Original Article

Efficacy and safety of combined treatment with pembrolizumab in patients with locally advanced or metastatic esophageal squamous cell carcinoma in the real world

Pei Zhang[1#], Xiaobin Hou[2#], Boning Cai[1], Wei Yu[1], Jing Chen[1], Xiang Huang[1], Ye Li[1], Mingyue Zeng[1], Zhipeng Ren[2], Emmanuel Gabriel[3], Baolin Qu[1], Fang Liu[1]

[1]Department of Radiotherapy, The First Medical Center of Chinese PLA General Hospital, Beijing, China; [2]Department of Thoracic Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing, China; [3]Department of Surgery, Division of Surgical Oncology, Mayo Clinic, Jacksonville, FL, USA

Contributions: (I) Conception and design: F Liu, B Qu, X Hou, P Zhang; (II) Administrative support: X Hou, F Liu, B Qu; (III) Provision of study materials or patients: F Liu, X Hou; (IV) Collection and assembly of data: P Zhang, B Cai, W Yu, J Chen, X Huang, Y Li, M Zeng, Z Ren; (V) Data analysis and interpretation: P Zhang, F Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Fang Liu, MD; Baolin Qu. Department of Radiotherapy, The First Medical Center of Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. Email: liufangfsq@163.com; qubl6212@sina.com.

Background: Treatments for patients with advanced esophageal cancer are still limited. Pembrolizumab has demonstrated antitumor activity in patients with advanced esophageal cancer in previous studies. Few studies have assessed safety and efficacy in routine clinical practice. We investigated the real-world outcomes of pembrolizumab for patients with advanced esophageal cancer.

Methods: This retrospective, observational study collected 57 advanced esophageal squamous cell carcinoma (ESCC) patients from October 1, 2019 to October 1, 2021, 57 who received different patterns of treatments according to the staging were collected. Briefly, patients diagnosed with locally advanced and surgically resectable ESCC received neoadjuvant therapy followed by surgery. For patients with locally advanced, unresectable ESCC, the treatment regimen including chemoradiotherapy combined with pembrolizumab was performed. Patients with metastatic ESCC or those not suitable for radiotherapy received pembrolizumab plus chemotherapy. Safety was assessed in all treated patients. The objective response rate (ORR) was used to evaluate the efficacy.

Results: The ORR was 74.1% (40/54) among all patients. The most common adverse events (AEs) were leukopenia (36.8%, 21/57), nausea (28.1%, 16/57), and thrombocytopenia (14%, 8/57). Grade III and higher AEs were observed in 9 of the 57 patients (15.8%).

Conclusions: For patients with advanced ESCC, combined treatment with pembrolizumab was effective and safe. Multicenter studies should be carried out for further confirmation.

Keywords: Esophageal cancer; pembrolizumab; real-world analysis

Submitted Apr 01, 2022. Accepted for publication Jun 20, 2022.
doi: 10.21037/atm-22-2779
View this article at: https://dx.doi.org/10.21037/atm-22-2779

Introduction

Worldwide, esophageal cancer is the ninth most common cancer and the sixth most frequent cause of cancer-related death (1). Esophageal squamous cell carcinoma (ESCC) accounts for almost 90% of cases in the Asian population (2). In China, ESCC is the fourth most common cancer and more than half of the global cases of ESCC occur in China (3). However, there are limited options for the

treatment of patients with locally advanced or metastatic esophageal cancer. Furthermore, the prognosis is still poor in patients with metastatic esophageal cancer, with 5-year survival rates of less than 5% (4).

Recently, accumulating data showed promising efficacy and safety of anti-PD-1 antibodies in patients with advanced or metastatic ESCC (5-9). In the first-line treatment of patients with advanced or metastatic disease, the phase 3 KEYNOTE-590 study (5,10) showed an improvement in overall survival (OS) in patients with ESCC and a PD-L1 combined positive score (CPS) of 10 or more [median 13.9 (95% CI: 11.1–17.7) *vs.* 8.8 (95% CI: 7.8–10.5) months; hazard ratio (HR): 0.57 (95% CI: 0.43–0.75); P<0.0001]. Although neoadjuvant chemoradiotherapy before surgery has been strongly recommended for resectable ESCC patients (11,12), the 5-year OS rate was about 47%, and 49% of patients developed either locoregional progression or distant progression (12). The PLACE-1 study investigated the safety and activity of preoperative pembrolizumab combined with concurrent chemoradiotherapy (PPCT) in patients with resectable ESCC (6). It showed that PPCT was safe, and induced a pathologic complete response (pCR) in 55.6% of resected tumors. However, further phase 3 multicenter studies are required for confirmation.

