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ORIGINAL ARTICLE

Predictor Value of PD-L1 for Radiotherapy Response in Locally Advanced Non-Small Cell Lung Cancer

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OBJECTIVE

The discovery of PD-L1 receptors triggered a great interest in immunotherapeutics for the management of locally advanced non-small-cell lung cancer (NSCLC). The efficacy of immunotherapeutics for overall survival (OS) in locally advanced NSCLC has been proven in several clinical trials. However, no data exist for the relationship between radiotherapy (RT) response and programmed death-ligand (PD-L1) receptor positivity in the literature. In this regard, we aimed to investigate the predictor value of PD-L1 receptors for RT response.

METHODS

Eighty patients who were diagnosed as having locally advanced NSCLC were selected from among patients in whom PD-L1 status was assessed in the Gazi University pathology laboratory. The relationship between PD-L1 and progression-free survival (PFS), OS, metastasis-free survival (MFS), RT response, and RT doses was evaluated using Kaplan-Meier and Cox regression analysis. Chi-square and t-tests were used for descriptive statistics.

RESULTS

The median follow-up was 16.1 months. The mean age was 61.1 years. PD-L1 positivity was detected in 34 patients. One year and 2-year OS and PFS ratios were found as 87%, 54% and 65%, 30%, respectively. The median OS and PFS were 26.8 and 15.1 months, respectively. There was no statistically significant difference between PD-L1 receptor status and OS and PFS (p=0.736 and p=0.372, respectively). In the PD-L1 positive subgroup analysis for OS, doses higher than 60 Gy (n=28, mean dose 64.6±1.53) were found superior to the 60 Gy dose (n=6) (p=0.034). The median MFS was 33 months.

CONCLUSION

PD-L1 status did not seem to be a predictor for RT response. However, despite the low number of patients in the 60 Gy group, our study showed that dose-escalation could improve survival in PD-L1 positive locally advanced NSCLC.

Keywords: NSCLC; PD-L1; RT.

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Introduction

Lung cancer is responsible for 18% of all cancer-related deaths around the world. Lung cancer is also frequently seen in Turkey due to the high cigarette consumption rates.[1,2] Non-small-cell lung cancer (NSCLC) accounts for approximately 80-85% of total lung cancers.[3] NSLCL represents Stage 3 disease in nearly 20-35% of all diagnosed patients.[4] Gross tumor volume (GTV), tumor diameter, nodal volume, pleural effusion, and low-performance scores are generally accepted as prognostic factors for locally advanced lung cancer.[5] However, the prognosis of the disease is dismal. Only 15-30% of patients remain alive at 5 years. The median survival for locally advanced lung cancer was calculated as around 28 months.[6,7]

The standard approach for Stage 3 NSCLC contains multimodality therapy with combinations of systemic therapy including chemotherapy and immunotherapy, radiotherapy (RT), and surgery. However, the selection of proper tools based on disease characteristics is still argued. Despite significant debate about the standard treatment for Stage 3 NSCLC (especially for Stages 3A and 3B), definitive concurrent chemoradiation is preferred for a substantial portion of patients according to the size, the location and extension of primary disease, lymph node involvement, low-performance status, and surgical resectability of tumors. Furthermore, as a result of recent Phase 3 studies, durvalumab was added to standard care for Stage 3 NSCLC in consolidation therapy.[8,9]

Programmed death-ligand (PD-L1) receptors are found on the surface of membranes of tumor cells and are members of the B7 protein family.[10] When PD-L1 receptors activate with PD-1 proteins on the surface of T cells, B cells, and myeloid cells, autoimmunity retreats.[11,12] Several sequential events such as apoptosis of activated T cells, limitation of T cell proliferation, and increasing activity of immunosuppressive T regulatory cells allow tumor cells to escape from the immune system of the body.[13] Concordant with this knowledge, PD-L1 positivity was associated with poor prognosis in lung cancer.[14] Furthermore, preclinical studies revealed that PD-L1 expression was upregulated in tumor cells after chemoradiotherapy (CRT).[15-17] However, clinical studies suggested improved survival in patients with PD-L1 positive lung cancer with PD-L1 inhibitors.[8,9,18]

Due to the promising outcomes with PD-L1 inhibitors in locally advanced and metastatic lung cancer because of the synergistic interaction between RT and immunotherapeutics, great interest was directed toward this topic. Therefore, the effects of RT on PD-L1 receptors have been intensely investigated in the literature. However, the predictive value of PD-L1 status for RT response is still unknown. In this regard, we aimed to investigate this relationship in our study.

