Turkish Journal of Thoracic and Cardiovascular Surgery 2022;30(4):602-610
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2022.22154

Original Article / *Özgün Makale*

The effects of the degree of pleural invasion on survival in patients with non-small cell lung cancer undergoing surgical resection

Cerrahi rezeksiyon uygulanan küçük hücreli dışı akciğer kanserli hastalarda plevral invazyon derecesinin sağkalıma olan etkisi

Volkan Yılmaz[1], Burçin Çelik[1], Yurdanur Süllü[2], Ayşen Taslak Şengül[1], Yasemin Bilgin Büyükkarabacak[1], Selçuk Gürz[1], Mehmet Gökhan Pirzirenli[1], Ahmet Başoğlu[1]

[1]Department of Thoracic Surgery, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye
[2]Department of Pathology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Türkiye

ABSTRACT

Background: The aim of this study was to evaluate the degree and size of pleural invasion in non-small cell lung cancer patients and to compare its relationship with the survival time.

Methods: Between January 2008 and June 2019, a total of 164 patients (143 males, 21 females; median age: 64.65 years; range 39 to 92 years) who underwent surgical resection with a diagnosis of non-small cell lung cancer and who were found to have pleural invasion histopathologically were retrospectively analyzed. The control group consisted of 105 patients (95 males, 10 females; median age: 61.7 years; range, 32 to 82 years) who underwent surgical resection but who were not found to have pleural invasion histopathologically during the same time period. Survival time was compared between the groups.

Results: Median survival was 52 months in the group with pleural invasion, while it was 70.6 months in the group without pleural invasion. In the pleural invasion group, the patients who underwent sublobar resection had shorter survival. The degree of pleural invasion (p=0.028), advanced age (p=0.022), and lymph node involvement (p=0.011) were found to be poor prognostic factors for survival.

Conclusion: In non-small cell lung cancer patients, the increase in the degree and size of pleural invasion is negatively correlated with the survival time and this is thought to be associated with advanced disease stage.

Keywords: Invasion, non-small cell lung carcinoma, pleura, survival.

ÖZ

Amaç: Bu çalışmada, küçük hücreli dışı akciğer kanserli hastalarda plevral invazyon derecesi ve boyutu değerlendirildi ve sağkalım süresi ile olan ilişkisi karşılaştırıldı.

Çalışma planı: Ocak 2008 - Haziran 2019 tarihleri arasında küçük hücreli dışı akciğer kanseri tanısı ile cerrahi rezeksiyon uygulanan ve histopatolojik olarak plevra invazyonu tespit edilen toplam 164 hasta (143 erkek, 21 kadın; ort. yaş: 64.65 yıl; dağılım, 39-92 yıl) retrospektif olarak incelendi. Kontrol grubu aynı dönemde cerrahi rezeksiyon uygulanan ancak histopatolojik olarak plevra invazyonu tespit edilmeyen 105 hastadan (95 erkek, 10 kadın, ort. yaş: 61.7 yıl; dağılım, 32-82 yıl) oluşuyordu. Gruplar arasında sağkalım süreleri karşılaştırıldı.

Bulgular: Plevra invazyonu olan grupta medyan sağkalım 52 ay iken, plevra invazyonu olmayan grupta 70.6 ay idi. Plevra invazyonlu grupta, sublober rezeksiyon uygulananların sağkalım süresi daha kısa idi. Plevral invazyon derecesi (p=0.028), ileri yaş (p=0.022) ve lenf nodu tutulumu (p=0.011) sağkalımın kötü prognostik faktörleri olarak tespit edildi.

Sonuç: Küçük hücreli dışı akciğer kanserli hastalarda plevral invazyonun derece ve boyut artışı ile sağkalım süresi negatif ilişkili olup, bu durumun ileri evre hastalık ile ilişkili olduğu düşünülmektedir.

Anahtar sözcükler: İnvazyon, küçük hücreli dışı akciğer karsinomu, plevra, sağkalım.

Received: May 17, 2021 *Accepted*: August 31, 2021 *Published online*: October 31, 2022

Correspondence: Volkan Yılmaz, MD. Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, 55280 Atakum, Samsun, Türkiye.
Tel: +90 507 - 960 58 76 e-mail: drvolkan71@gmail.com

Cite this article as:
Yılmaz V, Çelik B, Süllü Y, Taslak Şengül A, Bilgin Büyükkarabacak Y, Gürz S, et al. The effects of the degree of pleural invasion on survival in patients with non-small cell lung cancer undergoing surgical resection. Turk Gogus Kalp Dama 2022;30(4):602-610

©2022 All right reserved by the Turkish Society of Cardiovascular Surgery.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes (http://creativecommons.org/licenses/by-nc/4.0/).