Taken together, PD-1 inhibitors have demonstrated promising safety and efficacy as therapies for patients with different stages of ESCC. However, data are currently lacking on the real-world treatment patterns in patients with locally advanced or metastatic ESCC in routine clinical practice. This study was conducted to evaluate the safety and efficacy of combined treatment with pembrolizumab therapy in a diverse population of patients with different ESCC clinical stages in a high-incidence, real-world setting. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2779/rc).

Methods

Study design

This single-center, observational, retrospective, single-arm study was performed in the First Medical Center of Chinese PLA General Hospital, and registered consecutive patients with previously untreated, locally advanced, or metastatic ESCC from October 1, 2019 to October 1, 2021 were included. Staging was based on the American Joint Committee on Cancer (AJCC) Staging Manual, version 8. Patients were categorized by different clinical stages with different treatment patterns, which were at the clinician's discretion. The objective response rate (ORR; defined as the percentage of patients whose best response was complete or partial response) was reported. Treatment-related adverse events (AEs) of any grade were closely monitored and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Chinese PLA General Hospital (No. S2021-460-03) and the informed consent of all patients participating in this study was obtained.

Therapeutic regimen

Neoadjuvant therapy plus surgery

Patients diagnosed with locally advanced (T2–4a with or without lymph node involvement and had no evidence of metastatic disease) and surgically resectable ESCC received neoadjuvant therapy followed by surgery. Patients received chemotherapy (platinum and nab-paclitaxel) plus pembrolizumab once every 3 weeks for 2 or 3 cycles. After neoadjuvant therapy, physical examination, routine laboratory tests, echocardiography, pulmonary function tests, and contrast-enhanced chest computed tomography (CT) were performed. Surgery was performed within 4 to 6 weeks after completion of neoadjuvant therapy.

Chemoradiotherapy plus pembrolizumab

For patients with locally advanced, unresectable ESCC, the treatment regimen including chemoradiotherapy combined with pembrolizumab was used. In addition, patients with metastatic disease of the supraclavicular lymph nodes (SLNs) were also included. Platinum and nab-paclitaxel combined with pembrolizumab were administered once every 3 weeks for 2 cycles. Subsequently, patients received concurrent chemoradiotherapy. Radiotherapy was delivered by means of external-beam radiation, which started within 1 week of chemotherapy. A total radiation dose of 54 Gy was given by 30 fractions, with 5 fractions per week and 1.8 Gy each fraction. Meanwhile, patients received a boost of 9 Gy to the tumor sites, for a total dose of 64 Gy delivered in 30 fractions. Treatment continued until radiographic progression was confirmed, or until unacceptable toxicity or completion of 35 cycles of pembrolizumab (approximately 2 years).

Table 1 Baseline demographics and clinical characteristics (n=57)

Characteristics	N (%)
Age (years)	
Median	61
Range	44–74
Sex	
Male	45 (78.9)
Female	12 (21.1)
Tumor location	
Proximal third	19 (33.3)
Middle third	27 (47.4)
Distal third	11 (19.3)
Clinical stage	
II	12 (21.1)
III	19 (33.3)
IV	26 (45.6)
Lesions for evaluation	
Non-measurable lesions	21 (36.8)
Measurable lesions	33 (57.9)
Not evaluable	3 (5.3)
Subgroups	
Neoadjuvant therapy plus surgery	20 (35.1)
Chemoradiotherapy plus pembrolizumab	22 (38.6)
Chemotherapy plus pembrolizumab	15 (26.3)

Chemotherapy plus pembrolizumab

Patients with metastatic ESCC or those not suitable for radiotherapy received pembrolizumab plus chemotherapy (platinum plus nab-paclitaxel) once every 3 weeks for 4 cycles. Treatment continued until radiographic progression was confirmed, or until unacceptable toxicity or completion of 35 cycles of pembrolizumab (approximately 2 years).

