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Alleviation of neoadjuvant immunochemotherapy for esophageal squamous cell carcinoma and its relationship with expression and changes of PD-L1

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The alleviation of neoadjuvant immunochemotherapy (NICT) and neoadjuvant chemoradiotherapy (NCRT) was compared for esophageal squamous cell carcinoma (ESCC), and the correlation between the expression and changes of PD-L1 and the efficacy of NICT was evaluated in this study. Fourteen patients with ESCC who received preoperative NICT were included in group A, and fourteen patients with ESCC who received preoperative NCRT were included in group B. Next, group A was divided into CR (complete response), PR (partial response), and NR (no response) according to the degree of pathological response. Also, the expression and changes of PD-L1 (CPS, TPS, IPS) before and after treatment were compared between the groups. We observed that after the treatment, the expression of PD-L1 in both groups was higher than before treatment. In group B, the expression of PD-L1 was elevated in 92.8% of patients, which was higher than that in group A, which had significantly increased IPS ($p<0.05$). In group A, 9 (64.2%) patients with CPS <10 achieved partial or complete response. There was no significant difference in pathological response and reduction of tumor thickness between the two groups or significant differences in CPS and TPS among CR, PR, and NR groups before treatment. The IPS was the highest in the CR group; however, the difference was not statistically significant. The differences in IPS change were significant among the three groups ($p<0.05$). In conclusion, NICT and NCRT could upregulate the expression of PD-L1. NCRT more significantly upregulated the expression of PD-L1, mainly of PD-L1 in immune cells in the tumor microenvironment. NICT was not less effective than NCRT in pathological response and tumor thickness changes. The preoperative CPS and TPS scores of PD-L1 did not effectively predict the degree of pathological response, but the high IPS and high IPS downregulation could be related to the degree of pathological response. Some patients with low preoperative expression of PD-L1 could still achieve a good response by NICT. As NCRT can upregulate the expression of PD-L1, the low preoperative expression of PD-L1 is no contraindication for immunotherapy, which provides a new basis and prognostic indexes for chemoradiotherapy combined with immunotherapy.

Key words: PD-L1, neoadjuvant chemoradiotherapy, neoadjuvant immunochemotherapy, esophageal squamous cell carcinoma, pathological response

Esophageal cancer is the fourth leading cause of death from malignant tumors in China. Squamous cell carcinoma is the most common pathological type of esophageal cancer [1–3]. In China, most patients have locally advanced tumors at the time of diagnosis so comprehensive anti-tumor therapy, which includes surgery, chemoradiotherapy, and immunotherapy, is urgently needed.

Recent studies have shown that neoadjuvant chemoradiotherapy (NCRT) has an important role in the comprehensive anti-tumor strategy for locally advanced esophageal cancer [4]. According to previous studies, chemoradiotherapy has an immunosuppressive effect; however, it has been shown that chemoradiotherapy can activate the immune system through a variety of mechanisms, including inducing immunogenic cell death (ICD), promoting the production and release of inflammatory factors into the tumor microenvironment, promoting the expression and presentation of tumor antigens, and activating T cells [5–7]. Recently, preclinical studies have suggested that radiotherapy can activate cytotoxic T lymphocytes and increase the expression of programmed death ligand 1 (PD-L1) in the tumor microenvironment of mice with breast cancer and colorectal cancer [8]. Clinical studies on breast cancer and rectal cancer have also shown that chemoradiotherapy can reverse tumor

immunosuppressive microenvironment [9], thus encouraging the combination of NCRT with immunotherapy [10, 11].

PD-L1 is an important co-repressor [12] that can inhibit T cell proliferation and cytokine production by binding with PD-1 in T cells, participating in immune escape. It plays an important role in regulating host tumor microenvironment and systemic anti-tumor immune responses [13, 14]. Over recent years, the development of monoclonal antibodies that inhibit PD-1 or PD-L1 has promoted the use of immunotherapy in the treatment of a variety of malignant tumors, including esophageal cancer. According to the results of the KEYNOTE-181 clinical trial, for patients with advanced esophageal squamous cell carcinoma (ESCC) who had a combined positive score (CPS) ≥10, PD-L1 inhibitor alone could significantly prolong progression-free survival (PFS) and overall survival (OS) [15]. Based on this, immunotherapy for esophageal cancer has been recommended in NCCN guidelines [16]. Therefore, pathological evaluation of PD-L1 has become particularly important. The evaluation method, necessity, and clinical significance of PD-L1 before and after NCRT need to be further explored.

Standardized preoperative NCRT is still in the exploratory stage, and the studies on the effect of neoadjuvant chemotherapy combined with immunotherapy on tumor microenvironment and PD-L1 in ESCC are limited. Considering the pathological specimens of neoadjuvant chemotherapy combined with immunotherapy, it is not clear whether CPS, tumor proportion score (TPS) or immunocyte proportion score (IPS) should be used for PD-L1 evaluation. Therefore, it is very important to study the effects of NCRT and immunotherapy on the expression of PD-L1 for evaluating the prognosis of esophageal cancer and even exploring an individualized treatment model.

