Review Article

Quality of life measures in lung cancer

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Abstract

Lung cancer is one of the leading causes of cancer death worldwide. Survival has not improved significantly in spite of newer therapies. In view of the high-symptom burden and severe morbidity, evaluation of quality of life (QOL) becomes important in these patients. Several instruments are now available for this purpose, and have demonstrated good correlation with performance status, symptoms, and survival. Quality of life assessments also help in comparing different therapeutic regimes, thus allowing selection of the appropriate modality. Problems of inconsistent interpretability and high-patient dropout rate poses a challenging problem that needs to be tackled. In spite of these drawbacks, QOL is now considered to be an essential component of lung cancer management and should be performed routinely. Such a practice will help the physician plan appropriate treatment strategies and set practical therapeutic goals.

Key-words: Lung cancer, Performance status, Quality of life

Introduction

Lung cancer is one of the leading causes of cancer deaths globally. It carries a greater mortality than colorectal, breast and prostate cancers collectively. In the year 2000 alone, lung cancer was responsible for 692 000 male and 156 000 female deaths.[1] Approximately 85% of patients with lung cancer are diagnosed at an advanced stage that is not amenable to surgical intervention. As a result, these patients require chemotherapy and/or radiotherapy. In spite of several advancements in the chemotherapeutic regimens and the addition of many newer drugs, the 5-year survival has improved only marginally from 5% in the 1950s to approximately 14% by 1996.[2] The overall 1-year survival is less than 20%. Moreover, lung cancer is not just associated with a high mortality but a high morbidity as well, with a significant proportion of patients severely incapacitated by disease-related symptoms such as chest pain, cough, hemoptysis, and dyspnea.[3] In such a grim scenario, the evaluation and improvement of quality of life (QOL) as well as alleviation of symptom distress assumes great importance in the overall management of these patients.

Definition of quality of life

The assessment of a patient of cancer broadly includes two sets of endpoints – cancer outcomes and patient outcomes. Cancer outcomes measure the response of a patient to treatment, duration of response, symptom free period, and early recognition of relapse. Patient outcomes, on the other hand, assess the survival benefit attained after treatment as measured by the increase in life span, and the QOL before and after therapy. Unfortunately, physicians tend to concentrate on the cancer-related outcomes only. Consequently, assessment of QOL remains a neglected area.

Quality of life is a broad, subjective, and multidimensional concept that includes:

- Physical health and symptoms.
- Functional status and activities of daily living.

Mental well being and social health, including social role functioning.

Quality of life can also be simply defined as the effect of an illness and its therapy upon a patient's physical, psychological, and social well being as perceived by the patient himself.[4] However, being a highly subjective variable, there can be no universal consensus over this definition. The intra- and inter-observer variation can be large, and more importantly, may even vary at different points of time. Since it is impossible to define any universally agreed standard for comparison, the subject and observer usually have different perceptions of the same outcome. Furthermore, significant subjective variability may exist within the same patient regarding his problems. For example, he may endure pain for a short while without compromising his daily activities, but over an extended period, this pain may dominate his life and cause significant impairment of various activities.

Over the past few years, increasing attention is being paid to the evaluation of QOL in various diseases, including lung cancer. Numerous instruments have been developed, mainly in the form of questionnaires, which were subsequently validated in different settings and translated in several languages. However, other techniques, such as personal or telephone interviews, may also be used for this purpose. Measuring QOL is especially useful in phase-III trials since it allows the investigator to make, in most cases, definite conclusions regarding the efficacy of a particular therapeutic regimen. Quality of life assessments should be given due priority whenever it is expected that the survival differences between the treatment groups is going to be small (a frequent occurrence), or when the difference in at least one factor predicting QOL is expected to be large. The effect of two different therapeutic modalities on QOL and overall survival helps select the better modality. In fact, a particular treatment may be preferred if it improves the QOL even if the survival is not superior to the other. On the other hand, a treatment may be unsatisfactory and may be rejected if the QOL remains similar or worsens compared to another modality, without offering any survival advantage. However, two situations present a difficulty: one, if the treatment improves QOL but worsens survival, and, when QOL deteriorates but survival improves. In these situations, the choice of treatment is usually made jointly by the physician and the patient after detailed consideration of all relevant aspects.

Attributes of an ideal quality of life instrument[5]

Any QOL questionnaire should possess the following attributes:

- Reproducibility: ability to yield the same results repeatedly under the same conditions.
- Validity: accuracy with which it measures what it is supposed to measure.
- Responsiveness: ability to detect clinically significant changes over time.
- Interpretability: ability to provide results that can make sense.

