

Immunotherapy benefits PD-L1-positive gastric-type endocervical adenocarcinoma: A multicenter, retrospective study

JING LI^{1*}, DIAN WANG^{2*}, NING SU³, MIN WANG² and YULU WANG¹

¹Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450000, P.R. China;

²Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450000, P.R. China;

³Department of Gynecologic Oncology, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, Henan 450000, P.R. China

Received December 14, 2024; Accepted January 28, 2025

DOI: 10.3892/mco.2025.2841

Abstract. Gastric-type endocervical adenocarcinoma (GEA) usually exhibits notable aggressiveness and resistance to current therapies. A high expression of programmed death-ligand 1 (PD-L1) was previously reported in GEA and indicated it might benefit from immunotherapy targeting programmed cell death protein 1 (PD-1)/PD-L1. In the present study, the efficacy of immunotherapy in a panel of patients with GEA was explored, aiming to provide the first-hand evidence on this topic. A total of 44 pathologically diagnosed patients with GEA were recruited from the First Affiliated Hospital of Zhengzhou University and the Cancer Hospital of Zhengzhou University. The clinical and pathological information including age, tumor stage, treatments and prognosis were retrieved from our medical records system. Kaplan-Meier analysis was conducted to evaluate the role of immunotherapy on patients' overall survival (OS) and progression-free survival (PFS). According to the treatments, patients with GEA were divided into two groups: The immunotherapy group (n=19) and the non-immunotherapy group (n=25, the control group). In the immunotherapy group, 9 patients received PD-1/PD-L1 inhibitors as part of their primary treatment, while the remaining 10 received it after tumor recurrence/metastasis. Compared with the control group, the use of immunotherapy during primary treatment significantly extended PFS (median PFS: 14 vs. 6 months, $P=0.004$) and OS (median OS: 24 vs. 16 months, $P=0.019$). However, in the 10 patients who initiated immunotherapy after tumor recurrence/metastasis, the survival benefits were only

observed for OS (median OS: 33.5 vs. 16 months, $P=0.013$) but not PFS. Furthermore, the efficacy of immunotherapy was more significant in patients with PD-L1-positive GEA than those PD-L1-negative cases, which improved both the PFS (median PFS: 17 vs. 7 months, $P=0.002$) and OS (median OS: 36 vs. 16 months, $P<0.001$). This is the first study, to the best of our knowledge, reporting the efficacy of immunotherapy for GEA. It was demonstrated that the earlier use of PD-1/PD-L1 inhibitors was significantly associated with an improved prognosis, and PD-L1 status could predict the response of immunotherapy. These preliminary findings warrant further validations in the future.

Introduction

Cervical cancer ranks as the fourth most common malignancy in women, with endocervical adenocarcinoma (ECA) accounting for ~20-25% of all cases (1-3). According to the World Health Organization (WHO) classification, ECA is divided into HPV-associated (HPVa) and HPV-independent (HPVi) types (4). Among HPVi subtypes, gastric-type endocervical adenocarcinoma (GEA) is the most prevalent, comprising 80% of all HPVi cases. In addition to being unrelated to high-risk HPV infection, GEA lesions mainly develop in the deep cervical canal, leading to a high failure rate using the current screening methods (high-risk HPV test and cervical cytology) (5,6). In the near future, with the implementation of large-scale HPV vaccination programs, a decline in the incidence of HPVVa could be anticipated, potentially leading to an increased proportion of GEA.

In clinical practice, patients with GEA are more likely to present with bulky mass, deep stromal invasion, lymph node and ovarian metastasis, contributing to poor prognosis (7-9). Over the past decade, several studies have confirmed the poor prognosis of GEA in different populations. In a pivotal study conducted by Kojima *et al* (10), the post-operative survival outcomes of the patients with stage IB-IIIB GEA [according to International Federation of Gynecology and Obstetrics (FIGO)] were compared with those of patients without GEA. It was reported that patients with GEA obtained a markedly worse five-year disease-free survival when compared with the patients without GEA (25 vs. 75%). Additionally, the five-year

Correspondence to: Dr Jing Li, Department of Oncology, The First Affiliated Hospital of Zhengzhou University, 1 Longzhu Zhonghuan Road, Zhengzhou, Henan 450000, P.R. China
E-mail: fcclijl@zzu.edu.cn

*Contributed equally

Key words: gastric-type endocervical adenocarcinoma, immunotherapy, programmed cell death protein 1/programmed death-ligand 1 inhibitors, progression-free survival, overall survival

disease-specific survival rate was also lower in GEA group (30 vs. 77%) (10). In another study, Karamurzin *et al* (8) found that the five-year disease-specific survival rate for GEA was as low as 42%. Furthermore, in a retrospective analysis involving 95 patients with GEA and 233 patients with usual-type ECA (UEA) at FIGO stage IA-IIB and treated by the surgery, the median PFS for GEA was notably shorter than UEA (42 vs. 61.1 months) (7). Unfortunately, owing to its rarity, high-level evidences from prospective or randomized studies about GEA were not available yet. In clinical practice, current treatment strategies for GEA were mostly copied from that for common cervical cancers, while presented limited efficacy. Therefore, to explore individualized treatments based on the unique features of GEA becomes an urgent issue for our gynecologic oncologists.

