

Original Article

Efficacy of tislelizumab combined with nab-paclitaxel and nedaplatin in advanced esophageal squamous cell carcinoma and its impact on serum tumor markers

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Abstract: Objective: To evaluate the efficacy and safety of tislelizumab combined with nab-paclitaxel plus nedaplatin for advanced esophageal squamous cell carcinoma (ESCC), and its effects on serum tumor markers and inflammatory cytokines. Methods: A total of 228 advanced ESCC patients were retrospectively enrolled and divided into an observation group (tislelizumab combined with nab-paclitaxel plus nedaplatin, n=114) and a control group (chemotherapy alone: nab-paclitaxel plus nedaplatin, n=114). Related serological indicators, T lymphocyte subsets, quality of life, short-term efficacy, pathological response, survival outcomes and adverse reactions were compared. Independent prognostic factors were analyzed via univariate and multivariate Cox regression. Results: After treatment, both groups exhibited decreased levels of tumor markers, inflammatory cytokines, soluble PD-1, PD-L1, VEGF and MMP-9, with lower levels in the observation group (all $P<0.05$). The observation group had improved immune function, higher SF-36 scores, as well as higher objective response rate, disease control rate, and pathological response indexes (all $P<0.05$). Moreover, patients in the observation group had longer progression-free survival and overall survival (both $P<0.05$). Advanced TNM stage was an adverse prognostic factor, while combined immunochemotherapy reduced mortality risk. Conclusion: Tislelizumab plus the dual chemotherapy regimen can effectively reduce serum tumor markers and alleviate tumor-related inflammation, improve immune status, quality of life and survival of patients with advanced ESCC with acceptable safety, supporting its potential for broader clinical application.

Keywords: Tislelizumab, chemotherapy, esophageal squamous cell carcinoma

Introduction

Esophageal cancer is the 8th most common malignant tumor worldwide and the 6th leading cause of cancer-related death. China is a high-incidence area, with an age-standardized incidence of approximately 21.3/100,000, of which over 90% being esophageal squamous cell carcinoma (ESCC) [1, 2]. Most patients are diagnosed at an unresectable locally advanced or metastatic stage, and even with standard platinum-based chemotherapy, the 5-year survival rate remains low, and the prognosis is unsatisfactory [3, 4]. Although traditional chemotherapy can control tumor burden, it is frequently accompanied by significant toxic effects and immunosuppression, making it difficult to achieve lasting clinical benefits [5, 6].

Molecular profiling studies have indicated that ESCC exhibits a high tumor mutational burden and a high programmed death ligand 1 (PD-L1) positivity rate, providing a theoretical basis for the application of immune checkpoint inhibitors (ICIs) [7]. Recent studies have confirmed that ICIs, particularly anti-programmed death receptor 1 (PD-1) antibodies, combined with platinum-based chemotherapy can improve objective response rates and prolong survival in advanced or recurrent/metastatic ESCC, with generally manageable safety [8, 9]. Tislelizumab, a PD-1 inhibitor independently developed in China, specifically blocks the PD-1/PD-L1 pathway and restores anti-tumor T-cell function, and has been increasingly used in the systemic treatment of advanced ESCC.

However, current data on the use of tislelizumab combined with chemotherapy in real-world patients with advanced ESCC remain relatively limited, particularly regarding its effects on serum tumor markers, angiogenic factors, and inflammatory cytokines. Therefore, this retrospective study analyzed patients with advanced ESCC who received tislelizumab combined with nab-paclitaxel plus nedaplatin, comparing them with patients receiving chemotherapy alone, to explore its clinical efficacy, safety, and effects on serum tumor markers, immune factors, and T lymphocyte subsets, aiming to provide clinical evidence for individualized immunotherapy strategies for advanced ESCC.

Materials and methods

Data source and study population

This was a single-center retrospective-controlled study. Clinical data of patients with advanced ESCC who received systemic antitumor therapy at Zhangzhou Affiliated Hospital of Fujian Medical University from January 2023 to December 2023 were collected. Clinical data were mainly obtained from the hospital's electronic medical record system, laboratory information system, imaging archives and communication system, and outpatient and inpatient medical records. Follow-up data were obtained from structured records of the hospital's patient follow-up management system, outpatient follow-up records, and telephone follow-up records. Two physicians with intermediate-level qualifications and statistical training independently extracted data from the above-mentioned sources. The extracted data included demographic characteristics, clinicopathological tumor features, treatment regimens, laboratory test results, imaging assessments, and survival follow-up information. The mentioned data were verified by a third party and entered into Microsoft Excel 2019 software to establish an initial database. Prior to propensity score matching (PSM), patients were divided into an observation group (tislelizumab combined with nab-paclitaxel plus nedaplatin, n=147) and a control group (chemotherapy alone: nab-paclitaxel plus nedaplatin, n=122) according to their initial treatment regimen. Key demographic and disease characteristics (age, sex, clinical stage, tumor diameter, baseline PD-L1, differentiation grade, and Eastern Cooperative

Oncology Group (ECOG) score) influencing treatment selection and prognosis in patients with advanced esophageal cancer were selected as matching variables. A 1:1 nearest neighbor matching method was applied with a caliper width of 0.2, and successful matching was defined by an absolute standardized mean difference (SMD) <0.2. Before matching, the absolute SMD values for clinical stage, tumor diameter, and PD-L1 level were all >0.1 in both groups, suggesting a potential imbalance between the groups before matching. After PSM, a total of 228 patients were successfully matched, with 114 patients in each group. After matching, the standardized differences of each matched variable decreased significantly. The baseline characteristics between groups achieved generally good balance and were comparable (**Table 1**). The detailed research process is shown in **Figure 1**. This study was approved by the Ethics Committee of Zhangzhou Affiliated Hospital of Fujian Medical University.

Inclusion criteria: (1) age ≥ 18 years; (2) clinical stage III-IV or recurrent disease with lesions located in the thoracic segment; (3) no prior systemic antitumor therapy for esophageal squamous cell carcinoma (except for previous local radiotherapy or endoscopic treatment); (4) ECOG score of 0-2 points; (5) completion of the prescribed treatment regimen; (6) complete clinical records.

