

PD-L1 and PD-1 Expression in Early Stage Uterine Endometrioid Carcinoma

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Abstract. *Background/Aim:* Immune checkpoint inhibitors (ICI) and tumor-infiltrating lymphocytes (TILs) for cancer treatment in clinical oncology have revolutionized patient care. However, no gold standard exists for the criteria of analytical validity of TILs of different types of cancer. *Materials and Methods:* Clinicopathological data from 60 patients with endometrioid carcinoma (EC) who had undergone surgical treatment at the Gyeongsang National University Hospital between January 2002 and December 2009, were investigated. The programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PDL1) expression levels were characterized by immunohistochemical staining patterns, and the interpretations derived from machine learning morphometric analysis (Genie) and the pathologists' assessments were compared. In solid tumors, pathologists assessed the proportion of positive cells in each core of the tissue microarray. For Genie, the proportion of positive cells in the entire core and the number of positive cells per 1 mm² were used. *Results:* Both the pathologists and Genie identified the same trend in association with tumor size, with significant differences ($p=0.026$, $p=0.033$). Genie expression showed a significant association with PD1 expression, and pathologists identified a significant association with PDL1 expression in immune cells. *Conclusion:* The PD1 expression levels identified in immune

cells of EC specimens were similar between the pathologists and Genie, suggesting that there is little resistance to the introduction of morphometric analysis. To our knowledge, this is the first study to introduce and validate machine learning as an integrated method for predicting prognosis and treatment based on PD1 expression in EC tumor microenvironments.

Recently, the use of immune checkpoint inhibitors (ICI) to treat cancer in clinical oncology has revolutionized patient care and improved survival rates (1). This is no exception in triple-negative breast cancer, which has led to a number of studies suggesting that patients are more likely to benefit from ICIs through the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PDL1) signaling axis, especially if PDL1 is expressed along with immunogenic lymphocyte infiltration (1). A representative ICIs is pembrolizumab, which induces the binding of the PD-1 receptor expressed on immune cells to its ligand, PD-L1, thereby preventing immune evasion by cancer cells (2, 3). This binding activates T-cell-mediated immune responses against cancer cells, allowing tumor-infiltrating lymphocytes (TIL) to recognize and remove cancer cells (2, 3). The presence of TILs in the tumor and surrounding tumor microenvironment (TME) purportedly reflects the antitumor host immune response and is believed to predict the effectiveness of chemotherapy, targeted therapy, and immune therapy. However, no gold standard criteria exist for analytical validity of TILs because of the heterogeneity of TMEs in different cancer types (1). In many cancers, the complex TME has driven the development of various techniques, including molecular multi-omics profiling, multiplex imaging, and transcriptomics, to quantify TIL distribution, orientation, and frequency in individual cancer types. The classification of specific immune cell subtypes or cancer types using a limited number of TILs has proven challenging when employing these technologies or platforms (1).

Traditional biomarkers of immune checkpoint inhibitors consist of three stems: PDL1 immunohistochemistry (IHC),

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deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H), and high tumor mutational burden (TMB-H) (4). Among them, PDL1 IHC uses various cutoff criteria and scoring systems for specific antibody clones for particular solid cancer patients to be approved as a companion diagnosis for pembrolizumab. Three major scoring systems are used for PD-L1 IHC: the tumor proportion score (TPS), combined positive score (CPS), and immune cell score (IC). The CPS denotes the number of PD-L1 stained tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells, multiplied by 100. The TPS is the number of stained tumor cells divided by the number of viable tumor cells, multiplied by 100. The IC denotes the number of PD-L1 stained lymphocytes and macrophages divided by the tumor area and multiplied by 100 (5). In this study, pathologists assessed solid tumors by dividing them into TCs and ICs and describing the proportion of positive cells in each (6). For machine learning morphometric analysis, the approach was used to describe the percentage of positive cells in the entire core and the number of positive cells per 1 mm², as previously determined by our team (7).

Identifying a new method to categorize uterine cervical cancer disease subgroups based on PD-L1 expression is a current research hotspot (8). In this study, we characterized the clinicopathological features of patients with early stage uterine endometrioid carcinoma. The expression levels of PD1/PDL1 were investigated by immunohistochemical staining. Finally, the interpretation of PD1 and PDL1 by machine learning morphometric analysis and eyeball estimation by pathologists were compared. The usefulness of these biomarkers in assessing EC was validated using machine learning analysis.

