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The predictive role of PD-L1 expression and CD8 + TIL levels in determining the neoadjuvant chemotherapy response in advanced ovarian cancer

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Abstract

Objective To analyze how the PD-L1 expression and CD8 + tumor infiltrating lymphocyte (TIL) levels in biopsy samples before neoadjuvant chemotherapy (NACT) can predict chemotherapy response score and survival for advanced high-grade serous ovarian cancer (HGSC).

Methods We retrospectively analyzed 45 patients with advanced epithelial ovarian cancer between 2010 and 2018, who had received at least three cycles of NACT. PD-L1 expression and CD8 + TIL levels were evaluated by immunohistochemical staining in the pre-NAC tumor samples from which the patients had been diagnosed. The post-NACT tissue samples taken during interval debulking surgery (IDS) were used to evaluate the chemotherapy response score (CRS).

Results Among all the patients, CRS 1 (no response) was found in 8 patients, CRS 2 (partial response) in 28 patients, and CRS 3 (complete response) in 9 patients. A total of 20 (44.4%) patients had high intratumoral CD8 + TILs (iCD8 + TILs) levels, and 35 (77.8%) patients had high expression stromal CD8 + TILs (sCD8 + TILs). No statistically significant relationship was found between high and low expression of i/s CD8 + TILs levels with PFS and CRS. The study found that 33 (73.3%) patients had high levels of stromal PD-L1 (sPD-L1) expression and 28 (62.2%) patients had high levels of intratumoral PD-L1 (iPD-L1) expression. In the iPD-L1 group, patients with low expression had a PFS of 28 months, whereas those with high expression had a PFS of 17 months ($p = 0.028$). Among the patients with high iPD-L1 expression, 23 (82.1%) patients showed CRS2, 4 (14.3%) showed CRS3, and only 1 (3.6%) showed CRS1 ($p < 0.001$). However, high or low expression sPD-L1 did not significantly affect PFS and CRS ($p = 0.928$ and $p = 0.305$; respectively).

Conclusions We found that iPD-L1 expression levels in diagnostic biopsy in ovarian cancer can predict the chemotherapy response score in interval debulking surgery.

Keywords Ovarian cancer, Neoadjuvant chemotherapy, PD-L1, TILs, CRS

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Introduction

One of the most common gynecologic cancers is ovarian cancer, which has a high mortality rate. Approximately 75% of patients are diagnosed at an advanced stage, and the 5-year survival rate is less than 30% [1]. The standard treatment of ovarian cancer consists of extensive surgical staging followed by platinum-based chemotherapy. Despite the recent efforts on new chemotherapeutic regimens and targeted therapies, there has not been a significant increase in survival rates.

Ovarian cancer is defined by a specific tumor microenvironment that disrupts immune surveillance, impairing the immune system's ability to detect and fight against cancer. Various studies indicate that tumor cells activate immunosuppressive mechanisms to evade antitumor immunity. The PD-1/PDL-1 pathway is one of the most well-defined adaptive mechanisms utilized by tumor cells. In tumors, PD-L1 binding to PD-1 on immune cells can impede the effector function of cytotoxic T lymphocytes, leading to immune evasion and tumor progression [2]. Studies have shown that PD-L1 expression is linked to worse outcomes in several types of solid cancers, including melanoma, kidney, and lung cancer [3]. The role of PDL1 in the development and treatment of ovarian cancer is currently not well understood. There is limited data available on how PD-L1 expression affects the prognosis of ovarian cancer, and results are mostly controversial. Some studies found a positive prognostic effect of PD-L1 expression on survival outcomes [4], while others observed a negative impact on overall survival [5], and some found no effect [6].

Primary debulking surgery (PDS) has been the only ovarian cancer treatment with a proven survival advantage since it was established in the 1970s. The existing literature suggests that for certain patients with extensive disease that cannot be effectively removed through surgery, or those who are not good candidates for it, interval debulking surgery (IDS) may be a suitable alternative to PDS after neoadjuvant chemotherapy. All patients, particularly those in these categories, should be evaluated for IDS [7]. The chemotherapy response score (CRS) evaluates the histological impact of neoadjuvant chemotherapy on ovarian cancer and the complete pathological response was significantly associated with improved survival [8]. Although previous studies have shown that various clinical variables, including CA125 and HE4, can be used as prognostic indicators for patients with HGSC who receive neoadjuvant chemotherapy there are still unmet needs in terms of predictive markers that can precisely identify which patients are more likely to have good responses to NACT and achieve a better CRS [9].

