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Prognostic Factors and Survival Data of Stage I Lung Cancer: A Single-Center Experience

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ABSTRACT

Objective: Even in stage I lung cancer, the heightened risk of recurrence may lead to diminished survival rates. Only a few reports on prognostic factors have been published for stage I disease using the most recent staging system. This study was designed to identify predictive factors of recurrence and survival in early-stage lung cancer (LC) staged according to the eighth edition of the Tumor, Node, Metastasis (TNM) classification.

Materials and Methods: The clinicopathological characteristics, treatment, and follow-up data of 100 stage I patients monitored between 2013 and 2023 were retrospectively reviewed. The association between clinicopathological factors and survival was analyzed to identify prognostic factors.

Results: The median age was 61 years (range, 35–76). All patients had a histologic diagnosis of non-small cell lung cancer, with 62% being adenocarcinoma. During a median follow-up of 40.3 months (range, 1–183.5), 20 patients experienced recurrence and 16 died. The two-year and five-year disease-free survival (DFS) rates were 81% and 73%, respectively, while overall survival (OS) rates for the same periods were 86% and 77%. Multivariate analysis revealed that a smoking history greater than 40 pack-years (p=0.021) and perineural invasion (PNI) (p=0.049) were predictors of recurrence, while the presence of lymphovascular invasion (LVI) was significantly associated with OS (p=0.019).

Conclusion: Smoking significantly increases the risk of LC development and recurrence, making it crucial to promote smoking cessation. Patients with positive LVI or PNI in early-stage LC should be monitored more closely, although further research is warranted.

Keywords: Lung cancer, lymphovascular invasion, perineural invasion, smoking, stage I.

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INTRODUCTION

With more than 2 million new diagnoses and an estimated 1.8 million deaths by 2020, lung cancer (LC) remains a global health problem.[1] Its incidence has declined as a result of effective anti-smoking policies implemented in recent decades.[2] In addition, screening programs for individuals at risk have increased detection rates at earlier stages.[3] However, survival from LC has improved only slightly, and when all stages are taken into account, the overall five-year prognosis is below 25%.[4,5]

The majority of diagnosed cases (approximately 85%) are non-small cell lung cancer (NSCLC).[6] Early diagnosis with surgical resection is crucial for improving survival rates, as the clinical stage is considered the strongest prognostic indicator in NSCLC.[6–8] However, over time, defining early-stage disease has become more challenging. Goldstraw et al.[7] reclassified stage I LC into four subgroups (IA1, IA2, IA3, and IB) and reported notable differences in five-year survival rates: 92%, 83%, 77%, and 68% for stages IA1, IA2, IA3, and IB, respectively. This substantial survival difference within early-stage disease suggests that additional clinicopathological factors should be considered in this node-negative cohort. To guide appropriate disease monitoring and inform future treatment strategies, identifying prognostic factors in early-stage NSCLC is crucial.

Numerous studies in the literature have discussed prognostic factors for stage I disease, referencing earlier NSCLC Tumor-Node-Metastasis (TNM) staging editions.[8] Only a few studies have been published on prognostic factors and survival data for stage I disease staged according to the most recent eighth edition of the TNM system. In this study, we examined clinicopathological features, follow-up data, and survival outcomes in early-stage NSCLC patients to identify factors predictive of recurrence and associated with survival.

KEY MESSAGES

- Despite early diagnosis, lung cancer has a high rate of recurrence that significantly impacts survival outcomes.
- Smoking is not only a leading cause of lung cancer but is also associated with an increased risk of disease recurrence and mortality.
- Further studies are needed to support the potential predictive and prognostic role of factors such as lymphovascular invasion and perineural invasion, which could be evaluated through histopathological evaluation.

MATERIALS AND METHODS

Study Design and Patient Selection

This was a retrospective, single-institution cohort study. Medical records of histopathologically confirmed LC patients registered at the Medical Oncology Department of SBU Antalya Training and Research Hospital between June 2013 and June 2023 were evaluated. The study was approved by the Ethics Committee of SBU Antalya Training and Research Hospital on 08/06/2023 under approval number 8/19. Informed consent was waived with the awareness of the ethics committee, given the retrospective design. All procedures were conducted in accordance with the Declaration of Helsinki.

