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Clinicopathological characteristics and prognosis of non-small cell lung cancer in Algeria: a single-center retrospective study

Mohamed Lahmadi[1]*, Leila Beddar[2], Souad Ketit[2], Tarek Makhbouche[3], Narriman Laouar[4] and Taha Filali[4]

Abstract

Background　Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in men in Algeria. Little is known about the characteristics of lung cancer in Algeria. This study aimed to determine the clinicopathological characteristics and prognosis of non–small cell lung cancer (NSCLC) patients in Algeria.

Methods　This retrospective study was performed on 269 pathologically confirmed cases of NSCLC at the Benbadis University Hospital of Constantine (2015–2023). Of these, 95 patients were included in the survival analysis. The clinicopathological and outcome data were investigated based on the patients' medical records.

Results　This study showed male predominance with sex ratio of 5.7, with a mean age of 61.8 years. Histologically, 67.3% of cases had adenocarcinoma (ADC) and 22.7% squamous cell carcinoma (SCC). ADC and SCC occurred more frequently in female ($p = 0.02$) and male ($p = 0.003$) patients, respectively. Smoking was estimated at 82.2% in men. Over 28% were non-smokers, of which 50.7% were women, and presented at younger age ($p = 0.04$). Most of our patients (75.5%) have an advanced stage at diagnosis. Around 70% of patients underwent chemotherapy (CT) as first-line treatment, with medians diagnostic and treatment delays of 4 and 1 months, respectively. The median overall survival (mOS) was estimated at 10.3 and 6.7 months in I-III and IV stages, respectively. Other factors that negatively impact OS were age > 65 years ($p = 0.01$), and the presence of symptoms ($p = 0.005$) and comorbidity ($p = 0.004$) in stage IV, and delayed treatment ($p = 0.03$) and receiving CT alone ($p = 0.03$) in stages I-III cases. Medians progression free survival (mPFS) in stage IV, III, and II patients were 4.1, 5.2, and 8.3 months, respectively, and negatively affected by the comorbidity (stage IV, $p = 0.03$) and receiving CT alone (stages II-III, $p = 0.03$).

Conclusions　NSCLC presents at an early age and advanced stage in Algerian patients. ADC is the most frequent histological subtype and smoking remains the most important risk factor in men. Furthermore, the prognostic factors affecting survival are stage, age, comorbidity, symptoms, and treatment. Thus, tobacco control, early detection program, and access to novel therapies may be the best strategies to reduce NSCLC morbidity and mortality.

Keywords　Non–small-cell lung cancer, Clinicopathologial features, Prognosis, Algeria

*Correspondence:
Mohamed Lahmadi
m.lahmadi@crbt.dz
[1]Division of Biotechnology and Health, Biotechnology Research Centre (CRBt), Constantine, Algeria
[2]Department of Anatomical Pathology, Benbadis Hospital, University Constantine 3, Constantine, Algeria
[3]Department of Thoracic Surgery, Benbadis Hospital, University Constantine 3, Constantine, Algeria
[4]Department of Medical Oncology, Benbadis Hospital, University Constantine 3, Constantine, Algeria

Background

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death in 2020, representing 11.4% cancers diagnosed and 18% deaths of total cases. In men, lung cancer is the leading cause of cancer morbidity (14.3%) and mortality (21.5%), whereas, in women, it ranks third for incidence (8.4%) and second for mortality (13.7%) [1]. Lung cancer remains the most commonly diagnosed cancer among men in North-West Africa or the Maghreb region, including Algeria, Morocco, Tunisia, and Libya, posing a real public health problem. In Algeria, the overall lung cancer incidence rates in 2018 and 2020 have been estimated to be 1.3 and 1.4 cases per 100,000 people, respectively. It is the most common cancer among men, which accounts for about 15.2% of total cases of male cancers, and the third in both sexes. Lung cancer is the leading cause of cancer-associated death, for all ages, responsible for more than 4,300 deaths representing 13.2% of cases [2].

