



Immune checkpoint inhibitors combined with chemotherapy in conversion therapy for stage IV gastric cancer: a multicenter retrospective cohort study

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Received: 20 April 2025 / Accepted: 25 August 2025
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Abstract

Objectives To evaluate the efficacy of combining PD-1 inhibitors with chemotherapy in conversion therapy for patients with stage IV gastric cancer and to determine the populations most likely to benefit from this regimen.

Methods Data from patients with stage IV gastric cancer who received conversion therapy with PD-1 inhibitors combined with chemotherapy between January 2018 and December 2022 at multiple centers were retrospectively reviewed. Patients who underwent conversion surgery were categorized into a surgery group, while those who did not were placed into a palliative group. The survival outcomes between the two groups and the potential biomarkers that may predict the effectiveness of combining PD-1 inhibitors with chemotherapy were analyzed.

Results A total of 105 patients were included in the analysis, with 48 patients in the surgery group and 57 patients in the palliative group, resulting in a conversion rate of 45.7%. R0 resection was performed in 40 patients (83.3%) in the surgery group. The median survival time (MST) was not reached in the surgery group, while it was 12.0 months in the palliative group ($P < 0.001$). There were significant differences in 1-year and 3-year overall survival (OS) between the two groups (1-year OS: 93.7% vs. 45.6%, $P < 0.001$; 3-year OS: 52.1% vs. 4.0%, $P < 0.001$). Subgroup analysis revealed that patients with PD-L1 CPS ≥ 1 had significantly higher overall response rates (62.5% vs. 38.5%, $P = 0.016$) and conversion rates (60.4% vs. 32.7%, $P = 0.005$). For patients with peritoneal metastasis, a significant survival benefit was observed in those who received HIPEC treatment compared to those who did not (MST: 18.0 months vs. 9.0 months, $P = 0.039$). The incidence of treatment-related adverse events was similar to previous observations, with no new safety signals identified.

Conclusions The combination of PD-1 inhibitors with chemotherapy in conversion therapy is feasible for patients with stage IV gastric cancer. Individuals who exhibit improved responses to chemoimmunotherapy potentially experience survival benefits, particularly those with PD-L1 positivity.

Keywords Gastric cancer · Stage IV · Conversion therapy · Immune checkpoint inhibitor · Chemotherapy · Efficacy

Abbreviations

AEs Adverse events

AGC Advanced gastric cancer

CPS Combined positive score

CR Complete response

CT Computed tomography

CTCAE Common terminology criteria for adverse event

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|---------|--|
| DCR | Disease control rate |
| dMMR | MMR deficiency |
| EBV | Epstein–Barr virus |
| EBVaGC | Epstein–Barr virus-associated gastric cancer |
| HIPEC | Hyperthermic intraperitoneal chemotherapy |
| ICIs | Immune checkpoint inhibitors |
| IHC | Immunohistochemistry |
| MDT | Multidisciplinary team |
| MMR | Mismatch repair |
| MPR | Major pathological response |
| MST | Median survival time |
| ORR | Overall response rate |
| OS | Overall survival |
| pCR | Pathological complete response |
| PD | Progressive disease |
| PD-1 | Programmed cell death protein-1 |
| PD-L1/2 | Programmed death ligand-1/2 |
| PFS | Progression-free survival |
| PR | Partial response |
| RECIST | Response evaluation criteria in solid tumors |
| SD | Stable disease |

Introduction

Gastric cancer is the fifth most common human malignancy and the fifth leading cause of cancer-related mortality worldwide [1]. Tumor recurrence and distant metastasis are the main causes of cancer-related death and the dismal prognosis [2, 3]. Unfortunately, by the time some patients are diagnosed with gastric cancer, they have already progressed to stage IV of the disease. For such patients, the primary treatment goals are typically palliative, focusing on symptom control, disease management, and life extension. Although the optimal treatment strategy for advanced gastric cancer (AGC) has not yet been developed, a combination of a fluoropyrimidine and platinum-based regimen is generally preferred as the foundational treatment for most patients [4, 5]. Nevertheless, the relatively low tumor response rates and limited survival benefits of chemotherapy alone remain unsatisfactory, leading to a poor prognosis with a median survival time (MST) of approximately one year [6, 7]. Therefore, there is an urgent need to develop and identify more effective treatment strategies for patients with stage IV gastric cancer.

Recently, conversion therapy, including chemotherapy, radiation therapy, and immunotherapy, or a combination of these therapies, has emerged as a promising treatment strategy to improve the prognosis of patients with AGC, with the goal of achieving an R0 resection in those initially deemed unresectable or marginally resectable [8]. However, the optimal treatment regimen and population screening protocols for conversion therapy have yet to be clarified, and different

management strategies are still under exploration. Results from previous studies demonstrated that a sequence of chemotherapy followed by gastrectomy as conversion therapy effectively improved overall survival (OS) in patients with stage IV gastric cancer, which has deepened our understanding of the implications of conversion therapy for these patients [9–11]. Additionally, the emergence of immune checkpoint inhibitors (ICIs) has yielded significant clinical benefits for patients with AGC [5, 12–14]. The CheckMate 649 [15] and ORIENT-16 [16] clinical trials have revealed that the combination of PD-1 inhibitors with chemotherapy, as palliative treatment, could significantly improve OS and PFS for patients with unresectable or metastatic advanced gastric cancer or gastroesophageal junction adenocarcinoma. This suggests that the synergistic effects of immunotherapy and chemotherapy offer promising prospects for treating gastric cancer patients in advanced stages. Subsequently, anti-PD-1/PD-L1 treatment has been established as a standard first-line therapy for stage IV cases. However, the clinical benefits of conversion therapy comprising chemotherapy and anti-PD-1 therapy for stage IV gastric cancer are yet to be fully elucidated, and further exploration is necessary to identify the population most likely to benefit from this conversion therapy.