The potential of using markers including PD-L1 and CD8 + TILs in cancer tissues to predict the response to neoadjuvant chemotherapy is being investigated in recent studies. This topic is controversial, with some studies suggesting that high PD-L1 expression is linked to lower pCR and resistance to certain drug combinations in breast cancer [10], supporting the hypothesis that immune escape mechanisms play a role in resistance, while other studies indicate that PD-L1 is associated with greater pCR after neoadjuvant chemotherapy and longer patient survival [11, 12]. The high baseline TILs are also associated with increased pCR probability [13]. The majority of research on this topic has been conducted on breast cancer patients. There is insufficient data to determine a relationship between PD-L1 expression, TILs level, and neoadjuvant chemotherapy response in ovarian cancer. The purpose of this article is to assess this relationship.

Materials and methods

We retrospectively analyzed 45 patients with epithelial ovarian cancer who attended Hacettepe University Hospital between 2010 and 2018. The study was approved by the Hospital's Research Ethics Committee (KA 19101). An 'Informed Consent Form' was obtained from the patients. Demographic and clinicopathological data of the patients were collected using hospital medical records. The stage was evaluated according to the International Federation of Gynecology and Obstetrics (FIGO).

PD-L1 expression and CD8 TIL level evaluations were performed in tissue samples taken via laparoscopy before NACT. Post-treatment tissue samples were obtained through IDS and evaluated for CRS.

Immunohistochemistry staining and interpretation of PD-L1 expression

Three sections were taken from the paraffin blocks of the patients and placed into separate slides with a thickness of 4 μm. One of these sections was stained with Hematoxylin and Eosin (H&E) in order to confirm tissue diagnosis. The other two sections were then stained with CD8 + and PD-L1, according to Leica Bond-Max staining protocols.

CD8 + score

Immunohistochemical staining was performed using a primary antibody (product code Leica NCL-L-CD8 + -295, mouse monoclonal antibody, clone 1A5, Newcastle, UK) at a dilution of 1:50. It was evaluated separately for tumor cells and stroma. An area in the stroma that showed a high CD8 + staining was chosen. Using the 40X magnification area of the Nikon Eclipse E200 brand microscope, CD8 + stained lymphocytes were counted in this area and its surrounding areas, and the

mean values were calculated. The expression of CD8 + in the stroma was categorized into five groups according to the intensity of the staining as follows: score 0 (average lymphocyte count is 0), score 1(average lymphocyte count is 1–2), score 2 (average lymphocyte count is 3–19, Fig. 1A), score 3 (average lymphocyte count is 20–50), score 4 (average lymphocyte count > 50, Fig. 1B. Expression of score 3 and score 4 was considered high [14]. The expression of CD8 + in the tumor cells was categorized into three groups. Score 0 (no positive cells), score 1 (only a few positive cells, Fig. 1C), score 2 (many positive cells, Fig. 1D). Expression of score 2 was considered high.

PD-L1 score

Immunohistochemical staining was performed using a primary antibody (product code Leica PA0832, rabbit primary antibody, clone 73–10, Newcastle, UK) at a dilution of 1:400. Tumor and stroma were evaluated separately. Only membranous staining was considered positive. Using the 20X magnification of the Nikon ECLIPSE E200 brand microscope, we evaluated the area occupied by PD-L1 positive cells in the tumor and stroma. This area was divided by the total area of the tissue and multiplied by 100 to determine the percentage of staining (Fig. 3). Immunohistochemical expression for PD-L1 was analyzed semi-quantitatively in 5% increments, scoring positive cells from 0 to 100% of the total number of cells. The percentage of positive tumor cells in an entire section was determined by two gynecological pathologists without access to patient IDs or clinicopathological data. Any inconsistencies between the two pathologists were eliminated by consensus. It is important to note that there is no established standard cutoff for PD-L1 positivity in ovarian cancer. Some studies define a tumor as PD-L1 positive if positive staining is observed in > 1%, > 5%, or > 10% of the cells [15]. In our study, the PD-L1 expression was categorized into two groups: high expression (PD-L1 ≥ 1%, Fig. 1E), and low expression (PD-L1 < 1%).