Patients were excluded if they did not have a diagnosis of invasive LC, had stage II-IV disease according to the eighth edition of the TNM staging system, had insufficient archival records, or were lost to follow-up. Patient demographics (age, gender, smoking history, and comorbidities), symptoms and performance status (PS) at diagnosis (defined by the Eastern Cooperative Oncology Group), histopathological features, treatment data, and follow-up information were retrieved from medical archive records and the hospital information system. Smoking history was assessed in pack-years, defined as smoking 20 cigarettes daily for one year. Patients who had not been staged using the eighth edition of the TNM system were restaged based on pathology records. Disease-free survival (DFS) was calculated from the time of diagnosis to the first loco-regional or distant recurrence, death from LC, or the last date the patient was seen free of recurrence. Overall survival (OS) was defined as the interval from diagnosis to death from LC or to the last follow-up date for survivors.

Patient Follow-up

All patients were monitored every three to six months for the first two years, then every six to twelve months through the fifth year, and annually thereafter. Follow-up examinations included a physical assessment, laboratory analyses, and chest and abdominal imaging (with computed tomography [CT]) at intervals determined by international guidelines. Patients with symptoms suggestive of local recurrence and/or metastasis underwent further evaluation, including CT scans of the neck, thorax, and abdominal cavity; brain imaging; positron emission tomography/computed tomography (PET/CT) scanning; and bone imaging.

Statistical Analysis

Histograms and the Kolmogorov-Smirnov test were used to assess data normality. For descriptive statistics, the median (interquartile range [IQR] or range) was reported for continuous variables, and numbers with percentages were reported for categorical data. Age and smoking history were grouped according to their median values. The Kaplan-Meier method was used to estimate survival curves, with significance assessed using the log-rank test. Associations between clinicopathological factors and survival were analyzed using multivariate Cox regression, including variables with p-values <0.20 in univariate analysis. Statistical analyses were conducted using SPSS 26.0 (IBM Corp., NY, USA), and figures were generated with GraphPad Prism 6.0 (San Diego, CA, USA). All p-values were two-tailed, with values <0.05 considered statistically significant. Because of the smaller number of stage I patients compared to those diagnosed at other stages, along with the single-center nature of the study, the entire patient

Table 1. Clinical characteristics of patients (n=100)

Characteristics	
Median age at diagnosis (years) (min–max, IQR)	61 (35–76, 13)
Gender, n (%)	
Female	20 (20.0)
Male	80 (80.0)
Smoking (pack-years) (min–max, IQR)	40 (0–150, 30)
Comorbidity, n (%)	
Present	44 (44.0)
Absent	56 (56.0)
Symptom at diagnosis, n (%)	
Asymptomatic or incidental	61 (61.0)
Symptomatic	39 (39.0)
ECOG PS, n (%)	
0	52 (52.0)
1–2	48 (48.0)
Primary tumor site, n (%)	
Right lung	57 (57.0)
Left lung	43 (43.0)

Min: Minimum; Max: Maximum; IQR: Interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status.

Table 2. Pathologic characteristics of patients (n=100)

Characteristics	
Histologic type, n (%)	
Adenocarcinoma	62 (62.0)
Squamous	31 (31.0)
Other	7 (7.0)
Median tumor diameter (cm) (IQR)	2.25 (1.5)
Stage (AJCC TNM 8th edition), n (%)	
IA1	12 (12.0)
IA2	25 (25.0)
IA3	33 (33.0)
IB	30 (30.0)
Grade, n (%)	
Well differentiated	16 (16.0)
Moderately differentiated	32 (32.0)
Poorly differentiated	25 (25.0)
Unknown	27 (27.0)
Lymphovascular invasion, n (%)	
Present	29 (29.0)
Absent	57 (57.0)
Unknown	14 (14.0)
Perineural invasion, n (%)	
Present	16 (16.0)
Absent	68 (68.0)
Unknown	16 (16.0)
Visceral pleural involvement, n (%)	
Present	14 (14.0)
Absent	86 (86.0)

IQR: Interquartile range; AJCC: American Joint Committee on Cancer; TNM: Tumor node metastasis.

population for which archival and follow-up information was available was included. Consequently, no sample size calculation was performed.