Lung cancer is likely to continue as a major health problem well through the first half of this century with the increasing global trends in its incidence and mortality [3]. The overall survival rate for lung cancer patients is still poor and depends mainly on the stage of disease. Patients diagnosed with localized disease, NSCLC type, have the best 5-year survival rate [4]. However, the survival of advanced NSCLC has relatively improved in recent years by therapeutic advances [5]. Tobacco smoking is the major risk factor in the development of lung cancer. Other risk factors thought to contribute to lung cancer risk, implicating occupational exposures, air pollution, pulmonary conditions, dietary factors, and genetic susceptibility [6]. Disparities in lung cancer incidence, mortality, and survival have been reported by gender and geographical differences. Besides, the observed epidemiological variations are influenced by histological and molecular characteristics [3]. Over the past years, changes have been remarked on in some epidemiological factors such as gender, smoking, and histology [7].

There is limited published data associated with lung cancer reported from Algeria. This study aimed to investigate the clinicopathological and prognosis aspects of patients with NSCLC in the Eastern region of Algeria, based on a referral hospital record, which might reflect a national landscape and could lead to better recognition of this type of cancer in the North African population.

Methods

Patients

We retrospectively reviewed the clinical and pathological data of 269 patients with primary NSCLC diagnosed and/or treated at the Benbadis University Hospital of Constantine (UHC) for 8 years, between February 2015 and March 2023. Of these, 95 patients who underwent CT and/or radiotherapy (RT) were included in the survival analysis. Most patients admitted to the Benbadis UHC came mainly from the eastern regions of Algeria.

Diagnostic and staging were determined on the basis of imaging and anatomopathological testing. Patients underwent chest X-ray and computed axial tomography (CAT), abdominal (CAT or ultrasound), and brain (CAT or magnetic resonance imaging) imaging. Positron emission tomography-CAT was also performed for a proportion of patients. The tissue biopsy was obtained via either bronchoscopy, CAT-guided biopsy, or surgical lung biopsy, and thoracentesis for pleural fluid. Samples were subjected to histopathological (H&E staining) and immunohistochemical (Cytokeratins, TFF1, p40/63 markers) examination. The histopathological classification was confirmed on the basis of the WHO classification of lung tumors (2015). Furthermore, patients were staged according to the 8th edition of the American Joint Committee on Cancer (AJCC) TNM system.

Data collection

The data of NSCLC patients were obtained from the patients' medical records, at the departments of Anatomical Pathology, Thoracic Surgery, Pneumology, and Medical Oncology. The data collected comprised demographic characteristics and clinicopathological features of patients, including gender, age, smoking status, histological type, stages of the disease, treatment approach, and follow-up times.

Diagnostic delay was measured from first symptom onset to formal diagnosis, and treatment delay from diagnosis to the date of the first consultation in the center. The OS and PFS were defined as the interval from the date of diagnosis and the date of the first treatment to the date of the last follow-up or untill December 31, 2022.

Statistical analysis

The data were constructed and sorted with Excel (Microsoft Office, 2019). Quantitative and qualitative variables were represented with means/medians and percentages, respectively. The differences between groups were assessed using Chi-squared or Fisher test for categorical variables and Mann–Whitney test for continuous variables. Two-sided *p* values of <0.05 were considered statistically significant. GraphPad Prism version 7.05 (GraphPad Software, San Diego, CA) was used for statistical analysis.

Results

Clinicopathological characteristics of patients

The main clinicopathological characteristics of the patients included in this study are presented in Table 1. A total of 269 cases of NSCLC primary lung cancer were

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Table 1 Clinical and demographic characteristics of the patients

