Original Article

Comprehensive analysis of clinical, radiological, pathological findings, and survival outcomes in non-smoker non-small cell lung cancer patients

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Abstract:

BACKGROUND AND AIM: Lung cancer in non-smokers exhibits distinct epidemiological and biological characteristics. Despite a global decline in cigarette consumption, the incidence of lung cancer in non-smokers is on the rise. Regrettably, screening programs often overlook these patients. This study seeks to explore the clinical, radiological, and pathological features, as well as survival results, among non-smoker patients with non-small cell lung cancer (NSCLC).

METHODS: The study included 74 non-smoker patients among 315 diagnosed with NSCLC between January 2013 and May 2023. Patient characteristics, survival outcomes, and factors predicting overall survival (OS) were examined.

RESULTS: The mean age at diagnosis was 57.6±13.3 years (range: 23-82 years), and 57 patients (77%) were female. Upon diagnosis, 90% of patients were symptomatic, and 69% were at stage 3 or 4. The median follow-up time was 3.7 years (range: 0.2-8.9), and the 5-year progression-free survival (PFS) and OS rates were 20.7±4.8% and 36.2±6.3%, respectively. Median PFS was 1.6 years (95% confidence interval [CI]: 1.16-2.04) and median OS was 4.04 years (95% CI: 3.16-4.93). In multivariate Cox regression analysis, stage 4 disease at diagnosis (hazard ratio [HR]: 3.656, p<0.001) and non-adenocarcinoma histology (HR: 2.896, p=0.019) were independent predictors of OS.

CONCLUSIONS: Approximately one-quarter of NSCLC patients are non-smokers, with the majority being women diagnosed with adenocarcinoma. Individuals are commonly diagnosed after symptoms begin, usually at an advanced or locally advanced stage. Stage IV disease at diagnosis and non-adenocarcinoma histology were independent predictors of worse prognosis. Since current screening studies have primarily targeted the smoking population, there is a pressing need for research to identify additional risk factors, especially for the inclusion of non-smokers in screening programs.

Keywords:

Non-smoker, lung cancer, non-small cell lung cancer (NSCLC), screening

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Smoking is the best-defined risk factor for lung cancer and accounts for over 80% of lung cancer cases. Advanced age, environmental tobacco smoke/toxins, occupational exposures, chronic respiratory diseases, oncogenic viruses, hormonal factors, and family history of lung cancer have been suggested as risk factors for lung cancer in non-smokers.[2,3] Although global lung cancer rates have somewhat declined in recent decades with the implementation of tobacco control programs, lung cancer among non-smokers remains a developing and unique phenomenon.[4] Lung cancer in non-smokers differs in its natural history, biology, and epidemiology.[5] It predominantly occurs in female patients with adenocarcinoma histology.[6] Small cell lung cancer (SCLC) is an aggressive tumor commonly associated with smoking. Nevertheless, 1.8–2.5% of SCLC cases can develop in individuals who do not smoke. A significant portion of non-smoker SCLC cases is documented to occur in females (range: 66–80%).[7,8]

Non-smokers constitute 10–25% of all lung cancer patients.[9,10] However, lung cancer screening guidelines focus only on individuals who are current or former smokers.[11,12] This study aims to investigate the clinical, radiological, and pathological characteristics, as well as survival outcomes, in non-smoker patients diagnosed with non-small cell lung cancer (NSCLC).

Materials and Methods

This was a retrospective cohort study conducted in a referral university hospital over an approximately 10-year period. Data on 315 adult patients [91 (29%) women and 224 (71%) men] diagnosed with NSCLC between January 2013 and May 2023, whose smoking status was recorded, were examined retrospectively.

The study included 74 (23%) non-smoker NSCLC patients. Demographic characteristics, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), initial symptoms, radiological findings at diagnosis, histopathological subtype, presence of driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS oncogene 1 (ROS1), programmed cell death-ligand 1 (PD-L1) positivity, TNM staging (pathological in patients who underwent surgery, clinical in patients who did not), treatment protocols, and survival data were evaluated. The patients were staged based on the 8th TNM classification.[13] The study protocol was approved by Hacettepe University of Health Sciences Research Ethics Committee (Approval Number: 23/032, 2023/01-11, Date: 05.09.2023). Artificial intelligence-assisted technologies were not used in the production of the study. The study adhered to ethical standards outlined in the 1964 Helsinki Declaration and its subsequent amendments for all procedures involving human participants. Due to the retrospective nature of the study, formal informed consent was not acquired.