Table 1. Clinical and pathological characteristics of A and B group.

Clinical characteristics	Total	Cohort A	(%)	Cohort B	(%)	p-value
Sex						
Male	23	9	64.3	14	100	0.041
Female	5	5	35.7	0	0.0	
Age						
>60	15	6	42.9	9	64.3	0.449
≤60	13	8	57.1	5	35.7	
T Stage						
T2	1	0	0.0	1	7.1	0.041
T3	23	14	100	9	64.3	
T4	4	0	0.0	4	28.6	
N Stage						
N0	1	1	7.1	0	0.0	0.121
N1	11	8	57.1	3	21.4	
N2	13	4	28.6	9	64.3	
N3	3	1	7.1	2	14.3	
Differentiation						
High	7	4	28.6	3	21.4	0.797
Medium	10	4	28.6	6	42.9	
Low	11	6	42.9	5	35.7	
Location						
Upper	2	1	7.1	1	7.1	1.000
Middle	24	12	85.7	12	85.7	
Lower	2	1	7.1	1	7.1	

Patients and methods

Study objects. The surgical specimens were obtained from ESCC patients treated at Sichuan Cancer Hospital and Institute, China, from 2017 to 2021. Inclusion criteria were the following: 1) patients with primary ESCC; 2) patients with no other malignant tumors; 3) patients underwent preoperative concurrent NCRT or NICT; 4) patients underwent radical resection of esophageal carcinoma after NCRT; 5) patients with no autoimmune diseases.

This retrospective study included a total of 28 patients. Among them, 14 patients received preoperative NICT (paclitaxel 210 mg ivgtt d1+carboplatin 500 mg ivgtt d1+toripalimab 240 mg ivgtt d1) (group A), and 14 patients received preoperative NCRT (paclitaxel 210 mg d1 ivgtt+cisplatin 40 mg d1-3 ivgtt) (group B). Radiotherapy was used for primary tumors, positive lymph nodes, subclinical lesions, and lymph node drainage area. Image-guided intensity-modulated radiation therapy (IMRT) was also performed. The fraction dose was GTV 2.0 Gy/f, GTVInL 2.0 Gy/f, GTVInR 2.0 Gy/f and GTV1 1.8 Gy/f for 20 cycles. All patients in group A received 2 cycles of NICT treatment, chemotherapy and immunotherapy were performed simultaneously, and surgery was performed 29.7±3.5 (22–36) days after treatment. Patients in group B received NCRT treatment, including 2 patients in cycle 1, 11 patients in cycle 2, and 1 patient in cycle 3. Radiotherapy was performed simultaneously in the first cycle of chemotherapy. Surgery was performed 30.8±7.1 (22–54) days after NCRT treatment. Group A was further divided into CR (complete response), PR (partial response), and NR (no response) subgroups according to the degree of pathological responses. There were no significant differences in age, gender, preoperative tumor staging, tumor differentiation, and tumor location among the three groups (Tables 1 and 2).

Ethical approval has been obtained from the Regional Ethical Committee (Nos: SCCHEC-02-2017-043).

Sample processing. The specimens were fixed in 10% neutral formalin, embedded in paraffin, routinely sectioned, and stained with H&E. Streptavidin-peroxidase (SP) method was used for immunohistochemical study, and the staining steps were carried out on automated immunohistochemistry (IHC) staining instrument according to the manufacturer's instruction. PD-L1 (Dako 22c3) was positively stained in the cytoplasm and cell membrane, and Roche Ventana benchmark IHC staining platform was applied. The cross-platform use of PD-L1 antibodies was confirmed to be reliable [17].

Result interpretation. Three physicians who performed PD-L1 assessment participated in the training for the PD-L1 interpretation masters held by Targos Advance Training and Consulting and obtained the qualification certificate. The median of interpretation results was obtained. For biopsy specimens, we counted all cells on the slide section, and for excised specimens, we selected four different areas on the slide, and cells in 10 high power fields were counted in each area. Tumor cells, lymphocytes, and macrophages with positive cell membrane staining were determined under an OLYMPUS BX43 20× field microscope.

Three methods were mainly adopted for PD-L1 scoring: CPS (combined positive score) = (number of positive tumor cells in PD-L1 membrane + number of PD-L1 positive tumor-associated immune cells)/total number of tumor cells × 100%; TPS (tumor proportion score) = number of positive tumor cells in PD-L1 membrane/total number of tumor cells × 100%; IPS (immunocyte proportion score) = number of positive tumor-associated immune cells in PD-L1 membrane and cytoplasm of any intensity/total number of tumor-associated immune cells × 100% [15].