Exclusion criteria: (1) lesions located in the cervical segment or gastroesophageal junction; (2) previous subtotal gastrectomy; (3) previous treatment with PD-1/PD-L1 inhibitors, CTLA-4 antibodies, or other immune checkpoint inhibitors; (4) active autoimmune disease or a definite history of autoimmune disease; (5) pregnant or lactating women; (6) significant neurological or psychiatric disorders that may impair compliance with treatment and follow-up; (7) poor adherence to the treatment regimen and inability to complete the entire course.

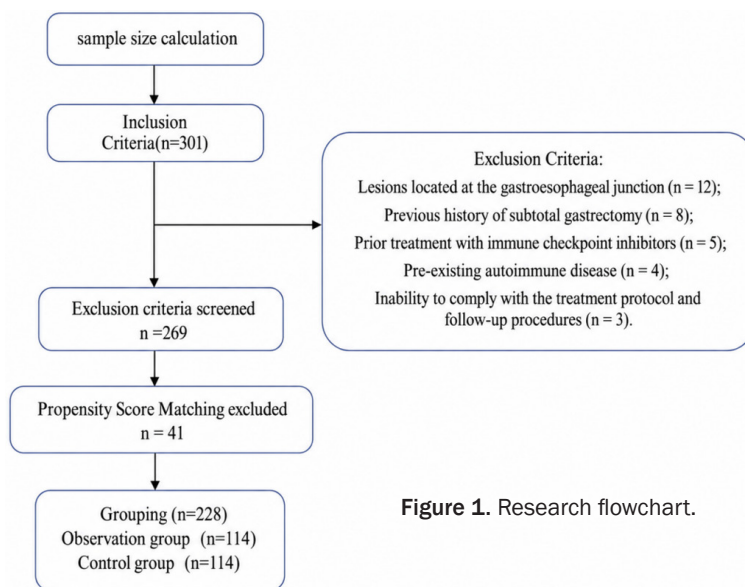
Treatment regimens and implementation

The control group received nab-paclitaxel plus nedaplatin. On day 1 of each treatment cycle, nab-paclitaxel was administered intravenously at 260 mg/m², together with intravenous nedaplatin at 80-100 mg/m². One cycle lasted three weeks, with a planned total of four cycles.

Table 1. Comparison of Baseline Characteristics of Patients Before and After Propensity Score Matching

Variable	Before PSM			After PSM		
	Observation group (n=147)	Control group (n=122)	SMD	Observation group (n=114)	Control group (n=114)	SMD
Ages (Years)	63.1 ± 6.3	62.5 ± 7.8	0.08	62.9 ± 5.8	63.4 ± 7.2	0.08
Sex (Male)	98 (66.67%)	75 (61.48%)	0.11	78 (68.42%)	73 (64.04%)	0.09
cTNM (IV)	40 (27.21%)	26 (21.31%)	0.18	23 (20.18%)	26 (22.81%)	0.08
Tumor diameter (cm)	6.35 ± 1.95	5.98 ± 1.93	0.19	6.21 ± 1.88	6.13 ± 1.91	0.04
Hb (g/L)	119.8 ± 15.2	122.5 ± 16.00	0.18	121.6 ± 14.8	120.9 ± 15.3	0.05
PD-L1 (pg/mL)	363.98±44.23	374.04±50.96	0.22	361.74±35.42	365.99±42.24	0.09
ECOG (0-1)	134 (91.16%)	114 (93.44%)	0.03	110 (96.49%)	108 (94.74%)	0.09
Differentiation grade (High/Medium)	115 (78.23%)	97 (79.51%)	0.04	95 (83.33%)	91 (79.82%)	0.09

Note: Propensity Score Matching (PSM); programmed cell death ligand 1 (PD-L1); Eastern Cooperative Oncology Group (ECOG); hemoglobin (Hb).

**Figure 1.** Research flowchart.

The observation group received the same chemotherapy regimen as the control group, combined with tislelizumab. On day 1 of each treatment cycle, tislelizumab injection was administered at a fixed dose of 200 mg intravenously. The nab-paclitaxel and nedaplatin administration regimen was the same as the control group, and patients received 4 cycles of the treatment.

Patients with lesions deemed resectable by multidisciplinary assessment after 2 cycles of systemic therapy, and who gave informed consent, then underwent radical resection, followed by the remaining 2 cycles of postoperative chemotherapy. Perioperative and pathological data were analyzed as exploratory endpoints.

Study endpoints and assessment procedures

Tumor-related factor testing: Fasting venous blood (3 mL) was collected from all patients before the first treatment and after completing four cycles of treatment. Serum was separated, and one tube was used to detect the levels of squamous cell carcinoma antigen (SCCA), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), and carbohydrate antigen 19-9 (CA19-9) using an electrochemiluminescence immunoassay.

Detection of T lymphocyte subset:

Fasting venous blood (3 mL) was collected from all patients before the first treatment, after completing two cycles, and after completing four cycles. Peripheral blood T lymphocyte subsets, including CD4⁺, CD8⁺, and the CD4⁺/CD8⁺ ratio, were detected by flow cytometry.

Detection of cytokines: Before treatment and after 4 treatment cycles, the concentrations of serum C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), soluble PD-1, PD-L1, vascular endothelial growth factor (VEGF), and matrix metalloproteinase 9 (MMP-9) were quantitatively detected by enzyme-linked immunosorbent assay (ELISA). All reagent kits used were from R&D Systems (IL-6 kit: Cat. No. JL20256, CRP kit: Cat. No. DCRP00, TNF-α kit: Cat. No. DTA00C, PD-1 kit: Cat. No.

D120, PD-L1 kit: Cat. No. DB7H10, VEGF kit: Cat. No. DVE00, MMP-9 kit: Cat. No. DMP900), and all were used according to the kit instructions.

Quality of life assessment: The quality of life of all patients was assessed using the SF-36 scale before and after treatment. The SF-36 scale includes daily living, physical health, mental health, and social functioning. Higher scores indicate better quality of life.

Efficacy and safety assessment

Clinical efficacy evaluation: Clinical efficacy was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [10]. Complete remission (CR): lesions completely disappear and last for more than 4 weeks; partial remission (PR): the sum of the longest diameters of the baseline lesions shrinks by more than 50%; stable disease (SD): the sum of the longest diameters of baseline lesions decreased but did not meet the criteria for PR; progressive disease (PD): lesion enlargement or new lesions occurred.

All imaging data were independently interpreted and measured by two radiologists with senior professional titles. In case of inconsistent evaluations, a chief radiologist made the final decision.

