ORIGINAL ARTICLE

Retrospective Study

Programmed death ligand-1 expression and its prognostic role in esophageal squamous cell carcinoma

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Abstract

AIM
To investigate the expression and prognostic role of programmed death ligand-1 (PD-L1) in locally advanced esophageal squamous cell carcinoma (ESCC).

METHODS
A total of 200 patients with ESCC who underwent radical esophagectomy with standard lymphadenectomy as the initial definitive treatment in Seoul National University Hospital from December 2000 to April 2013 were eligible for this analysis. Tissue microarrays were constructed by collecting tissue cores from surgical specimens, and immunostained with antibodies directed against PD-L1, p16, and c-Met. Medical records were reviewed retrospectively to assess clinical outcomes. Patients were divided into two groups by PD-L1 status, and significant differences in clinicopathologic characteristics between the two groups were assessed.

RESULTS
Tumor tissues from 67 ESCC patients (33.5%) were PD-L1-positive. Positive p16 expression was observed in 21 specimens (10.5%). The H-score for c-Met expression was $\geqslant$ 50 in 42 specimens (21.0%). Although PD-L1-positivity was not significantly correlated with any clinical characteristics including age, sex, smoking/alcoholic history, stage, or differentiation, H-scores for c-Met expression were significantly associated with PD-L1-positivity (OR = 2.34, 95%CI: 1.16-4.72, P = 0.017). PD-L1 expression was not significantly associated with a change in overall survival (P = 0.656). In contrast, the locoregional relapse rate tended to increase (P = 0.134), and the distant metastasis rate was significantly increased (HR = 1.72, 95%CI: 1.01-2.79, P = 0.028) in patients with PD-L1-positive ESCC compared to those with PD-L1-negative ESCC.

CONCLUSION
PD-L1 expression is positively correlated with c-Met expression in ESCC. PD-L1 may play a critical role in distant failure and progression of ESCC.

Key words: Esophageal neoplasm; Programmed death ligand-1 protein; c-Met protein; Prognosis; p16INK4A protein

Core tip: The clinical significance of expression of programmed death ligand-1 (PD-L1) in esophageal squamous cell carcinoma (ESCC) has not yet been fully established. We analyzed tissue microarrays of surgical specimen of 200 ESCC patients by immunohistochemistry with antibodies directed against PD-L1, p16, and c-Met.

Our results suggest that tumors from approximately one-third of the ESCC patients are positive for PD-L1 expression, and PD-L1 expression is positively correlated with c-Met expression. Although PD-L1 positivity was not found to be associated with survival of ESCC patients, we show that it may play a critical role in distant failure and progression of ESCC.

INTRODUCTION

Esophageal cancer is one of the most common gastrointestinal malignancies and is highly prevalent in Asia. Esophageal squamous cell carcinoma (ESCC) represents the most common histological type of esophageal cancer, accounting for more than 90% of all cases in Asian patients[1]. Although the 5-year survival rate for patients with ESCC has improved in recent decades, the prognosis remains unfavorable due to the invasive nature of the disease and the frequency of late diagnosis[2].

An improved understanding of immunobiology has uncovered the interaction between programmed death ligand-1 (PD-L1) and programmed death 1 (PD-1) as one of mechanisms by which cancer cells evade immune surveillance. PD-1 is a negative co-stimulatory factor that inhibits T cell activation when activated by PD-L1 or one of its other ligands[3,4], PD-L1 is a cell surface glycoprotein that belongs to the B7 family and is expressed not only on normal cells, such as T cells, B cells, monocytes, macrophages, and dendritic cells, but also on cancer cells[4-7]. The PD-L1/PD-1 interaction has been found to be associated with poor prognosis and clinical outcomes in various cancers such as non-small cell lung cancer, breast cancer, gastric cancer, soft tissue sarcomas and meningioma[8]; however, its prognostic value is still controversial. Immune checkpoint-blocking agents directed at this interaction have been clinically successful and have been shown to produce a durable clinical response in esophageal cancer patients[9].