In patients diagnosed with non-small cell lung cancer (NSCLC), identifying prognostic factors is critical to improve survival, understand tumor biology, and predict the outcome. The main determinant factors of survival are tumor size, lymph node metastasis, distant metastasis, and a complete resection in which the tumor is completely removed with regional and mediastinal lymph nodes.[1]

In 1970s, Brewer[2] found that prognosis in subpleural tumors was much worse than those in lung parenchyma. Shimizu et al.[3] reported that tumors which invaded elastic layer of visceral pleura showed worse prognosis and these tumors had strong growth and aggressive invasion characteristics.

In NSCLC, pleural invasion (PI) is considered as a significant negative prognostic factor and the degree of invasion should be correctly evaluated histopathologically. The degree of PI is classified histopathologically as PI0, PI1, PI2 and PI3.

In the present study, we aimed to evaluate the degree and size of PI in NSCLC and to compare its relationship with histological subtype, lymph node metastasis, surgical resection type, and survival times.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Ondokuz Mayıs University, Faculty of Medicine, Department of Thoracic Surgery between January 2008 and June 2019. A total of 164 patients (95 males, 10 females; median age: 61.7 years; range, 32 to 82 years) who underwent surgical resection with a diagnosis of NSCLC and who were found to have PI histopathologically were included in the study. A total of 105 patients (95 males, 10 females; median age: 61.7 years; range, 32 to 82 years) who underwent surgical resection but who were not found to have PI histopathologically during the same time period were included as control group to compare survival through random selection from clinical archive.

Positron emission tomography/computed tomography (PET/CT), brain magnetic resonance imaging (MRI), bronchoscopic biopsy, and transthoracic needle aspiration biopsy were held as a preoperative assessment. Routine blood, laboratory tests, and pulmonary function tests (PFTs) were performed for surgery preparation. For selected patients, ventilation/perfusion scintigraphy was taken. Surgical treatment was applied after routine anesthesia examination. Patients with NSCLC pre-diagnosis and pathology in the postoperative process are diagnosed with primary NSCLC were included. Patients with secondary tumors were not included in the study.

All patients included in the study underwent lung resection and mediastinal lymph node dissection. Pathology preparations of the patients were taken from Ondokuz Mayıs University Faculty of Medicine, Faculty of Medicine, Department of Pathology archive and reassessed. Pathology results were classified in terms of their histological types according to the current World Health Organization (WHO) classification and restaged according to 8th Tumor, Node, Metastasis (TNM) staging.[4]

Pathology preparations of the patients who were found to have PI were evaluated in terms of the degree and size of PI. Hematoxylin and eosin (H&E)-stained specimens were evaluated under a light microscope by a single pathologist (Nikon, Eclipse, Ni-U; Nikon Corporation, Tokyo, Japan). Pleural invasion degree was grouped as PI1, PI2, and PI3. The size of PI was calculated by measuring the area of the tumor invaded pleura in millimeters under the microscope and grouped as 1-10 mm, 11-19 mm, and 20 mm and above (Figure 1).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Comparison according to the degree and size of PI was made using the Pearson chi-square test.

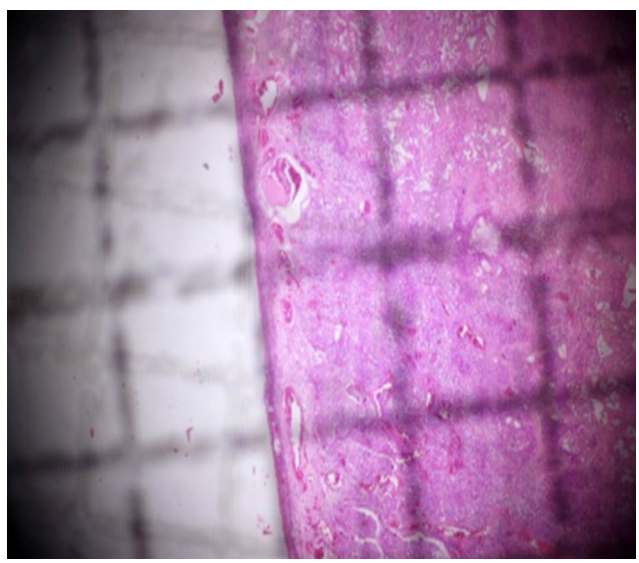

Figure 1. Microscopic measurement of pleural invasion size with millimetric ruler (×40).

