Variation in quality of life among patients with small and non-small cell lung cancer may be explained by other factors, such as patients' socioeconomic backgrounds, rather than just disease- or treatment-related side effects. Since little is known about the role of these factors, further investigation in this area is recommended.

In addition, creation of a supportive environment may help patients overcome their problems. Relatives, clinicians, social work departments, and cancer support groups all have an important role to play in this matter. Of these, the role of clinicians in recognizing these symptoms and referring patients to appropriate care is very crucial. This can be achieved by simple measures of quality of life, for example, the HADS, which is a good screening tool to identify patients in need.

Although there are still deficiencies in both quality of life measurement and research design, this review clearly shows that during the last 25 years, there have been promising developments in many areas of quality of life-related research. For example, there now are several valid instruments to measure quality of life, quality of life is increasingly becoming integrated as part of clinical trials, and quality of life by itself is becoming an issue of interest both for patients and clinicians. Patients themselves have expressed a wish for more emphasis on research into quality of life issues.[113] In contrast, the explosion of so many new instruments without critical appraisal, poor presentation of their data in published articles, complex statistical analyses, and lack of guidelines all can be seen as major causes of confusion. However, these recent developments should not prevent clinicians and oncologists from using the new instruments, provided that they have evaluated them critically.

The most difficult problem in studies of quality of life come from the many methodologic issues such as data collection, analysis, and barriers to the interpretation of the results. Since these could be counterproductive, there is an urgent need to provide simple and constructive guidelines to help researchers and clinicians in administering these measures.

The role of family, relatives, social life, economic, and leisure time received less attention in quality of life investigations. Focusing only on disease- or treatment-related symptoms makes quality of life studies very limited. There is an urgent need to investigate these issues more comprehensively, since lung cancer patients have indicated that family or leisure times are as important as their health.

Furthermore, communication between clinicians and patients needs to be improved.[114] Understanding lung cancer patients' feelings and concerns may help to improve the quality of care and the quality of life. There is evidence that patients do not necessarily share clinicians' priorities or place the same emphasis on different types of morbidity.[115]

In conclusion, while research into quality of life has made substantial progress in a relatively short time, there is an urgent need to include a broader concept of quality of life in future studies despite the methodologic difficulties. At present, comprehensive lung cancer care requires a cyclical process that includes prevention, early detection, specific therapy, improvement in survival, and supportive care strategies. In the future, the real challenge in the management of lung cancer lies in improving quality of life.

REFERENCES

1 Parkin DM, Pisani P, Ferlay J. Estimation of the worldwide incidence of 18 major cancers in 1985. Int J Cancer 1993; 54:594-606

2 Gillis CR, Hole D, Lamont DW, et al. The incidences of lung cancer and breast cancer in women in Glasgow. BMJ 1992; 305:1331

3 Martini N. Operable lung cancer. CA Cancer J Clin 1993; 43:201-15

4 Yarnold J. Ensuring an optimal quality of life in patients with lung cancer. In: Ventafridda V, van Dam FSAM, Yancik R, et al., eds. Assessment of quality of life and cancer treatment. Amsterdam: Elsevier, 1986; 139-44

5 Silberfarb PM. Ensuring an optimal quality of life in patients with lung cancer: a psychiatrist's perspective. In: Ventafridda V, van Dam FSAM, Yancik R, et al, eds. Assessment of quality of life and cancer treatment. Amsterdam: Elsevier, 1986; 145-50

6 Hurny C, Benhard J. Problems in assessing quality of life (QL) of lung cancer patients in clinical trials. Chest 1989; 96:102S-05S

7 Feld R. Quality of life assessment in patients with carcinoma of the lung. Chest 1989; 96:105S-07S

8 Geddes DM. quality of life in lung cancer. Respir Med 1991; 85(suppl B):7-11

9 Houston SJ, Kendall JA. Psychosocial implications of lung cancer. Nurs Clin North Am 1992;27:681-90

10 Schmitt R. Quality of life issues in lung cancer: new symptom management strategies. Chest 1993; 103:51S-55S

11 Feld R. Quality of life in patients with non-small cell lung cancer treated with chemotherapy. Eur J Cancer Clin Oncol 1987; 23:357-59

12 Fayers P. Quality-of-life assessment in small cell lung cancer. Pharmacoeconomics 1992; 2:181-88

13 Gralla RJ. Lung cancer quality of life: a two-part symposium [abstract]. Lung Cancer 1994; 11(suppl 2):239-40

14 Abratt RP. IASLC workshop on improving quality of life and supportive management of patients with lung cancer. Lung Cancer 1994; 10:375-80

