ORIGINAL RESEARCH

Feasibility and Safety of PD-1 Blockades Among Elderly Patients with Metastatic Esophageal Squamous Cell Carcinoma: A Real-World Study

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Objective: This study aimed to identify the effectiveness and safety of PD-1 blockades among elderly patients with metastatic esophageal squamous cell carcinoma (ESCC) clinically.

Methods: A total of 78 elderly patients with previously treated metastatic ESCC aged ≥65 years who received PD-1 blockades monotherapy were included retrospectively. Demographic characteristics, therapeutic effectiveness and adverse reactions of the elderly patients who underwent PD-1 blockade therapy were recorded. Regular follow-up was conducted for all patients. The analysis aimed to identify potential risk factors for OS by examining the correlation between prognosis and subgroups based on baseline characteristics.

Results: The median age of the 78 elderly patients was 73 years, ranging from 65 to 87 years. Among the 78 patients, 18 cases showed partial response, 26 cases had stable disease, 29 cases experienced progressive disease and 5 cases were not assessable for response, yielding an ORR of 23.1%, a DCR of 56.4%. The prognostic outcomes indicated that among the 78 patients with metastatic ESCC who received PD-1 blockades, the median PFS was 3.1 months [95% confidence interval (CI): 1.64–4.56], and the median OS was 10.9 months (95% CI: 6.02–15.78), 24-month OS rate was 22.7% (95% CI: 12.8–34.2%). In terms of the safety profile, among the 78 patients with metastatic ESCC during PD-1 blockades single-agent treatment, a total of 61 patients (78.2%) experienced any grade adverse reactions and the incidence of grade ≥3 adverse reactions were 20.5%. Briefly, the common adverse reactions manifested as fatigue (32.1%), gastrointestinal reaction (24.4%), diarrhea (19.2%), anemia (17.9%) and rash (16.7%). Overall tolerability of PD-1 blockade monotherapy in elderly patients with metastatic ESCC was acceptable and manageable.

Conclusion: PD-1 blockades single agent demonstrated encouraging effectiveness and acceptable safety profile for elderly patients with previously treated metastatic ESCC in clinical practice. Prospective study should be performed to elucidate the conclusion in this study subsequently.

Keywords: elderly patients, esophageal squamous cell carcinoma, PD-1 blockades, effectiveness, safety

Introduction

Esophageal cancer (EC) was recognized as a prevalent gastrointestinal tumor and ranked as the eighth most common solid tumor globally on an annual basis.[1] According to the epidemiological data in 2020, there were an estimated 604,000 new cases of EC and approximately 544,000 deaths worldwide.[2] China had the highest incidence of EC all over the world, there were approximately 324,000 new cases of EC and around 301,000 deaths annually, accounting for over half of the prevalence and death of EC globally.[3] A significant disparity was observed regarding the histological types of EC between Eastern and Western nations, which suggested that esophageal adenocarcinoma prevailed as the predominant

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form in Western countries, whereas in China, approximately 95% of EC cases were classified as esophageal squamous cell carcinoma (ESCC) clinically.[4] Considering the distinct etiology and molecular characteristics, treatment of EC in China was of unique attributes, necessitating the development of separate treatment strategies to optimize patient outcomes for ESCC as opposed to esophageal adenocarcinoma in Western countries.[5] Surgery and definitive chemoradiotherapy remained the primary therapeutic options for patients with early-stage ESCC who were eligible for resection. However, it was unfortunate that the majority of patients with ESCC were initially diagnosed with locally advanced or metastatic disease in China clinically.[6]

Noteworthily, EC was usually diagnosed at a relatively old age and the incidence of EC rose dramatically with the increase in age.[7] A recent data highlighted that approximately 69.8% of EC in males were found in those older than 60 years and another phase III clinical trial in China indicated that the median onset age of ESCC in clinical practice was approximately 63 years old.[8,9] Regrettably, due to the common practice of implementing stringent age screening criteria in most clinical trials (typically restricting eligibility to individuals under the age of 75), it seemed that the percentage of patients aged ≥75 years who could participate in these trials was likely less than 10%,[10] resulting in a scarcity of clinical trials available to shape clinical guidelines for elderly patients with metastatic ESCC.[11] Precisely, the exclusion of elderly patients from most clinical trials might be attributed to a range of specific factors. These factors often encompassed advanced age, less favorable physical performance status, lack of robust social support, cognitive impairment, higher incidence of comorbidities and hesitancy to undergo treatment regimens associated with greater toxicity.[12] Collectively, these factors contributed to the clinical rationale behind restricting the inclusion of elderly patients in clinical trials. In view of these particular physical conditions of elderly patients with ESCC, previous research indicated that elderly patients with EC experienced a higher frequency of treatment-related toxicities and complications during the conventional treatment.[13] In terms of EC, it was a debilitating condition, with elderly patients being particularly susceptible to the complications of dysphagia, malnutrition and sarcopenia, which helped to result in the worse physical performance status and compromised the chance to receive intensive therapeutic options clinically. Still and all, there was a growing demand for efficacious treatment strategies tailored to elderly ESCC patients. And these strategies must take the unique challenges posed by functional limitations and the presence of comorbidities into account among this population.[14] Interestingly, a previous study exhibited that when a patient was at 75 years of age, life expectancy could be more than 10 years,[15] suggested that elderly patients should not be automatically excluded from intensive treatments solely based on their age and there was a pressing need for the development of treatment guidelines specifically designed to address the needs and considerations of this population.[16] As a result, all these factors mentioned above highlighted that efficacious therapeutic options with lower toxicity should be explored for elderly patients with metastatic ESCC in depth. Among these therapeutic options, PD-1 blockades might be one promising candidate in clinical practice.

Fortunately, programmed cell death protein 1 (PD-1) blockades had showcased impressive anti-tumor effectiveness and manageable toxicity profile when employed as second-line or subsequent-line therapies for previously chemotherapy treated patients with advanced or metastatic ESCC from Keynote-181 trial in recent years, yielded an objective response rate (ORR) of approximately 20%, a median progression-free survival (PFS) ranging from 1.6 to 2.6 months, and a median overall survival (OS) ranging from 8.3 to 10.9 months, respectively.[17] Notably, within China, pembrolizumab, nivolumab, camrelizumab and tislelizumab had delivered substantial survival advantages when utilized as second-line monotherapy.[18] Subsequently, significant breakthroughs were observed with the integration of PD-1 blockades alongside chemotherapy since Keynote-590 trial, produced an ORR ranged from 45% to 72.1%, a median PFS varied between 5.8 and 7.2 months and a median OS spanned from 12.4 to 17.0 months, respectively.[19] Notably, the administration of pembrolizumab, nivolumab, camrelizumab and other PD-1 blockades in combination with chemotherapy as first-line treatments yielded varying degrees of improvement in terms of prognosis for patients with advanced ESCC.[20] Therefore, PD-1 blockade monotherapy or its combination with chemotherapy had established as the standard of care for patients with metastatic ESCC in the second-line and first-line treatment settings, respectively.[21] Nonetheless, it was important to highlight that the majority of participants in these trials were younger patients (<75 years). For instance, the median age was 60 years in the ESCORT trial that involved 457 patients with advanced ESCC receiving camrelizumab monotherapy.[22] Collectively, these existing evidence-based trials regarding PD-1 blockade monotherapy in patients with metastatic ESCC mainly centered on relatively younger individuals, which underscored that there was still a lack

of comprehensive evidence regarding the effectiveness and safety of PD-1 blockades in ESCC patients aged 65 and older and prospective clinical trials was ongoing.[23] Noteworthily, PD-1 blockades usually demonstrated a favorable safety profile compared to conventional chemotherapy with manageable adverse effects,[24] which was particularly important for elderly patients who often had reduced physiological reserves and might not tolerate the toxicities associated with chemotherapy. Previous studies highlighted that older adults could derive comparable benefits from PD-1 blockades without a significant increase in adverse events.[25] Therefore, understanding the efficacy and safety of PD-1 blockades in the elderly ESCC patient population was crucial for optimizing treatment strategies.