Materials and Methods

Case selection. The clinicopathological data of 60 patients with endometrioid carcinoma who underwent surgical treatment at the Gyeongsang National University Hospital between January 2002 and December 2009 were analyzed. Tumor size, TNM stage, and FIGO histologic grade were collected based on the pathological diagnosis. The tissue slides were reviewed by two pathologists. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital, and the requirement for informed consent was waived (IRB No. GNUH-2020-04-006).

Tissue microarray and Immunohistochemical staining. Tissue microarray samples were prepared as previously described (9). Primary antibodies against PD1 (1:100, ab52587, Abcam, Cambridge, UK) and PDL1 (1:200, E1L3N, Cell Signaling Technology, Danvers, MA, USA) were used. Additional immunostaining methods have been described previously (9). Stained slides were examined by two pathologists. The proportion of positive cells for both PD1 and PDL1 was recorded, and tumor and immune cells were separately assessed against the criteria described in another paper (6). If there was a disagreement between the pathologists, the result value was agreed upon through sufficient discussion.

Table I. Clinicopathological data of 60 patients with endometrioid carcinoma included in the study.

Variable	Number of patients (%)
Age	
Mean	51 [35~78]*
T	
T1	55 (92)
T2	3 (5)
T3	2 (3)
N	
N0	55 (92)
N1	3 (5)
N2	2 (3)
M	
M0	59 (98)
M1	1 (2)
Histologic grade	
1	40 (66.7)
2	15 (25)
3	5 (8.3)
PD1_TC	
Positive/Negative	1/59
PD1_IC	
≤5%	37 (62)
>5%	23 (38)
PDL1_TC	
Positive/Negative	10/50
PDL1_IC	
≤5%	34 (56.7)
>5%	26 (43.3)

*Range; T, T stage; N, N stage; M, M stage; Histologic grade, FIGO histologic grade; PD1_TC, PD1 expression in tumor cells; PD1_IC, PD1 expression in immune cells; PDL1_TC, PDL1 expression in tumor cells; PDL1_IC, PD1 expression in immune cells.

Morphometric analysis using the Genie analysis tool. Morphometric analysis was performed as previously described (7). All stained slides were scanned using an Aperio AT2 slide scanner. The scanned image files were analyzed for membrane staining signals using the Genie analysis tool (Leica Biosystems, Wetzlar, Germany). The number of positive cells per 1 mm² was measured in each core of the tissue microarray slide, and the ratio of the number of positive cells to the total number of cells per core was calculated. It was not possible to measure tumor cells and immune cells separately.

Statistical analysis. Correlation analysis was performed using Fisher's exact and chi-square tests. All factors were tested using SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

Results

Patient characteristics. Sixty patients with endometrial cancer were enrolled in the study. The clinicopathological data of EC patients are summarized in Table I. The mean patient age was 51 years (range=35-78 years). Among the 60