In previous years, the immunotherapies represented by PD-1/PD-L1 inhibitors have achieved significant advancements in various human cancers, particularly among patients with positive PD-L1 expression (11-13). Pembrolizumab, the first commercial monoclonal antibody targeting PD-1, has demonstrated efficacy and manageable safety profiles in patients with persistent, recurrent, or metastatic cervical cancer (14,15). Based on the PFS and OS benefits observed in the KEYNOTE-826 study, NCCN recommend Pembrolizumab in combination with cisplatin/paclitaxel or carboplatin/paclitaxel and bevacizumab as a first-line treatment for PD-L1-positive recurrent or metastatic cervical cancer (16-18). Additionally, results from the KEYNOTE-158 study indicated that Pembrolizumab exhibits significant antitumor activity in previously treated patients with advanced cervical cancer, with an overall response rate of 12.2% (19). Furthermore, the recent KEYNOTE-A18 study reported that the combination of Pembrolizumab with radiotherapy and chemotherapy significantly enhanced PFS in newly diagnosed patients with high-risk locally advanced cervical cancer (20). Unfortunately, all these clinical trials focused on common histological patterns such as squamous cell carcinoma and UEA, while rarely recruiting patients with rare tumors including GEA and neuroendocrine carcinoma. Two reasons may account for this phenomenon: First, GEA was markedly more aggressive and progressed rapidly, making it an unsuitable candidate for most clinical trials; second, the incidence of GEA was notably lower than other subtypes, which introduced significant challenges in patients' recruitment. Therefore, a retrospective analysis may be a more feasible approach in clinical practice.

As two previous studies reported, positive expression of PD-L1 (CPS $\geq$ 1) was detected in 87.5% (n=32) and 75.9% (n=58) patients with GEA, which strongly indicated that anti-PD-1/PD-L1 treatments might constitute a potent strategy for this lethal malignancy (21,22). In the present study, the survival benefits were retrospectively analyzed in a cohort of patients with GEA who received PD-1/PD-L1 inhibitors, aiming to provide the real-world evidence on this topic.

Materials and methods

Selection of patients. Between February 2012 and October 2023, a total of 44 patients with pathological diagnosis of GEA were enrolled in the First Affiliated Hospital of Zhengzhou University and the Cancer Hospital of Zhengzhou University. The present

study was approved (approval nos. 2022-KY-1433-002 and 2024-246) by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University and the Cancer Hospital of Zhengzhou University (Zhengzhou, China). Informed consent was obtained from all individual participants included in the study. All the slides were re-evaluated by our pathologists to confirm the diagnosis of GEA. The clinical and pathological characteristics were directly extracted from the medical record system, including patient age at diagnosis, FIGO stage, depth of invasion, lymphovascular space invasion (LVSI), lymph node metastasis (LNM), treatment details and the results of follow-up.

Patients follow-up. After treatments completed, the follow-up was conducted every 2 or 3 months in the first and second years, and extended to every 6 months in the third and fourth years, and then once a year in the fifth year and later. The contents of follow-up comprised the physical examination (especially the pelvic examination), cervical cytology, serum tumor markers and imaging tests (ultrasonography, computed tomography, magnetic resonance imaging, positron emission tomography-computed tomography and single photon emission-computed tomography were chosen appropriately). PFS1 was defined as the interval from the pathological diagnosis of GEA to the first tumor recurrence. PFS2 was the interval from the first tumor recurrence to the second disease progression. PFSi meant the interval from the initiation of immunotherapy to the subsequent disease progression. OS was the time frame from the diagnosis of GEA to the patient death.

Determination of PD-L1 status in GEA tissues. Tissue slides were obtained from all the 19 patients from immunotherapy group and immunohistochemical staining was performed to investigate the expression of PD-L1. The procedure was performed in the laboratory of the Department of Pathology using a commercial kit for the detection of PD-L1 (DAKO; Agilent Technologies, Inc.; clone number: 22-C3) by drying 4- μ m thick formalin-fixed paraffin-embedded whole tissue sections on positively charged slides at 56-60°C for 1 h, followed by complete immersion of the slides in preheated (65°C) EnVision FLEX Target Extraction Solution and incubation at 97°C for 20 min for deparaffinization, rehydration, and target extraction; the slides were then immediately immersed in the washing buffer 5 times. The slides were evaluated by experienced pathologists and the combined positive score (CPS) was calculated as previously reported (22). In the present study, a CPS $\geq$ 1 was set as PD-L1-positive.

Statistical analysis. Chi-square and Fisher's exact tests were used to determine the correlation between categorical variables. Kaplan-Meier analysis was used to determine the efficacy of PD-1/PD-L1 inhibitors on prognosis of patients with GEA. All statistical analyses were conducted using SPSS 27.0 (IBM Corp.). P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline clinical and pathological characteristics of patients with GEA. Among the 44 patients, 19 cases who received PD-1/PD-L1 inhibitors in combination with routine treatments

Table I. Baseline characteristics of patients with gastric-type endocervical adenocarcinoma.