Pathological evaluation of tumor regression after NCRT and immunotherapy was evaluated using the Becker score [18], where 0 indicated complete response with no residual tumor cells; 1 indicated almost complete response, with residual of single or few small focal tumor cells; 2 represented partial response, with obvious degeneration of residual tumor cells, but residual of single or small focal tumor cells; and 3 represented extensive residual tumor cells, with no obvious degeneration. Those with a score of 0–1 point, 2, and 3 points were assigned to the CR (complete response), PR (partial response), and NR (no response) subgroup, respectively.

Statistical analysis. Wilcoxon signed-rank test, chi-square test, Fisher exact test, and Kruskal Wallis one-way analysis of variance by rank were used to compare the clinical and pathological data among different groups. SPSS software (ver. 20.0) and GraphPad Prism 5 were used for all statistical analysis and plotting. A p-value <0.05 was considered statistically significant.

Results

The clinical and pathological characteristics of group A and group B before and after treatment are shown in Figure 1. PD-L1 scoring of 14 patients in group A revealed that CPS was increased in 10 (71.4%) and decreased in 4 patients (28.5%); TPS was increased in 8 (57.1%) and unchanged in 6 patients (42.9%); IPS was increased in 7 (50.0%), decreased in 6 (42.9%), and unchanged in 1 patient (7.1%). In group A, 14 patients (100%) had a CPS <10, and 9 of them (64.3%) achieved a complete or a partial response (Figure 1A). In group B, CPS, TPS, and IPS were increased in 13 patients (92.8%), CPS and IPS were decreased in 1 patient (7.2%), while TPS remained unchanged. The response rate was 64.3% in group A and 71.4% in group B. T restaging was 21.4% in group A and 42.8% in group B, and N restaging was 42.8% in group A and 78.6% in group B (Figure 1B). All 14 patients were followed up until June 15, 2021. Thirteen patients survived, 1 patient was lost to follow-up, and 1 patient had relapsed tumor. The follow-up time for most patients was less than 2 years.

Table 2. Clinical and pathological characteristics of CR, PR and NR subgroups.

Clinical characteristics	Total	CR	(%)	PR	(%)	NR	(%)	p-value
Sex								
Male	9	2	22.2	4	44.4	3	33.3	1.000
Female	5	1	20.0	2	40.0	2	40.0	
Age								
>60	8	2	25.0	4	50.0	2	25.0	0.800
≤60	6	1	16.7	2	33.3	3	50.0	
T Stage								
T3	14	3	21.4	6	42.9	5	35.7	1.000
N Stage								
N0	1	0	0.0	0	0.0	1	100.0	0.357
N1	8	2	25.0	5	62.5	1	12.5	
N2	4	1	25.0	1	25.0	2	50.0	
N3	1	0	0.0	0	0.0	1	100.0	
Differentiation								
High	4	0	0.0	2	50.0	2	50.0	0.769
Medium	4	1	25.0	1	25.0	2	50.0	
Low	6	2	33.3	3	50.0	1	16.7	
Location								
Upper	1	0	0.0	1	100.0	0	0.0	1.000
Middle	12	3	25.0	5	41.7	4	33.3	
Lower	1	0	0.0	0	0.0	1	100.0	

The changes in PD-L1 expression in groups A and B after treatment are shown in Figure 2. Post-treatment PD-L1 score in group A increased compared with pretreatment values, the differences in CPS and TPS were statistically significant ($p<0.05$) (Figures 2A, 2B), and the difference in IPS was not statistically significant ($p>0.05$) (Figure 2C). PD-L1 scores (CPS, TPS, IPS) in group B increased after treatment, and the differences in CPS, TPS, and IPS were statistically significant ($p<0.05$) (Figures 2D–2F). The increases in CPS and IPS in group B were higher than those in group A, and the difference in the increase in IPS was statistically significant ($p<0.05$).

The representative immunohistochemical micrograph of patients is shown in Figure 3.

There were no significant differences in pathological response score, tumor thickness, and tumor thickness change between the two groups ($p>0.05$), as shown in Figure 4.

The changes in PD-L1 expression in CR, PR, and NR groups after treatment are shown in Figure 5. Before treatment, there were no significant differences in PD-L1 scores among CR, PR, and NR groups ($p>0.05$). After treatment,