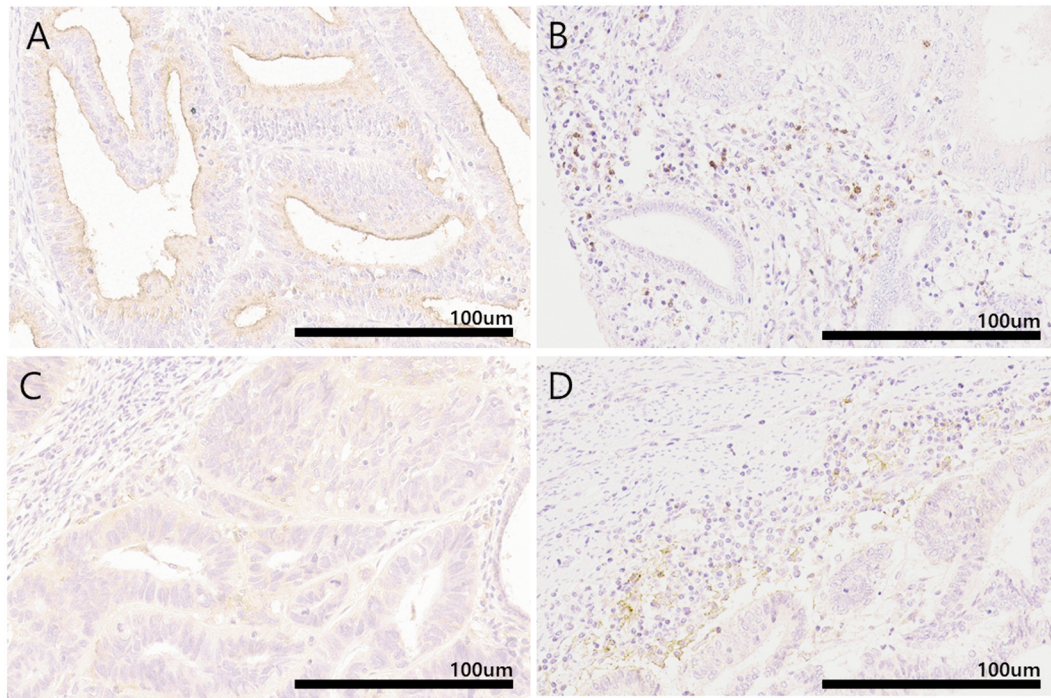


Figure 1. *PD1* expression, scored as positive, in membrane on the luminal border of tumor cells ($\times 200$) (A), and in nucleus of immune cells ($\times 200$) (B). *PDL1* expression, scored as positive, in the cytoplasm of tumor cells ($\times 200$) (C), and cytoplasm of immune cells ($\times 200$) (D). *PD-1*: Programmed cell death protein 1; *PDL1*: programmed cell death ligand 1.

patients with endometrial cancer, one had a more advanced stage of disease (M1 according to the TNM staging system). The distribution of T stages was as follows: 1: 55 (92%), 2: 3 (5%), 3: 2 (3%); and for N stages, 0: 55 (92%), 1: 3 (5%), 2: 2 (3%). The distribution of histological grades was as follows: 1: 40 (66.7%), 2: 15 (25%), 3: 5 (8.3%).

PD1 and PDL1 expression in tumor cells and immune cells in endometrioid cancer. With respect to PD1 expression, membranous expression on the luminal border of tumor cells and nuclear expression on immune cells were scored as positive. Cytoplasmic expression of PDL1 in the tumor and immune cells was scored as positive. Stromal fibroblasts negative for PDL1 were used as native controls. With respect to the PD1 expression in TC, among the 60 cores, one was positive, while 59 were negative. Regarding the percentage of ICs expressing PD1, 23 (38%) samples had a score of $>5\%$, whereas 37 (62%) samples had a score of $<5\%$. In contrast, 10 cores were positive and 50 cores were negative for PDL1 expression in TC. Considering the percentage of ICs that expressed PDL1, 26 (43.3%) had a score higher than 5%, and 34 (56.7%) had a score lower than 5%. Immunohistochemical staining for PD1 and PDL1 in TC and IC is shown in Figure 1A-D.

Relationship between PD1/PDL1 expression and clinico-pathological data by pathologists and by the Genie method. The degree of PD1 and PDL1 expression in tissue microarray slides including the number of PD1 positive cells in 1 mm^2 , measured by Genie analysis tool (PD1_N), the proportion of PD1 positive cells in section of a core, measured by Genie analysis tool (PD1_P), the number of PDL1 positive cells in 1 mm^2 , measured by Genie analysis tool (PDL1_N), the proportion of PD1-positive cells in section of a core, measured by the Genie analysis tool (PDL1_P), the proportion of PD1 expressed tumor cells in a core, measured by pathologists (PD1_TC), the proportion of PD1-expressed immune cells in a core, measured by pathologists (PD1_IC), the proportion of PDL1-expressed tumor cells in a core, measured by pathologists (PDL1_TC), and the proportion of PDL1-expressed immune cells in a core, measured by pathologists (PDL1_IC) are demonstrated in Table II. There was a statistically significant difference between the proportion of PD1 positive cells in a section of the core measured using the Genie analysis tool (PD1_P), tumor size, and histological grade ($p=0.033$ and 0.028 , respectively). Regarding the proportion of PD1-expressed immune cells in the core, as measured by pathologists (PD1_IC), tumor size showed a statistically significant difference ($p=0.026$). The proportion of PDL1-expressed immune cells in the core, as

Table II. Degree of PD1 and PDL1 expression in tissue slides.