We carried out a multi-center retrospective analysis to assess the effectiveness of combining PD-1 inhibitors with chemotherapy in conversion therapy for stage IV gastric cancer patients, and to investigate potential biomarkers that could predict response to this therapeutic approach.

Methods

Study design

This was a multi-center, retrospective study conducted on patients initially diagnosed with clinical stage IV gastric cancer who underwent conversion therapy at Zhejiang Cancer Hospital (Hangzhou, China), Second People's Hospital of Yuhang District (Hangzhou, China), Huzhou Central Hospital (Huzhou, China), and The First People's Hospital of Fuyang (Hangzhou, China), from January 2018 to December 2022. The study was approved by the Ethics Committee of Zhejiang Cancer Hospital (approval number: IRB-2022–278), and informed consent was obtained from each participating patient. All procedures were conducted in strict accordance with the Declaration of Helsinki. This study was registered with ClinicalTrials.gov as NCT05385809 on May 23, 2022.

The data on patients' demographic information, tumor characteristics, therapeutic interventions, and survival status were collected and selected to form an analytical cohort. The main selection criteria were: (1) Age 18–75 years;

(2) Histologic confirmation of gastric/gastroesophageal junction adenocarcinoma; (3) Patients at clinical stage IV with no more than two distant metastasis sites, including the peritoneum, liver, retroperitoneal lymph nodes, and ovaries; (4) Eastern Cooperative Oncology Group performance status 0–1; (5) Blood index and organ function indicating that patients could tolerate chemoimmunotherapy or/and surgery (white blood cells $\geq 3.5 \times 10^9/L$, neutrophils $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, serum total bilirubin $\leq 1.5 \times$ the upper limit of the normal range (ULN), serum creatinine $\leq 1.2 \times$ ULN, and serum aspartate transaminase and alanine transaminase levels $\leq 1.5 \times$ ULN); (6) No prior treatment, such as chemotherapy, radiotherapy and targeted therapy, etc. The exclusion criteria were: (1) A history of gastrectomy; (2) Expected survival time less than three months; (3) With concomitant malignancies or refractory autoimmune diseases; (4) Incomplete clinicopathological data.

Treatment and efficacy assessment

Chemoimmunotherapy and clinical response assessment

All patients enrolled in the present study received PD-1 blockade in combination with chemotherapy. Trastuzumab was additionally administered to patients with HER2-positive status. The same treatment regimens were repeated until either disease progression, patient refusal, or the possibility of conversion surgery with R0 resection. The same treatments were continuously administered to patients who underwent conversion surgery. Dose reduction, delay, cessation, or regimen alteration was performed in patients with unacceptable toxicity or disease progression.

Hyperthermic intraperitoneal chemotherapy (HIPEC) was conducted in some patients with peritoneal metastasis. Approximately 3 L of normal saline containing paclitaxel (120 mg) were heated to 43 ± 0.3 °C and infused into the peritoneal cavity at 500 mL/min using a high-precision hyperthermic perfusion system (BR-TRG-II, Bright Medical Technology Co., Ltd., Guangzhou, China). The heated perfusion was circulated for 60 min and drained after the procedure.

Responses of the primary tumor were assessed every 2–4 treatment cycles using computed tomography (CT) or magnetic resonance imaging (MRI) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1), and were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [17]. The latest version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, V.5.0) was used to grade the adverse events associated with chemoimmunotherapy [18].

Conversion surgery and pathological response assessment

Based on the findings of imaging examinations and a comprehensive evaluation by a multidisciplinary team (MDT), conversion surgery was considered for patients who demonstrated a positive response to chemoimmunotherapy, assuming that complete resection (R0) was possible for such patients. In the present study, patients who underwent conversion surgery were categorized into surgery group, while those without conversion surgery were categorized into palliative group. All patients in the surgery group underwent radical gastrectomy along with D2 or D2 + lymphadenectomy according to the Japanese Gastric Cancer Treatment Guidelines [19]. The extent of surgery, including distal gastrectomy and total gastrectomy, was determined based on tumor location. Extended surgery (combined resection) was performed in some patients with the aim of curative resection. For reconstruction methods, standard Billroth II gastrojejunostomy were performed in patients who underwent distal gastrectomy, while Roux-en-Y esophagojejunostomy was performed in patients who underwent total gastrectomy. Postoperative complications of surgery were assessed based on the Clavien–Dindo classification [20].

The pathological regression of the resected primary tumor was evaluated by two experienced pathologists and categorized into TRG1a, TRG1b, TRG2, and TRG3 based on the Becker criteria [21]. Surgical specimens free of residual tumor cells were classified as pCR, which is equivalent to TRG1a. Specimens containing less than 10% residual tumor cells after preoperative treatment were categorized as MPR.