15 Hopwood P, Stephens RJ, Machin D. Approaches to the analysis of quality of life data: experiences gained from a medical research council lung cancer working party palliative chemotherapy trial. Qual Life Res 1994; 3:339-52

16 Burke G. Quality of life endpoints for cancer trials [abstract]. Lung Cancer 1994; 11(suppl 2):23

17 Ganz PA. Quality of life issues in lung cancer treatment and research [abstract]. Lung Cancer 1994; 11(suppl 2):68-69

18 Gralla RJ. Measuring quality of life in patients with lung cancer [abstract]. Lung Cancer 1994; 11(suppl 2):70-71

19 Bakker W, ed. Studies in lung cancer treatment: impact on survival and quality of life. Leiden, Netherlands: 1986

20 Gralla RJ, Moinpour CM, eds. A guide for clinicians: monograph from the Lung Cancer Quality of Life Symposium presented June 26-27, 1994, Colorado Springs, Colo. New York: NCM Publishers, 1995

21 Kaasa S. Psychological aspects of patients with lung cancer

in controlled clinical trials. Cancer Treat Res 1989; 45: 325-55

22 Bernhard J, Ganz PA. Psychosocial issues in lung cancer patients (part 1). Chest 1991; 99:216-23

23 Bernhard J, Ganz PA. Psychosocial issues in lung cancer patients (part 2). Chest 1991; 99:480-85

24 Hopwood P, Thatcher N. Current status of quality of life measurement in lung cancer patients. Oncology 1991; 5:159-66

25 Fergusson RJ, Cull A. quality of life measurement for patients undergoing treatment for lung cancer. Thorax 1991; 46:671-75

26 Bergman B. Psychosocial issues in the treatment of patients with lung cancer. Lung Cancer 1992; 8:1-20

27 Hopwood P, Cull A. Quality of life. In: Thatcher N, Spiro S, eds. New perspectives in lung cancer. London: BMJ Publishing, 1994; 161-76

28 Bergman B, Aarenson NK. Quality-of-life and cost-effectiveness in lung cancer. Curr Opin Oncol 1995; 7:138-43

29 Bernhard J, Ganz PA. Psychosocial issues in lung cancer patients. Cancer Treat Res 1995; 72:363-90

30 Montazeri A, McEwen J, Gillis CR. Quality of life in patients with ovarian cancer: current state of research. Support Care Cancer 1996; 4:169-79

31 Hollen PJ, Gralla RJ, Kris MG, et al. Quality of life assessment in individuals with lung cancer: testing the Lung Cancer Symptoms Scale (LCSS). Eur J Cancer 1993; 29A(suppl 1):S51-58

32 Cella DF, Bonomi AE, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995; 12:199-220

33 Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994; 30A:635-42

34 Hollen PJ, Gralla RJ. Comparison of instruments for measuring quality of life in patients with lung cancer. Semin Oncol 1996; 23(suppl 5):31-40

35 Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. Eur Respir J 1994; 7:1350-64

36 Carlens E, Dahlstrom G, Nou E. Comparative measurements of quality of survival of lung cancer patients after diagnosis. Scand J Respir Dis 1970; 51:268-75

37 Nou E, Aberg T. Quality of survival in patients with surgically treated bronchial carcinoma. Thorax 1980; 35: 255-63

38 Eguchi K, Fukutani M, Kanazawa M, et al. Feasibility study on quality of life questionnaire for patients with advanced lung cancer. Jpn J Clin Oncol 1992; 22:185-93

39 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85:365-76

40 Buccheri GF, Ferrigno D, Tamburini M, et al. The patient's perception of his own quality of life might have an adjunctive prognostic significance in lung cancer. Lung Cancer 1995; 12:45-58

41 Osoba D, Murray N, Gelmon K, et al. Quality of life, appetite, and weight change in patients receiving dose-intensive chemotherapy. Oncology 1994; 8:61-65

42 Hopwood PH, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. Br J Cancer 1995; 71: 633-36

43 Cody M, Nichols S, Brennan C, et al. Psychiatric morbidity in patients with advanced lung cancer [abstract]. Qual Life Res 1993; 2:57

44 Schag CA, Ganz PA, Wings DS, et al. Quality of life in adult survivors of lung, colon, and prostate cancer. Qual Life Res 1994; 3:127-41

45 Schaafsma J, Osoba D. The Karnofsky performance status scales re-examined: a cross-validation with the EORTC-30. Qual Life Res 1994; 3:413-24

