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Research Article

Risk factors analysis for mortality among a cohort of lung cancer patients

Hager Yehia Mohamed [1], Azza Farag Said [1], Amel Mahmoud Kamal Eldin 2, Shady E Anis [3], Zainab Hassan Saeed [1]

[1]Faculty of Medicine, Pulmonary Medicine Department, Minia University, Minia, Egypt
[2]Faculty of Medicine, Clinical Pathology Department, Minia University, Minia, Egypt
[3] Faculty of Medicine, Pathology Department, Cairo University, Cairo, Egypt

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Abstract

Background: Over the last few decades, the worldwide burden of cancer has been increased. More than half of the 18.1 million people diagnosed with cancer in 2018 died. Lung cancer diagnoses and deaths are on the rise. So that it is very important to investigate the factors that influence lung cancer mortality. The aim is to assess the characteristics of lung cancer patients and the factors influencing mortality due to lung cancer. **Methods:** A cross-sectional observational study was performed on 58 lung cancer patients (48 with Non-Small Cell Lung cancer(NSCLC) and 10 with Small Cell Lung Cancer(SCLC) with a mean age 58.9 yrs. Forty-nine of them were males, one third were current smokers and 56% of them had advanced stage of lung cancer (stage III and IV). Survival was calculated from the date of enrollment in the study to the date of the last follow-up visit (3 years) or death. **Results:** Seventy-five of the studied patients died with an average survival duration of 19 months for NSCLC patients in comparison to 12 months for SCLC patients. Patients > 60 yrs., those with SCLC, current smokers and those with performance status ≥ 2 had a low survival time. Univariate regression analysis identified that advanced stage of cancer had a 6-fold increase in mortality (p=0.0001). **Conclusion:** Age more than 60, performance status ≥ 2 and stage III and IV were found as significant independent factors linked with raised mortality rate.

Keywords: Non- Small Cell Lung Cancer, Small Cell Lung Cancer, survival time, mortality rate

Introduction

Globally, lung cancer has been the most common type of cancer diagnosed over the last few decades. Lung cancer is a main cause of cancer mortality and produces a significant burden of disease, so lung cancer takes more attention from multiple authorities[(1)].

There were 2.1 million new lung cancer cases Globally in 2018[(1,2)]. This underscores the significance of this cancer in oncological researches.

Lung cancer is caused by multiple risk factor. Active smoking is the leading cause of lung cancer[(3)], accounting for 85 % of all cases [(1)]. Passive smokers face a significantly high risk, according to studies from the United States, Europe, and the United Kingdom [(4)]. In the United States, radon gas exposure is the second largest cause of lung cancer, with around 21,000 deaths per year [(5)]. Lung cancer is considered to be caused by outdoor air pollution in 1-2 % of cases [(6)]. Indoor air pollution from the burning of wood, charcoal, dung or agricultural residue for cooking and heating appears to raise the risk of lung cancer [(7)].Asbestos is linked to several lung illnesses, including cancer[(8)] . Lung cancer is caused by hereditary factors

in about 8% of cases [9]. Lung cancer risk is known to be influenced by polymorphism on chromosomes 5,6 and 15 [10].
All lung cancer types , NSCLC and SCLC, have a 5-year relative survival rate of 19%, with NSCLC patients having a higher 5-year survival rate (23%) than SCLC patients (6 %)[11, 12].
Multiple mechanisms lead to death from lung cancer; tumor burden with extensive metastasis and organ failure[13] and pneumonia secondary to bronchial obstruction by tumor[14]. Lung cancer can cause fatal pulmonary thromboembolism due to its hypercoagulable status [15]. Despite the higher mortality rates and poorer survival outcomes associated with lung cancer diagnosis, the newly developed generation of targeted medicines and the development of immune checkpoint inhibitors have demonstrated significant long-term survival in many patients [16].Knowing the contributory causes of death could help direct treatments to help these patients live longer[17].
The aim of this study was to evaluate the characteristics of a cohort of lung cancer patients, as well as possible risk factors for mortality.

