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ORIGINAL ARTICLE PULMONOLOGY

The relationship between the degree of visceral pleural invasion and survival in non-small cell lung cancer

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ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the relationship between the degree of visceral pleural invasion (VPI) and survival in patients operated for non-small cell lung cancer (NSCLC).

METHODS: Between 2013 and 2015, 202 patients who were diagnosed with NSCLC in our center and followed up in our clinic were retrospectively evaluated. To examine the preoperative and postoperative prognostic factors of the patients, postoperative pathology results, demographic data and data on recurrence status were obtained from our hospital database and patient files.

RESULTS: VPI Survival analysis was performed by dividing 3 groups: PL0, PL1 and PL2. Mean survival (MS) was calculated as 39.528±1.469 (36.655–42.402; 95% CI) months for PL0, 35.136±3.115 (29.031–41.240; 95% CI) months for PL1, and 24.688±3.697 (17.441–31.934; 95% CI) for PL2 (p=0.020). When we consider PL0 and PL1 as a single group and compare it with PL2, the MS time of the PL0-PL1 group was 38.358±1.346 (35.721–40.995; 95% CI) months, while the MS time of the PL2 group was 24.688±3.697 (17.441–31.934; 95% CI) months (p=0.020).

CONCLUSION: Although PL0, PL1 and PL2 were classified into a single group (all considered as T2), this study showed that the presence of PL2 was associated with a poor prognosis in terms of survival, independent of lymph node involvement, histopathological subtype of the tumor and tumor size.

Keywords: Lung cancer; survival; visceral pleura.

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Lung cancers, whose incidence has steadily increased over the last 30 years, remain the most common cause of cancer-related deaths in the world [1]. Lung cancers are roughly divided into 2 groups histopathologically: small cell lung cancer (SCLC) (15%) and non-small cell lung cancer (NSCLC) (85%) [2]. Accurate staging in NSCLC is crucial for selecting appropriate treatment and predicting survival. The 8th staging system for lung cancer recommended by the International Association for the Study of Lung Cancer (IASLC) was introduced in January 2017.8. According to the TNM staging system, the presence of visceral pleural invasion (VIP), even

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if the tumor size is less than 3 cm, is a descriptor that increases T staging from T1 to T2. VIP is categorized as follows: PL0 indicates superficial invasion of the tumor into the pleural connective tissue within the subpleural parenchyma or under the elastic layer; PL1 indicates invasion of the tumor beyond the elastic layer of the visceral pleura; and PL2 indicates invasion of the visceral pleural surface [3]. Accordingly, PL1 and PL2 definitions are accepted as VPI. In the presence of VPI, it is thought to be associated with poor prognosis, considering that cancer cells can spread more easily into the pleural cavity [4]. However, it is not yet clear whether there is a difference between VPI grades (PL1 and PL2) and prognosis.

In this study, we aimed to examine the effect of visceral pleural invasion grades on survival in patients who underwent resection for NSCLC.

MATERIALS AND METHODS

In our study, 202 patients who were diagnosed with NSCLC in our center and followed up in our clinic between 2013 and 2015 were retrospectively evaluated. This study was approved by the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Committee (approval date/no: 04.10.2017/62-1). The study was conducted in accordance with the Declaration of Helsinki. To examine the preoperative and postoperative prognostic factors of the patients, postoperative pathology results, demographic data and data on recurrence status were obtained from our hospital database and patient files. Patients who did not undergo complete resection, had parietal pleural invasion and needed neoadjuvant or chemoradiotherapy were excluded.

Statistical Analysis

Statistical analysis of the study was performed using the demo version of the SPSS 22.0 (SPSS Inc., Chicago, IL) package program. Independent groups were compared with independent samples t test/one-way analysis of variance (ANOVA) in terms of normally distributed variables, and Mann Whitney U/Kruskal Wallis H test for non-normally distributed variables. Kaplan-Meier survival analysis was applied to compare the survival times of the groups. Log rank test was performed to determine whether there was a significant difference between the survival times of the groups. Statistical significance level was determined as $p<0.05$.