Characteristics	N (%)
Age, Mean (years)	61.8
< 50	32 (11.9%)
50–59	77 (28.6%)
60–69	95 (35.3%)
≥ 70	65 (24.2%)
Gender	
Male	229 (85.1%)
Female	40 (14.9%)
Smoking statue	
Smoker/ex-smoker	178 (66.2%)
Non-smoker	77 (28.6%)
Unkown	14 (5.2%)
Histological type	
ADC	181 (68%)
SCC	61 (23%)
LCC	4 (1.5%)
ADC-SCC	3 (1.1%)
NOS	7 (2.6%)
Others	10 (3.8%)
Tumor grade	
Well differentiated	53 (33.4%)
Moderately	71 (44.6%)
Poorly	35 (22%)
Pathological stage	
T1–2	37 (13.7%)
T3	49 (18.2%)
T4	89 (33%)
N0–1	71 (26.4%)
N2–3	106 (39.4%)
M1	136 (50.5%)
Mx	13 (4.8%)
Clinical stage	
Stage I	8 (3.0%)
Stage II	40 (14.9%)
Stage III	54 (20.1%)
Stage IV	149 (55.4%)
Unspecified	18 (6.6%)
Site of metastasis	
Bone	62 (40.8%)
Brain	34 (22.4%)
Liver	19 (12.5%)
Adrenal	8 (5.3%)
Other organs	5 (3.2%)
Pleural Effusion	24 (15.8%)
Symptoms (n = 238)	
Cough	76 (31.9%)
Thoracic pain	55 (23.1%)
Dyspnea	51 (21.4%)
Hemoptysis	20 (8.4%)
Pain	14 (5.9%)
Weight loss	8 (3.4%)
Others	16 (6.7%)
Comorbidity	

Table 1 (continued)

Characteristics	N (%)
Hypertension	43 (36.1%)
Diabetes	32 (26.9%)
Respiratory diseases (RD)	
COPD	9 (7.6%)
Tuberculosis	4 (3.4%)
Other RD	6 (5%)
Cardiovascular diseases	7 (5.9%)
Benign prostatic hyperplasia	7 (5.9%)
Others	11 (9.2%)
Occuptional exposure (n = 106)	
Present	24 (22.5%)
Absent	82 (77.5%)
Treatment type (n = 206)	
CT	144 (69.9%)
RT (+ CT)	34 (16.5%)
Surgery (+ RT/CT)	28 (13.6%)
Delays, Median (IQR)	
Diagnosis, Months	4 (2–6)
Treatment, Days	31 (14–71)

*Statistically significant

included, of which 229 (85.1%) were men and 40 (14.9%) women, with a sex ratio male-to-female (M/F) of 5.7. The mean age of patients at the time of presentation was 61.8 years. The age group range from 50 to 69 years represented 63,9% of cases, while about 12% with an age fewer than 50 years.

In terms of smoking history, 178 (66.2%) were smokers, including ex-smokers, and 77 (28.6%) were non-smokers. Taking into account that only one (2.5%) woman patient was a smoker and unavailable data for 14 (5.2%) patients, the rate of smoking was estimated at 82.2% in male patients. Non-smokers tend to present at a younger age compared to smokers (mean: 59.6 vs. 62.8 years ; 44.4% ≤50 vs. 28.1% >50 years, $p=0.04$). Also, 50.7% of non-smoker patients were women. On the other hand, of 106 patients with data of occupational exposure, the history of profession-related to increased risk of NSCLC was observed in 24 (22.67%) male patients, the most frequent were the professional driver (8.5%).

The data for symptoms and comorbidity were available for 238 (88.5%) cases. The frequent symptoms at diagnosis were cough (31.9%), thoracic pain (23.1%), dyspnea (21.4%), hemoptysis (8.4%), and non-respiratory symptoms (16%). Regarding comorbidity, 19 (11.4%) patients had a comorbid pulmonary disease, including mainly chronic obstructive pulmonary disease (COPD) and tuberculosis, while 75 (31.5%) cases had chronic diseases, the most common were hypertension (18.1%) and diabetes (13.4%).