Furthermore, genuine therapeutic challenge associated with PD-1 blockade monotherapy in current clinical practice revolved around the disappointing ORR (approximately 20%). And this was especially notable when the expression of PD-L1 combined positive score (CPS) < 10, ORR of PD-1 blockade monotherapy was only 11.9%.[26] Consequently, it became imperative to investigate the correlation between baseline characteristics and the clinical outcomes of those with metastatic ESCC undergoing treatment of PD-1 blockades, aiming to uncover the specific patient population that might potentially derive significant benefits from the treatment of PD-1 blockade monotherapy clinically.

As a result, the primary objective of this study was to retrospectively provide real-world evidence concerning the effectiveness and tolerability of PD-1 blockade among elderly patients with metastatic ESCC in clinical practice.

Materials and Methods
Study Design and Eligibility Criteria

Many elderly patients with metastatic ESCC were treated with PD-1 blockade monotherapy in clinical practice currently. Consequently, this study was conducted retrospectively, focusing on individuals who received single-agent PD-1 blockade treatment between October 2018 and January 2023 at the Department of Gastrointestinal Medical Oncology of Tianjin Medical University Cancer Institute and Hospital consecutively. To generate more rigorous data, precise eligibility criteria were meticulously applied to ensure the accurate presentation of efficacy and safety associated with PD-1 blockade therapy for elderly patients with metastatic ESCC: (1) Histologically diagnosed of ESCC with advanced or metastatic stage; (2) Aged of ≥65 years or older, adhering to the age criterion outlined by the World Health Organization for elderly individuals; (3) Appropriate physical performance status with an Eastern Cooperative Oncology Group (ECOG) score ranging from 0 to 2 score; (4) Patients in the study had previously undergone at least one systemic treatment regimen and experienced disease progression or intolerant of the respective regimens, including PD-1 plus chemotherapy or systemic chemotherapy regimens; (5) Patients were treated with PD-1 blockades single agent as their treatment after previous therapy in clinical practice, whether the treatment was combined with local treatment such as radiotherapy was permitted;[27] (6) Appropriate target lesions were available to assess anticancer activity. Additionally, main exclusion criteria were as follows: (1) patients had a history of autoimmune disease or they currently were receiving steroids or other immunosuppressive drugs; (2) patients had one or more additional primary tumors or serious underlying medical conditions that might potentially jeopardize their survival in the assessment of investigators; (3) patients were absent of a substantial amount of baseline characteristics data, or the therapeutic process data were not available; (4) patients with significant organ dysfunction that might preclude the safe administration of PD-1 blockades, which included severe hepatic, renal or cardiac impairment, as defined by specific laboratory thresholds.

We reviewed the treatment history of the patients from the medical records system of our hospital to identify patients who met the inclusion criteria and excluded those who met the exclusion criteria. The collected data included patient's demographics, diagnosis details, treatment modalities, follow-up outcomes and any complications or side effects encountered. Finally, a total of 78 elderly patients with previously treated metastatic ESCC were suitable to be included in this study. And the study profile was illustrated in Figure 1.

Given that this study was designed as a retrospective analysis and OS was the most objective and reliable evaluation endpoint in clinical practice, the primary endpoint was OS in this study and other endpoints encompassed ORR, disease control rate (DCR), duration of response (DOR), PFS and safety profile. Moreover, the exploratory endpoint involved performing an association analysis between baseline characteristic subgroups and OS. This retrospective analysis protocol and the use of electronic medical records were approved by the ethics committees of the Tianjin Medical
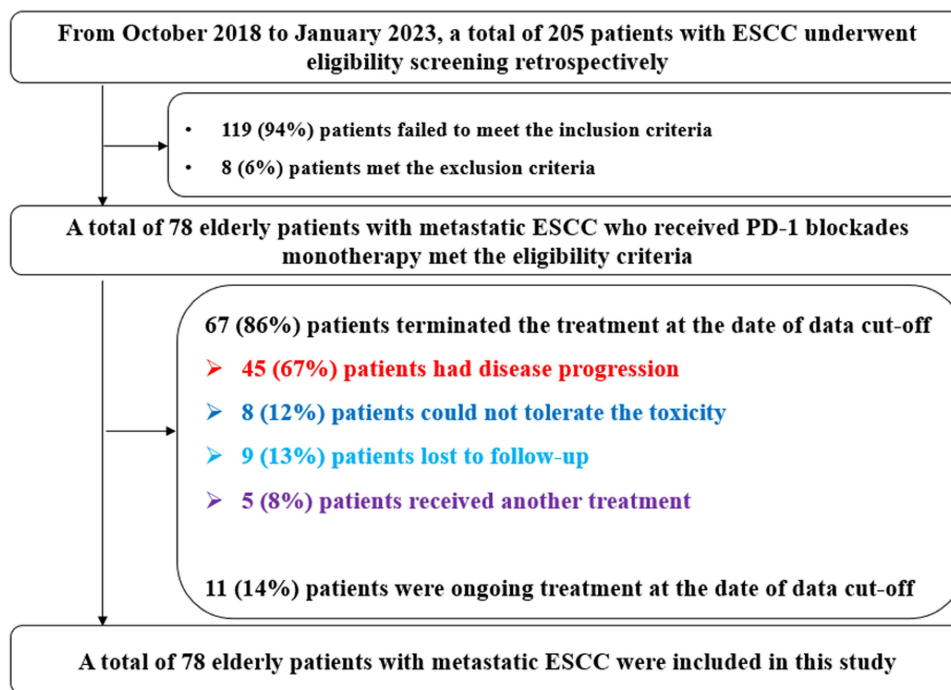
Figure 1 Study profile of this retrospective study regarding PD-1 blockades among elderly patients with previously treated metastatic ESCC.

University Cancer Institute and Hospital (approved number: E20230166). Written informed consent was obtained from all patients participating in this study, following the principles of the Declaration of Helsinki. The consent process involved providing detailed information regarding PD-1 blockade therapy, including potential benefits and risks. Special attention was given to the elderly patient population, highlighting age-specific risks and the importance of monitoring for adverse events. Patients and their families were encouraged to ask questions, and healthcare providers ensured that all information was understood before consent was given. And comprehensive information regarding the study was provided in clear language. Patients were encouraged to involve family members or caregivers, ensuring they had adequate support to understand the study and its implications.