Independent group comparisons for more than two were tested using the Kruskal-Wallis H test. The significance of survival times in terms of groups was tested using the Kaplan-Meier test and the statistical comparisons between the curves were conducted by using the log-rank test. The prognostic factors influencing survival time were determined using the Cox proportional hazard model. In parameters which were found to have a significant difference, the Bonferroni-corrected Mann-Whitney U test was conducted to find out the groups which caused the difference and corrected significance value was taken as $p<0.017$ ($0.05/3 = 0.017$). A p value of <0.05 was considered statistically significant.

RESULTS

In the group with PI, there were 104 patients diagnosed with adenocarcinoma (ADC) and 60 patients with squamous cell carcinoma (SCC), while there were 46 patients diagnosed with ADC and 59 patients diagnosed with SCC in the group with no PI. Demographic data of the patients included in the study are shown in (Table 1). Lobectomy was the most common procedure in the patients in both groups (Table 2).

The median follow-up was 59.1 (range, 6 to 144) months. The mean survival was found as 52±10.5 months in the group with PI, while the mean survival

Table 1. Demographic data of the patients

			Pleural invasion				No pleural invasion			
	Total		ADC		SCC		ADC		SCC	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	238	88.4	85	81.8	58	96.7	37	80.4	58	98.3
Female	31	11.6	19	18.2	2	3.3	9	19.6	1	1.7
Weight (kg)	226	73.9	90	75.6	55	72	37	74.7	44	72.3
Height (cm)	225	166.1	89	165.9	55	167.1	37	165	44	166.7
BMI (kg/m^2)	225	26.6	89	27.6	55	25.7	37	27.5	44	25.6
Smoking (box/year)	198	40.1	64	46.7	52	47	30	37.4	37	37.1
RFT										
FEV1 (L)	222	2.62	88	2.64	52	2.56	38	2.73	44	2.55
FVC (L)	222	3.37	88	3.33	52	3.33	38	3.49	44	3.36
FEV1/FVC (%)	222	77.2	88	79.7	52	75.8	38	78	44	75.4
Stage										
1A	32	11.8	0	0	0	0	17	36.9	15	25.4
1B	69	25.6	42	40.38	12	20	3	6.5	12	20.3
2A	14	5.2	4	3.8	3	5	2	1.9	5	8.4
2B	80	29.7	31	29.8	21	35	12	26	16	27.1
3A	63	23.4	19	18.2	22	36.6	11	23.9	11	18.6
3B	5	1.8	4	3.8	0	0	1	2.1	0	0
4A-B	6	2.2	4	3.8	2	3.3	0	0	0	0
ASA										
1	72	30.3	33	31.7	21	35	13	36.1	15	31.9
2	86	36.2	34	32.6	13	21.6	18	50	21	44.6
3	54	22.7	28	26.9	11	18.3	5	13.9	10	21.4
4	25	10.5	9	8.6	15	25	0	0	1	2.1

ADC: Adenocarcinoma; SCC: Squamous cell carcinoma; BMI: Body mass index; RFT: Respiratory function test; FEV1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; ASA: American Society of Anesthesiologists.

Table 2. Pleural invasion distribution by the resection type performed

	Pleural invasion		No pleural invasion	
Resection type	n	%	n	%
Wedge resection	12	7.3	9	8.5
Segmentectomy	6	3.7	3	2.8
Lobectomy	115	70.1	74	70.4
Bilobectomy	15	9.1	9	8.5
Pneumonectomy	16	9.8	10	9.5
Total	164	100	105	100

was calculated as 70.6±5 months in the group with no PI. There was a statistically significant relationship between the two groups in terms of survival (p=0.013 and p<0.05) (Figure 2). The patients' survival according to the degree of PI (PI1, PI2, PI3) and their comparison with PI0 patients are given in Table 3 and Figure 2. Patients with PI0 were found to have higher survival rates, indicating a statistically significant difference (p=0.013).