Highlight key points

- Lung cancers constitute a significant share of cancer-related causes of death.
- Although all pleural invasions (PL0, PL1 and PL2) are classified as T2 according to TNM classification, survival may differ according to the degree of pleural invasion.
- In the 8th TNM staging, a more detailed classification for the degree of pleural invasion would be useful.

RESULTS

Patient Characteristics

11 of 202 patients were excluded because they did not meet the necessary criteria. The median survival time (MST) was 37.542±1.313 (34.969–40.116; 95% CI) months. According to the degree of VPI; 135 (70.7%) patients were PL0, 40 (20.9%) patients were PL1, and 16 (8.4%) patients were PL2. The patients included in the study were analyzed according to their characteristics (Table 1). A statistically significant difference was found between VPI grades and tumor histopathological types (p=0.021) (Chi-Square Test).

Survival

VPI Survival analysis was performed by dividing 3 groups: PL0, PL1 and PL2. The MS was calculated as 39.528±1.469 (36.655–42.402; 95% CI) months for PL0, 35.136±3.115 (29.031–41.240; 95% CI) months for PL1, and 24.688±3.697 (17.441–31.934; 95% CI) for PL2. (p=0.031) (Fig. 1A). When subgroup analysis was performed according to the degree of visceral pleural invasion, there was no statistically significant difference between PL0 and PL1, PL1 and PL2 (respectively p=0.205 p=0.216), while a statistically significant difference was found between PL0 and PL2 (p=0.015). When we examined the patients in two groups as VPI (+) (PL1 or PL2) and VPI (-) (PL0), the MST of the VPI (+) group was 33.336±2.651 (28.140–38.533; 95% CI) months; The MST of the VPI (-) group was found to be 39,360±1,469 (36,481–42,239; 95% CI) months, and a statistically significant difference was found between the two groups in terms of survival time (p=0.031) (Fig. 1B).

In addition, when we consider PL0 and PL1 as a single group and compare it with PL2, the MST of the PL0-PL1 group was 38.358±1.346 (35.721–40.995; 95% CI) months, while the MST of the PL2 group was 24.688±3.697 (17.441–1.934; 95% CI) months. (p=0.020) (Fig. 1C).

Table 1. Basal characteristics of the patients with visceral pleural invasion (n=191)

	PL0	PL1	PL2	p
Total number (%)	135 (70.7)	40 (20.9)	16 (8.4)	
Sex, (%)				0.236
Female	9.6	15.0	–	
Male	90.4	85.0	100.0	
Age, years, mean±SD	59.57±7.56	60.35±7.84	62.75±6.65	0.355
Min–max	42–91	34–74	49–73	
Histology, (%)				**0.021**
Squamous cell carcinoma	59.3	45	18.8	
Adenocarcinoma	34.1	47.5	62.5	
Others	6.7	7.5	18.8	
Site of the tumor, (%)				0.184
Right	52.6	42.5	31.3	
Left	47.4	57.5	68.8	
Resection type, (%)				0.803
Lobectomy	57.8	67.5	50	
Pneumonectomy	34.7	25	43.8	
Bilobectomy	6.7	7.5	6.3	
Segmentectomy	0.7	–	–	
Tumor size, cm (%)				0.290
≤2 cm	15.4	7.5	6.3	
>2 cm	84.4	92.5	93.7	
≤3 cm	37.8	20	18.8	
>3 cm	62.2	80	81.2	
≤5 cm	76.6	16.9	6.5	
>5 cm	59.7	28.4	11.9	
Nodal status, (%)				0.539
N0	67.4	62.5	68.8	
N1	25.9	22.5	18.8	
N2	6.7	15	12.5	

SD: Standard deviation

N Nodal Status

No statistically significant difference was found when N0, N1 and N2 patients were evaluated separately according to the degree of VPI (PL0, PL1 and PL2) in terms of survival. No significant difference was found when N0, N1 and N2 patients were evaluated with VPI (+) (PL1 and PL2) and VPI (-) (PL0) groups in terms of survival (p=0.223, p=0.112 and p=0.527, respectively).