To ensure patient privacy and data confidentiality, all collected data were de-identified and stored in a secure, encrypted database. Access to the data was restricted to authorized personnel, and all activities were logged. The study complied with relevant data protection regulations, maintaining strict adherence to legal and ethical standards for data protection.

Therapeutic Regimens of PD-1 Blockades

All the subjects included in this study were those who progressed the previous systemic treatment and received PD-1 blockades single-agent therapy clinically. All the PD-1 blockade monotherapy used in this study were those approved in mainland China and accessible for Chinese patients in clinical practice, including camrelizumab (Jiangsu Hengrui Pharmaceutical Co., LTD), tislelizumab (BeiGene, LTD), sintilimab (Innovent Biopharmaceutical (Suzhou) Co., LTD), pembrolizumab (Merck (China) Co., LTD) and nivolumab (Bristol-Myers Squibb (China) Investment Co. LTD). Five PD-1 blockades were ultimately administered in this study. Except for nivolumab, other four PD-1 blockades were administered intravenously at a dosage of 200mg on day 1, while nivolumab was intravenously used at a dosage of 360mg on day 1. This regimen was repeated every 21 days, constituting one therapeutic cycle. The dosage of these five PD-1 blockades was determined according to the Esophageal Cancer Diagnosis and Treatment guidelines of the Chinese Society of Clinical Oncology (CSCO). The treatment could be discontinued in the event of disease progression or intolerable adverse reactions occurred.

Protocol for Evaluating Therapeutic Outcomes and Tolerability

Given that the efficacy resulted from the treatment of PD-1 blockades, the iRECIST criteria were employed for assessing the therapeutic activity of the patients as per the investigator's judgment.[28] Individually, computed tomography (CT) was used to assess target lesions in the chest, while CT or magnetic resonance imaging (MRI) was adopted for target lesions in other anatomical positions both before and after the administration of PD-1 blockades. CT or MRI images were reviewed and interpreted by experienced radiologists and surgeons who were blinded to the clinical outcomes. And the assessment of target lesions occurred either every two therapeutic cycles or as needed during clinical visits, particularly when patients exhibited worsening clinical symptoms. Therapeutic activity included ORR and DCR, which was computed by evaluating the best overall response observed during PD-1 blockade administration. ORR was determined by calculating the percentage of patients who achieved a complete response (CR) or partial response (PR) among all subjects included. DCR was calculated as the percentage of patients who achieved CR, PR, or stable disease (SD) among all subjects included. PR was also iPR, defined as a decrease of ≥30% in tumor burden compared to baseline and non-unequivocal progression of non-target lesions and no new lesions. SD was also iSD, defined as neither PR nor PD. PD was classified as immune unconfirmed PD (iUPD) and immune confirmed PD (iCPD). IUPD was defined as increase ≥20% of the sum of longest diameters compared with nadir (minimum 5mm) or progression of non-target lesions or new lesions, and confirmation of progression recommended minimum 4 weeks after the first iUPD assessment. ICPD was defined as increased size of target or non-target lesions, or increase in the sum of new target lesions >5mm, or progression of new non-target lesions, or appearance of another new lesion.

Furthermore, baseline demographic characteristics and disease progression status of each patient were gathered, and follow-up assessments were conducted to acquire prognostic data. The subsequent follow-up predominantly took place via telephone monthly: therapeutic regimens of the patients following the progression of PD-1 blockade administration were documented. To ascertain the patients' death status after progression, communication with themselves or their relatives was primarily relied upon, a method adopted from a previous study.[29] Finally, the data cut-off date of this study was July 13, 2023, producing a median follow-up duration of 10.6 months (follow-up range: 0.4–29.8 months).

Regarding the toxicity assessment, the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria were employed to assess the therapeutic toxicity among the patients. Comprehensive toxicity profile of all patients treated with PD-1 blockades were systematically collected to specifically outline the safety profile of PD-1 blockade monotherapy among elderly patients with metastatic ESCC. Adverse events were closely monitored through regular clinical assessments, including laboratory tests and physical examinations. A standardized reporting system documented all adverse reactions. Early detection protocols for severe events involved immediate clinical intervention, with treatment adjustments made as necessary. Comprehensive patient safety measures, including supportive care, were implemented to manage severe adverse reactions effectively during the study.

Statistical Analysis

All the data presented in this study were statistically carried out using SPSS (version 25.0). Statistical variables were presented in the format of median (range) for continuous data and number of patients (percentage) for categorical data, as appropriate for the respective data category. DOR was defined as the duration from the date when patients first achieved complete response (CR) or partial response (PR) to the date of PD or death from any cause, whichever occurred first. Other prognostic indicators (PFS and OS) were followed on the criteria established in prior studies, patients who failed to experience disease progression or death events at the data cut-off date were considered as censored data in the analysis.29 DOR, PFS and OS survival curve were estimated using the Kaplan–Meier method and compared using the Log rank test for between-group differences. Correlation between OS and baseline characteristic subgroups was assessed using the Log rank test. Besides, multivariate Cox regression analysis was conducted incorporating variables that were found to be statistically significant in the univariate analysis. To validate the proportional hazards assumption in the Cox proportional hazards model, Schoenfeld residual was employed, which confirmed that the assumption was met. Additionally, multi-collinearity among the covariates was assessed using the variance inflation factor (VIF). All VIF values were below 5, indicating an acceptable level of multicollinearity. Therefore, all covariates were retained in the model. Median follow-up

was calculated by the reverse Kaplan–Meier method. The 95% confidence interval (CI) of the ORR and DCR was calculated by the Clopper–Pearson method. In the safety analysis, frequency data was adopted to estimate the incidence of various adverse reactions. P < 0.05 was considered suggestive.

Results
Baseline and Demographic Characteristics

Baseline and demographic characteristics of the 78 elderly patients with metastatic ESCC were illustrated in Table 1. All the subjects included in this study were older ≥65 years with the median age of 73 years (ranging from 65 to 87 years). These elderly patients with metastatic ESCC included in our study were of clinically representative. Interestingly, a total of 41 patients were positive of PD-L1 expression (52.6%). Besides, five PD-1 blockades were used in this study, camrelizumab, tislelizumab, sintilimab, pembrolizumab and nivolumab were used in 25, 22, 19, 9 and 3 patients, respectively. As described in Figure 1, at the date of data cut-off, 67 patients terminated the treatment and 11 patients were still ongoing the treatment of PD-1 blockades.

