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PD-L1 and ALK expressions in stages III and IV colorectal cancer and their correlation with clinicopathological features

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Abstract

Colorectal cancer (CRC) is a type of cancer with a high recurrence rate. Studies are in the progress to identify effective treatments for CRC patients. We aimed to compare the expression of programmed death-ligand 1 (PD-L1) and anaplastic lymphoma kinase (ALK) in stages III and IV CRC patients and evaluate the clinicopathological significance associated with their expression. A total of 169 stages III and IV CRC specimens was tested for ALK (D5F3) and PD-L1 (SP142 and SP263) expression using immunohistochemistry on formalin-fixed paraffin-embedded specimens. Clinicopathological characteristics were obtained through a review of the medical records and hematoxylin and eosin slides. Expression of PD-L1 SP142 and PD-L1 SP263 was detected in 17.8% and 28.4% of CRC patients, respectively. ALK D5F3 expression was detected in 4 cases. PD-L1 SP142 expression was significantly correlated with tumor site and serum carcinoembryonic antigen (CEA) level. PD-L1 SP263 expression was associated with serum tumor marker level and tumor-infiltrating lymphocytes. In univariate analysis, PD-L1 expression was correlated with shorter survival in CRC patients. PD-L1 SP263 expression was an independent indicator of shorter survival in multivariate analysis. PD-L1 expression was associated with poor prognostic factors, including shorter survival. Further investigation is needed to understand the mechanisms of the association between PD-L1 expression and unfavorable CRC prognosis.

Abbreviations: ALK = anaplastic lymphoma kinase, CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, CT = computed tomography, FFPE = formalin-fixed paraffin-embedded, H&E = hematoxylin and eosin, HR = hazard ratio, ITWG = International TIL Working Group, NSCLC = non-small cell lung carcinoma, OS = overall survival, PD-1 = programmed death receptor-1, PD-L1 = programmed death-ligand 1, RFS = relapse-free survival, TC = tumor cell, TILs = tumor-infiltrating lymphocytes, TMA = tissue microarray.

Keywords: colorectal cancer, immunohistochemistry, programmed death-ligand 1

1. Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer mortality worldwide. In 2022, the number of newly diagnosed CRC cases was approximately 2 million, and the number of deaths was estimated to be 903,859. The incidence rates of CRC varied across countries. In high-income countries, the incidence rate of CRC is high, while it is low in low-income countries.[1] The difference of the incidence depends on a variety of factors, including environmental and molecular factors, intestinal microbiota, and metabolites.[2] While surgery is a major treatment option for stages I and II CRC due to its low recurrence rate, the National Comprehensive Cancer Network guideline recommends individually tailored treatment for stages III and IV CRC. Recent studies have emphasized comprehensive treatment including chemotherapy, targeted therapy, radiotherapy, and immunotherapy.[3,4]

Immunotherapy targeting programmed death receptor-1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade emerged as a

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The authors have no conflicts of interest to declare.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The study was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No. 2024-05-019).

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novel treatment for solid tumors such as non-small cell lung carcinoma (NSCLC) and malignant melanoma. Recent studies have also demonstrated the efficacy of immunotherapy in patients with metastatic CRC.[5] PD-L1, a ligand for PD-1, is a well-known biomarker assayed by immunohistochemistry for its response to immunotherapy. Previous studies have reported that high expression of PD-L1 is correlated with clinical benefits from immunotherapy. The correlation between PD-L1 expression and response to immunotherapy in patients with CRC has not been fully elucidated.[5,6]

Anaplastic lymphoma kinase (ALK), which is the kinase partner associated with anaplastic lymphoma, is widely studied biomarker analyzed by molecular genetic study and immunohistochemistry. Recently, ALK inhibitors have been approved in the treatment of NSCLC and *ALK* fusion harboring tumor.[7] Immunohistochemical staining for ALK has been demonstrated as a screening test for evaluation of *ALK* fusion harboring tumor. Although the incidence of ALK-positive CRC is low, ALK inhibitors may become a target therapy for CRC based on the evaluation of ALK expression. Previous literatures have shown that genetic alterations can influence the engagement of the immune system within tumors. EML4-ALK fusions activate the PD-1/PD-L1 pathway via PD-L1 upregulation.[8] We hypothesized that expression of PD-L1 and ALK in patients with CRC are functionally interwined. In this study, we evaluated ALK and PD-L1 expression in 169 stages III and IV CRC specimens and analyzed their association with clinicopathological features.