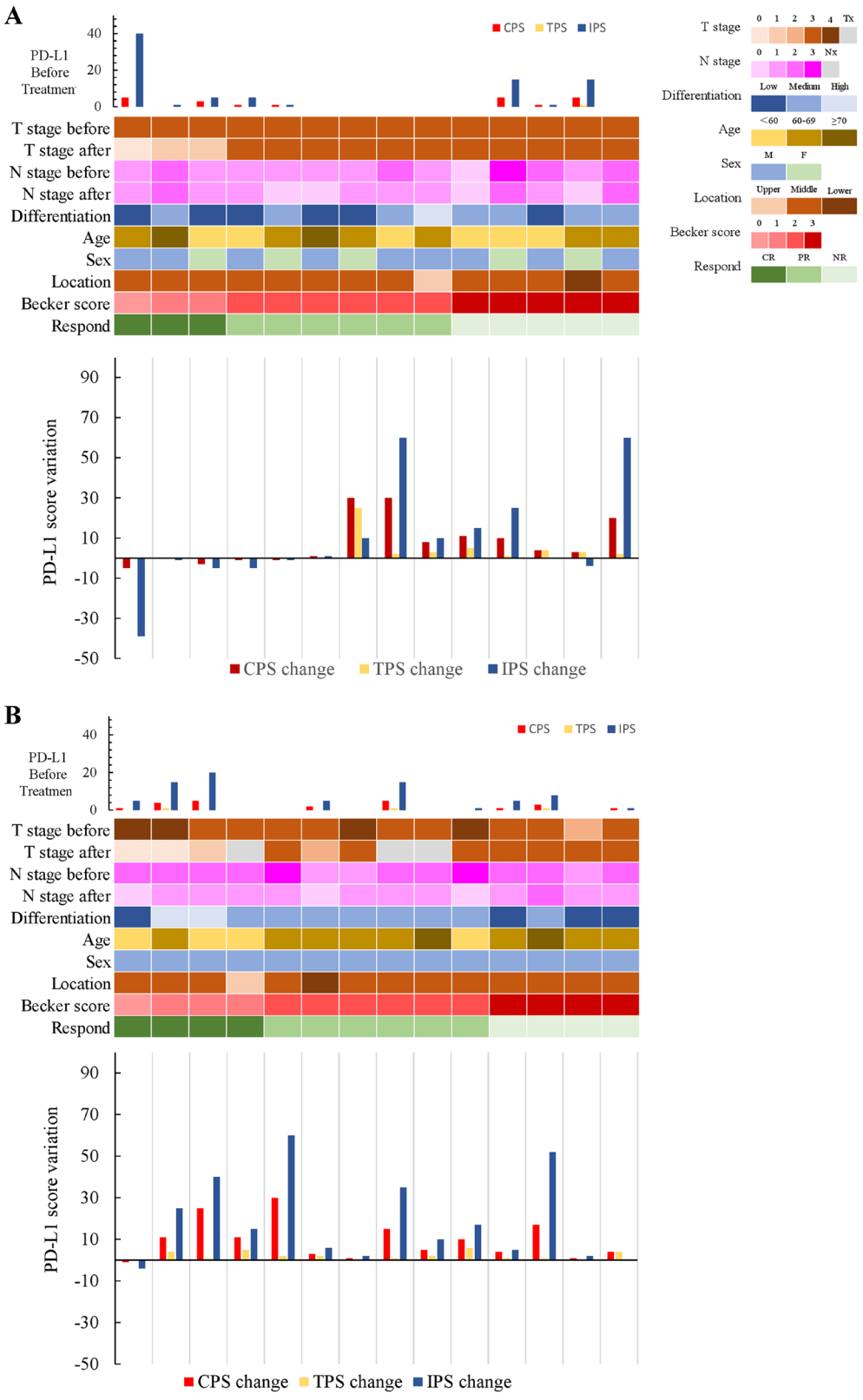

Figure 1. A) Clinical characteristics of group A patients, and PD-L1 CPS, TPS, and IPS scores and changes after treatment. B) Clinical condition of group B patients, and PD-L1 CPS, TPS, and IPS scores and changes after treatment.

