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ORIGINAL ARTICLE / ÖZGÜN MAKALE

The prognostic significance of PD-1 and its ligands in non-small cell lung cancer

Küçük hücreli dışı akciğer kanserinde PD-1 ve ligandlarının prognostik önemi

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ABSTRACT

Background: In this study, we aimed to investigate the prognostic value of programmed cell death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and programmed cell death ligand 2 (PD-L2) expressions on immune and cancer cells in terms of survival in patients with lung adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Methods: Between January 2000 and December 2012, a total of 191 patients (172 males, 19 females; mean age: 60.3±8.4 years; range, 38 to 78 years) who were diagnosed with non-small cell lung cancer and underwent anatomic resection and mediastinal lymph node dissection were retrospectively analyzed. The patients were evaluated in three groups including lung squamous cell carcinoma (n=61), adenocarcinoma (n=66), and large-cell carcinoma (n=64). The survival rates of all three groups were compared in terms of immunohistochemical expression levels of PD-1, PD-L1, and PD-L2.

Results: The mean follow-up was 71.8±47.9 months. In all histological subtypes, PD-1 expressions on tumor and immune cells were observed in 33% (61/191) and in 53.1% (102/191) of the patients, respectively. Higher expression levels of PD-L1 and PD-L2 at any intensity on tumor and immune cells were defined only in lung adenocarcinomas, and PD-L1 and PD-L2 values were detected in 36.4% (22/64) of these patients. The PD-L1 expressions on tumor and immune cells were observed in 41.7% (10/24) and 25% (6/24) of the patients, respectively. The PD-L2 expressions on tumor and immune cells were detected in 16.7% (4/24) and 8.4% (2/24) of the patients, respectively. Univariate and multivariate analyses revealed that PD-1 expression in tumor cells was an independent prognostic factor in all histological subtypes.

Conclusion: Our study results suggest that PD-1 expression is a poor prognostic factor for overall survival in patients with completely resected adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Keywords: Non-small cell lung cancer, prognosis, programmed cell death ligand 1, programmed cell death ligand 2, programmed cell death protein 1, survival.

ÖZ

Amaç: Bu çalışmada akciğer adenokarsinom, skuamöz hücreli karsinom ve büyük hücreli karsinomlu hastalarda programlı hücre ölüm proteini 1 (PD-1), programlı hücre ölüm ligandı 1 (PD-L1) ve programlı hücre ölüm ligandı 2 (PD-L2) ekspresyonlarının sağkalım açısından immün ve kanser hücreleri üzerindeki prognostik değeri araştırıldı.

Çalışma planı: Ocak 2000 - Aralık 2012 tarihleri arasında anatomik rezeksiyon ve mediastinal lenf nodu diseksiyonu yapılan küçük hücreli dışı akciğer kanseri tanılı toplam 191 hasta (172 erkek, 19 kadın; ort. yaş: 60.3±8.4 yıl; dağılım, 38-78 yıl) retrospektif olarak incelendi. Hastalar akciğer skuamöz hücreli karsinom (n=61), adenokarsinom (n=66) ve büyük hücreli karsinom (n=64) olmak üzere üç grupta incelendi. Üç grubun sağkalım oranları PD-1, PD-L1, ve PD-L2 immünhistokimyasal ekspresyon düzeyleri açısından karşılaştırıldı.

Bulgular: Ortalama takip süresi 71.8±47.9 ay idi. Tüm histolojik alt tiplerde, tümör ve immün hücreler üzerinde PD-1 ekspresyonu hastaların sırasıyla %33'ünde (61/191) ve %53.1'inde (102/191) gözlendi. Tümör ve immün hücreler üzerinde herhangi bir yoğunlukta PD-L1 ve PD-L2 ekspresyonları yalnızca adenokarsinomlarda tanımlandı ve bu hastaların %36.4'ünde (22/64) PD-L1 ve PD-L2 değerleri saptandı. Tümör ve immün hücreler üzerinde PD-L1 ekspresyonu hastaların sırasıyla %41.7 (10/24) ve %25'inde (6/24) gözlendi. Hastaların sırasıyla %16.7 (4/24) ve %8.4'ünde (2/24) tümör ve immün hücreler üzerinde PD-L2 ekspresyonu saptandı. Tek değişkenli ve çok değişkenli analizlerde tümör hücrelerinde PD-1 ekspresyonu tüm histolojik alt tiplerde bağımsız bir prognostik faktör olarak bulundu.