2. Materials and methods

2.1. Patients and tissue samples

A total of 224 patients with CRC who underwent surgical resection at Jeonbuk National University Hospital between

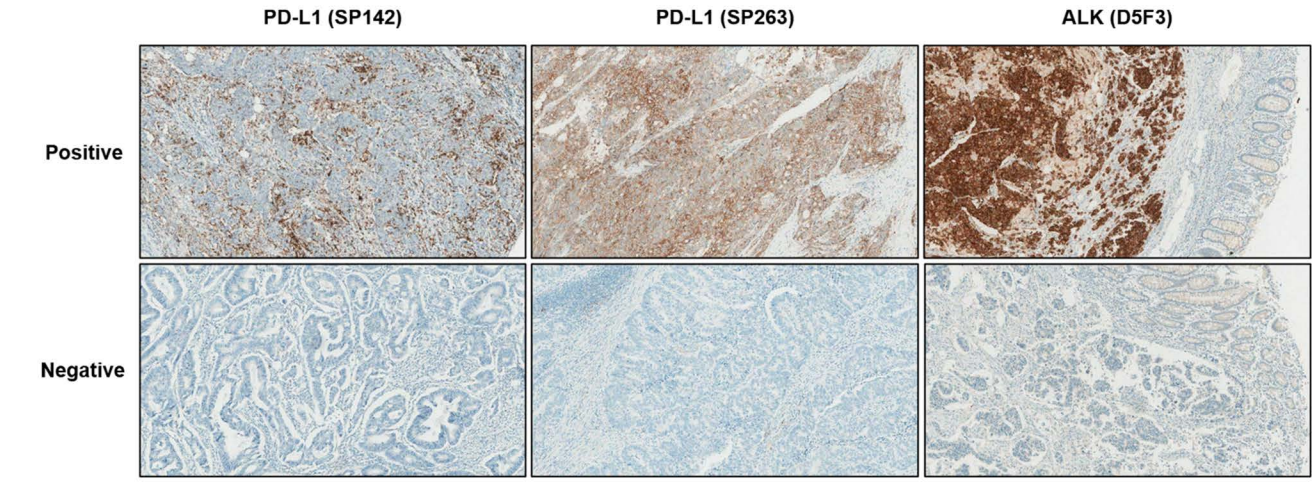

Figure 1. Positive and negative expression patterns of PD-L1 (SP142), PD-L1 (SP263), ALK (D5F3) antibodies. ALK = anaplastic lymphoma kinase, PD-L1 = programmed death-ligand 1.

Table 1

Association between patterns of PD-L1 (SP142) expression and clinicopathological characteristics.

Characteristics		No	PD-L1 negative (n = 139)	PD-L1 positive (n = 30)	*P*
Age, yr	≦70	79	66 (83.5%)	13 (16.5%)	.680
	>70	90	73 (81.1%)	17 (18.9%)	
Sex	Male	93	79 (84.9%)	14 (15.1%)	.310
	Female	76	60 (78.9%)	16 (21.1%)	
Tumor site*	Right	60	44 (73.3%)	16 (26.7%)	.024
	Left	109	95 (87.2%)	14 (12.8%)	
Serum CEA	Normal	82	76 (92.7%)	6 (7.3%)	<.001
	Elevation	87	63 (72.4%)	24 (27.6%)	
Serum CA19-9	Normal	151	122 (80.8%)	29 (19.2%)	.152
	Elevation	18	17 (94.4%)	1 (5.6%)	
TNM stage	III	94	75 (79.8%)	19 (20.2%)	.349
	IV	75	64 (85.3%)	11 (14.7%)	
TIL	Low	152	125 (82.2%)	27 (17.8%)	.991
	High	17	14 (82.4%)	3 (17.6%)	
ALK (D5F3)	Negative	165	138 (83.6%)	27 (16.4%)	.002
	Positive	4	1 (25.0%)	3 (75.0%)	
Death	Absent	127	117 (92.1%)	10 (7.9%)	<.001
	Present	42	22 (52.4%)	20 (47.6%)	
Relapse	Absent	107	100 (93.5%)	7 (6.5%)	<.001
	Present	62	39 (62.9%)	23 (37.1%)	

Left colon: defined as the segment from the distal one-third of the transverse colon to the rectum.

