



## Symptoms Burden, Quality of Life and Its Determinant Factors in Advanced Lung Cancer Patients

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### Authors' contributions

This work was carried out in collaboration between all authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and the first draft of the manuscript. Authors MD, IB, RC, FE, MN and NB managed the analyses of the study. Author MD managed the literature searches. All authors read and approved the final manuscript.

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### ABSTRACT

**Aims:** To assess in advanced lung cancer patients', reported symptoms burden, their QOL, and to identify determinant factors associated with their QOL in 2 healthcare departments.

**Study Design:** A cross sectional study.

**Place and Duration of the Study:** The study was carried out during 03 months from February 1st to 30 April 2016 in the Pneumology department and an oncology unit from 2 different University Hospitals in Tunisia.

**Methodology:** We recruited 60 patients with advanced lung cancer by convenience sampling. QOL was assessed by the SF-36 questionnaire and Symptom's burden by Lung Cancer

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Symptom Scale (LCSS).

**Results:** The mean LCSS score was 43.07 (SD, 21.45). Loss of appetite and fatigue were rated as the most severe symptoms. The mean overall score of SF36 was 39.3 (SD, 15.4). The physical and emotional limitations had the lowest scores.

Unemployment ( $p < 0.014$ ), smoking cessation after diagnosis ( $p < 0.013$ ), consumption of analgesic ( $p < 0.002$ ) and the indication of an analgesic radiotherapy ( $p < 0.001$ ) were revealed as independent determinants of QOL.

**Conclusion:** A built in support of lung cancer patients would better control the symptoms and promote their QOL.

*Keywords: Quality of life; lung cancer; metastasis; symptoms burden.*

## 1. INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total cancers) [1]. It's the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five of total death. In 2012, the age standardized incidence rate (ASR) in the world was 23.1 per 100,000. In Tunisia, the ASR for Lung cancer in 2012 was 16 per 100,000 and it's the leading cause of cancer mortality (21%) [1]. Despite recent advances in treatment of the lung cancer patients, the prognosis remains poor. Thus, in USA, only 15% of Lung Cancers are diagnosed at "in situ" stage [2]. Common symptoms associated with advanced lung cancer include cough, hemoptysis, and dyspnea [3], all of this symptoms can significantly debilitate and diminish quality of life (QOL) [4]. Despite the advent of targeted therapies, symptom burden seems to be high in the advanced lung cancer patients compared to other tumors [5]. Meaningful palliation refers to symptom relief and prolongation of good-quality survival in lung cancer patients. Therefore, it's important to focus on QOL as well as survival.

Our main objectives were to assess in patients with advanced lung cancer from two university hospitals: (1) Their reported symptom burden, (2) their reported QOL, (3) and to identify predictors factors of QOL.

## 2. MATERIALS AND METHODS

### 2.1 Study Design and Data Collection

Our study used a cross-sectional design. It was carried out from over the period of 03 months from February 1st to 30 April 2016. Patients were recruited in two department of health care:

Pneumology department in a University Hospital in Sousse (Central-east of Tunisia), and the oncology unit in the University Hospital of Kairouan (Center of Tunisia).

### 2.2 Study Participants

Patients with advanced stage (III and IV) [6] of lung cancer who were hospitalized or admitted in the day hospital were recruited by convenience sampling. The following inclusion criteria were applied: Histological evidence of lung cancer, the consent to participate in the survey, no neurologic or psychological problems that would interfere with the ability to comprehend and complete the LCSS. There were no limits on age or type of treatment, and there was no distinction between newly diagnosed patients versus patients whom cancer is already diagnosed.

The non-inclusion criteria were: intellectual or physical disorders, and non-consent of the patient.