Objective response rate (ORR) = (CR+PR)/total number of cases in the group. Disease control rate (DCR) = (CR+PR+SD)/total number of cases in the group.

Pathological assessment: Postoperatively, patients were assessed using the Tumor Regression Grading (TRG) system according to the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) for esophageal cancer [11]: Grade 0: No residual tumor; Grade 1: Residual tumor <10%; Grade 2: Residual tumor 10%-50%; Grade 3: Residual tumor >50%.

All pathological assessments were independently performed by two pathologists with senior professional titles. In case of inconsistent evaluations, a third senior pathologist performed the final interpretation.

R0 resection: Complete tumor resection with no cancer cells found in the surgical margin tissue.

Pathological complete remission (pCR): No residual cancer cells were found in the postoperative tumor specimen.

Major pathological remission (MPR): TRG grade 0-1.

Perioperative indicators: Perioperative indicators for both groups of patients were recorded, including intraoperative blood loss, operation time, and postoperative hospital stay.

Adverse reactions and treatment principles: Adverse reactions during treatment were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 [12].

Adverse reactions were managed according to a standardized protocol: Grade 1: Close observation without specific intervention; treatment continued as per the original regimen. Grade 2: Symptomatic supportive care (e.g., antiemetics, leukocyte increasing agents, hepatoprotective agents) was administered without treatment delay. Grade 3: Treatment was temporarily suspended, and intensified supportive care was provided. Treatment was resumed after the adverse event improved to Grade 1 or lower. Grade 4: Treatment was permanently discontinued, and the patient was hospitalized for active intervention.

Immune-related adverse reactions were managed in accordance with the CSCO Guidelines for the Management of Immune Checkpoint Inhibitor-Related Toxicity, primarily involving corticosteroid therapy and specialist consultations.

Supportive care (including granulocyte colony-stimulating factor, antiemetics, hepatoprotective agents, etc.) was administered according to uniform institutional protocols to ensure consistency in management across both groups.

Follow-up: All patients were followed up via outpatient visits and telephone contact until January 2025 or at the time of death. Disease progression and survival outcomes were documented. Progression-free survival (PFS) was

defined as the time from the date of first treatment administration to the first radiographic or clinically confirmed disease progression or death; overall survival (OS) was defined as the time from the date of first treatment administration to death or the last follow-up date.

Statistical analysis

SPSS 22.0 software was used for statistical analysis, and PSM was used for matching between the two groups. Count data were described as n (%), and comparisons were performed using the chi-square test. Fisher's exact test was applied when theoretical frequencies were small. Ordinal data were compared using the rank-sum test. Continuous variables were expressed as mean $\pm$ standard deviation and compared using the t-test. Kaplan-Meier survival curve analysis was used to analyze the PFS and OS. Log-rank test was used for inter-group comparison. Univariate and multivariate Cox regression analyses were applied to identify factors associated with OS. Pearson correlation analysis was conducted to evaluate the correlations between post-treatment tumor-related factors, cytokines and DCR, PFS, as well as OS in the observation group. A *P*-value <0.05 was considered statistically significant.

Bias control strategies

(1) Confounding bias control: Baseline characteristics were compared between the two groups to ensure comparability. PSM was applied to verify the robustness of primary outcomes.

(2) Information bias control: Imaging efficacy was independently evaluated by two senior radiologists/oncologists. Disagreements were resolved through joint discussion. Laboratory indicators were tested using the same platform and batch of reagents, and standardized quality control procedures were implemented.

Results

Comparison of baseline characteristics

There were no statistically significant differences between the two groups in terms of age, sex, smoking history, alcohol consumption history, family history, tumor location, tumor diameter, T stage, N stage, clinical stage, differentiation

grade, ECOG score, comorbidities (such as hypertension, diabetes, and heart disease), history of previous radiotherapy, history of previous endoscopic local treatment, hemoglobin, or albumin levels, indicating that baseline characteristics were comparable (all $P>0.05$, **Table 2**).

Comparison of tumor-related factor levels

Before treatment, there were no statistically significant differences in serum levels of SCCA, CEA, CA125, and CA19-9 between the two groups (all $P>0.05$). After treatment, the levels of these indicators in both groups decreased significantly from baseline, and were significantly lower in the observation group than in the control group (all $P<0.05$, **Table 3**).

Comparison of cytokine levels

After treatment, serum levels of IL-6, TNF- α , CRP, soluble PD-1, PD-L1, VEGF, and MMP-9 in both groups were significantly lower than before treatment (all $P<0.05$), with the observation group showing significantly lower levels than the control group (all $P<0.05$, **Table 4**).

Comparison of T lymphocyte subsets

Before treatment, there were no statistically significant differences between the two groups in peripheral blood CD4⁺, CD8⁺, or CD4⁺/CD8⁺ ratio (all $P>0.05$). After 2 and 4 cycles, the CD4⁺ levels and CD4⁺/CD8⁺ ratio in both groups increased compared with before treatment, while the CD8⁺ levels decreased. Furthermore, the CD8⁺ levels in the observation group progressively decreased from 35.56 $\pm$ 5.27 to 30.24 $\pm$ 3.30 after 2 cycles, and to 26.73 $\pm$ 3.64 after 4 cycles; the ratio of CD4⁺/CD8⁺ increased from 0.81 $\pm$ 0.22 before treatment to 1.30 $\pm$ 0.21 after 2 treatment cycles, and further increased to 1.51 $\pm$ 0.29 after 4 treatment cycles ($P<0.05$, **Table 5**).

Comparison of quality of life

After treatment, scores on all dimensions of the SF-36 scale increased in both groups, with the observation group showing significantly higher scores than the control group ($P<0.05$). See **Table 6**.