Materials and Methods

Eighty patients who were diagnosed as having Stage 3 NSCLC and their biopsy materials tested for PD-L1 status in the Gazi University Pathology laboratory were included in the study. All patients were treated with definitive RT (n=2) or definitive radiochemotherapy (n=78). Patients with incomplete definitive treatment or who needed breaks during the RT course were excluded from the study. The data of the patients were gathered from the electronic databases of hospital and patient files, retrospectively. Demographic information; smoking status; histology of tumors; PD-L1 status and percentage; other molecular profiles (epidermal growth factor receptor, reactive oxygen species, anaplastic lymphoma kinase); tumor size; tumor, node, and metastasis stages; chemotherapy regimens; RT techniques, fields, and doses; second-line therapies; treatment responses; metastasis sites, and recurrence data were noted and extracted to an Statistical Package for the Social Sciences file (Table 1). The relationship between PD-L1 status and progression-free survival (PFS), overall survival (OS), metastasis-free survival (MFS), treatment response, and RT doses were evaluated using Kaplan-Meier survival analysis, Cox regression, and the log-rank test. Chi-square and t-tests were used for descriptive statistics.

Computed tomography (CTsim) (1 mm slices) was performed for all patients before RT planning. Positron emission tomography (PET/CT) images were fused with CTsim for determining the gross tumor target volume (GTV). GTV was contoured on both PET/CT and CTsim images and summed. FDG-positive lymph nodes on PET images and nodes larger than 1 cm were also contoured as GTV. An additional 5-8 mm margin was added to the GTV for the clinical target volume (CTV). Planning target volumes (PTV) were defined with 1-1.5 cm expansion from the CTV for three-dimensional conformal RT plans. Internal target volumes include all CTV positions during the breathing cycle used for image-guided RT plans.[19] Sixty to 68 gray RT doses were prescribed for the patients. No elective mediastinal irradiation was used.

Table 1 Patient characteristics

Variables	Patient number and ratio		Variables	Patient number and ratio	
	n=80	%		n=80	%
Gender			Molecular profile		
Female	4	5	EGFR+	3	4
Male	76	95	ROS+	1	1
Age	Mean 61.1		ALK+	1	1
<65	59	74	Definitive therapy		
>65	21	26	CRT	78	98
Smoking			RT	2	2
Yes	71	89	RT technique		
No	9	11	3D-CRT	68	85
Comorbidity			IGRT	12	15
Yes	36	45	RT dose	Mean 63.8 Gy	
No	44	55	60 Gy	12	15
Histology			>60 Gy	68	85
SCC	53	66	RT field		
Adenocarcinoma	24	30	Primary+Mediastinum	72	90
Other	3	4	Primary only	8	10
Tumor size	Mean 6		Chemotherapy regimen	n=78	
<5 cm	19	24	Cisplatin+Paclitaxel	7	9
5-7 cm	23	29	Carboplatin+Paclitaxel	61	78
>7 cm	38	47	Cisplatin+Etoposide	4	5
T stage			Other	6	8
T1	8	10	Timing	n=78	
T2	13	16	Concurrent CRT	56	73
T3	21	26	Sequential CRT	22	27
T4	38	48	Treatment response		
N stage			Complete	6	8
N0	8	10	Partial	62	78
N1	6	8	Stable	10	13
N2	51	64	Progressive	2	1
N3	15	18	Local recurrence		
Clinical stage			Yes	38	48
3A	28	35	No	42	52
3B	40	50	Distant metastasis		
3C	12	15	Yes	22	28
PD-L1			No	58	72
Positive	34	43	Metastasis site	n=22	
Negative	46	57	Bone	8	36
PD-L1 percentage	n=34		Brain	7	32
<1%	3	9	Lymph node	3	14
1-50%	18	53	Other	4	18
>50%	13	38	Second-line therapies		
			Second-line chemotherapy	41	
			Palliative RT	15	

SCC: Squamous cell carcinoma; PD-L1: Programmed death-ligand; EGFR: Epidermal growth factor receptor; ROS: Reactive oxygen species; ALK: Anaplastic lymphoma kinase; CRT: Chemoradiation; RT: Radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy; IGRT: Image-guided radiotherapy; Gy: Gray

RT started simultaneously with chemotherapy regimens. However, 2-4 cycles of chemotherapy were administered before RT for patients with bulky disease to minimize the RT field and complications. Paclitaxel 45-50 mg/m^2 weekly and carboplatin area under the curve (AUC) 2 were administrated with concurrent RT. The paclitaxel dose was upregulated to 200 mg/m^2 every 21 days and carboplatin AUC 6 for an additional two cycles. The doses of cisplatin were 50 mg/m^2 on days 1, 8, 29, and 36 and etoposide was 50 mg/m^2 days 1-5 and 29-33.