### 2.3 Measurements

For the purposes of our study, we used a questionnaire administrated and completed by a trained interviewer. This questionnaire is composed of three parts:

#### 2.3.1 Demographic characteristics, clinical and therapeutic information's

Information abstracted from participants medical records included:

- \*Demographics, underlying illnesses.
- \*Clinical information: WHO Performance Status [7]
- \*Lung cancer histology, staging.
- \*Treatment classification and toxicity [8]

### **2.3.2 QOL measurements**

Based on the SF-36 questionnaire [9,10], a generic and multipurpose questionnaire. It measures 2 main health concepts (physical and mental health) with 36 items and 8 multi-item scales:

1/ physical functioning (PF) 2/Role limitations due to Physical health (RP) 3/ Role limitations due to Emotional problems (RE) 4/ vitality (VT) 5/ Mental Health (MH) 6/ Social Functioning (SF) 7/ Bodily Pain (BP) 8/ General Health (GH).

Internal consistency of this scale was assessed in many studies [11,12] and it had a good coherence with Cronbach's alpha between 0.77 and 0.93.

We used the Arab and validated version (Cronbach's alpha: 0.94) of this questionnaire in our survey [13].

### **2.3.3 QOL scoring method**

Scores are assembled using summing ratings; the raw scores are then transformed to a 0 to 100 scale (with 0 and 100 assigned to the lowest and highest possible value, respectively). The highest value indicates better health [14]. The eight SF-36 scales can also be combined into two summary scales: the Physical Component Summary score and the Mental Component Summary score [15]. An average score was calculated, and by reference to the threshold value of Lean and al [16], it was admitted that subjects with an average score less than 66.7 were classified as having a poor health concept, and those with 66.7 or above were considered having a good health concept.

### **2.3.4 Symptom's burden measurement**

reported symptoms were assessed using the Lung Cancer Symptom Scale (LCSS): a disease-specific and site-specific symptoms' burden instrument that describe the experience of lung cancer through two complementary scales, one for patients and an optional counterpart for health professionals as observers [17], only the patient scale was used in this study. The patient is asked to focus on describing lung cancer symptoms in the past day, based on the rationale that the scale items represent states or conditions that fluctuate quickly, and not enduring traits [18]. It consists of nine items focusing primarily on the physical and functional

status of patients suffering from lung cancer [19]. Six items measures major symptoms for lung malignancies: appetite, fatigue, dyspnea, cough, blood in sputum and pain, and 03 summation items related to total symptomatic distress, activity status and overall quality of life. The intensity of patient response is measured by visual analogue scale varying from 0 corresponding to the lowest (the best) rating and 100 corresponding to the highest (worst) rating (highest degree of severity of symptoms) [18].

The feasibility, reliability and validity of the LCSS questionnaire have been shown in many studies especially in multicenter trial [17,20–22], in an earlier study it has a high Cronbach's alpha = 0.89 [19].

This scale is only available in English language. For our purposes, we have opted for a translation to Arab Language by a sworn translator. The Arab version was approved by an oncologist, an epidemiologist and a psychologist before being administrated to patients.

### **2.3.5 Symptoms burden scoring method**

Overall symptoms (items1-8) and QOL (item 9 of LCSS) were assessed as scales (from 0 to 100) and as binary variables. An average score for every symptom, and an average score were calculated and compared with normative scores established by Patricia J. Hollen and al [18].

These tools were tested with 05 patients before the beginning of the study to check the comprehension of questions.

## **2.4 Statistical Analysis**

Statistical analysis was performed using SPSS version 10.0.

Demographic characteristics, clinical and therapeutic information's were expressed as means with SD's for quantitative variables and as frequencies and percentages for qualitative ones.

To identify factors influencing QOL in Lung cancer, a univariate statistical analysis was carry out to determine the association between SF-36 scores and different variables, using T-test for binary variables, ANOVA test for variables with more than 2 categories and correlation for continuous variables. Then, a linear regression analysis was used, wherein the variables with  $p <$

0.2. All tests were two-tailed, and a *p*-value of < 0.05 was considered significant.

## 2.5 Ethical Considerations

After getting authorization for collecting data in the 2 hospitals, informed consent was obtained from all participants. Data were collected by only a trained interviewer. Confidentiality and anonymity were assured.