Considering the clinical importance of PD-L1, there is great interest in understanding the mechanisms that regulate its expression. PD-L1 upregulation has been reported in human papilloma virus (HPV)-associated malignancies, including uterine, cervical, and head and neck cancers[10-12]. PD-L1 expression may be associated with HPV infection, which represents one of the potential causes of ESCC[13]. Furthermore, c-Met, a receptor tyrosine kinase that is aberrantly activated
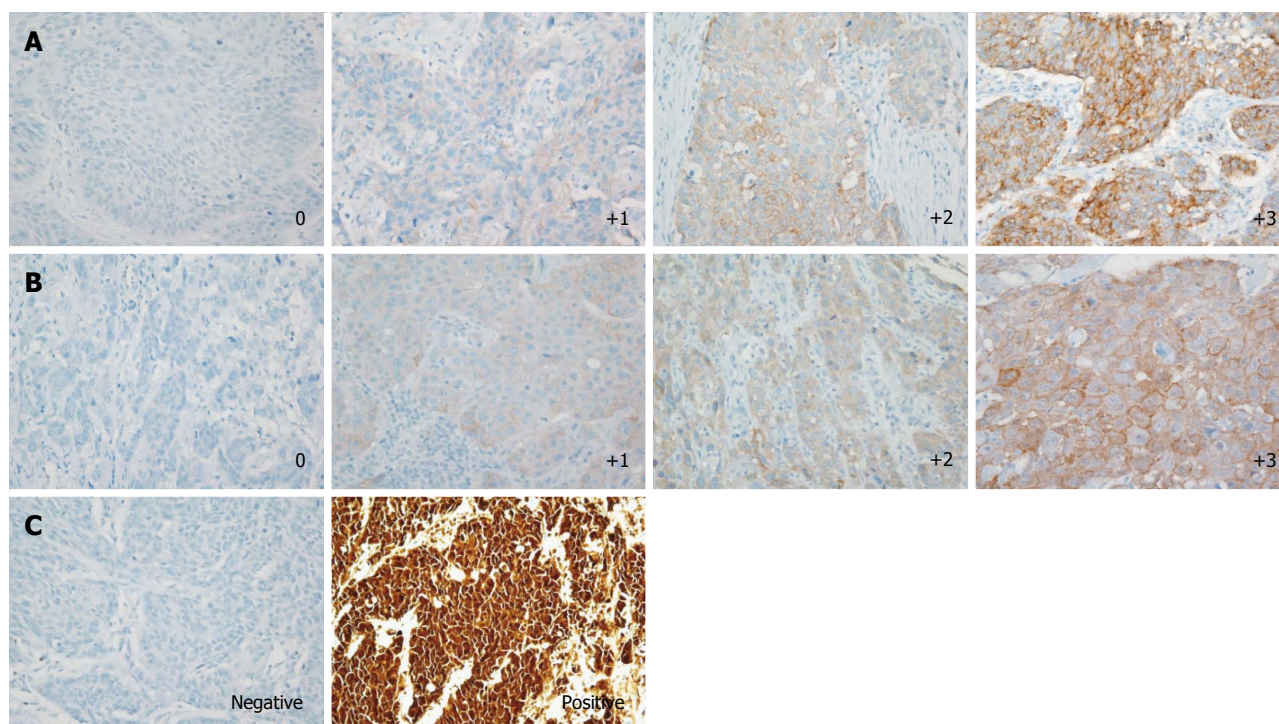
Figure 1 Representative immunohistochemical images of programmed death ligand-1, c-Met, and p16 expression in esophageal squamous cell carcinoma tissues. A: PD-L1 expression was scored from 0 to 3+. Cases with scores of 0 were considered PD-L1-negative; B: c-Met intensity was scored from 0 to 3+. The H-score was calculated for each case. Cases with H-scores ≥ 50 were considered positive for c-Met expression; C: p16 expression was scored as negative or positive (Original magnification, × 400). PD-L1: Programmed death ligand-1.

in numerous human cancers[14], has been shown to promote PD-L1 overexpression in renal cell and pulmonary squamous cell carcinoma[15,16]. However, a comprehensive analysis of the correlation between PD-L1 and c-Met expression in ESCC has not yet been reported.

In this study, we aimed to investigate the expression of PD-L1 in ESCC and explore the correlation between PD-L1 expression and c-Met, as well as p16, a surrogate marker for HPV infection[17]. Additionally, we evaluated the potential for a prognostic role for PD-L1, p16, and c-Met expression in ESCC.

MATERIALS AND METHODS

Patients and samples

Patients with ESCC who underwent radical esophagectomy with standard lymphadenectomy (two-field or three-field lymphadenectomy) as the initial definitive treatment in Seoul National University Hospital from December 2000 to April 2013 were eligible for this retrospective analysis. All tumor tissues were confirmed to be ESCC through hematoxylin and eosin staining after surgical resection. Tissue microarrays (TMAs; 2 mm in diameter) were constructed by collecting tissue cores from representative intratumoral areas from surgical specimens. The pathologic tumor-node-metastasis (TNM) stage was characterized according to the 7th American Joint Committee on Cancer Guidelines[18].