Pre- and postoperative treatments of patients with PI are summarized in Table 4. In cases diagnosed with ADC histopathologically, the mean survival was calculated as 63±7.6 months in the group with PI and as 66.5±7.4 months in the group with no PI. This difference was not statistically significant (p=0.488). In patients diagnosed with SCC histopathologically, mean survival was calculated as 45.2±5.6 months in the group with PI and as 72.8±5.9 months in the group with no PI. This difference was statistically significant (p=0.002). When the degree of PI was evaluated according to histopathological types, median survival was calculated as 96 months in PI1, 64 months in PI2, and 37 months in PI3 in ADC cases with PI and as 25 months in PI1, 23 months in PI2, and 14 months in PI3 in SCC patients (Figure 3 and Figure 4).

According to the survival analysis in terms of PI size, survival time became shorter, as the PI size increased. However, no statistically significant

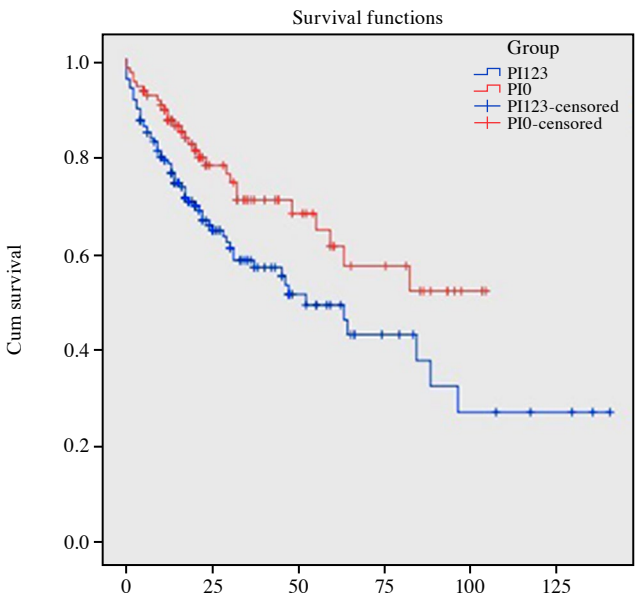

Figure 2. Survival chart in terms of the degree of pleural invasion.
PI: Pleural invasion.

Table 3. Comparison of survival in terms of pleural invasion

		Survival		
	n	n	%	*p*
Pleural invasion (PI1-PI2-PI3)	164	97	59.1	0.013
No pleural invasion (PI0)	105	76	72.4	
Total	269	173	64.3	

PI: Pleural invasion.

Table 4. Preoperative and postoperative oncological treatments in pleural invasion group

	Preoperative		Postoperative	
Oncologic treatment	n	%	n	%
No	150	91.5	46	28.0
Chemoradiotherapy	7	4.3	27	16.5
Chemotherapy	5	3	85	51.8
Radiotherapy	2	1.2	6	3.7
Total	164	100	164	100

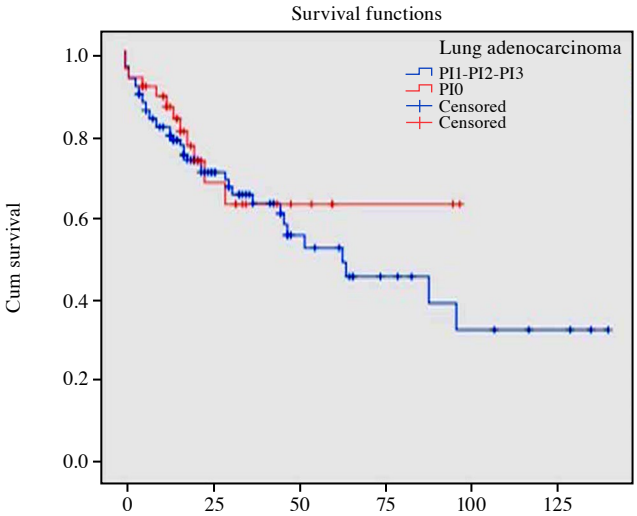

Figure 3. Survival chart of patient groups diagnosed with adenocarcinoma; red chart is PI0 in adenocarcinoma, blue chart is pleural invasion in adenocarcinoma.
PI: Pleural invasion.

