Symptom Assessment for Patients with Non-small Cell Lung Cancer Scheduled for Chemotherapy

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Abstract. *Aim: This study assessed the symptoms and health-related quality of life (HRQOL) of patients with advanced non-small cell lung cancer (NSCLC) and examined the symptom-associated characteristics. Patients and Methods: The symptoms of 122 patients with NSCLC scheduled for chemotherapy before starting treatment were surveyed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire and Edmonton Symptom Assessment Scale (ESAS). Results: The most prevalent symptoms were coughing (EORTC score 41.7), dyspnea (33.9), fatigue (31.9), insomnia (30.3) and pain (21.8). The mean EORTC score for global QoL was 56.9 (SD=23.5). Physical, cognitive and emotional functioning, insomnia, diarrhea, and dyspnea had a significant influence on the HRQOL ($p<0.05$). ESAS assessment correlated with these results and thus was an easy-to-use tool for symptom assessment (correlation coefficient range=0.546-0.865, $p<0.0001$ for all symptoms). Conclusion: Patients with advanced NSCLC suffer from multiple symptoms influencing HRQOL. ESAS provides a symptom assessment tool that is as reliable as but simpler to use than the EORTC questionnaire.*

Patients with advanced lung cancer often present with a high symptom burden (1). Among newly-diagnosed patients with lung cancer, more than one-half experience severe pain and fatigue, and more than one-third experience insomnia and difficulty with appetite (2). Breathlessness is also one of the common symptoms (3). Consequently, symptom assessment and control, and quality-of-life (QoL) issues should be the focus of treatment of advanced lung cancer. To accomplish this task, a simple symptom assessment tool for use in daily practice is necessary.

At the time of diagnosis, two-thirds of patients with NSCLC suffer from inoperable locally advanced or metastatic disease (4). Standard treatment with chemotherapy improves the overall survival of these patients, but the major goal of the treatment is still to alleviate the symptoms. Patients with advanced NSCLC may regard the improvements in progression-free survival (PFS) that are achieved with chemotherapy valuable only if their disease symptoms are mild. In patients with severe disease symptoms, small improvements in PFS may be regarded as harmful (5).

The current study assessed the symptoms and QoL of Finnish patients with advanced NSCLC scheduled for chemotherapy. The user-friendliness and validity of ESAS with patients with NSCLC was tested, to our knowledge for the first time, by comparing the results with the results of the simultaneously completed EORTC questionnaire.

Patients and Methods

This prospective symptom assessment study was performed at the Turku University Hospital in Turku, Finland, between August 2008 and August 2011. Patients with newly diagnosed NSCLC subjected to chemotherapy were eligible for the study. Those patients who were scheduled for an operation or curative radiotherapy or whose diagnosis was over 1 year old were excluded.

During the study period, 154 patients were asked to participate in the study consecutively. Of this group, 22 patients refused to participate, and 10 patients did not meet the inclusion criteria. In total, 122 patients (79% of total addressed) were thus included in the study.

All demographic patient data were collected from hospital records. These data included age, gender, performance status, histopathological diagnosis, TNM classification, smoking status, concurrent diseases, and medication at the time of diagnosis.

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The patients were asked to complete three different surveys. Health-related quality-of-life data and symptoms were measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) (6) and lung cancer-specific questionnaire (QLQ-LC13) (7). The core QLQ-C30 questionnaire had five functional scales (physical, role, cognitive, emotional, social), one global health status, three symptom scales (fatigue, pain, nausea/vomiting) and five single items (constipation, diarrhea, sleep, dyspnea, financial problems). The QLQ-LC13 included 13 questions that assessed lung cancer-associated symptoms (cough, hemoptysis, dyspnea, site-specific pain), treatment-related side-effects (sore mouth, dysphagia, peripheral neuropathy, alopecia) and pain medication. These scores ranged from 0 to 100. A high score for a functional scale represents a high level of functioning, and a high score for QoL represents a high QoL, while a high score for a symptom item represents a high level of symptomatology. Reference data for the QLQ-C30 were obtained from the EORTC reference values (8).

At the same time, the patients filled in the Edmonton Symptom Assessment Scale (ESAS) questionnaire that was developed for symptom assessment of patients with cancer (9). The original ESAS questionnaire was translated in Finnish and slightly modified to gather a separate registration of pain at rest and pain at effort. Items for constipation and sleeplessness were also added. Thus, the questionnaire had 11 items that included 10 symptoms. The forms were completed by the patient without any staff help. The assessment date was mostly the date for commencement of treatment with chemotherapy.