Characteristics	Immunotherapy group (n=19)	Non-immunotherapy group (n=25)	P-value
Median age, years (range)	45 (34-68)	49 (34-67)	0.759
FIGO Stage at diagnosis, n (%)			0.47
I	1 (5.3)	2 (8)	
II	1 (5.3)	0 (0)	
III	10 (52.6)	9 (36)	
IV	7 (36.8)	14 (56)	
Depth of stromal invasion, n (%)			0.17
Unknown	4 (21.1)	2 (8)	
≤1/2	4 (21.1)	2 (8)	
>1/2	11 (57.9)	21 (84)	
Lymph node metastasis, n (%)			0.164
Negative	7 (36.8)	4 (16)	
Positive	12 (63.2)	21 (84)	
Lymphovascular space invasion, n (%)			0.387
Negative	5 (26.3)	10 (40)	
Positive	11 (57.9)	14 (56)	
Unknown	3 (15.8)	1 (4)	

(including chemotherapy and radiotherapy) were defined as the immunotherapy group, and the remaining 25 patients treated without immunotherapy were set as the control group. Baseline characteristics of patients with GEA were provided in Table I. As shown, the median age was 45 years (ranged from 34 to 68 years) in the immunotherapy group, and 49 years (ranged from 34 to 67 years) in the control group. In the immunotherapy group, there were 1, 1 and 17 patients at stage I, II and III/IV when diagnosed with GEA, respectively. Among of them, 12 (63.2%) cases presented pelvic/para-aortic LNM, and 11 (57.9%) cases were positive with LVSI and deep stromal invasion. In the control group, 23 patients (92.0%) were stage III/IV at diagnosis. The positive rates of LNM, LVSI and deep stromal invasion were 84, 56 and 84%, respectively. Statistical analysis showed that there were no significant differences between the two groups in terms of patients age ($P=0.759$), tumor stage at diagnosis ($P=0.47$), LNM ($P=0.164$), LVSI ($P=0.387$), or deep stromal invasion ($P=0.17$).

The efficacy of PD-1/PD-L1 inhibitors as primary treatment in GEA. In the immunotherapy group, nine patients received PD-1/PD-L1 inhibitor as part of the primary treatment (seven received the combination of surgery and chemoradiotherapy, and the other two only underwent chemotherapy and/or radiotherapy) (Table II). As demonstrated, the median PFSi was 14 months (range: 8-38 months), which was markedly longer than that of the control group (median PFSi: 6 months, ranged from 2 to 39 months) (Table III) (Fig. 1A, $P=0.004$). Consistently, a significant benefit of OS was also detected in the immunotherapy group (median OS: 24 vs. 16 months, Fig. 1B, $P=0.019$).

The efficacy of PD-1/PD-L1 inhibitors in recurrent/metastatic GEA. In the immunotherapy, 10 patients started their use of

PD-1/PD-L1 inhibitors after tumor recurrence (Table IV). The median PFSi was 6.5 months in immunotherapy group (ranged from 2 to 21 months), and 6 months (ranged from 2 to 48 months) in the control group. As revealed in Fig. 2A, survival analysis showed that PD-1/PD-L1 inhibitors were not beneficial for these patients with GEA regarding PFS ($P=0.545$). Interestingly, a significant longer OS was observed in the immunotherapy group (median OS: 33.5 vs. 16 months; Fig. 2B, $P=0.013$).

The association between PD-L1 status and the response to immunotherapy in patients with GEA. Meanwhile, the association between PD-L1 status and the efficacy of immunotherapy was further evaluated in patients with GEA. According to the immunostaining results, 63.2% (12/19) patients with GEA were PD-L1-positive, with CPS ≥ 10 in eight cases (Fig. 3A-D). Compared with the PD-L1-positive group (median PFSi=17 months, ranged from 2-38 months), the median PFSi in PD-L1-negative patients was notably shorter (median PFSi=7 months, ranged from 2 to 14 months; Fig. 3E, $P=0.002$). Regarding OS, the PD-L1-positive group had a longer median OS of 36 months, which was only 16 months in PD-L1-negative group (Fig. 3F, $P<0.001$).

Discussion

Currently, the treatment strategy for GEA is similar to those for common cervical cancers, primarily involving surgery, radiotherapy and chemotherapy (18). However, owing to its significant aggressiveness and resistance to current therapies, the prognosis of GEA is considerably poorer (23). Thus, novel therapeutic approaches are urgently needed in clinical settings.

As previously reported, a substantial proportion of GEA cases exhibit positive PD-L1 expression, suggesting that immunotherapy targeting the PD-1/PD-L1 axis may offer

Table II. Treatment details of patients with gastric-type endocervical adenocarcinoma using PD-1/PD-L1 inhibitors in primary treatment.

Case no.	PD-L1	FIGO stage	Primary treatment	First line treatment after recurrence	Second line
1	Negative	IV	Sur + Che + Rad + Sin	Sur	
2	Positive	IV	Sur + Che + Tis	Sur	
3	Positive	III	Sur + Che + Rad + Sin		
4	Positive	III	Sur + Che + Rad + Pem		
5	Negative	III	Che + Rad + Cam	Che + Cad	Che
6	Negative	IV	Sur + Che + Sin		
7	Positive	III	Sur + Che + Rad + Cam		
8	Positive	III	Che + Rad + Cam		
9	Positive	III	Sur + Che + Rad + Cam		

Sur, surgery; Che, chemotherapy; Rad, radiotherapy; Sin, sintilimab; Tis, tislelizumab; Pem, pembrolizumab; Cam, camrelizumab; Cad, cadonilimab; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1.