Statistical analyses were conducted using SPSS (Statistical Package for the Social Sciences, version 28, IBM Inc., Armonk, NY) software. Descriptive statistics were reported as frequency (percent) or mean ± standard deviation (SD). The period from diagnosis to death from any cause was designated as overall survival (OS), while the duration from diagnosis to progression or death was termed progression-free survival (PFS). Survival rates were computed through the Kaplan-Meier method, and the log-rank test was utilized to detect independent effects on OS and PFS. A significance level of $p<0.05$ was considered statistically significant.

Results

The characteristics of 74 non-smoker NSCLC patients are presented in Table 1. Among them, 55 (77%) were female, and 17 (23%) were male, with a mean age of 57.6±13.3 years (range: 23–82 years) at the time of diagnosis. Three (4.1%) patients had a family history of lung cancer, while four (5.4%) patients had a history of asbestos exposure. Sixty-five percent of the patients (n=48) had comorbidities, with hypertension being the most common (n=35, 47.3%). Sixty-seven (90.5%) patients were symptomatic at diagnosis. The presenting symptoms included cough (52.7%), shortness of breath (29.7%), weight loss (17.6%), back pain (10.8%), hemoptysis (8.1%), chest pain (6.8%), and hoarseness (4.1%). The ECOG-PS was 0 in 73% of patients and 1 in the remainder.

The characteristics of the tumors and therapies applied are presented in Table 2. The histological subtype was adenocarcinoma in 66 (89.2%) patients. The tumor was central in 57 (77%) patients and peripheral in 17 (23%) patients. Disease stages at diagnosis were stage I in 16 (21.6%) patients, stage II in seven (9.5%) patients, stage

Table 1: Characteristics of study subjects (n=74)

Characteristics	Frequency	
	n	%
Female	57	77
Male	17	23
Age at diagnosis, mean±SD, years	57.6±13.3	
Range (years)	23–82	
≥65 years	30 (40.5)	
Family history of lung cancer	3	4.1
Asbestos exposure	4	5.4
Comorbidity(ies)	48	64.9
Hypertension	35	47.3
Diabetes	15	20.3
Coronary artery disease	6	8.1
Connective tissue disease	5	6.8
Malignancy	3	4.1
COPD	1	1.4
Others	19	25.7
Symptom(s) at admission	67	90.5
Cough	39	52.7
Shortness of breath	22	29.7
Weight loss	13	17.6
Back pain	8	10.8
Hemoptysis	6	8.1
Chest pain	5	6.8
Hoarseness	3	4.1
ECOG-PS		
0	54	73
1	20	27

SD: Standard deviation, COPD: Chronic obstructive pulmonary disease, ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

Table 2: Characteristics of tumors and applied therapies (n=74)

Characteristics	Frequency	
	n	%
Histological subtypes		
Adenocarcinoma	66	89.2
SCC	5	6.8
Adenosquamous carcinoma	2	2.7
NSCLC-NOS	1	1.4
Central	57	77
Peripheral location	17	23
Staging		
Stage I	16	21.6
Stage II	7	9.5
Stage III	13	17.6
Stage IV	38	51.4)
Distant metastasis sites		
Bone	20	27
Liver	10	13.5
Adrenal gland	7	9.5
Pleural/pericardial effusion	5	6.8
Brain (n=30)	4/30	13.3
Others	11	14.9
Driver mutations		
EGFR (n=46)	20/46	43
ALK (n=34)	9/34	26
ROS1 (n=25)	6/25	24
PD-L1 (n=9)		
<1% negative	4/9	44.4
1–49% positive	4/9	44.4
≥50% positive	1/9	11.1
Treatments		
Only surgery	14	18.9
Surgery + Adjuvant CT	12	16.2
Definitive treatment with CRT	10	13.5
Systemic therapy	37	50
Cytotoxic	24	32.4
Targeted	23	31.1
Immunotherapy	1	1.4
Supportive care	1	1.4

SCC: Squamous cell carcinoma, NSCLC-NOS: Non-small cell lung cancer, not otherwise specified, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, ROS1: ROS oncogene 1, PD-L1: Programmed cell, CT: Chemotherapy, CRT: Chemoradiotherapy

III in 13 (17.6%) patients, and stage IV in 38 (51.4%) patients. The most common site of distant metastasis was the bone (n=20, 27%). EGFR, ALK, and ROS1 mutations were detected in 43% (20/46), 26% (9/34), and 24% (6/25) of the cases, respectively. PD-L1 was tested in nine patients and was ≥1% positive in five patients. Twenty-six (35.1%) patients underwent surgery; of these, 12 received adjuvant chemotherapy (CT). Ten (13.5%) patients received definitive CT and radiotherapy (RT). Thirty-seven (50%) patients received systemic therapy. Only one (1.4%) patient received supportive care.