The patients signed a written informed consent before their inclusion. The study protocol was approved by the Ethical Committee of the Hospital District of South West Finland (Clinical trial information: NCT00818402). The study was performed in accordance with the Declaration of Helsinki.

Statistical analysis. Quantitative data was summarized by mean, together with a standard deviation or range, and categorical data as counts and percentages. The Pearson correlation was calculated using age, EORTC QLQ-C30 and QLQ-LC13 scores. Association between QoL score and several specific factors [sex, stage, pathological diagnosis, age class (≤60, 60-70, >70 years), the number of pack years of smoking, metastases in bone or brain] were examined using multi-way analysis of variance. A similar model was performed for the association between QoL and lung cancer-specific questionnaire scores. Modelling was performed separately because of the multi-co-linearity aspects. The severity of dyspnea was compared by the number of pack years of smoking using the Kruskal–Wallis test. The Spearman correlation coefficient was calculated for EORTC symptoms and the corresponding ESAS symptoms. A *p*-value of less than 0.05 (two-tailed) was considered statistically significant. The statistical analyses were performed using SAS® software (Version 9.3 for Windows; SAS Institute Inc. Cary, NC, USA).

Results

Baseline characteristics. The patient characteristics are summarized in Table I. The respondents consisted of 76 males (62%) and 46 females (38%). The mean age was 67 years (range=45-86 years). Only 16 patients (13%) were non-smokers. Of the patients, most (90%) had a diagnosis of adenocarcinoma or squamous cell carcinoma, and 10% had a large cell carcinoma, a poorly differentiated carcinoma, or NSCLC without a specified histology. Of these patients, 14

Table I. *Patients' characteristics (n=122).*

		n (%)
Gender	Male	76 (62.3)
	Female	46 (37.7)
Age, years	<60	22 (18.0)
mean=67.1,	60-70	60 (49.2)
range=45-86 years	>70	40 (32.8)
Diagnosis	Adenocarcinoma	66 (54.1)
	Squamous cell carcinoma	44 (36.1)
	Other	12 (9.8)
Smoking history	Never	16 (13.1)
	Former	58 (47.5)
	Current	46 (37.7)
	Not known	2 (1.6)
Total pack years:	Under 10	5 (4.8)
	11-40	62 (59.6)
	Over 40	37 (35.6)
TNM Stage	I	4 (3.2)
	II	5 (4.1)
	III	34 (27.9)
	IV	79 (64.8)
Metastases at time of diagnosis	Lymph nodes	98 (80.3)
	Pleura	34 (27.9)
	Bone	19 (15.6)
	Liver	7 (5.7)
	Brain	15 (12.3)
	Adrenal gland	18 (14.8)
ECOG performance status	0	26 (21.3)
	1	81 (66.4)
	2	13 (10.7)
	3	2 (1.6)
Concurrent disease	Lung	29 (23.7)
	Cardiovascular	62 (50.8)
	Gastrointestinal/hepatic	9 (7.4)
	Kidney	2 (1.6)
	Neurological	6 (4.9)
	Psychiatric	6 (4.9)
	Rheumatic	7 (5.7)
	Musculoskeletal	18 (14.8)
	Endocrine	17 (13.9)
	Urological	8 (6.6)
	Previous cancer	21 (17.2)
Possible treatment of lung cancerbefore the beginning of the study	Chemotherapy	0 (0)
	Surgery	14 (11.5)
	Lobectomy	11
	Pneumonectomy	1
	Wedge resection	2
	RT	18 (14.8)
	Radical RT	1
	Brain metastases RT	10
	SDR RT	3
	Bone metastases RT	2
	Other palliative RT	2

RT: Radiotherapy; SDR: superior *vena cava* syndrome.

Table II. *Symptoms at baseline assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaires. All of the scales and single-item measures ranged in score from 0 to 100. A high score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/quality of life (QoL) represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.*

Questionnaire	Symptom	N	Mean score	SD
EORTC QLQ-C30[1]	Global QoL	120	56.9	23.5
	Physical functioning	121	64.4	23.1
	Role functioning	120	63.5	30.9
	Cognitive functioning	121	82.8	21.3
	Emotional functioning	121	75.2	21.3
	Social functioning	120	81.1	25.5
	Fatigue	121	31.9	21.0
	Nausea and vomiting	120	5.0	13.2
	Pain	121	21.8	25.3
	Dyspnea	121	33.9	29.8
	Insomnia	121	30.3	29.8
	Appetite loss	121	19.3	26.1
	Constipation	121	16.0	25.9
	Diarrhea	120	5.8	14.1
	Financial difficulties	117	23.1	30.0
EORTC QLQ-LC13[2]	Dyspnea	113	32.7	22.2
	Coughing	119	41.7	27.9
	Hemoptysis	120	7.2	17.9
	Sore mouth	119	9.5	18.0
	Dysphagia	120	8.3	20.8
	Peripheral neuropathy	120	11.9	21.1
	Alopecia	120	10.3	24.7
	Chest pain	118	17.8	20.3
	Arm pain	118	18.6	25.2
	Other pain	112	22.6	27.3