Table III. Treatment details of patients in the non-immunotherapy group.

Case no.	FIGO stage	Recurrent/metastatic sites	Primary treatment	First line treatment after recurrence
1	IV	Liver/pelvic cavity	Sur + Che	Rad
2	IV	Pelvic cavity /abdominal cavity	Sur + Che + Rad	Sur
3	III	Pelvic cavity /abdominal cavity	Sur + Che + Rad	Che
4	IV	Lung	Che	Che + Rad
5	III	Bone	Sur + Che	Che
6	IV	Liver/lung/pelvic cavity/peritoneum	Sur + Che + Rad	
7	IV	Colon/greater omentum	Sur + Che	Che
8	IV	Greater omentum	Sur + Che + Rad	Che
9	IV	Greater omentum/distant lymph node	Sur + Che	Che
10	III	Peritoneum	Sur + Che + Rad	Che
11	IV	Pelvic cavity	Sur + Che	
12	IV	Lung	Sur + Che + Rad	Che + Rad
13	III	Bone	Sur + Che + Rad	Che
14	IV	Lung/pelvic cavity/peritoneum	Sur + Che	Che
15	III	Abdominal cavity/pelvic cavity	Sur + Che + Rad	Che
16	IV	Abdominal cavity	Sur + Che	Rad
17	IV	Greater omentum	Sur + Che + Rad	Che
18	IV	Abdominal cavity/distant lymph node	Sur + Che + Rad	Che
19	III	Pelvic cavity/peritoneum	Sur + Che + Rad	Che
20	I	Vaginal cuff	Sur + Che + Rad	Rad
21	III	Distant lymph node	Sur + Che	Rad
22	I	Vaginal cuff	Sur + Che + Rad	Che
23	IV	Liver/distant lymph node	Sur + Che	Rad
24	III	Bone	Sur + Che	Che
25	III	Peritoneum/pelvic cavity	Sur + Che + Rad	Che

Sur, surgery; Che, chemotherapy; Rad, radiotherapy.

therapeutic benefits. in the present study, by retrospectively analyzing GEA cases in our centers, preliminary evidences to support the potential benefits of immunotherapy for this lethal

cancer were provided. However, it is important to note that GEA has previously been reported to have a low median tumor mutational burden and a high proportion of KRAS and STK11

Table IV. Treatment details of patients treated with PD-1/PD-L1 inhibitor after recurrence/metastasis.

Case no.	PD-L1	FIGO stage	Recurrent/metastatic sites	Primary treatment	First line treatment after recurrence	Second line
1	Negative	III	Bone	Che + Rad	Che + Tis	
2	Positive	IV	Vaginal cuff/lung/peritoneum/distant lymph node	Sur + Che + Rad	Che + Cam	Cam
3	Negative	IV	Rectum	Sur + Che	Che + Tis	
4	Positive	II	Pelvic cavity	Sur + Che + Rad	Che + Tis	
5	Positive	III	Vaginal cuff	Sur + Che + Rad	Che + Rad	Che + Sin
6	Positive	III	Bone	Sur + Che + Rad	Che + Tor	
7	Positive	I	Lung	Sur + Che + Rad	Che	Che + Sin
8	Positive	IV	Vaginal cuff	Sur + Che + Rad	Che + Sin	
9	Negative	IV	Pelvic cavity/abdominal cavity/vaginal cuff/lung	Sur + Che + Rad	Che	Che + Cam
10	Negative	III	greater omentum	Sur + Che + Rad	Che + Pem	

Sur, surgery; Che, chemotherapy; Rad, radiotherapy; Sin, sintilimab; Tis, tislelizumab; Pem, pembrolizumab; Cam, camrelizumab; Tor, toripalimab.