Treatment strategies

Treatment decisions were made via a multidisciplinary team-based approach. All patients without clinical evidence of metastatic disease were treated with radial esophagectomy. The type of esophageal resection was dictated by the size, stage, and location of the primary tumor. According to the clinician's judgment, selected patients were offered neoadjuvant or adjuvant chemotherapy with or without radiation therapy. The chemotherapy regimen was fluoropyrimidine-/taxene-based and was selected based on the performance statuses, comorbidities, and toxicity profiles of individual patients.

Immunohistochemistry

Immunohistochemistry (IHC) was performed using the Benchmark XT automated staining system (Ventana Medical Systems, Tucson, AZ, United States) to estimate the expression of PD-L1, p16, and c-Met. A rabbit anti-PD-L1 (E1L3N) XP® monoclonal antibody (mAb) (Cell Signaling Technology, Danvers, MA, United States), a mouse anti-p16 (E6H4) mAb (Ventana), and a rabbit anti-c-Met (SP44) mAb (Ventana) were used for staining. PD-L1 IHC was evaluated based on the intensity and proportion of membranous staining and/or cytoplasmic staining in tumor cells and was scored as 0 (no or any staining less than 10% of cells), 1+ (weak), 2+ (moderate), or 3+ (strong staining in more than 10% of tumor cells) (Figure 1A). Cases

Table 1 Clinicopathologic characteristics of esophageal squamous cell carcinoma patients *n* (%)

Characteristics	Total (*n* = 200)	PD-L1 status		*P* value
		Negative (*n* = 133)	Positive (*n* = 67)	
Age, median years (range)	65 (41-83)	65 (50-83)	64 (41-82)	0.519[1]
Sex				
Male	188 (94.0)	125 (94.0)	63 (94.0)	
Female	12 (6.0)	8 (6.0)	4 (6.0)	1.000
Smoking history	168 (84.9)	110 (84.0)	58 (86.6)	0.630
Alcoholic intake	166 (84.3)	110 (84.0)	56 (84.9)	0.873
Stage				
I	66 (33.0)	47 (35.3)	19 (28.4)	
II	59 (29.5)	41 (30.8)	18 (26.9)	
III	71 (35.5)	44 (33.1)	27 (40.3)	
IV	4 (2.0)	1 (0.8)	3 (4.5)	0.200
Differentiation				
W/D	41 (23.0)	36 (27.1)	10 (14.9)	
M/D	131 (65.5)	83 (62.4)	48 (71.6)	
P/D	23 (11.5)	14 (10.5)	9 (13.4)	0.152
Treatment				
Surgery alone	122 (61.0)	83 (62.5)	39 (58.2)	
Surgery → Adj.	58 (29.0)	38 (28.6)	20 (29.9)	
Neoadj. → Surgery	14 (7.0)	9 (6.8)	5 (7.5)	
Neoadj. → Surgery → Adj.	6 (3.0)	3 (2.3)	3 (4.5)	0.927
Surgery results				
R0 resection	176 (88.0)	121 (91.0)	55 (82.1)	
R1, R2 resection	24 (12.0)	12 (9.0)	12 (17.9)	0.068
p16				
Negative	179 (89.5)	121 (91.0)	58 (86.6)	
Positive	21 (10.5)	12 (9.0)	9 (13.4)	0.616
H-score				
< 50	158 (79.0)	112 (84.2)	46 (68.7)	
⩾ 50, < 100	31 (15.5)	16 (12.0)	15 (22.4)	
⩾ 100, < 200	11 (5.5)	5 (3.8)	6 (9.0)	0.036
Follow-up duration, median months (range)	33.2 (0.6-178.7)	33.9 (0.6-176.7)	31.7 (2.3-178.7)	0.790[1]

[1]Estimated by Mann-Whitney test. N: Number; W/D: Well differentiated; M/D: Moderately differentiated; P/D: Poorly differentiated; Adj.: Adjuvant chemotherapy; Neoadj.: Neoadjuvant chemotherapy.

with scores of 1+, 2+, or 3+ were considered to be PD-L1-positive. c-Met expression was analyzed by the membranous and/or cytoplasmic staining pattern and the positivity was evaluated by H-score. The c-Met staining intensity was scored as 0 (none or staining in less than 10% tumor cells), 1 (weak), 2 (moderate), or 3 (strong) based on membranous and/or cytoplasmic staining as previously reported[19,20] (Figure 1B), and each score multiplied by the percentage of cells (0%-100%). Therefore, H-score was ranged from 0 to 300. The median value 50 of c-Met H-score among samples with positive c-Met IHC staining was arbitrarily defined as the cutoff value for c-Met positivity. Samples were considered positive for p16 staining if diffuse strong nuclear and cytoplasmic immunostaining was observed in more than 50% of the tumor cells (Figure 1C)[21]. All slides were blinded with respect to clinical characteristics and outcome and were reviewed and scored by two experienced pathologists (Kwon D

and Jeon YK).