Chemotherapy response score evaluation

The Chemotherapy Response Score was used to evaluate the histopathological response to neoadjuvant chemotherapy. The College of American Pathologists and the International Collaboration on Cancer Reporting have used a 3-tier CRS [16]. The criteria are given below:

> CRS 1: Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration
> CRS 2: Appreciable tumor response amid viable tumor that is readily identifiable. The tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with a viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory

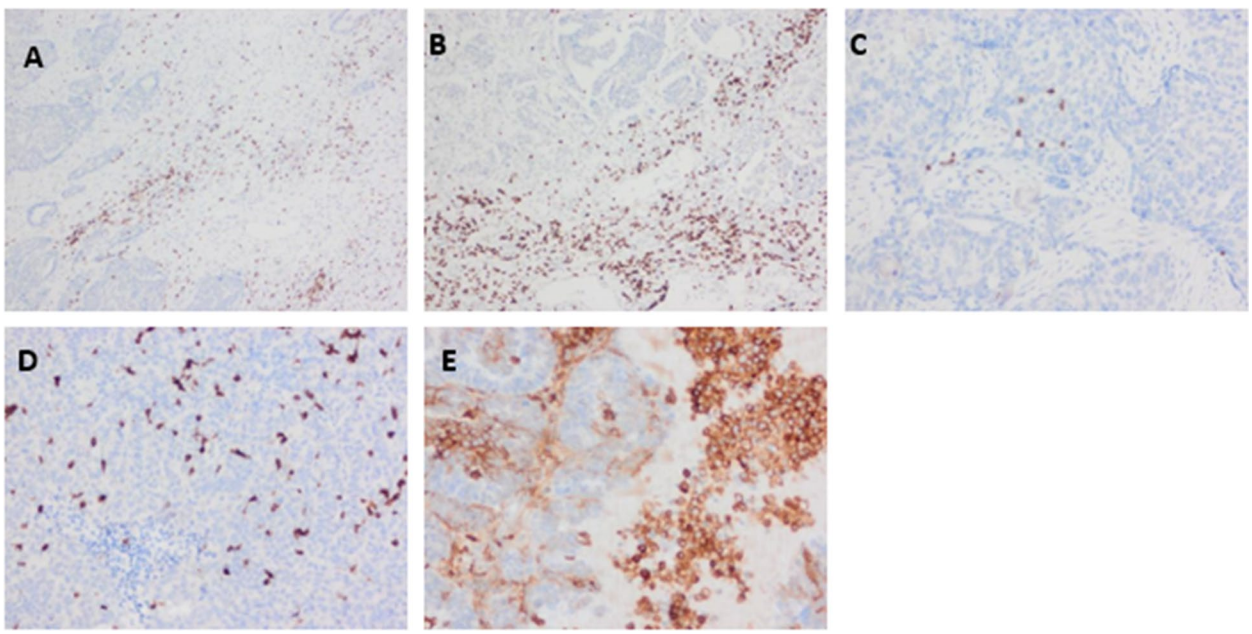

Fig. 1 Immunohistochemical staining pattern of CD8 and PDL-1 (**A** low expression stromal CD8; **B** high expression stromal CD8; **C** low expression intratumoral CD8; **D** high expression intratumoral CD8; **E** high expression PD-L1)

changes with a multifocal residual tumor, which are easily identifiable.

CRS 3: Complete or near-complete response with no residual tumor or minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases no or very little residual tumor in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumor or whether there is a microscopic residual tumor present.

Statistical analysis

Statistical analyses were performed using the SPSS package program (IBM SPSS Statistics 23). Fisher's exact test was used to analyze categorical variables. Survival functions were evaluated using the Kaplan–Meier method, and the difference in survival was compared using the log-rank test. The correlation between two variables was evaluated using Spearman's rank correlation coefficient (rho). A statistically significant effect was determined if the *p*-value was less than 0.05 unless otherwise stated.