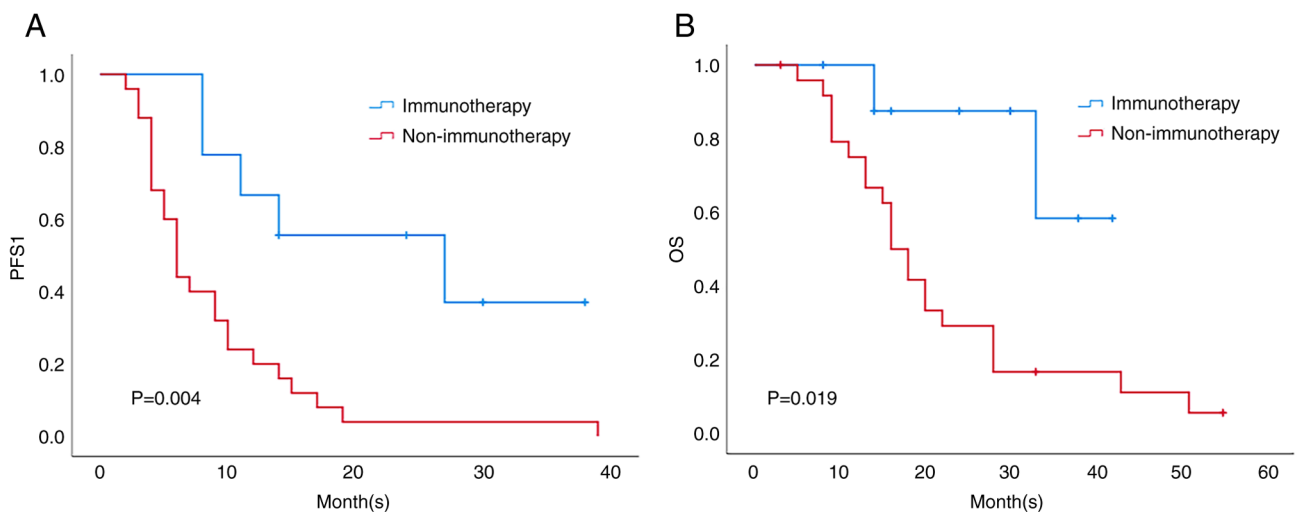


Figure 1. Comparison of PFS and OS between the immunotherapy and non-immunotherapy groups. (A) Immunotherapy prolonged PFS ($P=0.004$) and (B) OS ($P=0.019$) in patients who initiated the therapy in the primary treatment. PFS, progression-free survival; OS overall survival.

mutations, suggesting that GEA may exhibit resistance to checkpoint inhibitors. However, it was concluded that checkpoint inhibitors have a therapeutic effect on GEA. Several factors may account for this discrepancy. From a sampling perspective, the participants in the present study are drawn from the Chinese population, whereas the sample source in the previous study differs (23). Variations in genetic background, regional characteristics, living environment and other factors among patients may influence the tumor's response to immunotherapy. Regarding treatment options, the majority of patients in the present study received a combination of chemotherapy or radiotherapy, and PD-1/PD-L1 inhibitors, which may produce a synergistic effect that enhances the efficacy of immunotherapy. By contrast, earlier studies may not have adequately addressed the effects of combination therapy. Future studies should aim to expand the sample size and further

investigate the mechanisms by which these factors influence the efficacy of immunotherapy, in order to more accurately evaluate the role of checkpoint inhibitors in the treatment of GEA. The present findings supported that PD-1/PD-L1 inhibitors were beneficial for patients with PD-L1-positive GEA and who started immunotherapy as part of their primary treatment. Interestingly, among patients with GEA who initiated immunotherapy following tumor recurrence/metastasis, it was observed that immunotherapy significantly prolonged OS while having limited effects on PFS. After reviewing the data, it was hypothesized that subsequent treatments following PD-1/PD-L1 inhibition may partially account for this unexpected finding (data not shown), which will be further explored in our future work.

To the best of our knowledge, this is the first case series study aimed at exploring the efficacy of immunotherapy in

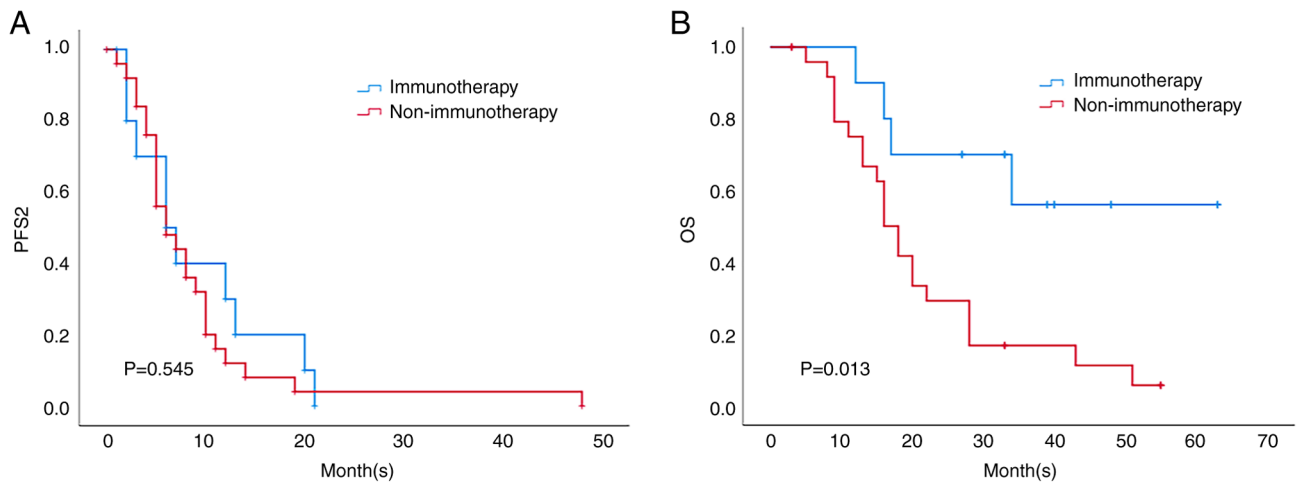


Figure 2. Comparison of PFS and OS between the immunotherapy and non-immunotherapy groups. (A) There was no significant improvement in PFS for patients receiving programmed cell death protein 1/programmed death-ligand 1 inhibitors following metastasis/recurrence (P=0.545). (B) A significant difference in OS was observed between the two groups (P=0.013). PFS, progression-free survival; OS overall survival.