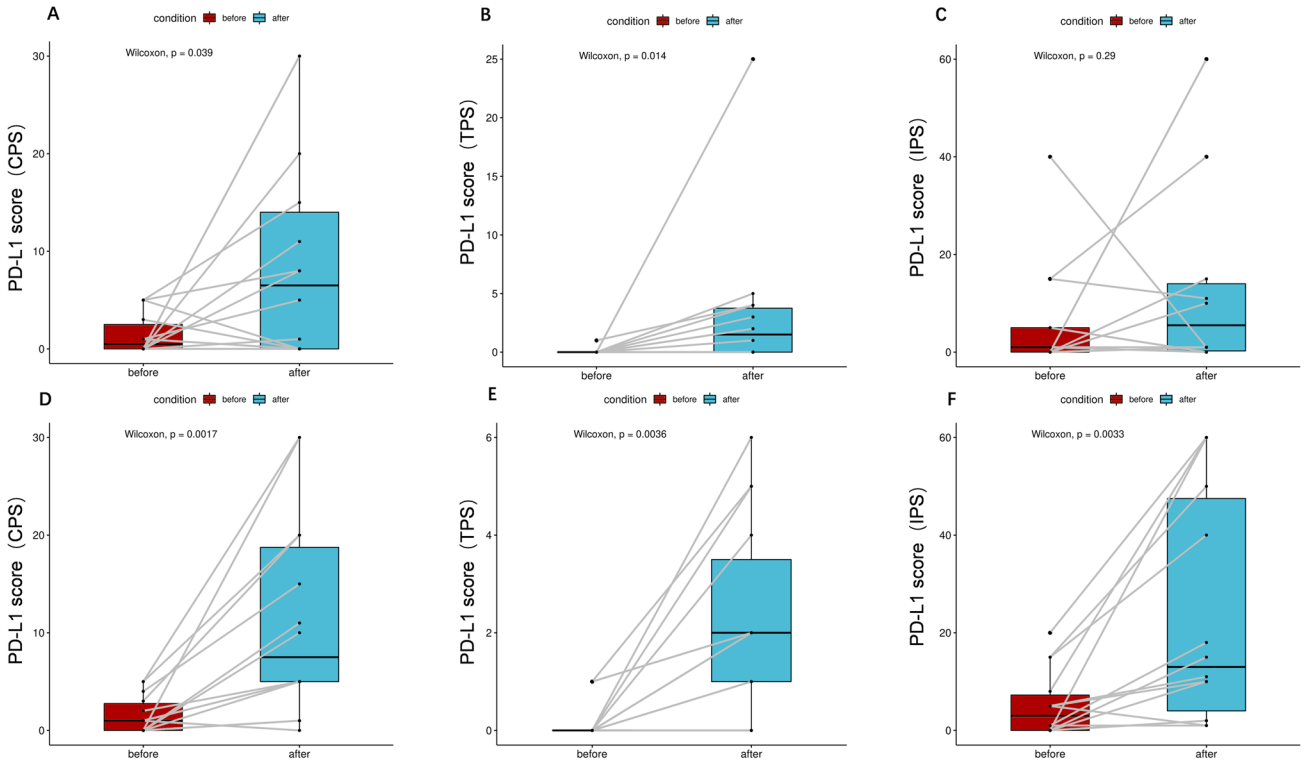

Figure 2. PD-L1 scores of group A and B before and after treatment A) CPS of group A before and after treatment; B) TPS of group A before and after treatment; C) IPS of group A before and after treatment; D) CPS of group B before and after treatment; E) TPS of group B before and after treatment; F) IPS of group B before and after treatment.

for group A, IPS was decreased in CR subgroup, while it was significantly increased in PR and NR subgroups ($p<0.05$) (Figure 5A and Supplementary Figure S1). There were no significant differences in post-treatment PD-L1 scores among CR, PR, and NR subgroups ($p>0.05$) in group B (Figure 5B).

Discussion

Tumor cells can express a variety of immunosuppressive proteins, leading to immune cell dysfunction and apoptosis [19]. Among them, programmed death-ligand 1 (PD-L1; also known as B7-H1 or CD274) is one of the most important repressors promoting tumor immune escape [20]. PD-L1 is expressed on antigen-presenting cells and tumor cells. It is an immune checkpoint protein that can negatively regulate the anti-tumor immune response. Inhibition of this immune checkpoint protein can promote anti-tumor immunity, thus eliminating tumor cells. Although the relationship between the expression of PD-L1 and the prognosis of tumor patients is controversial, anti-PD-L1 therapy has been shown to have good safety in clinical application and has a good effect in the treatment of a variety of tumors, including esophageal cancer [21–27].

Previous studies on PD-L1 expression after immunotherapy for esophageal cancer showed that compared with the pretreatment biopsy tissues, the expressions of PD-L1 were increased in the postoperative tumor tissues of 19 patients undergoing NCRT [28]. The result of this study showed that NICT and NCRT could upregulate the expression of PD-L1, and NCRT had a more obvious effect, which was consistent with previous reports. Moreover, our results further revealed that the increase in PD-L1 IPS score was more significant after NCRT. This suggests that NCRT may exert a more significant effect on immune cells in the tumor microenvironment, allowing patients with low expression of PD-L1 to benefit from immunotherapy, which has become a clinical alternative modality for ESCC.

Considering the protocol selection and the effectiveness of neoadjuvant combination therapy, in the present study, we compared the degree of pathological response, response rate, and tumor shrinkage between NICT and NCRT groups, and found that both groups had a higher response rate. NICT showed non-inferiority to NCRT and was safer than chemoradiotherapy. A single-arm, multicenter phase II clinical trial in Japan also confirmed that PD-1 immune checkpoint inhibitor monotherapy was safer and more effective than chemoradiotherapy in the treatment of chemotherapy-resis-

