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Research Article

Clinicopathogical Correlation of PD-L1 in Endometrial Cancer

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Abstract

Background: In Thailand, Endometrial cancer (EC) is the fifth female cancer. Immunity is a hallmark of cancer development and regulates tumor growth. PD-L1 intensity correlated with the immune evasion and the prognosis of disease. Many studies showed that PD-L1 is expressed in EC and its intensity associates with the response of anti-PD-L1.

Objective: To evaluate the frequency of PD-L1 of EC patients and to compare expression of PD-L1, CD3, CD45, MSH6, PMS2, p53 with clinicopathological character.

Material and Methods: A retrospective cohort study was collected of endometrial cancer patients who diagnosed and underwent surgery at Rajavithi Hospital from January 2013 to December 2014. The demographic data and survival data were collected. Specimens were reviewed and immunohistochemistry data was interpreted by pathologist. Kaplan-Meier method, log-rank tests and the multivariable Cox proportional hazards regression analyses were used for statistical analysis.

Results: Of 129 Thai EC patients, 33 patients (25.6%) were positive for PD-L1, 61 patients (47.3%) were absented mismatch repair (MMR) protein, 42 patients (32.6%) were abnormal p53. Tumor-infiltrating lymphocyte (TIL) reported in 110 patients (85.3%) and tumor-infiltrating T cell lymphocyte found in 107 patients (82.9%). The rate of positive PD-L1 in high grade was 46.67% and low-grade EC was 28.78%. Non-endometrioid histology, deep myometrial invasion, FIGO staging, poorly-differentiated histology, pelvic lymph node metastasis, lymphovascular invasion and cervical involvement were bad prognosis to overall survival significantly. In poorly-differentiated tumor subgroup, overall survival was affected by pelvic lymph node metastasis significantly. In well-differentiated tumor, deep myometrial invasion affected on survival outcome.

Conclusion: The rate of PD-L1 in EC patient was approximately 25% and more expression found in high-grade EC. The PD-L1 expression, MMR protein deficiency, p53 abnormal and TIL might not be a prognostic biomarker but tumor differentiation was the best survival marker.

Keywords: *CA Endometrium; Corpus; Endometrial Carcinoma; Corpus Uteri; PD-L1; Immune Checked Point; Program Death Ligand 1*

Introduction

In Thailand, Endometrial cancer (EC) is the fifth female cancer and the mortality rate has been increased every year since 2010 [1,2]. Most of patients who diagnosed at early stage were treated with surgery and some were suffered from complication of radiation or

chemotherapy as an adjuvant treatment. In additional, 5-year overall survival rate is significant difference among disease extension, which were 96%, 67%, and 17% for localized, regional and metastatic EC respectively [3].

Bokhman., *et al*. reported that EC was classified into two groups by clinicopathologic appearance and pathogenesis [4]. 70% of patients are type 1 which is well-differentiated endometrioid adenocarcinoma and associated with unopposed estrogen, endometrial hyperplasia and metabolic syndrome. Some of genetic mutations were found in related with type 1 endometrial cancer such as PTEN, PIK3CA, PIK3R1, and KRAS [5]. In contrary, type 2 EC which is poorly-differentiated endometrioid, serous or clear cell adenocarcinoma is worse prognosis than type 1 and commonly found p53 gene mutation [6].

The cancer genome atlas project classified EC into 4 types by genomic aberration, transcriptomic, and proteomic. POLE ultramutated, microsatellite instability hypermutated, copy-number low, and copy-number high were 4 types of EC that associated with survival rate [7]. It was complicated to apply the genomic classification in clinical practice so Aline Talhouk., *et al*. simplified those classification using immunohistochemistry technique [8].

Immunity is a hallmark of cancer development and regulates tumor growth [9]. Programmed cell death protein 1 (PD-1) receptor on T-helper 1 cytotoxic cells inhibited the over activity of immunity while the cancer cells use this process to evade immune system furthermore, programmed cell death protein ligand 1 (PD-L1) binded and activated PD-1 expression in many cells such as activated T-cell, epithelium cell, and cancer cell [10,11]. PD-L1 intensity correlated with the immune evasion and the prognosis of disease [12].