Results

A total of 45 female patients with ovarian cancer were included in the study, with a mean age of 61.60 ± 9.94 years (range: 42–82 years). All patients had serous histologic type ovarian cancer. High-grade ovarian cancer was detected in 41 (91.1%) patients, and the grade could not be determined in the remaining 4 (8.9%) patients. Of 45 patients, 32 (71.1%) were stage III, and 13 (28.9%) were stage IV at the time of diagnosis. Out of the 45 patients, 41 received intravenous carboplatin (area under the curve [AUC] 5) and intravenous paclitaxel (175 mg/m^2 by body surface area) on day 1 of every 21-day cycle as neoadjuvant treatment. Of these, one patient received five courses and another received six courses of neoadjuvant chemotherapy due to disease progression after a radiological evaluation, while the remaining 39 patients received a total of three courses. No treatment discontinuations or dose reductions were noted in this cohort. The other 4 patients were treated with different regimens. In terms of chemotherapy response scores, CRS 1 was found in 8 (17.8%) patients, CRS 2 in 28 (62.2%) patients, and CRS 3 in 9 (20.0%) patients. Recurrence was observed in 21 (46.7%) of 45 patients, and exitus developed in 6 patients (13.3%). The defined follow-up period from the date of diagnosis to the last follow-up or the date of death of all patients was 19 months. The median PFS of the group was 13 months. Baseline characteristics of patients are summarized in Table 1.

PD-L1 expression and patient prognosis

Patients with high levels of intratumoral PD-L1 expression had a lower PFS of 17 months compared to those with low PD-L1 expression, who had a higher PFS of 28 months ($p = 0.029$). However, there was no significant

Table 1 Demographic and clinical features of patients

	Number of patients (%)
Total	45
Age, mean (Min–Max) (year)	61,60 ± 9,946 (42–82)
PFS, median (month)	13
Average follow-up time, median (month)	19
ECOG	
0	35 (77.8)
1	10 (22.2)
Stage at the time of diagnosis	
Stage IIIB	1 (2.2)
Stage IIIC	31 (68.9)
Stage IVA	1 (2.2)
Stage IVB	12 (26.7)
Grade	
High grade	41 (91.1)
Unknown	4 (8.9)
Chemotherapy response score	
CRS 1	8 (17.8)
CRS 2	28 (62.2)
CRS 3	9 (20.0)
Chemotherapy regimen	
Carboplatin + paclitaxel	41 (91.1)
Others	4 (8.9)
Intratumoral CD8 + TILs	
Low expression	25 (55.6)
High expression	20 (44.4)
Stromal CD8 + TILs	
Low expression	10 (22.2)
High expression	35 (77.8)
Intratumoral PD-L1	
Low expression (< 1%)	17 (37,8)
High expression (≥ 1%)	28 (52.2)
Stromal PD-L1	
Low expression (< 1%)	12 (26,7)
High expression (≥ 1%)	33 (73,3)
Recurrence	
Yes	21 (46.7)
No	24 (53.3)
Latest Status	
Live	39 (86.6)
Dead	6 (13.3)