Patients and methods

This prospective study included (58) lung cancer patients recruited to Chest Department, Cardiothoracic Minia University Hospital during the period from February 2018 to February 2020.
All aspects of patient care and bronchoscopy were carried out according to the local guidelines of the Ethical Committee of the Faculty of Medicine of Minia University. All patients signed a written consent before bronchoscopy indicating their acceptance to participate.
All the patients in the study had a lung cancer diagnosis that was confirmed by either bronchoscopic lung biopsy or presence of malignant cells in bronchoalveolar lavage (BAL). None of them had a metastatic lung disease or other forms of extra-pulmonary malignancy. All patients underwent bronchoscopic examination after chest CT.
Fiberoptic bronchoscope (PENTAX, EB-1970(2.8), Japan) was done in bronchoscopy unit of Chest Department under local anesthesia using 2% lidocaine spray and conscious sedation by intravenous midazolam 3-5 mg were used. The bronchoscope was most generally administered through the nose and a routine assessment of the tracheobronchial tree has been performed, in the presence of endobronchial lesion, 3-5 samples were taken by forceps biopsy that were collected in a 10% buffered formalin solution and embedded in paraffin. Then the slides were stained with hematoxylin and eosin for further histopathological examination. In absence of lesion on bronchoscope, BAL was performed by wedging the bronchoscope into an affected lobar or segmental bronchus at the site of a shadow on CT, injecting 120 mL of saline solution into the segment bronchus, and suctioning it out; the total volume of returned aspirate ranged from 40 to 50 mL The retrieved aspirates were examined for cytologic assessment.

All the patient's clinical data was collected including their age, sex, smoking status and pack year, TNM staging system (eighth edition)[18],histopathological type of cancer and Eastern Cooperative Oncologic Group (ECOG) performance status.
According to the WHO/IASLC (2015) classification of lung cancer, Patients were separated into two groups based on histological results; (48) NSCLC patients and (10) SCLC patients.

From the time of inclusion until the last follow-up (February 2021) or death, survival was calculated.

Statistical analysis

The SPSS for Windows release 10.0 package application was used for statistical analysis. The data between the different variables was compared using the Chi-square test. Survival analysis was computed according to the method of Kaplan Meier. A Cox Regression was performed to evaluate predictors of mortality using both univariate and multivariate analyses. A value of $p< 0.05$* was accepted as statistically significant.

Results:

Table (1) shows demographics among the studied patients, (48) patients with non-small cell carcinoma (NSCLS) and (10) patients with small cell carcinoma(SCLC). NSCLS group was subdivided into:(20) patients with adenocarcinoma, (14) patients with squamous cell carcinoma, (12) patients with large cell carcinoma, and (2) patients with adenosquamous carcinoma. There was no significance difference between NSCLC patients and SCLC patients as regard mean age, gender distribution, smoking history, and performance status($p>0.05$). Patients with stage IV were significantly higher in SCLC than those of NSCLC (70% vs 29.2%, $p=0.014$).

Regarding lines of treatment that were used in lung cancer patients, 62% of them received chemotherapy in form of (gemcitabine/cisplatin) for those with NSCLC and (etoposide/cisplatin) for those with SCLC, while 15.5% used targeted therapy (gefitinib), all of them in NSCLC patients. In our study (12) patients were alive and (46) patients were dead, with a significant higher time of survival in NSCLC than SCLC patients (19.1 ± 8.6 months' vs 12.1 ± 6 respectively, $p= 0.008$) (Table 2).

Table (3) represents the general characteristics of dead and alive lung cancer patients, we found that survived patients were significantly younger than dead ones. Dead patients had a higher performance status and TMN staging. As regard comorbidity, 33% of survived patients had one comorbidity, while 93.5% of dead patients had more than one comorbidity (diabetes mellitus and systemic hypertension).

Fig. (1) shows that survival time was significantly increased in patients younger than 60 years old than patients older than 60 years old ($p=0.035$). At the 20-month follow-up, around 40% of patients over 60 years old were still alive, whereas approximately 68 percent of patients under 60 years old were still alive. After 30 months of follow-up, roughly 20% of patients over 60 years old were still alive, whereas about 50% of patients under 60 years old were still alive.

Kaplan Meier survival curves shows that survival time was significantly increased in NSCLC patients more than patients with SCLC ($p=0.006$) (Fig.2). At 10 months of follow up about 60% of patients of SCLC were alive corresponding to about 78% of patients with NSCLC. While at 30 months of follow up all patients with SCLC were died corresponding to about 20% of patients with NSCLC were still alive.

