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

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**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 previous 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 HPVa 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-IIB 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

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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≥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-$\mu$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 ≥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 PFS1: 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.

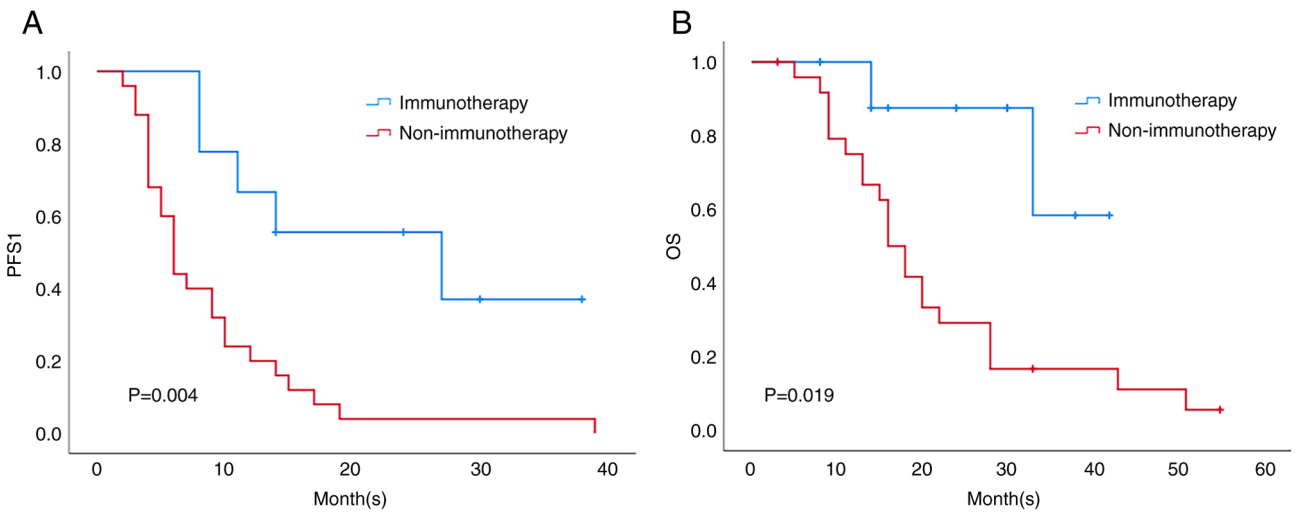


Figure 1. Comparison of PFS and OS between the immunotherapy and non-immunotherapy groups. (A) Immunotherapy prolonged PFS (P=0.004) and (B) OS (P=0.019) in patients who initiated the therapy in the primary treatment. PFS, progression-free survival; OS overall survival.

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

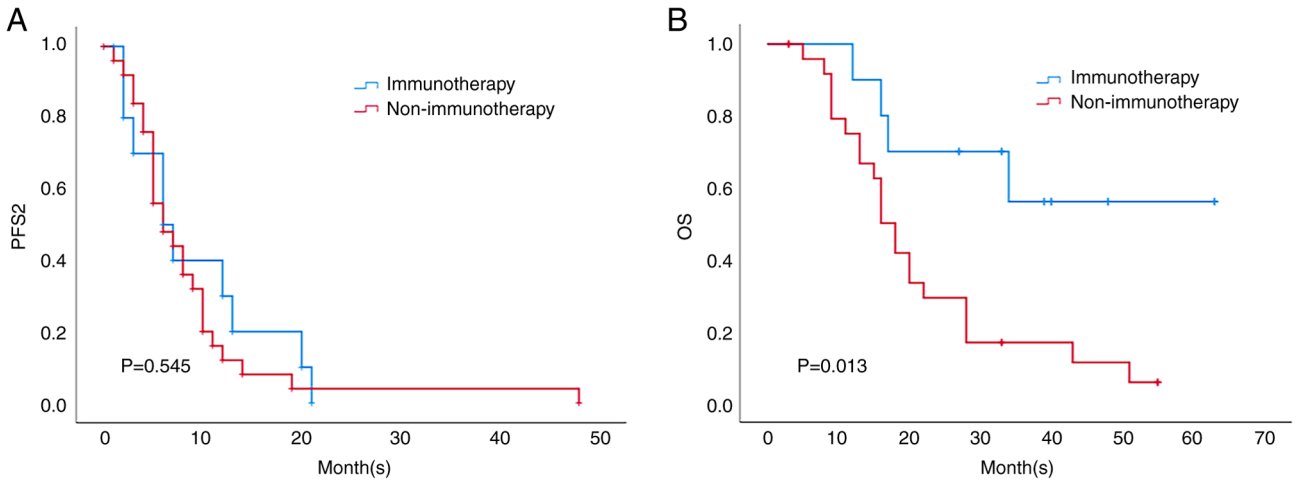


Figure 2. Comparison of PFS and OS between the immunotherapy and non-immunotherapy groups. (A) There was no significant improvement in PFS for patients receiving programmed cell death protein 1/programmed death-ligand 1 inhibitors following metastasis/recurrence (P=0.545). (B) A significant difference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