Table 2. Comparison of General Information between the Two Groups

Index	Observation group (n=114)	Control group (n=114)	t/ χ^2	P
Age (Years)	62.9±5.8	63.4±7.2	0.577	0.564
Sex				
Male	78 (68.42)	73 (64.04)	0.490	0.484
Female	36 (31.58)	41 (35.96)		
History of smoking				
Yes	51 (44.74)	45 (39.47)	0.648	0.421
NO	63 (55.26)	69 (60.53)		
History of drinking				
Yes	42 (36.84)	39 (34.21)	0.172	0.678
NO	72 (63.16)	75 (65.79)		
Family history				
Yes	15 (13.16)	18 (15.79)	0.319	0.572
NO	99 (86.84)	96 (84.21)		
Tumor location				
Upper	14 (12.28)	17 (14.91)	0.521	0.771
Middle	62 (54.39)	63 (55.26)		
Lower	38 (33.33)	34 (29.82)		
Tumor diameter (cm)	6.21±1.88	6.13±1.91	0.319	0.75
T stage				
T2	15 (13.16)	17 (14.91)	0.983	0.612
T3	72 (63.16)	76 (66.67)		
T4	27 (23.68)	21 (18.42)		
N stage				
N0	23 (20.18)	21 (18.42)	0.397	0.941
N1	29 (25.44)	30 (26.32)		
N2	45 (39.47)	43 (37.72)		
N3	17 (14.91)	20 (17.54)		
cTNM				
II	22 (19.30)	20 (17.54)	0.286	0.867
III	69 (60.53)	68 (59.65)		
IV	23 (20.18)	26 (22.81)		
Differentiation grade				
High/Medium	95 (83.33)	91 (79.82)	0.467	0.494
Low	19 (16.67)	23 (20.18)		
ECOG				
0-1	110 (96.49)	108 (94.74)	0.418	0.518
2	4 (3.51)	6 (5.26)		
Complications				
Diabetes	7 (6.14%)	9 (7.89%)	0.269	0.604
Hypertension	8 (7.02%)	6 (5.26%)	0.304	0.581
Heart disease	9 (7.89%)	9 (7.89%)	0.000	1.000
Previous history of radiotherapy (yes)	21 (18.42%)	24 (21.05%)	0.249	0.618
Previous history of local endoscopic treatment (yes)	12 (10.53%)	10 (8.77%)	0.201	0.654
Hemoglobin (g/L)	121.6±14.8	120.9±15.3	0.351	0.726
Albumin (g/L)	39.8±4.6	39.2±4.8	0.964	0.336

Tislelizumab with chemotherapy in advanced ESCC

Table 3. Comparison of tumor-related factor levels between the two groups

Groups	SCCA (μg/L)		CEA (ng/mL)		CA125 (U/L)		CA199 (U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=114)	26.24±2.28	12.05±1.07**	13.77±2.09	4.14±1.02**	72.98±7.21	41.33±4.45**	101.04±10.36	62.93±7.71**
Control group (n=114)	26.41±2.91	14.38±1.25**	14.03±2.48	5.26±1.09**	73.47±8.02	45.02±4.17**	99.87±11.42	68.95±8.22**
t	0.491	15.119	0.856	8.011	0.485	6.460	0.810	5.703
P	0.624	<0.001	0.393	<0.001	0.628	<0.001	0.419	<0.001

Note: Compared with before treatment within the same group, **P<0.001. SCCA: Squamous cell carcinoma antigen; CEA: Carcinoembryonic antigen; CA: Carbohydrate Antigen.

Table 4. Comparison of serum inflammatory factor levels between the two groups ($\bar{x} \pm s$)

Groups		Observation group (n=114)	Control group (n=114)	t	P
IL-6 (pg/ml)	Before treatment	46.23±8.86	47.38±7.26	1.072	0.285
	After treatment	30.18±3.06**	35.25±2.11**	14.564	<0.001
TNF-α (pg/ml)	Before treatment	20.95±5.12	21.23±5.08	0.414	0.679
	After treatment	11.61±1.81**	14.38±1.56**	12.377	<0.001
CRP (mg/L)	Before treatment	14.03±5.11	14.30±5.02	0.402	0.688
	After treatment	5.41±2.05**	8.78±1.01**	15.745	<0.001
PD-1 (pg/mL)	Before treatment	291.54±26.15	294.08±27.13	0.720	0.472
	After treatment	218.27±19.85**	250.17±20.22**	12.020	<0.001
PD-L1 (pg/mL)	Before treatment	361.74±35.42	365.99±42.24	0.823	0.411
	After treatment	317.65±29.88**	332.81±26.54**	4.050	<0.001
VEGF (pg/mL)	Before treatment	554.92±61.74	551.03±72.18	0.437	0.662
	After treatment	109.76±22.37**	148.91±25.98**	12.193	<0.001
MMP-9 (pg/mL)	Before treatment	244.11±17.83	241.59±21.16	0.972	0.332
	After treatment	54.63±7.78**	94.10±10.24**	32.770	<0.001

Note: Compared with before treatment within the same group, **P<0.001. IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; PD-1: Programmed cell death receptor 1; PD-L1: Programmed cell death ligand; VEGF: Vascular endothelial growth factor; MMP-9: Matrix metalloproteinase 9.

Table 5. Comparison of T lymphocyte subpopulation levels between the two groups

Groups		Treatment group (n=114)	Control group (n=114)	t	P
CD4+					
	Before treatment	28.31±4.42	28.66±5.19	0.548	0.584
	After two treatment cycles	35.07±2.29	31.48±3.14	9.863	<0.001
	After four treatment cycles	40.66±4.12**	34.41±4.25**	11.274	<0.001
CD8+					
	Before treatment	35.56±5.27	35.73±5.93	0.229	0.819
	After two treatment cycles	30.24±3.30	32.79±2.14	6.922	<0.001
	After four treatment cycles	26.73±3.64*	30.28±3.37*	7.641	<0.001
CD4+/CD8+					
	Before treatment	0.81±0.22	0.83±0.26	0.627	0.531
	After two treatment cycles	1.30±0.21	0.98±0.17	12.646	<0.001
	After four treatment cycles	1.51±0.29*	1.15±0.28*	9.535	<0.001

Note: Compared with before treatment within the same group, *P < 0.05, **P < 0.001.

Comparison of clinical efficacy

The observation group achieved an ORR of 53.51% and a DCR of 74.56%, compared with 31.58% and 57.89%, respectively, in the control group (both P<0.05, **Table 7**).

Comparison of pathological outcomes

Compared with the control group, the observation group showed superior TRG, R0 resection rate, pCR rate, and MPR rate (all P<0.05, **Table 8**).

Table 6. Comparison of quality of life scores between the two groups

Groups	Daily life		physical health		Mental health		Social functioning	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=114)	58.19±2.12	76.01±3.38**	52.19±2.29	76.45±4.26**	53.74±3.35	74.59±3.31**	54.80±4.28	71.07±3.24**
Control group (n=114)	57.83±1.98	71.42±3.02**	51.87±2.93	70.12±4.48**	54.01±2.86	68.94±3.64**	55.12±3.99	63.88±2.95**
t	1.325	10.812	0.919	10.933	0.654	12.261	0.584	17.520
P	0.186	<0.001	0.359	<0.001	0.513	<0.001	0.560	<0.001

Note: Compared with before treatment within the same group, **P<0.001.