## 3. RESULTS

### 3.1 Basic Descriptive Information

#### 3.1.1 Characteristics of patients

During the study period, 60 patients consented to complete symptom and quality of life questionnaires at a single point time (72% were recruited from day hospital). The majority of patients were male (88%), age ranged from 21 to 79 years with a mean of 60.5 years. Most of patients (n= 52), were smokers before the first lung cancer diagnosis, among whom, 80% were in smoking cessation after lung cancer diagnosis announcing (Table 1).

#### 3.1.2 Clinical and therapeutic information's

Among patients, 48 (80%) were diagnosed as having non-small cell lung carcinoma (NSCLC). The average time since first lung cancer diagnosis was 240 days ± 292.

Approximately, 60% (n=36) of patients were in stage IV, 25% in stage IIIa and 15% in stage IIIb. Bone metastasis and visceral metastasis represented 33.3% (n= 12) and 26.7% (n= 16) % of total number of metastasis. Furthermore, among patients, 56% of whom were in complete remission or in stable disease stage, and 42% were in progression stage of cancer.

Almost, all patients (n=57), were under first line chemotherapy, among them, 12 patients had received second line chemotherapy. Concerning radiotherapy, only 4 patients had received chest radiotherapy, and 29 patients (48.3%) had received cerebral radiotherapy.

As 78.3% of patients were exposed to moderate-severe pain, supportive care therapy was especially focused on pain management. Drugs were prescribed according to WHO Analgesic Ladder. None of patients had benefit of psychological support.

**Table 1. Patient demographics and baseline disease characteristics**

Variables	No. (%)
Mean (SD*) age (y)	60.5 (9.9)
Sex	
Women	7 (12)
Men	53 (88)
Origin	
Urban	34 (57)
Rural	26 (43)
Marital status	
Married	55 (91.7)
Single	2 (3)
Widowed	3 (5)
Professional status	
Unemployed	41 (68.3)
Employee	16 (26.6)
Retired	3 (5)
Smoking history	
Current smoker	4(6.6)
Smoking cessation	48(80)
Never smoked	8(13.3)
Family history of cancer	
Yes	17 (28.3)
No	43 (71.7)
Histology	
Adenocarcinoma	33 (55)
Squamous	15 (25)
Small Cell	10 (17)
Other	2 (3)
Time since diagnosis (days)	
Mean (SD)	240 (292)
Lung cancer stage	
IIIa	15 (25)
IIIb	9 (15)
IV* (metastases)	36 (60)
Site of metastases (n=36)	
Visceral	20 (55.6)
Bone	12 (33.3)
Visceral+ Bone	4 (11.1)
WHO Performance Status	
OMS<2	31 (51.7)
OMS≥ 2	29 (48.3)
Chemotherapy first line	
Yes	57 (95)
No	3 (5)
Chemotherapy Second line	
Yes	12 (20)
No	48 (80)
Analgesic	
Yes	38 (63.3)
No	22 (36.6)
Analgesic radiotherapy	
Yes	5 (8.3)
No	55 (91.7)
Decompressive radiotherapy	
Yes	3 (5)
No	57 (95)

\*Standard Deviation

Furthermore demographic, clinic and therapeutic data are available in Table 1.

### 3.2 Patients Reported Symptom Scores

Within 31% of patients, 5 co-occurring symptoms at least were present. The majority of patients reported scores greater than zero in the LCSS for each of the lung cancer symptoms: fatigue (98.3%), loss of appetite (90%), pain (78.3%), shortness of breath (71.1%), cough (71.7%) and blood in sputum (18.3%). The mean LCSS (SD) was 43.1 (21.4). The mean (SD) severity scores for individual symptoms are shown in Table 2. Loss of appetite and fatigue were rated as the most severe symptoms.