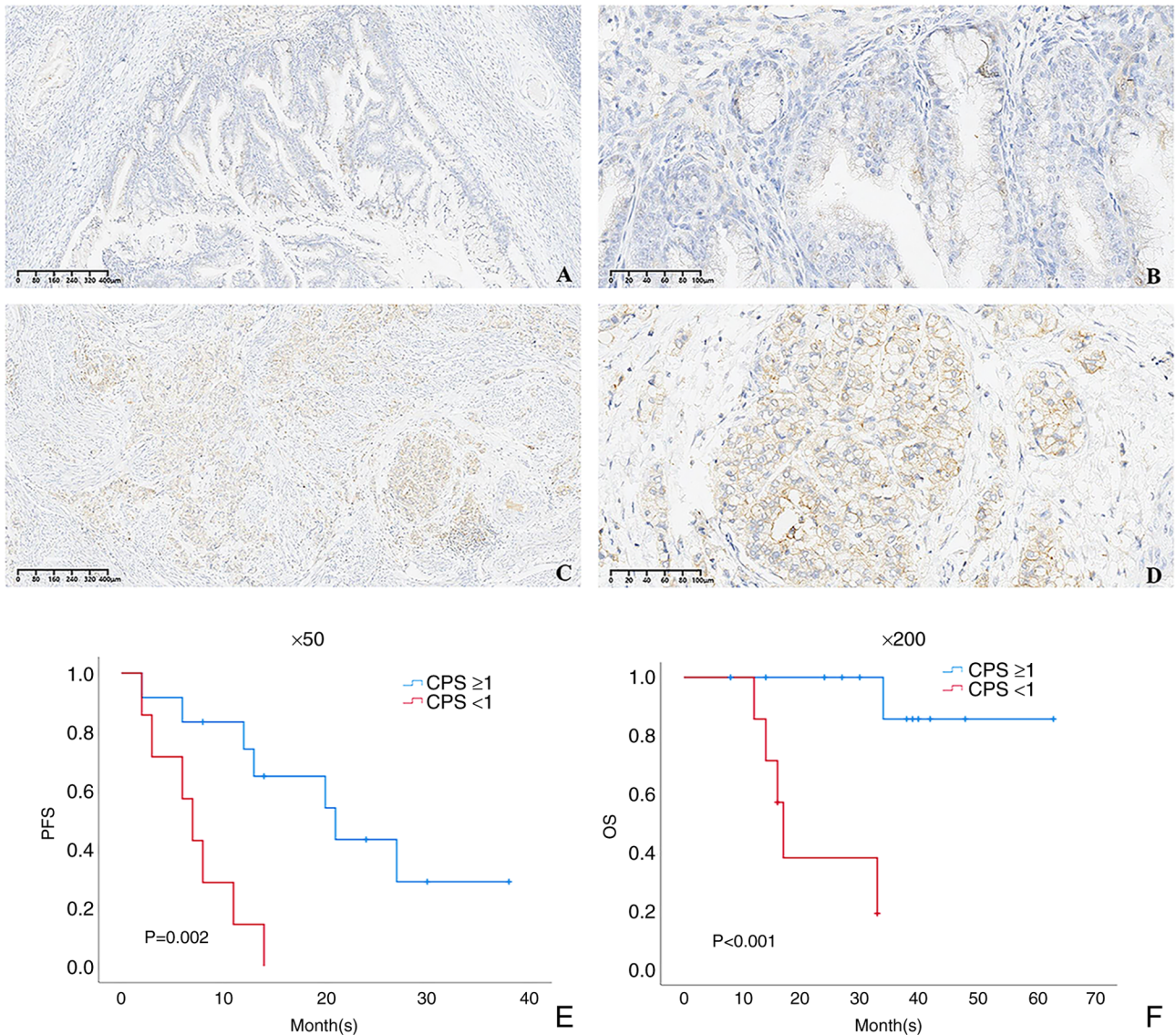


Figure 3. PD-L1 predicts tumor response to immunotherapy in GEA. (A and B) Representative images of PD-L1-negative GEA tissues. (C and D) Representative images of PD-L1-positive GEA cases. (E and F) Treatments with PD-1/PD-L1 inhibitors achieved markedly more benefits in patients with PD-L1-positive GEA (for PFS: P=0.002; for OS: P<0.001). PD-L1, programmed death-ligand 1; GEA, gastric-type endocervical adenocarcinoma; PFS, progression-free survival; OS overall survival.

GEA, which might shed some light on treating this rare and lethal malignancy. As a preliminary study, several limitations should be acknowledged. First, the retrospective nature and small sample size limited the statistical power of the analysis and may not adequately mitigate potential biases; second, the majority of patients in our cohort received a combination of treatments, including chemotherapy, radiotherapy and PD-1/PD-L1 inhibitors, which might not fully reveal the efficacy of immunotherapy and introduce unpredicted interference for the evaluation of tumor response.