During a median follow-up time of 3.7 (0.2–8.9) years, the disease progressed in 59 (79.7%) patients, and 48 (64.9%) patients died. Median PFS was 1.6 years (95% confidence interval [CI: 1.16–2.04), and median OS was 4.04 years (95% CI: 3.16–4.93). The 5-year PFS and OS were 20.7±4.8% and 36.2±6.3%, respectively. Univariate analyses showed that age ≥65 years at diagnosis, ECOG-PS 1 (versus 0), central tumor location, stage IV disease (versus I, II, and III), non-adenocarcinoma histology, and systemic or pal-

liative treatment were related to mortality. The multivariate analysis assessed the independent impacts of factors identified as significant in the univariate analyses. Since systemic or palliative therapy had a strong correlation with stage IV disease, it was excluded from the model. Finally, stage IV disease at diagnosis (hazard ratio [HR]: 3.656, 95% CI: 1.779–7.513, p<0.001) and non-adenocarcinoma histology (HR: 2.896, 95% CI: 1.191–7.041, p=0.019) were found to be independent predictors of OS (Table 3). The survival curves are shown in Figure 1a and 1b.

Table 3: Cox regression analysis for overall survival

Risk factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age at diagnosis ≥65 years	2.055	1.135–3.721	**0.017**	1.357	0.641–2.876	0.425
Female sex	0.757	0.393–1.458	0.406	–	–	–
Presence of comorbidity(ies)	0.759	0.425–1.357	0.353	–	–	–
Presence of symptom(s) at admission	1.892	0.583–6.144	0.289	–	–	–
ECOG-PS 1 (versus 0)	2.649	1.476–4.757	**0.001**	1.492	0.718–3.100	0.283
Central tumor location	3.259	1.377–7.716	**0.007**	1.341	0.501–3.590	0.560
Stage IV disease (versus I, II, and III)	4.058	2.148–7.667	**<0.001**	3.656	1.779–7.513	**<0.001**
Non-adenocarcinoma histology	2.320	1.029–5.231	**0.042**	2.896	1.191–7.041	**0.019**
Systemic or palliative treatment	4.308	2.282–8.132	**<0.001**	–	–	–

Bold text indicates statistical significance at p<0.05 level. HR: Hazard ratio, CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group - Performance Status

Discussion

It is widely accepted that the prevalence of lung cancer in non-smokers is increasing, and further evaluation is warranted. This study investigated the clinical, radiological, and pathological characteristics, as well as survival outcomes, in non-smoker patients diagnosed with NSCLC. The patients were selected from a pool of 315 patients diagnosed with NSCLC during a 10-year period (January 2013 - May 2023), with recorded smoking status. A significant proportion of the patients, approximately one-quarter, were non-smokers (n=74, 23%). Most of the patients were female (77%), and nearly 90% of the patients had adenocarcinoma. Ninety percent of the patients were symptomatic at diagnosis, and 70% had locally advanced or advanced-stage disease. Stage IV disease at diagnosis and non-adenocarcinoma histology were independent predictors of worse prognosis.

The ratio of non-smoker NSCLC patients was found to be 23%, consistent with the current literature.[14] Adenocarcinomas are the most common histological subtype in non-smoker lung cancer patients.[3] Epidemiological studies reveal that non-smoker lung cancer cases are predominantly in females, accounting for 59.5% in the US.[15] The findings obtained in our study are consistent with previous literature. Females represented 77% of the study population, and 90% of the cases were adenocarcinoma. Risk factors other than smoking, such as a family history of lung cancer, asbestos exposure, or the presence of respiratory disease, were present in less than 5% of the cases.

