

# Recombinant human-endostatin combined with sintilimab and chemotherapy in first-line treatment of locally advanced or metastatic esophageal squamous cell carcinoma

SHIYUN CUI<sup>1,2\*</sup>, LEI FAN<sup>3,4\*</sup>, XINNAN SUN<sup>5</sup>, YUCHENG CAI<sup>5</sup>,  
TING WANG<sup>1</sup>, PING LI<sup>1</sup>, RONG WANG<sup>1</sup> and LIANKE LIU<sup>1</sup>

<sup>1</sup>Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029, P.R. China;

<sup>2</sup>Department of Oncology, Chongqing Hospital of Jiangsu Province Hospital (The People's Hospital of Qijiang District), Chongqing 401420, P.R. China; <sup>3</sup>Department of General Surgery, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210028, P.R. China; <sup>4</sup>Department of General Surgery, Jiangsu Province Academy of Traditional Chinese Medicine, Nanjing, Jiangsu 210028, P.R. China; <sup>5</sup>Department of Clinical Medicine, The First Clinical Medical College of Nanjing Medical University, Nanjing, Jiangsu 211166, P.R. China

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**Abstract.** Esophageal cancer is a type of digestive system tumor with a high degree of malignancy. In recent years, research has been conducted on immunotherapy, chemotherapy and radiation therapy for esophageal cancer. However, there are still shortcomings in the improvement of 5-year survival rates. In order to explore more therapy options, the present study evaluated the efficacy and safety of recombinant human-endostatin (rh-endostatin) combined with sintilimab and chemotherapy for the first-line treatment of locally advanced or metastatic esophageal squamous cell carcinoma (ESCC). This retrospective study included data from 31 patients with unresectable locally advanced or metastatic esophageal cancer treated between January 2019 and December 2023, and was approved by the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). All patients received first-line treatment combining rh-endostatin with sintilimab, paclitaxel liposome and platinum. Following the completion of 6 cycles, maintenance therapy with sintilimab was administered until disease progression occurred. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) time, overall survival (OS) time and adverse events (AEs) were observed. Symptomatic or supportive care was administered as needed, according to

the clinical discretion of the treating physician. As of July 17, 2024, the median follow-up time was 13.07 months, with a median PFS time of 8.30 months (95% confidence interval, 3.442-13.158 months). For these 31 patients, the ORR was 67.7% (21/31), while the DCR was 93.5% (29/31). The median OS time reached 23.07 months. Furthermore, 77.4% of patients experienced at least one treatment-related AE (TRAE), and grade 3 TRAEs occurred in 8 patients (25.8%). No unexpected AEs were observed. In conclusion, rh-endostatin combined with sintilimab and chemotherapy exhibited positive efficacy and safety in patients with advanced ESCC, providing a promising treatment regimen for these patients.

## Introduction

Esophageal cancer is a highly malignant tumor of the digestive system, characterized by high incidence and mortality rates. According to the World Health Organization (WHO), in 2020, 53.7% of the global esophageal cancer cases (324,000 new cases) and 55.4% of the associated deaths (301,000 cases) were reported in China, thus China ranked first in the world in terms of both new cases and associated deaths. In light of current data, the prognosis of esophageal cancer is not ideal. Based on data from 60 countries and regions around the world, the age-standardized 5-year survival rate of esophageal cancer is only 10.0-30.0% (1). As a result, esophageal cancer poses a major threat to human health.

Numerous clinical studies have clarified the status of synchronous radiotherapy in the treatment of locally advanced esophageal cancer (2-4). Due to their efforts, the survival rate of patients has greatly improved. However, the 5-year survival rate remains at a low level. More than two-thirds of patients are diagnosed at advanced stages, where surgical options are no longer viable. Immune checkpoint inhibitors (ICIs), as novel therapeutic tools in clinical practice, have gradually changed the treatment paradigm of esophageal cancer by exhibiting durable response rates in some refractory tumors. Over the last

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*Correspondence to:* Dr Lianke Liu, Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Gulou, Nanjing, Jiangsu 210029, P.R. China  
E-mail: liulianke@j sph.org.cn

\*Contributed equally

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5 years, numerous large randomized controlled studies have actively explored the efficacy and safety of immunotherapy combined with chemotherapy in esophageal squamous cell carcinoma (ESCC) in first-line clinical treatment (5-9). However, survival benefits are still limited, highlighting the need for further exploration of improved treatment strategies.