TMA No.	Tumor size	H	PD1_N	PD1_P	PDL1_N	PDL1_P	PD1_TC	PD1_IC	PDL1_TC	PDL1_IC
1	2 (cm)	2	554	29.24	816	83.33	0	15.00	0	40.00
2	5	2	1,016	10.41	754	3.82	0	5.00	0	1.00
3	3	1	1,536	5.34	1269	6.72	0	2.00	0	1.00
4	3	2	896	27.51	633	33.92	0	10.00	0	20.00
5	2	1	1,478	17.11	1,373	15.14	0	10.00	0	5.00
6	4	1	544	7.43	369	10.18	0	2.00	0	5.00
7	2	1	1,201	46.12	1,362	85.63	0	30.00	0	40.00
8	4	1	1,283	5.53	1,380	52.91	0	2.00	35.00	5.00
9	8	1	2,135	6.26	1,733	3.84	0	2.00	0	0
10	3	1	2,296	41.40	1,934	39.24	0	30.00	0	30.00
11	4	1	1,512	10.56	995	9.53	0	5.00	0	10.00
12	1	1	2,152	11.88	1,854	17.92	0	5.00	0	10.00
13	4	3	2,449	19.04	1,419	71.31	0	20.00	25.00	15.00
14	4	1	3,003	5.76	2,877	7.86	0	2.00	0	2.00
15	2	2	2,365	42.49	2,408	21.62	0	40.00	0	20.00
16	10	2	2,099	9.13	2,090	14.98	0	2.00	0	20.00
17	2	1	3,128	2.85	3,185	1.82	0	2.00	0	5.00
18	10	1	983	22.87	997	9.17	0	15.00	0	5.00
19	1	1	2,311	10.72	1,296	50.19	0	2.00	0	20.00
20	5	1	1,878	10.39	1,128	26.77	0	2.00	0	0
21	2	1	3,391	31.31	2,355	44.92	0	20.00	0	30.00
22	2	2	2,274	22.98	2,033	35.03	0	15.00	0	30.00
23	8	1	959	10.72	985	14.19	0	2.00	0	5.00
24	4	1	627	6.63	797	28.15	0	2.00	10.00	5.00
25	3	1	490	58.10	429	45.41	0	10.00	0	15.00
26	1	3	1,778	94.60	1,434	85.30	0	50.00	0	40.00
27	6	1	827	72.65	460	26.99	0	20.00	0	10.00
28	4	2	791	32.83	902	33.88	0	30.00	10.00	10.00
29	3	2	695	6.81	613	36.48	0	5.00	0	20.00
30	8	1	281	22.61	446	27.10	0	10.00	0	10.00
31	8	1	1,761	13.49	1,444	10.84	0	5.00	0	2.00
32	6	1	993	3.52	550	1.84	0	2.00	0	0
33	6	1	756	3.32	423	3.21	0	2.00	0	0
34	6	3	1,260	.91	914	.69	0	2.00	1.00	0
35	5	1	1,418	2.14	903	2.76	0	2.00	0	1.00
36	2	2	1,211	20.26	859	17.75	0	10.00	5.00	10.00
37	0	1	2,169	3.44	1,236	2.82	0	5.00	0	1.00
38	Ni	1	3,637	1.63	1,865	3.42	0	2.00	2.00	0
39	2	1	2,051	6.06	1,384	5.99	0	2.00	0	1.00
40	3	1	1,816	18.19	1,045	8.59	0	10.00	0	15.00
41	4	3	3,656	3.45	2,814	3.00	0	5.00	0	10.00
42	Ni	1	2,502	14.83	3,041	6.94	0	5.00	0	1.00
43	Ni	1	1,688	6.86	1,276	5.03	0	5.00	0	5.00
44	Ni	1	2,295	5.37	1,683	3.79	0	2.00	0	5.00
45	3	1	1,708	3.97	1,472	1.54	0	2.00	0	0
46	2	2	3,605	15.52	3,103	72.23	0	20.00	0	80.00
47	6	2	2,777	11.39	1,733	7.69	0	10.00	0	10.00
48	4	2	2,069	54.21	1,894	26.45	0	40.00	0	20.00
49	3	2	1,354	11.80	1,457	11.45	0	5.00	0	5.00
50	5	1	2,620	59.18	2,323	46.13	70.00	2.00	70.00	0
51	2	1	2,069	3.81	1,936	8.35	0	2.00	0	3.00
52	3	1	2,363	12.14	1,877	5.81	0	10.00	0	3.00
53	4	2	1,545	1.48	973	4.07	0	2.00	0	1.00
54	2	1	1,868	9.38	1,750	25.08	0	10.00	0	15.00
55	1	1	920	36.00	1,562	40.07	0	20.00	5.00	25.00
56	8	3	494	21.68	767	6.22	0	5.00	0	0
57	3	1	335	14.41	487	12.73	0	2.00	0	0