Table 1 Baseline and Demographic Characteristics of the 78 Elderly Patients with Metastatic ESCC

Baseline Characteristics	Total (N=78)	Percentage
Age (year)		
Median (range)	73 (65–87)	
Gender		
Male	63	80.8%
Female	15	19.2%
ECOG performance status		
0–1	53	67.9%
2	25	32.1%
Pathological staging		
III	6	7.7%
IV	72	92.3%
Previous surgical treatment		
Yes	15	19.2%
No	63	80.8%
Lines of PD-1 blockades monotherapy		
Second line	43	55.1%
Third line or more line	35	44.9%
Combination with radiotherapy		
Yes	16	20.5%
No	62	79.5%
Previous immunotherapy-related treatment		
Yes	18	23.1%
No	60	76.9%
Distant metastasis		
Yes	69	88.5%
No	9	11.5%
Number of metastatic lesions		
≤3	54	69.2%
>3	24	30.8%
PD-L1 expression status		
Positive	41	52.6%
Negative	9	11.5%
NA	28	35.9%

(*Continued*)

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Table 1 (Continued).

Baseline Characteristics	Total (N=78)	Percentage
PD-1 blockades		
Camrelizumab	25	32.1%
Tislelizumab	22	28.2%
Sintilimab	19	24.4%
Pembrolizumab	9	11.5%
Nivolumab	3	3.8%

Abbreviations: ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PD-1, Programmed death ligand 1.

Effectiveness of 78 Elderly Patients with Metastatic ESCC Who Received PD-1 Blockades Single Agent

This study included 78 patients and the assessment of optimal response among elderly patients during PD-1 blockade administration by each radiological assessment using CT or MRI was collected and recorded, which was evaluated in accordance with the efficacy assessment criteria established in iRECIST. Unfortunately, 5 patients were not available for the therapeutic response. Among the remaining 73 patients, no CR was detected, PR was observed in 18 cases, SD was noted in 26 cases and progressive disease was found in 29 patients, which yielded an ORR of 23.1% [95% confidence interval (CI): 14.3–34.0%] and a DCR of 56.4% (95% CI: 44.7–67.6%). Briefly, the waterfall plot for the best percentage change in target lesion of the 78 elderly patients with metastatic ESCC who received PD-1 blockades single agent was depicted in Figure 2. Obviously, considerable elderly patients experienced a dramatic reduction in the size of their target lesions with a total of 18 patients achieving a partial response (over 30% reduction) following treatment with PD-1 blockades monotherapy. And the median percentage changes in target lesions of the 73 patients was 10.1% (range: −61.1%~68.9%). Furthermore, we chose one case of a male patient who was unable to receive surgical resection due to the older age, and only system treatment was available. Figure 3 presents the CT scans of the target lesions in the esophagus site before and after treatment with tislelizumab monotherapy. The target lesion of this patient exhibited
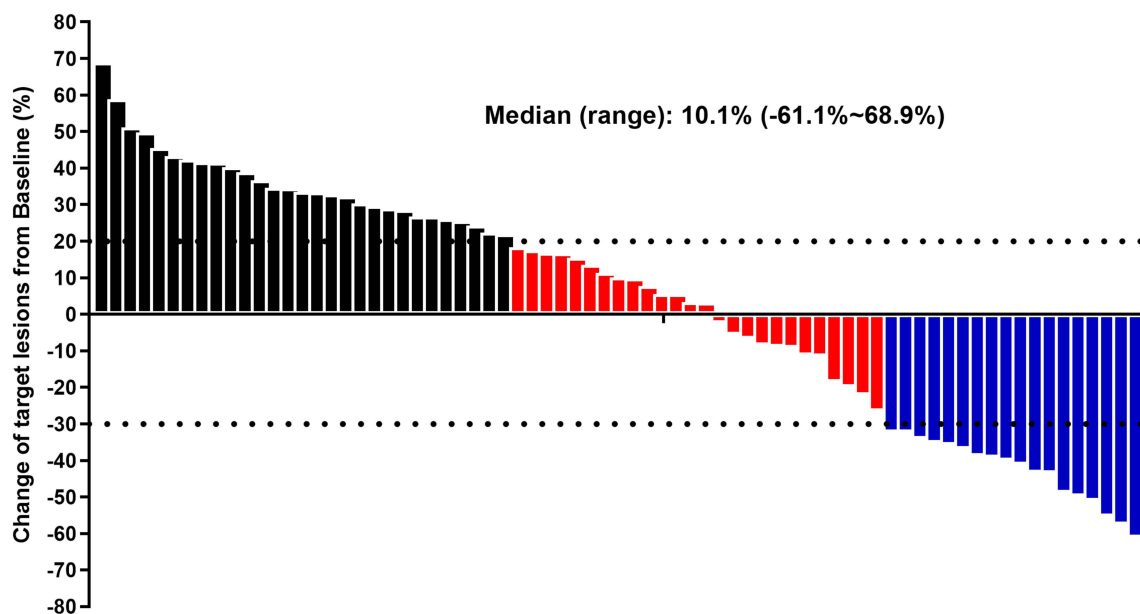

Figure 2 Waterfall plot for the variation of target lesions from baseline among the 78 elderly patients with metastatic ESCC who were treated with PD-1 blockades single agent (blue columns represent PR, red columns represent SD and black column represents PD according to the optimal response).
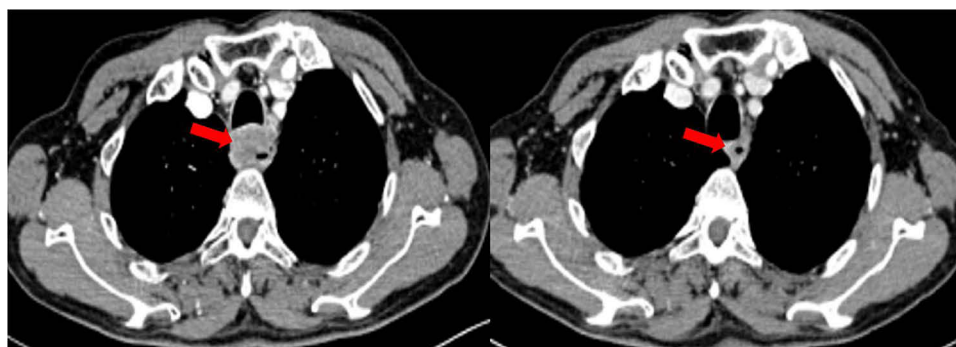
Figure 3 CT scan results of the changes for target lesions in the primary esophagus site of a male patient with metastatic ESCC before and after the treatment using tislelizumab (red arrows indicated the locations of the target lesions).

a remarkable reduction and the dysphagia symptoms were significantly relieved after tislelizumab administration, indicating a substantial benefit from the tislelizumab monotherapy for this elderly male patient.