Sintilimab is a human IgG4 monoclonal antibody that binds to programmed cell death receptor-1 (PD-1) in order to block the interaction of PD-1 with its ligands [programmed cell death-ligand 1 (PD-L1) and polyclonal antibody to mitochondrial ribosomal protein L2] and consequently help to restore the endogenous antitumor T-cell response (10). Due to its potential advantages, sintilimab has been investigated extensively in China, and was recently approved by the State Drug Administration of China for the treatment of classical Hodgkin's lymphoma, natural killer/T cell lymphoma, non-small cell lung cancer (NSCLC) and hepatocellular carcinoma. To explore its broader applications, sintilimab is undergoing phase I, II and III development for use in various solid tumors, including glioblastoma, osteosarcoma and pancreatic adenocarcinoma, in China (11-13). Based on the results of the ORIENT-15 study, sintilimab in combination with chemotherapy has been approved for first-line treatment of ESCC (14).

When combined with anti-angiogenesis agents, such as bevacizumab and ramucirumab, ICIs have exhibited synergistic antitumor effects in preclinical studies (15,16). Recombinant human-endostatin (rh-endostatin) is a broad-spectrum anti-angiogenic drug, which is a novel recombinant human vascular endothelial inhibitor drug independently developed in China. Rh-endostatin inhibits endothelial cell migration, impedes angiogenesis and reduces tumor blood supply, thereby suppressing tumor growth and metastasis. Additionally, the drug enhances the local tumor microenvironment and induces tumor cell death, potentially prolonging patient survival (17). It has also been reported that rh-endostatin combined with conventional chemotherapy can improve therapeutic outcomes in numerous malignant tumors, including lung, breast and colorectal cancer (18-21). However, its combination with chemotherapy for advanced ESCC remains underexplored.

Considering the potential therapeutic benefits of rh-endostatin combined with sintilimab and chemotherapy, the present study collected clinicopathological data from 31 patients with unresectable locally advanced or metastatic ESCC treated with rh-endostatin combined with sintilimab, paclitaxel liposome and platinum (TP regimen) as a first-line treatment. Subsequently, the overall effective rate, incidence of adverse events (AEs) and survival times were assessed.

The present study aimed to provide effective combination medication regimens and supportive evidence to improve the efficiency of first-line treatment for advanced ESCC, improve the prognosis of patients and provide a theoretical basis for the clinical exploration of novel treatment regimens.

## Patients and methods

**Study design.** The present retrospective analysis included data from 31 patients with unresectable locally advanced or metastatic esophageal cancer who received treatment with rh-endostatin in combination with sintilimab and the TP

regimen at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) between January 2019 and December 2023. The objective was to assess the clinical efficacy and AEs associated with this regimen.

**Patient eligibility.** A total of 31 patients with unresectable locally advanced or metastatic esophageal cancer treated with rh-endostatin in combination with sintilimab and the TP regimen on a first-line basis were retrospectively included. All the patients included in this study provided written informed consent agreeing to the use of their clinical data and biological samples.

The inclusion criteria were as follows: i) Patients with histologically confirmed unresectable locally advanced, recurrent or metastatic ESCC; ii) patients who were underwent first-line treatment with rh-endostatin in combination with sintilimab and the TP regimen; iii) patients with at least one evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) classification (22); iv) patients with an expected survival time  $\geq 3$  months; and v) patients with adequate heart, lung, liver and kidney function.

The exclusion criteria were as follows: i) Patients who were severely malnourished (weight  $< 40$  kg or body mass index  $< 18$ ), or who required tube feeding; ii) patients who had major surgery within 30 days prior to study treatment; iii) patients with other malignant tumors that have not been cured within 2 years (except for patients with a combination of other early-stage tumors that have been treated radically and are assessed by the investigator to be at low risk of recurrence in the short term); iv) patients with active infections who still require systemic therapy 7 days prior to administration of the first dose of treatment in this study; v) patients who are allergic to the drugs or related ingredients involved in this study; vi) patients who are currently enrolled in other interventional clinical studies; vii) patients who have not recovered from prior antitumor-related AEs to CTCAE Grade 1 prior to the first dose; viii) patients with a tendency or history of thrombosis or bleeding, regardless of severity, within 60 days prior to the first dose; and ix) patients with any serious or unstable medical condition or mental illness; patients with known active alcohol or drug abuse or dependence.

**Data collection.** The patients in this study were selected from the biobank of the First Affiliated Hospital of Nanjing Medical University. All donors of clinical data had provided informed written consent, agreeing that the related information could be used for all medical research. Medical records for this study were collected and obtained in January 2024. During the survival follow-up process, follow-up surveys were conducted via telephone with patients who had previously used the drug or with their family members.