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Table 2 Descriptive statistics according to the PD-L1 status (Chi-square independence test and independent sample t-test)

Variables	All patients (n=80)	PD-L1 negative (n=46)	PD-L1 positive (n=34)	p
Age	61.14±9.05 (41-85)	61.13±9.55 (41-85)	61.15±8.46 (41-76)	0.994
Gender				
Female	4	2	2	0.756
Male	76	44	32	
Histology				
Adenocarcinoma	24	16	8	0.425
SCC	53	29	24	
Other	3	1	2	
T Stage				
T1	8	5	3	0.474
T2	13	5	8	
T3	21	12	9	
T4	38	24	14	
N Stage				
N0	8	5	3	0.940
N1	6	4	2	
N2	51	29	22	
N3	15	8	7	
Stage				
3A	28	15	13	0.745
3B	40	23	17	
3C	12	8	4	
Treatment				
CRT	78	45	33	0.828
RT	2	1	1	
RT technique				
3DCRT	68	40	28	0.569
IGRT	12	6	6	
RT dose	63.87 Gy±2.16 (60-68)	64.24 Gy±2.12 (60-68)	63.38±2.14 (60-66)	0.077
60 Gy	12	6	6	0.569
>60 Gy	68	40	28	
Treatment response				
Complete	6	2	4	0.400
Partial	62	36	26	
Stable	10	6	4	
Progressive	2	2	0	
Local recurrence				
No	42	23	19	0.602
Yes	38	23	15	
Distant metastasis				
No	**58**	**29**	**29**	**0.028**
Yes	**22**	**17**	**5**	
Progression				
No	32	16	16	0.268
Yes	48	30	18	
First progression cause				
Local	38	22	16	0.199
Distant	10	8	2	
Exitus	34	19	15	0.505
Concurrent CRT				
Karboplatin+Paclitaxel	56	30	26	0.550
Sequential CRT				
Cisplatin+Gemsitabine	1	0	1	0.255
Cisplatin+Etoposide	4	3	1	
Carboplatin+Paclitaxel	17	9	8	
Tumor size	6.06±2.13 (2.1-14.2)	6.26±2.24 (2.1-14.2)	5.79±1.95 (2.4-12.3)	0.76

Distant metastasis distribution was inhomogenous between PD-L1 positive and negative groups. PD-L1: Programmed death-ligand; SCC: Squamous cell carcinoma; CRT: Chemoradiation; RT: Radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy; IGRT: Image-guided radiotherapy; Gy: Gray

Table 3 Log-rank test results for overall survival

Variables	Patient number	Mean (months)	Standard deviation	CI %95 (Lower-upper)	Log rank p
Overall survival	80	30.99	2.98	25.17-36.83	
PD-L1					
Positive	34	33.13	4.74	23.84-42.41	0.736
Negative	46	28.42	3.22	22.11-34.73	
Gender					
Male	76	31.27	3.30	24.79-37.74	0.922
Female	4	32.00	8.41	15.52-48.48	
Age					
≤65	59	27.76	2.39	23.08-32.43	0.353
>65	21	35.77	6.78	22.48-49.05	
Histology					
Squamous	53	33.83	3.99	26.00-41.64	0.372
Adeno	24	28.63	4.85	19.13-38.13	
Others	3	16.27	5.33	5.84-26.71	
T Stage					
T1	8	32.25	6.86	18.82-45.68	0.898
T2	13	35.43	6.40	22.90-47.95	
T3	21	28.99	5.65	17.93-40.06	
T4	38	25.10	2.22	20.76-29.45	
N Stage					
N0	8	35.62	9.02	17.94-53.30	0.857
N1	6	25.00	4.89	15.42-34.58	
N2	51	32.64	3.90	24.99-40.29	
N3	15	18.05	1.08	15.93-20.17	
Stage					
3A	28	34.13	4.13	26.03-42.22	0.458
3B	40	26.97	3.62	19.87-34.06	
3C	12	18.79	0.83	17.16-20.43	
Radiation dose					
60 Gy	12	20.38	1.97	16.52-24.24	0.359
>60 Gy	68	32.47	3.28	26.04-38.90	
Response					
Complete	6	38.20	0.0	38.20-38.20	**0.036**
Partial	62	31.78	3.42	25.07-38.49	
Stable	12	23.18	3.90	15.54-30.82	
Progressive	2	8.69	.07	8.55-8.82	
PD-L1 Level					
≤1%	3	25.26	17.98	0.00-60.50	0.720
1-50%	18	33.60	4.03	25.70-41.51	
≥50%	13	22.88	2.66	17.64-28.09	

Tretment response was the only significant factor for OS. CI: Confidence interval; PD-L1: Programmed death-ligand; Gy: Gray

RECIST criteria version 1.1 were used for evaluating the RT response. In terms of RECIST criteria, complete response requires the disappearance of all target and non-target lesions and a short axis of all lymph nodes smaller than 1 cm; partial response (PR) requires a >30% decrease in the sum of the longest diameters of the target lesions compared with baseline; stable disease requires neither PR nor progressive disease (PD); PD requires >20% increase in the sum of the longest diameter of target lesions compared with the smallest sum recorded, or the appearance of one or more new lesions, or unequivocal progression of non-target lesions, and at least 5 mm absolute increase of target lesions.[20] Furthermore, the Hopkins criteria