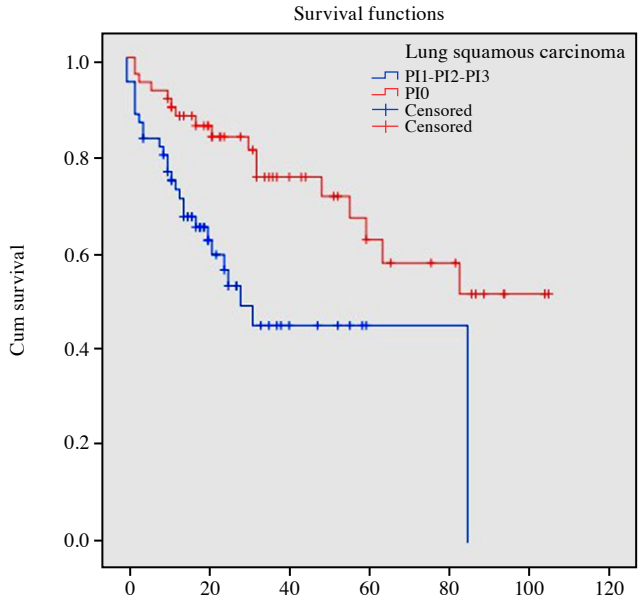

Figure 4. Survival chart of patient groups diagnosed with squamous carcinoma; red chart is PI0, blue chart is pleural invasion in squamous carcinoma.
PI: Pleural invasion.

relationship was found between the invasion sizes (p=0.842) (Table 5 and Figure 5).

In this study, a statistically significant relationship was found between type of surgical resection and survival in patients with PI. There was also a statistically significant difference between wedge resection and lobectomy (p=0.015 and p<0.05), and segmentectomy and pneumonectomy (p=0.033 and p<0.05) in terms of survival. In the patient group with PI, survival was found to be shorter in patients who underwent sublobar resection (Table 6 and Figure 6). No statistically significant relationship was found between type of surgical resection and survival in the group with no PI (Table 6).

In 36 (22%) of 164 patients with PI, lymph node metastasis was found. A statistically significant relationship was observed between the pathological diagnosis and lymph node metastasis (p=0.007 and p<0.05). In addition, SCC patients (30%) were found to have a higher lymph node metastasis rate compared to ADC patients (17.3%). Table 7 shows the relationship between the degree of PI and lymph node factor. No statistically significant relationship was found between the degree of invasion and lymph node metastasis (p=0.385 and p>0.05). However, in PI3 patients, lymph node metastasis was found to be significantly higher compared to the others (31.4%).

Table 5. Survival in terms of pleural invasion size

		Survival		Median survival (months)	
	n	n	%	n	*p*
Pleural invasion size (mm)					
1-10	63	39	61.9	63	0.842
11-19	63	37	58.7	52	
≥20	38	21	55.3	45	
Total	164	97	59.1	52	

The area tumour is invaded to pleura in millimeters under the microscope and grouped as 1-10 mm, 11-19 mm and 20 mm and above.

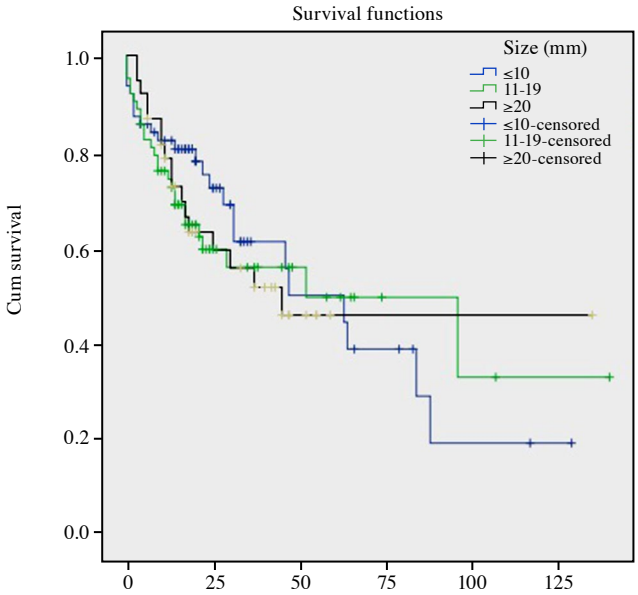

Figure 5. Pleural invasion size and survival chart.