Response evaluation

Radiological responses were recorded according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. For patients without measurable disease, we used the RECIST system to assess the primary esophageal lesions by measuring the longest tumor radius. Measurement was performed on contrast-enhanced CT scans. The target area was measured at a site with different contrast enhancement and thickness compared to the normal esophageal wall. Tumor radius were measured using the horizontal slice at the thickest part. The longest radius was defined as the maximum distance between the inner and outer tumor margins, and was used to evaluate responses according to the RECIST system. All the measurements were further reviewed by the superior physician in routine clinical practice.

Statistical analysis

As a single-center, real-world study, 57 patients met study criteria and analyzed. Continuous variables were recorded as median with range or mean with standard deviation (SD). Categorical variables were presented as frequency with percentage. All data were processed and analyzed using the Statistical Package for the Social Sciences software package version 19.0 (Armonk, NY, USA).

Results

Baseline demographics and characteristics

From 1 October, 2019 to 1 October, 2021, 57 patients with ESCC were enrolled (*Table 1*). Most patients were male (45/57, 78.9%), and 12 patients were female. The median age was 61 (range, 44–74) years. Most tumors were located in the middle third of the esophagus (27/57, 47.4%). Clinical stage IV ESCC accounted for about half of these patients (26/57, 45.6%). For primary esophageal tumors and lymph nodes of insufficient size, lesions for evaluation were classified as non-measurable. In this study, more than half of the patients (33/57, 57.9%) had non-measurable lesions.

Treatment patterns

Patients received different treatment patterns according to clinical staging (*Figure 1*). In this study, 20 patients received neoadjuvant therapy followed by surgery, and 38.6% of these patients received chemoradiotherapy combined with pembrolizumab. These patients were referred as locally advanced, unresectable cases. In addition, patients with SLN metastasis (M1) were also included, as radiotherapy could be performed to cover that lymph node basin. The other 15 patients with metastatic disease or not suitable for radiotherapy received chemotherapy plus pembrolizumab.