Exploration of efficacy-related factors

Potential efficacy-related biomarkers, including PD-L1 expression, mismatch repair (MMR) status, Epstein–Barr virus (EBV) status, and HER-2 status, were assessed in patients with available formalin-fixed, paraffin-embedded biopsy samples. As described in our previous study [22], PD-L1 expression (Clone 22C3; Dako) and MMR status (MLH1, clone ES05, Dako; MSH2, clone FE11, Dako; MSH6, clone EP49, Dako; PMS2, clone EP51, Dako) were assessed by immunohistochemistry (IHC), while EBV status (EBV-0050; EBER ISH Kit, MXB) was evaluated using *in situ hybridization*. Patients with a PD-L1 CPS of 1 or greater were classified as PD-L1 positive. Loss of any of the four MMR proteins (MLH1, MSH2, MSH6, and PMS2) was defined as MMR deficiency (dMMR). HER-2 expression was determined by IHC (Clone 4B5; Roche), and tumor tissues with scores of 2+ were further analyzed by fluorescence *in situ hybridization* (FISH) (GSP HER-2/CSP 17) [23]. Further analysis of the relationships between these biomarkers and treatment efficacy was conducted.

Endpoints and follow-up

The primary endpoint was the conversion rate, while the second endpoints were R0 resection, pathological response, and OS. The interval from the date of diagnosis to the date of last follow-up or death was defined as OS. Routine follow-up was performed for all enrolled patients every 3 months during the initial 2 years, followed by a schedule of every 6 months thereafter. The follow-up examination included regular CT scans, routine laboratory tests (including tumor markers), or gastrointestinal endoscopy, etc. The last follow-up was performed on June 30, 2024.

Statistical analysis

Categorical variables were presented as frequencies and percentages, and comparisons were made using the Chi-square test or Fisher's exact test. Continuous variables were expressed as the median or mean with range and compared using the Mann–Whitney U test. The cumulative OS rates were calculated using the Kaplan–Meier method and compared using the log-rank test. The Cox regression model was used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) for both univariable and multivariable analyses. A two-sided P -value < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA).

Results

Clinicopathological characteristics

As illustrated in Fig. 1, a total of 154 patients diagnosed with stage IV gastric cancer underwent conversion therapy combining anti-PD-1 with chemotherapy between January 2020 and June 2022. Forty-nine patients were excluded as they had more than two unresectable factors ($n=28$) or insufficient data ($n=21$). Consequently, 105 patients formed the analytical cohort, comprising 66 males and 39 females, with a median age of 62 (26–75). Of these 105 patients, 61 (58.1%) patients had one unresectable factor, while the remaining 44 (41.9%) had two unresectable factors. Predominant distant metastasis sites included the peritoneum ($n=59$, 56.2%), liver ($n=36$, 34.3%), retroperitoneal lymph nodes ($n=36$, 34.3%) and ovaries ($n=14$, 13.3%). No significant differences were observed between the baseline characteristics of the surgery group and the palliative group in terms of age, gender, T stage, N stage, number of metastases, and metastasis sites. The detailed information regarding patient characteristics is presented in Table 1.

Treatment outcomes

All patients enrolled in the present study received at least two cycles of PD-1 blockade along with chemotherapy. A total of 891 treatment cycles were administered, with a median of eight cycles (2–27). PD-1 blockade was achieved using PD-1 antibodies, including sintilimab, camrelizumab, and nivolumab, while the chemotherapy regimens were