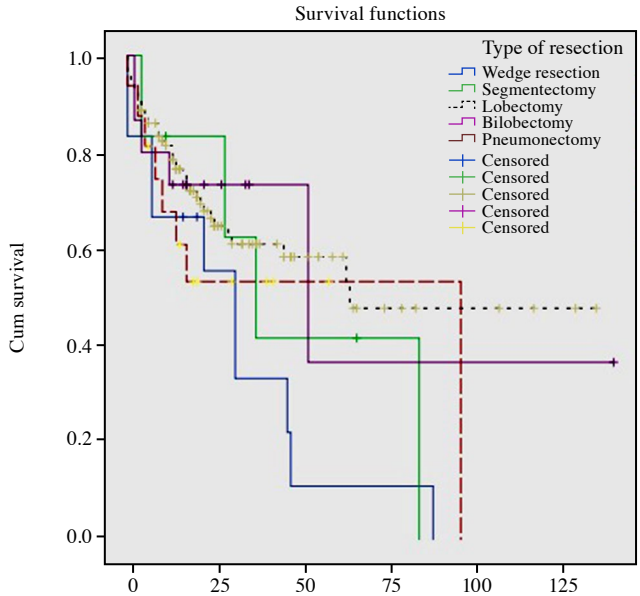

Figure 6. Type of resection and survival chart in patients with pleural invasion; blue chart is wedge resection, green chart is segmentectomy, black chart is lobectomy, purple chart is bilobectomy, red chart is pneumonectomy.

When the PI size and lymph node factor were compared, it was found that lymph node metastasis rate also increased, as the invasion size increased; there was a higher involvement rate particularly in N1 lymph nodes in the area close to the tumor and this was more prominent in cases diagnosed with SCC (Table 8).

In cases with PI, stage-survival relationship was statistically significant. When survival was evaluated among the factors of tumor stage, T factor and N factor were found to be statistically significant (Table 9).

DISCUSSION

The pleura covers the lung parenchyma and maintains intrapleural fluid balance. In addition, pleura is an oncologically important structure that should be well-known due to both its exposure to tumor metastasis and its role in distant organ spread. In the visceral pleura, there is a very rich lymphatic network in connective tissue under the mesothelial covering and this network connects to lung lymph circulation.[5] Lymphatic drainage of the pleura is critical for the management of intrathoracic malignancy. In their study, Miura et al.[6] showed mesothelial cells in two structures as microvilli and stoma and they reported that the passage of malignant cells was through the same mechanism through mesothelial cells and that distant organ spread could be explained this way.

Table 6. Survival in terms of resection types in patients with and without pleural invasion

	Pleural invasion			No pleural invasion		
		Survival (months)			Survival (months)	
Resection type	n	n	*p*	n	n	*p*
Wedge resection	12	31	0.127	9	30	0.411
Segmentectomy	6	37		3	15	
Lobectomy	115	64		74	72	
Bilobectomy	15	52		9	91	
Pneumonectomy	16	96		10	58	
Total	164	52		105	71	

Table 7. Relationship between degree of pleural invasion and lymph node metastasis

	Lymph node stage						
	N0		N1		N2		
	n	%	n	%	n	%	*p*
Degree of pleural invasion							
PI1	52	81.3	9	14.1	3	4.7	0.385
PI2	41	83.7	6	12.2	2	4.1	
PI3	35	68.6	13	25.5	3	5.9	
Total	128	78.0	28	17.1	8	4.9	

Table 8. Relationship between pleural invasion and lymph node metastasis

	Lymph node								
	N0		N1		N2		Total		
	n	%	n	%	n	%	n	%	*p*
Pleural invasion size (mm)									
1-10	52	82.5	7	11.1	4	6.3	63	100	0.287
11-19	48	76.2	14	22.2	1	1.6	63	100	
≥20	28	73.7	7	18.4	3	7.9	51	100	
Total	128	78.0	28	17.1	8	4.9	164	100	

Table 9. Tumor, Node, Metastasis and survival statistics

Factor	*p*	Survival effect
T	0.045	1.386
N	0.011	1.682
M	0.331	1.349

The cadaveric study conducted by Fourdrain et al.[7] is the first study to evaluate visceral pleura tract specifically and fully for lymphatic drainage of the lung. In this study, 21 cadavers were dissected and 2 mL of triphenylmethane blue dye solution was injected subpleurally to each lung segment. The lymphatic drainage of the visceral pleura was found to be segmental in 44.2% of the injections and intersegmental in 55.8%. The authors suggested that the presence of missing fissures or accessory fissures might affect lymphatic drainage in visceral pleura and that further researches should be conducted to evaluate the effect of lymphatic drainage of visceral pleura in lung cancer surgery, particularly in sublobar resections such as segmentectomy.