**Treatment plan.** All included patients received rh-endostatin combined with sintilimab and the TP regimen. Based on the dosage applied in previous studies, the continuous intravenous infusion of cisplatin ( $25 \text{ mg/m}^2$ ) was administrated consecutively from the first day to the third day, with paclitaxel liposome ( $135 \text{ mg/m}^2$ ) administrated on day 1, sintilimab ( $200 \text{ mg}$ ) on day 1 and continuous intravenous infusion of rh-endostatin ( $135 \text{ mg/m}^2$ ) on day 1 for 96 h (14). All treatments

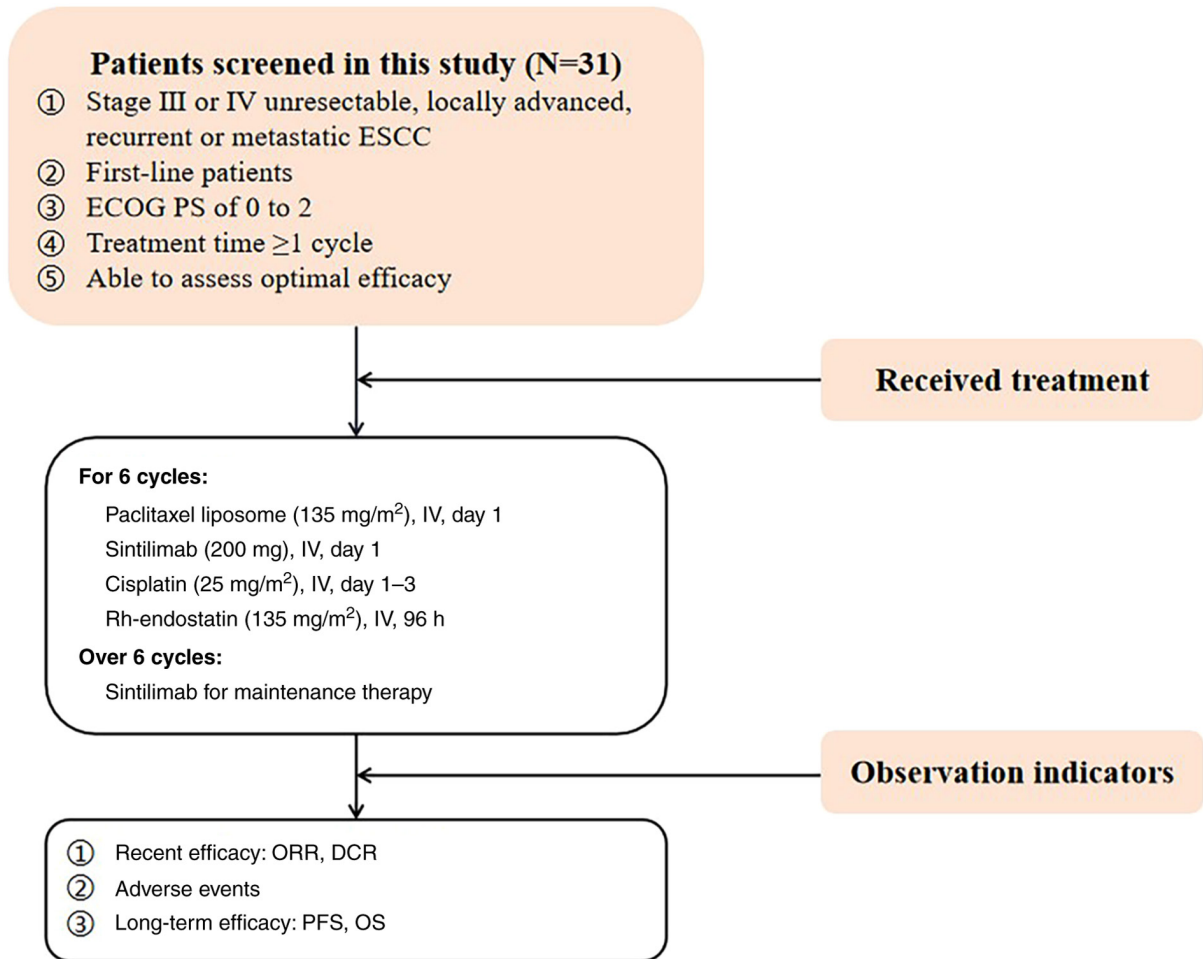


Figure 1. Flowchart of the inclusion and exclusion procedure. ESCC, esophageal squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; rh-endostatin, recombinant human-endostatin; IV, intravenous; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

were applied intravenously every 3 weeks as one cycle, with 6 cycles completed. Following the completion of 6 cycles, maintenance therapy with sintilimab was administered until disease progression occurred (Fig. 1).

**Baseline and follow-up assessment.** Baseline assessments included age, sex, pathological type, stage, metastasis, PD-L1 tumor proportion score (TPS) (23), Eastern Cooperative Oncology Group performance status (ECOG PS) (24) and smoking status. AEs were monitored weekly during treatment. Efficacy was assessed every two treatment cycles based on the RECIST 1.1 guidelines (22).