Lung cancer is the leading cause of cancer-related death worldwide.[1] The overall 5-year survival rate of lung cancer is 19%, with a median survival time of 12 months.[16] Despite significant advancements in understanding the biology, oncogenesis, and immunology of cancer, coupled with the development of groundbreaking systemic therapies, the overall survival rate remains notably low. This poor survival rate is primarily due to the asymptomatic nature of the disease, which leads to diagnosis at advanced stages when curative therapies are unlikely with currently available treatment options. Thus, screening and early diagnosis are key factors for improving lung cancer survival rates.
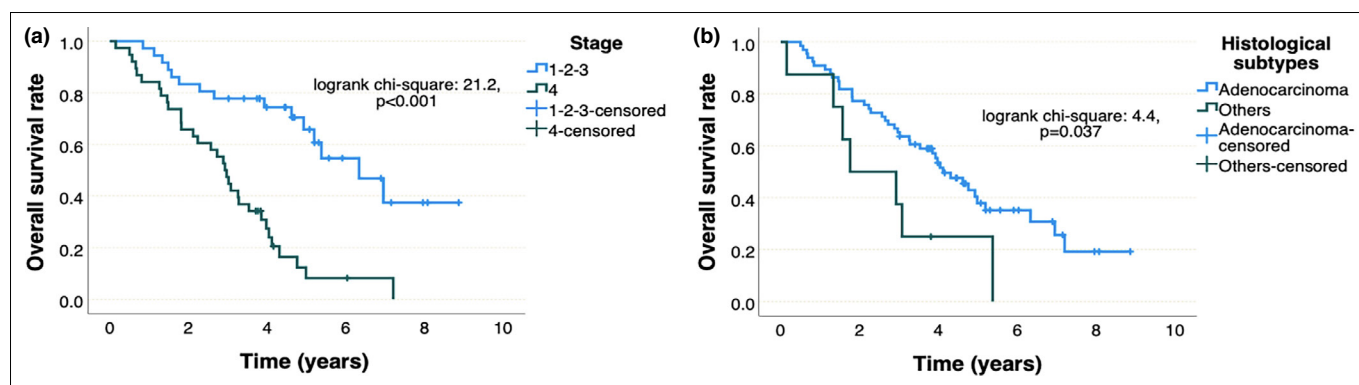

Figure 1: Overall survival curves according to disease stage (a) and histological subtypes (b)

[17,18] Our study revealed that, similar to their smoker counterparts, 90% of non-smoker NSCLC patients are diagnosed when they become symptomatic, and nearly 70% are diagnosed at a locally advanced or advanced stage. However, guidelines for lung cancer screening advise individuals aged 50 to 80 years with a smoking history of at least 20 pack-years, including both current smokers and those who quit smoking within the past fifteen years.[11,12] Notably, these guidelines exclude non-smokers. Despite the small number of patients and the retrospective nature of our study, it highlights the scientific gap concerning lung cancer screening in non-smokers. Further studies with a larger number of patients from different geographical regions are needed to identify additional risk factors for the development of lung cancer in this population and to include this patient group in screening programs.

In the present study, as expected, stage IV disease at diagnosis and non-adenocarcinoma histology were independent predictors of a worse prognosis. The 5-year OS rate (36.2±6.3%) and median survival (4 years) were comparatively higher than those reported in smoker lung cancer patients in the current literature. This difference can be primarily attributed to the higher usage of targeted therapies in advanced-stage patients. The growing literature on the genomic landscape of non-smoker lung cancer patients reveals distinctive features compared to smokers. EGFR is the most common driver mutation, reported in 40–60% of patients depending on the study population.[19–22] In our study population, driver mutations could not be examined in all patients due to difficulties in accessing these tests at the beginning of the study period. Despite these challenges, EGFR was studied in 46 patients and was found to be mutated in 43%.

The study's limitations include its retrospective design and a comparatively small patient cohort. Additionally, other risk factors for lung cancer could not be identified, as this information might have been neglected during the initial patient history. Not comparing patients with smokers can be considered another limitation. A significant strength of our study was the examination of various clinical, histological, and molecular attributes in non-smoker patients diagnosed with NSCLC. The follow-up time was adequate for determining PFS and OS rates. A significant finding for clinicians is that targetable mutations are prevalent in this group of patients, contributing to prolonged survival.

Conclusion

Approximately one-quarter of patients with NSCLC are non-smokers, with the majority being women diagnosed with adenocarcinoma. Patients are frequently diagnosed following the onset of symptoms, typically at an advanced or locally advanced stage. Stage IV disease at diagnosis and non-adenocarcinoma histology were independent predictors of worse prognosis. Since current screening studies have primarily targeted the smoking population, there is a pressing need for research to identify additional risk factors, especially for the inclusion of non-smokers in screening programs.

Ethics Committee Approval
The study was approved by the Hacettepe University of Health Sciences Research Ethics Committee (No: 2023/01-11, Date: 05/09/2023).

Authorship Contributions
Concept – R.I., D.K.; Design – D.K.; Supervision – S.S., S.K; Funding – U.I., F.S.A.; Materials – U.I.; Data collection &/or processing – U.I., R.I.; Analysis and/or interpretation – R.I.; Literature search – R.I.; Writing – U.I., R.I.; Critical review – D.K.

Conflicts of Interest
There are no conflicts of interest.

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