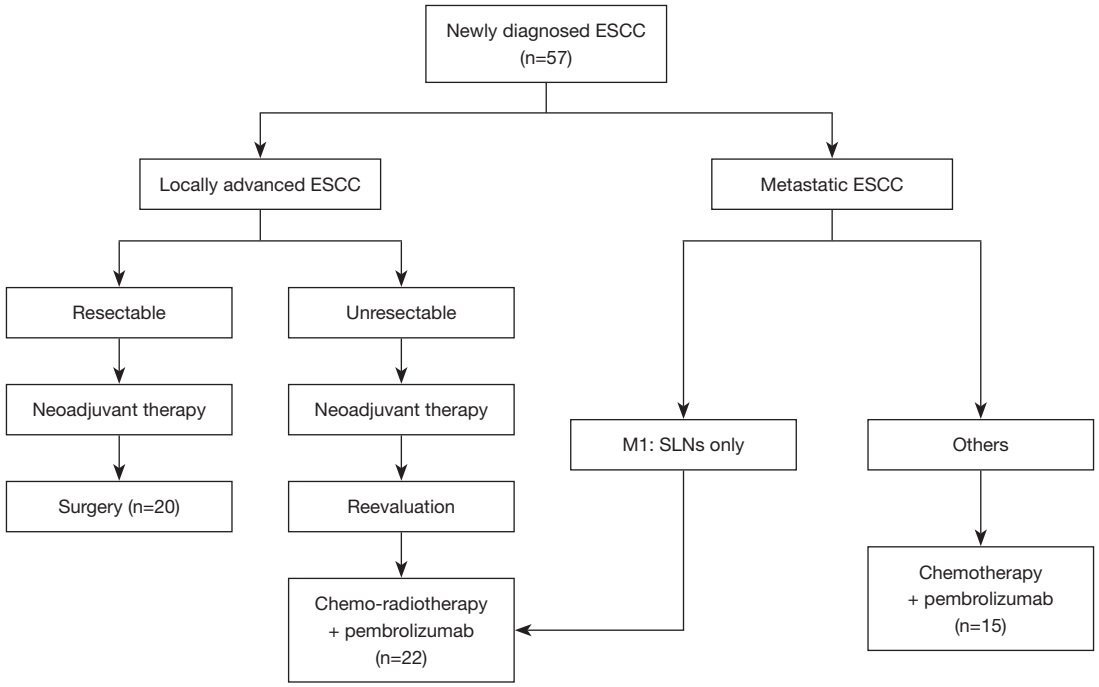

Figure 1 Treatment patterns of patients with different staging. ESCC, esophageal squamous cell carcinoma; SLNs, supraclavicular lymph nodes.

Table 2 Summary of treatment-related AEs

Toxicity	All patients (n=57)	
	Any	Grade ≥ III
All events, n (%)	39 (68.4)	9 (15.8)
White blood cell count decreased, n (%)	21 (36.8)	10 (17.5)
Nausea, n (%)	16 (28.1)	0
Platelet count decreased, n (%)	8 (14.0)	4 (7.0)
Diarrhea, n (%)	2 (3.5)	0
Increased blood creatinine, n (%)	2 (3.5)	0
Increased aspartate aminotransferase, n (%)	3 (5.3)	3 (5.3)
Rash, n (%)	2 (3.5)	0
Pneumonitis, n (%)	1 (1.7)	0

AEs, adverse events.

Safety and feasibility

During the combined treatment period, 39 (68.4%) patients developed treatment-related AEs of any grade (*Table 2*). The most common AEs were leukopenia (36.8%, 21/57), nausea (28.1%, 16/57), and thrombocytopenia (14%, 8/57). Most AEs were grade I or II. In 9 of the 57 patients (15.8%), grade III and higher AEs were observed. The most frequent grade III AE was leukopenia, which was improved after granulocyte colony-stimulating factor treatment.

Short-term efficacy

In this study, 57 patients were included, and 3 patients did not receive response evaluation for loss of follow-up. According to the radiological evaluation methods mentioned above, the ORR was 74.1% (40/54) among all patients (*Figure 2*). For patients who received neoadjuvant therapy plus surgery, the ORR was 68.4% (13/19; *Table 3*). R0 resection was achieved for all patients who underwent surgery. Two patients (2/20, 10.0%) had pCR in both the primary tumor and lymph nodes. One patient showed complete response at the primary tumor site, though had residual cancer cells in resected lymph nodes. After neoadjuvant therapy, 3 patients who were classified as unresectable were reevaluated as resectable and received surgery. Seventeen patients (17/21, 81%) were downstaged after neoadjuvant therapy. For patients who received chemoradiotherapy plus pembrolizumab, the ORR was 76.2% (16/21; *Table 3*), and 78.6% (11/14) of patients who