[1]EORTC Quality of life questionnaire QLQ-C30; [2]EORTC lung cancer-specific questionnaire EORTC QLQ-LC13. SD: Standard deviation.

had had lung surgery before the study. Eighteen patients had received radiotherapy, but only one of these was with a curative intent.

The majority of the patients had stage III (28%) or IV (65%) NSCLC. The main sites of metastasis were lymph nodes (80%) and pleura (28%). A few patients had liver, bone, brain, or adrenal gland metastases (see Table I).

Symptoms. The mean EORTC score for global QoL was 56.9 [standard deviation (SD) 23.5] (see Table II). Cognitive functioning scores (mean=82.8, SD=21.3) and social functioning scores (mean=81.1, SD=25.5) were the highest, showing that there was no marked impairment in this field. The lowest scores were for physical and role functioning (mean=64.4, SD=23.1, and mean=63.5, SD=30.9, respectively).

Table III. *The association of Edmonton Symptom Assessment Scale (ESAS) to the European Organisation for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30).*

EORTC	ESAS	Correlation coefficient	*p*-Value
QOL	Total well-being	−0.577	<0.0001
Pain	Pain at rest or upon effort	0.763	<0.0001
Fatigue	Fatigue	0.704	<0.0001
Nausea and vomiting	Nausea	0.546	<0.0001
Dyspnea	Dyspnea	0.800	<0.0001
Loss of appetite	Loss of appetite	0.761	<0.0001
Insomnia	Insomnia	0.819	<0.0001
Constipation	Constipation	0.865	<0.0001

Of the symptom scales for QLQ-C30, the most prominent symptoms were dyspnea with a mean score of 33.9 (SD=29.8), fatigue (mean=31.9, SD=21.0), and insomnia (mean=30.3, SD=29.8). Pain (score=21.8, SD=25.3) and financial difficulties (mean=23.1, SD=29.8) were distracting for the patients.

The lung cancer module QLQ-LC13 revealed the highest score for coughing at 41.7 (SD=27.9). Dyspnea received nearly the same scores (mean=32.7, SD=22.2). Pain (other than arm or chest pain) was measured and offered the third highest scores (mean=22.6, SD=27.3).

In a multivariate analysis, several items of the questionnaire QLQ-C30 had a significant influence on HRQOL: physical functioning (p=0.013), cognitive functioning (p=0.003), emotional functioning (p=0.041), insomnia (p=0.037) and diarrhea (p=0.020).

A statistical analysis of the influence of the items for the lung cancer module QLQ-LC13 on HRQOL was made, and the only symptom that had a significant negative effect on affecting HRQOL was dyspnea (p=0.0002). The number of pack years did not have a significant influence on the symptom of dyspnea.

The effect of dyspnea on the items of QLQ-C30 was examined, and it was found that dyspnea had a significant negative effect on physical function (p<0.0001).

The influence of patient characteristics on symptoms. The demographic variables, such as age, sex, stage, pathological diagnosis, the pack years smoked, or the location of the metastases (brain or bone) were not significantly associated with the symptoms or the QoL of these patients.

The association of ESAS with the EORTC questionnaire. When the symptoms were measured using the ESAS questionnaire, the median ranged from 0-2 (on a scale of

0-10). There was a strong positive correlation with the results from the EORTC questionnaire (Table III). Most of the correlation coefficients were over 0.7 (range=0.546-0.865, $p<0.0001$ for all symptoms).

EORTC reference values. The results for the EORTC questionnaire were linked to the EORTC reference values of patients with NSCLC representing all stages and those representing all cancer patients (Figure 1). Physical functioning scores in this study were noticeably lower (score=64.4) than NSCLC reference scores (score 78.4) and the all-cancer patient reference score (score=76.7). Dyspnea was regarded as a distressing symptom, with a score of 33.9, which was almost at the same level as the NSCLC reference score (score=38.5), but still markedly higher than the score for all cancer patients (score=21.0). The HRQOL score was almost the same for all groups (score 56.9, 58.8, and 61.3, respectively). Our patient population reported more financial difficulties (score=23.1) than the reference group of patients with NSCLC (score=12.8). Coughing was one of the most distressing symptoms (score=41.7), similar to the reference value (score=38.4).