Table II. Continued

Table II. *Continued*

TMA No.	Tumor size	H	PD1_N	PD1_P	PDL1_N	PDL1_P	PD1_TC	PD1_IC	PDL1_TC	PDL1_IC
58	7	1	1,688	3.15	1,751	3.40	0	2.00	0	1.00
59	2	1	712	10.33	599	5.79	0	5.00	0	1.00
60	1	2	933	13.72	889	22.31	0	5.00	5.00	5.00

TMA No., the number of core in tissue microarray; H, FIGO histologic grade; PD1_N, the number of PD1 positive cells in 1 mm², measured by the Genie analysis tool; PD1_P, the proportion of PD1 positive cells in section of a core, measured by Genie analysis tool; PDL1_N, the number of PDL1 positive cells in 1 mm², measured by Genie analysis tool; PDL1_P, the proportion of PD1 positive cells in section of a core, measured by Genie analysis tool; PD1_TC, the proportion of PD1 expressed tumor cells in a core, measured by pathologists; PD1_IC, the proportion of PD1 expressed immune cells in a core, measured by pathologists; PDL1_TC, the proportion of PDL1 expressed tumor cells in a core, measured by pathologists; PDL1_IC, the proportion of PDL1 expressed immune cells in a core, measured by pathologists; Ni, not informative.

Table III. *The correlation between PD1/PDL1 expression and clinicopathological information.*

	PD1_P (11)*			PDL1_P (12)			PD1_IC (5)			PDL1_IC (5)			PDL1_TC (0)		
	≤11	>11	<i>p</i>	≤12	>12	<i>p</i>	≤5	>5	<i>p</i>	≤5	>5	<i>p</i>	=0	>0	<i>p</i>
Age (51)															
≤51	16	10	0.118	15	11	0.297	19	7	0.112	18	8	0.086	22	4	0.550
>51	14	20		15	19		18	16		16	18		28	6	
Tumor size (3)															
≤3	10	19	0.033	10	19	0.063	13	16	0.026	12	17	0.058	26	3	0.199
>3	17	10		16	11		20	7		18	9		21	6	
Histologic grade															
≤1	24	16	0.028	23	17	0.100	28	12	0.060	28	12	0.003	35	5	0.194
2,3	6	14		7	13		9	11		6	14		15	5	
T stage															
≤1	27	28	0.500	26	29	0.177	33	22	0.358	31	24	0.628	46	9	0.612
2,3	3	2		4	1		4	1		3	2		4	1	

PD1_P, Proportion of PD1 positive cells in section of a core, measured by Genie analysis tool (Leica Biosystems, Wetzlar, Germany); PDL1_P, the proportion of PD1 positive cells in section of a core, measured by Genie analysis tool; PD1_IC, the proportion of PD1 expressed immune cells in a core, measured by pathologists; PDL1_IC, the proportion of PDL1 expressed immune cells in a core, measured by pathologists; PDL1_TC, the proportion of PDL1 expressed tumor cells in a core, measured by pathologists; (N)*, N is a median number. Bold values indicate statistical significance.

measured by the pathologists (PDL1_IC), showed a statistically significant difference ($p=0.003$). Correlations between PD1/PDL1 expression and clinicopathological characteristics are shown in Table III.

Comparison between the results from pathologists and the Genie analysis tool. The staining patterns of PD1 were more appropriate than those of PDL1 for comparing the results of the pathologists with those of the Genie analysis tools (Table III). In PD1 immunostaining, no tumor cell expression was observed, except in one specimen, #50, in which all positive cells were immune cells. This was a more suitable environment for the Genie analysis. The comparison of PD1_P and PD1_IC revealed different trends in the two groups of patients aged 51 and over 51 years, that is, there was a common trend of fewer PD1-expressing cells in patients under 51 years, but in patients over 51 years, the PD1_P and PD1_IC trends were not similar.