Abbreviations: ALK = anaplastic lymphoma kinase, CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, PD-L1 = programmed death-ligand 1, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

* Right colon: defined as the segment from the cecum to the proximal two-thirds of the transverse colon

April 2019 and August 2020 initially was included. After excluding patients who had received neoadjuvant chemotherapy or radiotherapy (n = 55), a final cohort of 169 was enrolled in the research. For clinical stages I to 8 III patients with CRC, resectional surgery was the first choice of treatment option. Stage IV patients with CRC underwent palliative resectional surgery and received adjuvant chemotherapy. The inclusion criteria of this study are stages III and IV patients with CRC based on advanced-stage (stages III and IV) CRC patients need additional treatment after surgery. The patients group received no adjuvant treatment including chemotherapy, radiotherapy and immunotherapy. Two pathologists (KYJ and ARA) blinded to the clinical information reviewed the CRC specimens from 169 CRC patients. The hematoxylin and eosin (H&E) slides of all formalin-fixed paraffin-embedded (FFPE) tissue blocks from CRCs were reviewed based on the WHO classification of tumors of the digestive system. The Tumor-Node-Metastasis stage of the patients was classified by the American Joint Committee on Cancer staging system 8th edition. Assessment of tumor-infiltrating lymphocytes (TILs) was performed using the International TIL Working Group (ITWG) methodology. For analysis, the TIL level were classified as low or high based on a cutoff of 55%. Preoperative serum cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) were measured with cutoff levels of 37 kU/L and 5.0 ng/mL, respectively. For analysis, the entire colon was divided into right and left -sides. The right-sided colon was defined as the segment including the cecum, the ascending colon, and the proximal two-thirds of the transverse colon. The left-sided colon was the segment including the distal one-third of the transverse colon, the descending colon, the sigmoid colon, and the rectum. Postoperative surveillance with abdominal computed tomography (CT) for CRC patients was performed every 3 months to detect recurrence and metastasis. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Jeonbuk National University Hospital (IRB No. 2024-05-019). Informed consent was waived.

2.2. Immunohistochemical staining for ALK and PD-L1

Immunohistochemical staining was performed for ALK and PD-L1 in all cases. Tissue microarrays (TMA) comprising 2-mm-diameter cores were created from FFPE tissue blocks for immunohistochemistry. The following commercially available antibodies were used: ALK (clone: D5F3, dilution: Ready to use; Roche), PD-L1 (clone: SP142, dilution: Ready to use; Roche), and PD-L1 (clone: SP263, dilution: Ready to use; Roche). Immunohistochemical staining of FFPE sections was performed by the Ventana BenchMark ULTRA (Roche Diagnostics, Mannheim, Germany).

2.3. Evaluation of ALK and PD-L1 expression

The slides that had been stained for ALK and PD-L1 were evaluated by 2 pathologists (JKY and ARA) who were blind to the clinicopathologic data. Interpretation of the ALK (D5F3), PD-L1 (SP142), and PD-L1 (SP263) assays was based on Ventana interpretation guide for all cases. The positivity of ALK (D5F3) was defined as the presence of strong granular cytoplasmic staining in tumor cells (TCs) of any percentage. TC and immune cell scoring was performed according to the Ventana interpretation guide for PD-L1 (SP142). A case was considered positive for PD-L1 (SP142) if it showed ≥ 50% TC or ≥ 10% IC. Specimens with ≥ 1% TC were defined as PD-L1 (SP263) positive (Fig. 1).

2.4. Statistical analysis

Clinicopathologic predictors of patients with CRC were assessed using the chi-square test and Cox proportional hazards regression analysis. The prognosis of CRC patients was evaluated for overall survival (OS) and relapse-free survival (RFS) through December 2022. In the OS analysis, patient death by CRC was treated as an event. OS was defined from the date of pathologic diagnosis to the date of death or the last follow-up. RFS was defined from the date of pathologic

Table 2

Association between patterns of PD-L1 (SP263) expression and clinicopathological characteristics.