Outcome measurements

The primary objectives of this study were to evaluate PD-L1 expression in ESCC and to evaluate the correlations between PD-L1 expression and other clinicopathologic features, including p16 and c-Met expression. The secondary objective was to assess the prognostic value of PD-L1, p16, and c-Met expression for overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the date of diagnosis until either death due to any cause or the last follow-up date. PFS was defined as the time from the first day of definitive treatment until locoregional/distant relapse or progression, death, or last follow-up. Locoregional relapse refers to regional lymph node metastasis or tumor recurrence at the primary site. OS of patients who received palliative chemotherapy and/or radiotherapy (OSpall) was measured from the date of relapse or surgery (if R0 resection was not achieved) until either death due to any cause or the last follow-up date.

Statistical analysis

Patients were divided into two groups by PD-L1 status. Significant differences in clinicopathologic characteristics between the two groups were assessed using the Mann-Whitney test for continuous variables and the χ^2 (or Fisher's exact test, if appropriate) for categorical variables. Significant correlations between clinicopatholoic factors and PD-L1-positivity were assessed by logistic regression analysis. Survival analyses were performed using the Kaplan-Meier method and were compared using a log-rank test. Univariate and multivariate analyses using the Cox proportional hazard regression model were applied to determine the hazard ratio (HR) for specific variables with respect to OS and PFS. For all statistical analyses, two-sided *P* values < 0.05 were considered statistically significant. All statistical analyses were carried out using STATA version 12 (StataCorp LP, College Station, TX, United States).

RESULTS

Patient characteristics

A total of 200 ESCC patients were included in our analysis. The clinicopathologic characteristics of the patients are summarized in Table 1. Most of the patients (94.0%) were males who ranged in age from 41 to 83 years (median age, 65 years). A majority of the patients were ex/current-smokers (84.9%) or alcohol drinkers (84.3%). All patients underwent radical esophagectomy as an initial definitive treatment, and R0 resection was achieved in 176 patients (88.0%). Twenty patients (10.0%) received neoadjuvant chemotherapy prior to surgery, and 64 patients (32.0%) received adjuvant chemotherapy.

Table 2 Univariate and multivariate logistic regression analysis for clinicopathologic factors affecting programmed death ligand-1 expression

Factors	Ref.	OR (95%CI)	*P* value
Univariate analysis			
Age[1]		0.98 (0.94-1.02)	0.323
Sex	Male *vs* Female	1.01 (0.29-3.48)	0.99
Smoking	Yes *vs* No	1.23 (0.53-2.86)	0.63
Alcohol	Yes *vs* No	1.07 (0.47-2.42)	0.873
CEA[1]		0.86 (0.66-1.11)	0.234
TNM stage	Ⅲ/Ⅳ *vs* Ⅰ/Ⅱ	1.59 (0.87-2.89)	0.133
Differentiation	M/D or P/D *vs* W/D	2.12 (0.98-4.58)	0.058
Neoadj.	Yes *vs* No	1.37 (0.53-3.53)	0.517
p16	Positive *vs* Negative	1.56 (0.62-3.92)	0.34
c-Met H-score	≥ 50 *vs* < 50	2.43 (1.21-4.88)	0.012
Multivariate analysis			
Differentiation	M/D or P/D *vs* W/D	2.01 (0.92-4.40)	0.08
c-Met H-score	≥ 50 *vs* < 50	2.34 (1.16-4.72)	0.017

[1]Treated as continuous variables. OR: Odds ratio; CEA: Carcinoembryonic antigen; TNM: Tumor-node-metastasis; W/D: Well differentiated; M/D: Moderately differentiated; P/D: Poorly differentiated; Neoadj.: Neoadjuvant chemotherapy.