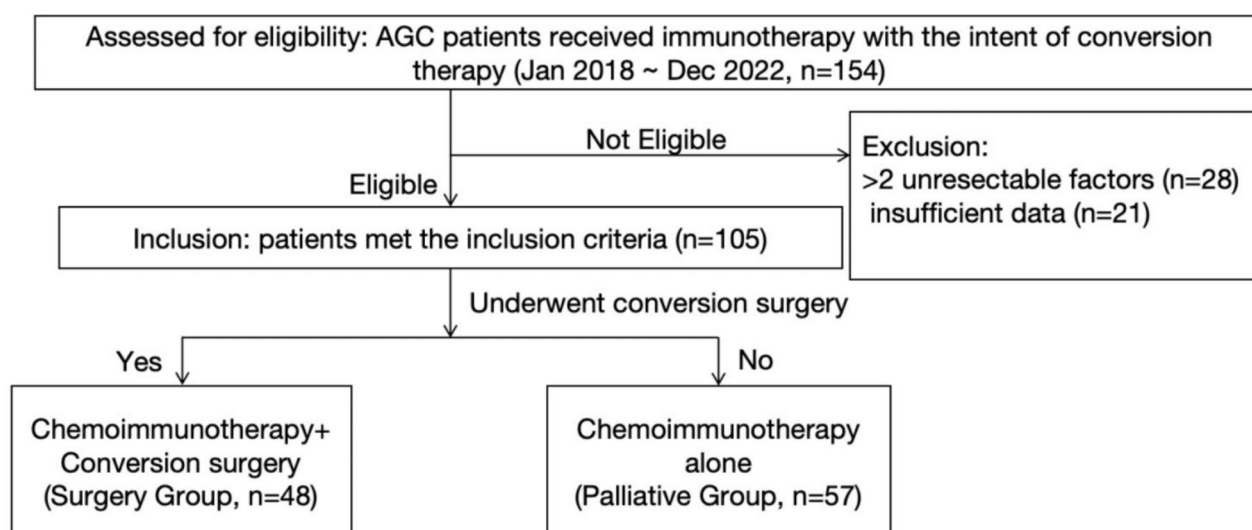


Fig. 1 Flow diagram of the patient selection process

Table 1 Clinicopathological characteristics

| | Total (n = 105) | Surgery group (n = 48) | Palliative group (n = 57) | P-value |
|-------------------------------|-----------------|------------------------|---------------------------|---------|
| <i>Age (years)</i> | | | | 0.582 |
| ≤60 | 49 (46.7) | 21 (43.8) | 28 (49.1) | |
| >60 | 56 (53.3) | 27 (56.3) | 29 (50.9) | |
| <i>Gender</i> | | | | 0.945 |
| Male | 66 (62.9) | 30 (62.5) | 36 (62.2) | |
| Female | 39 (37.1) | 18 (37.5) | 21 (36.8) | |
| <i>Primary tumor location</i> | | | | 0.274 |
| Upper | 28 (26.7) | 10 (20.8) | 18 (31.6) | |
| Middle | 21 (20.0) | 13 (27.1) | 8 (14.0) | |
| Lower | 49 (46.7) | 21 (43.8) | 28 (31.6) | |
| Total stomach | 7 (6.7) | 4 (8.3) | 3 (5.3) | |
| <i>Primary tumor size</i> | | | | 0.134 |
| ≤5 | 14 (13.3) | 9 (18.8) | 5 (8.8) | |
| >5 | 91 (86.7) | 39 (81.3) | 52 (91.2) | |
| <i>T-category</i> | | | | 0.658 |
| 3 | 29 (27.6) | 15 (31.3) | 14 (24.6) | |
| 4a | 75 (71.4) | 33 (68.8) | 42 (73.7) | |
| 4b | 1(1.0) | 0 (0.0) | 1 (1.8) | |
| <i>N-category</i> | | | | 0.347* |
| 0 | 3 (2.9) | 0 (0.0) | 3 (5.3) | |
| 1 | 14 (13.3) | 6 (12.5) | 8 (14.0) | |
| 2 | 51 (48.6) | 22 (45.8) | 29 (50.9) | |
| 3 | 37 (35.2) | 20 (41.7) | 17 (29.8) | |
| <i>Number of metastases</i> | | | | 0.356 |
| 1 | 65 (61.9) | 32 (66.7) | 33 (57.9) | |
| 2 | 40 (38.1) | 16 (33.3) | 24 (42.1) | |
| <i>Metastatic sites</i> | | | | |
| Peritoneum | 59 (56.2) | 30 (62.5) | 29 (50.9) | 0.232 |
| Liver | 36 (34.3) | 12 (25.0) | 24 (42.1) | 0.066 |
| Retroperitoneal lymph node | 36 (34.3) | 15 (31.3) | 21 (36.8) | 0.548 |
| Ovary | 14 (13.3) | 7 (14.6) | 7 (12.3) | 0.730 |
| <i>Preoperative CEA</i> | | | | 0.239 |
| ≤5 | 75 (71.4) | 37 (77.1) | 38 (66.7) | |
| >5 | 30 (28.6) | 11 (22.9) | 19 (33.3) | |
| <i>Preoperative CA125</i> | | | | 0.006 |
| ≤35 | 59 (56.2) | 34 (70.8) | 25 (43.9) | |
| >35 | 46 (43.8) | 14 (29.2) | 32 (56.1) | |
| <i>Preoperative CA199</i> | | | | 0.033 |
| ≤37 | 77 (73.3) | 40 (83.3) | 37 (64.9) | |
| >37 | 28 (26.7) | 8 (16.7) | 20 (35.1) | |

Significant values are highlighted in bold *CEA* Carcinoembryonic antigen, *CA125* Carbohydrate antigen 125 *CA199* Carbohydrate antigen 199

Table 2 Clinical response of chemoimmunotherapy-based conversion therapy

| | Total (n = 105) | Surgery group (n = 48) | Palliative group (n = 57) | P-value |
|--------------------------|-----------------|------------------------|---------------------------|---------|
| <i>Clinical response</i> | | | | <0.001 |
| CR | 3 (2.9) | 3 (6.3) | 0 (0.0) | |
| PR | 51 (48.6) | 40 (83.3) | 11 (19.3) | |
| SD | 37 (35.2) | 5 (10.4) | 32 (56.1) | |
| PD | 14 (13.3) | 0 (0.0) | 14 (24.5) | |
| ORR | 54 (51.4) | 43 (89.6) | 11 (19.3) | <0.001 |
| DCR | 91 (86.7) | 48 (100.0) | 43 (75.4) | <0.001 |

CR Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease, *ORR* Objective response rate, *DCR* Disease control rate

mainly platinum-based and paclitaxel-based, including SOX (S-1 and oxaliplatin), XELOX (capecitabine and oxaliplatin), and PS (paclitaxel and S-1). According to the RECIST ver.1.1 guidelines, CR was achieved in 3 (2.9%) patients, PR in 51 (48.6%) patients, SD in 37 (35.2%) patients, and PD in 14 (13.3%) patients. Thus, the ORR was 51.4% and the DCR was 86.7% (Table 2).

Based on the treatment response results and the evaluation by the MDT, conversion surgery was deemed feasible for three patients with CR, 42 patients with PR and six patients with SD through D2/D2 + gastrectomy or extensive resection. Additionally, three patients declined to undergo surgery. Finally, conversion surgery was conducted on 48 patients (surgery group), resulting in a conversion rate of 45.7%. Chemoimmunotherapy was continued as palliative treatment in patients who declined to receive conversion surgery or for whom conversion surgery was not applicable (palliative group, n = 57).