Characteristics		No	PD-L1 negative (n = 121)	PD-L1 positive (n = 48)	*P*
Age, yr	≦70	79	56 (70.9%)	23 (29.1%)	.848
	>70	90	65 (72.2%)	25 (27.8%)	
Sex	Male	93	68 (73.1%)	25 (26.9%)	.628
	Female	76	53 (69.7%)	23 (30.3%)	
Tumor site*	Right	60	40 (66.7%)	20 (33.3%)	.292
	Left	109	81 (74.3%)	28 (25.7%)	
Serum CEA	Normal	82	76 (92.7%)	6 (7.3%)	<.001
	Elevation	87	45 (51.7%)	42 (48.3%)	
Serum CA19-9	Normal	151	104 (68.9%)	47 (31.1%)	.023
	Elevation	18	17 (94.4%)	1 (5.6%)	
TNM stage	III	94	63 (67.0%)	31 (33.0%)	.140
	IV	75	58 (77.3%)	17 (22.7%)	
TIL	Low	152	105 (69.1%)	47 (30.9%)	.030
	High	17	16 (94.1%)	1 (5.9%)	
PD-L1 (SP142)	Negative	139	112 (80.6%)	27 (19.4%)	<.001
	Positive	30	9 (30.0%)	21 (70.0%)	
ALK (D5F3)	Negative	165	118 (71.5%)	47 (28.5%)	.879
	Positive	4	3 (75.0%)	1 (25.0%)	
Death	Absent	127	109 (85.8%)	18 (14.2%)	<.001
	Present	42	12 (28.6%)	30 (71.4%)	
Relapse	Absent	107	104 (97.2%)	3 (2.8%)	<.001
	Present	62	17 (27.4%)	45 (72.6%)	

Left colon: defined as the segment from the distal one-third of the transverse colon to the rectum

Abbreviations: ALK = anaplastic lymphoma kinase, CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, PD-L1 = programmed death-ligand 1, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

* Right colon: defined as the segment from the cecum to the proximal two-thirds of the transverse colon

diagnosis to the date of relapse, death, or final follow-up. Survival curves were plotted using the Kaplan–Meier method and analyzed using the log-rank test. The statistical analysis was performed using SPSS software version 29.0 (IBM Corp., Armonk, NY, USA). *P*-values < 0.05 were considered statistically significant.

3. Results

3.1. Immunohistochemical staining and the correlations with clinicopathological characteristics in stages III and IV CRC patients

The mean age was 70.26 years and 45.0% of patients were female. Relapse occurred in 62 (36.7%) patients and death occurred in 42 (24.9%) during follow-up. For each patient, the date of the last follow-up was that of the last contact or of death of patient up to December 2022. The follow-up period was about 3 years. PD-L1 (SP142) positivity was found in 30 of 169 cases (17.8%). The results revealed that PD-L1 (SP142) positive cases were significantly associated with right-sided colon cancer ($P = .024$), CEA elevation ($P < .001$), and ALK (D5F3) positivity ($P = .002$) (Table 1). PD-L1 (SP263) positivity was observed in 48 of 169 cases (28.4%). PD-L1 (SP263) expressions was significantly associated with CEA elevation ($P < .001$) and CA19-9 elevation ($P = .023$) and inversely correlated with high TILs ($P = .030$) (Table 2). ALK (D5F3) positivity was found in only 4 of 169 cases (2.4%) and showed no significant correlation with any clinicopathological factors. In addition, PD-L1 (SP142) expression was positively correlated with PD-L1 (SP263) expression ($P < .001$).