Table 3 Univariate and multivariate Cox proportional hazard regression analysis for clinicopathologic factors overall survival

Factors	Ref.	HR (95%CI)	*P* value
Univariate analysis			
Age[1]		1.03 (1.00-1.05)	0.023
Sex	Male *vs* Female	6.29 (1.55-25.4)	0.010
Smoking	Yes *vs* No	1.36 (0.80-2.33)	0.261
Alcohol	Yes *vs* No	1.30 (0.80-2.13)	0.286
CEA[1]		1.07 (0.95-1.20)	0.269
TNM stage	Ⅲ/Ⅳ *vs* Ⅰ/Ⅱ	2.77 (1.97-3.90)	< 0.001
Differentiation	M/D or P/D *vs* W/D	1.23 (0.82-1.85)	0.308
Neoadj.	Yes *vs* No	1.70 (1.04-2.78)	0.032
Adj.	Yes *vs* No	1.73 (1.23-2.45)	0.002
Operation result	R1/R2 *vs* R0	3.53 (2.25-5.52)	< 0.001
p16	Positive *vs* Negative	0.49 (0.24-1.01)	0.053
c-Met H-score	≥ 50 *vs* < 50	1.12 (0.73-1.72)	0.601
Multivariate analysis			
Age[1]		1.03 (1.01-1.06)	0.001
Sex	Male *vs* Female	4.31 (1.06-17.6)	0.042
TNM stage	Ⅲ/Ⅳ *vs* Ⅰ/Ⅱ	2.52 (1.64-3.87)	< 0.001
Neoadj.	Yes *vs* No	1.26 (0.73-2.19)	0.405
Adj.	Yes *vs* No	0.91 (0.58-1.44)	0.685
Operation result	R1/R2 *vs* R0	2.53 (1.48-4.32)	0.001
p16	Positive *vs* Negative	0.51 (0.25-1.05)	0.069

[1]Treated as continuous variables. CEA: Carcinoembryonic antigen; TNM: Tumor-node-metastasis; W/D: Well differentiated; M/D: Moderately differentiated; P/D: Poorly differentiated; Neoadj.: Neoadjuvant chemotherapy; Adj.: Adjuvant chemotherapy.

Correlation of PD-L1 expression with p16 and c-Met expression in ESCC

IHC was performed to assess PD-L1, p16, and c-Met expression in surgical specimens collected from a total of 200 ESCC patients (Table 1). Tumor tissues from 67 patients (33.5%) were PD-L1-positive, and the remaining specimens (133 patients, 66.5%) were PD-L1-negative. PD-L1-positivity was not significantly correlated with any clinical characteristics, including age, sex, smoking/alcoholic history, stage, or differentiation (Table 1). A total of 21 samples were positive for p16 expression (10.5%), 12 of which were PD-L1-negative and 9 of which were PD-L1-positive. The c-Met H-scores were ≥ 50 in 42 of 200 samples (21.0%). Of these cases, 21 were PD-L1-negative, and the remaining 21 were PD-L1-positive.

The factors associated with PD-L1 expression were investigated by univariate and multivariate analyses using a logistic regression model (Table 2). Most clinical characteristics, including age, sex, smoking/alcoholic history, carcinoembryonic antigen (CEA) level, TNM stage and neoadjuvant chemotherapy were not significantly associated with PD-L1 expression. Moderately or poorly differentiated ESCC tended to be PD-L1-positive compared to well-differentiated ESCC in both univariate (*P* = 0.058) and multivariate analysis (*P* = 0.080). PD-L1 expression was not significantly associated with p16 expression (*P* = 0.340), but elevated c-Met expression (H-score ≥ 50) was significantly associated with PD-L1-positivity compared to lower c-Met expression (H-score < 50) (OR = 2.34, 95%CI: 1.16-4.72, *P* = 0.017 in multivariate analysis).

Prognostic implications of PD-L1, p16, and c-Met expression for ESCC

In our cohort of ESCC patients, there was no significant difference in the OS (*P* = 0.656) according to PD-L1 expression (Figure 2A). Modifying the threshold for PD-L1-positivity by IHC score (*e.g.*, 1+, 2+ or 3+) also did not yield a significant difference (data not shown). However, the locoregional relapse rate tended to increase (*P* = 0.134; Figure 2B), and the distant metastasis rate was significantly increased in patients with PD-L1-positive ESCC compared to those with PD-L1-negative ESCC (HR = 1.72, 95%CI: 1.06-2.79, *P* = 0.028; Figure 2C). To investigate the prognostic factors for OS in ESCC, univariate and multivariate Cox regression analyses were carried out (Table 3). There was no significant difference in OS according to c-Met expression (*P* = 0.601; Figure 3A). However, there was a trend toward improved OS in patients with p16-positive ESCC compared to those with p16-negative ESCC in univariate analysis (HR = 0.49; 95%CI: 0.24-1.01, *P* = 0.053; Figure 3B) and multivariate analysis (HR = 0.51, 95%CI: 0.25-1.05, *P* = 0.069). This tendency became statistically significant in PD-L1-positive ESCC patients (HR = 0.23, 95%CI: 0.06-0.96, *P* = 0.043; Figure 3C), but not in PD-L1-negative ESCC patients (*P* = 0.932; Figure 3D). Interestingly, the OS$_{pall}$ was significantly better in patients with PD-L1-positive ESCC compared to those with PD-L1-negtvie ESCC (HR = 0.59, 95%CI: 0.36-0.96, *P* = 0.034; Figure 4).