Duration of Response Among 18 Elderly Patients Who Received PD-1 Blockades Single Agent

As described previously, a total of 18 patients achieved PR who were suitable to perform the DOR analysis. The data cut-off date of this study was July 13, 2023, resulting in a median follow-up duration of 10.6 months among the 78 elderly patients with metastatic ESCC (follow-up range: 0.4–29.8 months). As exhibited in Figure 4, the median DOR of the 18 patients who achieved PR was 8.8 months (95% CI: 5.99–11.61). Furthermore, the 12-month DOR and 20-month DOR rate were 44.4% (95% CI: 21.6–65.1%) and 33.3% (95% CI: 11.0–57.9%), respectively.
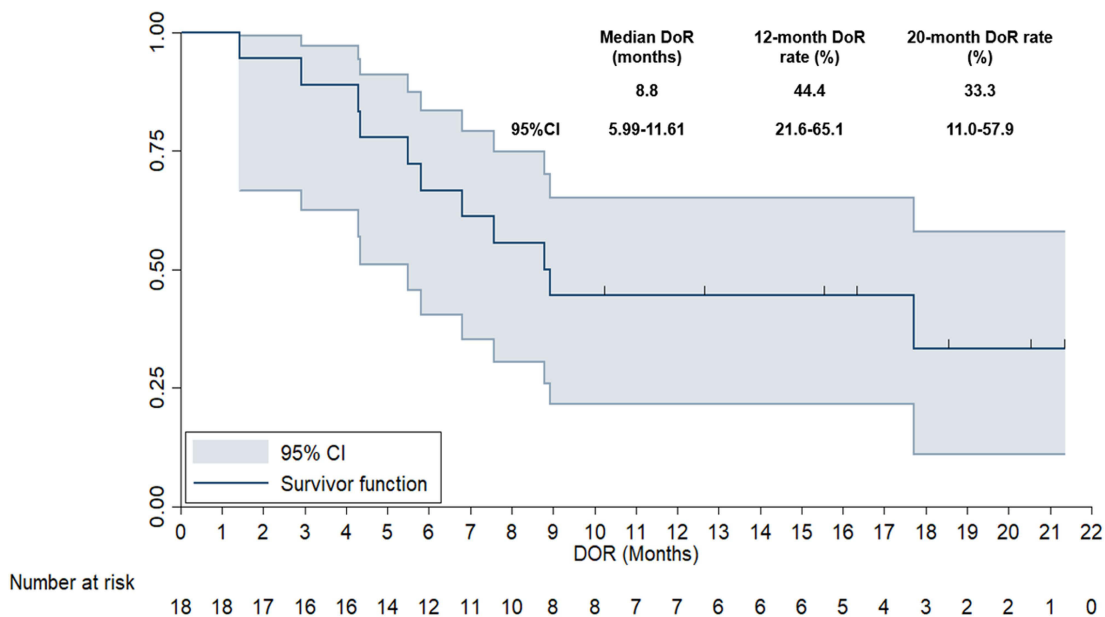

Figure 4 Duration of response among the 18 elderly patients with metastatic ESCC who received PD-1 blockades monotherapy and achieved partial response.

Prognosis of 78 Elderly Patients with Metastatic ESCC Who Received PD-1 Blockades Single Agent

After a median follow-up duration of 10.6 months, a total of 57 subjects were detected of progression or death events, yielding a maturity for PFS data of 73.1%. As illustrated in Figure 5, the median PFS of the 78 elderly patients with metastatic ESCC who received PD-1 blockades monotherapy was 3.1 months (95% CI: 1.64–4.56). The 6-month, 12-month and 24-month PFS rate was 40.9% (95% CI: 29.9–51.5%), 30.2% (95% CI: 19.8–41.4%) and 10.9% (95% CI: 2.7–25.6%), respectively. Besides, a total of 14 elderly patients with metastatic ESCC achieved a durable PFS benefit of over one year.

Furthermore, after a sufficient follow-up duration, we also obtained the available OS data. At the date of data cut-off, a total of 54 death events were observed, which resulted in a maturity for OS data of 69.2%. As exhibited in Figure 6, the
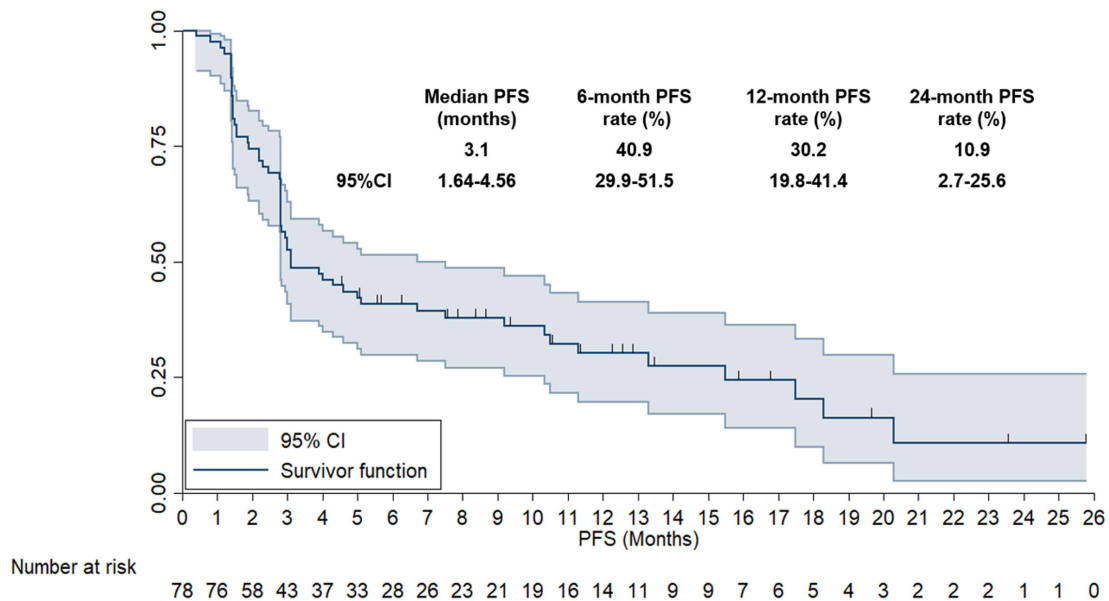

Figure 5 Progression-free survival of the 78 elderly patients with metastatic ESCC who received PD-1 blockades single agent.
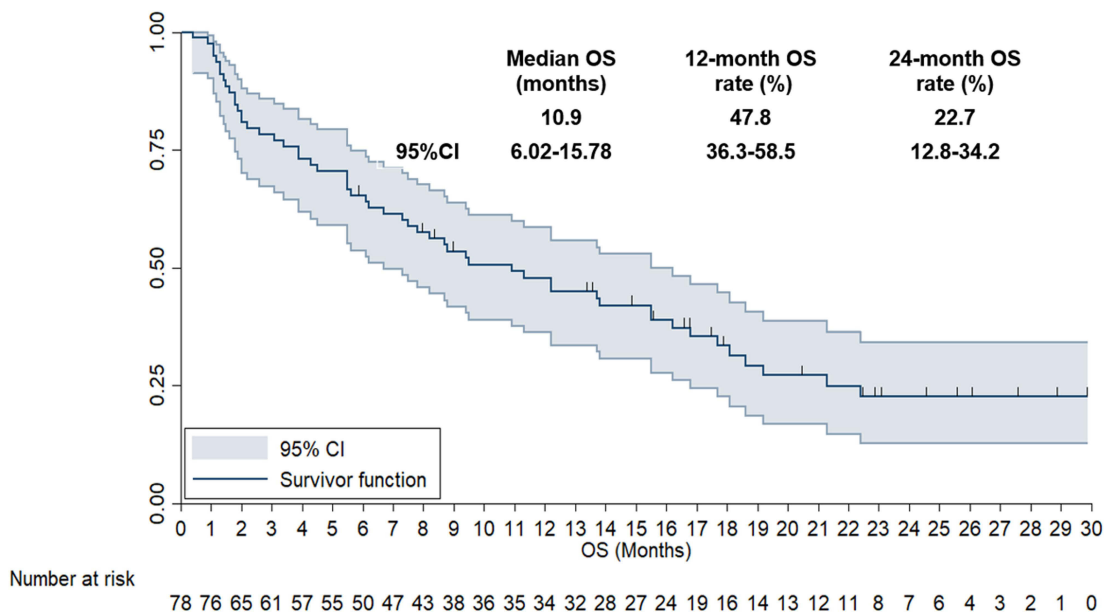