The study subjects had the following histological distribution: 181 (67.3%) ADC, 61 (22.7%) SCC, and 27 (10%)

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other types [Large cell carcinoma (LCC), Adenosquamous carcinoma (ADC-SCC), not otherwise specified (NOS), carcinoid]. A significant association was found between the histological type and gender, in which a high rate of ADC was found in women in comparison to men (82.5% vs. 64.6%, *p*=0.02) and SCC in men in comparison to women (25.8% vs. 5%, *p*=0.003). Also, there was an association between the histological type and smoking statute, but not statistically significant, ADC was more frequent in non-smokers (76.6% vs. 65.7%, *p*=0.08) and SCC in smokers (24% vs. 14.3%, *p*=0.08) (Tables 2 and 3). Furthermore, 106 (39.4%) cases had moderately or poorly differentiated tumor while 53 (19.7%) had well differentiated.

Regarding the clinical stage of the disease and treatment approach, 149 (55.4%) cases were at the metastatic disease (stage IV) and 102 (38%) were in non-metastatic stages (stages I-III). Over 75% of patients presented with advanced stages (stage III/IV). The major distant metastatic sites were bone (23%) and brain (12.6%), followed by liver (7.1%) and adrenal gland (3%). These results reflected the received treatment, around 70% of cases undergoing chemotherapy as a first-line treatment, while 16.5% and 13.6% of patients were treated with radiotherapy and surgery, respectively. On the other hand, among patients with metastatic stage, 17 (11.4%) cases benefited from epidermal growth factor receptor (EGFR) mutation testing, of which 6 (35.3%) had positive EGFR mutation. Furthermore, of the 165 patients with data regarding symptoms, the medians of the diagnostic and treatment delay were 4 months (IQR 2–6 months) and 31 days (IQR 14–71 days), respectively.

Prognostic factors

As reported in Tables 4 and 5, various clinicopathological variables were evaluated on a group of treated patients to determine potential prognostic factors for survival. The mOS was estimated at 10.3 months and 6.7 months in non-metastatic and metastatic disease, respectively (*p*=0.03). The univariate analysis revealed that a shorter mOS was significantly associated with advanced stage [T4 stage, N2-3 stage, clinical stage IV, two or more sites of metastasis (*p*<0.05)], age at diagnosis≥65 years (*p*=0.01), and the presence of symptoms (*p*=0.005) and comorbidity (*p*=0.004) in stage IV, and the treatment delay>2 months (*p*=0.018) and receiving CT alone (*p*=0.025) in stage I-III cases. According to this analysis, OS was not influenced by other variables including gender, smoking status, histological type, tumor grade, and diagnostic delay. Furthermore, the mPFS was estimated at 4.1 months in metastatic stage and significantly associated with the presence of comorbidity (*p*=0.03), while it was at 5.5 months in non-metastatic stages (Table 6), of which 5.2 months in stage III (*p*=0.32) and 8.3 months in

Table 2 Characteristics of the study population according to gender

	Male	Female	*p*
Age, Mean (years)	62	61.1	0.66
Smoking statute			
Smoker	176 (82.2%)	1 (2.5%)	<0.0001*
Non-smoker	38 (17.8%)	39 (97.5%)	
Histology			
ADC	148 (64.6%)	33 (82.5%)	0.026*
SCC	59 (25.8%)	2 (5.0%)	0.003*
Others	22 (9.6%)	5 (12.5%)	
Clinical stage			
Non-metastatic	93 (42.7%)	11 (31.4%)	0.2
Metastatic	125 (57.3%)	24 (68.6%)	

*Statistically significant

Table 3 Characteristics of the study population according to smoking status

	Smoker	Non-smoker	*p*
Age (years) Mean	62.8	59.6	0.043*
Gender			
Male	176 (99.4%)	38 (49.3%)	<0.0001*
Female	1 (0.6%)	39 (50.7%)	
Histology			
ADC	115 (65.7%)	59 (76.6%)	0.085
SCC	42 (24.0%)	11 (14.3%)	0.082
Others	18 (10.3%)	7 (9.1%)	
Clinical stage			
Non-metastatic	71 (41.5%)	25 (35.2%)	0.36
Metastatic	100 (58.5%)	46 (64.8%)	

*Statistically significant

Table 4 Overal survival of the study population according to the stage of disease