Ex-smokers and passive smoker patients had significantly longer lifetimes than current smokers($p=0.002$), as seen in Fig. (3).

Table (4) represents Cox Regression analysis of variables predict death among lung cancer patients. It was found that advanced stages of cancer (stage III&IV) had a significant risk factor for death (HR=6.661) than early lung cancer stages (stage I&II) in both univariate and multivariate analysis ($p=0.0001$). Performance status equal to or more than 2 was also a significant risk factor of mortality (HR=3.514) than performance status less than 2. Patients with NSCLC had a significant lower risk of mortality in comparison to those with SCLC ($p=0.01$ in univariate analysis and $p=0.003$ in multivariate analysis).

Table 1: Demographics of the studied patients

	NSCLC (48)	SCLC (10)	Total (58)	p value
Age	53.5 ± 12.1	60 ± 10.1	58.9 ± 10.7	0.07
Gender				
Males	41 (85.4%)	8 (80%)	49 (84.5%)	0.667
Females	7 (14.6%)	2 (20%)	9 (15.5%)	0.667
Smoking status				
Non-smoker	6 (12.5%)	0	6 (10.3%)	0.238
Current smoker	15 (31.3%)	5 (50%)	20 (34.5%)	0.258
Pack year < 10	5 (10.4%)	1 (10%)	6 (10.3%)	0.968
Pack year ≥ 10	31 (64.6%)	7 (70%)	38 (65.5%)	0.741
Passive smoker	6 (12.5%)	2 (20%)	8 (13.8%)	0.528
Ex-smoker	21 (43.8%)	3 (30%)	24 (41.4%)	0.423
TMN Staging				
Stage I	5 (10.4%)	0	5 (8.6%)	0.284
Stage II	18 (37.5%)	2 (20%)	20 (34.5%)	0.289
Stage III	11 (22.9%)	1 (10%)	12 (20.7%)	0.357
Stage IV	14 (29.2%)	7 (70%)	21 (36.2%)	0.014*
Performance status				
< 2	28 (58.3%)	3 (30%)	31 (53.4%)	0.103
≥2	20 (41.7%)	7 (70%)	27 (46.6%)	0.103
Comorbidities				
No comorbidity	7 (14.6%)	0	7 (12%)	
≥ 1comorbidity	41 (85.4%)	10 (100%)	51 (88%)	0.197

Data are presented as mean±SDand number (%).

Table (2): Treatment options and survival data among lung cancer patients

	NSCLC (48)	SCLC (10)	Total (58)	p value
Line of treatment:				
Surgery	6 (12.5%)	1 (10%)	7 (12.1%)	0.82
Chemotherapy	31 (64.6%)	5 (50%)	36 (62.1%)	0.38
Chemoradiotherapy	2 (4.2%)	4 (40%)	6 (10.3%)	0.007
Targeted therapy	9 (18.8%)	0	9 (15.5%)	0.136
Survival				
Alive	12 (25%)	0	12 (20.7%)	
Dead	36 (75%)	10 (100%)	46 (79.3%)	0.07
Survival time (months)	19.1 ± 8.6	12.1 ± 6	21.4 ± 10.7	0.008

Data are presented asnumber (%) and mean±SD.

Table (3): Clinical variables of the patients analyzed with survival outcome

	Survival		p value
	Alive (n=12)	Dead (n=46)	
Age: < 60 ≥60	 8 (66.7%) 4 (33.3%)	 16 (34.8%) 30 (65.2%)	 0.004* 0.045*
Sex: Male Female	 11 (91.7%) 1 (8.3%)	 38 (82.6%) 8 (17.4%)	 0.44 0.44
Type of lung cancer: SCLC NSCLC	 0 12 (100%)	 10 (21.7%) 36 (78.3%)	 0.075
Performance status: <2 ≥ 2	 12 (100%) 0	 19 (41.3%) 27 (58.7%)	 0.028* _
TMN staging Stage I&II Stage III&IV	 12 (100%) 0	 13 (28.3%) 33 (71.7%)	 0.001* _
Comorbidity: No Comorbidity ≥ 1Comorbidity	 4 (33.3%) 8 (66.7%)	 3 (6.5%) 43 (93.5%)	 0.001* 0.011*

Data are illustrated as number (%).