RESULTS

Baseline Characteristics

This study included 100 patients diagnosed with stage I LC. Table 1 summarizes the clinical characteristics of the patients. The median age was 61 years (IQR: 13), and 80% were male. The median smoking history was 40 pack-years (IQR: 30). At the time of diagnosis, most patients were asymptomatic or diagnosed incidentally. Among symptomatic patients, cough was the most common presenting symptom.

Baseline histopathological characteristics are shown in Table 2. All enrolled patients had NSCLC histology, with adenocarcinoma being the predominant histologic subtype (62%). Seven patients (7%) did not present with adenocarcinoma or squamous cell histology; these included one patient with pleomorphic, two with large cell, and four with adenosquamous histology.

Treatment and Follow-up Data

Anatomical resection, either lobectomy or pneumonectomy, was performed in most cases (78%). Two patients with histopathologically proven NSCLC, without radiological evidence of mediastinal lymph node invasion or distant metastasis, were not operated on because they were medically unfit for surgery. These two patients received definitive radiotherapy. Thirteen patients at high risk of recurrence (tumor size >4 cm, non-anatomic resection, visceral pleural involvement, high-grade tumors, or large cell histology) received four cycles of adjuvant cisplatin-based chemotherapy.

During the median follow-up of 40.3 months, disease recurrence occurred in 20 patients (20%), including nine cases with distant metastases (contralateral lung, liver, bone, or brain). The median DFS was 101.2 months, with two- and five-year DFS rates of 81% and 73%, respectively. There were 16 deaths during the follow-up period. The two- and five-year OS rates were 86% and 77%, respectively. Notably, the median OS had not yet been reached.

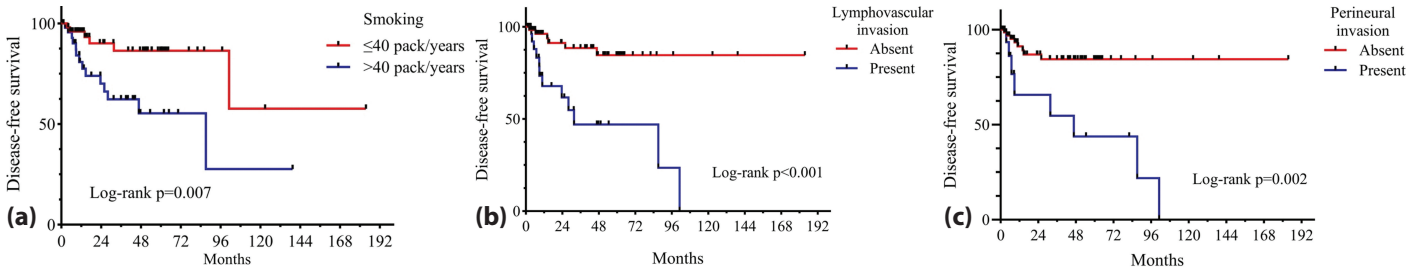

Figure 1. Kaplan-Meier curves of disease-free survival by **(a)** smoking status, **(b)** lymphovascular invasion, and **(c)** perineural invasion.

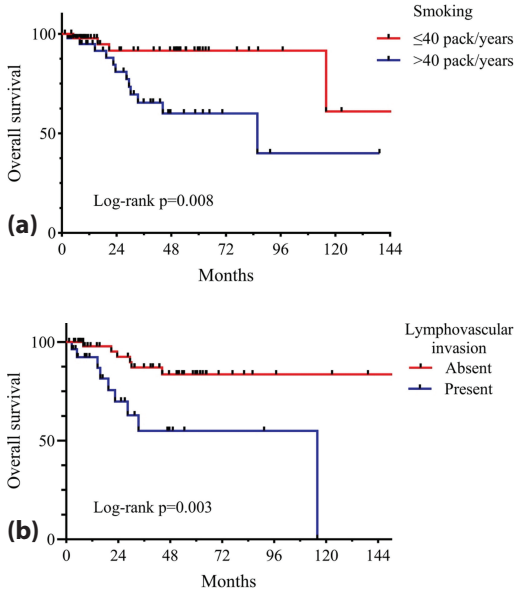

Figure 2. Kaplan-Meier curves of overall survival by **(a)** smoking status and **(b)** lymphovascular invasion.