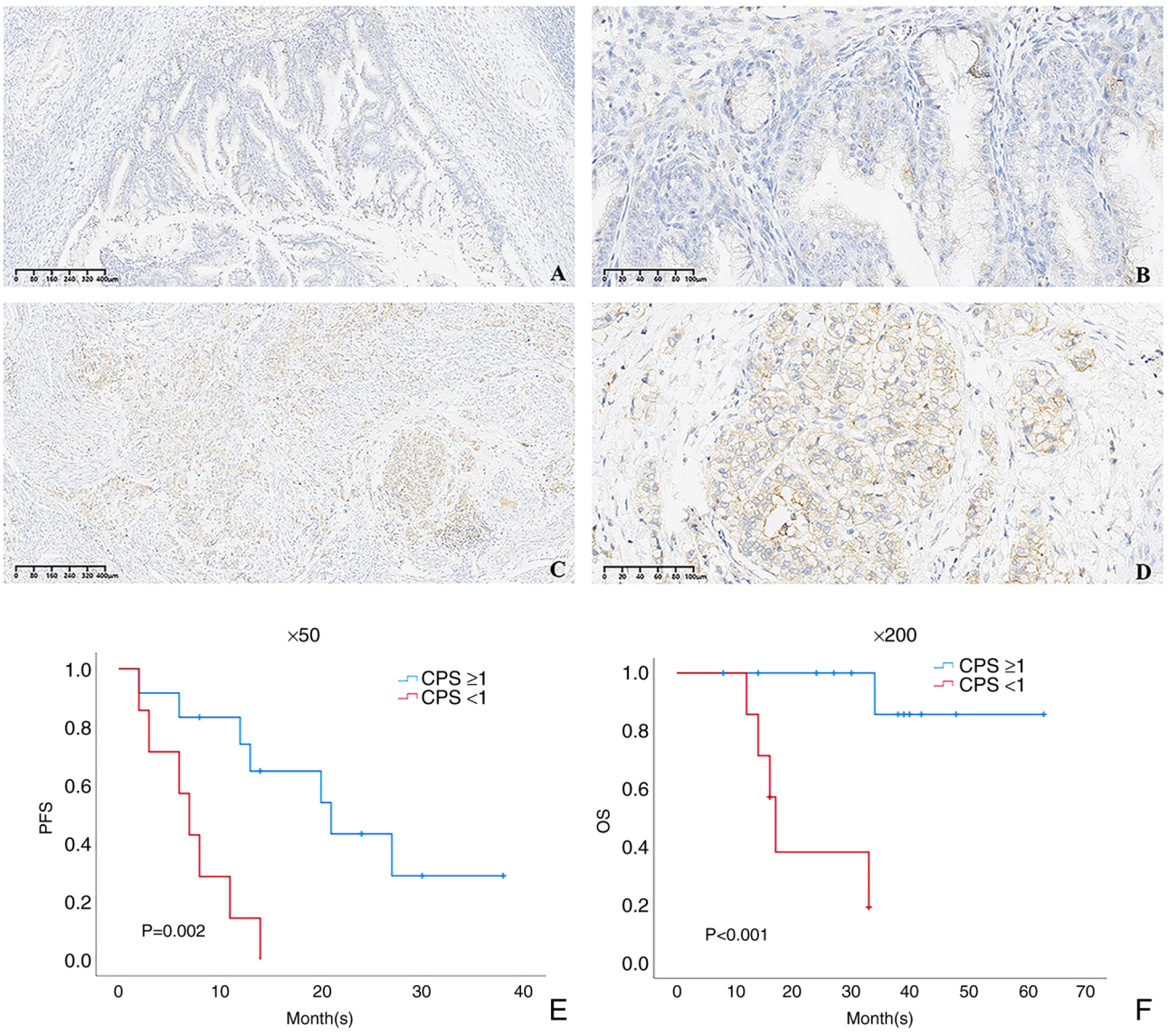


Figure 3. PD-L1 predicts tumor response to immunotherapy in GEA. (A and B) Representative images of PD-L1-negative GEA tissues. (C and D) Representative images of PD-L1-positive GEA cases. (E and F) Treatments with PD-1/PD-L1 inhibitors achieved markedly more benefits in patients with PD-L1-positive 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.

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## Availability of data and materials

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

## Authors' contributions

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.

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