In another study, Jiang et al.[8] found that visceral pleural invasion (VPI) and tumor size together had a synergetic effect on survival in negative lymph node with NSCLC. The effect of VPI on survival increased with the size of the tumor. As the size of the tumor increases, the negative effect of VPI on survival also increased. In our study, when T stage was evaluated with the degree of PI, its effect on survival was found to be more prominent. The T factor ($p=0.045$ and $p<0.05$) and N factor ($p=0.011$ and $p<0.05$) were found to be statistically significant in terms of survival, and T factor was found to increase the mortality risk 1.38 times, while N factor was found to increase the mortality risk 1.68 times.

In a study investigating poor prognostic factors in cases with an SCC diagnosis, Zhao et al.[9] reported that, of 132 cases, 40% had PI and, in these cases, the five-year-survival was shorter compared to the

cases that did not have PI (30% *vs*. 76%). In our study, while the mean survival time was 28±4.9 months in PI1, PI2, PI3 groups in cases diagnosed with SCC, the mean survival time was 63±5.9 months in PI0 and this rate was found to be statistically different.

In a meta-analysis of 16 studies, Wang et al.[10] found that the overall survival rate was lower in PI1 or PI2 patients compared to PI0 patients and that PI2 patients showed a lower overall survival than PI1 patients. When the five-year survival rates of PI1 or PI2 patients were examined, they had lower rates than PI0 patients. Similarly, in our study, the survival time decreased, as the degree of invasion increased. A statistically significant relationship was found between PI0 and PI1-PI2-PI3, between PI1 and PI3 and between PI2 and PI3 in terms of survival. The five-year survival was higher in patients with PI0 tumor (60%) and PI1 tumor (45%), compared to the patients with PI3 tumor (36%). Sakakura et al.[11] also reported that PI0-PI1 tumor results were different from PI2 tumors. Likewise, Osaki et al.[12] reported that PI0 had a better prognostic value than PI1-PI2, regardless of the N state and tumor size.

To examine the effects of VPI on patients' prognosis in terms of tumor size, Tian et al.[13] classified 521 patients into four groups according to the tumor size (≤2, 2-3, 3-5, and 5-7 cm). The results showed that VPI did not have a significant effect on prognosis in patients with a tumor of ≤2 cm. The rate of patients with regional or distant metastases was significantly higher in those with VPI compared to those without VPI. In our study, survival was evaluated particularly in terms of the invasion size, since the invasion size would increase with the tumor size. Survival size was found to decrease, as PI size increased. The average survival was found to be 63 months in the group with a pleural size of 10 mm and below, while it was found to be 45 months in the group with a pleural size of 20 mm and above.

Lymphatic metastasis is an important prognostic factor in NSCLC. Patients with multi-station mediastinal lymph node metastasis (≥2 stations) were found to have a significantly worse prognosis compared to those with a single station mediastinal lymph node metastasis. Manac'h et al.[14] reported that tumor cells were more prone to disintegration throughout the lymphatic system, when the tumor invaded visceral pleura. Supporting these studies, they showed that the probability of mediastinal lymph node metastasis in patients with NSCLS who underwent lung resection was significantly higher in patients with VPI compared to those without VPI. In addition, they reported that these patients were more vulnerable to multi-station mediastinal lymph node metastasis.

Jiwangga et al.[15] reported that the most common forms of recurrence of VPI and Stage 1 lung ADC were pleural metastasis and bilateral lung metastasis. They, therefore, reported that patients with VPI and Stage 2B lung cancer should be followed carefully in terms of distant recurrence. In our study, lymph node metastasis rate increased, as the degree of PI increased and, consistent with the literature, a statistically significant relationship was found between metastatic lymph node number and survival ($p=0.003$ and $p<0.01$). Lymph node metastasis was found in 36 (22%) of 164 patients, and a statistically significant relationship was observed between pathological diagnosis and lymph node metastasis ($p=0.007$ and $p<0.01$). In SCC patients, the stage was more advanced, survival was shorter, and N1 stage was more prominent. As in Oyama et al.'s[16] study, we found that, as the degree of PI increased, survival time decreased and N stage increased.

The main limitation of this study is its single-center, retrospective design. In addition, evaluations were made on specimens obtained from the pathology clinic archive. Another limitation is the small sample size. Further multi-center, prospective studies in which specimens are macroscopically examined would provide more reliable conclusions with a better comparison.

In conclusion, the degree of PI was a negative prognostic factor alone or with the tumor size (T stage), lymph node involvement (N stage), and overall survival. The survival time of patients with a squamous cell carcinoma and PI was found to be shorter compared to those with an adenocarcinoma. We believe that, in non-small cell lung cancer patients with PI, anatomic resection should be performed and sublobar resection should be avoided as much as possible.