For patients in the surgery group, the median number of preoperative treatment cycles was 4 (2–6), and the median number of postoperative treatment cycles was 4.5 (1–16). The median time between preoperative treatment and conversion surgery was 28.5 (21–89) days and the median time between surgery and postoperative treatment was 37.5 (28–71) days. The median postoperative hospitalization time was 8 days (7–29). Meanwhile, for patients in the palliative group, a total of 429 treatment cycles were administered, with a median of 6 cycles (2–27).

Among the 48 patients who underwent conversion surgery, distal gastrectomy was performed in 25 patients and total gastrectomy in 23 patients (Supplementary Table S1). R0 resection was conducted in 40 patients (83.3%) and non-R0 resection in eight patients (16.7%). Combined resection was performed in four patients due to tumor invasion or splenic hilum lymph node metastasis, including splenectomy in two patients, pancreatectomy in one patient, and colectomy in another.

According to the pathological response of primary tumors, 5 (10.4%) patients achieved pCR (TRR1a), while 12 (25.0%), 23 (47.9%), and 8 (16.7%) patients achieved TRG1b, TRG2, and TRG3, respectively. Thus, the pCR and MPR rates of patients who underwent conversion surgery were 10.4% and 35.4%, respectively (Supplementary Table S2).

Metastasectomy was performed on 22 patients in the surgery group, including oophorectomy in seven patients, para-aortic lymph node dissection in six patients, peritoneal resection in three patients, partial hepatectomy in five patients, and radiofrequency ablation in one patient. For patients with pyloric obstruction, gastrointestinal bypass surgery was conducted on five patients in the surgery group before their conversion surgery, and on eight patients in the palliative group. Additionally, laparoscopic exploration was performed on 29 patients in the palliative group.

Surgical complications

Surgical complications of Clavien–Dindo grade 3 or above occurred in eight patients (16.7%) in the surgery group, including chylous leakage in three patients, anastomotic leakage in two patients, pneumonia in two patients, and intestinal obstruction in one patient. After symptomatic treatment, these patients' conditions improved, and there were no deaths related to surgery.

Safety profile

Adverse events (AEs) of grade 3 or 4 were observed in 27.6% (29/105) patients in the entire cohort. AEs were identified in 29.2% (14/48) of patients during the preoperative treatment period and in 22.9% (11/48) of patients during the postoperative treatment period in the surgery group, whereas they were observed in 22.8% (13/57) of patients in the palliative group throughout the entire treatment period. No significant difference was observed between the two groups ($P=0.229$). In the entire cohort, the most common hematological toxicities were neutropenia (12.4%), thrombocytopenia (6.7%), and leucopenia (5.7%). Meanwhile, transaminase elevation (8.6%) emerged as the most commonly reported non-hematological toxicity, followed by vomiting (2.9%) and pneumonia (1.9%). Additionally, two patients experienced immune-related AEs, including one case of grade 2 hypothyroidism and one case of grade 1 hyperthyroidism. The condition of all patients with AEs improved after symptomatic treatment. No treatment-related deaths occurred in the entire cohort.

Survival outcomes

All patients underwent follow-up, and the median follow-up time was 29.0 months (3.0–41.0 months). For the entire cohort, the MST was 18.0 months (95% CI: 13.8–22.2 months), with 1- and 3-year OS rates of 67.6% and 28.6%, respectively, as shown in Fig. 2A.

Furthermore, a subgroup analysis revealed that the MST was not reached in the surgery group, while that of the palliative group was 12.0 months (3–39 months, 95% CI 9.5–14.5 months, $P<0.001$). The 1-year OS rate was 93.7% for the surgery group and 45.6% for the palliative group, with a statistical difference ($P<0.001$). Similarly, there was a significant difference in the 3-year OS rate (52.1% vs. 4.0%, $P<0.001$) between the two groups (Fig. 2B).

Exploration analysis based on the Yoshida classification

According to the Yoshida classification [8], the conversion rates of category 1, 2, 3, and 4 were 87.5% (7/8), 34.2% (13/38), 61.3% (19/31) and 32.1% (9/28), respectively. An analysis of OS revealed a significant difference in each category between the surgery group and the palliative group. (category 1, MST not reached vs. 12.0 months, $P=0.008$; category 2, MST not reached vs. 15.0 months, $P<0.001$; category 3, MST 31.0 months vs. 10.0 months, $P<0.001$; category 4, MST 18.0 months vs. 9.0 months, $P=0.018$; Supplementary Fig. 1). For patients with peritoneal metastasis (categories 3 and 4), a total of 38 (64.4%) patients were treated with HIPEC. A further exploratory analysis revealed a significant difference in the OS between patients treated with HIPEC and those who were not ($P=0.039$, Supplementary Fig. 2), with MSTs of 18.0 months and 9.0 months, respectively.

Univariate and multivariate analyses

Univariate analysis showed that the metastasis number, peritoneal metastasis, preoperative CA125 level, treatment response and conversion surgery were associated with patient prognosis. Furthermore, multivariate analysis revealed that peritoneal metastasis and conversion surgery were independent predictors of OS (Table 3).