	N=95 (%)	mOS (mths)	95% CI	*p*
Pathological stage				
T1–3	33 (34.7%)	11.4	9.1–14.5	0.008*
T4	39 (41.0%)	5	5.1–9.3	
N0–1	24 (25.2%)	10.8	7.9–15.0	0.022*
N2–3	45 (47.3%)	6.2	5.9–9.8	
M1a	19 (20.0%)	11	7.4–16.5	0.019*
M1b–c	38 (40.0%)	5.3	4.9–13.5	
Clinical stage				
Stages I-II	11 (11.6%)	10.2	5.3–20.6	0.035*
Stages III	23 (24.2%)	10.5	8.1–12.6	0.077
Stages IV	57 (60.0%)	6.7	7.0–13.4	
Sites of metastasis				
Single organ	27 (28.4%)	7.2	5.3–16.8	0.032*
Two or more	14 (14.7%)	3.5	1.2–10.5	

*Statistically significant, mOS: Median overall survival time, Months: Mths

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Table 5 Characteristics and univariate analysis of prognostic factors affecting OS stratified by stage of disease

	N	Stage IV			Stages I-III		
		mOS (mths)	95% CI	p	mOS (mths)	95% CI	p
Total	95 (100%)	6.7	7.0–13.4	/	10.3	8.1–20.6	/
Age (years)							
>65	47 (49.5%)	5.3	4.3–7.7	0.02*	11.2	8.6–13.9	0.42
≤65	48 (50.5%)	9.4	8.1–18.9		9.2	5.6–15.8	
Gender							
Male	79 (83.2%)	6.4	6.0–11.5	0.12	10.9	8.9–14.4	0.052
Female	16 (16.8%)	9.5	3.5–27.9		5.6	1.7–10.0	
Smoking statue							
Yes	68 (71.6%)	6.7	5.9–12.2	0.26	10.5	5.9–12.2	0.26
No	26 (28.4%)	6.8	4.7–20.7		6.9	4.7–20.7	
Symptoms							
Symptomatic	66 (69.5%)	5.8	5.6–11.4	0.028*	8.3	5.6–11.4	0.1
Asymptomatic	29 (30.5%)	10.3	5.5–24.5		12	5.5–24.5	
Comorbidity							
Present	40 (42.1%)	5.3	4.2–10.2	0.033*	9.1	4.2–10.2	0.59
Absent	55 (57.9%)	10.1	7.6–19.1		10.5	7.6–19.1	
Histology							
ADC	72 (75.8%)	6.7	6.4–14.4	0.96	8.4	6.4–14.4	0.23
Non-ADC	23 (24.2%)	7.6	4.3–15.0		11.3	4.3–15.0	
Tumor grade							
Well differentiated	14 (14.8%)	7.3	3.5–11.2	0.87	9.1	0.07–21.4	0.96
Moderately/Poorly	53 (55.8%)	5.2	5.0–14.8		9.3	7.2–12.5	
Diagnosis delay							
≥4 months	59 (62.1%)	6.2	5.2–16.5	0.44	9.1	5.2–16.5	0.67
<4 months	36 (37.9%)	10	6.4–14.1		8.3	6.4–14.1	
Treatment delay							
≥60 days	47 (49.5%)	7.2	3.3–22.4	0.26	10.3	8.0–12.4	0.018*
<60 days	48 (50.5%)	6.4	5.9–12.8		27	12.8–33.7	
Treatment type							
CT	76 (80.0%)	6.4	6.5–11.7	0.17	8.3	6.6–11.9	0.025*
CT and/or RT	18 (19.0%)	10	7.9–47.1		12	9.1–19.9	

*Statistically significant, mOS: Median overall survival time, Mths: Months

Table 6 Univariate analysis of PFS according to age, comorbidity, and treatment type stratified by stage of disease