46 Buccheri GF, Ferrigno D. Karnofsky and ECOG performance status in lung cancer: equivalence, construct validity, and predictive validity [abstract]. Lung Cancer 1994; 11(suppl 1):s87

47 Ruckdeschel JC, Piantadosi S. Quality of life in lung cancer surgical adjuvant trials. Chest 1994; 106:324S-28S

48 Ganz PA, Lee JJ, Siau J. Quality of life assessment: an independent prognostic variable for survival in lung cancer. Cancer 1991; 67:3131-35

49 Cella DF, Bonomi AE, Lloyd S, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument [abstract]. Lung Cancer 1994; 11(suppl 1):s89

50 Hughes JE. Depressive illness and lung cancer: II. Follow-up of inoperable patients. Eur J Surg Oncol 1985; 11:21-24

51 Berglund G, Sjoden PO. Communication problems with medical staff: a correlate of distress in cancer patients. Scand J Behav Ther 1987; 16:111-20

52 Sakai H, Yoneda S, Noguchi Y, et al. The investigation of telling the truth to lung cancer patients [abstract]. Lung Cancer 1994; 11(suppl 1):s86

53 Ahmedzai S, Morton A, Reid JT, et al. Quality of death from lung cancer: patients' reports and relatives' retrospective opinion. In: Watson M, Greer S, Thomas G, eds. Psychosocial oncology. Oxford, UK: Pergamon Press, 1988; 187-92

54 Buccheri GF, Vola F, Ferrigno D. Aspects of quality of life in patients with lung cancer: a three observer evaluation study. Int J Oncol 1993; 2:537-44

55 Stephens RJ. Quality of life (QL) in randomised clinical trials: are the doctors' assessment as valid as patients'? [abstract]. Lung Cancer 1994; 11(suppl 1):s81

56 Wolf M, Pritsch M, Drings P, et al. Cyclic-alternating versus response-oriented chemotherapy in small-cell lung cancer: a German multicentre randomised trial of 321 patients. J Clin Oncol 1991; 9:614-24

57 Bergman B, Sullivan M, Sorenson S. Quality of life during chemotherapy for small cell lung cancer: I. An evaluation with generic health measures. Acta Oncol 1991; 30:947-57

58 Bergman B, Sullivan M, Sorenson S. 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. Acta Oncol 1992; 31:19-28

59 Flehinger BJ, Melamed MR. Current status of screening for lung cancer. Curr Perspect Thorac Oncol 1994; 4:1-15

60 Muers MF. How much investigation? In: Thatcher N, Spiro S, eds. New perspectives in lung cancer. London: BMJ Publishing, 1994; 77-104

61 Geddes DM, Law KS, Spiro SG, et al. Quality of life in small cell carcinoma of the lung: a comparison of two chemotherapy regimens using diary cards [abstract]. Lung Cancer 1988; 4(suppl):A182

62 Spiro SG, Souhami RL, Ash CM, et al. Randomised trial of planned as required chemotherapy in small cell lung cancer (SCLC) [abstract]. Lung Cancer 1988; 4(suppl):A101

63 Earl HM, Rudd RM, Spiro SG, et al. A randomised trial of planned versus as required chemotherapy in small cell lung

cancer: a Cancer Research Campaign trial. Br J Cancer 1991; 64:566-72

64 Wolf M, Pritsch M, Drings P, et al. Standard vs palliation chemotherapy in metastatic small cell lung cancer: an analysis on treatment efficacy and quality of life [abstract]. Lung Cancer 1994; 11(suppl 1):s92

65 Joss RA, Alberto P, Hurny C, et al. Quality versus quantity of life in the treatment of patients with advanced small-cell lung cancer? a randomised phase III comparison of weekly carboplatin and teniposide versus cisplatin, adiamycin, etoposide alternating with cyclophosphamide, methotrexate, vincristine and lomustine. Ann Oncol 1995; 6:41-48

66 Joss RA, Bacchi M, Hurny C, et al. Early versus late alternating chemotherapy in small-cell lung cancer. Ann Oncol 1995; 6:157-66

67 Gower NH, Rudd RM, Ruiz de Elvira MC, et al. Assessment of quality of life using daily diary card in a randomised trial of chemotherapy in small-cell lung cancer. Ann Oncol 1995; 6:575-80

68 Bleehen NM, Fayers PM, Girling DJ, et al. Controlled trial of 12 versus six courses of chemotherapy in the treatment of small-cell lung cancer. Br J Cancer 1989; 59:584-90