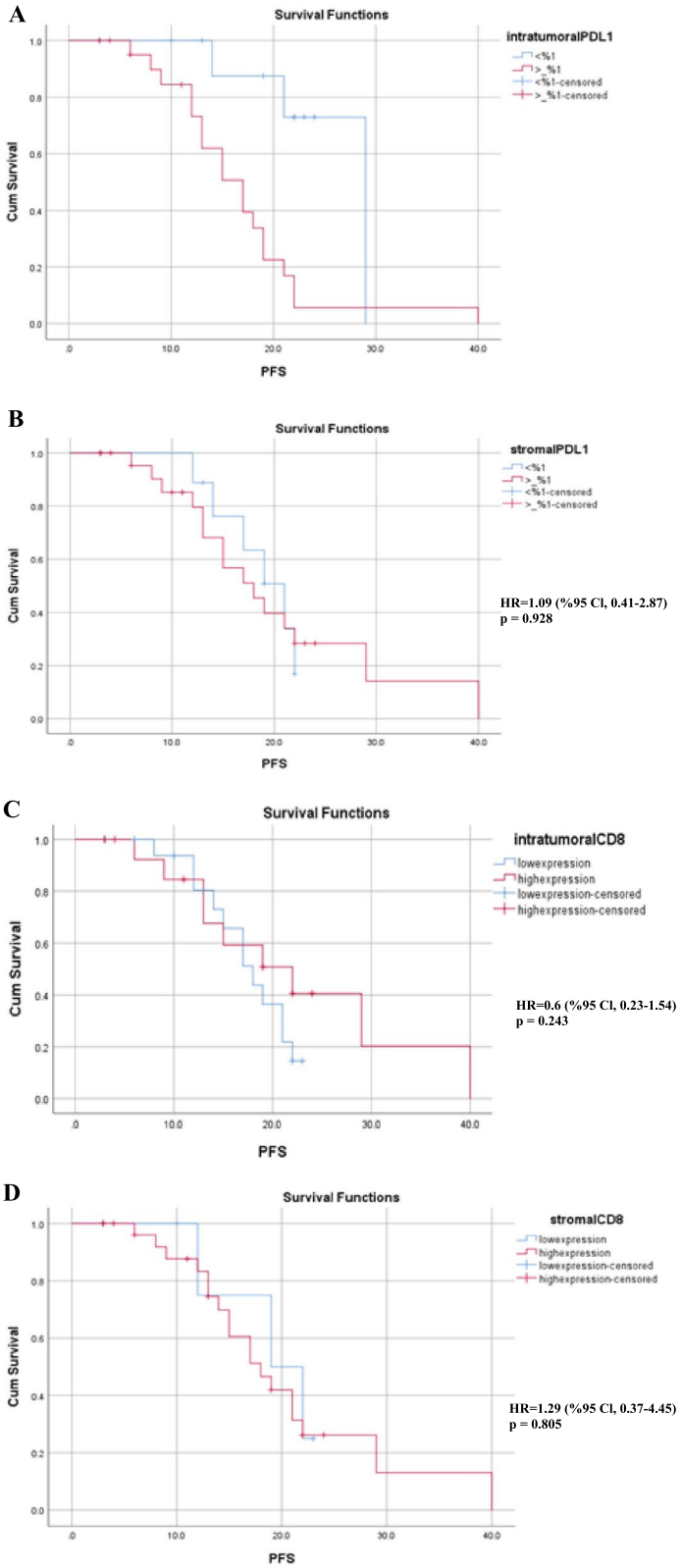

Fig. 2 **A** Kaplan–Meier plotter for Intratumoral PD-L1 and PFS; **B** Stromal PD-L1 and PFS; **C** Kaplan–Meier plotter for Intratumoral CD8 + TILs and PFS; D. Stromal CD8 + TILs and PFS

Table 2 Distribution of CRS according to intratumoral and stromal PD-L1

Intratumoral PD-L1		CRS 1 N, (%)	CRS 2 N, (%)	CRS 3 N, (%)	Total N	p
	Low expression	7(41.2%)	5(29.4%)	5(29.4%)	17	< 0.001
	High Expression	1 (3.6%)	23(82.1%)	4 (14.3%)	28	
Stromal PD-L1						
	Low Expression	4(33.3%)	6(50.0%)	2(16.7%)	12	0.305
	High Expression	4(12.1%)	22(66.7%)	7(21.2%)	33	

relationship found between stromal PD-L1 levels and PFS, as both groups had similar PFS of 20 and 17 months ($p=0.928$) (Fig. 2A,B and Supplementary Table 2A).

CD8 + TIL expression and patient prognosis

No statistically significant relationship was found between high and low expressions of intraepithelial and stromal CD8 + levels and PFS ($p=0.243$ and $p=0.805$; respectively) (Fig. 2C, D and Supplementary Table 2B).

PD-L1 expression and chemotherapy response scoring

Of all the patients, 28 (62.2%) showed a high level of intratumoral PD-L1 expression (PD-L1 ≥ 1%), and 33 (73.3%) exhibited high stromal PD-L1 expression (PD-L1 ≥ 1%). We found that as the level of PD-L1 expression increased in both areas, there was a correlated increase in the number of patients with CRS2 and CRS3 and a decrease in the number of patients with CRS1 (Table 2). Of the patients with high intratumoral PD-L1 expression, 23 patients experienced CRS2, 4 patients experienced CRS3, and only 1 patient experienced CRS1 ($p<0.001$). These results showed that there is a significant relationship between intratumoral PD-L1 expression and chemotherapy response scoring. Chemotherapy response was significantly increased in patients with high PD-L1 levels. Although the CRS2 and CRS3 levels tend to increase with high stromal PD-L1 levels, this was not found to be statistically significant ($p=0.305$) (Fig. 3A, B).

CD 8 expression and chemotherapy response scoring

As a result of the IHC evaluation high expression intraepithelial CD8 + TIL levels were observed in 20 (44.4%) patients and high stromal CD 8 + TIL expression in 35 (77.8%) patients (Table 3). It was shown that there was no relationship between intratumoral and stromal CD8 + TIL levels and chemotherapy response score ($p=0.303$ and $p=0.396$; respectively) (Fig. 3C, D).