The follow-up assessment included recent efficacy, AEs and long-term efficacy. The recent efficacy of patients was classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), and the total efficacy rate was calculated as CR + PR, according to the WHO solid tumor efficacy evaluation criteria (25). The objective response rate (ORR) and disease control rate (DCR) can be calculated from the CR, PR, SD and PD. The ORR was defined as the percentage of patients achieving CR and PR. The DCR was defined as the percentage of patients achieving CR, PR and SD. The AE evaluation was performed within 5 months after the administration of the drug according to the

RECIST 1.1 guidelines. Treatment-related AEs (TRAEs) were graded according to the National Cancer Institute-Common Terminology Criteria Adverse Events 4.0 guidelines (26). For long-term efficacy, survival statistics were obtained for the 31 patients by telephone follow-up or outpatient follow-up. The survival time was defined as the time from the initial chemotherapy to death or the follow-up cut-off date.

**Statistical analysis.** Statistical analysis was performed using SPSS 24.0; measurements are expressed as median (Q3-Q1), and comparisons were made using Wilcoxon's rank-sum test and Kruskal-Wallis test. Counts are expressed as percentages, and the test level was  $\alpha=0.05$ . The median follow-up period, progression-free survival (PFS) time and overall survival (OS) time were analyzed by the Kaplan-Meier method.

A clinical heterogeneity analysis was performed using Wilcoxon's rank-sum test and Kruskal-Wallis test, with the overall population stratified into groups based on different subgroup characteristics. Wilcoxon's rank-sum test was used to compare quantitative efficacy between two groups and the Kruskal-Wallis test was used for multiple groups. The specific dataset consisted of the PFS time and the total follow-up time of the groups.  $P<0.05$  was used to indicate a statistically significant difference.

## Results

**Baseline characteristics.** A total of 31 patients with unresectable locally advanced or metastatic esophageal cancer were included in the present study. Of these, 83.9% (26/31) were male and 16.1% (5/31) were female, with a median age of 68 years (range, 56-77 years). All patients had histologically confirmed ESCC, and metastasis occurred in the liver (5 cases), lung (5 cases), bone (1 case) and peritoneum (1 case) (Table I).

**Clinical efficacy.** The data cut-off date for the analysis was July 17, 2024, with a median follow-up duration of 13.067 months (95% CI, 10.267-15.866 months). In the overall sample, a total of 31 patients were eligible for efficacy analysis. For the whole cohort, the ORR was 67.7% and the DCR was 93.5%. The data showed that of the 12 patients who received <4 treatment cycles, 0% achieved CR, 50.0% achieved PR, 33.3% achieved SD and 16.7% achieved PD. Additionally, of the 19 individuals who received ≥4 treatment cycles, 10.5% achieved CR, 68.4% achieved PR and 21.1% achieved SD. For patients with <4 treatment cycles, the ORR reached 50%, and the DCR reached 83.3%. Compared with fewer treatment cycles, both ORR and DCR were improved with ≥4 treatment cycles, reaching 78.9 and 100.0%, respectively (Table II; Fig. 2).

In subgroup analyses, patients were grouped according to characteristics, including age, sex, stage, TPS, ECOG PS and smoking status. Each subgroup member had a corresponding PFS time and total follow-up time, and Wilcoxon's rank-sum test or Kruskal-Wallis test was performed between subgroups. No significant differences were found between the different subgroups based on age, sex, stage, PD-L1 TPS, ECOG PS or smoking status in terms of PFS (Table III). The OS in some subgroups was not reached, making statistical comparison infeasible.

For the entire cohort, the median PFS time was 8.30 months (95% CI, 3.442-13.158 months) and the median OS time reached 23.07 months (Fig. 3).

**AEs.** The AEs are outlined in Table IV. Among the 31 patients with ESCC included in the safety analysis, 24 (77.4%) experienced at least one TRAE, with 35.5% (11/31) reporting grade ≥3 TRAEs. The most common TRAEs were anemia (83.9%; 26/31), thrombocytopenia (38.7%; 12/31) and neutropenia (32.3%; 10/31). The most serious AEs, including grade ≥3 events, were neutropenia and anemia; each was observed in 9.7% (3/31) of patients. No unexpected AEs were observed during the study.

## Discussion

The present retrospective study evaluated the efficacy and safety of rh-endostatin in combination with sintilimab and chemotherapy in patients with advanced ESCC. The exploratory findings suggested that, compared with the chemotherapy combined with immunotherapy regimens, rh-endostatin in combination with sintilimab and chemotherapy exhibited favorable efficacy in improving survival and treatment outcomes in patients with locally advanced or metastatic ESCC, with a manageable safety profile.