Association between potential biomarkers and treatment efficacy

Information regarding the PD-L1 expression, MMR status, HER-2 status and EBV-positivity was detected in patients with available untreated cancer tissue samples, and further analysis of the relationships between these biomarkers and treatment efficacy was performed (Supplementary Table S3).

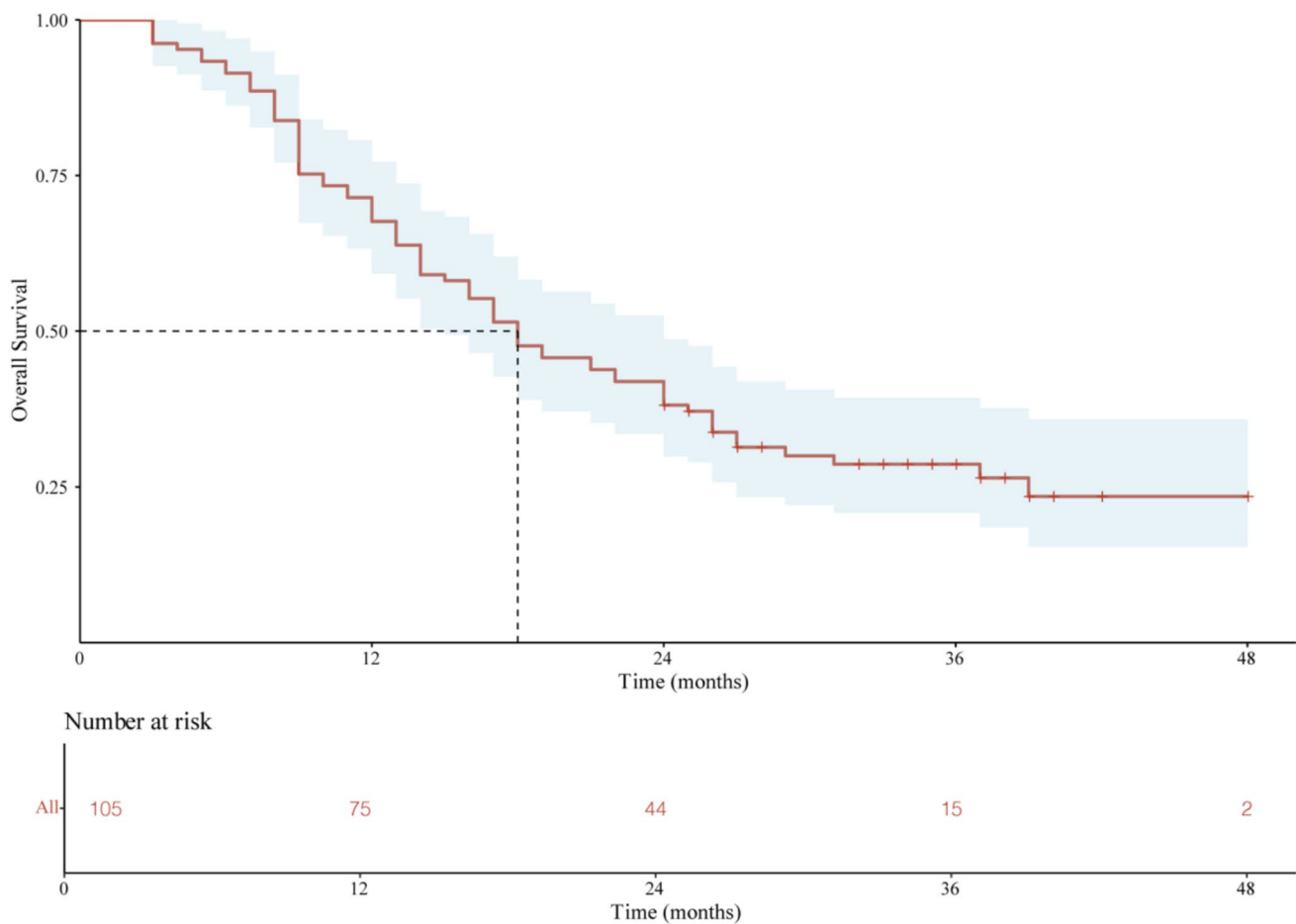


Fig. 2 A Kaplan–Meier estimates of the overall survival of all enrolled patients. Figure 2B Kaplan–Meier estimates of the overall survival of patients in the surgery group and palliative group

As shown in Table 4, information on PD-L1 was obtained for 100 patients. Regarding the treatment response, the ORRs of PD-L1-positive and -negative patients were 62.5% and 38.5% ($P = 0.016$), and the DCRs were 87.5% and 86.7% ($P = 0.886$), respectively. As a result, a significantly higher conversion rate was achieved in PD-L1-positive patients compared to PD-L1-negative patients (60.4% vs. 32.7%, $P = 0.005$). Furthermore, for patients who underwent conversion surgery, the pCR rate in patients with PD-L1 CPS ≥ 5 was significantly higher than in those with PD-L1 CPS < 5 (22.2% vs. 0.0%, $P = 0.019$). No significant difference was observed between the PD-L1-positive and PD-L1-negative patients (13.8% vs. 0.0%, $P = 0.281$). Additionally, there was no significant difference in the MPR rate when the cut-off value of CPS was set at either 1 or 5 (Supplementary Table S2). The subgroup analysis showed that the OS of PD-L1-positive patients was significantly better than that of PD-L1-negative patients, with MST values of 31.0 and 14.0 months, respectively ($P < 0.001$, Fig. 3).