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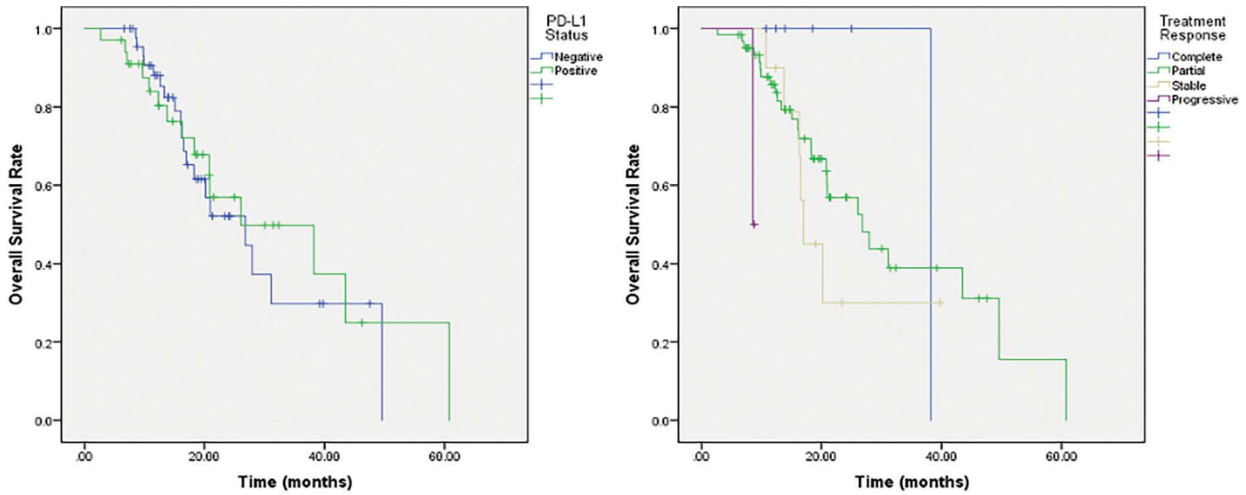

Fig. 1. Effect of PD-L1 status and treatment response on OS (p=0.736 and p=0.036, respectively).
PD-L1: Programmed death-ligand.

were employed to evaluate FDG uptake assessment after definitive therapy.[21] Responses to the treatment were calculated 3 months after the cessation of RT.

Ethical approval for the study was given by Gazi University Clinical Researches Ethics Committee on February 17, 2021.

Results

The mean follow-up of the study was 16.08±11.28 (range, 2.69-60.79) months. The median OS was 26.8 months. The 2-year and 2-year OS ratios were 87% and 54%, respectively. The median PFS was 15.1 months. The 2-year and 2-year PFS ratios were 65% and 30%, respectively. The median MFS was 33 months.

The descriptive statistics for PD-L1-positive and negative groups and comparisons between them are shown in Table 2.

PD-L1 status, age, sex, histology, stage of disease, recurrence, distant metastasis, RT dose, chemotherapy timing, tumor size, and treatment response were analyzed for survival using the log-rank test (p=0.736, p=0.353, p=0.922, p=0.372, p=0.458, p=0.36, p=0.075, p=0.359, p=0.525, p=0.167, and p=0.036, respectively). Only the complete response showed a statistically significant survival advantage (p=0.036) (Table 3 and Fig.1). The median OS for the PD-L1-negative group was 26.7 months and was 26.1 months for the PD-L1-positive group (p=0.736). The 1- and 2-year OS ratios were reported as 88% and 52% for patients with PD-L1-negative disease and 84% and 57% for patients with PD-L1-positive disease.

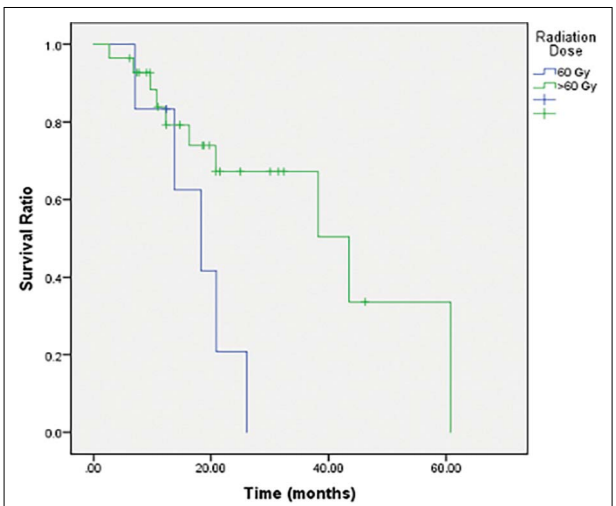

Fig. 2. PD-L1 positive subgroup analysis for RT dose-OS relationship (p=0.034)
PD-L1: Programmed death-ligand; RT: Radiotherapy; OS: Overall survival.

When PD-L1 positive subgroup analysis was performed, doses higher than 60 Gy (n=28) were found superior to the 60 Gy dose group (n=6) according to the OS (p=0.034) (Fig. 2). PD-L1 percentage, histology, stage, recurrence, distant metastasis, and tumor size were not statistically significant (p=0.72, p=0.204, p=0.837, p=0.076, p=0.247, and p=0.422, respectively).