Besides immunotherapies, the latest studies also reported two candidates for target therapy of GEA, HER2 and Claudin 18.2. In a Chinese GEA cohort, Wang *et al* (24) revealed that 17.2 and 15.5% patients presented HER2 overexpression and amplification, which was closely related with a worse prognosis. Shi *et al* (25) also reported that HER2 amplification/over-expression was more common in GEA comparing to UEA (14.7 vs. 4.5%). Interestingly, several studies have also indicated potential benefits of anti-HER2 treatment in other gynecologic malignancies such as ovarian mucinous carcinoma and uterine serous carcinoma (26,27). These findings support that anti-HER2 therapy might be a candidate choice for GEA and warrant further investigations.

As a member of the claudins family, Claudin18.2 primarily regulates the tight junctions on the cell surface and is typically expressed in cancers originating from the digestive system. In recent years, a series of clinical trials have demonstrated that targeting Claudin18.2 can lead to significant improvements in PFS and OS in advanced gastric, gastroesophageal junction and esophageal carcinomas. Notably, a recent study found that Claudin18.2 was positively stained in 95.2% of gastroesophageal adenocarcinoma tissues, with 58.0% of cases exhibiting moderate to strong staining (28), while it was rarely detected in common cancers or normal cervical tissues. These findings suggest that targeting Claudin18.2 may represent a viable strategy for treating advanced GEA.

As a member of the claudins family, Claudin18.2 mainly participates in regulating the tight junctions on cell surface, which is usually specifically expressed in cancers originated from the digestive system (29,30). Recently, a series of clinical trials have demonstrated that targeting Claudin18.2 can lead to significant improvements in PFS and OS in advanced gastric, gastroesophageal junction and esophageal carcinomas (31,32). Notably, a latest study proved that Claudin18.2 was positively stained in 95.2% GEA tissues (58.0% cases presented a moderate or strong staining), while scarcely detected in common cancers or normal tissues of cervix (28). This result proposed that targeting Claudin18.2 might be a reasonable strategy for treating advanced GEA.

In conclusion, the present study provides the first case series about the efficacy of PD-1/PD-L1 inhibitors for treating GEA. The present results suggest that immunotherapy could be given as part of the primary treatments and patients with high expression of PD-L1 would obtain more survival benefits. These findings are helpful for guiding our clinical practice, which warrants further investigations in large populations.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

JL designed the study, prepared and modified the manuscript. DW and MW performed literature search, data analysis and manuscript preparation. YLW and NS collected patient information and conducted follow-up. All authors read and approved the final version of the manuscript. JL and DW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved (approval nos. 2022-KY-1433-002 and 2024-246) by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University and the Cancer Hospital of Zhengzhou University (Zhengzhou, China). Informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 74: 229-263, 2024.
2. Smith HO, Tiffany MF, Qualls CR and Key CR: The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States-a 24-year population-based study. *Gynecol Oncol* 78: 97-105, 2000.
3. Adegoke O, Kulasingam S and Virnig B: Cervical cancer trends in the United States: A 35-year population-based analysis. *J Womens Health (Larchmt)* 21: 1031-1037, 2012.
4. International Agency for Research on Cancer (IARC): Female Genital Tumours. In: *WHO Classification of Tumours*. Vol 4. 5th edition. IARC, Lyon, pp374-375, 2020.
5. Takatsu A, Shiozawa T, Miyamoto T, Kurosawa K, Kashima H, Yamada T, Kaku T, Mikami Y, Kiyokawa T, Tsuda H, *et al*: Preoperative differential diagnosis of minimal deviation adenocarcinoma and lobular endocervical glandular hyperplasia of the uterine cervix: A multicenter study of clinicopathology and magnetic resonance imaging findings. *Int J Gynecol Cancer* 21: 1287-1296, 2011.
6. Kido A, Mikami Y, Koyama T, Kataoka M, Shitano F, Konishi I and Togashi K: Magnetic resonance appearance of gastric-type adenocarcinoma of the uterine cervix in comparison with that of usual-type endocervical adenocarcinoma: A pitfall of newly described unusual subtype of endocervical adenocarcinoma. *Int J Gynecol Cancer* 24: 1474-1479, 2014.