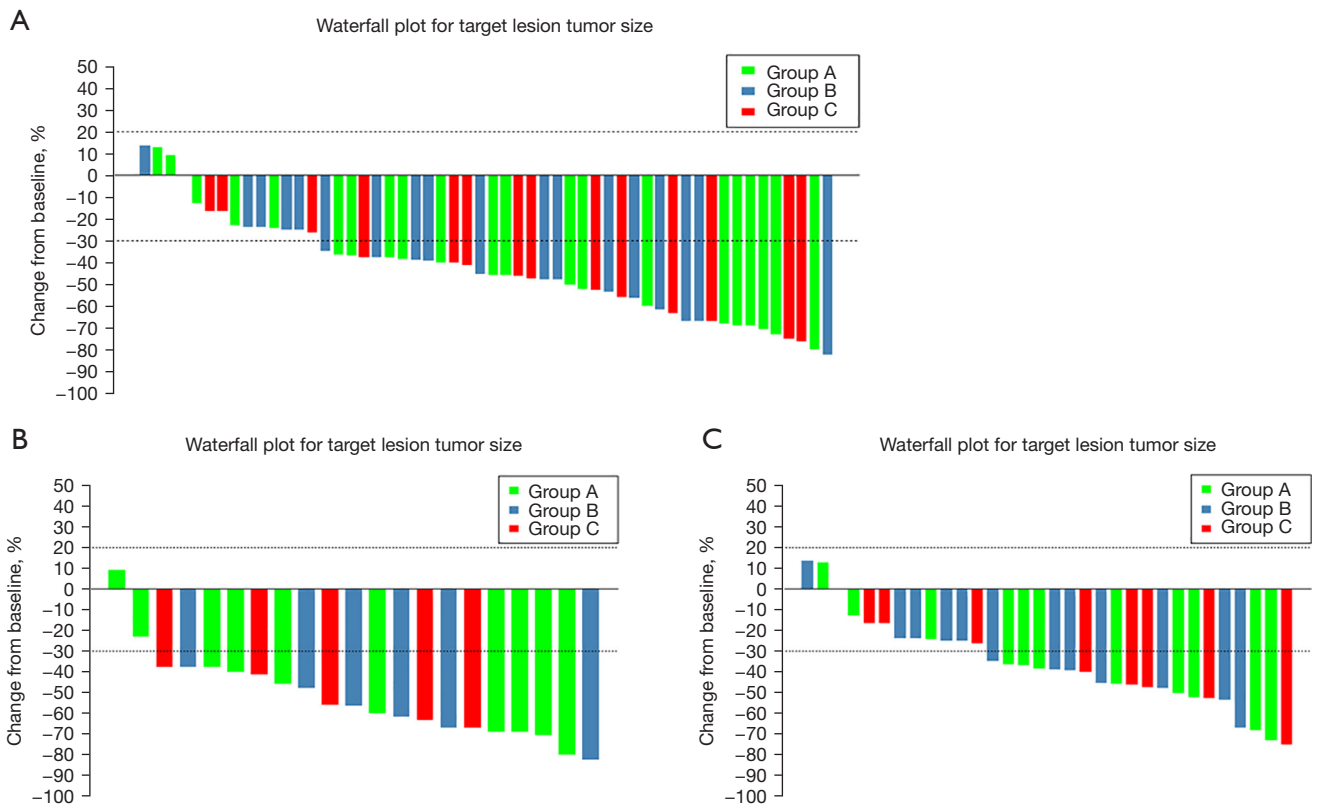

Figure 2 Changes of target lesion during treatment. (A) A waterfall plot of the maximum change in tumor size of all patients. (B) Patients with measurable disease were evaluated based on the RECIST system. (C) Patients with non-measurable disease were evaluated according to the methods mentioned in this study. Group A: chemoradiotherapy plus pembrolizumab; group B: neoadjuvant therapy; group C: chemotherapy plus pembrolizumab. RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3 Antitumor activity

Overall response rate	Group A (n=21)	Group B (n=19)	Group C (n=14)
Objective response, n (%)	16 (76.2)	13 (68.4)	11 (78.6)
Best overall response, n (%)			
Complete response	0	0	0
Partial response	16 (76.2)	13 (68.4)	11 (78.6)
Stable disease	5 (23.8)	6 (31.6)	3 (21.4)
Progressive disease	0	0	0

Group A: chemoradiotherapy plus pembrolizumab; group B: neoadjuvant therapy; group C: chemotherapy plus pembrolizumab.

received chemotherapy plus pembrolizumab achieved an objective response (*Table 3*). The median progression-free survival (PFS) and OS were not analyzed in this study as the follow-up time varied significantly.

Discussion

This study used data from the real world to analyze the safety and efficacy of combination therapy with pembrolizumab in routine clinical practice in China. Among the patients diagnosed with locally advanced or metastatic ESCC, 3 different treatment patterns were administered. The results demonstrated that combination treatment was associated with relatively manageable treatment-related AEs, and showed a satisfactory ORR.

For resectable ESCC patients, preoperative chemoradiotherapy followed by surgery is strongly recommended according to the NEOCRTEC5010 trial (11,13), CROSS trial (14), and FFCD-9901 trial (15). However, the disease progression rate was about 49%, and 39% of patients developed distant metastasis. Therefore, novel strategies of systemic therapy seems to be necessary. Furthermore, concurrent chemoradiotherapy is not commonly achieved in clinical practice in China.