	N	Stage IV			Stages II-III		
		mPFS (mths)	95% CI	p	mPFS (mths)	95% CI	p
Total	85 (100%)	4.1	4.0–8.8	/	5.5	5.4–14.5	0.08
Age (years)							
>65	38 (43%)	3	2.9–8.7	0.12	4.5	2.0–11.2	0.09
≤65	47 (57%)	6.2	5.3–10.6		6.2	5.0–18.9	
Comorbidity							
Present	39 (46%)	3.3	2.6–5.5	0.03*	6.3	5.5–14.1	0.46
Absent	46 (54%)	7.5	5.9–12.1		5	2.3–17.5	
Treatment type							
CT	70 (82.3%)	4.1	4.8–9.5	0.98	4.8	3.5–14.8	0.04*
CT and/or RT	15 (17.7%)	4.8	1.6–7.2		6.4	5.6–16.1	

*Statistically significant, mPFS: Median pregression free survival time, Mths: Months

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stage II ($p = 0.07$). A shorter mPFS was also significantly associated with receiving CT alone in non-metastatic stages ($p = 0.04$). Moreover, 50% (6/12) of stage II and merely 25% (5/20) of stage III cases were treated with CT and/or RT.

Discussion

To the best of our knowledge, this is the first study to investigate the clinicopathological and prognosis features of NSCLC in Algeria. The present study is a retrospective investigation of NSCLC in a public referral hospital in Constantine, an Eastern Province of Algeria. The analysis of the collected data allowed us to evaluate some clinicopathological characteristics and prognostic factors of this type of cancer in Algeria.

In our cohort, NSCLC showed a male predominance with a sex ratio (M/F) of 5.7. Comparable results were reported from studies in Algeria [8–11], Tunisia, and Morocco [12–17], with a sex ratio (M/F) varying between 6 and 13.2. In the same line, according to global estimates based on Globocan 2020, the sex ratio (M/F) varies widely across regions, ranging from 1.2 in Northern America to 5.6 in Northern Africa [1]. The low incidence of NSCLC in women in the region of North Africa largely reflects differences in tobacco consumption which represents about 2-5.6% among women versus 27–55% among men [18]. Besides, women have less access to professions with high occupational exposure to pulmonary carcinogens [11].

We found that NSCLC mainly affects patients older than 50 years at the moment of diagnosis, with a mean age of 61.8 years, which is similar to that reported in other Algerian studies [8–11]. These findings are also close to those found in studies carried out in Maghreb countries [12–15, 17, 19]. NSCLC is often considered a disease in elderly patients with a median age at diagnosis of 70 years old [20]. The young age observed in NSCLC patients in Northern Africa may be explained by the fact that our population is younger compared to other populations, in particular in Europe and North America [21].

Our findings indicate that the male smoking rate was over 82%. This rate is close to the previous Algerian study conducted by Kefti et *al* [11]., while other studies in the Maghreb region have reported higher rates varying between 90% and 94%. Concerning female smoking, one patient (2.5%) in our study was a smoker; similar findings were obtained in studies conducted in our region with rates of 0–4% [8, 10, 13–15]. Although tobacco smoking remains the most important risk factor in men, about 10–25% of lung cancer patients report no history of regular smoking [22]. In our study, we found a high prevalence (28.6%) of non-smokers, and this non-smoking-related NSCLC was associated with younger age, women and ADC subtype. As reported in literature, neversmokers with NSCLC present distinct clinicopathological characteristics and different patterns of molecular alterations. Never-smoker patients are more likely to be female and have ADC [23]. Shan et *al*. found that non-smoker with lung ADC showed a younger age [24]. This should increase our interest to understanding the biological and clinical features of this subset of patients.

Other risk factors such as occupational exposure, air pollution, respiratory diseases, and genetic susceptibility, may be related to an increased risk of lung cancer [6]. In terms of respiratory comorbidities, they represent 11.4% among our patients, the most common were COPD and tuberculosis, whereas hypertension and diabetes were the most common chronic diseases. These comorbidities may be an important prognostic factor in treatment choice [25]. Additionally, according to the study by Kefti et *al*., approximately 50% of Algerian patients with lung cancer had occupational exposure to a carcinogen in their workplace, such as diesel exhaust gases, silica, PAHs, welding fumes, and asbestos [11]. Taking into account that data in our study was not readily available for all patients, the history of occupational exposure was observed in 22.6%, mostly related to professional drivers. As demonstrated in a meta-analysis by Tsoi et *al*., there is an 18% excess risk of lung cancer linked to professional drivers, potentially exposed to diesel exhaust [26]. Thus, it is needed to research potential non-tobacco-related risk factors in NSCLC.