Discussion

Identifying new therapeutic targets and biomarkers is an important area of research for oncogenesis and the progression of ovarian cancer. Previous research has demonstrated that the presence of PD-L1 and TILs could be used to predict the outcome of ovarian cancer. According to some studies, the presence of both tumor PD-L1 expression and intraepithelial CD8 + TILs infiltration are prognostic factors for patients with HGSC. The relationship between PD-L1 expression and survival outcomes appears to be variable across different studies. Esfahani et al. and Webb et al. reported that high PD-L1 expression is associated with improved survival outcomes [4, 17]. Conversely, Hamanashi et al. identified high PD-L1 expression as a poor prognostic indicator [5]. Additionally, Hyun-Soo Kim et al. observed no significant impact of PD-L1 expression on survival outcomes [18]. When analyzing PD-L1 expression in ovarian cancer through meta-analyses, distinct cancer-specific trends emerge. Li-Jun Huang et al. suggests that PD-L1 predicts a poorer prognosis in Asian ovarian cancer patients but indicates a better prognosis in non-Asian populations [19]. In contrast, Lin Wang et al. meta-analysis questions the overall prognostic significance of PD-L1 in ovarian cancer, while a bioinformatics study suggests that PD-L1 correlates with worse PFS [20]. Our study showed that lower iPD-L1 expression levels were associated with reduced survival rates, which is consistent with the findings of Hamanashi et al. [5]. We determined that patients with low-expression iPD-L1 (PD-L1 < 1%) had a greater PFS than those with high-expression iPD-L1 (PD-L1 > 1%) (28 versus 17 months, respectively). However, sPD-L1 did not significantly affect PFS.

This variability is also observed in the relationship between TILs and survival outcomes. CD4 + memory TILs, particularly iCD4 +, are often positively associated with DFS or OS, but this association is inconsistent for sCD4 + TILs. Significant infiltration of CD8 + TILs generally correlate with a positive prognostic effect on OS [21]. However, some studies find no significant impact [22–24], and some indicate negative effects on survival [17, 25, 26]. We could not demonstrate a correlation between CD8 + TILs and PFS. We believe that this may be related to the relatively small number of our patients and short follow-up time.