Table I. Baseline characteristics of included patients (n=31).

Baseline characteristics	n (%)
Age, years	
<65	7 (22.6)
≥65	24 (77.4)
Sex	
Male	26 (83.9)
Female	5 (16.1)
Pathological type	
Adenocarcinoma	0 (0.0)
Squamous carcinoma	31 (100.0)
Others	0 (0.0)
Stage	
III	17 (54.8)
IV	14 (45.2)
No. of metastatic sites	
<2	14 (45.2)
≥2	17 (54.8)
Liver metastasis	
Absent	26 (83.9)
Present	5 (16.1)
Bone metastasis	
Absent	30 (96.8)
Present	1 (3.2)
Lung metastasis	
Absent	26 (83.9)
Present	5 (16.1)
Peritoneal metastasis	
Absent	30 (96.8)
Present	1 (3.2)
PD-L1 tumor proportion score	
<10%	12 (38.7)
≥10%	2 (6.5)
Could not be evaluated	17 (54.8)
ECOG PS	
0-1 points	29 (93.5)
2 points	2 (6.5)
Smoking status	
Never	14 (45.2)
Former/current	17 (54.8)

PD-L1, programmed cell death-ligand 1; ECOG PS, Eastern Cooperative Oncology Group performance status.

In the ORIENT-15 study, the PFS and OS times of the treatment modality involving sintilimab combined with chemotherapy were found to be 7.2 and 16.7 months, respectively. This indicated that, compared with the traditional radiotherapy and chemotherapy regimens, sintilimab combination chemotherapy markedly prolonged OS, improved PFS and increased the overall remission rate in patients with locally advanced, recurrent or metastatic ESCC. Additionally,

Table II. Results of clinical efficacy.

Best response	Overall (n=31)	<4 cycles (n=12)	≥4 cycles (n=19)
CR, n (%)	2 (6.5)	0 (0.0)	2 (10.5)
PR, n (%)	19 (61.3)	6 (50.0)	13 (68.4)
SD, n (%)	8 (25.8)	4 (33.3)	4 (21.1)
PD, n (%)	2 (6.5)	2 (16.7)	0 (0.0)
ORR, %	67.7	50.0	78.9
DCR, %	93.5	83.3	100.0

CR, complete response; DCR, disease control rate; PR, partial response; ORR, objective response rate; PD, progressive disease; SD, stable disease.

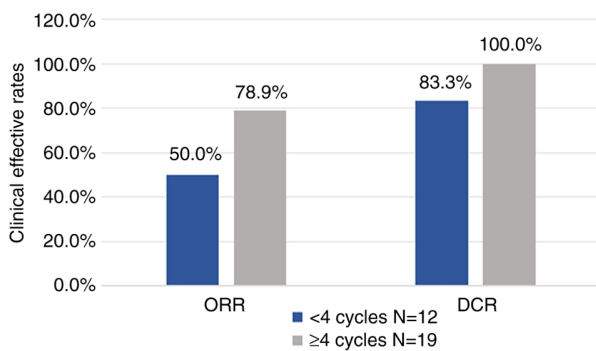


Figure 2. Histogram of clinical efficacy. ORR, objective response rate; DCR, disease control rate.

this combination therapy had a manageable safety profile compared with placebo-based chemotherapy, regardless of the PD-L1 expression level (14). Therefore, sintilimab in combination with chemotherapy is recommended as a novel first-line standard treatment for locally advanced, recurrent or metastatic ESCC by the Chinese Society of Clinical Oncology guidelines (27).

Vascular endothelial growth factor (VEGF) serves a crucial role in the development of ESCC; it is upregulated in the tumor microenvironment, leading to the formation of abnormal and incomplete blood vessel networks around the tumor, which limits immune cell infiltration. The blood vessels formed under the influence of VEGF are often structurally abnormal, resulting in impaired blood flow. These VEGF-induced vessels typically exhibit leakage, fluid accumulation and irregular barrier functions. The abnormal vasculature also contributes to increased interstitial pressure within the tumor microenvironment. As a result, poor blood flow, leakage and high interstitial pressure hinder the effective penetration of immune cells into the tumor tissue, thereby weakening the antitumor response of the immune system (28,29).