**Table 2. Lung cancer symptom scale (LCSS) scores<sup>a</sup>**

Item	Mean	SD <sup>b</sup>
Appetite	49.6	25.7
Fatigue	58.2	15.5
Cough	31.2	27.1
Dyspnea	35.3	27.02
Hemoptysis	7.8	19.05
Pain	34.8	25.1
Overall symptomatic distress	60	17.1
Normal activity	60.7	17.6
Overall quality of life	50.0	18.7
Mean LCSS	<b>43.1</b>	<b>21.4</b>

*a scores for each symptom and the mean LCSS score can range from 0 to 100 with higher scores indicating greater symptom severity. b Standard Deviation*

The average scores for all symptoms were significantly higher ( $p < 0.001$ ) than the normative scores.

### 3.3 SF36 Scores

The results of administration of the SF36 are shown in Table 3. The mean scores for the 8

domains of the SF-36 ranged from 26.66 (Role limitations due to Emotional problems, SD 29.3) to 46.39 (Pain, SD 25.90). The average score (SD) for QOL was 39.3(15.44). The mean summed physical and mental scores of the SF-36 were 38.76 (SD 16.02) and 39.84 (SD 16.32), respectively. By reference to the threshold value of Lean and al, 96.7% of patients were classified as having a poor health status.

**Table 3. Quality of life scores obtained by application of the short form health survey in patients with lung cancer**

Domain	Mean	SD
Physical functioning	45.66	23.65
Role physical	27.91	23.95
Bodily pain	46.39	25.9
General health	34.92	14.83
<b>Physical component summed score</b>	<b>38.76</b>	<b>16.02</b>
Vitality	35.91	13.51
Social functioning	52.29	25.15
Role emotional	26.66	29.30
Mental Health	44.51	15.57
<b>Mental component summed score</b>	<b>39.84</b>	<b>16.32</b>
<b>Mean SF-36 score</b>	<b>39.3</b>	<b>15.44</b>

### 3.4 Multiple Analysis

Table 4 shows results from univariate and multivariate analysis between the mean SF-36 score and various patient's demographics and baseline disease characteristics. Having an employment ( $p=0.014$ ) and non-smoking cessation ( $p=0.013$ ) were found to be positive predictors of patient reported QOL. Provision of supportive care therapy represented by analgesic medication ( $p=0.001$ ) and analgesic radiotherapy ( $p=0.002$ ), were revealed to be negative predictors of QOL.

**Table 4. Independent predictors of QOL. Univariate and multivariate analysis**

Variables	n	Univariate analysis		Multivariate analysis	
		Mean SF-36±SD	p value	Coefficients	p value <sup>a</sup>
<b>Characteristics of patients</b>					
Age :					
≤ 65	46	38.12±15.25	0.28		
> 65	14	43.16±15.99			
Gender:					
Male	53	39.87±15.13	0.43		
Women	7	34.99±18.29			
Origin:					
Urban	34	36.99±15.40	0.18		
Rural	26	42.32±15.25			
Professional status:					
Unemployed	41	36.68±15.28	0.05	0.236	0.014

Variables	n	Univariate analysis		Multivariate analysis	
		Mean SF-36±SD	p value	Coefficients	p value <sup>a</sup>
Employee	19	44.96±14.59			
Marital status:					
Married	55	38.03±38.03	0.03		
Single	5	53.19±9.61			
<b>Smoking</b>					
Smoking cessation:					
Yes	48	38.58±15.14	0.02	0.238	0.013
No	4	56.46±6.21			
<b>Clinical data</b>					
Time since diagnosis					
<3 months	13	42.24±14.68			
3-6 months	27	42.89±16.01	0.05		
>3 months	20	32.51±13.42			
WHO Performance Status					
<2	31	42.79±13.05	0.06		
≥ 2	29	35.56±17.07			
Histology					
Adenocarcinoma	33	38.50±15.78	0.66		
Other	27	40.27±15.24			
Stage					
IIIa/IIIb	24	45.38±13.73	0.011		
IV	36	35.24±15.34			
Site of metastases					
Visceral	20	31.79±15.45			
Bone	12	42.24±14.72	0.36		
Visceral+ Bone	4	29.45±14.95			
<b>Therapeutic data</b>					
Chemotherapy first line					
Yes	57	39.33±15.44	0.93		
No	3	38.61±18.79			
Chemotherapy Second line:					
Yes					
No	12	33.69±14.68	0.16		
	48	40.70±15.45			
Analgesic:					
Yes	38	35.60±13.24	0.004	-0.52	0.001
No	22	50.87±11.81			
Analgesic radiotherapy					
Yes	5	21.04±10.49	0.005	-0.30	0.002
No	55	40.96±14.78			
Decompressive radiotherapy:					
Yes	3	26.09±14.89	0.12		
No	57	39.99±15.27			