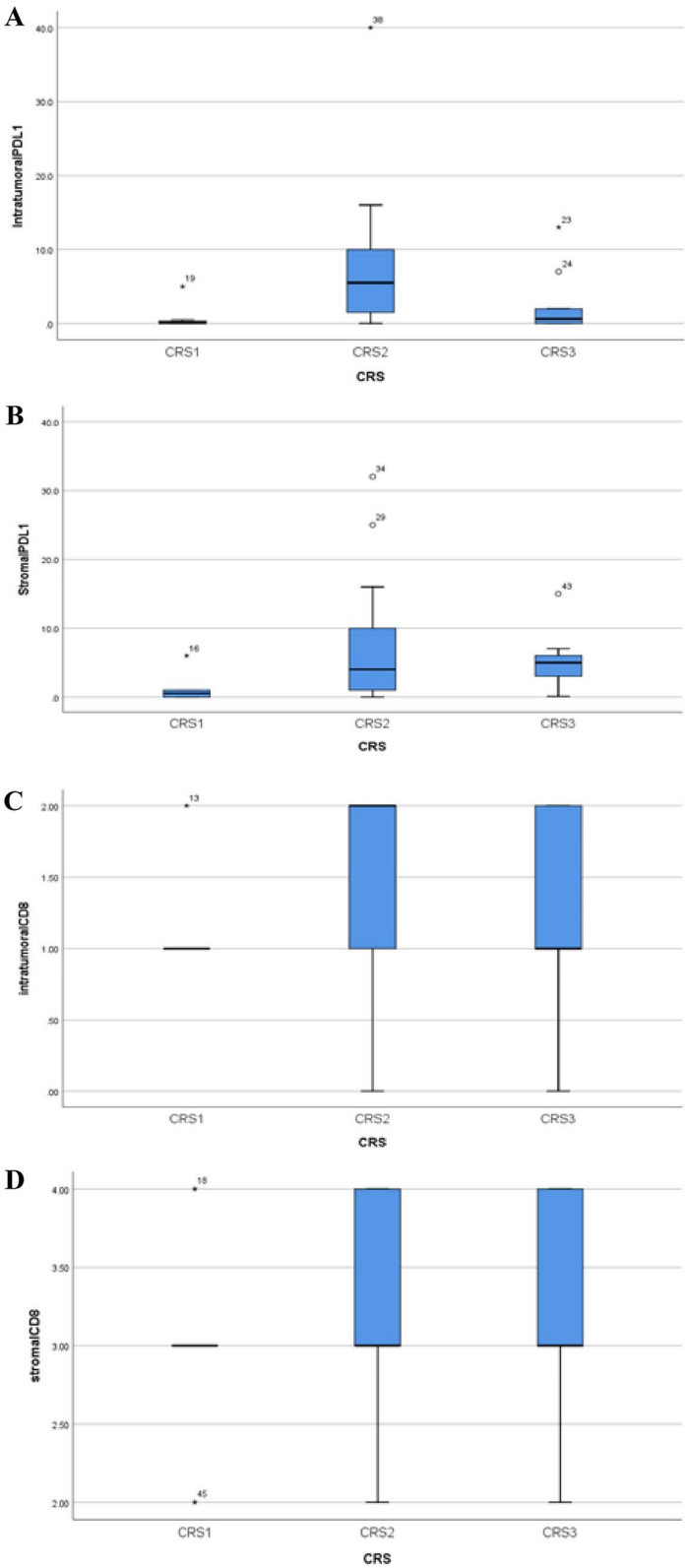

Fig. 3 Intratumoral PD-L1 (panel **A**), stromal PD-L1 (panel **B**), intratumoral CD8 + TILs (panel **C**), stromal CD8 + TILs (panel **D**) by CRS strata. On each box, the middle line indicates the median value, and the bottom and top edges of the box represent the 25th and 75th percentiles, respectively

Table 3 Distribution of CRS by intratumoral and stromal CD8 + TILs

Intraepithelial CD8 + TILs		CRS 1 N, (%)	CRS 2 N, (%)	CRS 3 N, (%)	Total N	p
	Low expression	6 (24.0%)	13 (52.0%)	6 (24.0%)	25	0.303
	High Expression	2(10.0%)	15(75.0%)	3 (15.0%)	20	
Stromal CD8 + TILs						
	Low expression	3(30.0%)	6(60.0%)	1(10.0%)	10	0.396
	High Expression	5(14.3%)	22(62.9%)	8(22.9%)	35	

We believe that the variations in PD-L1 expression/TILs and survival outcomes are likely influenced by several factors. These factors include the selection of PD-L1 and TILs antibodies, which can affect the accuracy and reliability of their detection, differences in scoring methods, and threshold levels. Moreover, the specific cell types that exhibit PD-L1 positivity within the tumor microenvironment play a critical role in modulating immune responses and clinical implications. Additionally, the unique genetic, molecular, clinical, and immunological characteristics inherent to different histological subtypes of EOC contribute significantly to the observed variations in PD-L1 and TILs profiles across patient cohorts. Additionally, we believe differences between optimally debulked and suboptimal debulked cases contribute to these variations.

Recent studies have demonstrated that the tumor microenvironment not only affects a patient's overall prognosis but also their response to conventional anti-cancer medications. In the study by Bohm et al., CD8 + T-cells and CD45RO + memory cells remained unchanged after NACT, but Treg cells decreased, and PD-1, CTLA4, and PD-L1 expression increased. Patients with a complete response (CRS3) showed higher T-cell activation and lower Treg cell infiltration compared to those with a poor response (CRS2) [16]. Mesnage et al. found that chemotherapy increased PD-L1 and iTILs/sTILs levels in post-NACT tissue, with high sTILs being prognostic for PFS. However, iTILs and PD-L1 expression did not significantly impact prognosis [27]. In contrast Kim et al. found that PD-L1 and TILs in post-NACT tissue did not impact survival [18].

For the last 20 years, the question of whether primary debulking surgery or interval debulking surgery after neoadjuvant chemotherapy should be preferred in ovarian cancer surgery has been one of the most debated topics. Prospective studies have not shown the superiority of either of the two surgical options over the other [28, 29]. Although this approach (NACT-IDS) may be associated with lower morbidity, there is a need for international consensus criteria for selecting patients and for parameters to predict which patients would benefit from neoadjuvant therapy.