Sonuç: Çalışma sonuçlarımız PD-1 ekspresyonunun, komplet rezeksiyon uygulanmış adenokarsinom, skuamöz hücreli karsinom ve büyük hücreli karsinomlu hastalarda genel sağkalım açısından kötü bir prognostik faktör olduğunu göstermektedir.

Anahtar sözcükler: Küçük hücreli dışı akciğer kanseri, prognoz, programlı hücre ölüm ligandı 1, programlı hücre ölüm ligandı 2, programlı hücre ölüm proteini 1, sağkalım.

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Lung cancer is the most common cause of cancer-related deaths worldwide. Mountain et al.[1] adapted the Tumor, Node, Metastasis (TNM) classification to lung cancer staging in 1974 that has been updated approximately every five to seven years so far. However, significant survival differences have been observed in stages of cancer which affect the choice of treatment and prognostic prediction.[2] These problems would be overcome at molecular level and with mutational analysis in the near future. Particularly, in this context, identifying the functioning and physiopathology of the immune system is a promising development facilitating the treatment and prognostic evaluation of cancer patients.[3]

Currently, immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have become popular in the medical treatment of patients with non-small cell lung cancer (NSCLC).[4,5] In the literature, the expression of PD-1 and/or PD-L1 in patients with resected NSCLC has been examined extensively. In these studies, PD-1 and/or PD-L1 expression has been shown to have a positive prognostic value in some and a negative prognostic value in other studies.[6-11] However, PD-L1 expression is not a useful parameter for either prognostic or adjuvant chemotherapy in patients with early-stage NSCLC, independent of the cut-off values chosen.[12] Uncertainty still remains regarding the prognostic predictive values of PD-1, PD-L1, and programmed cell death ligand 2 (PD-L2) in NSCLC.

In the present study, we aimed to investigate the prognostic value of PD-1, PD-L1, and PD-L2 expressions on immune and cancer cells in terms of survival in patients diagnosed with adenocarcinoma (AC), squamous cell carcinoma (SQC), and large cell carcinoma (LCC) who underwent complete resection.

PATIENTS AND METHODS

This two-center, retrospective cohort study was conducted at Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, and Dokuz Eylül University, Institute of Health Sciences, Department of Thoracic Surgery and Basic Oncology between January 2000 and December 2012. A total of 191 patients (172 males, 19 females; mean age: 60.3±8.4 years; range, 38 to 78 years) diagnosed with NSCLC and underwent anatomic resection and mediastinal lymph node dissection were included. The patients were evaluated in groups of SQC (n=61; 31.6%), AC (n=66; 35.2%), and LCC (n=64; 33.2%) and classified according to the 8th TNM staging system.[2] Immunohistochemical expression levels of PD-1 were assessed in all three groups and immunohistochemical expression levels of two ligands of this protein, PD-L1 and PD-L2, were evaluated only in the AC group and compared to their survival rates. Patients who were lost to follow-up, patients, who died in the first 30 days, and those who underwent incomplete resection were excluded from the study.

The sections were stained with hematoxylin and eosin and immunohistochemical methods. The expressions of PD-1, PD-L1, and PD-L2 on cancer cells and lymphocytes were evaluated and presented as a percentage of the total tumor area. The staining results were, then, correlated with patient characteristics, including age, sex, smoking status, tumor size, stage, presence of necrosis, type of surgery, and patient survival.