Tumor Size

We examined tumor size into 3 categories: ≤2 cm, ≤3 cm, and ≤5 cm.

When the VPI (+) and VPI (-) groups were compared in patients with tumor size ≤2 cm, there was no difference in survival (p>0.05). On the other hand, a statistically significant difference was found between the VPI (+) and VPI (-) groups in terms of survival in those with tumor size ≤3 cm (p=0.006). When subgroup analysis was performed in patients with tumor size ≤3 cm, there was no difference between PL0-PL1 and PL1-PL2 (p=0.163; p=0.224, respectively), while there was a significant difference between PL0-PL2 (p=0.009). While there was no significant difference between PL0 and PL1 in cases with tumor size ≤5 cm, a significant difference was found between PL1-PL2 (0.021) and PL0-PL2 (p=0.009).

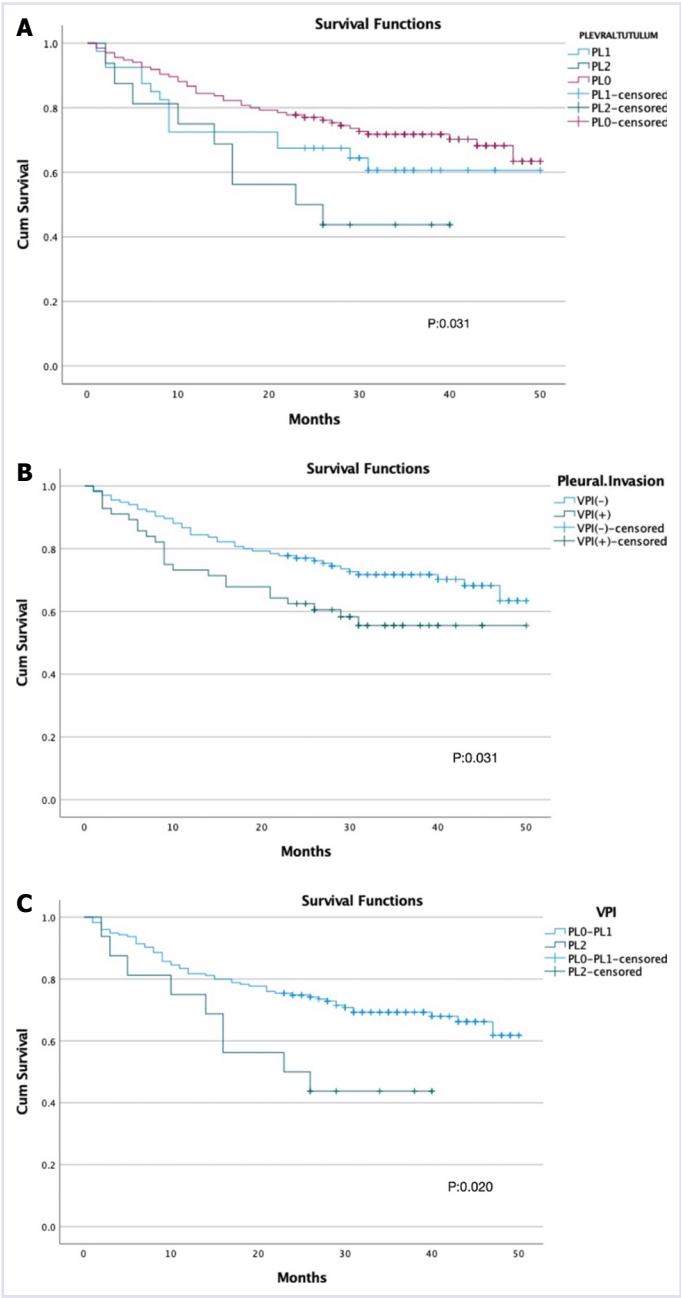

FIGURE 1. **(A)** Kaplan Meier survival curves according to VPI invasion levels. **(B)** Kaplan Meier survival curves between VPI (+) and (-) groups. **(C)** Kaplan Meier survival curves between PL0-PL1 and PL2 groups.