Regarding lung cancer incidence by histological subtypes, our findings indicate that ADC was the most common subtype, followed by SCC. Recent studies from the region of Maghreb have reported similar proportions of ADC compared with SCC [10, 11, 13–15]. Although comparable to previous studies in our region, the SCC subtype predominantly occurred [8, 12]. Indeed, the rates of ADC increased over time and surpassed SCC as the most frequent lung cancer subtype. Moreover, there are disparities in the distribution of histological subtypes according to gender and smoking status. Contrary to the SCC, which is more associated with tobacco smoking, ADC is seen with a higher incidence among women and neversmokers [27]. Although ADC is most commonly found in women and non-smokers in our study, men smokers also showed a high proportion of ADC. It has been suggested that cigarette filter ventilation has contributed to the rise in ADC among smokers [28].

Lung cancer patients are more likely to have advanced disease upon diagnosis. In the same line, most patients in our serie presented with advanced disease. Furthermore, the extra-thoracic metastatic sites are frequently seen in the order of bone, brain, and liver. Our findings are close to those reported in the literature, but hepatic metastases were less frequent [29]. The delayed diagnosis of lung cancer is relatively attributed to the lack of validated

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screening tools and non-specific symptoms [3]. However, evidence from several cohort studies indicated that low-dose CAT screening allows for the early detection of lung cancer in high-risk patients [1]. On the other hand, promoting awareness of lung cancer symptoms may lead to improved clinical outcomes. In our study, the dominant symptoms that prompted consultation were mainly cough and chest pain, followed by dyspnea and hemoptysis, which are consistent with reported in previous large-scale studies [30, 31]. In terms of delays in the diagnosis and treatment of our patient, contrary to a reasonable time of treatment delay, the diagnostic delay seems excessive in comparison to the recommendation by professional organizations (2–4 weeks) [32]. Our findings are comparable with those in Western Algeria and Morocco, with median times of 83 days and 75 days, respectively [33, 34]. Thus, our patients experience substantial delays from the onset of symptoms to treatment initiation. Future efforts should focus on developing efficient strategies for early detection, based on improving lung cancer diagnosis intervals accompanied by implementing a screening program.

The survival rate of NSCLC depends mainly on the stage of disease. Patients with advanced NSCLC usually have a poor prognosis [4]. In our study, the mOS was estimated at 10.3 and 6.7 months in non-metastatic and metastatic stages, respectively. These findings are generally consistent with data of NSCLC patients received CT and CRT [35]. We found that the advanced stage was associated with a poor prognosis, especially having T4, N2-3, or metastatic stage, particularly with two or more distant metastases. Furthermore, older age (≥65 years) and the presence of symptoms and comorbidity were associated with a poor prognosis in patients with metastatic disease. This is in line with the results of a regional study in Tunisian patients with advanced NSCLC, which reported a mOS of 6 months, and the stage, performance status, comorbid conditions, delay of management, and treatment were identified as prognostic factors [36]. The age and comorbidity have been reported yet as independent prognostic factors in lung cancer [37]. Besides, asymptomatic lung cancer patients at diagnosis exhibit a better prognosis. This underlines the importance of an early diagnosis [38]. On the other hand, our data showed that delayed treatment and receiving CT alone were associated with a poor prognosis in patients with non-metastatic disease. These results were consistent with previous findings showing that patients with stages I-III NSCLC who received delayed treatment had a higher risk of mortality [39, 40].