The independent variables of our study were age and sex, while the dependent variables were disease stage, lung cancer differentiation, pathological subtype, type of operation, results of PD-1 immunohistochemical expression, PD-L1 and PD-L2 gene copy number analyses.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The normality of the distribution of numerical variables was evaluated using the Shapiro-Wilk test. Categorical variables were compared using the chi-square or Fisher exact probability test. Continuous variables were expressed in mean ± standard deviation (SD), while categorical variables were expressed in number and frequency. Survival analyses were performed using the Kaplan-Meier method. Log-rank test was used to compare survival rates. Variables that may have an effect on survival were evaluated with univariate and multivariate (Cox-regression analysis) analyses. Correlations between variables were analyzed using the Pearson correlation test. A p value of <0.05 was considered statistically significant.

RESULTS

The distribution of the characteristic features of the patients according to histological subtypes is summarized in Table 1. The mean follow-up was 71.8±47.9 (range, 1 to 178.6) months.

In NSCLC subgroups, PD-1 expression on cancer cells was observed to be between 0 and 50% and over 50% of the cases, while PD-1 expression on lymphocytes was detected to between 0 and 50%

Table 1. Demographic characteristics of the patients

	Adenocarcinoma (n=66)			Squamous cell carcinoma (n=61)			Large cell carcinoma (n=64)			Total (n=191)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			59.9±7.4			63.2±8.1			58.1±9.1			60.3±8.4	0.002
<65	53	80.3		34	55.7		49	76.6		136	71.2		0.005
>65	13	19.7		27	44.3		15	23.4		55	28.8		
Sex													0.098
Female	10	15.2		3	4.9		6	9.4		19	10		
Male	56	84.8		58	95.1		58	90.6		172	90		
Tobacco use													0.040
No	15	22.7		4	13.8		10	15.6		29	15.2		
Yes	51	77.3		57	93.4		54	84.4		162	84.8		
Tumor size (cm)			3.8±1.9			4.3±2.3			4.6±2.2			4.2±2.2	0.095
Neoadjuvant therapy													0.48
No	57	86.3		51	83.6		58	90.6		166	87		
Yes	9	13.6		10	16.4		6	9.4		25	13		
Resection type													0.009
Lobectomy	55	83.3		39	63.9		47	73.4		141	73.8		
Bilobectomy	6	9.1		5	8.2		1	1.6		12	6.2		
Pneumonectomy	5	7.6		17	27.9		16	25		38	20		
Stage													0.59
I	21	31.8		25	41.0		25	39.1		80	41.9		
II	26	39.4		13	21.3		20	31.2		50	26.2		
III	19	28.8		23	37.7		19	29.7		61	31.9		
Presence of necrosis													0.01
No	52	78.8		24	39.3		27	40.3		103	53.9		
Yes	14	21.2		37	60.7		37	59.7		88	46.1		

SD: Standard deviation.

and over 50% of the cases. When these values were evaluated for each cancer subgroup, protein expressions on both cancer cells and lymphocytes were found to be statistically significant in AC patients (p<0.001).

In the subgroup analysis, survival time decreased as the PD-1 tumor cell expression rate increased in patients with AC histology. The worst survival rates were seen in the patient group where PD-1 expression was seen in more than 50% of cancer cells (p<0.001). Similar distribution of survival rates was also seen among patients with PD-1 expression on lymphocytes. Statistically significantly worse survival rates were observed in the group with PD-1 expression seen on more than 50% of lymphocytes compared to the other groups (p<0.001).

The mean survival time was shorter in the group with rates of PD-1 expression on cancer cells were above 50% in patients with SQC histology without a statistically inter-group significant difference (p=0.321). The patients with SQC who did not demonstrate PD-1 expression on lymphocytes had statistically significantly (p=0.027) increased survival rates compared to those with PD-1 expression rates between 0 and 50% and above 50%.

In patients with the diagnosis of LCC, the five-year survival was not observed in the group with rates of PD-1 expression on cancer cells or lymphocytes were above 50% (p<0.001). In this group of patients, high rates of PD-1 expression on cancer cells and lymphocytes were associated with poor survival rates.