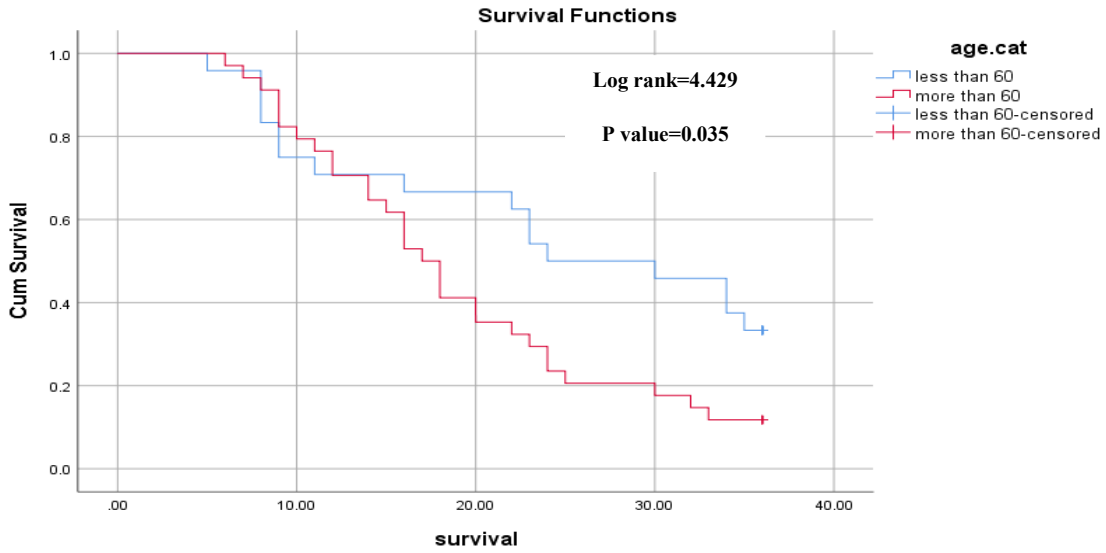

Fig. (1): Kaplan Meier survival curves for lung cancer patients in relation to age.

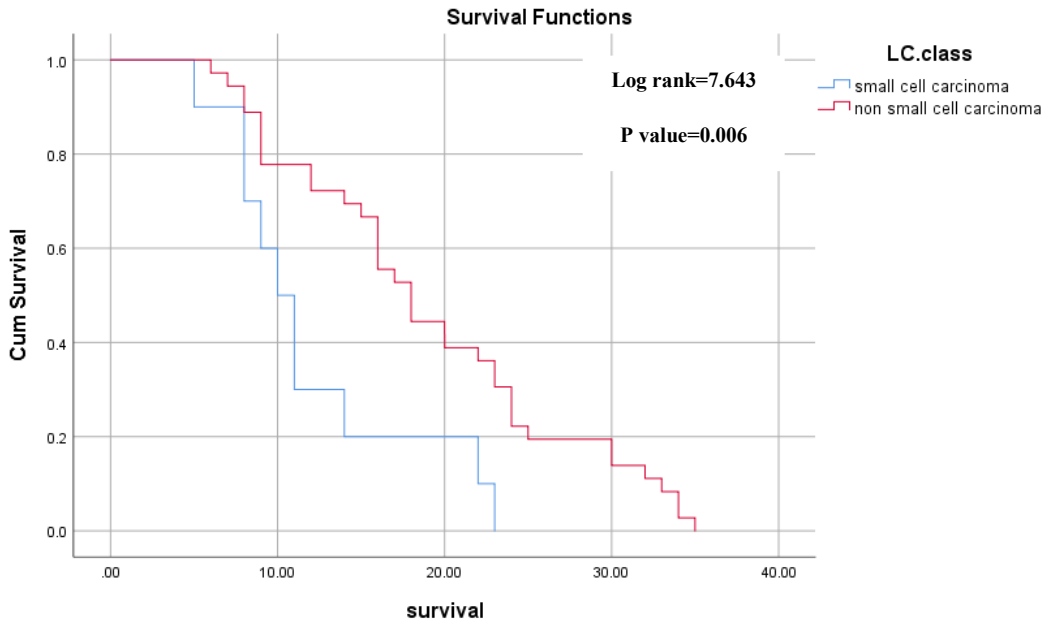

Fig. (2): Kaplan Meier survival curves for lung cancer patients in relation to cancer type.