3.2. Relationship between PD-L1 expression and the prognostic impact of patients with stages III and IV CRC

To evaluate the relationship between PD-L1 expression and the prognostic impact of patients with stages III and IV CRC, we

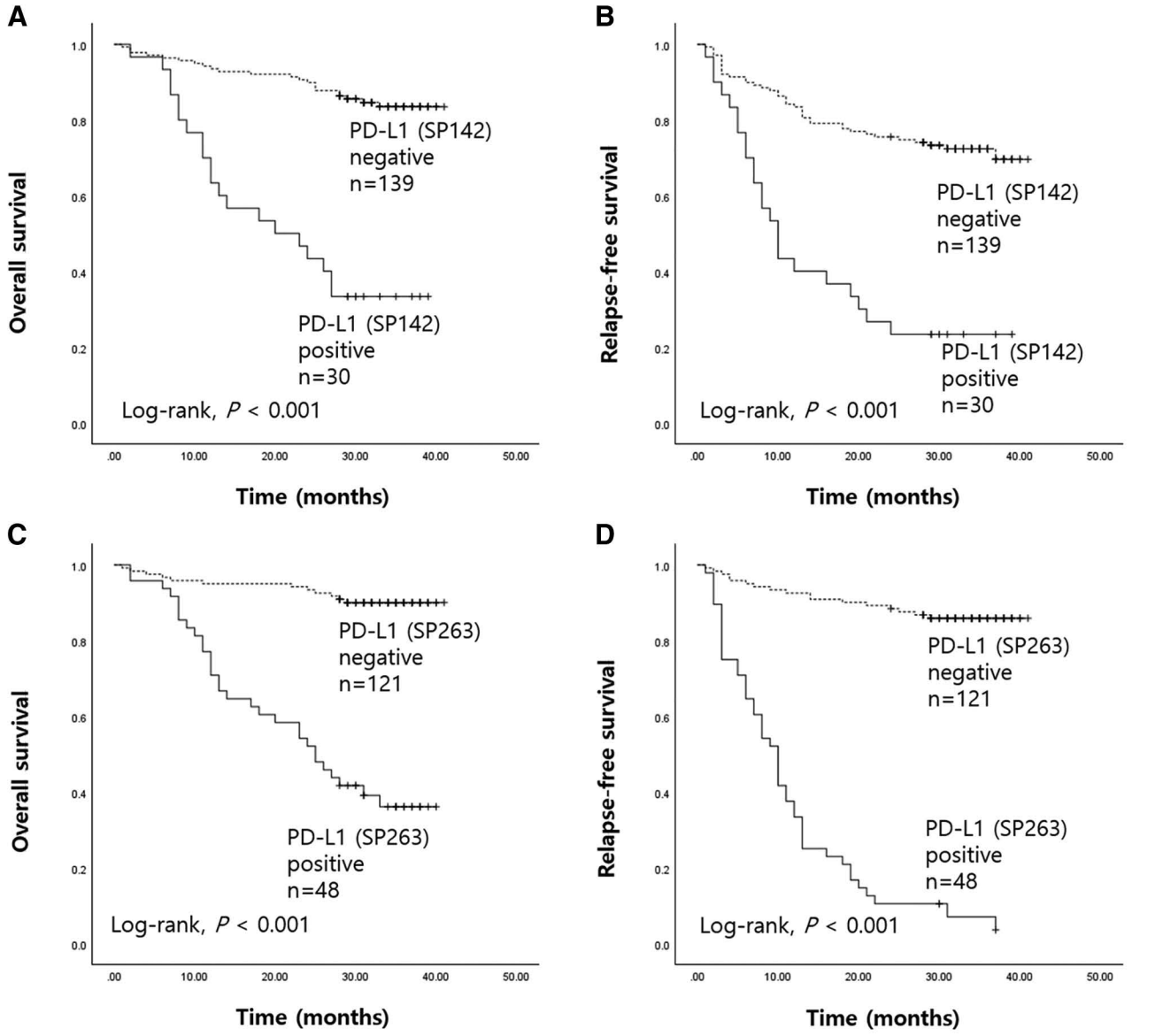

Figure 2. Kaplan–Meier curves of overall survival (OS) and relapse-free survival (RFS). (A) Kaplan–Meier curves for OS PD-L1 (SP142) expression in stages III, IV colorectal cancers. (B) Kaplan–Meier curves for RFS PD-L1 (SP142) expression in stages III, IV colorectal cancers. (C) Kaplan–Meier curves for OS PD-L1 (SP263) expression in stages III, IV colorectal cancers. (D) Kaplan–Meier curves for RFS PD-L1 (SP263) expression in stages III, IV colorectal cancers. PD-L1 = programmed death-ligand 1.