7. Nishio S, Mikami Y, Tokunaga H, Yaegashi N, Satoh T, Saito M, Okamoto A, Kasamatsu T, Miyamoto T, Shiozawa T, *et al*: Analysis of gastric-type mucinous carcinoma of the uterine cervix-An aggressive tumor with a poor prognosis: A multi-institutional study. *Gynecol Oncol* 153: 13-19, 2019.
8. Karamurzin YS, Kiyokawa T, Parkash V, Jotwani AR, Patel P, Pike MC, Soslow RA and Park KJ: Gastric-type endocervical adenocarcinoma: An aggressive tumor with unusual metastatic patterns and poor prognosis. *Am J Surg Pathol* 39: 1449-1457, 2015.
9. Jung H, Bae GE, Kim HM and Kim HS: Clinicopathological and molecular differences between gastric-type mucinous carcinoma and usual-type endocervical adenocarcinoma of the uterine cervix. *Cancer Genomics Proteomics* 17: 627-641, 2020.
10. Kojima A, Mikami Y, Sudo T, Yamaguchi S, Kusanagi Y, Ito M and Nishimura R: Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol* 31: 664-672, 2007.
11. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, McDermott DF, Powderly JD, Gettinger SN, *et al*: Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 515: 563-567, 2014.
12. Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, Bellmunt J, Burris HA, Petrylak DP, Teng SL, *et al*: MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* 515: 558-562, 2014.
13. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro G Jr, Srimuninnimit V, Laktonov KK, Bondarenko I, *et al*: Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): A randomised, open-label, controlled, phase 3 trial. *Lancet* 393: 1819-1830, 2019.
14. Frenel JS, Le Tourneau C, O'Neil B, Ott PA, Piha-Paul SA, Gomez-Roca C, van Brummelen EMJ, Rugo HS, Thomas S, Saraf S, *et al*: Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: Results from the phase Ib KEYNOTE-028 trial. *J Clin Oncol* 35: 4035-4041, 2017.
15. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, Manzuk L, Piha-Paul SA, Xu L, Zeigenfuss S, *et al*: Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol* 37: 1470-1478, 2019.
16. Monk BJ, Colombo N, Tewari KS, Dubot C, Caceres MV, Hasegawa K, Shapira-Frommer R, Salman P, Yañez E, Gümüş M, *et al*: First-Line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: Final overall survival results of KEYNOTE-826. *J Clin Oncol* 41: 5505-5511, 2023.
17. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Usta EH, Yañez E, *et al*: Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 385: 1856-1867, 2021.
18. Abu-Rustum NR, Yashar CM, Arend R, Barber E, Bradley K, Brooks R, Campos SM, Chino J, Chon HS, Crispens MA, *et al*: NCCN guidelines® insights: Cervical cancer, version 1.2024. *J Natl Compr Canc Netw* 21: 1224-1233, 2023.
19. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, *et al*: Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 study. *J Clin Oncol* 38: 1-10, 2020.
20. Lorusso D, Xiang Y, Hasegawa K, Scambia G, Leiva M, Ramos-Elias P, Acevedo A, Sukhin V, Cloven N, de Santana Gomes AJ, *et al*: Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): A randomised, double-blind, phase 3 clinical trial. *Lancet* 403: 1341-1350, 2024.
21. Chen L, Lucas E, Zhang X, Liu Q, Zhuang Y, Lin W, Chen H and Zhou F: Programmed death-ligand 1 expression in human papillomavirus-independent cervical adenocarcinoma and its prognostic significance. *Histopathology* 80: 338-347, 2022.
22. Sun Y, Zhou X, Lucas E, Chen L, Zhang H, Chen H and Zhou F: Expression of B7-H3 and TIM-3 in gastric-type endocervical adenocarcinoma: Prevalence, association with PD-L1 expression, and prognostic significance. *J Pathol Clin Res* 10: e345, 2024.
23. Ehmann S, Sassine D, Straubhar AM, Praiss AM, Aghajanian C, Alektiar KM, Broach V, Cadoo KA, Jewell EL, Boroujeni AM, *et al*: Gastric-type adenocarcinoma of the cervix: Clinical outcomes and genomic drivers. *Gynecol Oncol* 167: 458-466, 2022.
24. Wang S, Zhou X, Niu S, Chen L, Zhang H, Chen H and Zhou F: Assessment of HER2 in gastric-type endocervical adenocarcinoma and its prognostic significance. *Mod Pathol* 36: 100148, 2023.
25. Shi H, Shao Y, Lu W and Lu B: An analysis of HER2 amplification in cervical adenocarcinoma: Correlation with clinical outcomes and the international endocervical adenocarcinoma criteria and classification. *J Pathol Clin Res* 7: 86-95, 2021.
26. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, Chambers SK, Secord AA, Havrilesky L, O'Malley DM, *et al*: Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. *J Clin Oncol* 36: 2044-2051, 2018.
27. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, Chambers S, Secord AA, Havrilesky L, O'Malley DM, *et al*: Randomized phase II trial of carboplatin-paclitaxel compared with carboplatin-paclitaxel-trastuzumab in advanced (Stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): Updated overall survival analysis. *Clin Cancer Res* 26: 3928-3935, 2020.
28. Yang J, Peng Y, Ding Y, Liu Y, Wang Y, Liu Y and Liu C: The clinicopathological and molecular characteristics of endocervical gastric-type adenocarcinoma and the use of claudin18.2 as a potential therapeutic target. *Mod Pathol* 37: 100569, 2024.
29. Niimi T, Nagashima K, Ward JM, Minoo P, Zimonjic DB, Popescu NC and Kimura S: claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. *Mol Cell Biol* 21: 7380-7390, 2001.
30. Sahin U, Koslowski M, Dhaene K, Usener D, Brandenburg G, Seitz G, Huber C and Türeci O: Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. *Clin Cancer Res* 14: 7624-7634, 2008.
31. Qi C, Liu C, Gong J, Liu D, Wang X, Zhang P, Qin Y, Ge S, Zhang M, Peng Z, *et al*: Claudin18.2-specific CAR T cells in gastrointestinal cancers: Phase 1 trial final results. *Nat Med* 30: 2224-2234, 2024.
32. Liang Z, Liu L, Li W, Lai H, Li L, Wu J, Zhang H and Fang C: Efficacy and safety of zolbetuximab for first-line treatment of advanced Claudin 18. 2-positive gastric or gastro-esophageal junction adenocarcinoma: A systematic review and meta-analysis of randomized controlled trials. *Front Oncol* 13: 1258347, 2023.



Copyright © 2025 Li *et al*. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.