Similarly, when PD-L1 negative subgroup analysis was performed, only the stage of disease presented as statistically significant for OS (p=0.035). Histology, RT dose, recurrence, and distant metastasis were not

Table 4 Log-rank test results for progression-free survival

Variables	Patient number	Mean (months)	Standard deviation	CI %95 (Lower-upper)	Log rank p
Progression free survival	80	19.33	1.60	16.20-22.46	
PD-L1					
Positive	34	20.69	2.38	16.03-25.35	0.372
Negative	46	18.82	2.19	14.53-23.10	
Age					
≤65	59	17.81	1.64	14.59-21.03	0.091
>65	21	23.47	3.65	16.31-30.63	
Histology					
Squamous	53	18.81	1.75	15.39-22.23	0.770
Adeno	24	20.98	3.66	13.81-28.14	
Others	3	15.71	7.82	0.40-31.02	
T Stage					
T1	8	21.81	5.35	11.33-32.29	0.993
T2	13	20.37	4.56	11.44-29.31	
T3	21	14.50	0.86	12.83-16.18	
T4	38	18.53	1.73	15.13-21.92	
N Stage					
N0	8	28.34	7.06	14.51-42.17	**0.017**
N1	6	11.38	1.20	9.04-13.73	
N2	51	19.98	1.79	16.48-23.48	
N3	15	13.11	1.52	10.13-16.09	
Stage					
3A	28	20.33	2.87	14.71-25.95	0.023
3B	40	19.90	1.77	16.44-23.37	
3C	12	12.40	1.49	9.49-15.32	
Radiation dose					
60 Gy	12	18.25	3.65	11.06-25.40	0.945
>60 Gy	68	19.33	1.76	15.88-22.77	
Response					
Complete	6	18.58	3.69	11.34-25.82	**<0.001**
Partial	62	20.62	1.87	16.96-24.28	
Stable	12	13.40	1.74	9.99-16.82	
Progressive	2	6.67	2.03	2.68-10.65	

Disease stage, N stage and treatment response seemed to be effective for PFS. CI: Confidence interval; PD-L1: Programmed death-ligand; Gy: Gray

significantly associated with OS (p=0.528, p=0.369, p=0.805, and p=0.127, respectively).

PFS analysis was performed using the log-rank test for different variables. PD-L1 status, age, histology, T stage, RT dose, and tumor size were found not significant for PFS (p=0.372, p=0.091, p=0.77, p=0.993, p=0.945, and p=0.456, respectively). N stage, clinical stage, and treatment response showed statistical significance for PFS (p=0.017, p=0.023, and p<0.001, respectively) (Table 4 and Fig. 3). Furthermore, treatment response was determined as an independent factor for PFS in Cox multivariate analysis (p=0.015). PFS for patients with N0, N1, N2, and N3 disease was 42.9, 11.2, 16.3, and 11.8 months, respectively (p=0.017). Similarly, PFS for patients with Stages 3A, 3B, and 3C diseases was 14.7, 17.2, and 11.8 months, respectively (p=0.023). PFS for complete and PR and stable and PD was 23.8, 16.1, 11.4, and 4.6 months, respectively (p<0.001). The median PFS for the PD-L1-positive group was 17.2 months and it was 13.8 months for the PD-L1-negative group p=0.372).

When PD-L1-positive subgroup analysis was performed, the PD-L1 expression percentage was seen to be associated with PFS (p=0.024). The median PFS for the <1% PD-L1 expression group was 8.4 months, 1-50% was 18 months, and >50% was 30.7 months.