69 Fayers PM, Bleehen NM, Girling DJ, et al. Assessment of quality of life in small-cell lung cancer using a daily diary card developed by the Medical Research Council Lung Cancer Working Party. Br J Cancer 1991; 64:299-306

70 Geddes DM, Dones L, Hill E, et al. Quality of life during chemotherapy for small cell lung cancer: assessment and use of daily diary card in a randomised trial. Eur J Cancer 1990; 26:484-92

71 Flechtner H, Holle R, Heim ME, et al. Quality of life assessment in small cell lung cancer: results from three consecutive German multicentre randomised trials [abstract]. Qual Life Res 1993; 2:63

72 Hopwood P, Cull A. Quality of life. In: Thatcher N, Spiro S, eds. New perspectives in lung cancer. London: BMJ Publishing, 1994; 161-76

73 Bernhard J, Flechtner H, Havemann K, et al. Quality-of-life (QL) assessment in Swiss and German multicentre randomised phase III trial for small cell lung cancer (SCLC): intercultural comparison of QL-questionnaire [abstract]. Lung Cancer 1988; 4(suppl):A188

74 Hurny C, Bernhard J, Joss R, et al. Fatigue and malaise as a quality of life indicator in small cell lung cancer. Support Care Cancer 1993; 1:316-20

75 Osoba D. Lessons learned from measuring health-related quality of life in Oncology. JAMA 1994; 12:608-16

76 Abratt RP. IASLC workshop on improving quality of life and supportive management of patients with lung cancer. Lung Cancer 1994; 10:375-80

77 Pignon JP, Arriagada R, Ihde D, et al. A meta-analysis of thoracic radiotherapy for small cell lung cancer. N Engl J Med 1992; 327:1618-24

78 Rosenman J, Noah CC. Improved quality of life of patients with small cell lung carcinoma of the lung by elective irradiation of the brain. Int J Rad Oncol Biol Phys 1982; 8:1041-43

79 Bleehen NM, Fayers PM, Girling DJ, et al. Survival, adverse reactions and quality of life during combination chemotherapy compared with selective palliative treatment for small-cell lung cancer. Respir Med 1989; 83:51-58

80 Cull A, Gregor A, Hopwood P, et al. Neurological and cognitive impairment in long-term survivors of small cell lung cancer. Eur J Cancer 1994; 30(A):1067-74

81 Thatcher N, Ranson M, Lee SM, et al. Chemotherapy in non-small cell lung cancer. Ann Oncol 1995; 6(suppl 1): s83-95

82 Bakker W. Quality of life of lung cancer patients. In: Bakker W, ed. Studies in lung cancer treatment: impact on survival and quality of life. Leiden, Netherlands: 1986: 69-106

83 Finkelstein DM, Cassileth BR, Bonomi PD, et al. A pilot study of the Functional Living Index-Cancer (FLIC) Scale for the assessment of quality of life for metastatic lung cancer patients: an Eastern Cooperative Oncology Group Study. Am J Clin Oncol 1988; 11:630-33

84 Moreno I, Rosell R, Abad A, et al. Subjective evaluation in non-small cell lung cancer (NSCLC): comparison of observer assessment with patient generated visual analogue scales (VAS) [abstract]. Lung Cancer 1988; 4(suppl):A183

85 Fernandez C, Rosell R, Abad-Esteve A, et al. Quality of life during chemotherapy in non-small cell lung cancer patients. Acta Oncol 1988; 28:29-33

86 Pujol JL, Monnier A, Berille J, et al. Phase II study of nitrosourea fotemustine as single-drug chemotherapy in poor-prognosis non-small cell lung cancer. Br J Cancer 1994; 69:1136-40

87 Gralla RJ, Hollen PJ, Eberley S, et al. Quality of life score predicts both response and survival in patients receiving chemotherapy for non-small cell lung cancer [abstract]. Support Care Cancer 1995; 3:378-79

88 Hollen PJ, Gralla RJ, Kris MG. Measurement of quality of life in patients with lung cancer in multicentre trial of new therapies: psychometric assessment of the Lung Cancer Symptom Scale. Cancer 1994; 73:2087-98

89 Buccheri GF, Ferrigno D, Curcio A, et al. Continuation of chemotherapy versus supportive care alone in patients with inoperable non-small cell lung cancer and stable disease after two or three cycles of MACC: results of a randomised prospective study. Cancer 1989; 63:428-32