Analyses of Prognostic Factors

Kaplan-Meier analysis showed significant differences in DFS according to smoking history >40 pack-years (p=0.007), positive lymphovascular invasion (LVI) (p<0.001), and positive perineural invasion (PNI) (p=0.002) (Fig. 1). For OS, Kaplan-Meier analysis demonstrated significant differences based on smoking history >40 pack-years (p=0.008) and positive LVI (p=0.003) (Fig. 2).

On univariate Cox regression analysis, smoking history of 40 pack-years (p=0.012), positive LVI (p=0.001), and PNI (p=0.001) were associated with DFS. Multivariate Cox regression analysis showed that smoking history >40 pack-years (p=0.021) and PNI (p=0.049) were significant prognostic factors for DFS (Table 3). In terms of OS, univariate Cox regression analysis showed that a smoking history of more than 40 pack-years (p=0.015), positive LVI (p=0.006), and squamous histology (p=0.041) were associated with OS. Multivariate regression analysis revealed that positive LVI (p=0.019) was the only significant prognostic factor for OS (Table 4).

DISCUSSION

The focus of our study was to explore potential prognostic indicators related to survival and recurrence in early-stage NSCLC, staged according to the eighth edition of the TNM classification. We found that a smoking history greater than 40 pack-years and PNI were associated with recurrence, while only LVI was a significant factor for poor OS in stage I LC.

All patients in the present study had stage I NSCLC, and male gender was more common, consistent with current literature.[9,10] Compared with symptomatic patients, the proportion of asymptomatic or incidentally diagnosed patients was much higher. Although LC screening has not yet been implemented in our country, the development and widespread use of imaging modalities, as well as the increase in thoracic imaging during the Coronavirus Disease 2019 (COVID-19) outbreak, may have contributed to this rise in asymptomatic or incidental diagnoses.

The primary cause of poor survival in LC is recurrence.[11,12] Recurrence rates in early-stage NSCLC are still high despite complete resection, with most loco-regional and distant recurrences occurring within the first two years.[13] Consistent with previous reports,[8,14,15] we observed a 20% recurrence rate, 55% of which was loco-regional. In early-stage LC, recurrence and survival have been associated with numerous clinicopathological factors, including age, smoking history, tumor size, stage, poor differentiation, LVI, pleural invasion, histologic type, and extent of resection.[8,12] However, our study did not identify any correlation between recurrence or survival and factors such as age, gender, PS, histologic type, grade, pleural invasion, or extent of resection. One potential factor contributing to the absence of statistical significance observed in the present study may be the relatively limited sample size.

Table 3. Results of Cox regression analysis for disease-free survival

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age group (years)						
≤61	Ref.					
>61	1.17	0.48–2.83	0.720			
Gender						
Female	Ref.			Ref.		
Male	4.73	0.63–35.4	**0.130**	2.74	0.34–21.9	0.340
Smoking (pack-years)						
≤40	Ref.			Ref.		
>40	3.45	1.31–9	**0.012**	3.45	1.20–9.87	**0.021**
Comorbidity						
Absent	Ref.					
Present	1.35	0.53–3.39	0.521			
ECOG PS						
0	Ref.					
1-2	1.49	0.6–3.68	0.378			
Histologic type						
Adenocarcinoma	Ref.					
Squamous	1.71	0.7–4.16	0.238			
Stage (AJCC TNM 8th edition)						
IA1	Ref.					
IA2	1.53	0.3–7.62	0.603			
IA3	1.07	0.2–5.66	0.929			
IB	1.46	0.29–7.28	0.639			
Grade						
Well differentiated	Ref.					
Moderately differentiated	6.47	0.01–1.30	0.899			
Poorly differentiated	9.50	0.01–1.91	0.896			
Lymphovascular invasion						
Absent	Ref.			Ref.		
Present	5.72	2.13–15.3	**0.001**	3.01	0.90–10	0.072
Perineural invasion						
Absent	Ref.			Ref.		
Present	5.23	1.94–14.1	**0.001**	2.70	1.04–9.12	**0.049**
Visceral pleural involvement						
Absent	Ref.					
Present	1.23	0.35–4.27	0.738			
Extent of resection						
Lobectomy/pneumonectomy	Ref.					
Segmentectomy/wedge resection	0.96	0.27–3.32	0.950			
None	3.24	0.42–24.8	0.257			