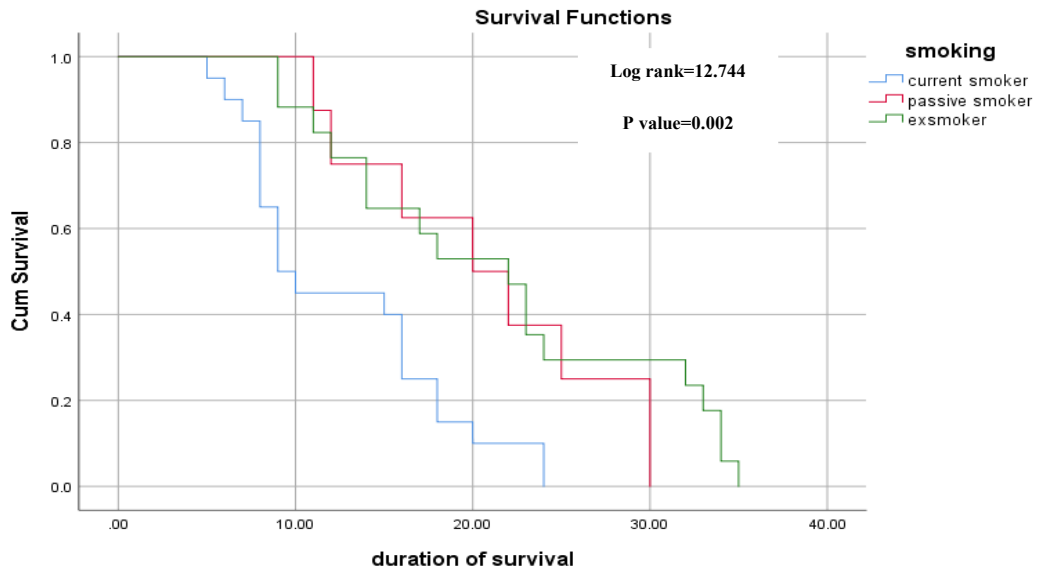

Fig. (3): Kaplan Meier survival curves for lung cancer patients in relation to smoking status

Table (4) Variables related to lung cancer mortality using Cox Regression

Variable	Total (n=58)	Univariate analysis		Multivariate c analysis	
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age: Less than 60 More than 60	 24 (41.4%) 34 (58.6%)	 1 1.541 (0.79-2.99)	 0.202	 1 0.796 (0.33-1.90)	 0.607
Sex: Male Female	 49 (84.5%) 9 (15.5%)	 1 0.809 (0.37-1.75)	 0.593	 1 0.166 (0.01-2.10)	 0.167
Lung cancer type: SCLC NSCLC	 10 (17.2%) 48 (82.8%)	 1 0.374 (0.17-0.79)	 0.01*	 1 0.24 (0.09-0.61)	 0.003*
Performance status: < 2 ≥ 2	 31 (53.4%) 27 (46.6%)	 1 3.514 (1.79-6.87)	 0.0001*	 1 2.13 (0.94-4.81)	 0.069
TMN Staging: Stage I & II Stage III & IV	 25 (43.1%) 33 (56.9%)	 1 6.661 (2.69-6.46)	 0.0001*	 1 8.14 (2.54-28.14)	 0.0001*
Comorbidity: No comorbidity ≥ 1 comorbidity	 20 (34.5%) 38 (65.5%)	 1 1.271 (0.60-2.66)	 0.527	 1 0.13 (0.01-1.811)	 0.13

Discussion

Lung cancer is a leading cause of cancer-related death and produces a significant burden . According to the GLOBOCAN estimations, there will be 18.1 million new cases of cancer in 2018, with 9.6 million people dying from it [(1)]. As a result, we wanted to identify clinical characteristics of lung cancer patients at the time of diagnosis as well as significant predictors of mortality for patients with lung cancer throughout a 36-month duration.

Our study involved 58 patients with lung cancer(males,49(84.5%);females,9(15.5)) showing that Males had a higher incidence of lung cancer than females, which is consistent with most global reports[(19)] . Lung cancer was also found to be more common in elderly persons as consistent with most worldwide reports. In our study, the median age of patients was 58.9 ± 10.7 which is slightly lower than other studies(19).This may have resulted from difference of sample size , racial variation and availability of early diagnostic methods.