Table 3

Univariate Cox proportional hazards regression analysis for the overall survival and relapse-free survival of stages III and IV CRC patients.

		OS		RFS	
Characteristics	**No.**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, yr, >70 (vs ≦ 70)	90/169	2.192 (1.139–4.217)	.019	1.216 (0.736–2.010)	.445
Sex, female (vs male)	76/169	1.371 (0.748–2.514)	.307	1.055 (0.639–1.741)	.833
Tumor site, Left colon (vs Right colon)	109/169	0.637 (0.347–1.170)	.146	0.888 (0.530–1.488)	.652
CEA elevation (vs Normal range)	87/169	3.458 (1.699–7.039)	<.001	3.353 (1.895–5.933)	<.001
CA 19-9 elevation (vs Normal range	18/169	0.391 (0.094–1.617)	.195	0.494 (0.179–1.365)	.174
TNM stage, IV (vs III)	75/169	0.739 (0.396–1.378)	.341	0.747 (0.448–1.246)	.264
TIL High (vs Low)	17/169	0.415 (0.100–1.718)	.225	0.397 (0.124–1.268)	.119
PD-L1 (SP142) Positive (vs Negative)	30/169	6.417 (3.472–11.861)	<.001	4.284 (2.539–7.229)	<.001
PD-L1 (SP263) Positive (vs Negative)	48/169	8.896 (4.532–17.460)	<.001	15.655 (8.703–28.162)	<.001

Abbreviations: CA19-9 = cancer antigen 19-9, CEA = carcinoembryonic antigen, CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, OS = overall survival, PD-L1 = programmed death-ligand 1, RFS = relapse-free survival, TILs = tumor-infiltrating lymphocytes, TNM = Tumor-Node-Metastasis.

analyzed the OS rate and RFS rate according to PD-L1 expression. Kaplan–Meier curves based on the positivity of PD-L1 (SP142) and PD-L1 (SP263) showed significantly shorter OS and RFS (Fig. 2). Table 3 shows the univariate analysis for OS and RFS in patients with stages III and IV CRC. The factors significantly associated with shorter OS were age (hazard ratio [HR], 2.192; 95% confidence interval [CI], 1.139–4.217; $P = .019$), preoperative serum level CEA elevation (HR, 3.458; 95% CI, 1.699–7.039; $P < .001$), PD-L1 (SP142) positivity (HR, 6.417; 95% CI, 3.472–11.861; $P < .001$) and PD-L1 (SP263) positivity (HR, 8.896; 95% CI, 4.532–17.460; $P < .001$). Preoperative serum level CEA elevation (HR, 3.353; 95% CI, 1.895–5.933; $P < .001$), PD-L1 (SP142) positivity (HR, 4.284; 95% CI, 2.539–7.229; $P < .001$), and PD-L1 (SP263) positivity (HR, 15.655; 95% CI, 8.703–28.162; $P < .001$) were all significantly associated with shorter RFS. We also performed multivariate analysis for OS and RFS of patients with stages III or IV CRC (Table 4). For the OS, older age (HR, 2.433; 95% CI, 1.256–4.712; $P = .008$), PD-L1 (SP142) expression (HR, 2.996; 95% CI, 1.536–5.847; $P = .001$) and PD-L1 (SP263) expression (HR, 6.841; 95% CI, 3.259–14.206; $P < .001$) were independent prognostic factors. PD-L1 (SP263) expression (HR, 15.655; 95% CI, 8.703–28.162; $P < .001$) was an independent indicator of shorter RFS.

Table 4

Multivariate Cox regression analysis for the overall survival and relapse-free survival of stages III and IV CRC patients.

	OS		RFS	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, yr, >70 (vs ≦ 70)	2.433 (1.256–4.712)	.008		
PD-L1 (SP142) Positive (vs Negative)	2.996 (1.536–5.847)	.001		
PD-L1 (SP263) Positive (vs Negative)	6.841 (3.259–14.206)	<.001	15.655 (8.703–28.162)	<.001

Variables considered in multivariate analysis for overall survival were age, sex, tumor site, CEA elevation, CA19-9 elevation, Tumor-Node-Metastasis stage, tumor-infiltrating lymphocytes, PD-L1 (SP142) Positive, and PD-L1 (SP263) Positive.