DISCUSSION

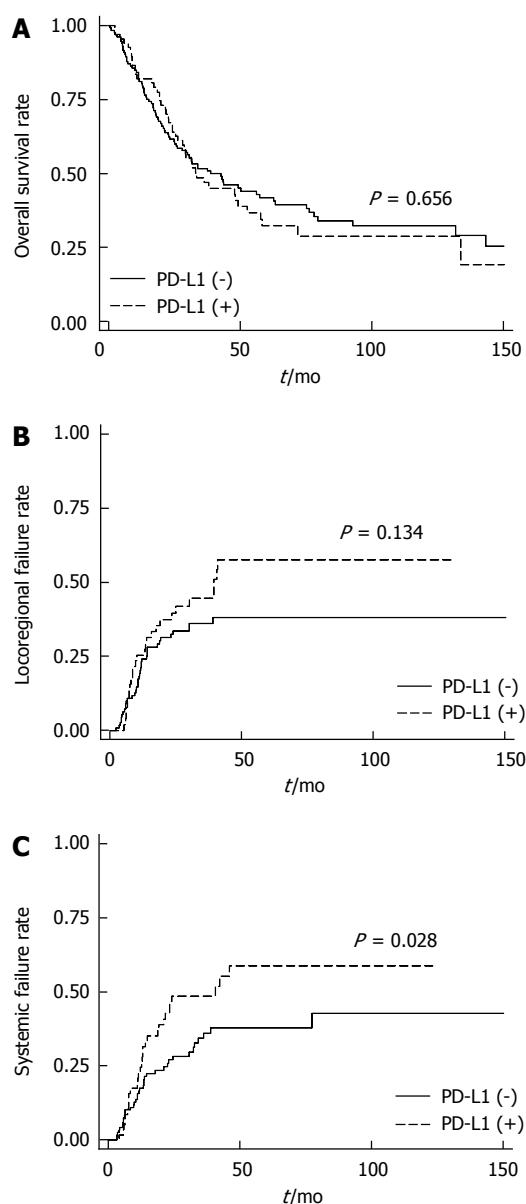In this study, we report that approximately one-third of

Figure 2 Kaplan-Meier plots for esophageal squamous cell carcinoma patients stratified by programmed death ligand-1 expression. A: Overall surviva; B: Locoregional relapse rate; C: Distant metastasis rate.

ESCC cases were positive for expression of PD-L1, and that PD-L1 expression was positively correlated with c-Met-positivity. Although PD-L1-positivity appeared to have no prognostic value for OS, it was associated with increased rate of distant failure. Expression of p16, a marker for HPV infection, was not correlated with the PD-L1 expression.

Because the PD-L1/PD-1 interaction has a negative regulatory function in T cell activation, cancer patients with elevated PD-L1 expression often exhibit a poor prognosis and clinical outcomes[8]. With respect to ESCC, Ohigashi *et al*[22] analyzed data from 41 patients with ESCC and showed that PD-L1 can serve as a prognostic biomarker for ESCC. Similarly, Chen *et al*[23] reported that PD-L1 expression was significantly associated with patient survival by analyzing 99

patients with ESCC. In contrast, we found no significant difference in survival of ESCC patients according to PD-L1 expression. The discrepancies among these studies can be partially explained by variations in the antibodies used for detection, as well as differing IHC cut-off definitions for PD-L1-positivity. ESCC specimens with any positive immunohistochemial staining using the rabbit anti-PD-L1 (E1L3N) XP® mAb were considered positive in our analysis. However, Ohigashi *et al*[22] performed immunostaining with a mouse anti-PD-L1 immunoglobulin G1 mAb (MIH1) and considered specimens with $\geq$ 10% PD-L1-positive tumor cells to be positive. In contrast, Chen *et al*[23] used the H-score method to assess PD-L1 immunostaining with a rabbit anti-human PD-L1 mAb (NBP1-03220). In addition to these variations in technique, differences in the multidisciplinary approach to treatment, such as use of palliative chemotherapy, radiotherapy, and supportive care might have also influenced OS. Furthermore, differences in tissue preparation and processing variability could have confounded results regarding the use of PD-L1 IHC as a prognostic marker for ESCC.