When the patients with AC histology were evaluated in terms of PD-L1 tumor expression rates, the worst survival rate was seen in the group with an expression rate of more than 50%. This difference between the survival rates was statistically significant (p=0.018). However, in the same group, no significant survival difference was observed according to PD-L1 expressions on lymphocytes (p=0.744) (Figure 1).

When PD-L1 expression on tumor cells and lymphocytes were grouped as negative/positive in patients with AC histology, there was no significant difference in their distribution according to disease stages (Stage I-II-III, p=0.059, and p=0.39, respectively), whereas PD-L1 tumor cell expression and PD-L1 lymphocyte expression were found to be associated with poor survival (p<0.001 and p=0.049, respectively).

However, no PD-L2 expression was detected in cases with SQC and LCC. Among patients diagnosed with AC, PD-L2 expressions were detected on cancer cells (n=4; 16.7%), and lymphocytes (n=2; 8.4%) in indicated number of patients. Due to these low PD-L2 expression rates, they were not included in the univariate and multivariate analyses.

When all NSCLC patients included in the study were divided into three groups according to their rates of PD-1 expression on lymphocytes, the worst prognosis was seen in the group demonstrating expression rates more than 50% (median survival 55.7 months, p<0.001). Similarly, the group with rates of PD-1 expression on cancer cells above 50% had a statistically significantly shorter survival than the

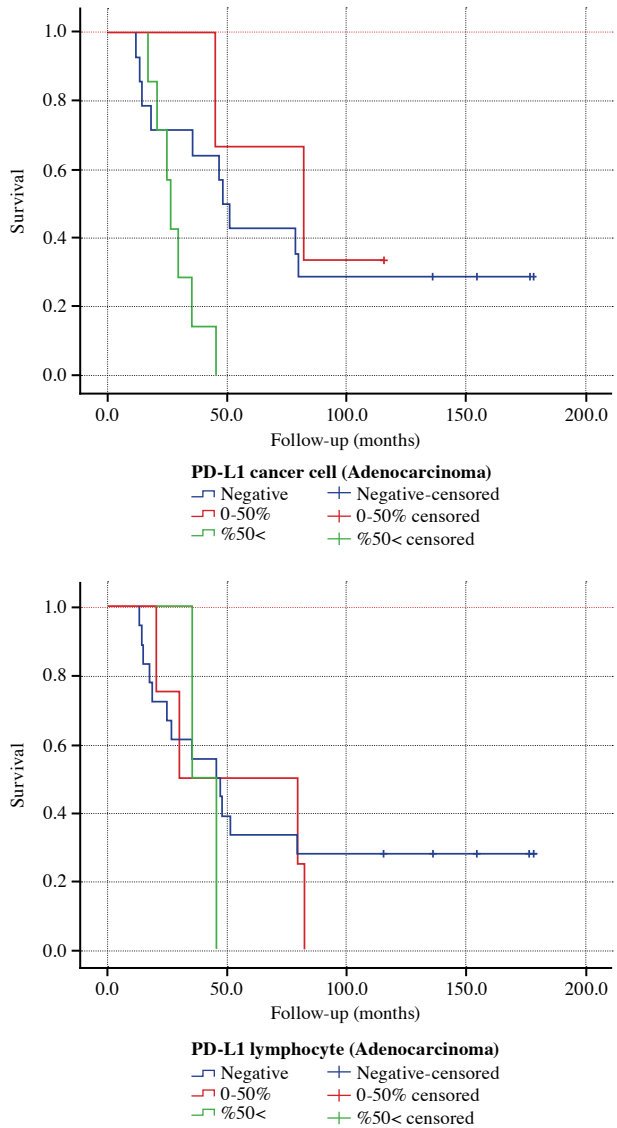

Figure 1. Survival analyses according to cut-off value of 50% in cases with PD-L1 expression on cancer cells and PD-L1 expression on lymphocytes in adenocarcinoma.

PD-L1: Programmed death-ligand 1.