Table 7. Comparison of clinical efficacy between the two groups

Indexs	Observation group (n=114)	Control group (n=114)	χ^2	P
CR	32 (28.07)	15 (13.16)		
PR	29 (25.44)	21 (18.42)		
SD	24 (21.05)	30 (26.32)		
PD	29 (25.44)	48 (42.11)		
ORR	61 (53.51)	36 (31.58)	11.214	0.001
DCR	85 (74.56)	66 (57.89)	7.079	0.008

Note: CR: Complete remission; PR: Partial remission; SD: Stable condition; PD: Disease progression; ORR: Objective relief rate; DCR: Disease control rate.

Table 8. Comparison of pathological indicators between the two groups

Indexs	Observation group (n=114)	Control group (n=114)	Z/ χ^2	P
TRG classification			3.642	<0.001
0	39 (34.21)	24 (21.05)		
1	43 (37.72)	31 (27.19)		
2	25 (21.93)	39 (34.21)		
3	7 (6.14)	20 (17.54)		
R0 excision	98 (85.96)	86 (75.44)	4.055	0.044
pCR	38 (33.33)	23 (20.18)	5.036	0.025
MPR	82 (71.93)	55 (48.25)	13.332	<0.001

Note: TRG: Tumor regression grading; pCR: Pathological complete remission; MPR: Major pathological remission.

Comparison of adverse reactions and immune-related adverse events

There were no statistically significant differences in the incidence of adverse reactions and immune-related adverse events between the two groups during treatment (all $P>0.05$, **Table 9**).

Comparison of perioperative indicators

There were no statistically significant differences between the two groups in operation time, intraoperative blood loss, or postoperative hospital stay (all $P>0.05$, **Figure 2**).

Comparison of PFS

At the end of follow-up, 39 patients in the observation group experienced disease progression, with a non-progression rate of 65.79%; 58 patients in the control group experienced disease progression, with a non-progression rate of 49.12%. Kaplan-Meier analysis showed that the median PFS of the observation group was not reached during the follow-up period, while the median PFS of the control group was 21.85 months. The difference in PFS curves between the two groups was statistically significant (HR=0.490, 95% CI=0.326-0.737, Log-rank $\chi^2=12.282$, $P<0.001$, **Figure 3**).

Comparison of OS

At the end of follow-up, 34 deaths occurred in the observation group, with an overall survival rate of 70.18%; 50 deaths occurred in the control

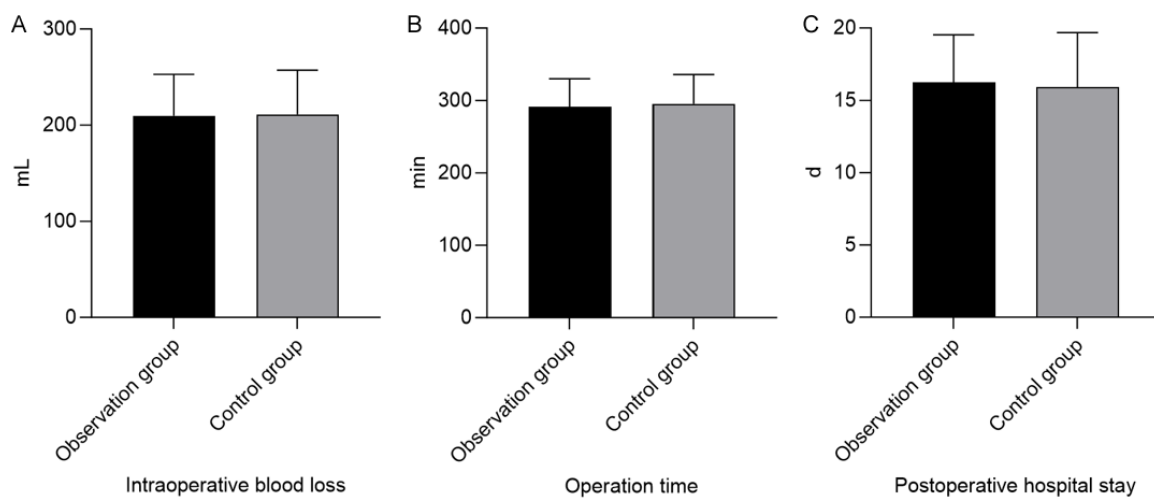
group, with an overall survival rate of 56.14%. Kaplan-Meier analysis showed that the median OS was not reached in the observation group during the follow-up period, whereas the median OS in the control group was 23.24 months. The difference in OS curves between the two groups was statistically significant (HR=0.498, 95% CI=0.322-0.772, Log-rank $\chi^2=10.131$, $P=0.001$, **Figure 4**).

Comparison of factors between the survival and death groups

The results showed statistically significant differences between the survival (n=144) and

Table 9. Comparison of Incidence of Adverse Reactions and Immune-related adverse events During Treatment in the Two Groups

Adverse drug reaction	Observation group (n=114)	Control group (n=114)	Statistical value	P
Common adverse reactions				
Decreased white blood cell count				
1	8 (7.02)	9 (7.89)	0.536	0.592
2	9 (7.89)	9 (7.89)		
3	3 (2.63)	5 (4.39)		
Nausea and vomiting				
1	24 (21.05)	29 (25.44)	0.981	0.327
2	9 (7.89)	11 (9.65)		
Liver dysfunction				
1	9 (7.89)	11 (9.65)	0.388	0.698
2	4 (3.51)	4 (3.51)		
Hypothyroidism				
1	5 (4.39)	5 (4.39)	0.213	0.831
2	8 (7.02)	9 (7.89)		
rash				
1	7 (6.14)	6 (5.26)	0.246	0.805
2	5 (4.39)	7 (6.14)		
Immune-related adverse events				
Hypothyroidism			0.213	0.831
1	5 (4.39)	5 (4.39)		
2	8 (7.02)	9 (7.89)		
Rash			0.246	0.805
1	7 (6.14)	6 (5.26)		
2	5 (4.39)	7 (6.14)		
Immune-Related Pneumonitis			-	0.122
1	3 (2.63)	0 (0.00)		
2	1 (0.88)	0 (0.00)		
Immune-Related Colitis			-	0.498
1	2 (1.75)	0 (0.00)		

**Figure 2.** Comparison of perioperative indicators between the two groups. A: Intraoperative blood loss; B: Operation time; C: Postoperative hospital stay.