The MMR status was confirmed in 104 patients, including 5 (4.8%) patients with dMMR and 99 (95.2%) patients with pMMR. A favorable conversion rate of 60.0% (3/5) was achieved in patients with dMMR (one achieved pCR; the others achieved TRG 2). All three of these patients had a CPS > 5 and were negative for HER-2 and EBV.

EBV information was available for 96 patients, of whom only 7 (7.3%) were identified as EBV-positive. Three (42.9%) of these seven patients underwent conversion surgery (one achieved pCR, while the others achieved MPR).

HER-2 data were available for 97 patients, of whom 11 (11.3%) were confirmed as positive. Among these 11 HER-2-positive patients, seven (73.6%) underwent conversion surgery. TRG1a, TRG1b, TRG2, and TRG3 were achieved in two, one, two, and two patients, respectively.

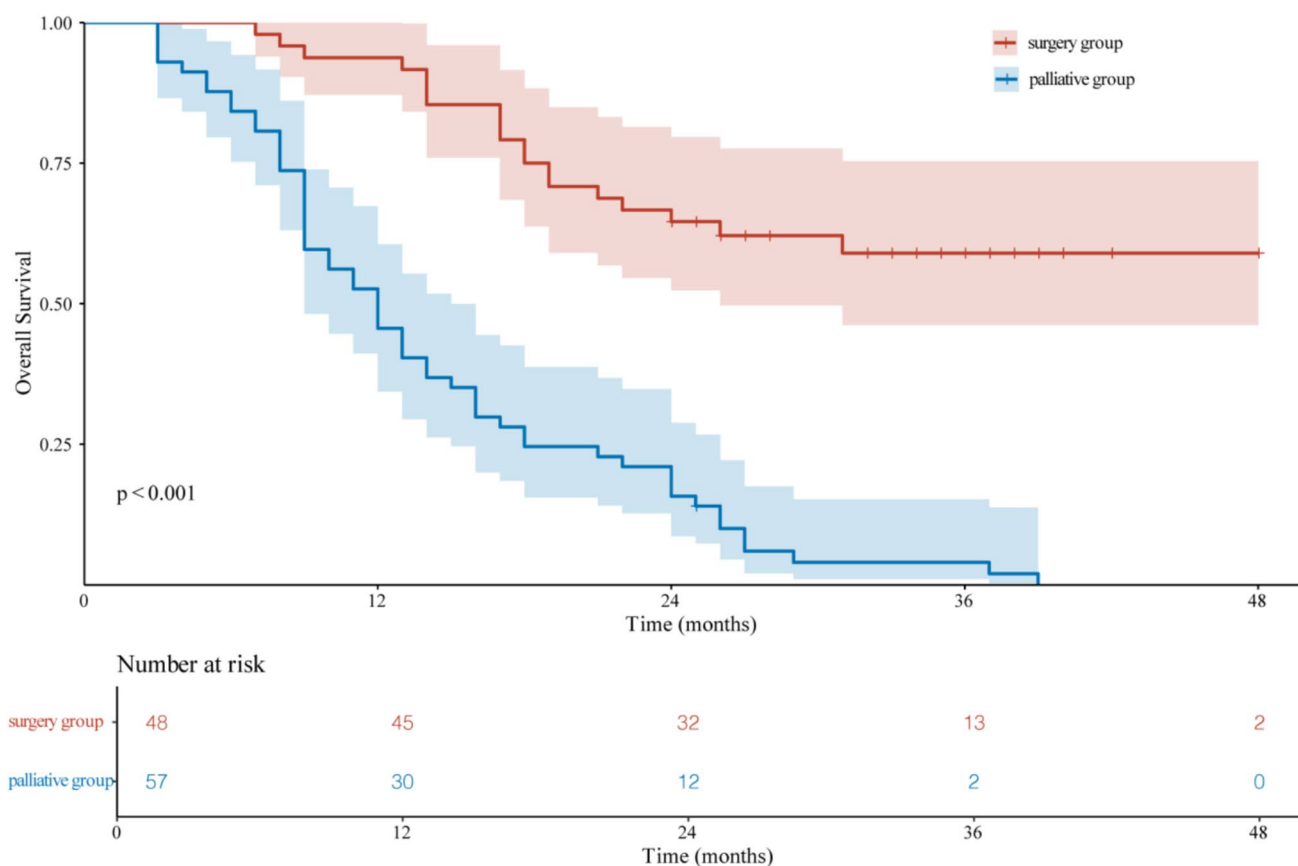


Fig. 2 (continued)

Table 3 Relationship between PD-L1 expression and the clinical response of patients across the entire cohort

| Variable | Total (n=100) | CPS < 1 (n=52) | CPS ≥ 1 (n=48) | P-value | CPS < 5 (n=74) | CPS ≥ 5 (n=26) | P-value |
|--------------------------|---------------|----------------|----------------|---------|----------------|----------------|---------|
| <i>Clinical response</i> | | | | 0.040 | | | 0.063 |
| CR | 2 (2.0) | 0 (0.0) | 2 (4.2) | | 0 (0.0) | 2 (7.7) | |
| PR | 48 (48.0) | 20 (38.5) | 28 (58.3) | | 34 (45.9) | 14 (53.8) | |
| SD | 37 (37.0) | 25 (48.1) | 12 (25.0) | | 31 (41.9) | 6 (23.1) | |
| PD | 13 (13.0) | 7 (13.5) | 6 (12.5) | | 9 (12.1) | 4 (15.4) | |
| ORR | 50 (50.0) | 20 (38.5) | 30 (62.5) | 0.016 | 34 (45.9) | 16 (61.5) | 0.171 |
| DCR | 87 (87.0) | 45 (86.5) | 42 (87.5) | 0.886 | 65 (87.8) | 22 (84.6) | 0.737 |