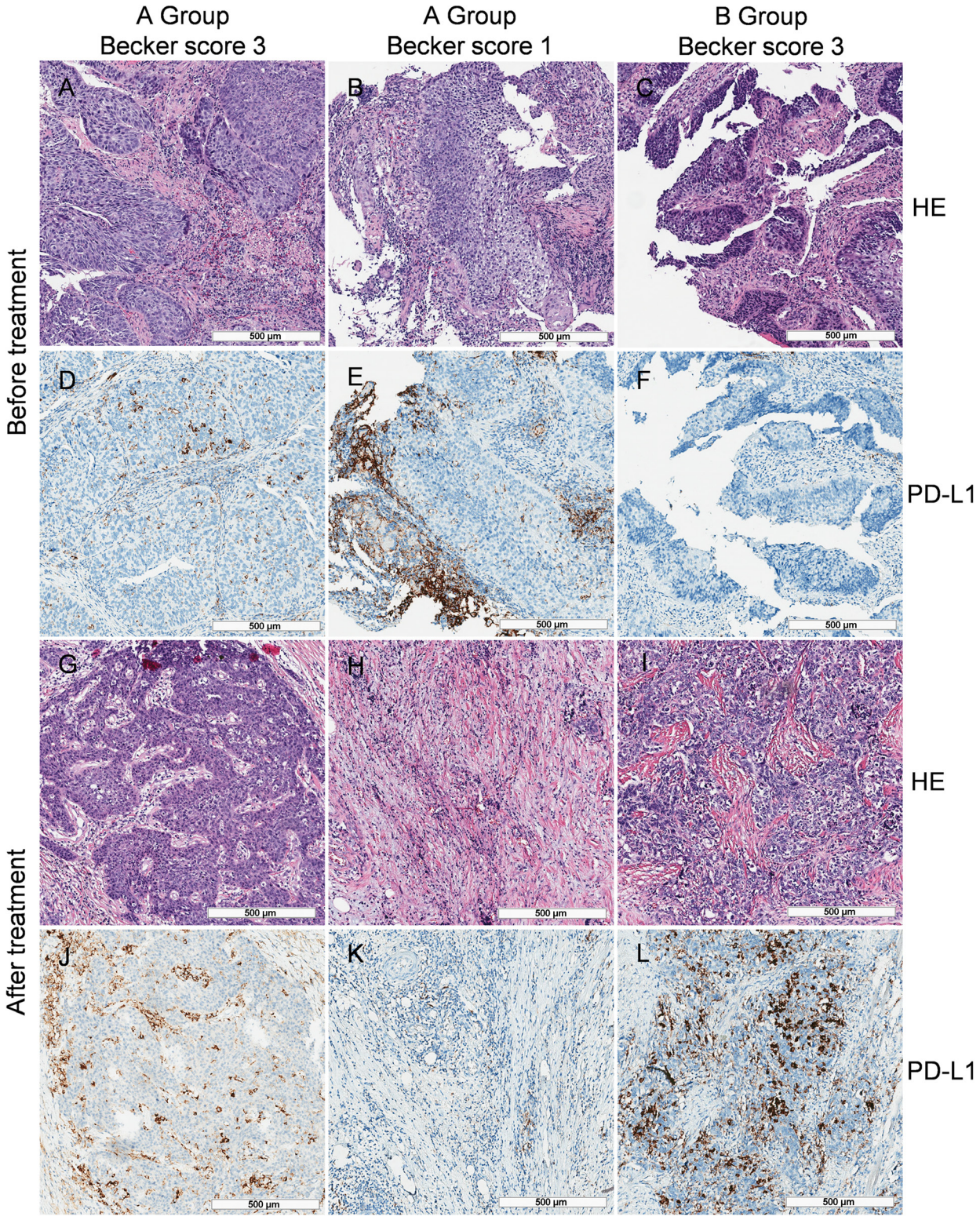

Figure 3. A–C) Pathological characteristics before treatment. D–F) PD-L1 expression before treatment. G, I) Pathological sections of one patient with Becker score of 3 in group A and group B, respectively; extensive residual tumor cells, with no obvious degeneration. J, L) The expression of PD-L1 is upregulated compared with that before treatment and is mainly expressed on immune cells; the change of PD-L1 expression in tumor cells is obvious. H) Pathological section of one patient with Becker score of 1 in group A after treatment, showing an almost complete response of the tumor cells, obvious degeneration, and residual of single or few small focal tumor cells. K) The expression of PD-L1 is downregulated after treatment. HE, ×100.

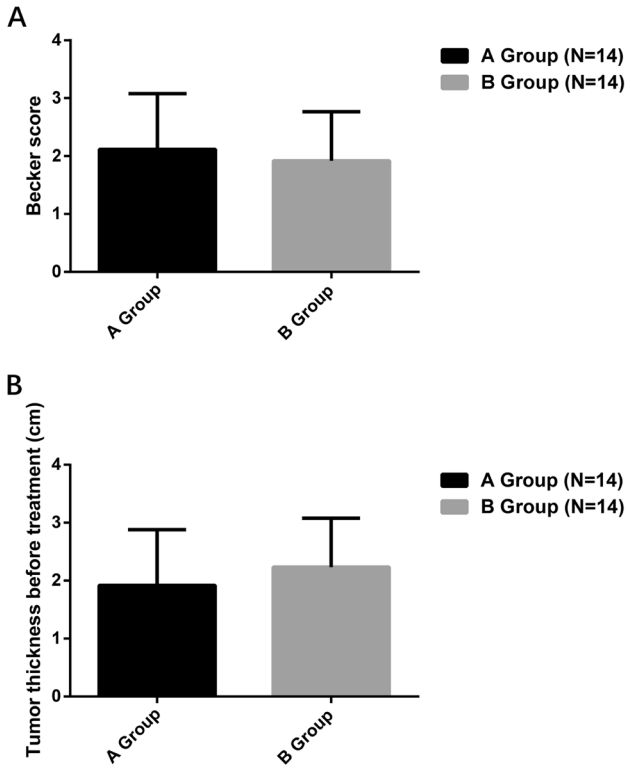

Figure 4. A) Pathological response score. B) Tumor thickness.