<sup>a</sup> a p<0.05 is considered significant

#### 4. DISCUSSION

Until recently, self-reported QOL has been rarely assessed in patients with lung cancer in Tunisia. Our study was conducted in two department of health care: Pneumology department in a University Hospital in Sousse, and the oncology unit in the University Hospital of Kairouan. Current Symptom burden and QOL were assessed using respectively 2 questionnaires: LCSS and SF-36, which are valid and well-recognized QOL tools. The other strength of our study lies in the variety of collected data and the good response rate (100%).

Data from our study showed that 31% of patients reported more than 05 co-occurring symptoms. This finding is similar to some previous studies. An assessment of symptom burden within lung cancer patients was performed by Patricia J. Hollen et al. [18] and revealed that 36% of patients were suffering from more than 05 co-occurring symptoms. Symptom cluster [23], defined as two or more concurrent symptoms, have been reported in lung cancer [24]. The development of fatigue in lung cancer has been correlated with other symptoms such as dyspnea, appetite loss, and depression [25]. In a qualitative study conducted on lung cancer

patients in the United Kingdom [26], cough, breathlessness and fatigue were identified as symptom cluster, which co-occur and influence each other, Both fatigue and appetite loss, were frequently reported by patients recruited in our study (98.3% and 90%) and also rated as the most severe symptoms. The mean LCSS score was 43.1 (SD 21.4). This is consistent with previous studies [3,19,27]. Shrividya Iyer et al. [5] in a multicenter study (France and Germany) including 1213 patients with advanced lung cancer, and using the LCSS scale, found that fatigue and loss of appetite were reported by 98% of patients. Their mean scores were; 54.4 (SD 29.1) and 47.1 (SD 30.0), respectively. The same study conducted in USA [2] revealed that the most common symptom was fatigue (75.3%), the mean LCSS score was 42.3 (SD 21.5), and the greater rated symptoms were fatigue and appetite loss. However, Patricia J. Hollen [18] found that dyspnea was the most reported symptom (87%). A Chinese study used another scale: Functional assessment of cancer therapy- Lung (FACT-L) [28], and confirmed that appetite loss was the most common symptom in lung cancer [29]. In terms of symptom severity, mean scores for individual symptoms were higher in the present study than in the normative data, this difference could be due to non-clinical trials settings and the inclusion of later line patients in our study. Normative data were established from clinical studies restricted to first line, and from which typically patients with extreme symptom severity were excluded.

The mean scores for the 8 domains of the SF-36 ranged from 26.66 (Role limitations due to Emotional problems, SD 29.3) to 46.39 (Pain, SD 25.90). The mean SF-36 score (SD) of QOL was 39.3(15.44). The mean summed physical and mental scores of the SF-36 were 38.76 (SD 16.02) and 39.84 (SD 16.32). In general, the SF-36 results were in line with those obtained in previous studies. Thus, Irawati Lemonnier et al. [30] in a study conducted on 230 patients with advanced lung cancer, reported a poor QOL with mean SF-36 score :36 ±9.8, mean summed physical and mental scores rated of 34.8 ±8.4 and 37.2±11.3. Role physical was the worst affected domain. A poor QOL was revealed in a study including 57 lung cancer patients using SF-36 scale; however role emotional domain was not under normative data [31]. The FACT-L scale showed in the study of Shrividya I et al. [5] that emotional limitation domain had the worst score.