Immunotherapy showed dramatically response in some metastatic cancer such as malignant melanoma and lung cancer [13]. In a result of that, monoclonal antibody against PD-L1 (Pembrolizumab, Nivolumab) was integrated in malignant melanoma treatment [14]. Many studies showed that PD-L1 is expressed in EC and its intensity associates with the response of anti-PD-L1 [12,14]. Thus, the information of immune alteration would affect treatment options. However, the incidence of PD-L1 expression and immunohistochemistry detection among endometrial cancer in Thailand is limited.

Objectives of the Study

The primary objective of this study was to evaluate the frequency of PD-L1 of EC patients. The secondary objective was to compare expression of PD-L1, CD3, CD45, MSH6, PMS2, p53 with clinicopathological character.

Materials and Methods

Endometrial tissue specimen

The 153 EC specimens which undergone surgery at Department of Obstetrics and Gynecology at Rajavithi hospital (Bangkok, Thailand) were retrospectively recruited between January 2013 and December 2014. The samples were paraffin-embedded tissue blocks. Pathological review was done to confirm diagnosis and pathological characters (cell type and histologic grade). Uterine sarcoma, unavailable paraffin block, and incomplete or unavailable medical records were excluded. This study was approved by institutional review board (IRB) of Rajavithi hospital.

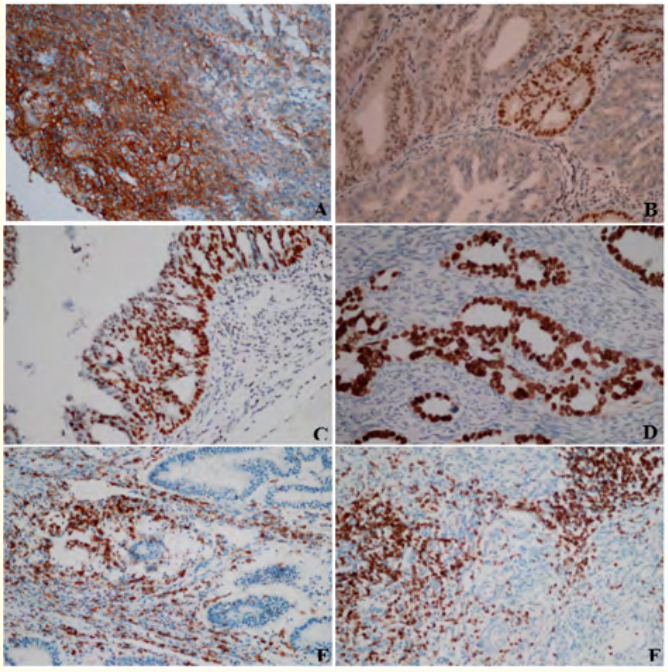
All medical records were reviewed including clinical character, pathologic risk, surgical procedure, adjuvant treatment, and treatment outcome. Survival data was provided by Population registration.

Immunohistochemistry

All of the specimens were cut at 4 μm, deparaffinized in xylene and rehydrated in a graded series of alcohol, and fully automated processed using IHC stained technique by Bench Mark XT Automated Slide Stainer. The primary antibodies used were VENTANA PD-L1 (SP263) Assay; Ventana, Cat.No.741-4905, CONFIRM anti-MSH6 (44); Ventana, Cat.No.790-4455, PMS2 (EPR3947) Rabbit

Monoclonal Antibody; Ventana, Cat.No.760-4531, p53 Protein Clone DO-7; DAKO, Code No-M7001, CD3;DAKO,Code No A0452, LCA Clone 2B11+PD7/26; DAKO, Code M0701. After end of the run, dehydrated slides in a graded alcohol, clearing with xylene and mounted slides with permanent mounting medium. The slides were viewed on an Olympus BX43 light microscope (Olympus, Tokyo, Japan) and assessed for presence of IHC staining in tumor cells.