All survival analyses were performed independently of the pathologic stage.

Histopathologically Type

When 191 patients were analyzed according to their histopathological types, 101 (52.9%) were squamous cell lung cancer, 75 (39.3%) adenocarcinoma and 15 (7.9%) other (large cell carcinoma, adenosquamous carcinoma and pleomorphic carcinoma). In the group with VPI (+), adenocarcinoma was 51.8%, while squamous cell carcinoma was 37.5%.

DISCUSSION

Visceral pleural invasion may have prognostic significance in NSCLC was first reported by Brewer in 1958 [5]. In 1977, the same person proved that VPI had poor prognostic significance in NSCLC [6]. The rate of VPI in NSCLC has been reported to be between 11.5% and 26.8% [4, 7]. This is a very serious rate. Visceral pleural invasion is still a controversial and important issue for clinicians (medical oncologists, radiation oncologists, thoracic surgeons, etc.) involved in the treatment and follow-up of lung cancer.

In the 7th staging system recommended by the IASLC, lung cancer is classified as T2a when VPI (+) and tumor size is 5 cm, and as T2b when VPI (+) and tumor size is 5–7 cm. In the 8th staging system, unlike the 7th staging system, those with VPI (+) are classified as T2a when tumor size is ≤4 cm. However, PL1 and PL2 were evaluated as the same group (VPI (+) and no clear statement was made about the effect of these two groups on prognosis separately [8].

In our study, when patients were divided into two groups as VPI (+) (PL1, PL2) and VPI (-) (PL0) and survival times were analyzed, the survival time of the VPI (+) group was found to be lower, but the difference was statistically significant (p=0.031). In other words, VPI was associated with poor prognosis in our patients. When MS analysis was performed between PL0, PL1 and PL2, a statistically significant difference was found (p=0.031). When subgroup analysis was performed for these three groups, no significant difference was found between PL0-PL1 (p=0.205) and PL1-PL2 (p=0.216) in terms of survival, while a significant difference was found between PL0-PL2 (p=0.015). Accordingly, the survival of PL0 was significantly higher than that of PL2. Although PL1 and PL2 were considered in the same category [both were considered VPI (+)], there was a difference in survival between these groups. Another study found a significant difference in survival between PL0 and PL1, but not between PL1, PL2 and PL3 [9].

Osaki et al. [10] showed that PL0 had a better prognosis than PL1 and PL2, independent of tumor size and N status. In the study of Tanju et al. [8], although there was no significant difference in survival between VPI (+)

and VPI (-), VPI (+) was associated with poor survival. In addition, in the same study, it was reported that there was a significant difference in survival times between PL0-PL2 and PL1-PL2 [8].

There are many studies reporting that VPI is associated with lymph node involvement [11, 12]. Since the visceral pleura is rich in lymphatic vessels, it has a strong structure that communicates with each other on the lung surface, and this connection penetrates the lung parenchyma and establishes a connection with bronchial lymph vessels draining to various hilar lymph nodes [13, 14]. In the study by Manac'h et al. [7], the MST of the VPI (+) group was found to be significantly lower than that of the VPI (-) group in N0 and N2 patients, whereas no difference was found between the VPI (+) and VPI (-) groups in the N1 group. In our study, when the survival analysis of the VPI (+) and VPI (-) groups in the N0 group was performed (38.562±2.964 months and 42.266±1.544 months, respectively), it was shown that the VPI (+) group was associated with poor prognosis, but no statistically significant difference was found in terms of survival time between N0, N1, N2 and the presence of VPI. Similar to our study, Osaki et al. [10] showed that PL0 was associated with a better prognosis than PL1 and PL2 independent of the N factor. Zhao et al. [15] showed that VPI was significantly associated with poor survival in N0 but not in N1 and N2. Another study showed that VPI affected prognosis only in the N0 patient group ($p<0.001$) but not in N1 and N2.