According to demographic factors (age, sex, origin), our study did not show a significant difference in mean SF-36 score of QOL. This finding corresponds to some studies. Yuxiang M et al. [29] proved that QOL (assessed by the FACT-L scale) was not influenced by sex and age. Moreover, Patricia J. Hollen et al. [18] found that age, sex and race were not significantly associated with QOL. Nevertheless, a study conducted on 230 patients with lung cancer [30] revealed that older patients and men had a poorer QOL. In univariate analysis, married patients had a lower QOL, but this association did not remain significant in multivariate analysis, which was concordant with results of a study conducted on 650 lung cancer patients [19]. The unemployed status was independently associated with a lower QOL in our study, however, in studies of Patricia J. Hollen et al. [18] and Shrividya et al. [5], professional status hadn't a significant effect on QOL. This discordance can be explained by the absence of unemployment benefit in our country, leading to financial problems and affecting negatively QOL.

Smoking cessation was a negative predictor of QOL in multivariate analysis. This finding is quite different from literature; Yuxiang M et al. [29] and Shrividya et al. [5] showed that smoking cessation was not meaningfully associated with QOL. Yolanda I et al. [32] assessed the relationship between cigarette smoking and QOL among lung cancer survivors, they proved that continued cigarette smoking is related to a relative deficit in their QOL. This discordance with literature is related to acute smoking cessation and absence of professional help and follow-up among smokers with difficulty of access to smoking cessation consultation for behavioral support.

Analgesic medication and analgesic radiotherapy were found to be negative predictors of QOL in our survey, however, shrividya et al. [5] revealed that provision of supportive care therapy contributed to a better QOL. Several factors explain that our patients under analgesic palliative care had deficit in their QOL; clinical symptoms especially pain and side effects of chemotherapy are not well tolerated within our patients. In fact, there is a deficit in care givers specialized in pain management. Moreover, availability of analgesic drugs in university hospitals is limited. Concerning analgesic radiotherapy, the limited number of radiotherapy centers (3 in all the country) contributes to restrict the prescription of this kind of palliative

care. In addition to that, the absence of psychological support and help is an important deficit in the advanced lung cancer patient's management.

Our study had a number of limitations. Results may not be totally generalizable to all patients with lung cancer in other settings due to the small sample size and the exclusion of the early stage lung cancer patients. It was a cross sectional and not prospective survey, hence the time effect on symptoms and QOL could not be studied. A prospective longitudinal approach is required to consider the changes and effectively evaluate the multiple factors that affect the QOL in lung cancer [3].

It's important to focus on improving the basis of palliative care in our hospitals by establishing departments specialized in this healthcare approach. Early palliative care visits emphasize managing symptoms, strengthening coping, and cultivating illness understanding and prognostic awareness in a responsive and time-sensitive model [33]. Researches has demonstrated that palliative care is associated with better QOL and mood, improved symptom control and increased patient and care givers satisfaction [33,34]. It's also imperative to raise awareness about the importance of early detection of lung cancer. Furthermore, it should be a primary concern to strengthen tobacco prevention measures and to set up smoking cessation consultations all over public healthcare institutions.

## 5. CONCLUSION

The results of our study re-emphasize that the burden of lung cancer-specific symptoms in patients with advanced disease is high, even among patients receiving treatment within current guidelines. Thus, It's important to assess symptoms both from an objective physician's perspective and from the subjective perspective of patients in order to capture a more comprehensive clinical picture that could help optimize therapy management outcomes [5]. Affected domains in QOL in SF-36 scale indicate the need to identify and intervene with patients who are at an elevated risk of diminished QOL soon after receiving a lung cancer diagnosis and undergoing cancer treatment. These actions are crucial for developing palliative care in our hospitals and needed to improve QOL of these patients.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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