Quality of life and lung cancer

Quality of life is closely linked to symptom burden and severity in lung cancer. Loss of physical functioning, psychological events such as depression, and reduced overall QOL is associated with uncontrolled symptoms.[6,7] In addition, depression has also been found to be an independent prognostic factor for lung cancer irrespective of stage.[8]

Physical functioning is possibly the easiest to evaluate in QOL studies. However, they have their own limitations. The commonest symptoms of lung cancer, i.e. cough, and dyspnea may be caused by chronic bronchitis also, whereas hemoptysis is usually transient. It has been suggested that pain and malaise are the most useful symptoms for assessing general well being in lung cancer. Likewise, nausea, vomiting, and hair loss are proposed to be the most suitable symptoms for evaluating treatment-related side effects.[9]

It is now universally accepted that assessment of QOL should be included in evaluating treatment outcomes in lung cancer. A recent review, that examined all prospective phase III randomized trials for the treatment of lung cancer found that only 14 out of 39 studies (36%) contained information about QOL.[10] Only five of these used QOL and symptom relief as primary end-points; majority of the remaining described patient-reported symptom assessment. A previous review that examined 151 QOL studies in lung cancer found that 83 focused specifically on either small cell cancer or nonsmall-cell lung cancer.[11] Of these 151 reports, 33 were validation/feasibility studies. The remaining studies were carried out with different objectives, using varying time intervals of measurement, different clinical outcomes, and different interpretations of QOL changes.

Over the last decade, over 50 instruments have been developed and used to measure QOL in lung cancer. Quality of life instruments are mainly classified in the following categories: generic or disease-specific. Generic instruments are further subclassified into Health profiles

Table 1: Classification of QOL instruments*

Generic		Disease specific
Health profiles	Utility measurements	
Nottingham	Visual analog scale	
Health profile (38)		Functional living index – cancer (22)
Short form-36		EORTC-WHOQOL30 (30)
Health survey		Daily dairy card (22)
Sickness impact profile (136)		Functional assessment of cancer therapy – lung (41)
		Lung cancer symptom scale (15)
		EORTC QOL- LC 13 (13)

*Numbers in parentheses indicate the number of items in each questionnaire

and Utility measurements [Table 1].

Health profiles are single instruments primarily used to measure each important facet of QOL. They have the advantage of being valid and reproducible over a wide variety of diseases, as well as being able to demonstrate change with treatment. However, they are not disease-specific and hence, may miss important aspects of QOL of the disease under evaluation. They are also lengthy and time-consuming compared to the recent site-specific questionnaires available.

Utility measurements, on the other hand, measure an individual's perception of a single symptom, e.g. dyspnea or chest pain. The commonest in use is the Visual analog scale (VAS). This is a vertical line 10 cm in length with two anchor points at each extreme. The two ends may be designated verbal descriptions such as none and maximum. The subject responds by marking a point on the line to indicate the intensity of the symptom as perceived by him. Visual analog scale eliminates the restrictions imposed by fixed responses (better/worse, or yes/no), and allows a flexible response in a continuum, thereby allowing finer descriptions and assessments of any subjective state. Visual analog scale has been extensively used in QOL studies, mostly to quantify dyspnea, and has been found to be a reliable and reproducible tool.[12,13]

Disease-specific questionnaires are those that incorporate questions relevant to a particular disease. These may include items pertaining to symptoms and treatment-related toxicities. The commonly used specific QOL instruments for lung cancer are the Functional Assessment of Cancer Therapy-Lung (FACT-L), Lung Cancer Symptom Scale (LCSS), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC-QLQ-LC 13).

Most of the instruments listed in [Table 1] have been widely applied in QOL assessment studies. However, there is a substantial heterogeneity in the outcome variable(s) used to evaluate QOL. Some questionnaires use changes in symptom burden and severity as the indicator of QOL, whereas others use subscale scores to measure change over time and with intervention. Some of the popular instruments, categorized according to the primary outcome measured, are shown in [Table 2]. These instruments are useful not only for baseline evaluation, but also to assess the efficacy of various therapeutic modalities (including surgery, chemotherapy, and radiotherapy) or a combination of any of the