Checkpoint inhibitors have shown good safety profiles and antitumor activity in ESCC in several clinical trials. Recently, several studies investigated the efficacy of checkpoint inhibitors used in neoadjuvant therapy. In the PALACE-1 trial (6), treatment with pembrolizumab combined with concurrent chemoradiotherapy was administered. Combination treatment showed a higher pCR rate, and grade III and higher AEs occurred at rate of about 65% (13/20). In our study, ORR was achieved for 16 of the 20 patients (80%) who received neoadjuvant therapy. However, only 2 patients (2/20, 10%) had pCR in both primary tumors and lymph nodes. The pCR rate was lower compared with reported studies. Previous research showed that a higher pCR rate after neoadjuvant therapy was related to better survival (16,17). However, with regard to combination with checkpoint inhibitors, further studies should be performed to confirm the rationality of pCR chosen as the end point. Furthermore, the safety of the combination of checkpoint inhibitors and radiotherapy should be a main priority. High-grade AEs, especially pneumonitis, should be investigated in phase 3 trials.

For ESCC patients who are ineligible for curative resection, definitive chemoradiotherapy is recommended as a standard option. The RTOG-8501 trial demonstrated that definitive chemoradiotherapy was superior to radiotherapy alone (18). Recently, the abscopal effect induced by radiotherapy has drawn increased attention. Studies have shown that radiotherapy could exert immunomodulatory effects that may result in antitumor responses, especially when combined with checkpoint inhibitors (19-21). Li and colleagues found that the expression of PD-1 was increased in patients receiving radiation, indicating the potential combination of PD-1 inhibitors and radiation (22). Generally, these studies demonstrate promising results with combination of radiation and PD-1 inhibitors. In this study, pembrolizumab was administered in combination with chemoradiotherapy. In consideration of treatment-related AEs, pembrolizumab was withdrawn when radiotherapy was performed. As a result, this treatment pattern was safe, and 83.3% of patients achieved an objective response. However, the optimal pattern of combination should be further investigated.

In previous study, the phase 3 KEYNOTE-590 trial investigated pembrolizumab in combination with chemotherapy as a first-line treatment in patients with advanced esophageal cancer. The combination pattern showed significant improvements in OS, PFS, and ORRs. In a previous study, we found that nab-paclitaxel was effective in patients with locally advanced ESCC, with mild adverse effects (23). Therefore, different from the chemotherapy regimen of 5-fluorouracil plus cisplatin in the KEYNOTE-590 trial, we used the nab-paclitaxel plus platinum regimen in the current study.

RECIST (version 1.1) (24) is now widely applied for evaluating treatment efficacy in various tumors. However, unlike other solid tumors, primary esophageal tumors are often classified as "non-measurable". In many clinical trials, patients with at least 1 measurable disease are required. However, ESCC patients with only non-measurable disease are often seen. In this study, more than half of the patients (36/57, 63.2%) were found to have non-measurable lesions. In addition, evaluating the effect on primary sites is also important in determining treatment strategies. A retrospective multicenter study (25) measured the longest and shortest tumor diameters on contrast-enhanced CT scans and analyzed the correlations between pathological and survival data in ESCC patients treated with neoadjuvant therapy followed by surgery. The results showed that the RECIST system is proper for assessing pathological response when using the longest radius of the primary tumor. This issue should be evaluated in sufficiently large cohorts.

As a real-world study, several limitations must be acknowledged. The sample size was small, and data were collected from a single center. However, real-world data can provide important insights into routine clinical practice and real-world patient care.

Conclusions

Our real-world analysis demonstrated that pembrolizumab in combination with chemotherapy or radiotherapy in ESCC patients with different clinical stages showed a favorable objective response and safety.