Figure 6 Overall survival of the 78 elderly patients with metastatic ESCC who received PD-1 blockades single agent.

median OS of the 78 elderly patients with metastatic ESCC who received PD-1 blockades was 10.9 months (95% CI: 6.02–15.78). And the 12-month and 24-month OS rate was 47.8% (95% CI: 36.3–58.5%) and 22.7% (95% CI: 12.8–34.2%), respectively. Besides, a total of 7 elderly patients obtained a durable OS benefit of over two years.

Additionally, the relationship between OS and subgroups of baseline characteristics was analyzed. The outcomes including median OS and 95% CI were presented in Table 2. Interestingly, it seemed that almost all the baseline characteristic subgroups might benefit from the PD-1 blockade monotherapy and demonstrated similar OS across the subgroups. Noteworthily, ECOG performance status score and number of metastatic lesions subgroups exhibited a dramatically different OS in the univariate analysis, highlighting that patients with ECOG performance status 0–1 score were associated with longer OS than those with 2 score (median OS: 12.2 vs 8.2 months, P = 0.014), patients with ≤3 metastatic lesions conferred a better OS than those with >3 metastatic lesions (median OS: 12.2 vs 7.8 months, P = 0.012). Interestingly, it should be noted that patients with positive PD-L1 expression had a trend for superior OS than the other, even the difference was not statistically significant (P = 0.067). As a result, to adjust the potential confounding factors, Cox multivariate analysis incorporated ECOG performance status and number of metastatic lesions and PD-L1 expression status, as detailed in Table 2. After multivariate adjustment, both ECOG performance status score (HR = 0.67, P = 0.021) and number of metastatic lesions (HR = 0.64, P = 0.019) remained statistically significant, suggesting that ECOG performance status and number of metastatic lesions served as independent factors to predict OS for elderly patients with metastatic ESCC underwent PD-1 blockade monotherapy. Additionally, PD-L1 expression status showed no significant association with OS after multivariate adjustment (HR = 0.86, P = 0.118).

Safety Profile of the 78 Elderly Patients with Metastatic ESCC

As described previously, comprehensive records of all adverse reactions experienced of the 78 elderly patients with metastatic ESCC during PD-1 blockade treatment were meticulously and retrospectively gathered. The highest levels of

Table 2 Association Analysis Between OS of the 78 Elderly Patients with Metastatic ESCC and Baseline Characteristic Subgroups in Univariate Analysis and Multivariate Cox Analysis

Baseline Characteristics	Median OS (95% CI)	P (univariate analysis)	Multivariate Analysis	
			HR (95% CI)	P
Age				
<73	12.2 (7.89–16.51)	0.315		
≥73	9.4 (6.78–12.02)			
Gender				
Male	9.4 (6.23–12.57)	0.258		
Female	12.2 (8.18–16.22)			
ECOG performance status score				
0–1	12.2 (7.92–16.48)	0.014	0.67 (0.41–0.91)	0.021
2	8.2 (5.87–10.53)			
Pathological staging				
IIIb	12.2 (9.33–15.07)	0.552		
IV	10.9 (7.79–14.01)			
Previous surgical treatment				
Yes	10.9 (7.34–14.46)	0.627		
No	9.5 (7.13–11.87)			
Lines of PD-1 blockades monotherapy				
Second line	11.3 (7.79–14.81)	0.418		
Third line or more line	9.4 (7.24–11.56)			
Combination with radiotherapy				
Yes	11.3 (8.12–14.48)	0.537		
No	10.9 (7.34–14.46)			

(Continued)

Table 2 (Continued).

Baseline Characteristics	Median OS (95% CI)	P (univariate analysis)	Multivariate Analysis	
			HR (95% CI)	P
Previous immunotherapy-related treatment				
Yes	9.4 (7.08–11.72)	0.429		
No	11.3 (8.31–14.29)			
Distant metastasis				
Yes	9.5 (7.11–11.89)	0.318		
No	12.2 (8.67–15.73)			
Number of metastatic lesions				
≤3	12.2 (9.08–15.32)	0.012	0.64 (0.38–0.88)	0.019
>3	7.8 (5.11–10.49)			
PD-L1 expression status				
Positive	12.2 (9.32–15.08)	0.067	0.86 (0.68–1.09)	0.118
Other	8.8 (6.34–11.26)			
PD-1 blockades				
Camrelizumab	9.4 (7.24–11.56)	0.378		
Tislelizumab	10.9 (8.11–13.69)			
Sintilimab	8.8 (6.04–11.56)			
Pembrolizumab	12.2 (9.24–15.16)			
Nivolumab	NA (NA)			

Abbreviations: OS, overall survival; ESCC, esophageal squamous cell carcinoma; ECOG: Eastern Cooperative Oncology Group; PD-1, Programmed death ligand 1; CI, confidence interval; HR, hazard ratio; NA, not available.

toxicity were documented and subsequently analyzed in detail, as presented in Table 3. A total of 61 patients with metastatic ESCC were detected of adverse reactions regardless of grade (78.2%). Among whom, 16 patients experienced grade ≥3 adverse reactions (20.5%). Regrettably, one male patient died from PD-1 blockade-related liver failure after two weeks of camrelizumab treatment and one female patient died from pneumonitis after one month of Tislelizumab therapy, which was deemed as grade 5 adverse reaction (2.6%).

Table 3 Tolerability of the 78 Elderly Patients with Metastatic ESCC Who Received PD-1 Blockades Monotherapy

Adverse Reactions	Total (N, %)	Grade 1–2 (N, %)	Grade ≥3 (N, %)
Adverse reactions	61 (78.2)		16 (20.5)
Fatigue	25 (32.1)	20 (25.7)	5 (6.4)
Gastrointestinal reaction	19 (24.4)	16 (20.6)	3 (3.8)
Diarrhea	15 (19.2)	13 (16.6)	2 (2.6)
Anemia	14 (17.9)	11 (14.1)	3 (3.8)
Rash	13 (16.7)	11 (14.1)	2 (2.6)
RCCEP	11 (14.1)	9 (11.5)	2 (2.6)
Hypothyroidism	10 (12.8)	9 (11.5)	1 (2.6)
Abnormal liver function	9 (11.5)	3 (3.8)	6 (7.7)
Nausea and vomiting	9 (11.5)	7 (8.9)	2 (2.6)
Pneumonitis	8 (10.3)	4 (5.1)	4 (5.1)
Esophagitis	6 (7.7)	6 (7.7)	0 (0.0)
Stomatitis	3 (3.8)	3 (3.8)	0 (0.0)

Abbreviations: ESCC: esophageal squamous cell carcinoma; RCCEP: Reactive cutaneous capillary endothelial proliferation; PD-1, programmed cell death protein 1.