Table 2: Popular QOL measuring instruments in lung cancer

Instruments	Number of items	Variables assessed
Generic outcomes		
SIP	136	Physical and psychological status, sleep, rest, work, recreation
Performance status		
KPS	11	Performance status
ECOG Scale	5	Performance status
Psychological assessment		
HAD	14	Anxiety, depression
Cancer specific		
DDC	5	Physical activity level, mood, anxiety, vomiting, overall condition
FLI-C	22	Physical symptoms and activity, mood
Symptom Distress	13	Cancer-related Scale symptoms (cough, pain, dyspnea, appetite, nausea, sleep, and concentration)
EORTC-QOL-C30	30	Cancer symptoms, physical symptoms, functioning (physical, role, emotional, and social), overall health, financial impact)

above. The description of how a particular treatment (or combination of treatments) influences the QOL and overall survival is important to assist in the selection of the best possible approach.[14] This has important implications for the patient who may, in fact, opt for the treatment that offers a better QOL even if the overall survival is not superior to that conferred by another treatment regimen.[4]

Among the instruments listed in [Table 1], the FACT-L, the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ C30) (along with its lung cancer specific module), and LCSS are the most widely used for QOL assessments in lung cancer clinical trials.

Functional assessment of cancer therapy-lung

The FACT instrument was developed to measure QOL in patients with cancer.[15] The original questionnaire, referred to as the FACT-General (FACT-G), comprised of 27 items. The lung cancer-specific module (FACT-L) incorporates the FACT-G with a symptom scale specific for lung cancer. The latest version (Version 4) is a 41-item self-reported questionnaire. Among these, 34 items pertain to five dimensions of general health-related QOL (physical, social and family, emotional, functional well-being, and relationship with the physician), and seven items to specific lung cancer symptoms (dyspnea, difficulty breathing, coughing, chest tightness, appetite, weight loss, and cognitive function). These items are marked on a 5-point Likert scale keeping a time frame of the past 1 week. This questionnaire has the disadvantage of putting less emphasis on treated related symptoms. However, in spite of these shortcomings, it has a high level of reliability and validity based on extensive psychometric testing.[16] Good sensitivity to change has also been demonstrated. A change of two points on the seven-item symptom scale is considered a clinically significant change in QOL.[17]

European organization for the treatment and research of cancer quality of life questionnaire (EORTC QLQ-C30) and EORTC QLQ LC 13

In order to overcome the shortcomings of the QOL instruments existing at the time, the EORTC initiated a large-scale multinational program in 1986 to try and develop a comprehensive questionnaire that covers all areas of QOL assessment. This program included 305 patients across 13 countries. The outcome was a 30-item questionnaire, which included five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and one global health and QOL scales. This instrument was tested in the USA, Australia, Europe, and Japan and demonstrated a high reliability and validity across the continents.[18]

The EORTC QLQ-LC 13 questionnaire was developed in 1994 as a lung cancer specific supplementary to the EORTC QLQ-C30. This is a 13-item instrument that assesses lung cancer related symptoms [cough and hemoptysis (one item each), dyspnea (three items)], treatment related side-effects [sore mouth or tongue, dysphagia, hair loss, tingling hands, and feet (one item each)], pain (three items), and pain medication (one item). All items are rated on a 4-point Likert scale and 7-point numerical analog scale with a reporting time frame of 1 week. Extensive field studies demonstrated significant changes in symptom and treatment toxicity subscale scores over time, with symptoms improving and treatment related side effects increasing during chemotherapy.[19] Thus, it was found to be a clinically valid and useful tool to assess disease and treatment-specific symptoms in lung cancer patients. The EORTC-QLQ C30 and EORTC-QLQ LC-13 are often used together in order to obtain a comprehensive evaluation of QOL in lung cancer. Over the last decade, it has been translated into 17 other languages and is now the most widely used QOL questionnaire in cancer patients.

Methods of analysis of this questionnaire and interpretation of clinically meaningful changes of QOL measures have varied. Some studies calculated changes in individual symptom scores whereas others used mean subscale scores of the various QOL domains to evaluate change.[20–22] Montazeri et al. compared EORTC scores in 129 patients divided into two groups, one who received treatment (chemotherapy, radiotherapy, or surgery) and the other that did not (called as receiving best supportive care).[23] They used the change in mean scores of individual symptoms as well as mean subscale domain scores to interpret the results. Some researchers categorized symptom changes into subgroups, such as improved, worsened, or unchanged.[24]

Lung cancer symptom scale

This questionnaire was developed in the mid-1980s at the Memorial Sloan-Kettering Cancer Center as a lung cancer-specific questionnaire that focuses primarily on the physical and functional dimensions of a patient. It comprises two different scales, one rated by the patient and the other by the physician. The patient scale contains nine items, including three summation and six symptom items. Each item is marked on a VAS of