Pathologist evaluated 10 representative high-power fields per tissue section. The intensity scores showed the average PD-L1, MSH6, PMS2, p53 staining intensity of positive staining: 0, None; 1, weak; 2, intermediate; and 3, strong and the area of straining was showed in the percentage. CD3 and CD45 were reported in negative (0 cell/ high power field (HPF)), weak (1-30 cells/10 HPF), moderate (31-50 cells/10 HPF) and dense (>50/10 HPF) (Picture 1).



Picture 1: *A: PD-L1 diffuse strong straining, B: PMS2 negative straining, C: MSH6 negative staining, D: p53: diffuse strong, E: CD45 dense peritumoral straining, F: CD3 dense peritumoral straining.*

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Descriptive statistics and comparisons between groups were performed using t-tests, x2, or Fisher's exact tests. Kaplan Mayer curve, log rank test, and cox proportional hazard model were used to calculate overall survival and progression free survival. Statistical significance was determined as P-value < 0.05.

Result

Of 129 Thai EC patients, 33 patients (25.6%) were positive for PD-L1, 61 patients (47.3%) were absented mismatch repair (MMR) protein, 42 patients (32.6%) were abnormal p53. Tumor-infiltrating lymphocyte was identified in 110 patient (85.3%) and tumor-infiltrating T cell lymphocyte was identified in 107 patients (82.9%). The rate of PD-L1 positive in high-grade was 46.67% and low-grade

EC was 28.78% (Table 1). Patients who were positive PD-L1 more presented in advanced stage, high-grade tumor, LVSI positive tumor, deep myometrial invasion and lymph node metastasis. In the absence of MMR protein group, most of tumors were well differentiation. Older age, non-endometrioid tumor, poorly-differentiated tumor and high death rates were found in abnormal p53 patients. Clinical characteristics and pathologic risk factors were showed in table 2.

	Total	PD-L1 positive	p-value
Tumor grade			
High grade	44	14 (46.7%)	0.24
Low grade	85	19 (28.8%)	
MMR			0.87
Deficient	61	16 (26.2%)	
MSH6 loss		7	
PMS2 loss		9	
Intact	68	17 (25.0%)	
p53			0.75
Mutate	42	10 (23.8%)	
Wild	87	23 (26.4%)	
CD45 TIL			
TIL	110	30 (27.3%)	0.29
No TIL	19	3 (12.8%)	

Table 1: *The number of PD-L1 positive.*

Characteristic	Overall	PD-L1 Expression	Absence MMR protein	Abnormal p53
	(N = 129)	(N = 33)	(N = 61)	(N = 42)
Age, years (SD)	57.57 (10.4)	57.85 (11.3)	56.89 (11.7)	60.6 (11.5)
BMI, kg/m^2 (SD)	27.46 (6.8)	25.9 (8.19)	27.59 (7.4)	26.6 (5.7)
Age of menopause, years (SD)	50.26 (3.9)	50.54 (3.0)	50.26 (3.5)	49.5 (3.8)
Diabetic mellitus, n (%)	34 (26.4)	5 (15.2)	18 (29.5)	9 (21.4)
Family history of Lynch related cancer, n (%)	10 (7.8)	4 (12.1)	7 (11.5)	5 (11.9)
Stage, n (%)				
Early stage	79 (61.2)	17 (51.5)	38 (62.3)	25 (59.5)
Advance stage	50 (38.8)	16 (48.5)	23 (37.8)	17 (40.5)
Pathology, n (%)				
Endometrioid	102 (79.0)	26 (78.8)	51 (83.6)	28 (66.7)
Non endometrioid	27 (21.0)	7 (21.2)	10 (16.4)	14 (33.3)
Grade, n (%)				
1	51 (39.5)	9 (27.3)	27 (44.3)	16 (38.1)
2	34 (26.4)	10 (30.3)	16 (26.2)	6 (14.3)