Lung cancer is well-known to be caused by smoking[(20)]. According to our study, the prevalence of lung cancer was higher among 44(75.9%)smoker than non-smokers 6 (10.3%) and passive smokers 8(13.8%) in agreement with previous studies[(19)]. To reduce the rate of smoking in our country, it appears that aggressive anti-smoking strategies such as smoking cessation medication and motivational interviewing are still required.

In addition , the proportion of patients with stage III- IV was higher (56.8%) than early stage with a significant higher proportion with stage IV in SCLC patients than those of NSCLC (70% vs 29.2%, p=0.014)as consistent with other studies[(19)] .These results may reflect the need to improve lung cancer screening processes especially among high risk individuals for early diagnosis and successful treatment in our country.

As regard performance status , we found that 46.6% of lung cancer patients with ECOG PS equal or more than 2 which confirmed the quite high prevalence of poor PS among lung cancer patients as consistent with other studies [(21)] . Significant higher deaths (58.7%) were present among patients with ECOG PS equal or more than 2 showing that a ECOG PS at least 2 was associated with poorer prognosis. Similar evidence has been shown by other studies [(22)].

Our study showed that one or more comorbidities affect 88 % of lung cancer patients and also were significantly present in a greater proportion of lung cancer deaths (93.5% , p=0.011) which revealed that comorbidities were frequent among lung cancer patients and had a great impact on their survival as consistent with many studies [(23, 24)].

Regarding lines of treatment offered for the studied patients, only 7patients (12.1%) received surgical treatment and the remaining 51 patients (87.9%) received treatment that involved chemotherapy, radiation therapy and targeted therapy. A significant higher proportion of SCLC patients received treatment in form of both chemotherapy and radiotherapy than those with NSCLC (40% vs 4.2% p=0.007). This may have resulted from the late lung cancer diagnosis in our study in contrast with other reports where early diagnosis and better prognosis seen in lung cancer patients [(19)].

Our study showing that Patients with NSCLC had a significantly longer survival duration than those with SCLC (19.1 ± 8.6months vs 12.1 ± 6 months, p=0.008) as seen in many studies [(19, 25, 26)].

In both genders, we discovered that increasing age, particularly after 60 years, was a significant risk factor for lower survival than patients younger than 60 years (19.176Months vs 24.458Months, p=0.035). Other studies have found that getting older has a negative impact on lung cancer patients' survival [(27-30)]. Treatment tolerance and health problems may be compromised in elderly. There are different viewpoints on the association between diagnostic age and lung cancer patient survival rates [(31, 32)].

In our study, we noticed that a significant better survival among ex-smokers and passive smoker than current smokers (21.41, 20.75months vs 12.7 months, respectively, p=0.002). These findings were consistent with other studies which confirmed that cigarette smoking is a well-known risk factor for lung cancer patients

and it has been shown to reduce survival rates considerably [26, 28, 33, 34].

For histological type and its impact on survival, patients with non-small cell lung cancer had a significant longer survival time than those with small cell lung cancer (19.056months vs 12.1 months p=0.006).Patients with NSCLC had a significant lower risk of mortality in comparison to those with SCLC(HR=0.374,p=0.01 in univariate analysis and HR=0.24 p=0.003 in multivariate analysis). Similar evidence has been shown by other studies[19, 25, 26].It was found also that advanced stages of cancer (stage III&IV) had a significant risk factor for death (HR=6.661) than early lung cancer stages (stage I&II) in both univariate and multivariate analysis (p=0.0001) and this is consistent with previous study[19].
As regard performance status, our study revealed that performance status equal to or more than 2 was also a significant risk factor of mortality(HR=3.514 and p=0.001) than performance status less than 2.Other publications on performance status and survival confirmed the significant longer survival in patient with lower performance status[19, 22, 35].

Conclusion

Some clinical factors (e.g., diagnostic age, smoking history, histological type, and performance status) play a major effect in lung cancer mortality, according to this study. In individuals with lung cancer, SCLC, advanced staging, and a lower performance status were all significant predictors of mortality. Lung cancer patients must be given more attention in order to receive an early diagnosis and a better prognosis.

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