Tislelizumab with chemotherapy in advanced ESCC

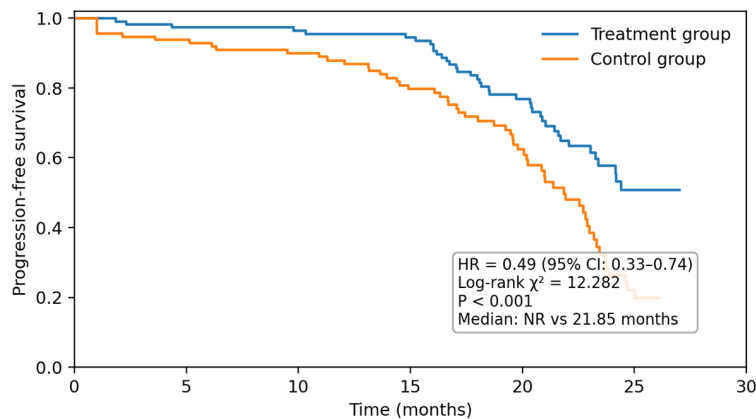


Figure 3. Kaplan-Meier survival curves of progression-free survival for the two groups.

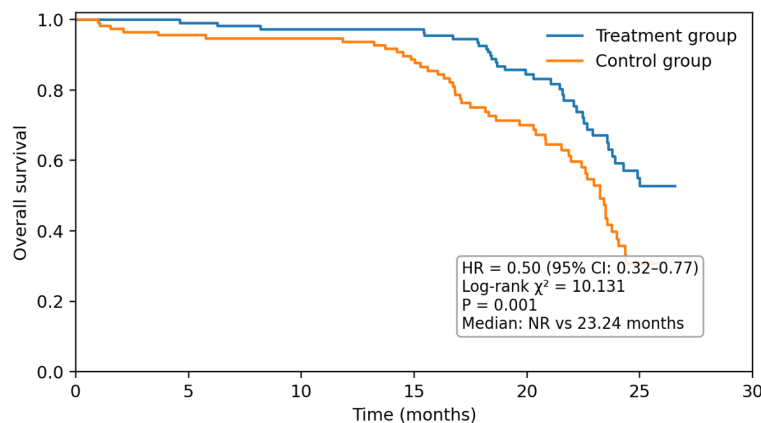


Figure 4. Kaplan-Meier survival curves of overall survival time for the two groups.

death (n=84) groups in terms of T, and cTNM stages (all $P < 0.05$, **Table 10**).

Univariate Cox regression analysis

Univariate Cox regression analysis showed that tislelizumab combined with platinum-based chemotherapy was associated with a lower risk of death, while family history and cTNM stage IV were associated with a higher risk of death (all $P < 0.05$). The associations between the remaining factors and the risk of death were not statistically significant (all $P > 0.05$, **Table 11**).

Multivariate Cox regression analysis

Treatment regimen, N stage and cTNM stage were incorporated into the multivariate Cox proportional-hazards regression model. The

results showed that tislelizumab combined with platinum-based chemotherapy was independently associated with a lower risk of death (HR=0.536, 95% CI: 0.345-0.831, $P = 0.005$); cTNM stage IV was independently associated with a higher risk of death (HR=3.268, 95% CI: 2.119-5.040, $P < 0.001$); the association between N stage and death risk was not statistically significant ($P = 0.671$, **Table 12**).

Correlation analysis

Pearson correlation analysis revealed that in the observation group, post-treatment VEGF level was weakly negatively correlated with PFS ($r = -0.222$, $P = 0.017$), and PD-1 level was weakly positively correlated with OS ($r = 0.198$, $P = 0.035$). The correlations of the remaining indicators with DCR, PFS and OS were not statistically significant (all $P > 0.05$, **Table 13**).

Discussion

In recent years, with the advancement of diagnostic and treatment technologies, the overall incidence and mortality of esophageal cancer have shown a downward trend. However, a considerable number of patients are already in unresectable locally advanced or metastatic stages at the time of diagnosis, and long-term survival with systemic chemotherapy alone remains unsatisfactory [13-16]. Previous studies have shown that although platinum-based chemotherapy can alleviate tumor burden to a certain extent, the ORR is limited, the duration of response is short, and it has a significant inhibitory effect on the body's immune function [17-20]. Guidelines such as the NCCN have included platinum-based chemotherapy combined with radiotherapy as one of the standard treatment modalities for advanced esophageal cancer, yet limitations still exist [21]. Against this backdrop, immune checkpoint inhibitors combined

Table 10. Comparison of various factors between the survival and death groups

Index	Survival group (n=144)	Death Group (n=84)	t/χ^2	P
Ages (Years)	63.4±6.7	62.8±6.3	0.670	0.504
Sex				
Man	102 (70.83)	49 (58.33)	3.706	0.054
Female	42 (29.17)	35 (41.67)		
History of smoking				
Yes	55 (38.19)	41 (48.81)	2.452	0.117
No	89 (61.81)	43 (51.19)		
History of drinking				
Yes	50 (34.72)	31 (36.90)	0.110	0.740
No	94 (65.28)	53 (63.10)		
Family history				
Yes	18 (12.50)	15 (17.86)	1.230	0.267
No	126 (87.50)	69 (82.14)		
Tumor location				
Upper	20 (13.89)	11 (13.10)	0.038	0.981
Middle	79 (54.86)	46 (54.76)		
Lower	45 (31.25)	27 (32.14)		
Tumor diameter	6.12±1.87	6.26±1.94	0.570	0.569
T				
T2-3	120 (83.33)	60 (71.43)	4.524	0.033
T4	24 (16.67)	24 (28.57)		
N				
N0-1	67 (46.53)	36 (42.86)	0.289	0.591
vN2-3	77 (53.47)	48 (57.14)		
cTNM				
II-III	133 (92.36)	46 (54.76)	44.451	<0.001
IV	11 (7.64)	38 (45.24)		
Complications				
Diabetes	8 (5.56)	8 (9.52)	1.280	0.258
Hypertension	8 (5.56)	6 (7.14)	0.232	0.630
Heart disease	11 (7.64)	7 (8.33)	0.035	0.851
Previous history of radiotherapy (yes)	25 (17.36)	20 (23.81)	1.393	0.238
Previous history of local endoscopic treatment (yes)	12 (8.33)	10 (11.90)	0.776	0.378
Hemoglobin (g/L)	121.3±15.7	121.1±13.8	0.107	0.915
Albumin (g/L)	39.7±5.0	39.1±4.1	0.991	0.323