The common drug-related adverse reactions were fatigue (32.1%), gastrointestinal reaction (24.4%), diarrhea (19.2%), anemia (17.9%), rash (16.7%), reactive cutaneous capillary endothelial proliferation (RCCEP, 14.1%), hypothyroidism (12.8%), abnormal liver function (11.5%), nausea and vomiting (11.5%), pneumonitis (10.3%), esophagitis (7.7%) and stomatitis (3.8%). Most adverse reactions were moderate of grade 1–2. Furthermore, grade ≥3 adverse reactions were found in fatigue (6.4%), gastrointestinal reaction (3.8%), diarrhea (2.6%), anemia (3.8%), rash (2.6%), RCCEP (2.6%), abnormal liver function (7.7%), nausea and vomiting (2.6%) and pneumonitis (5.1%), respectively.

Discussion

To the best of our knowledge, the present study represented the first retrospective analysis that shed light on real-world evidence concerning the feasibility and tolerability of PD-1 blockades among elderly patients with ESCC, offering valuable guidance and safety data regarding the administration of PD-1 blockade monotherapy for elderly patients with previously treated metastatic ESCC in clinical practice.

In this study, we defined those who were ≥65 years old as elderly patients in ESCC, which was in line with the previous original study regarding concurrent chemoradiotherapy with capecitabine and cisplatin for elderly patients with locally advanced ESCC.[30] Additionally, RAMONA trial that investigated nivolumab and ipilimumab as 2nd line therapy in elderly patients with advanced ESCC also recruited subjects who were ≥65 years old and this trial was still ongoing.[23] Since the definition of elderly patients remained a subject of debate, it was reasonable that our study adopted elderly patients as individuals aged over 65 years, aligning with the criteria set forth by the World Health Organization (WHO).[31] Incidence of EC in China demonstrated a consistent year-over-year increase with the estimated number of new cases reaching nearly 324,000 presently.[3] Within this trend, the number of elderly EC patients also showed a significant rise annually. Regrettably, this increase in age was often accompanied by a decrease in body fat percentage, a decline in liver and kidney function and deteriorating physical conditions.[32] Especially, some symptoms specific to elderly patients with advanced EC, such as dysphagia, malnutrition and sarcopenia, might also compromise the absorption, metabolism and excretion of PD-1/PD-L1 blockades clinically.[33] Therefore, elderly patients were consistently chosen with great caution, and age restrictions might be the predominant exclusion criteria in many clinical trials.[34] Furthermore, a previous survey investigated the clinical trials of cancer drug registration and highlighted a significant discrepancy between the proportion of elderly patients in the general population and the proportion in clinical trials: 67% vs 35%, which was a substantial underrepresentation, especially among patients aged 75 and above.[35] As a result, there was an urgent demand for effective and well-tolerated therapeutic regimens to augment the survival of considerable elderly patients with metastatic ESCC both in clinical trials and clinical practice.

All the 78 patients included in our study were elderly patients with a median age of 73 years old (range from 65 to 87 years) and the common metastatic ESCC clinically, which was consistent with the subjects included in the previous study of elderly ESCC.[36] Additionally, out of the total cohort, 43 patients underwent PD-1 blockade treatment as second-line therapy, while the remaining 35 patients received PD-1 blockades as third-line treatment or beyond. It should be noted that certain PD-1 blockades were approved for usage as second-line monotherapy for patients with metastatic ESCC in China.[37] Therefore, the utilization of PD-1 blockades in our study was considered both rational and ethical. Overall, five PD-1 blockades single agent among the 78 elderly patients with metastatic ESCC yielded an ORR and DCR of 23.1% and 56.4%, respectively, in clinical practice, which was basically consistent with the ORR and DCR of the phase III clinical trials (Keynote 181, ATTRACTION-3 and RATIONALE302) regarding PD-1 blockades monotherapy as second-line therapy for advanced ESCC (ranging from 19% to 20.3%).[17,26,27] It seemed that elderly patients with metastatic ESCC might also benefit from PD-1 blockade monotherapy.[12] Noteworthily, of the 18 patients with PR, the response seemed to be durable and efficacious with the median DOR of 8.8 months, which was in concert with the previous study regarding Nivolumab for ESCC among Korea population who achieved a median DOR of 6.5 months.[38] These findings provided further evidence that the response of immunotherapy was long-lasting and durable for responders, even among elderly patients, which was different from that of chemotherapy.[39]

Additionally, it should be noted that the median PFS of PD-1 blockades among the 78 elderly patients was 3.1 months, longer than the median PFS of the phase III clinical trials (Keynote 181, ESCORT, ATTRACTION-3 and RATIONALE302) numerically (median PFS of PD-1 blockades cohorts ranged from 1.6 to 2.5 months).[17,22,26,27] We

speculated that the discrepancy might lie in two aspects: firstly, iRECIST criteria was adopted in our study to assess the tumor response, while all the four phase III clinical trials employed RECIST v1.1 to evaluate the therapeutic response, which might contribute to the difference in median PFS across the studies to some extent. A previous meta-analysis highlighted that the application of iRECIST had a minor influence on the survival endpoint of PFS than RECIST v1.1 with a pooled difference of approximately 0.46 months.[40] Secondly, our study was designed as a retrospective trial, the selection bias of the 78 elderly patients included might be unrepresentative, and the non-randomized screening might exaggerate the therapeutic outcomes to some extent. This situation was reflected in the fact that elderly patients who could receive PD-1 blockade treatment as subsequent-line therapy had been selected after the front-line administration, and only those with better physical performance status and enough social support could be treated with corresponding therapy in clinical practice,[41] which might result in the superior median PFS in our study to a certain degree. Interestingly, we also noticed that another retrospective study explored gefitinib in elderly patients with non-small cell lung cancer and yielded superior therapeutic outcomes than that in clinical trials numerically.[42]