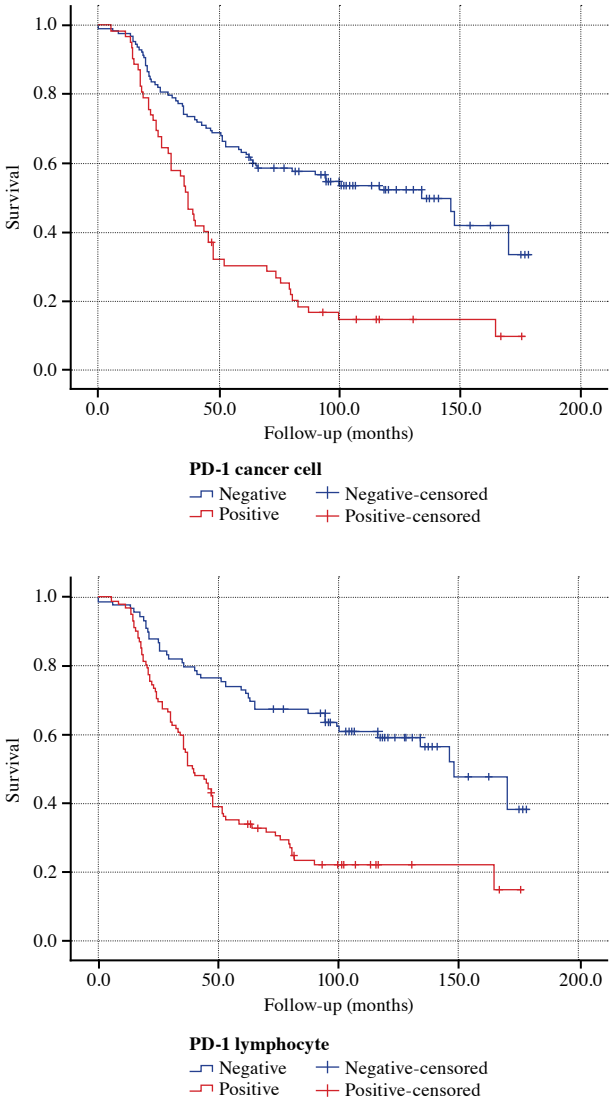

Figure 2. Survival analyses by presence of PD-1 expression on cancer cells and lymphocytes in all patients with non-small cell lung cancer.

PD: Programmed death 1.

other groups (median survival: 56.4 months, p<0.001) (Figure 2).

The relationship between PD-1 expression levels on cancer cells and lymphocytes was analyzed in terms of age and tumor size. Accordingly, a highly positive correlation was found between rates of PD-1 expression on cancer cells and on lymphocytes (r=0.689, p< 0.001).

Regardless of PD-1 expression on cancer cells, the patients included in the study only according to histological subtypes had SQC (31.1%), AC (41.8%), and LCC (42.2%). No statistically significant survival difference was observed among the three histological subtypes (p=0.292) (Table 2).

There were patients with Stages I, II, and III in all cancer types, although PD-1 expression on cancer cells and lymphocytes increased as the stage increased, but no significant difference was observed in the distribution of PD-1 expression rates (p=0.091 and p=0.080, respectively) (Table 3).

According to the Cox regression analysis, advanced-stage, PD-1 expression on cancer cells, and the presence of necrosis were found to be independent poor prognostic factors (Table 4).