Targeting the aforementioned mechanisms, recent studies have shown that combination of anti-angiogenic treatment with immunotherapy can improve antitumor efficacy (30,31). On the one hand, antiangiogenic drugs not only reverse the immunosuppressive effect caused by serum VEGF, but also normalize the tumor vascular system, promote the exudation

and perivascular accumulation of CD8<sup>+</sup> cytotoxic T lymphocytes expressing  $\gamma$ -interferon (IFN- $\gamma$ ), and may induce or increase active T-cell transit to specific tumor antigens or other effector cells of the immune system. On the other hand, ICIs can restore the immune-supportive microenvironment, normalize the tumor vascular system by activating effector T cells and upregulating the secretion of IFN- $\gamma$ , increase the infiltration and killing function of effector T cells, facilitate the delivery of drugs, reduce the dosage of ICIs and decrease the risk of AEs (32-36). Overall, the combination of anti-angiogenesis treatment and immunotherapy holds promise for improving the immune microenvironment while normalizing tumor vasculature, thereby enhancing therapeutic efficacy.

The Empower study, presented at the 2022 American Society of Clinical Oncology annual meeting, explored the efficacy of sintilimab in combination with recombinant human vascular endothelial inhibitor plus standard platinum-containing two-agent chemotherapy (pemetrexed + carboplatin/cisplatin) for the first-line treatment of advanced non-squamous NSCLC in driver-negative NSCLC (37). The combination therapy resulted in an ORR of 53% and a DCR of 93%. Most AEs were grade 1-2 AEs, suggesting that the combination of recombinant human vascular endothelial inhibitor, immunotherapy and chemotherapy offers promising efficacy and safety (18). The favorable safety and tolerability of the combination mode in the Empower study further supports the exploration and application of the combination regimen of immunological and antiangiogenic drugs.

In order to improve antitumor efficacy, the present retrospective study was theoretically based on anti-angiogenesis treatment combined with immunotherapy. The present study aimed to explore a potentially optimal treatment regimen by adding the anti-angiogenic agent rh-endostatin to a chemotherapy and immunotherapy protocol. The regimen seemed to have a promising clinical efficacy. Thus, the present study retrospectively analyzed the data from these patients. Although the analysis was retrospective, rigorous screening was performed in the patient selection process, and the treatment process was subjected to rigorous quality control, closely aligning with the requirements of a prospective trial.

In the short-term efficacy assessment, improved ORR and DCR were observed. The study demonstrated that the ORR and DCR were 67.7 and 93.5% respectively, while in the ORIENT-15 study, the ORR and DCR were 66.1 and 90.2% respectively. This indicated that the present results seemed to show an upward trend. However, this may be related to the relatively small sample size in the present study, and thus it should be interpreted with caution. In patients receiving longer cycles of treatment, the improvements in ORR and DCR seemed to be more marked. Specifically, the ORR was 78.9% for those receiving  $\geq 4$  cycles of treatment, compared with 67.7% for the overall cohort, and the DCR was 100.0% in patients receiving  $\geq 4$  cycles, compared with 93.5% in the overall cohort. These findings suggest that the treatment duration may be associated with therapeutic efficacy. Preliminary results indicated that the adequate  $\geq 4$ -cycle long regimen of rh-endostatin may be associated with more significant survival gain. However, the safety of combination therapy with rh-endostatin in full cycles still deserves to be explored.

Table III. Subgroup analysis of PFS and OS in the 31 patients.

Variable	Patients, n (%)	PFS, months <sup>a</sup>	OS, months <sup>a</sup>	P-value (PFS)
Age, years				0.422
<65	7 (22.6)	4.267 (3.400-15.767)	NR	
≥65	24 (77.4)	8.300 (4.333-23.067)	23.067 (5.733-NR)	
Sex				0.259
Male	26 (83.9)	5.733 (4.267-23.067)	23.067 (9.767-NR)	
Female	5 (16.1)	12.633 (9.933-15.767)	NR	
Stage				0.171
III	17 (54.8)	11.967 (4.800-23.067)	23.067 (5.733-NR)	
IV	14 (45.2)	5.367 (3.400-10.367)	NR	
PD-L1 tumor proportion score				0.814
<10%	12 (38.7)	9.933 (4.333-12.633)	13.067 (4.333-NR)	
>10%	2 (6.5)	4.333 (4.333-8.300)	NR	
Could not be evaluated	17 (54.8)	8.100 (4.067-23.067)	23.067 (23.067-NR)	
ECOG PS				0.634
0 points	14 (45.2)	9.033 (4.267-23.067)	23.067 (23.067-NR)	
≥1 points	17 (54.8)	5.733 (4.333-12.633)	NR	
Smoking status				0.937
Never	14 (45.2)	8.100 (4.800-NR)	NR	
Former/current	17 (54.8)	9.933 (3.367-15.767)	23.067 (13.067-NR)	

<sup>a</sup>Data are presented as median (Q3-Q1). PFS, progression-free survival; OS, overall survival; NR, not reached; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1.