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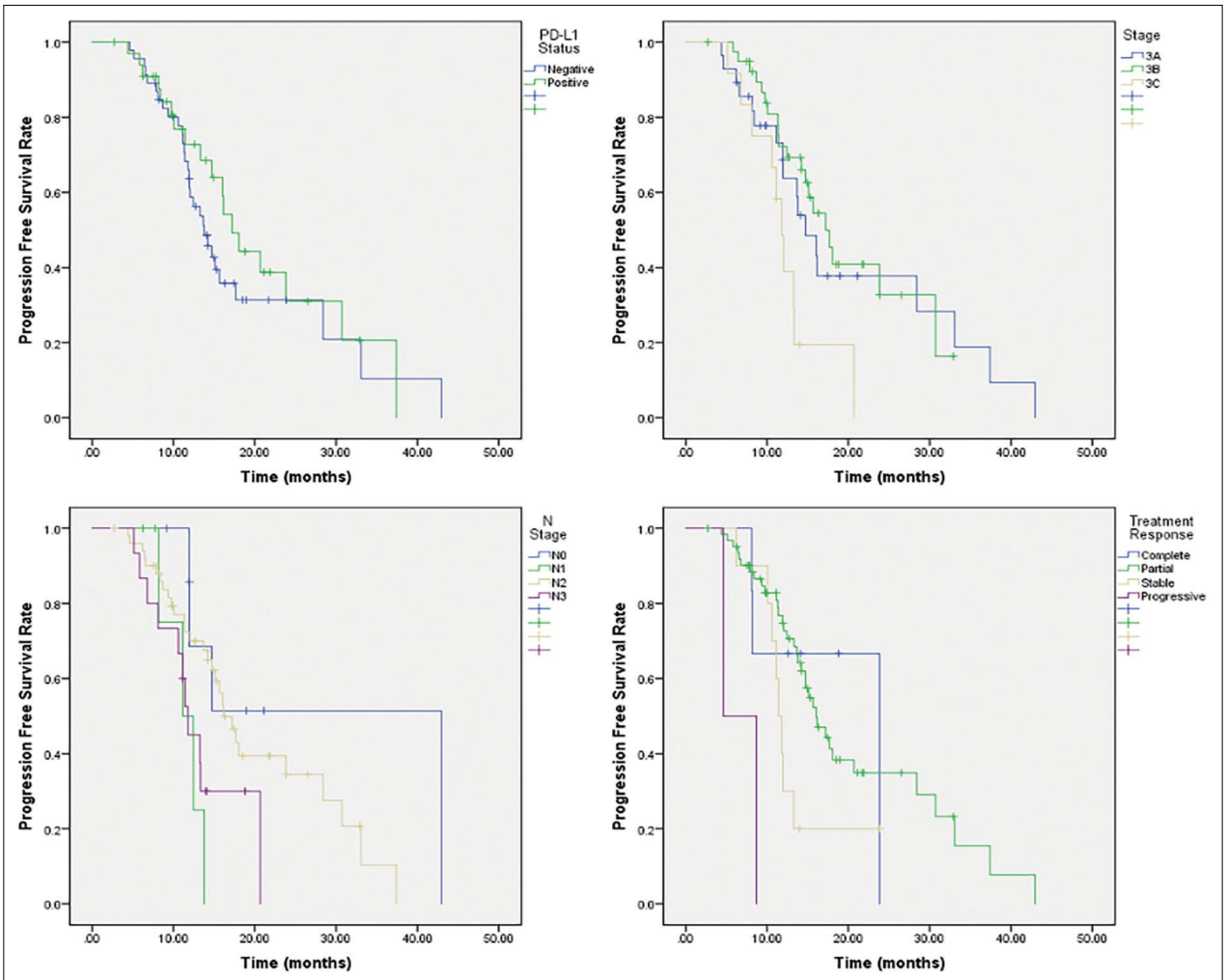

Fig. 3. Effect of PD-L1 status, N stage, disease stage, and treatment response on PFS (p=0.372, p=0.017, p=0.023, and p<0.001, respectively).
PD-L1: Programmed death-ligand.

PD-L1 status, histology, and clinical stage were found associated with MFS in the log-rank test (p=0.015, p=0.002, and p=0.039, respectively) (Table 5 and Fig. 4). The MFS for patients with PD-L1-positive and negative disease was 60.1 and 29 months, respectively. The MFS for SCC, adenocarcinoma, and other histologies were 60.1, 33, and 12 months, respectively. MFS for clinical Stages 3A, 3B, and 3C diseases was 33, 60.2, and 12 months, respectively. In Cox multivariate analysis for MFS, PD-L1 status and histology were determined as independent prognostic factors (p=0.017 and p=0.006, respectively). Age, RT dose, treatment response, recurrence, and tumor size were not significant for MFS (p=0.139, p=0.18, p=0.172, p=0.798, and p=0.36, respectively).

Cross-tabulations were used to analyze the relationship between the PD-L1 status and local recurrence; treatment response and PD-L1 status; PD-L1 expression rate and treatment response; and PD-L1 expression rate and local recurrence. None were statistically significant (p=0.602, p=0.4, p=0.468, and p=0.404, respectively).

Discussion

The median OS for patients with Stage 3 NSCLC treated with definitive CRT in Turkey has been reported as 20 months.[22] However, it was mentioned as 28 months in recent studies in the literature.[6,7] Similarly, with recent studies, we detected 26.8 months of survival in our study. Although PD-L1 inhibitors are not available in Turkey due to the reimbursement limitations of the social insurance system, close follow-up of pa-