DISCUSSION

After recognizing the significance of immune checkpoints in battling cancer, immunotherapy using checkpoint inhibitors such as PD-1 and PD-L1 has been applied to treat advanced NSCLC, notably to improve survival.[13-15] In the PACIFIC trial, a significant increase in progression-free survival (17 *vs.* 6 months) with conventional chemoradiotherapy and durvalumab highlights that immune response can also be improved with daily low-dose radiotherapy protocols.[13] However, the clinical benefit of durvalumab in the PACIFIC trial

Table 2. Overall survival in all patients with non-small cell lung cancer

	Patients with non-small cell lung cancer						
	Number of patients		5-year survival rate	Average survival rate (months)	95% CI (months)		
Histology	n	%	Mean±SD	Mean±SD	Upper limit	Lower limit	*p*
Squamous cell carcinoma	61	31.1	42.6±6.3	80.1±8.7	63.023	97.257	0.292
Adenocarcinoma	66	41.8	54.3±6.2	97.2±8.6	80.450	114.040	
Large cell carcinoma	64	42.2	59.4±6.1	94.5±8.3	78.165	110.889	
Total	191	100	52.3±3.6	91.4±5.0	81.496	101.214	

SD: Standard deviation.

Table 3. Distribution of PD-1 expression rates in cancer cells and lymphocytes according to stages

	Stage I		Stage II		Stage III		
	n	%	n	%	n	%	*p*
Squamous cell carcinoma							
PD-1 expression on cancer cells	8	32.0	6	46.2	9	39.1	0.68
PD-1 expression on lymphocytes	11	44.0	8	61.5	12	52.2	0.58
Adenocarcinoma							
PD-1 expression on cancer cells	10	32.3	7	41.2	12	63.2	0.09
PD-1 expression on lymphocytes	11	35.5	9	52.9	15	78.9	0.012
LCC							
PD-1 expression on cancer cells	1	4.2	6	30.0	3	15.8	0.065
PD-1 expression on lymphocytes	13	54.2	11	55.0	11	57.9	0.97
Overall							
PD-1 expression on cancer cells	19	23.8	19	38.0	24	39.3	0.091
PD-1 expression on lymphocytes	35	43.8	28	56.0	38	62.3	0.080

PD-1: Programmed death 1.

Table 4. Evaluation of demographic data with using univariate and multivariate analyzes

			Univariate analyzes		Multivariate analyzes	
Variables	n	%	*p*	Hazard ratio	*p*	Hazard ratio
Age (>65 years)	55	28.8	0.19	1.3	0.41	0.79
Tobacco use	162	84.8	0.59	0.87	0.42	1.35
Histology						
Squamous cell carcinoma	61	31.9	ref	ref	ref	ref
Adenocarcinoma	66	34.5	0.15	0.72	0.44	0.52
Large cell carcinoma	64	33.5	0.18	0.74	0.32	0.43
PD-1 expression on cancer cells	62	32.5	<0.001	2.60	0.01	3.39
PD-1 expression on lymphocytes	102	53.4	<0.001	2.86	0.73	1.15
Necrosis	88	46.1	<0.001	3.45	0.011	1.02
Stage						
I	80	41.9	ref	ref	ref	ref
II	50	26.2	<0.001	2.69	0.002	3.35
III	61	31.9	<0.001	3.61	<0.001	4.87

SD: Standard deviation; Ref: Reference value.

was not associated with PD-L1 expression. The use of immune checkpoint inhibitors in lung cancer has become more common, and these inhibitors are applied not only for inoperable lung cancer cases, but also for neoadjuvant therapy in the preoperative and adjuvant therapy in the postoperative period.[16-18]

Little is known about the prognostic and/or predictive value of PD-1 expression. In a large-scale study such as the PACIFIC trail, the possible explanation for the response in patients without PD-L1 expression may be that the presence of low levels of PD-L1 expression on cancer cells which

cannot be detected by current methods. However, the clinical benefit of durvalumab in the PACIFIC trial was not associated with PD-L1 expression.[16,19]

Currently, PD-L1 is the generally accepted predictive marker for response to immunotherapy.[20] The results of prognostic and predictive studies on PD-1 and its ligands are also highly variable. However, additional validation studies may be required to establish the validity of currently available immunohistochemistry tests of PD-1 and its ligands.[21] The difficulties in evaluating PD-1 expression on lymphocytes and the poor interobserver agreement concerning the evaluation of the immunocell staining results may necessitate conduction of additional validation studies.[22] Besides, the mechanisms regulating the expressions of PD-1, PD-L1, and PD-L2 have not been completely understood. In particular, the lack of standardized tests for PD-L1 is a major challenge in assessing its predictive and prognostic role.[23]