Discussion

The burden of lung cancer-specific symptoms in patients with advanced disease is high (1, 2, 4, 10, 11). Therefore, when treatments are planned, physicians need to assess those symptoms to follow the outcome and the need for symptom management.

Among our patients, the most distressing symptoms were coughing, dyspnea, fatigue, insomnia, and pain. Physical functioning and role functioning had the lowest scores on the functional scales. The mean EORTC score for global QoL was 56.9, suggesting that these patients' view of their QoL was weak at the beginning of chemotherapy. Dyspnea had a remarkable impact on the QoL of patients with lung cancer. Physical functioning deteriorated with increasing dyspnea, and it concurrently also worsened QoL.

QoL is an important feature of patients with NSCLC; however, the symptom assessment forms are time consuming. The mean EORTC score in our study population for global QOL was 56.9. That was quite weak. Nevertheless, the reference values showed that this result was similar to previous findings when compared to all other patients with cancer. QoL has been shown to be an independent prognostic factor for overall survival of patients with NSCLC (12). This indicates the importance of measuring QoL and being fully aware of the factors that influence QoL. With effective symptom palliation, QoL can be improved. Temel *et al*. found that early palliative care led to significant improvements in QoL and thus longer survival of patients with metastatic NSCLC (13).

No correlation was observed between the different background variables (age, sex, stage, and pathological diagnosis, amount of pack years smoked, or the location of metastases) and QoL or symptoms in the present study. This finding contradicted several previous findings (1, 12, 14, 15). In some of those studies, QoL was found to correlate with baseline factors (sex, stage, disease histology, and performance status). It has also been shown that younger patients experience more pain than older patients (14). Rowland *et al*. learned in their review that smoking was reported to significantly lower QoL. Current smokers reported significantly poorer QoL than did former smokers, and former smokers had poorer QOL than those who never smoked (16).

When comparing the current results with the EORTC reference values, the current results corresponded to previous perceptions. The severity of symptoms was on the same level as that found in the reference values. Nevertheless, the physical functioning score (mean=64.4) in our study was notably lower than the reference score for patients with NSCLC (mean=78.4) and all-cancer patients (mean=76.7), meaning that our patients felt their physical functioning had decreased more than the functioning of the patients in the reference groups. This difference can be partly explained by the fact that the majority of patients in our study had advanced (stage III-IV) cancer. Statistical comparison was not possible, however, because of the heterogeneity of the different groups. Osoba *et al*. showed that a mean change of 10 to 20 for the domains of QLQ-C30 questionnaire indicated a moderate change in symptoms (17). Therefore, there was a marked difference between our scores and the reference scores for physical functioning.

Dyspnea and coughing were the most distressing symptoms among our patients. Dyspnea also had a remarkable effect on QoL. The severity of dyspnea in our study group was notably higher than that in the reference group for all cancer (8). Dyspnea was not correlated to patient smoking history or concurrent diseases, which indicates that dyspnea of patients with NSCLC is a symptom that should be focused on and treated properly.

Pain was the third most distressing symptom. It also had a significant impact on QoL. In previous studies, the pain of patients with cancer was shown to be undertreated (18). Pain needs to be treated properly. Pain is associated with reduced QoL, and its treatment is associated with better outcomes in patients with NSCLC (12).

Contrary to the EORTC questionnaires, the ESAS forms were simple to fill out, and being just one page, made the paper easy for the patients and for the physician to use to gather valuable information about the patients' conditions. To our knowledge, there are only a few studies comparing the ESAS and EORTC questionnaires and none of the comparisons are made especially for patients with lung cancer. We found that symptom intensity detected from the results from the EORTC questionnaires strongly correlated with the