Acknowledgments

The authors would like to offer their sincere thanks to Dr. Runkun Yang from Merck & Co., Inc. Medical Affairs for his scientific comments on this manuscript. The authors appreciate the academic support from the AME Esophageal Cancer Collaborative Group.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the

STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2779/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2779/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2779/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Chinese PLA General Hospital (No. S2021-460-03) and the informed consent of all patients participating in this study was obtained.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424. Erratum in: CA Cancer J Clin 2020;70:313.
2. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. Chin J Cancer 2012;31:281-6.
3. Lin Y, Totsuka Y, He Y, et al. Epidemiology of esophageal cancer in Japan and China. J Epidemiol 2013;23:233-42.
4. Noone AM, Cronin KA, Altekruse SF, et al. Cancer Incidence and Survival Trends by Subtype Using Data from the Surveillance Epidemiology and End Results Program, 1992-2013. Cancer Epidemiol Biomarkers Prev 2017;26:632-41.
5. Kato K, Shah MA, Enzinger P, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced esophageal cancer. Future Oncol 2019;15:1057-66.
6. Li C, Zhao S, Zheng Y, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). Eur J Cancer 2021;144:232-41.
7. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:1506-17.
8. Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): a multicentre, randomised, open-label, phase 3 study. Lancet Oncol 2020;21:832-42.
9. Luo H, Lu J, Bai Y, et al. Effect of Camrelizumab vs Placebo Added to Chemotherapy on Survival and Progression-Free Survival in Patients With Advanced or Metastatic Esophageal Squamous Cell Carcinoma: The ESCORT-1st Randomized Clinical Trial. JAMA 2021;326:916-25.
10. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet 2021;398:759-71.
11. Yang H, Liu H, Chen Y, et al. Neoadjuvant Chemoradiotherapy Followed by Surgery Versus Surgery Alone for Locally Advanced Squamous Cell Carcinoma of the Esophagus (NEOCRTEC5010): A Phase III Multicenter, Randomized, Open-Label Clinical Trial. J Clin Oncol 2018;36:2796-803.
12. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090-8.
13. Yang H, Liu H, Chen Y, et al. Long-term Efficacy of Neoadjuvant Chemoradiotherapy Plus Surgery for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma: The NEOCRTEC5010 Randomized Clinical Trial. JAMA Surg 2021;156:721-9.
14. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or

junctional cancer. N Engl J Med 2012;366:2074-84.
15. Mariette C, Dahan L, Mornex F, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416-22.
16. Berger AC, Farma J, Scott WJ, et al. Complete response to neoadjuvant chemoradiotherapy in esophageal carcinoma is associated with significantly improved survival. J Clin Oncol 2005;23:4330-7.
17. Wan T, Zhang XF, Liang C, et al. The Prognostic Value of a Pathologic Complete Response After Neoadjuvant Therapy for Digestive Cancer: Systematic Review and Meta-Analysis of 21 Studies. Ann Surg Oncol 2019;26:1412-20.
18. Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 1999;281:1623-7.
19. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Invest 2014;124:687-95.
20. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic Radiation Therapy Augments Antigen-Specific PD-1-Mediated Antitumor Immune Responses via Cross-Presentation of Tumor Antigen. Cancer Immunol Res 2015;3:345-55.
21. Boustani J, Lecoester B, Baude J, et al. Anti-PD-1/Anti-PD-L1 Drugs and Radiation Therapy: Combinations and Optimization Strategies. Cancers (Basel) 2021;13:4893.
22. Li D, Guan Y, Dong Y, et al. Radiochemotherapy upregulates expression of checkpoint receptors on circulating T cells. Int J Radiat Biol 2021;97:1563-8.
23. Yan MH, Liu F, Qu BL, et al. Induction chemotherapy with albumin-bound paclitaxel plus lobaplatin followed by concurrent radiochemotherapy for locally advanced esophageal cancer. World J Gastrointest Oncol 2021;13:1781-90.
24. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
25. Taniyama Y, Murakami K, Yoshida N, et al. Evaluating the effect of Neoadjuvant chemotherapy for esophageal Cancer using the RECIST system with shorter-axis measurements: a retrospective multicenter study. BMC Cancer 2021;21:1008.

(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Zhang P, Hou X, Cai B, Yu W, Chen J, Huang X, Li Y, Zeng M, Ren Z, Gabriel E, Qu B, Liu F. Efficacy and safety of combined treatment with pembrolizumab in patients with locally advanced or metastatic esophageal squamous cell carcinoma in the real world. Ann Transl Med 2022;10(12):708. doi: 10.21037/atm-22-2779

