

Original Research Article**Symptoms Burden, quality of life and its determinant factors in advanced Lung Cancer patients.****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.

Methodolgy: We recruited 60 Lung cancer advanced stage patients' by convenience sampling. QOL was assessed by the SF-36 questionnaire and Symptom's burden using Lung Cancer 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 palliative lung cancer include cough, hemoptysis, and dyspnea [3], all of which 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 patient population compared to other tumors [5]. Meaningful palliation refers to symptom relief and prolongation of good-quality survival in lung cancer patients. It is therefore important that, the implication of focusing on QOL as well as survival needs to be well established.

Our main objectives were to assess in patients with advanced lung cancer from two university hospitals: (1) patient reported lung cancer symptom burden, (2) patient reported QOL, (3) 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, verbal 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 $\pm$ 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 prescript according to WHO Analgesic Ladder. None of patients had benefited of psychological support.

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

152 **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	
Smoking cessation	
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)
Median	
(Min, Max)	(530, 1920)
Lung cancer stage	
IIla	15 (25)
IIlb	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	154
Yes	5 (3.3)
No	55 (91.7)
Decompressive radiotherapy	156
Yes	15 (9.6)
No	57 (95)

*Standard Deviation

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 ^a

Item	Mean	SD ^b
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	43.1	21.4

^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 (Figure1).

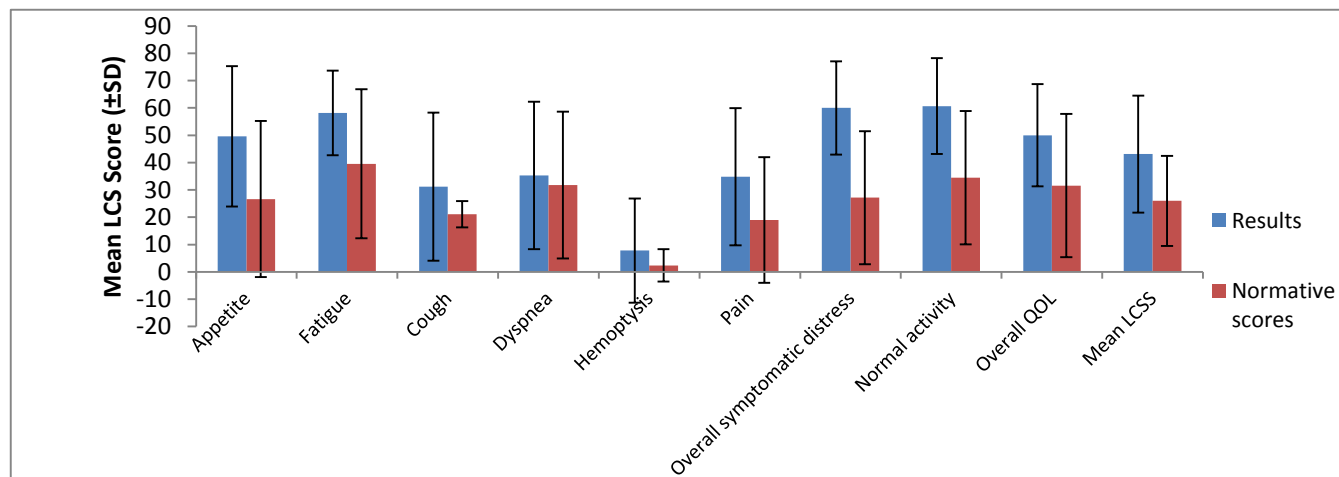


Fig.1. Symptom burden scores in the overall population compared with normative Data.

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 concept.

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
Physical component Summed score	38.76	16.02
Vitality	35.91	13.51
Social functioning	52.29	25.15
Role emotional	26.66	29.30
Mental Health	44.51	15.57
Mental component Summed score	39.84	16.32
Mean SF-36 score	39.3	15.44

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 ^a		
Characteristics of patients								
Age :	≤ 65	4	38.12±15.25	0.28	0.236	0.014		
	> 65	6	43.16±15.99					
		1						
Gender: male		4		0.43				
	women	5	39.87±15.13					
		3	34.99±18.29					
Origin: Urban		7		0.18				
	Rural	3	36.99±15.40					
		4	42.32±15.25					
		2						
		6						
Professional status:	Unemployed	4	36.68±15.28	0.053				
	Employee	1	44.96±14.59					
		1						
		9						
Marital status:	Married	5	38.03±38.03	0.034				
	Single	5	53.19±9.61					
		5						
Smoking								
Smoking cessation:	Yes	4	38.58±15.14	0.024	0.238	0.013		
	No	8	56.46±6.21					
		4						
Clinical data								
Time since diagnosis	<3 months	1	42.24±14.68	0.052				
	3-6 months	3	42.89±16.01					
	>3 months	2	32.51±13.42					
		7						
		2						
	0							

WHO Performance						
Status	31	42.79±13.05	0.069			
<2	29	35.56±17.07				
≥ 2						
Histology	33	38.50±15.78	0.66			
Adenocarcinoma	27	40.27±15.24				
Other						
Stage						
IIIa/IIIb	2	45.38±13.73	0.011			
IV	4	35.24±15.34				
	3					
	6					
Site of metastases						
Visceral	2	31.79±15.45				
Bone	0	42.24±14.72	0.36			
Visceral+ Bone	1	29.45±14.95				
	2					
	4					
		Therapeutic data				
Chemotherapy first line						
Yes	5	39.33±15.44	0.93			
No	7	38.61±18.79				
	3					
Chemotherapy Second line:	1	33.69±14.68	0.16			
Yes	2	40.70±15.45				
No	4					
	8					
Analgesic:						
Yes	3	35.60±13.24	0.004	-0.52	0.001	
No	8	50.87±11.81				
	2					
	2					
Analgesic radiotherapy						
Yes	5	21.04±10.49	0.005	-0.30	0.002	
No	5	40.96±14.78				
	5					
Decompressive radiotherapy:	3	26.09±14.89	0.12			
Yes	5	39.99±15.27				
No	7					

^a p<0.05 is considered significant

4. Discussion

Until recently, self-reported QOL has been assessed rarely 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]. Cough, breathlessness and fatigue were identified as symptom cluster, which co-occur and influence each other, in a qualitative study conducted in lung cancer patients in the United Kingdom [26].

Both fatigue and appetite loss, were most 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 most reported(87%). Using another scale: Functional assessment of cancer therapy- Lung (FACT-L) [28], a Chinese study 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 from our patients 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 of 36 $\pm$ 9.8, mean summed physical and mental scores rated of 34.8 $\pm$ 8.4 and 37.2 $\pm$ 11.3. Role physical was the worst appreciated 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 contribute 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 controlled within our patients. In fact, there is a deficit in care givers specialized in pain management. Moreover, availability of analgesic drogues 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 and 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]. Although LCSS scale and SF-36 scale are a well-recognized QOL tool

In light this study's findings, 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]. Research 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, strengthening tobacco prevention measures and setting up smoking cessation's consultations all over public healthcare institutions, should be a primary concern.

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.

Conflict of interest:

The authors declare no conflict of interest.

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