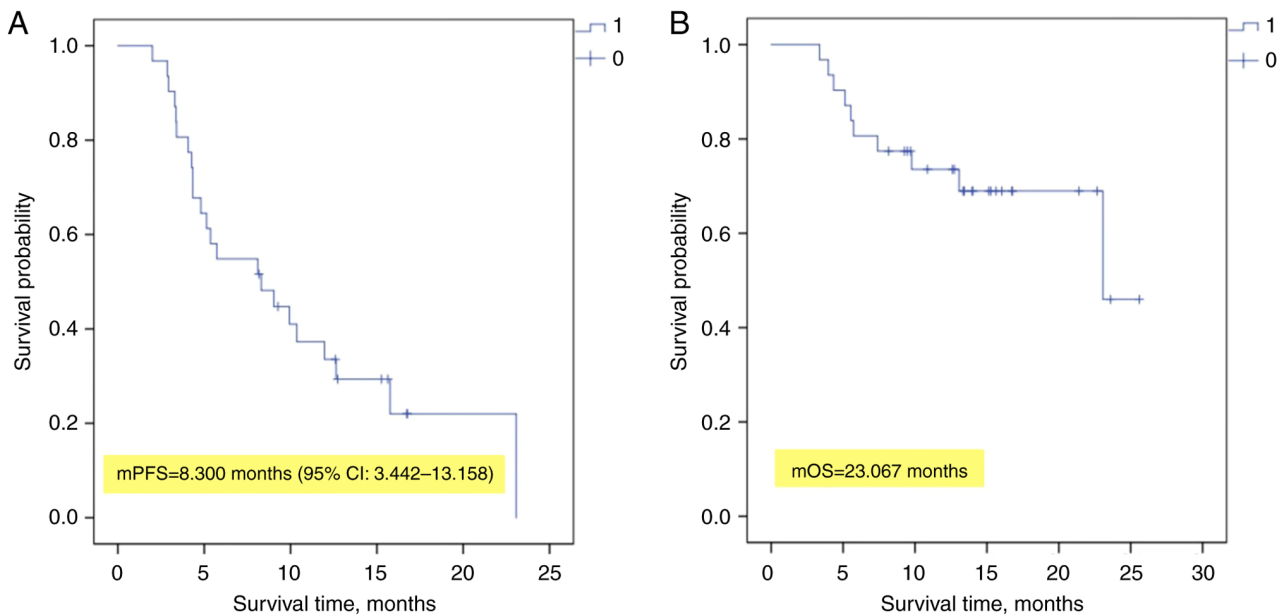


Figure 3. Kaplan-Meier curves for (A) PFS and (B) OS of the whole cohort. mPFS, median progression-free survival; mOS, median overall survival.

In addition to short-term efficacy assessment, it is also important to assess the long-term survival of patients. The median PFS time of patients treated with rh-endostatin combined with sintilimab and chemotherapy was 8.30 months (95% CI, 3.442-13.158 months), and the median OS time reached 23.07 months. In the ORIENT-15 study, the PFS and

OS of the treatment modality involving sintilimab combined with chemotherapy were found to be 7.2 and 16.7 months, respectively. It was observed that rh-endostatin-combined treatment tended to extend PFS and OS. However, as the present results were from a retrospective study, a head-to-head comparison could not be conducted. Therefore, further



Table IV. Profile of AEs in the 31 patients.

AEs	Any grade	Grade $\geq 3$
Hematological adverse event		
Neutropenia	10 (32.3)	3 (9.7)
Thrombocytopenia	12 (38.7)	2 (6.5)
Anemia	26 (83.9)	3 (9.7)
Non-hematological adverse events		
Nausea or vomiting	0 (0.0)	0 (0.0)
Rash	1 (3.2)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)
Hemorrhage	0 (0.0)	0 (0.0)
Immune-related adverse events		
Reactive cutaneous capillary endothelial proliferation	0 (0.0)	0 (0.0)
Immune-mediated pneumonitis	1 (3.2)	1 (3.2)
Liver injury	4 (12.9)	0 (0.0)
Kidney injury	2 (6.5)	1 (3.2)
Hypothyroidism	5 (16.1)	0 (0.0)
Diarrhea and colitis	0 (0.0)	0 (0.0)
Cardiac creatine kinase level change	3 (9.7)	1 (3.2)
Hair loss	9 (29.0)	0 (0.0)

AEs, adverse events.

prospective large-scale clinical trials are still needed for confirmation.