c-Met is one of the most important cancer-associated receptor tyrosine kinases and is activated through binding to its specific ligand, HGF[24]. c-Met has been reported to be involved in the development of a number of human primary tumors, such as gastric, breast, colorectal, liver, and rectal cancers[25]. Activation of the receptor enhances oncogenesis through a wide range of mechanisms, including the promotion of tumor cell invasiveness, angiogenesis, and the epithelial-to-mesenchymal transition[24,26]. Based on its many roles in regulation of pro-oncogenic pathways, we hypothesized that c-Met modulates PD-L1 expression in ESCC. Consistent with this hypothesis, c-Met-induced signaling has been reported to lead to PD-L1 overexpression in renal cancer cells[15]. Our analysis demonstrated that c-Met expression is significantly correlated with PD-L1-positivity in ESCC. However, in agreement with a previous report[27], c-Met overexpression had no prognostic value for OS[27]. Thus, the biological impact of the correlation between PD-L1 and c-Met expression should be further investigated in future studies.

HPV infection is one of the risk factors associated with esophageal cancer, oropharyngeal squamous cell carcinoma, and cervical cancer[13,28-30]. Previous reports have shown that HPV-positive tumors exhibit high PD-L1 expression compared to HPV-negative tumors[10-12]. With respect to ESCC, we did not observe any significant correlation between expression of PD-L1 and that of p16, a surrogate marker for HPV infection[17]. However, we did find that p16 expression has potential prognostic value for ESCC. This result was similar to that observed in patients with oropharyngeal squamous cell carcinoma[30,31]. Interestingly, the prognostic value of p16 expression was more significant in patients with PD-L1-positive ESCC.
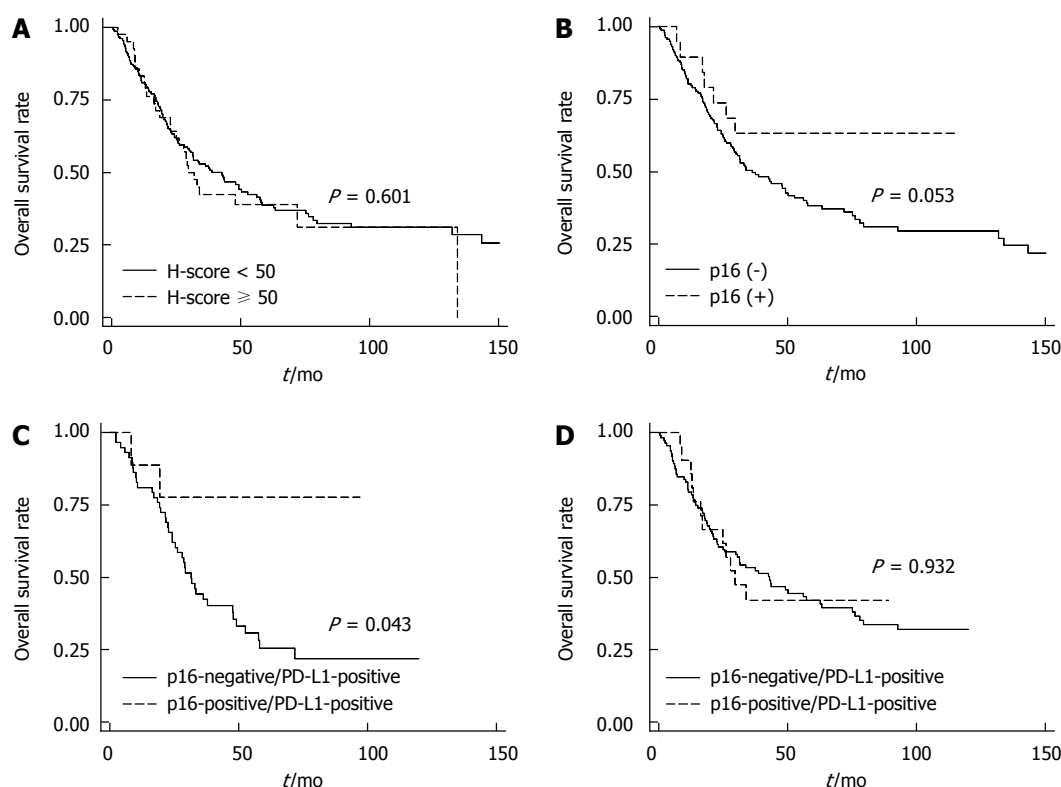
Figure 3 Overall survival according to c-Met, p16 expression. Kaplan-Meier plots of overall survival for all patients stratified by (A) c-Met expression and (B) p16 expression; Kaplan-Meier plots of overall survival stratified by p16 expression (C) for patients with PD-L1-positive esophageal squamous cell carcinoma; and (D) for patients with PD-L1-negative esophageal squamous cell carcinoma.
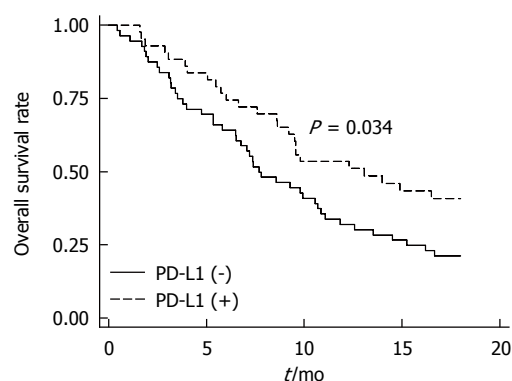