Furthermore, we found that mPFS in patients with stage IV, III, and II were 4.1, 5.2, and 8.3 months, respectively. The PFS was also negatively affected by the presence of comorbidity and receiving CT alone. These findings are under the expected range according to mOS, though a shorter mPFS in patients with stage III. Besides the stage of disease, the presence and severity of comorbid conditions along with age and performance status appear to be important determinants of PFS in NSCLC. The age and presence of comorbidity could have a significant impact on treatment decisions [41]. In patients with early-stage NSCLC, in addition to the impact of comorbidities on the qualification for surgical treatment, they contribute to increased postoperative complications [42, 43]. Multiple comorbidities also have a negative impact on elderly NSCLC patients with III and IV stages treated with CT or CRT [44, 45]. Additionally, PFS may vary depending on the specific treatment regimens and patient characteristics involved in each study. A multicenter retrospective study by Jazieh et *al.*, from 19 low-to-middle-income countries, reported that surgery plus CT and concurrent CRT (cCRT) as initial therapy predicted better mPFS in patients with stage III NSCLC compared to other different treatment regimens [46]. In the same line, Sakin et *al.* showed that performance status and CRT are the most important factors affecting PFS in elderly patients with inoperable stage III NSCLC, and the best survival was achieved in patients treated with cCRT [47]. Moreover, Flörsch et *al.* found that patients with inoperable stage III NSCLC treated (post cCRT) according to a multimodal treatment depending on the treatment time and pattern, demonstrated improved survival regardless of immunotherapy use. However, the implementation of immunotherapy has further enhanced patient outcomes [48]. This highlights the importance of timely initiation of specific therapy, along with treatment of comorbidity, to improve the outcome of NSCLC patients. Thus, we suggest further optimization strategies in the management of our NSCLC patients, taking into consideration these different factors.

As expected, our outcome is lower than the medians survival achieved with the use of novel therapies. Though the recent progress in targeted therapy and immunotherapy have changed the landscape for the treatment of advanced NSCLC, access to certain therapeutic modalities among the countries in the region is still limited [18]. Besides, EGFR and PDL1 have been proved as predictive biomarkers in advanced NSCLC for tyrosine kinase and PD1/PDL1 inhibitors, respectively [49, 50]. In conjunction with the predominance of ADC histological type in the current study, high rates of EGFR mutation and PDL1 overexpression (approximativly 40%) were observed in our patients with NSCLC, in particular in those with ADC [51, 52]. This suggests that a large number of Algerian patients with NSCLC are likely candidates for EGFR-targeted therapy and PD1/PDL1 immunotherapy. However, the rate of EGFR testing was admittedly low in this cohort of patients, even among patients with

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metastatic ADC. This may be explained by the socioeconomic status of our patients since there is limited access to diagnostic settings for molecular testing in public hospitals and anticancer centers. On the other hand, immunotherapy is much more likely to be accessed since PDL1 expression could be routinely assessed by immunohistochemistry. Thus, the establishment of precision medicine treatments at our anticancer centers is likely to improve survival outcomes.

Our study presents some limitations as being a single-center evaluation and based on retrospectively reviewed medical records. There was a proportion of cases without information for some parameters. Besides, the lack of molecular testing of some important markers (EGFR, ALK, ROS1) and PDL1 have not routinely introduced with the immunohistochemical report until most recently. Despite the limitations, our results could be an update on the clinicopathological and prognosis features of NSCLC in our population and help to conduct future research studies, particularly prospective investigations of the influence of novel therapies (targeted and immuno-therapies) and clinical parameters on NSCLC patients' survival.

Conclusion

In this Algerian cohort of patients with NSCLC, the majority of cases were male and diagnosed with advanced disease. The age at diagnosis was relatively younger and ADC was the predominant histological subtype. Tobacco smoking was the most important risk factor in men. On the contrary, neversmokers patients were more likely to be young and female. Furthermore, the prognostic factors affecting survival are stage, age at diagnosis, comorbidity, symptoms, and treatment. Therefore, we suggest that primary prevention, based mainly on tobacco control and early detection through screening program, and access to targeted therapy and immunotherapy may be the best strategies to reduce lung cancer morbidity and mortality. Future efforts should focus on identifying biological differences and potential etiological risk factors to improve NSCLC management in our population.

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