100 mm length, with zero denoting the lowest rating and 100 the highest. The mean of the six main symptoms is used to calculate the 'average symptom burden' of the patient. The physician scale consists of six items pertaining to the main lung cancer symptoms. These are rated as 0, 25, 50, 75, and 100 depending on symptom severity.[25]

A change of 10 mm or more on the patient scale is taken as a clinically meaningful change in QOL and has been found to correlate well with symptomatic change both for total score and for individual items.[26] A drawback of LCSS is that it ignores several important components of QOL, such as the social and emotional aspects. However, Hollen and Gralla compared LCSS with other QOL instruments and demonstrated a reasonably good reliability and validity.[27] Normative data is also available in a large cohort of NSCLC patients.[28] Consequently, LCSS remains popular and has been used in several studies for assessing QOL.[29,30]

Problems in measuring quality of life

Measuring QOL is beset with several problems. There is a large intra and inter-observer error, and perceptions may vary with time. There is no universal agreement regarding comparative standards. Except for the Nottingham Health Profile (NHP), which was developed through public participation, majority of questionnaires were devised by physicians.[31] As a result, subjective variability is high since different physicians may have different points of view. Barriers of language, culture, and religion also hinder accurate measurement of QOL. In addition, several other factors such as age, associated co-morbidities, and the quality of medical and palliative care provided to the patients influence many aspects of QOL. Comparing two studies is difficult since they invariably differ in the patient profile, timings of assessments, treatment modalities given, length of follow-up, and the QOL instrument used for evaluation. Furthermore, the short-term survival of lung cancer, rapid deterioration of performance status (PS), and drop-outs due to treatment related side effects may cause difficulty in collecting data and following-up the patients for a long period of time. This problem of 'missing data' causes difficulties in making accurate assessments and drawing conclusions from QOL studies. It has been suggested that comparative analysis of QOL should be stopped when less than 30% of the data is available.[32]

Performance status and quality of life

Performance status has been frequently used as a proxy of QOL since the 1970s. It is an important prognostic factor and predictor of survival of lung cancer patients.[8] There is good correlation between PS and global QOL, including psychological, physical, and symptomatic well-being. Performance status also correlates well with the number and severity of symptoms.[33] The most well established markers of PS are the Karnofsky Performance Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG). Karnofsky Performance Scale is a simple and widely used numerical instrument for rapidly quantifying the PS of an individual based on his level of independence.[34] This scale rates the PS of a patient in multiples of 10, from 0 (worst) to 100 (best) depending on the ability to perform his activities. Various studies have demonstrated a direct relationship between KPS and the perceived QOL in patients with cancer, including lung cancer.[8] In a study of 57 disease free survivors of lung cancer, KPS was found to be the best predictor of QOL.[35] However, another study that evaluated 139 patients of lung cancer receiving palliative treatment, KPS was found to be only weakly associated with the QOL as measured by EORTC QLQ C30.[36] Similar results have been observed in studies that used the ECOG Scale. This scale is a five-grade observer rating of patients' physical ability ranging from 0 (normal) to 4 (disabled).[37] Buccheri and Ferrigno performed a validation study using ECOG and KPS on a large sample of 471 patients and concluded that both instruments are valid, however, the ECOG was found to be slightly superior.[38] Aaronson et al. used the ECOG and EORTC QLQ-C30 to evaluate QOL in 354 patients with lung cancer undergoing chemotherapy or radiotherapy.[8] They found a strong correlation between the PS (assessed by ECOG scale) and physical, role, cognitive functioning, and overall QOL (assessed by EORTC QLQ-C30). These results suggest that measurement of PS by either KPS or ECOG may serve as a useful and simple surrogate marker of QOL.

Quality of life as a prognostic marker in lung cancer

There is sufficient evidence to suggest that initial QOL is a strong prognostic factor for survival in lung cancer. Ganz et al. demonstrated the predictive value of QOL [assessed by Functional Living Index-Cancer (FLI-C)] for survival in 40 patients receiving either chemotherapy or radiotherapy.[39] In another large study, the pretreatment QOL as assessed by the FLI-C strongly prognosticated a randomized sample of 437 patients undergoing two different therapeutic regimens.[40] Langendijk et al evaluated baseline QOL using EORTC QLQ C30 in 198 patients planned for radiotherapy and estimated the prognostic value of several parameters for

survival.[41] Performance status, weight loss, and N-classification were found to be independent prognostic factors. Global QOL was the strongest predictor of survival after multivariate analysis. A 3-month follow-up assessment of QOL in 129 patients showed that prediagnosis global QOL was the most significant predictor of the length of survival after adjusting for other known prognostic factors such as age and extent of disease.[23] Other important proposed prognostic markers are the subscales – pain, anorexia, fatigue, lung cancer symptoms, level of physical functioning, overall QOL, albumin, and the stage of disease.[42] There does not appear to be any significant correlation with histological subtype.