Table 5 Log-rank test results for metastasis-free survival

Variables	Patient number	Mean (months)	Standard deviation	CI %95 (Lower-upper)	Log rank p
Metastasis free survival	80	38.87	4.09	30.86-46.88	
PD-L1					
Positive	34	49.87	2.85	21.41-32.56	0.015
Negative	46	26.98	5.50	39.08-60.65	
Age					
≤65	59	31.34	3.01	25.44-37.23	0.139
>65	21	42.84	8.69	25.81-59.86	
Histology					
Squamous	53	45.46	5.39	34.90-56.02	0.002
Adeno	24	26.47	3.91	18.80-34.13	
Others	3	15.71	7.81	0.40-31.02	
T Stage					
T1	8	27.01	6.44	14.38-36.64	0.566
T2	13	37.02	4.37	28.46-45.58	
T3	21	42.94	8.84	25.61-60.26	
T4	38	28.96	2.86	23.35-34.57	
N Stage					
N0	8				
N1	6	21.35	4.80	11.95-30.75	0.075
N2	51	38.81	5.20	28.62-49.50	
N3	15	16.61	1.66	13.37-19.86	
Stage					
3A	28	34.36	3.61	27.28-41.43	**0.039**
3B	40	43.62	6.23	31.42-55.83	
3C	12	14.90	1.84	11.30-18.50	
Radiation dose					
60 Gy	12	23.16	3.50	16.30-30.02	0.180
>60 Gy	68	41.07	4.35	32.54-49.60	
Response					
Complete	6	24.63	3.02	18.71-30.54	0.172
Partial	62	39.28	4.61	30.24-48.32	
Stable	12	27.98	4.78	18.61-37.35	
Progressive	2	8.32	0.44	7.46-9.17	

Significant factors for MFS were PD-L1 status, histology, stage. CI: Confidence interval; PD-L1: Programmed death-ligand; Gy: Gray

tients and administering second-line therapies for all patients with recurrent and PD may provide better OS. The majority (73%) of the patients treated with concurrent CRT in our study and concurrent CRT was confirmed to be superior to sequential CRT for OS in the RTOG-9410 trial.[23] This may also contribute to the prolonged OS.

PD-L1 is the escape pathway of tumors from the immune system of the body. Concordant with this, preclinical evidence indicated poor prognosis with PD-L1 positivity.[14] However, it was shown that blockage of this pathway provides an enormous advantage for the control of the disease.[24] Then, the relationship between PD-L1 and CRT was frequently investigated in the literature. As a result of many studies, PD-L1 is upregulated according to the initial level after the RT or chemotherapy.[25-27] Deng et al.[16] associated this with the inflammatory effects of RT in the tumor microenvironment in their study. Furthermore, it is difficult to obtain tissue samples after RT for PD-L1 evaluation. However, Wang et al.[15] showed that circulating tumor cells could be used for assessing PD-L1 expression after CRT. Nevertheless, although there are numerous studies about the PD-L1-RT relationship, no study in the literature has investigated the predictive value of PD-L1 for RT response. Therefore, we aimed to inves-

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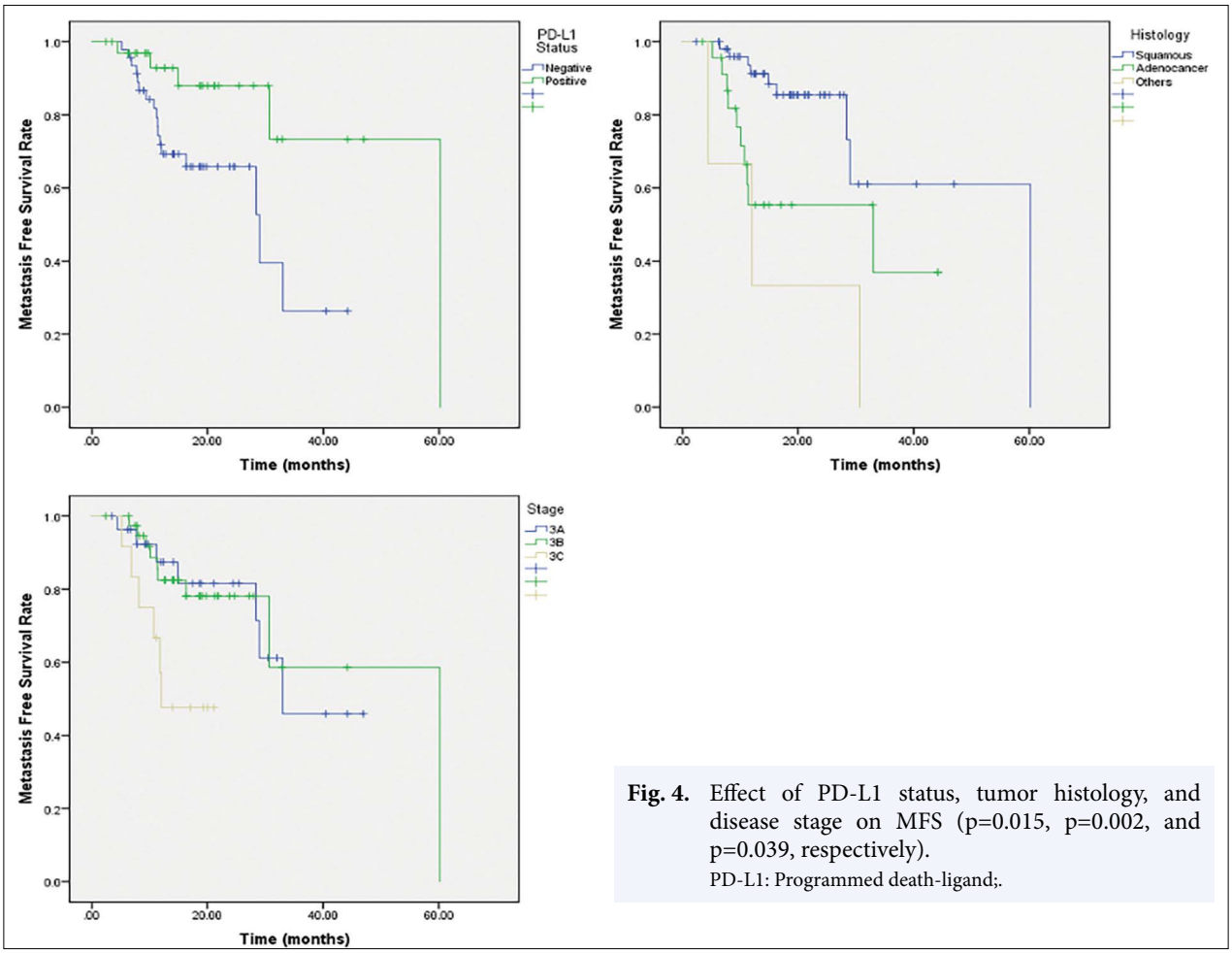