HR: Hazard ratio; CI: Confidence interval; Ref: Reference; ECOG PS: Eastern Cooperative Oncology Group performance status; AJCC: American Joint Committee on Cancer; TNM: Tumor node metastasis. Variables with p<0.2 in univariate analyses were included in multivariate analyses. Bold P values indicate significance.

Table 4. Results of Cox regression analysis for overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age group (years)						
≤61	Ref.					
>61	1.11	0.41–2.99	0.835			
Gender						
Female	Ref.					
Male	1.62	0.36–7.18	0.520			
Smoking (pack-years)						
≤40	Ref.			Ref.		
>40	4.14	1.32–12.9	**0.015**	3.46	0.95–12.5	0.059
Comorbidity						
Absent	Ref.					
Present	1.03	0.38–2.77	0.953			
ECOG PS						
0	Ref.					
1-2	1.59	0.57–4.41	0.373			
Histologic type						
Adenocarcinoma	Ref.			Ref.		
Squamous	2.83	1.04–7.68	**0.041**	1.15	0.35–3.79	0.813
Stage (AJCC TNM 8th edition)						
IA1	Ref.					
IA2	0.93	0.17–5.1	0.936			
IA3	1.35	0.26–6.84	0.716			
IB	0.76	0.13–4.32	0.766			
Grade						
Well differentiated	Ref.					
Moderately differentiated	6.31	0.01–4.24	0.903			
Poorly differentiated	6.62	0.01–4.45	0.902			
Lymphovascular invasion						
Absent	Ref.			Ref.		
Present	4.24	1.5–11.99	**0.006**	3.14	1.76–12.9	**0.019**
Perineural invasion						
Absent	Ref.					
Present	2.91	0.94–8.96	**0.062**	1.34	0.32–5.54	0.687
Visceral pleural involvement						
Absent	Ref.					
Present	0.97	0.21–4.35	0.969			
Extent of resection						
Lobectomy/pneumonectomy	Ref.					
Segmentectomy/wedge resection	1.27	0.35–4.58	0.708			
None	4.27	0.54–33.5	0.267			

HR: Hazard ratio; CI: Confidence interval; Ref: Reference; ECOG PS: Eastern Cooperative Oncology Group performance status; AJCC: American Joint Committee on Cancer; TNM: Tumor node metastasis. Variables with p<0.2 in univariate analyses were included in multivariate analyses. Bold P values indicate significance.

However, most studies with larger patient cohorts investigating these potential factors have included not only early-stage patients but also those with locally advanced or metastatic disease. Moreover, some used earlier TNM staging systems.[16,17] The main difference between our study and the aforementioned ones is that only early-stage (stage I) patients staged according to the TNM 8th staging system were included in our study. This could provide another reason why such factors were not found to be statistically significant in the current study.

With respect to age, relevant studies examining the impact of advanced age on prognosis have included patients of very advanced age (75 or 80 years and older) in their analyses.[8,16] A similar observation can be made in the context of PS. In studies that identified a relationship between PS and survival in localized NSCLC, the inclusion of patients with PS 3 or 4 in the analysis may have revealed a statistical relationship.[16,18] The inclusion of patients with less favorable clinical characteristics, including advanced age and poor PS, in contrast to the patient cohort in our study, may have led to the identification of these factors as indicators of poor prognosis. Prior research has also shown a correlation between male sex and poorer survival rates.[8,19,20] However, it should be noted that these studies encompassed a heterogeneous patient population. The findings of two studies, conducted in two distinct geographical regions and focusing only on stage I patients, showed no association between sex and survival outcomes.[15,21] These findings are consistent with the results of our study.