The association of QOL with chemotherapy has been evaluated in several studies [Table 3]. Helsing et al compared chemotherapy with best supportive care and demonstrated significant survival benefit in the chemotherapy group (29 weeks *vs* 11 weeks; 1-year survival, 28% *vs* 8%) along with significant improvement in dyspnea, pain, insomnia, and social function.[43] Similarly, the Elderly Lung Cancer Vinorelbine Study Group found significantly longer survival, less pain and dyspnea, better cognitive function and QOL, and better global health status in the vinorelbine group compared to controls.[44] In contrast, Bonomi et al. compared two chemotherapeutic regimes (paclitaxel/cisplatin *vs* etoposide/cisplatin) and found a significant decline in QOL over time inspire of improved survival in the paclitaxel/cisplatin arm.[45]
From the above evidence, therefore, it is clear that the benefit of chemotherapy over best supportive care is still questionable. A clear answer to this question would be difficult since most chemotherapeutic regimes have produced benefit in different aspects of the disease, such as survival, symptomatic relief, tumor regression, and QOL.

Table 3: Selected studies evaluating QOL in lung cancer (1994 – 2005)

Author (year)	Sample size	Instrument	Design	Treatment	Results/interpretation
Erridge et al. (2005)	149	HAD	P	RT (single fraction *vs* multiple fraction dose regimens)	Significant higher improvement in symptom score and palliation in single fraction RT regimen; no significant difference in survival
Cella et al. (2005)	216	FACT-L	P	Geftinib (250 mg/day *vs* 500 mg /day)	Rapid symptom improvement with both doses; significant QOL improvement with 250 mg/ day that correlated with survival
Esbensen et al. (2004)	101	EORTC - QLQ C30 + LC - 13	P	Baseline evaluation	Factors associated with poorer QOL were economic state, low level of hope, and need of help in activities of daily living
Garces and colleagues (2004)	1028	LCSS	P	CT	Seven LCSS components (appetite, fatigue, cough, shortness of breath, lung cancer symptoms, illness affecting normal activities, and overall QOL) were significantly different between never smokers and persistent smokers after diagnosis
Spiro et al. (2004)	725	EORTC - QLQ C30	P	BSC/CT + BSC	No significant difference in QOL; better survival in chemotherapy arm
Montazeri et al. (2003)	129	EORTC QLQ C30 + LC - 13, NHP	P	CT + RT/BSC	Improved physical mobility and disease-related symptoms in RT group
Herndon et al. (1999)	206	EORTC - QLQ C30 + LC - 13	P	CT + Hydrazine/placebo	QOL significantly related to ECOG performance status, weight loss, dyspnea and hypoalbuminemia
Cullen et al. (1999)	351	EORTC QLQ C30 + LC-13	P	CT + BSC	Better survival in CT group
Ruckdeschel et al. (1994)	437	FLI-C, KPS	P	Preoperative therapy + surgery/ Surgery + postoperative therapy	Baseline QOL strongest predictor of survival; FLI-C highly sensitive to clinical change
Bergman et al. (1994)	346	ECOG, EORTC	P	CT/RT	EORTC valid tool to assess disease-symptoms and therapy – related side effects

P, prospective; RT, radiotherapy; CT, chemotherapy; BSC, best supportive care

Conclusion

Lung cancer continues to claim thousands of lives every year globally. Several newer therapies have, as yet, failed to significantly prolong survival or offer curative benefit. In view of the high morbidity and short survival, assessment of QOL needs to be included as an end point in evaluation and treatment of lung cancer. Several instruments, mostly in the form of questionnaires, have been developed in the last decade, and subsequently translated and cross-validated in various geographical and cultural settings. Quality of life measurements also help in predicting survival, evaluating efficacy of various treatment regimens, as well as comparing one regimen with another. However, several problems, such as missing data due to a high-dropout rate, and lack of guidelines for uniform interpretation still exist that need to be addressed and improved upon in the future. In spite of these handicaps, QOL evaluation would greatly help in treatment planning and in the setting up of appropriate and practical therapeutic goals. As far as the patient is concerned, the primary goal of the physician should be to try and improve his overall QOL using all measures available.

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