Fig. 4. Effect of PD-L1 status, tumor histology, and disease stage on MFS (p=0.015, p=0.002, and p=0.039, respectively).
PD-L1: Programmed death-ligand;.

tigate this and found no statistically significant difference between the PD-L1 positive and negative groups according to the treatment response in our study. Furthermore, PD-L1 expression percentages were not relative to treatment response. Only distant metastasis incidence was significantly different between the PD-L1-positive and negative groups. Distant metastasis developed in five patients in the PD-L1-positive group, whereas it was 17 in the PD-L1-negative group.

Most patients (91%) in our study received carboplatin+paclitaxel chemotherapy. Therefore, the effect of chemotherapy was neglected while evaluating PD-L1 status and the RT response relationship. Steuer et al.[28] have already shown no difference between the chemotherapy regimens of carboplatin+paclitaxel and cisplatin+etoposide according to the OS, PFS, and treatment response. They also reported 58% of treatment responses with concurrent CRT. However, the total treatment response was 85% in our study. The reason for this may be the excess of concurrent CRT. Hence, Furuse et al.[29] indicated an improved response rate up to 84% with concurrent CRT.

Doses higher than 60 Gy were found superior to 60 Gy doses for OS in the PD-L1-positive subgroup analysis. These data contradict a landmark study of the RTOG for RT doses in lung cancer. The RTOG-0617 study showed no survival advantage for dose escalation up to 74 Gy in Stage 3 NSCLC.[30] However, RTOG-0617 did not contain any analysis for PD-L1 status. Therefore, despite all the disadvantages of the retrospective study, such as the non-homogeneous distribution of patients between the dose groups (n=6 for 60 Gy and n=28 for >60 Gy) and the insufficient number of patients for survival analysis, these data need further research. Furthermore, the mean RT dose was 63.4 Gy for the PD-L1-positive group in our study, and it was much lower than the dose in the RTOG-0617 study.

Dose escalation is a well-studied topic in locally advanced NSCLC. Prolongation of overall treatment time may cause increased repopulation and inferior

outcomes. Furthermore, the escalated dose may contribute to more severe complications and deteriorate the patient's general status.[31] Consequently, hyperfractionated and hypofractionated regimens are also being experimented with in locally advanced NSCLC. Theoretically, these regimens provide higher biologic effective doses and better protection of surrounding normal tissues while shortening the total treatment time. In this regard, one recent review about dose escalation in NSCLC concluded that several hypo and hyperfractionation regimens might present better treatment responses.[32] Furthermore, the authors noted that a stereotactic body radiation therapy boost for residual disease was very beneficial for local control.[32] None of these studies included data for PD-L1 status. Concordantly, the predictive value of PD-L1 status at the beginning of the treatment for dose escalation may need further research.

The primary endpoint of our study was to evaluate the predictive value of RT for the treatment response according to the PD-L1 status. Therefore, patients treated with similar chemotherapy regimens were selected to better distinguish the effect of RT for the treatment response. However, our study has main limitations such as the heterogeneity of the groups, and the insufficient total number of patients for survival analyses caused by the retrospective nature of our investigation. Nevertheless, we believe that some of our research data may guide further prospective studies.

Conclusion

PD-L1 status did not seem to be predictive for RT response. However, despite the low number of patients in the 60 Gy group, our study showed that dose escalation could improve survival in PD-L1 positive locally advanced NSCLC. There is a disparity between the RTOG 0617 study, which reported that dose-escalation did not affect OS, and our results. We are aware that our data are not strong enough to claim such a result. However, this finding may draw attention to dose escalation studies, and in the era of tailored therapy, this knowledge may provide valuable for selecting the correct RT dose for patients.

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