In terms of safety, the incidence of at least one TRAE associated with any level of treatment (sintilimab, placebo, cisplatin, paclitaxel or 5-fluorouracil) in the ORIENT-15 study was 98% (321/327). The incidence of TRAEs of rh-endostatin combined with sintilimab and chemotherapy in the present study was 77.4% (24/31), while the incidence of all adverse reactions was lower than that in the ORIENT-15 study. Anemia, thrombocytopenia and neutropenia were the most common AEs. However, the majority of these events were mild to moderate, with severe AEs being rare. The incidence of grade  $\geq 3$  AEs was 35.5% (11/31). In the ORIENT-15 study, the incidence of grade  $\geq 3$  TRAEs was 59.9% (196/327) in the sintilimab chemotherapy group. By contrast, the present study exhibited a significant decrease. The reduced incidence of these AEs may be associated with the lower dose of paclitaxel used in the present study. The chemotherapy regimen used in the present study had a dose of 135 mg/m<sup>2</sup> of paclitaxel liposome, which is in the low-dose range of paclitaxel liposome (135-175 mg/m<sup>2</sup>) (38), and the combined application of rh-endostatin can reduce the chemotherapy dose, which is conducive to the reduction of AEs of chemotherapy. The present data suggest that the addition of rh-endostatin treatment to sintilimab combination chemotherapy is beneficial on trend, both in terms of efficacy and safety, and that this can also lower the chemotherapy dose and reduce the incidence of toxic side effects; however, this needs to be further confirmed by prospective clinical trials with large samples.

In the subgroup analysis, there were no significant differences in PFS across subgroups based on age, sex, stage, PD-L1 TPS, ECOG PS or smoking status. This suggests that the response to treatment was similar across different subgroups, and the subgroup characteristics studied (age, sex, stage, PD-L1 TPS, ECOG PS and smoking status) are not key factors influencing treatment efficacy. Therefore, the treatment strategy exhibited broad effectiveness across different patient populations.

The present study also had certain limitations. Firstly, this investigation was a small sample size, single-center, retrospective analysis. With a sample size of 31 patients and the study being conducted solely at one institution, it is highly susceptible to the influence of random factors. This may potentially compromise the reliability and generalizability of the research findings. Secondly, the median follow-up duration in the present study was 13.067 months (95% CI, 10.267-15.866 months). The relatively short follow-up period may not be adequate to capture a sufficient number of target events, such as mortality and recurrence. This can introduce inaccuracies in the analysis of survival rates and treatment efficacy. Furthermore, short-term follow-up may impede the accurate assessment of safety. For instance, immune-related AEs (irAEs) are prevalent adverse reactions among patients with cancer undergoing ICI therapy. irAEs are characterized by latency and chronic persistence. Short-term follow-up may fail to detect these persistent or progressively deteriorating conditions. Additionally, the symptoms of irAEs are often non-specific and can be easily confounded with those of other common diseases or adverse reactions induced by treatment. As a result, short-term follow-up may overlook certain subtle symptoms, potentially leading to misdiagnosis or missed diagnosis. This could lead to an underestimation of the incidence of AEs in the statistical data.

In future studies, the following adjustments can be made to address the aforementioned limitations. Firstly, a prospective randomized controlled clinical trial could be set up to compare the clinical efficacy of rh-endostatin combined with sintilimab and chemotherapy against that of sintilimab combined with chemotherapy. Secondly, the follow-up time could be extended. The optimal follow-up time should be as long as 2 years, or even longer if possible. Thirdly, individualized monitoring programs could be added. Monitoring programs can be developed based on patients' underlying diseases and their previous adverse reaction histories. irAEs often involve multiple organ systems, and thus, timely and comprehensive assessments are crucial for the early detection of irAEs.

It is therefore necessary to conduct larger sample size, multicenter, long-term, randomized, controlled clinical trials to further validate the efficacy and safety of rh-endostatin in combination with sintilimab and chemotherapy for the first-line treatment of locally advanced or metastatic ESCC, and to confirm its long-term effectiveness and toxicity.

In conclusion, rh-endostatin combined with sintilimab and chemotherapy has a positive efficacy and safety in the first-line treatment of locally advanced or metastatic ESCC, suggesting that this regimen may be a potential treatment option for patients with advanced ESCC. Further randomized controlled trials are needed to study the efficacy and safety of rh-endostatin in combination with sintilimab and chemotherapy for advanced ESCC.

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## Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

SC and LF provided materials and contributed to the study conception and design. XS was responsible for writing the draft manuscript and conducting the analysis. YC and TW performed data analysis and interpretation. PL and RW contributed to the acquisition of data. LL participated in data analysis and study design. SC and LF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

Ethical approval was granted by the First Affiliated Hospital of Nanjing Medical University (Nanjing, China; approval no. 2024-SR-415). Written informed consent was gathered from the participants prior to initiation of the study.

## Patient consent for publication

In the present study, the patient, parent, guardian or next of kin as appropriate provided written informed consent for the publication of any associated data and accompanying images.

## Competing interests

The authors declare that they have no competing interests.

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