3	44 (34.1)	14 (42.4)	18 (29.5)	20 (47.6)
Size of tumor, cm (SD)	4.84 (2.4)	5.21 (2.5)	4.8 (2.5)	4.8 (2.5)
Lower uterine segment involvement, n (%)	62 (48.1)	17 (51.5)	32 (52.5)	21 (50.0)
Cervical involvement, n (%)	29 (22.5)	8 (24.2)	13 (21.3)	8 (19.0)
Lymphovascular invasion positive, n (%)	58 (45.0)	22 (66.7)	30 (49.2)	19 (45.2)
Deep myometrial invasion, n (%)	58 (45.0)	21 (63.6)	26 (42.6)	18 (42.9)
Pelvic lymph node metastasis, n (%)	20 (17.1)	7 (21.2)	12 (19.7)	5 (13.9)
Paraaortic lymph node metastasis, n (%)	11 (10.7)	4 (12.1)	7 (11.5)	3 (9.7)
Adjuvant treatment, n (%)				
No	63 (48.8)	13 (39.4)	30 (49.2)	24 (57.1)
Radiotherapy	32 (24.8)	7 921.2)	11 (18.1)	6 (14.3)
Chemoradiation	22 (17.0)	8 (24.2)	16 (26.2)	6 (14.3)
Chemotherapy	12 (9.3)	5 (15.2)	4 (6.6)	6 (14.3)
Recurrence, n (%)	13 (10.1)	3 (9.1)	6 (11.3)	4 (13.8)
Pelvic recurrence, n (%)	6 (46.2)	2 (66.7)	3 (50.0)	1 (25.0)
Death, n (%)	29 (22.5)	7 (21.2)	13 (21.3)	11 (26.2)

Table 2: *Demographic data.*

Non-endometrioid histology, deep myometrial invasion, FIGO staging, poorly-differentiated histology, pelvic lymph node metastasis, lymphovascular invasion, cervical involvement were bad prognosis of overall survival significantly (Table 3). After adjusted confounding factor, multivariate cox regression analysis showed only tumor grade significantly affected on overall survival. FIGO staging, poorly-differentiated histology, pelvic lymph node metastasis, cervical involvement and lower uterine segment involvement were negative affect on disease-free interval. Poorly-differentiated histology and pelvic lymph node metastasis significantly affected on disease-free survival in multivariate cox regression analysis.

Factors	**OS**				**DFI**			
	Hazard ratio	**P value**	**95CI**		**Hazard ratio**	**P value**	**95CI**	
			Lower	**Upper**			**Lower**	**Upper**
Obesity	1.55	0.28	0.70	3.41	2.36	0.06	0.98	5.70
Old	0.48	0.06	0.23	1.04	1.42	0.45	0.58	3.47
Deep myometrial invasion	3.09	<0.05	1.58	8.20	1.93	0.16	0.78	4.80
Large tumor size	0.98	0.97	0.34	2.82	0.90	0.87	0.26	3.07
Non endometrioid histology	3.00	<0.05	1.41	6.35	1.77	0.27	0.64	4.88
Tumor grade	4.01	<0.05	1.89	8.49	3.76	<0.05	1.54	9.20
Figo staging	3.38	<0.05	1.57	7.28	4.34	<0.05	1.67	11.30
Lymphovascular invasion	6.71	<0.05	1.55	29.41	2.61	0.15	0.72	9.52
Cervical involvement	2.33	<0.05	1.09	4.98	2.90	<0.05	7.19	1.16
Lower segment involvement	1.98	0.08	0.91	4.28	3.27	<0.05	1.18	9.07
Pelvic lymph node metastasis	3.09	<0.05	1.30	7.30	3.32	<0.05	8.62	1.29

Paraaortic lymph node metastasis	2.58	0.98	0.35	19.23	1.09	0.91	0.25	4.82
p53 abnormal	1.36	0.43	0.64	2.87	1.24	0.65	0.50	3.11
PD-L1 expression	0.95	0.90	0.41	2.23	1.17	0.75	0.45	3.04
CD45 TIL	0.84	0.73	0.32	2.21	0.39	0.05	0.15	1.01
CD3 TIL	0.83	0.68	0.34	2.03	0.48	0.13	0.18	1.25
MMR protein deficiency	0.85	0.67	0.41	1.77	0.86	0.73	0.36	2.07
Receiving adjuvant treatment	1.83	0.122	0.85	3.938	2.218	0.103	0.852	5.776