It is thought that as the tumor size increases, the tumor will occupy the peripheral area and thus the possibility of invading the visceral pleura will increase [15]. Manac'h et al. [7] showed that 10.4% of tumors <3 cm and 19.6% of tumors between 3–5 cm had VPI. In the same study, it was found that the frequency of VPI increased significantly in tumors >5 cm ($p <0.001$) [7]. In our study, no significant difference was found in terms of survival when patients with tumor size ≤2 cm were compared with patients with and without VPI (+) ($p=0.708$). When VPI (+) and non-VPI (-) patients with tumor size ≤3 cm were compared, it was observed that the survival time of the VPI (-) group was longer than that of the VPI (+) group ($p=0.016$). When patients with tumor size ≤3 cm were compared in terms of survival according to VPI invasion grades, no difference was found between PL0-PL1 and PL1-PL2 ($p=1.163$; $p=0.224$, respectively), while a statistically significant difference was found between PL0-PL2 ($p=0.009$).

Many studies have examined the relationship between tumor size and VPI. In the study of Zhao et al. [15], it was shown that those with VPI (-) had better survival than those with VPI (+) in ≤2 cm and ≤3 cm tumors. When we looked at tumors ≤5 cm in our study, we found a significant difference in survival between those with VPI (+) and those without ($p=0.022$). Again, when we performed subgroup analysis in this group, there was no difference in survival between PL0-PL1 ($p=0.626$), while a significant difference was found between PL1-PL2 and PL0-PL2 in terms of survival ($p=0.021$ and $p=0.009$, respectively). In another study, better survival was observed in the presence of PL0 in tumors ≤5 cm in size compared to PL1, PL2 and PL3 [9]. Tanju et al. [8] showed that the frequency of VPI increased with increasing tumor size.

When we look at the studies analyzing the frequency of VPI in different histological types of lung cancer, VPI was found to be the most frequent in adenosquamous lung cancer (45%) and lower in squamous cell lung cancer (13%) ($p<0.001$). In the study of Okada et al. [13], the rate of adenocarcinoma cell type was the highest (70.9%), while the rate of squamous cell lung cancer (20.0%) was lower ($p=0.010$). In our study, the most common cell type in the VPI (+) group was adenocarcinoma (51.8%), while squamous cell lung cancer was found less frequently (37.5%).

Conclusion

Although PL0, PL1 and PL2 were classified under a single group (all considered as T2), this study showed that the presence of PL2 was associated with poor prognosis in terms of survival independent of lymph node involvement, tumor histopathological subtype and tumor size. Some limitations of this study include its retrospective nature, single-center study, limited sample size and heterogeneous patient selection in terms of the presence of VPI. Considering these results, we think that PL0 and PL1 may be considered as a single group in the next TNM classification and PL1 may be evaluated in a different category than PL2. However, prospective randomized studies with larger patient groups are needed to understand the detailed effects of VPI on prognosis.

Ethics Committee Approval: The Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Scientific Committee granted approval for this study (date: 04.10.2017, number: 62-1).

Authorship Contributions: Concept – MK; Design – MK, SO; Supervision – SO, IG; Fundings – SO, IG; Materials – MK, SO; Data collection and/or processing – IG, SO; Analysis and/or interpretation – IG, SO, MK; Literature review – MK, SO; Writing – MK, SO, IG.

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