Abbreviations: CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, OS = overall survival, PD-L1 = programmed death-ligand 1, RFS = relapse-free survival.

4. Discussion

Evaluation of the expression of ALK and PD-L1 and analysis of the correlations between immunohistochemical expression and clinicopathological features in patients with stages III or IV CRC are beneficial for development of tailored treatment. *ALK* is a gene that encodes a receptor kinase protein that plays a crucial role in the pathogenesis of malignant tumor. Among solid tumors, *ALK* mutations are most common in lung cancer and rare in CRC.[9,10] In this study, ALK expressions was only observed in 4 of the 169 samples; these findings are consistent with those of previous studies. With only 4 ALK-positive cases, it is likely that the small sample size limits the significance of these findings. Therefore, as a prognostic marker, ALK assessment is of little value. A limitation of the current study is that the *ALK* mutation was only assayed by immunohistochemistry and the data on ALK are insufficient to draw any meaningful result.

In the current study, we investigated the immunohistochemical expression of PD-L1 (2 clones: SP142 and SP263) in human CRC tissues. Our results revealed PD-L1 (SP142) and PD-L1 (SP263) expression in 17.8% (30/169) and 28.4% (48/169) of stages III and IV CRC samples, respectively. PD-L1 (SP142) positive cases were correlated with right-sided colon cancer, CEA elevation, and ALK (D5F3) expression. PD-L1 (SP263) positive cases were correlated with CEA elevation and CA19-9 elevation. PD-L1 (SP142) and PD-L1 (SP263) expression was associated with shorter OS and RFS on univariate analysis. PD-L1 (SP142) was significantly associated with shorter OS on multivariate analysis, while PD-L1 (SP263) was significantly associated with shorter OS and RFS on multivariate analysis.

PD-L1, a ligand for the PD-L1 receptor, is expressed in the tumor immune microenvironment and TCs. The PD-1 receptor is an immune inhibitory receptor expressed on activated T cells, B cells, and myeloid cells. Immunotherapy has emerged as a novel treatment for malignant tumors. Immune checkpoint

inhibitors, which target PD-1 or PD-L1, have demonstrated significant responses in NSCLC, malignant melanoma, and urothelial carcinoma. The clinical benefit of immune checkpoint inhibitors remains controversial in CRC, and the mechanism of immune checkpoint inhibitors within the tumor microenvironment is unclear. Only microsatellite instable CRC revealed a favorable response to the immune checkpoint inhibitors pembrolizumab and nivolumab in the CheckMate 142 trial, KEYNOTE-177. These clinical trials have also demonstrated the diagnostic value of PD-L1 as a biomarker for the efficacy of pembrolizumab or nivolumab in patients with advanced CRC, although different antibodies and scoring systems are needed.[11]

The prognostic value of PD-L1 expression in patients with CRC remains controversial. PD-L1 expressions is thought to act as a biomarker for poor prognosis, poorly differentiated tumor, and lymphatic invasion in patients with CRC.[12] However, other studies have demonstrated that PD-L1 expression is a favorable prognostic factor in patients with CRC.[13] Therefore, the clinical significance of PD-L1 expression is controversial. The current study revealed that PD-L1 expression was correlated with unfavorable clinicopathologic factors and shorter OS and RFS in stages III and IV CRC patients. These findings suggest that stage III or IV CRC patients with PD-L1 expression are good candidates for immunotherapy and immune checkpoint inhibitors, which may improve the condition of patients with poor prognosis.

There are some limitations to this study. There is the potential underestimation of PD-L1 expression using TMAs compared to whole-tissue sections. Although the TMA consisted of 2 cores in each case, this may be a limiting factor due to the heterogeneous expression of PD-L1. Furthermore, the consistency between PD-L1 (SP142) and PD-L1 (SP263) based on the same cutoff and scoring system was not evaluated. In addition, the patients' clinical responses to immune checkpoint inhibitors could not be evaluated. Therefore, further studies are needed to clarify the therapeutic response of immunotherapy and interchangeability between the 2 clones within CRC.

Author contributions

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