Tumor size was the most interesting aspect in this comparison. Both PD1_P and PD1_IC showed the same trend, with statistically significant p -values (PD1_P=0.033 and PD1_IC=0.026). This indicated that the pathologists and algorithmic machine learning (Genie) achieved similar results. Regarding the association with histologic grade, algorithmic machine learning (Genie) found a statistically significant association between PD1 expression and PDL1_IC, a pathologist's assessment of PDL1 expression in immune cells. In conclusion, pathologists and algorithmic machine learning (Genie) showed similar results for PD1 expression in immune cells; however, there were some differences in other values.

Discussion

According to the NCCN guidelines version 2. 2023 of endometrial carcinoma, for first- or second-line systemic

therapy for recurrent diseases, biomarker-directed therapy such as pembrolizumab for TMB-H or MSI-H/dMMR tumors is recommended after prior platinum-based therapy, including neoadjuvant and adjuvant therapies (10).

There are several scoring systems and cutoff criteria for evaluating PD1/PDL1 expression using specific antibody clones for solid cancer patients to be approved as a companion diagnosis for pembrolizumab. The three major scoring systems used for PD1/PDL1 expression are the tumor proportion score (TPS), combined positive score (CPS), and immune cell score (IC) (5). In 2014, pembrolizumab received limited approval as immunotherapy for patients with advanced melanoma, because clinical trials showed similar treatment effects regardless of whether the patients had negative or positive PDL1 expression (11, 12). In contrast to melanoma, where the value of PDL1 as a biomarker of IC is unclear, in advanced non-small cell lung cancer (NSCLC), PDL1 expression has been shown to be associated with therapeutic benefits in several trials, including KEYNOTE-001, CheckMate 057, and POPLAR (13-15). Despite the US FDA approval of PDL1 expression as a companion diagnostic assay for pembrolizumab, some patients with low or no expression of PDL1 also respond to treatment. Therefore, identifying biomarkers that exhibit these characteristics and analyzing mismatch repair deficiency and mutation burden are urgent and might supplement current companion diagnostics. At this point, the utility of PDL1 expression as a biomarker must be confirmed by comparing pathologists' visual evaluations with machine learning analysis, as morphometric analysis has several advantages (16). This can reduce the workload of pathologists and significantly reduce inter-reader and inter-institutional disagreements.

In this study, in endometrioid carcinoma, pathological assessments of PD1 expression in immune cells were associated with tumor size only, and PDL1 expression in immune cells was associated with histological grade only. Morphometric analysis showed that PD1 expression in tumor and immune cells was associated with both tumor size and histologic grade, whereas PDL1 expression in these cells was not statistically associated with either tumor size or histologic grade (Table III). The need to distinguish between tumor cells and immune cells in the assessment of PDL1 and PD1 is due to the fact that the PDL1 evaluation differs for each tumor type. In head and neck cancer, CPS is associated with overall patient survival, while TPS, which is known to be functional in lung cancer, is not applicable, and *vice versa* (17). Therefore, a conclusive PDL1 scoring protocol cannot be applied to all cancers. This is because the efficacy of immunotherapy is strictly related to the TME, and stimulating the T-cell response increases the levels of co-stimulatory molecules and promotes antitumor alterations (18-20). While morphometric analysis has the advantage of being highly reproducible, this study showed that PD1 expression in uterine endometrioid carcinoma specimens was similar between pathologists and morphometric

analyses, suggesting that there is little resistance to the introduction of morphometric analysis. In addition, since there were statistically significant differences between histologic grade, size, and PD1 expression measured by Genie, we expect this tool to predict prognosis and apply immunotherapy even in small curettage biopsies of unresectable endometrial carcinomas. The disadvantage of the Genie method is that it is difficult to strictly train the staining pattern of PDL1 or PD1 in different types of cancer cells. We expect to deepen machine learning through algorithm development using more cases to integrate the Genie method into various types of cancers. In gynecological diseases that are difficult to treat, such as endometrioid cancer and ovarian cancer, new treatments not only immunotherapy, but hormonal therapy and LAT1 selective inhibition are currently being actively developed (21, 22). We hope to extend the Genie method described in this study to these new treatments to improve patient survival rates.

Conclusion

The PD1 expression in immune cells from endometrial cancer samples was statistically significant in terms of tumor size for both machine learning methods and pathologists. The significance of this study is that it introduced an integrated machine learning method to predict prognosis and treatment strategies based on PD1 expression in the tumor microenvironment of endometrioid cancers.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors Contributions

HJA, DHS designed and wrote the article, MHK, JWY analyzed and curated data, HJA reviewed the article, DHS supervised and reviewed the article.

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