As we mentioned in the methods part, the primary endpoint of this study was OS, which was the most objective and reliable endpoint in clinical practice. We observed that another retrospective study also used OS as the primary endpoint. After a median follow-up of 10.6 months, PD-1 blockades single agent yielded a median OS of 10.9 months (95% CI: 6.02–15.78) among the 78 elderly patients with metastatic ESCC clinically, which was comparable or slightly superior compared with the median OS of the phase III clinical trials (Keynote 181, ESCORT, ATTRACTION-3 and RATIONALE302) numerically (median OS of PD-1 blockades cohorts ranged from 8.3 to 10.9 months).[17,22,26,27] Even 44.9% elderly patients received PD-1 blockades as the third line or beyond in our study, the overall median OS reached 10.9 months, indicating that elderly patients with metastatic ESCC might benefit from PD-1 blockades enduringly. Additionally, we speculated that the possible explanation regarding the superior OS benefit in our study might be attributed to the fact that many PD-1/PD-L1 blockades and antiangiogenic targeted drugs were licensed in China since 2018.[43] Therefore, another immunotherapy or targeted drugs were still available for the elderly patients with metastatic ESCC when they progressed after PD-1 blockade administration without deteriorating their physical status due to the friendly safety profile of PD-1 blockades, thus providing the patients with survival benefits consecutively. Interestingly, we also performed the correlation analysis between OS and the baseline characteristic subgroups, it seemed that elderly patients with metastatic ESCC might potentially derive uniform benefits from PD-1 blockades monotherapy irrespective of various baseline characteristic subgroups, highlighting that the therapeutic activity of PD-1 blockades remained consistent and equitable across different baseline characteristic subgroups.[44] However, it should be noted that ECOG performance status and number of metastatic lesions were still significantly associated with OS after multivariate adjustment and might be prognostic indicators for OS, which was in concert with the previous retrospective study.[29] In our opinion, this finding should be interpreted with caution, since patients with ECOG performance status of 2 score and metastatic lesions of >3 trended to have an inferior prognosis regardless of the therapeutic regimens.[12,45] Additionally, patients with positive PD-L1 expression seemed to confer better OS than the other patients in univariate analysis (median OS: 12.2 vs 8.8 months, P = 0.067), which was consistent with the previous retrospective study and Keynote-181 trial found that positive PD-L1 expression predicted superior prognosis of patients with ESCC when treated with PD-1 blockades.[26,38] However, the predictive significance of PD-L1 expression status disappeared after multivariate adjustment. We speculated the reason might be the fact that considerable elderly patients (35.9%) were not available for the PD-L1 expression data in this retrospective study, and the treatment that integrated patients with PD-L1 negative and NA as one group might compromise the predictive significance of PD-L1 expression in the association analysis. Another interesting finding of our study was that the 18 patients who had been treated with immunotherapy-related therapy previously might benefit from PD-1 blockade monotherapy and no significant association was found in OS analysis when compared with those failed to receive immunotherapy-related regimens previously (median OS: 9.4 vs 11.3 months, P = 0.429). It seemed that PD-1 blockades rechallenge in metastatic ESCC was feasible; however, this finding should be further explored and subsequently evaluated in larger prospective clinical trials.

Besides, safety profile of PD-1 blockades in this study demonstrated that the incidence of adverse reactions with any grade was 78.2% and incidence of grade ≥3 adverse reactions was 20.5% among the 78 elderly patients with

metastatic ESCC, which was slightly higher than the incidence of adverse reactions in the phase III clinical trials (Keynote 181, ESCORT, ATTRACTION-3 and RATIONALE302) numerically (incidence of any grade adverse reactions ranged from 64.3% to 94%, incidence of grade ≥3 adverse reactions ranged from 18% to 21%), even the sample size was small and tolerability data was collected retrospectively.[17,22,26,27] It seemed that elderly patients might be more susceptible to the toxicity of systemic treatment due to the chronic disease and different comorbidities that compromised the patients' tolerability and functional reserve.[14] Previous studies also found that elderly patients might experience higher incidence of high-grade pulmonary toxicity when receiving intensive treatment.[46] We noticed that pembrolizumab and nivolumab monotherapy exhibited a ≥3 adverse reactions of 18.2% and 18% in Keynote 181 and Attraction-3 phase III clinical trials, respectively.[26,27] It seemed that the severe adverse actions in our study were higher than that in other studies. We speculated that this discrepancy might be attributed to the elderly patients included in our study, a previous study also found that elderly patients tended to experience more severe adverse actions than young patients.[47] Therefore, PD-1 blockades might be one of the most promising therapeutic options for elderly patients with metastatic ESCC owing to their encouraging efficacy and acceptable toxicity. Nevertheless, it should be crucial to give enough consideration to certain immunotherapy-related adverse reactions among elderly patients undergoing PD-1 blockade monotherapy.[48] We detected two patients who tragically passed away from liver failure and pneumonitis attributed to therapy of camrelizumab and Tislelizumab, respectively. This underscored the need for more proactive measures to manage the risk of severe pneumonitis and abnormal liver function when administered PD-1 blockades to elderly patients. Additionally, we also found that 6 out of 9 patients with abnormal liver function were deemed as grade ≥3 (7.7%). This incidence was slightly higher than what was presented in the RATIONALE-302 (<3%).[17] Similarly, pneumonitis with grade ≥3 was also more profound in our study. We speculated that this might be attributed to the fact that elderly patients usually had impaired liver and kidney function due to a higher prevalence of underlying comorbidities. Consequently, this might exacerbate liver function abnormalities following the administration of PD-1 blockade monotherapy. As a result, it was imperative to prioritize vigilance over pneumonitis and liver function when administering PD-1 blockade monotherapy to elderly patients in clinical practice. Still and all, the safety profile of elderly patients with metastatic ESCC who received PD-1 blockade monotherapy was basically acceptable and controllable.

Objectively speaking, we acknowledged several limitations in our study, primarily due to its retrospective design and relatively small sample size. These limitations compromised the statistical power of our analysis, particularly in exploratory subgroup analyses aimed at identifying potential prognostic factors for OS. As a result, we failed to apply multiple testing corrections, such as the Bonferroni correction, as these adjustments might further reduce statistical power, increasing the likelihood of Type II errors. Additionally, we thought the inherent bias in single-center and retrospective studies might exist in our study; this bias occurred when the selection of participants was not random or representative of the targeted population, which might result in an over- or under-representation of certain groups, potentially compromising the study results. And the potential for selection bias due to the retrospective design and the consecutive enrollment of patients who met the eligibility criteria might result in a study population with relatively better health status compared to the broader elderly metastatic ESCC population. Acknowledging this limitation, we recommended future prospective studies with broader inclusion criteria to ensure a more representative sample and validated the findings. Besides, our study did not include a control group of elderly patients who did not receive PD-1 blockade treatment, which might compromise the findings of our study in clinical practice. Future studies that included a comparative analysis between PD-1 blockades treated and untreated groups to comprehensively assess the impact of PD-1 blockades on survival outcomes in elderly patients were needed. Finally, five PD-1 blockades for elderly patients might introduce heterogeneity and diversity in terms of efficacy and toxicity. In a word, our findings should be interpreted with caution.

Conclusion

Collectively, our study provided real-world evidence regarding the effectiveness and tolerability of PD-1 blockade monotherapy for elderly patients with ESCC, suggesting PD-1 blockades might be a viable therapeutic option for elderly patients with previously treated metastatic ESCC. Identification of ECOG performance status and number of

metastatic lesions as significant prognostic factors provided valuable insights for personalized patient management. These findings suggested that patients with lower ECOG performance status scores and fewer metastatic sites might derive greater benefit from PD-1 blockades. Future research should focus on validating these factors in larger, prospective cohorts and exploring additional biomarkers that might further refine prognostic assessments. Furthermore, these results underscored the need for tailored treatment approaches based on individual patient characteristics, potentially guiding clinical decision-making in the management of elderly patients with metastatic ESCC.

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