Based on the available evidence, it appears that some factors can positively impact the survival of advanced ovarian cancer. These include achieving R0/1 cytoreduction after PDS or IDS, having a BRCA1/2 gene mutation, and having a complete or near-complete response [30]. BRCA1/2 status and the CRS are both reliable markers of chemosensitivity [31]. The CRS is a simple and consistent method for predicting the outcomes of patients with HGSC who have received NACT [8, 32].

Recently, studies have explored PD-L1 and TILs as predictive biomarkers of neoadjuvant chemotherapy response. Latest study indicate that breast cancer patients who demonstrate higher levels of PD-L1 expression experience a substantial improvement in their pCR [33]. Qi Du et al.'s meta-analysis demonstrated that breast cancer patients with higher PD-L1 expression had a notably greater pCR to neoadjuvant chemotherapy [34]. In addition, the presence of TILs during breast cancer diagnosis is a prognostic marker for achieving pCR after treatment with neoadjuvant chemotherapy [35, 36]. Currently, there is a lack of research in the literature that evaluates the relationship in ovarian cancer. Our study revealed that there is a relationship between high levels of iPDL1 expression and CRS. Specifically, we observed that the incidence of CRS2 and CRS3 was higher, and CRS1 was lower among individuals with high PD-L1 expression.

In our study, we observed that high iPD-L1 expression is associated with lower PFS but increased chemotherapy response. This phenomenon can be interpreted through several plausible explanations: (1) PD-L1 expression in ovarian cancer patients may have a dual effect; high PD-L1 levels could indicate a more aggressive disease phenotype, potentially leading to poorer PFS, while it also indicate an active immune microenvironment that responds well to chemotherapy, particularly in tumors heavily infiltrated by immune cells, (2) ovarian cancer's heterogeneity contributes to varied treatment responses among patients, influenced by intrinsic tumor characteristics that can impact treatment efficacy despite initial

responses. In summary, high PD-L1 expression in ovarian cancer patients can influence both chemotherapy response and PFS in complex and multifaceted ways.

Our study has some limitations, including being a retrospective study with a limited patient sample. Furthermore, the varying scoring systems and detection methods for PD-L1 across different studies may have contributed to conflicting results compared to our study. We suggest that developing and implementing a standardized pathology procedure could address this limitation. Unfortunately, due to the lack of Ki-67 and BRCA1/2 data in our patient cohort, we were unable to perform the multivariate analyses. The retrospective nature of our study and the limited resources available at the time of data collection prevented us from obtaining these specific data points.

In conclusion, our findings suggest that levels of iPD-L1 expression in a diagnostic biopsy of ovarian cancer could serve as predictive biomarkers for the effectiveness of neoadjuvant chemotherapy prior to undergoing interval debulking surgery. We believe that, if supported by large-scale prospective studies, the PD-L1 expression level in the tumor before chemotherapy may be used as a test to predict the chemotherapy response.

Abbreviations

CRS	Chemotherapy response score
DFS	Disease-free survival
FIGO	Federation of Gynecology and Obstetrics
HGSC	High-grade serous carcinoma
iCD4 +	Intraepithelial/intratumoral CD4 + T cells
iCD8 +	Intraepithelial/intratumoral CD8 + T cells
IDS	Interval debulking surgery
IHC	Immunohistochemistry
iPD-L1	Intraepithelial/intratumoral PD-L1
NACT	Neoadjuvant chemotherapy
OC	Ovarian cancer
OS	Overall survival
pCR	Pathologic complete response
PDS	Primary debulking surgery
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
sCD4 +	Stromal CD4 + T cells
sCD8 +	Stromal CD8 + T cells
sPD-L1	Stromal PD-L1
TILs	Tumor-infiltrating lymphocytes

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13048-024-01533-x.

Supplementary Material 1.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Hacettepe University Hospitals (decision number: KA-19101; date of approval: 26 September 2019).

Authors' contributions

Conceptualization, T.A. and Z.A.; methodology, T.A. and B.Y.A.; software, validation, investigation, formal analysis, data curation, T.A. and B.Y.A.; pathological staining and evaluation, F.G. and A.U.; writing—review and editing, T.A., B.Y.A., and E.C.; visualization, E.C.; supervision, Z.A.; project administration, T.A.; funding acquisition, Z.A. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all subjects involved in the study for molecular analysis.

Competing interests

The authors declare no competing interests.

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