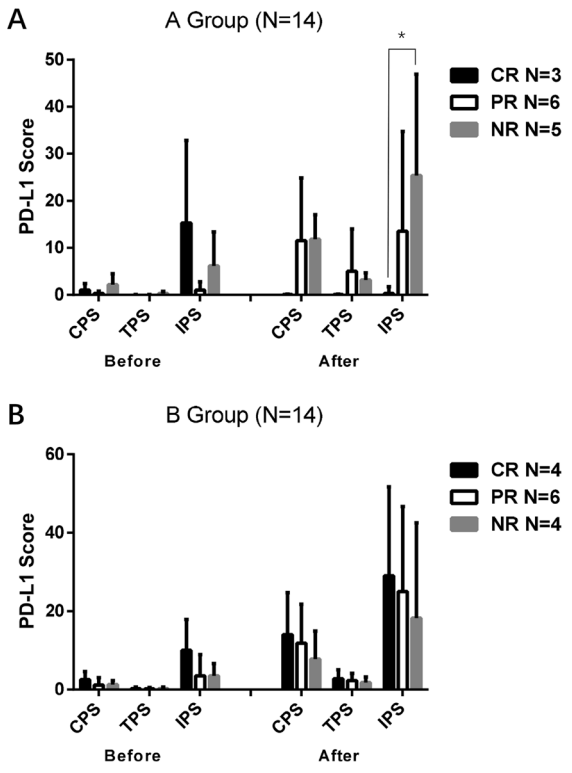

Figure 5. Expression of PD-L1 in CR, PR, and NR subgroups before and after treatment: group A (A) and group B (B). *p<0.05

tant or refractory advanced esophageal cancer [29]. Therefore, NICT may be a better choice for the treatment of ESCC.

Furthermore, considering the prognostic biomarkers for NICT, although PD-L1 can be expressed in both tumor and immune cells, the predictive value of these biomarkers and efficacy evaluation method for anti-PD-1/L1 therapy in various solid tumors is still controversial. Numerous studies have suggested that the PD-L1 CPS score can be used as a biomarker for the prognosis of patients with ESCC. In these patients, higher PD-L1 expression was associated with a poorer prognosis. In the aspect of anti-PD-1/L1 therapy, the PD-L1 TPS score could predict the clinical benefit of pembrolizumab [30–33]. In a single-arm study of patients with esophageal cancer pretreated with pembrolizumab, patients with a PD-L1 CPS value of 10 based on 22C3 PharmDx test had a better ORR (14%) compared with those (6% of patients) with a PD-L1 CPS value of <10 [34]. A randomized phase III clinical trial (KEYNOTE-181) comparing the efficacy of second-line pembrolizumab plus chemotherapy showed that the OS of patients with a CPS ≥10 was significantly improved, which eventually led to the US FDA approval of a CPS point ≥10 as the positive threshold in concomitant diagnosis [15]. Our study attempted to explore the correlation between the expression of baseline PD-L1 and the efficacy of neoadjuvant therapy. Although the IPS value of the CR subgroup was higher, the difference was not statistically significant ($p>0.05$). This might be due to the small sample size, and further investigation with a large sample size is needed. In addition, our results revealed that the difference in IPS change in three groups after treatment was statistically significant ($p<0.05$). The decrease in IPS may be related to better pathological responses. There were no significant differences in CPS and TPS scores among CR, PR, and NR subgroups before treatment, indicating that pretreatment CPS and TPS scores could not effectively predict the degree of pathological response. In this study, three patients (21.4%) achieved complete or almost complete response, and among patients receiving NICT with a CPS <10, 6 patients (42.8%) achieved a partial response. As neoadjuvant therapy can cause dynamic changes in PD-L1 expression, whether the PD-L1 CPS ≥10 criteria can be applied to the screening of patients for NICT needs to be further studied.

In conclusion, NCRT could upregulate the expression of PD-L1, significantly influencing the immune cells in the tumor microenvironment. The combination of neoadjuvant chemotherapy and PD-L1 immune checkpoint inhibitors may have a better synergistic anti-tumor effect, which may depend on the activation of cytotoxic T cells [8]. Therefore, IPS and the downregulation of IPS may be related to the degree of pathological response. But more data will be needed to verify this hypothesis. The prognostic values of these markers were not analyzed due to the short follow-up period.