Smoking not only increases the risk of LC but also has a detrimental effect on prognosis.[8,22] Compared to smokers, non-smokers with stage I NSCLC have been shown to have significantly better survival.[22,23] Some studies have stratified patients into never-smokers and ever-smokers, while others have applied different pack-year thresholds.[22–24] When patients were grouped by the median value, we observed that smoking more than 40 pack-years was an important predictor of recurrence and survival. Encouraging smoking cessation is essential, as smoking remains a substantial risk factor not only for LC development but, more importantly, for its recurrence.

Lymphovascular invasion refers to malignant cells found within the lumens of arterial, venous, or lymphatic vessels, as identified by histologic staining with hematoxylin and eosin. LVI is considered an unfavorable prognostic factor for both recurrence and survival in early-stage LC.[25–27] Our research showed that LVI was a significant predictor of OS in both univariate and multivariate analyses. However, LVI did not demonstrate the same level of predictive power for DFS. PNI refers to the dissemination of malignant cells into and along nerves and represents an alternative route of metastasis in addition to vascular or lymphatic invasion.[28] The prognostic role of PNI in LC is poorly studied, and the results of these studies are conflicting.[29] Moreover, the vast majority of these studies enrolled patients staged by earlier TNM staging systems and included patients beyond stage I. Our multivariate analyses indicate that the presence of PNI is indicative of recurrence, though not of OS, in stage I. Given the risk of recurrence or death observed in our study, both LVI and PNI should be documented in the postoperative pathology report. Patients with these adverse factors should be considered for close follow-up and may be candidates for treatment intensification. The prognostic role of PNI in early-stage LC remains an area for further investigation.

Visceral pleural invasion (VPI) refers to the infiltration of a tumor into the elastic layer of the visceral pleura or its direct extension to the surface of the visceral pleura.[30] Studies that identified a relationship with prognosis have explored the depth and localization of tumor involvement across distinct layers of the visceral pleura, categorizing VPI into three grades: PL0, PL1, and PL2.[8,30] In our study, archival pathology reports that identified VPI lacked clear information regarding the depth of involvement. Consequently, patients were divided into two groups based on the presence of VPI, which hindered the establishment of a relationship between the extent of pleural invasion and recurrence or survival. This limitation emphasizes the need for more detailed pathology reporting to better assess the implications of VPI on patient outcomes.

Lung cancer survival varies widely between stages and also within the same stage. As mentioned above, stage I has four distinct substages, and survival decreases from IA1 to IB.[7] In the present study, there was no statistical effect of stage on DFS and OS in either the univariate or multivariate analyses. This might be explained by the small number of enrolled patients and the relatively short follow-up duration.

This study, however, is subject to several limitations. First, it is a single-institution retrospective study. Second, there is an inevitable introduction of bias in the surgical approach because some patients were operated on at external centers. Third, smoking history was documented solely upon admission, with no data on smoking status during the postoperative and follow-up periods, which could potentially affect the course of the disease. Despite these limitations, restaging all patients according to the eighth edition of the TNM classification is a significant strength of our study, as it addresses a gap in the literature.

CONCLUSION

Smoking significantly increases the risk of LC development and recurrence, making it crucial to promote smoking cessation. Our study found that both LVI and PNI were correlated with an increased probability of recurrence or death, suggesting their potential inclusion as parameters in the standard pathology report. Closer monitoring and adjuvant treatment administration for patients with positive LVI or PNI in early-stage LC may be considered, but further multicenter and prospective studies are needed to draw firm conclusions.

Ethics Committee Approval: The SBU Antalya Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 08.06.2023, number: 8/19).

Informed Consent: Informed consent was waived with the awareness of the ethics committee, given the retrospective design.

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