Several studies investigating the relationship between the expressions of PD-1 and its ligands and the outcome of patients with completely resected NSCLC have gained momentum and different degrees of emphasis have been placed on their prognostic importance.[6-11,24,25] In the study of Paulsen et al.,[24] which included 536 patients diagnosed with NSCLC and underwent lung resection surgery, the prognostic significance of PD-1 and PD-L1 was evaluated and both PD-1 and PD-L2 were found to be independent positive prognostic factors in the multivariate survival analyses. Positive prognostic effects of PD-1 and PD-L1 were observed in two studies of European origin conducted with 149 and 271 cases, respectively.[7,9] However, a meta-analysis that included 12 studies from the continents of United States, Europe, and Asia demonstrated that the PD-L1 ligand had no prognostic value in terms of survival for NSCLC. However, a study from China included in the same meta-analysis indicated that PD-L1 expression was a poor prognostic factor.[26] Zaric et al.[27] found that PD-1 expression was an independent prognostic factor for disease-free survival (DFS) and overall survival (OS) in 159 patients diagnosed with AC and underwent complete resection, while PD-L1 was not correlated with DFS, but with correlated OS. Although we also found expressions of PD-1 and PD-L1 to be associated with OS, one of the limitations to our study was that we did not have DFS data.

In the current study, we showed that PD-1 expression on cancer cells and immune cells was a negative prognostic factor for OS in patients with completely resected lung AC, SQC, and LCC. In a similar study, PD-1 expression on immune cells in patients with resected lung AC was indicated as an independent positive prognostic factor in terms of both recurrence-free and OS.[27] Also in this study, PD-L1 expression was not associated with relapse-free survival, but correlated with longer survival. In our study, we observed that PD-L1 expression on cancer cells was a negative prognostic factor for survival in patients with pulmonary AC, SQC and LCC, whereas PD-L1 expression on lymphocytes did not affect survival. In the study of Parra et al.,[21] different antibody clones were compared in the immunohistochemical examination of PD-L1, and the need for further investigations and validation studies were emphasized as a concluding remark of the study.

Contrary to our study results, some studies in the literature described PD-L1 protein expression as a positive prognostic marker in patients with completely resected NSCLC.[7,25] Other studies have shown an association between PD-L1 expression and poor prognosis[5] or that PD-L1 expression has no prognostic value in these cases.[10,23,27]

The main limitations to our study included its retrospective design, relatively small sample size, inability to provide data regarding postoperative DFS, lack of standardization for immunohistochemical analysis of PD-1, PD-L1 and PD-L2, and failure to perform mutation analyses in lung cancer patients.

In conclusion, our study results suggest that the PD-1 protein expression may affect the prognosis of resected non-small cell lung cancer patients and influence survival. Moreover, in patients diagnosed with adenocarcinoma, the expression of PD-L1 affects prognosis. Further validation through additional examinations and standardization is needed due to existing literature. With the advancements in cancer immunotherapy, using PD-1 and its ligands as biomarkers can lead to personalized follow-up plans for lung cancer patients. These plans may aid in predicting recurrences or metastases and facilitate prompt administration of necessary treatments (chemo/radiotherapy or surgery). Centralized studies across diverse locations may provide guidance for future research in this area.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Non-invasive Research Ethics Committee (date: 18.01.2018, no: 2018/02-33). 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, design, analysis and/or interpretation, writing the article, critical review: O.U., Ö.E.G., A.E., T.Ç.A., G.B., Ş.Ö.K., A.Ü., Z.A., Z.A., İ.Ö., S.A.; Control/supervision: O.U., Ş.Ö.K., A.Ü., Z.A., Z.A., İ.Ö., S.A.; Data collection and/or processing, literature review; references and fundings; materials: O.U., Ö.E.G., A.E., T.Ç.A., G.B.

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