with chemotherapy have gradually become a research hotspot in the treatment of advanced esophageal squamous cell carcinoma. Tislelizumab is a class of PD-1 inhibitor independently developed in China. It specifically binds to PD-1 through the Fab segment, blocks the PD-1/PD-L1 signaling pathway, relieves T cell immunosuppression, and promotes the activation and proliferation of effector T cells, thereby exerting an anti-tumor effect [22-24]. Multiple

studies have indicated that PD-1 inhibitors, such as tislelizumab, combined with platinum-based chemotherapy can improve ORR and OS in advanced or recurrent/metastatic ESCC, with a manageable safety profile [25]. This study further validated the benefits of this combination regimen in a real-world population. Compared with chemotherapy alone, the ORR and DCR in the tislelizumab combined with nab-paclitaxel/nedaplatin group were signifi-

Table 11. Results of Univariate COX Regression Analysis

Factors	β	SE	Wald	P	HR	95% CI
Treatment plan (Tislelizumab + chemotherapy vs chemotherapy)	-0.696	0.223	9.738	0.002	0.498	0.322-0.772
Ages (Years)	-0.002	0.018	0.011	0.918	0.998	0.963-1.035
Sex (Women vs Man)	0.414	0.221	3.5	0.061	1.513	0.980-2.335
History of smoking (yes vs no)	0.242	0.218	1.231	0.267	1.274	0.831-1.954
History of drinking (yes vs no)	0.099	0.226	0.192	0.662	1.104	0.709-1.720
Family history (yes vs no)	0.579	0.287	4.066	0.044	1.784	1.016-3.131
Tumor location: Middle vs Upper	-0.056	0.337	0.028	0.868	0.945	0.488-1.831
Tumor location: Lower vs Upper	0.045	0.359	0.015	0.901	1.046	0.518-2.112
Tumor diameter (cm)	0.015	0.061	0.062	0.804	1.015	0.901-1.144
T (T4 vs T2-3)	0.454	0.242	3.524	0.06	1.575	0.980-2.531
N (N2-3 vs N0-1)	-0.002	0.221	0	0.992	0.998	0.648-1.538
cTNM (IV vs II-III)	1.223	0.22	30.973	<0.001	3.396	2.208-5.224
Diabetes (yes vs no)	0.411	0.372	1.218	0.27	1.508	0.727-3.127
Hypertension (yes vs no)	0.681	0.427	2.541	0.111	1.976	0.855-4.564
Heart disease (yes vs no)	-0.029	0.395	0.006	0.941	0.971	0.448-2.106
Previous history of radiotherapy (yes vs no)	0.263	0.256	1.054	0.305	1.301	0.787-2.150
Previous history of local endoscopic treatment (yes vs no)	0.131	0.337	0.151	0.698	1.14	0.589-2.207
Hb (g/L)	-0.001	0.007	0.016	0.901	0.999	0.985-1.013
ALB (g/L)	-0.003	0.023	0.022	0.883	0.997	0.952-1.043

Table 12. Results of Multivariate COX Regression Analysis

Factors	β	SE	Wald	P	HR	95% CI
Treatment plan (Tislelizumab + chemotherapy vs chemotherapy)	-0.624	0.224	7.781	0.005	0.536	0.345-0.831
N2-3 vs N0-1	-0.094	0.222	0.18	0.671	0.91	0.589-1.406
cTNM IV vs II-III	1.184	0.221	28.687	<0.001	3.268	2.119-5.040

Table 13. Correlation Analysis

Index	Statistical value	SCCA	CEA	CA125	CA199	IL-6	TNF- α	CRP	PD-1	PD-L1	VEGF	MMP-9
DCR	r	0.104	0.184	-0.052	-0.109	0.108	0.035	0.161	-0.133	0.023	-0.061	0.079
	P	0.271	0.050	0.583	0.250	0.253	0.713	0.087	0.159	0.810	0.523	0.404
PFS	r	-0.079	0.025	-0.041	-0.040	0.084	0.029	-0.043	0.078	-0.079	-0.222	0.062
	P	0.403	0.789	0.669	0.675	0.372	0.761	0.650	0.411	0.401	0.017	0.513
OS	r	0.108	0.166	-0.070	0.011	-0.067	0.026	-0.010	0.198	0.142	0.133	0.021
	P	0.255	0.077	0.457	0.911	0.479	0.781	0.913	0.035	0.131	0.159	0.827

DCR: Disease control rate; Progression-free survival (PFS); overall survival (OS); SCCA: Squamous cell carcinoma antigen; CEA: Carcinoembryonic antigen; CA: Carbohydrate Antigen; IL-6: interleukin-6; TNF- α : tumor necrosis factor- α ; CRP: C-reactive protein.; PD-1: Programmed cell death receptor 1; PD-L1: Programmed cell death ligand; VEGF: Vascular endothelial growth factor; MMP-9: Matrix metalloproteinase 9.

cantly improved, suggesting that the immunotherapy combination regimen can induce deeper and more durable tumor regression.

The results of this study demonstrated that serum levels of SCCA, CEA, CA125, and CA19-9 in both groups decreased from baseline after

treatment, with a greater decrease in the observation group, indicating that this combination regimen more effectively suppressed tumor growth and metastatic activity than chemotherapy alone. Regarding cytokines, IL-6, TNF- α , CRP, soluble PD-1, PD-L1, VEGF, and MMP-9 levels in both groups decreased signifi-

cantly after treatment compared with before treatment, with a greater decrease in the observation group, suggesting that tislelizumab combined with chemotherapy is superior to chemotherapy alone in controlling tumor-related inflammation. IL-6, TNF- α , and CRP are important indicators reflecting systemic inflammatory burden and tumor progression. Elevated levels are associated with poor prognosis in various malignant tumors, and lowering their levels can improve patient prognosis. Soluble PD-1 and PD-L1, as immune checkpoint molecules, can enhance the body's anti-tumor immune response by blocking their signaling pathways. VEGF and MMP-9 play important roles in tumor angiogenesis and invasion/metastasis; inhibiting their expression helps control tumor progression. The results suggest that combination therapy not only reduces tumor burden and alleviates inflammatory stimulation, but also improves the immune microenvironment by blocking the PD-1/PD-L1 pathway, providing a basis for survival benefits [26-28].