Table 3: *Prognostic factors.*

In poorly-differentiated tumor subgroup, overall survival deceased only upon pelvic lymph node metastasis significantly (Table 4). In well-differentiated tumor, deep myometrial invasion affects on survival outcome. Paraaortic lymph node metastasis relates with disease-free survival in multivariate cox regression analysis (Table 5).

	OS				**DFI**			
Factors	**Hazard ratio**	**P value**	**95CI**		**Hazard ratio**	**P value**	**95CI**	
			Lower	**Upper**			**Lower**	**Upper**
Obesity	0.57	0.54	1.11	1.00	1.77	0.29	0.61	5.11
Old	0.52	0.49	1.13	1.00	0.60	0.29	0.23	1.55
Large tumor size	0.45	0.29	0.10	1.98	0.30	0.12	0.06	1.36
Deep myometrial invasion	1.53	0.46	0.50	4.68	1.25	0.74	0.33	4.73
Non endometrioid histology	1.34	0.54	0.53	3.41	0.85	0.78	0.27	2.67
Figo staging	2.68	0.08	0.88	8.15	2.33	0.21	0.63	8.60
Cervical involvement	2.43	0.07	0.93	6.30	2.38	0.15	0.72	7.81
Lower segment involvement	1.78	0.28	0.63	5.06	2.04	0.29	0.54	7.69
Lymphovascular invasion	1.65	0.51	0.37	7.38	0.98	0.98	0.20	4.70
Pelvic lymph node metastasis	3.32	0.04	1.06	10.36	3.13	0.07	0.90	10.88
Paraaortic lymph node metastasis	0.30	0.25	0.04	2.32	0.03	0.30	0.00	21.45
p53 abnormal	0.70	0.45	0.28	1.76	0.95	0.93	0.30	2.99
PD-L1 expression	1.34	0.58	0.48	3.75	1.11	0.86	0.34	3.69
CD45 TIL	1.00	1.00	0.29	3.46	0.63	0.49	0.17	2.33
CD3 TIL	1.00	1.00	0.29	3.46	0.63	0.49	0.17	2.33
MMR protein deficiency	1.21	0.70	0.47	3.12	1.11	0.86	0.35	3.51
Receiving adjuvant treatment	0.45	0.10	0.17	1.16	0.74	0.65	0.20	2.72

Table 4: *Prognostic factors on Poorly-differentiated endometrial carcinoma.*

	OS				DFI			
Factors	**Hazard ratio**	**P value**	**95CI**		**Hazard ratio**	**P value**	**95CI**	
			Lower	**Upper**			**Lower**	**Upper**
Obesity	0.11	0.68	0.03	1.00	0.90	0.87	0.24	3.39
Old	1.13	0.68	2.76	1.00	0.32	0.10	0.09	1.22
Large tumor size	0.93	0.93	0.20	4.32	1.47	0.72	0.18	11.94
Deep myometrial invasion	4.13	0.02	1.21	14.19	1.34	0.69	0.32	5.63
Non endometrioid histology	2.43	0.40	0.31	19.01	0.05	0.71	0.00	379439.36
Figo staging	2.18	0.20	0.66	7.13	4.61	0.04	1.10	19.30
Cervical involvement	1.45	0.58	0.39	5.49	2.73	0.17	0.65	11.41
Lower segment involvement	1.52	0.49	0.46	4.97	4.13	0.08	0.83	20.45
Lymphovascular invasion	78.75	0.24	0.06	109565.68	3.58	0.27	0.37	34.44
Pelvic lymph node metastasis	1.70	0.50	0.37	7.89	2.24	0.32	0.45	11.08
Paraaortic lymph node metastasis	0.045	0.618	0	8698.985	6.883	0.021	1.332	35.552
p53 abnormal	1.84	0.44	0.39	8.57	1.10	0.91	0.22	5.44
PD-L1 expression	1.16	0.85	0.25	5.39	0.91	0.91	0.18	4.50
CD45 TIL	0.76	0.72	0.16	3.50	0.25	0.06	0.06	1.03
CD3 TIL	0.61	0.46	0.16	2.29	0.34	0.14	0.08	1.41
MMR protein deficiency	0.86	0.80	0.26	2.82	1.02	0.97	0.26	4.09
Receiving adjuvant treatment	4.001	0.041	1.061	15.087	2.601	0.191	0.621	10.896