90 Ganz PA, Figlin RA, Haskell CM, et al. Supportive care versus supportive care and combination chemotherapy in metastatic non-small cell lung cancer: does chemotherapy make a difference? Cancer 1989; 63:1271-78

91 Weeks JC, Cook EF, Tosteson ANA, et al. Quality of life in patients with unresectable non-small lung cancer: performance status as a measure of outcome [abstract]. Clin Res 1989; 37:327A

92 Jaakkimainen L, Goodwin PJ, Pater J, et al. Counting the costs of chemotherapy in a National Cancer Institute of Canada randomised trial in non-small cell lung cancer. J Clin Oncol 1990; 8:1301-09

93 Manegold C, Schwarz R. Quality of life and supportive care in the treatment of NSCLC. Chest 1996; 109:113S-14S

94 Gergor A. Radiotherapy of lung cancer. Ann Oncol 1995; 6(suppl 1):s37-41

95 Damstrup L, Poulsen HS. Review of the curative role of radiotherapy in the treatment of non-small cell lung cancer. Lung Cancer 1994; 11:153-78

96 Kaasa S, Mastekaasa A, Thorud E. Toxicity, physical function, and everyday activity reported by patients with inoperable non-small cell lung cancer in a randomised trial: chemotherapy versus radiotherapy. Acta Oncol 1988; 27: 343-49

97 Bleehen NM, Giling DJ, Fayers PM, et al. Inoperable non-small lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or 10 fractions. Br J Cancer 1991; 63:265-70

98 Hopwood P. Physical symptoms as a component of quality of life (QOL) in a prospective randomised trial of two radiotherapy regimens for non-small cell lung cancer (NSCLC) [abstract]. Lung Cancer 1991; 7(suppl 1):145

99 Bleehen NM, Girling DJ, Machin D, et al. A Medical Research Council (MRC) randomised trial of palliative

radiotherapy with two fractions or single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Br J Cancer 1992; 65:934-41

100 Hopwood P, Stephens RJ. Quality of life assessment in a multicentre randomised clinical trial of two policies of radiotherapy in inoperable non-small cell lung cancer [abstract]. Lung Cancer 1994; 11(suppl 1):s82

101 Marino P, Preatoni A, Cantoni A. Randomised trial of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb non-small cell lung cancer: a metaanalysis. Cancer 1995; 76:593-601

102 Arcangeli G, Righini R, Nervi C, et al. Pilot study of multiple-fraction daily radiotherapy alternating with chemotherapy in patients with stage IV non-oat cell lung cancer. Cancer Treat Rep 1985; 69:25-31

103 Minet P, Bartsch P, Chevalier PH, et al. Quality of life of inoperable non-small cell lung carcinoma: a randomised phase II clinical study comparing radiotherapy alone and combined radio-chemotherapy. Radiother Oncol 1987; 8:217-30

104 Ahmedzai S, Grzegorczyk EA, Teather BA, et al. Quality of life in patients with non-small cell lung cancer in a randomised trial of radiotherapy, chemotherapy+RT and palliative treatment [abstract]. Lung Cancer 1988; 4(suppl):A182

105 Dales RE, Dionne G, Leech JA, et al. Preoperative prediction of pulmonary complications following thoracic surgery. Chest 1993; 104:155-59

106 Dales RE, Belanger R, Shamji FM, et al. Quality of life following thoracotomy for lung cancer. J Clin Epidemiol 1994; 47:1443-49

107 Aisner J, Belani CP. Lung cancer: recent changes and expectations of improvements. Semin Oncol 1993; 20:383-93

108 Kosmidis P. Quality of life as a new end point. Chest 1996; 109:110S-12S

109 Cella DF, Orofiamma B, Holland JC, et al. The relationship of psychological distress, extent of disease, and performance status in patients with lung cancer. Cancer 1987; 60:1661-67

110 Krech R, Davis J, Walsh D, et al. Symptoms of lung cancer. Palliat Med 1992; 6:309-15

111 Stewart LA, Pignon JP. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 1995; 311:899-909

112 Smith IE. Palliative chemotherapy for advanced non-small cell lung cancer: time to reappraise its role. BMJ 1994; 308:429-30

113 Goodare H, Smith R. The rights of patients in research. BMJ 1995; 310:1277-78

114 Montazeri A, Milroy R, Macbeth FR, et al. Understanding patients: let's talk about it. Support Care Cancer 1996; 4:97-101

115 Turner S, Maher EJ, Young T, et al. What are the information priorities for cancer patients involved in treatment decisions? an experienced surrogate study in Hodgkin's disease. Br J Cancer 1996; 73:222-27