Figure 4 Kaplan-Meier plot of overall survival for esophageal squamous cell carcinoma patients who received palliative treatment. Overall survival was measured from the date of relapse or surgery (if R0 resection was not achieved) until either death by any cause or the last follow-up date.

There are several limitations that must be considered regarding the findings of this study. First, the retrospective design could bias the results. Second, there is no standard IHC threshold definition for PD-L1, p16 and c-Met positivity, and our definition was arbitrary. Therefore, one should be cautious when generalizing the results of our analysis. Third, we used p16 IHC as a surrogate marker instead of detecting HPV DNA to assess HPV infection. Fourth, although we identified a positive correlation between PD-L1 and c-Met expression, the biological meaning of the correlation was not investigated in this study.

Therefore, further follow-up studies including external validation are needed. Nevertheless, the present study represents the largest retrospective study to date with sufficient statistical power to assess PD-L1 expression and its prognostic implications in ESCC patients. Furthermore, the correlation between PD-L1 and c-Met expression in ESCC identified in this study is a novel finding.

In conclusion, approximately one-third of the ESCC patient samples analyzed were positive for PD-L1 expression, and PD-L1 expression was positively correlated with c-Met expression. Although PD-L1-positivity was not found to be associated with the prognosis of ESCC patients, it may play a critical role in distant metastasis and progression of ESCC. Because most cancer-related deaths are associated with distant metastasis, our findings provide a rationale for immunotherapy targeting PD-L1 for ESCC.

ACKNOWLEDGMENTS

COMMENTS

Background

Recently, an improved understanding of immunobiology has uncovered the interaction between programmed death ligand-1 (PD-L1) and programmed

death 1 (PD-1) as one of mechanisms by which cancer cells evade immune surveillance. The prognostic role of this interaction is controversial, and the mechanisms that regulate the expression of PD-L1 are obscure. There has been relatively scarce study examining the clinical meaning of PD-L1/PD-1 interaction in esophageal cancer, which is one of the most common gastrointestinal malignancies and is highly prevalent in Asia.

Research frontiers

PD-L1 upregulation has been reported in human papilloma virus-associated malignances such as esophageal squamous cell carcinoma (ESCC), and c-Met has been shown to promote PD-L1 overexpression in some type of cancers. However, a comprehensive analysis of the correlation between PD-L1 and c-Met expression in ESCC has not yet been reported.

Innovations and breakthroughs

This study revealed that PD-L1 play a critical role in distant failure and progression of ESCC. In addition, this study found that PD-L1 expression is positively correlated with c-Met expression, which is a novel finding.

Applications

PD-L1-positivity may play a critical role in distant metastasis and progression of ESCC. Because most cancer-related deaths are associated with distant metastasis, this finding provides a rationale for immunotherapy targeting PD-L1 for ESCC.

Terminology

PD-1 is a negative co-stimulatory factor that inhibits T cell activation when activated by PD-L1 or one of its other ligands. PD-L1 is a cell surface glycoprotein that belongs to the B7 family and is expressed not only on normal cells, such as T cells, B cells, monocytes, macrophages, and dendritic cells, but also on cancer cells.

Peer-review

The article focuses on the role of PD-L1 and another two markers, the authors are looking for new and different correlations.

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