Table 5: *Prognostic factors on Well-differentiated endometrial carcinoma.*

Discussion

Approximately 25% of EC patients were positive for PD-L1 in present study. Other studies also reported that the rate of PD-L1 positive EC was 17-44% [14,15]. The rate of positive PD-L1 EC in present study resembles other studies. On the other hand, the study from China reported that the rate of PD-L1 positive was quite high in primary EC (83%), 100% in metastatic stage and 68% in recurrent stage [16].

In subgroup analysis, the rate of PD-L1 positive in high-grade EC was higher than low-grade EC (46.7%, 28.8% respectively). Bregar and colleague reported that 56% of high-grade EC and 35% of low-grade EC were positive on PD-L1 [14]. Zhongfu Mo., *et al*. found that the rate of positive PD-L1 straining was 73.7% in poorly and moderate-differentiated EC, which was significantly higher than well-differentiated EC (45.9%, P = 0.014) [15].

The rate of PD-L1 expression in deficient MMR protein EC was 26.2% and intact MMR protein EC was 25%. Brooke E. and colleague reported that microsatellite-instable (MSI) EC expressed PD-L1 higher than microsatellite-stable EC (39% VS 13%, p = 0.02) [17]. Emily A. Sloan., *et al.* also reported more PD-L1 express in microsatellite-instable group (53% VS 10%, p = 0.0005). Most of deficient MMR protein EC were PD-L1 positive (53%) but only 10% of intact MMR protein EC showed PD-L1 expression; this was significantly lower than what was observed in deficient MMR protein EC (P = 0.0005) [14]. All cases of the MSH6 loss were positive in PD-L1 expression but in our study reported only 7 in 22 cases (31.8%) were positive in the PD-L1 expression.

In present study, poor-differentiated tumor affected on overall survival and poorly-differentiated tumor and pelvic lymph node metastasis affected on disease-free survival. PD-L1 expression, MMR deficiency and TIL were not associated with improving survival outcome and disease-free survival. In the contrary, Jia Liu., *et al*. reported that PD-L1 expression associated with prolongs survival [16]. However, this effect of PD-L1 expression resembled with previous study of malignant melanoma and mismatch repair-proliferated rectal cancer. Emily A. Sloan., *et al.* showed that there was no difference in survival and recurrent rate regarding on the MMR status and the PD-L1 expression [18]. Previous studies reported that ECs with dense TIL were associated with improved survival [19,20]. Based on uncertain evidence, the PD-L1 expression may not be a good prognostic biomarker but could be a biomarker for immunotherapy (PD-L1 inhibitor) in EC.

This study is limited due to retrospective study and sample size was small to make a different performance of prognostic prediction. Moreover, the natural history of EC was good thus 5-year mean follow up time might not be long enough in this study. All of the specimens were reviewed and selected for immunohistochemistry testing by pathologist. The pathologist was blinded in pathologic diagnosis and clinical outcome. Survival data was provided by population registration. As a result of that, the data was reliable.

The rate of PD-L1 in EC patient was approximately 25% and more expression in high-grade EC. Therefore high-grade EC may be candidate for screening for the PD-L1 expression and immunotherapy. The PD-L1 expression, MMR protein deficiency, p53 abnormal and TIL might not be a prognostic biomarker while tumor differentiation was probably the best survival marker.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgements

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