Changes in peripheral T lymphocyte subsets further confirmed the immunomodulatory effects. In this study, the CD8⁺ levels in the observation group decreased from 35.56 ± 5.27 before treatment to 30.24 ± 3.30 after 2 treatment cycles, and further decreased to 26.73 ± 3.64 after 4 treatment cycles; the CD4⁺/CD8⁺ ratio increased from 0.81 ± 0.22 before treatment to 1.30 ± 0.21 after 2 treatment cycles, and further increased to 1.51 ± 0.29 after 4 treatment cycles. These changes suggest that tislelizumab combined with nab-paclitaxel/nedaplatin may improve the peripheral immune status of patients with advanced esophageal squamous cell carcinoma [29, 30]. CD4⁺ T cells play an important auxiliary regulatory role in anti-tumor immune responses, and an increase in the CD4⁺/CD8⁺ ratio usually indicates that the cellular immune function of the body is recovering. The change in CD8⁺ levels may be related to the reduction of immunosuppressive T cell subsets, decreased tumor-related inflammatory load, and remodeling of the immune microenvironment after treatment. At the same time, PD-1 inhibitors can restore the anti-tumor activity of T cells by blocking the PD-1/PD-L1 pathway, and chemotherapy can reduce the tumor burden and promote the release of tumor antigens. Both may improve

the immune balance of the body. In this study, the CD8⁺ levels in the observation group were lower than those in the control group after 2 and 4 treatment cycles, and the CD4⁺ levels and CD4⁺/CD8⁺ ratio were higher than those in the control group. Moreover, the ORR, DCR, PFS, and OS of the observation group were better than those of the control group, suggesting that the changes in these immune indicators may be related to better disease control and survival benefits. However, this study did not further distinguish between effector cytotoxic T cells, exhausted T cells, and immune suppression-related subsets of CD8⁺ cells. Therefore, the specific immunological meaning of the decrease in CD8⁺ levels still needs to be further verified in subsequent studies by combining multi-parameter flow cytometry and tumor tissue immune infiltration analysis. In terms of safety, the incidence of immune-related adverse events such as immune-related pneumonia, immune-related colitis, hypothyroidism and skin rash was lower in the observation group, and there was no statistically significant difference in the overall incidence of adverse reactions between the two groups. It indicates that under standardized monitoring and management, tislelizumab combined with chemotherapy can improve the tumor immune microenvironment without significantly increasing toxicity. Besides, the improvement in SF-36 scores in the observation group was better than that in the control group, suggesting that patients' quality of life was also significantly improved on the basis of better tumor control. This may be related to the dual factors of reduced disease burden and no significant increase in toxic side effects.

Survival analysis showed that the observation group had superior PFS and OS compared with the control group. Neither the median PFS nor median OS was reached in the observation group during the follow-up period, while the median PFS and median OS in the control group were 21.85 months and 23.24 months respectively. Immunotherapy can achieve durable disease control for some patients with a sustained response [18, 19]. The prolonged PFS and OS in this study are likely closely related to the deeper remission, immune memory effects, and sustained improvement in the tumor microenvironment resulting from the

combination regimen. This study further showed that the post-treatment levels of soluble PD-1 and PD-L1 in the observation group were lower than those in the control group. Additionally, the post-treatment levels of soluble PD-1 and PD-L1 were negatively correlated with disease control status, PFS, and OS. This suggests that the improvement of indicators related to the PD-1/PD-L1 pathway may be associated with more durable disease control after combination therapy. Tislelizumab relieves the functional inhibition of T cells by blocking the PD-1/PD-L1 signaling pathway. Meanwhile, chemotherapy can reduce tumor burden and promote the release of tumor antigens. The two approaches may jointly improve the tumor immune microenvironment, thereby laying a foundation for the formation of the long-tail effect of immunotherapy. Notably, even in real-world populations, the survival benefit of the combination group remained relatively clear, suggesting that this regimen has potential for wider application in clinical practice. In addition, the multivariate Cox regression analysis demonstrated that tislelizumab combined with platinum-based chemotherapy was independently associated with a lower risk of death, whereas cTNM stage IV was independently associated with a higher risk of death. This result further emphasizes the importance of early application of immunotherapy combined with chemotherapy; timely intervention at a relatively early stage of the disease may be more conducive to improving patient prognosis. It also suggests that clinicians should comprehensively consider the patient's stage, physical condition, and treatment tolerance when selecting treatment regimens to develop individualized treatment strategies.

Regarding safety, there were no statistically significant differences in the incidence of adverse reactions and immune-related adverse events between the groups and no treatment discontinuations occurred in either group. As both groups followed the same management protocol, these measures did not affect treatment adherence or survival. This also suggested that within the dosage regimen and range used in this study, the combination of tislelizumab and chemotherapy did not significantly increase the toxicity burden, and its safety profile was largely consistent with previously reported literature [20, 21].

Nevertheless, this study has several limitations. First, as a single-center retrospective study, selection bias may exist in patient enrollment and treatment allocation. Second, the sample size was relatively limited, and the follow-up period was insufficient to comprehensively assess long-term survival and immune-related delayed adverse events. Furthermore, this study did not perform stratified analysis of biomarkers such as PD-L1 expression levels and tumor mutational burden, and therefore cannot answer which populations benefited more significantly. Future research requires multicenter, large-sample, prospective randomized controlled trials, combined with molecular subtyping and immunobiomarkers, to further validate the efficacy and safety of tislelizumab combined with chemotherapy in advanced ESCC, and to optimize population selection and treatment strategies.

In conclusion, compared with chemotherapy alone, tislelizumab combined with nab-paclitaxel plus nedaplatin for advanced esophageal squamous cell carcinoma can more effectively reduce serum tumor markers and immunosuppression-related factors, improve T-cell immune function, increase ORR and DCR, and significantly prolong PFS and OS without increasing treatment toxicity. This provides valuable reference for the clinical application of immunotherapy strategies in advanced ESCC.

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Disclosure of conflict of interest

None.

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