Ethics Committee Approval: The study protocol was approved by the Ondokuz Mayıs University Ethics Committee (date: 23.05.2019, no: 2019/423). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: V.Y., B.Ç., A.B., Y.S.; Design: V.Y., B.Ç., Y.S.; Control/supervision: V.Y.; Data collection and/or processing: V.Y., B.Ç., Y.S.; Analysis and/or interpretation: V.Y., B.Ç., A.B.; Literature review: V.Y., B.Ç.,

S.G.; Writing the article: V.Y., S.G., M.G.P.; Critical review: A.B.; References and fundings: B.Ç; Materials; V.Y., Y.B.K., Y.S., A.T.Ş.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Neri S, Menju T, Sowa T, Yutaka Y, Nakajima D, Hamaji M, et al. Prognostic impact of microscopic vessel invasion and visceral pleural invasion and their correlations with epithelial-mesenchymal transition, cancer stemness, and treatment failure in lung adenocarcinoma. Lung Cancer 2019;128:13-9.
2. Brewer LA. Patterns of survival in lung cancer. Chest 1977;71:644-50.
3. Shimizu K, Yoshida J, Nagai K, Nishimura M, Yokose T, Ishii G, et al. Visceral pleural invasion classification in non-small cell lung cancer: A proposal on the basis of outcome assessment. J Thorac Cardiovasc Surg 2004;127:1574-8.
4. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: Review of the changes and clinical implications. Quant Imaging Med Surg 2018;8:709-18.
5. Li J. Ultrastructural study on the pleural stomata in human. Funct Dev Morphol 1993;3:277-80.
6. Miura T, Shimada T, Tanaka K, Chujo M, Uchida Y. Lymphatic drainage of carbon particles injected into the pleural cavity of the monkey, as studied by video-assisted thoracoscopy and electron microscopy. J Thorac Cardiovasc Surg 2000;120:437-47.
7. Fourdrain A, Lafitte S, Iquille J, De Dominicis F, Havet E, Peltier J, et al. Lymphatic drainage of lung segments in the visceral pleura: A cadaveric study. Surg Radiol Anat 2018;40:15-9.
8. Jiang L, Liang W, Shen J, Chen X, Shi X, He J, et al. The impact of visceral pleural invasion in node-negative non-small cell lung cancer: A systematic review and meta-analysis. Chest 2015;148:903-11.
9. Zhao Y, Shen H, Qiu C, Zhang T, Hu P, Qu X, et al. Invasion types are associated with poor prognosis in lung squamous carcinoma patients. Medicine (Baltimore) 2015;94:e1634.
10. Wang T, Zhou C, Zhou Q. Extent of visceral pleural invasion affects prognosis of resected non-small cell lung cancer: A meta-analysis. Sci Rep 2017;7:1527.
11. Sakakura N, Mori S, Okuda K, Fukui T, Hatooka S, Shinoda M, et al. Subcategorization of lung cancer based on tumor size and degree of visceral pleural invasion. Ann Thorac Surg 2008;86:1084-90.
12. Osaki T, Nagashima A, Yoshimatsu T, Yamada S, Yasumoto K. Visceral pleural involvement in nonsmall cell lung cancer: Prognostic significance. Ann Thorac Surg 2004;77:1769-73.
13. Tian D, Pei Y, Zheng Q, Zhang J, Li S, Wang X, et al. Effect of visceral pleural invasion on the prognosis of patients with lymph node negative non-small cell lung cancer. Thorac Cancer 2017;8:97-105.
14. Manac'h D, Riquet M, Medioni J, Le Pimpec-Barthes F, Dujon A, Danel C. Visceral pleura invasion by non-small cell lung cancer: An underrated bad prognostic factor. Ann Thorac Surg 2001;71:1088-93.
15. Jiwangga D, Cho S, Kim K, Jheon S. Recurrence pattern of pathologic stage I lung adenocarcinoma with visceral pleural invasion. Ann Thorac Surg 2017;103:1126-31.
16. Oyama M, Miyagi Maeshima A, Tochigi N, Tsuta K, Kawachi R, Sakurai H, et al. Prognostic impact of pleural invasion in 1488 patients with surgically resected non-small cell lung carcinoma. Jpn J Clin Oncol 2013;43:540-6.