As mentioned above, chemoradiotherapy can activate the immune system and reverse the immunosuppressive state through various mechanisms, so an improved pathological response following immunotherapy may be promoted by neoadjuvant chemotherapy. Currently, the clinical trials of chemoradiotherapy combined with immunotherapy for non-small cell lung cancer, esophageal cancer, melanoma, and other solid tumors are in progress. Extensive preclinical evidence [11], as well as the current study, provided a reliable theoretical basis for the application of NCRT combined with immunotherapy in treating ESCC. However, the optimal time and sequence of NCRT combined with immunotherapy, as well as the location and fraction protocol of radiotherapy, chemotherapy dose, and similar issues still present problems that need to be urgently solved. Therefore, future clinical trials are needed to further explore this comprehensive anti-tumor treatment strategy.

Supplementary information is available in the online version of the paper.

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Alleviation of neoadjuvant immunochemotherapy for esophageal squamous cell carcinoma and its relationship with expression and changes of PD-L1

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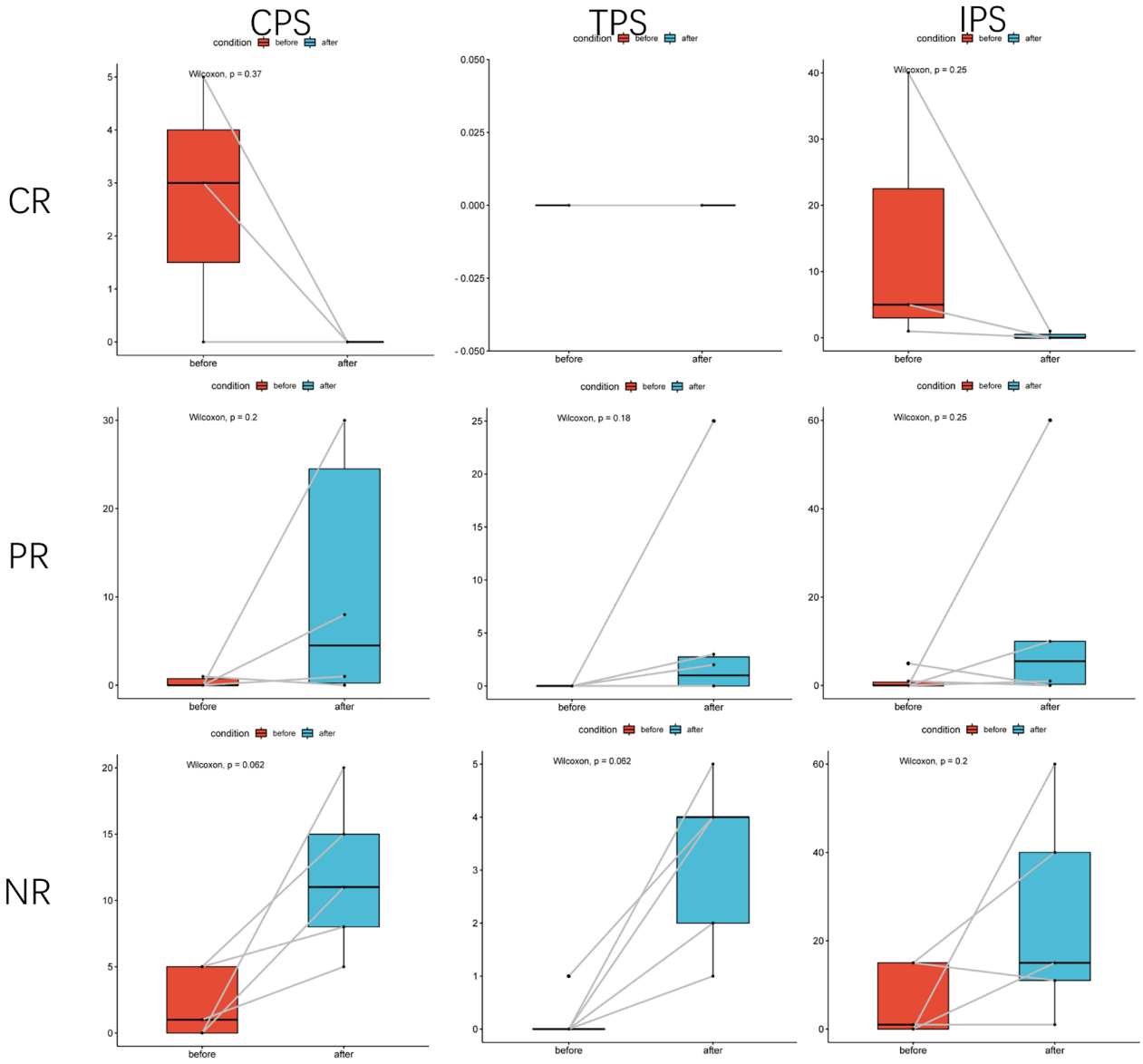
Supplementary Information



Supplementary Figure S1. Expression of PD-L1 in CR, PR, and NR subgroups in group A before and after treatment.