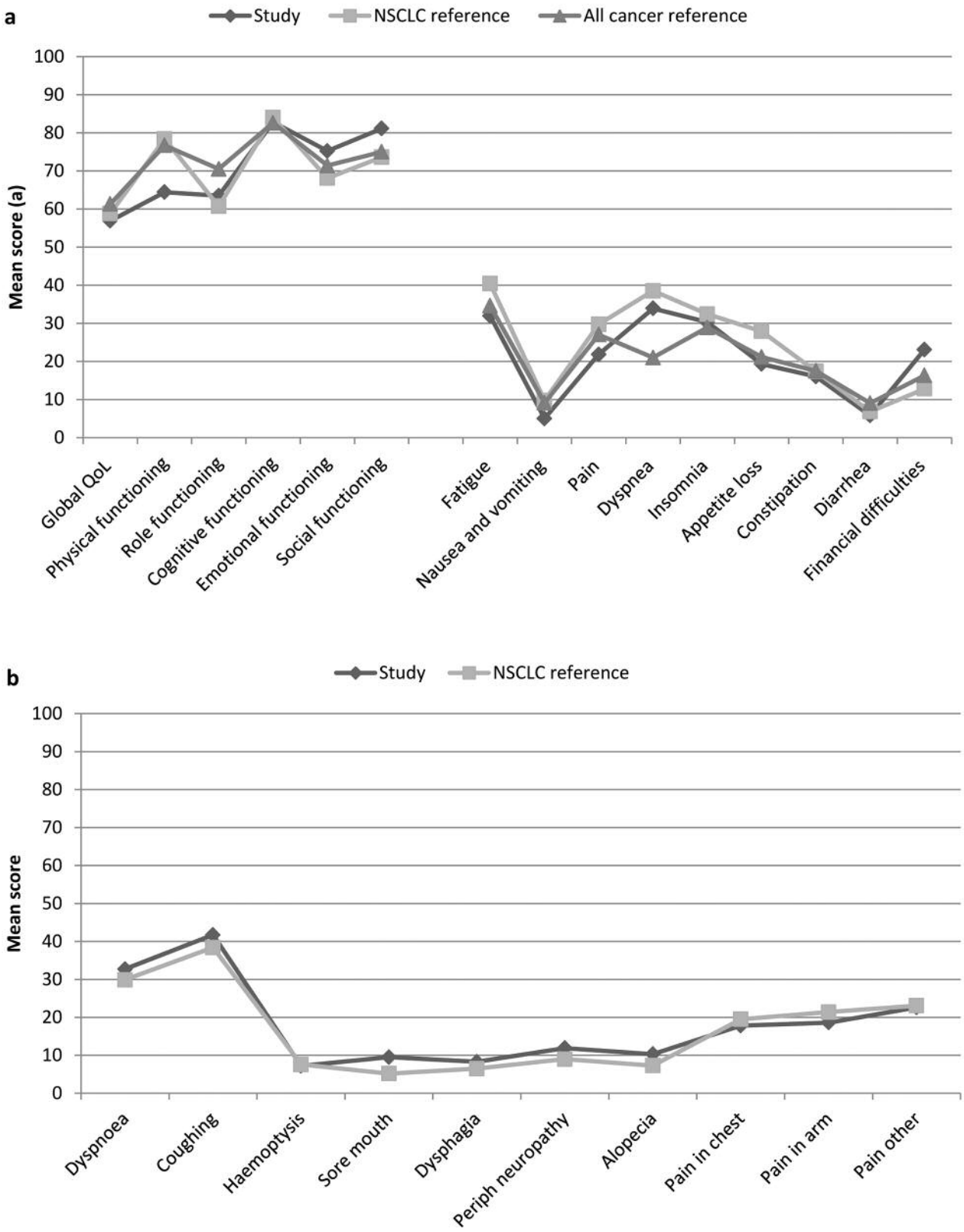

Figure 1. *Mean baseline scores for functional and symptom domains of the (a) European Organisation for Research and Treatment Quality of Life Questionnaire (EORTC QLQ-C30) and (b) lung cancer-specific questionnaire (QLQ-LC13) for study patients compared to a reference population of all-cancer patients and a reference population of patients with non-small cell lung cancer (NSCLC) at all stages.*

results from the ESAS questionnaire. Thus, the use of ESAS can be recommended for patients with lung cancer in a busy oncology practice and with patients who are not necessarily able to fill-in longer forms, as the questionnaire is easy to use and quickly completed. Our earlier experience with palliative patients has shown that patients appreciate giving a more comprehensive picture of their symptoms rather than their symptoms only being requested by the physician (3). They also appreciated that the form is easy to understand and fill out even for patients with current poor performance status.

Conclusion

Patients with NSCLC have a high symptom burden, and thus it is important to use symptom survey as a routine procedure in the management of lung cancer. For symptom assessment, ESAS appears to be a useful tool, as it is easy to fill out, and without any further analysis, ESAS gives the physician a comprehensive understanding of the patient's suffering and allows for positive planning of symptom-targeted management in addition to chemotherapy. The major symptoms affecting the QoL of patients with NSCLC were dyspnea and pain, and management of these symptoms should be the focus. Surveying using ESAS is thus recommended to guide the physician in daily practice in order to enable optimal symptom awareness and management of those symptoms to best help their patients with cancer.

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