CR Complete response, PR Partial response, SD Stable disease, PD Progressive disease ORR Objective response rate, DCR Disease control rate

Discussion

In this study, we retrospectively evaluated the efficacy of PD-1 inhibitors combined with chemotherapy as conversion therapy for patients who initially presented with unresectable metastatic AGC, focusing on the clinical benefits and potential biomarkers. An encouraging conversion rate (45.7%) was achieved in the present study. Additionally,

the MST, and 1- and 3-year OS rates of patients who responded well to chemoimmunotherapy and subsequently underwent conversion surgery were significantly higher than those who did not. Furthermore, subgroup analysis revealed that PD-L1-positivity was associated with improved efficacy.

The management strategies for patients with initially unresectable AGC have been widely explored in recent decades. In a multi-institutional retrospective study, Sato et al.

Table 4 Univariate and multivariate analyses

| Variable | Univariate | | Multivariate | |
|--|---------------------|---------|---------------------|---------|
| | HR (95%CI) | P-value | HR (95%CI) | P-value |
| <i>Gender</i> | | | | |
| Female/male | 1.143(0.717–1.822) | 0.573 | | |
| <i>Age (year)</i> | | | | |
| > 60/≤ 60 | 0.988(0.628–1.554) | 0.957 | | |
| <i>T-category</i> | | | | |
| T4/T3 | 0.964(0.578–1.609) | 0.890 | | |
| <i>N-category</i> | | | | |
| N2-3/N0-1 | 0.879(0.491–1.574) | 0.665 | | |
| <i>Metastasis number</i> | | | | |
| Two/One | 1.783(1.121–2.834) | 0.015 | 1.073(0.655–1.757) | 0.781 |
| <i>Peritoneal metastasis</i> | | | | |
| Yes/no | 1.812(1.132–2.899) | 0.013 | 2.458(1.381–4.376) | 0.002 |
| <i>Liver metastasis</i> | | | | |
| Yes/no | 1.312(0.821–2.099) | 0.256 | | |
| <i>Retroperitoneal lymph node metastasis</i> | | | | |
| Yes/No | 0.739(0.442–1.237) | 0.250 | | |
| <i>Ovary metastasis</i> | | | | |
| Yes/no | 0.878(0.451–1.710) | 0.702 | | |
| <i>Preoperative CEA</i> | | | | |
| > 5/≤ 5 | 1.516(0.931–2.468) | 0.094 | | |
| <i>Preoperative CA125</i> | | | | |
| > 35/≤ 5 | 2.324(1.461–3.696) | < 0.001 | 0.903(0.504–1.616) | 0.731 |
| <i>Preoperative CA199</i> | | | | |
| > 37/≤ 37 | 1.428(0.870–2.343) | 0.158 | | |
| <i>Differentiation</i> | | | | |
| Median/poor | 0.716(0.318–1.612) | 0.419 | | |
| <i>Conversion surgery</i> | | | | |
| Without/with | 5.859(3.421–10.033) | < 0.001 | 6.999(3.716–13.186) | < 0.001 |
| <i>Treatment response</i> | | | | |
| CR&PR/SD&PD | 0.302(0.186–0.488) | < 0.001 | 1.236(0.640–2.387) | 0.528 |

CEA Carcinoembryonic antigen, CA125 Carbohydrate antigen 125, CA199 Carbohydrate antigen 199, CR Complete response, PR Partial response, SD Stable disease, PD Progressive disease

[24] reported that conversion surgery following chemotherapy safely achieved a favorable conversion rate (33.0%) and pathological response rate (78.8%) in patients with inoperable AGC, contributing to an extended OS. Furthermore, another retrospective study demonstrated a significantly prolonged MST in patients who underwent conversion surgery compared with those who did not [25]. These results have indicated that conversion therapy, utilizing chemotherapy with the goal of converting initially unresectable gastric cancer to a resectable form, may represent a viable treatment approach for patients with AGC. Additionally, previous studies have demonstrated that the antitumor activity of chemotherapeutic agents may be enhanced by the synergistic effect of immunotherapy [26, 27]. Moreover, further research suggests that chemotherapy combined with ICIs can lead to better efficacy and improved prognosis for patients with AGC

[13, 15, 16, 28]. However, the feasibility and clinical benefits of this combination regimen in a conversion therapy setting still remain unclear.

Liang et al. [29] reported a comparable ORR of 58.8% and a conversion rate of 30.9% in stage IV gastric cancer patients treated with immunochemotherapy for conversion therapy in a retrospective study. Additionally, those who underwent conversion surgery achieved an improved pCR rate of 16.7%, with 1-year OS and PFS rates of 96.6% and 89.1%, respectively. Similarly, our study reported promising DCR, ORR, and conversion rates, with encouraging pCR and MPR rates achieved in patients who underwent conversion therapy. Consequently, the MST and 1- and 3-year OS rates were significantly higher in the conversion surgery group compared to those in the palliative group. Furthermore, conversion surgery was identified as one of the

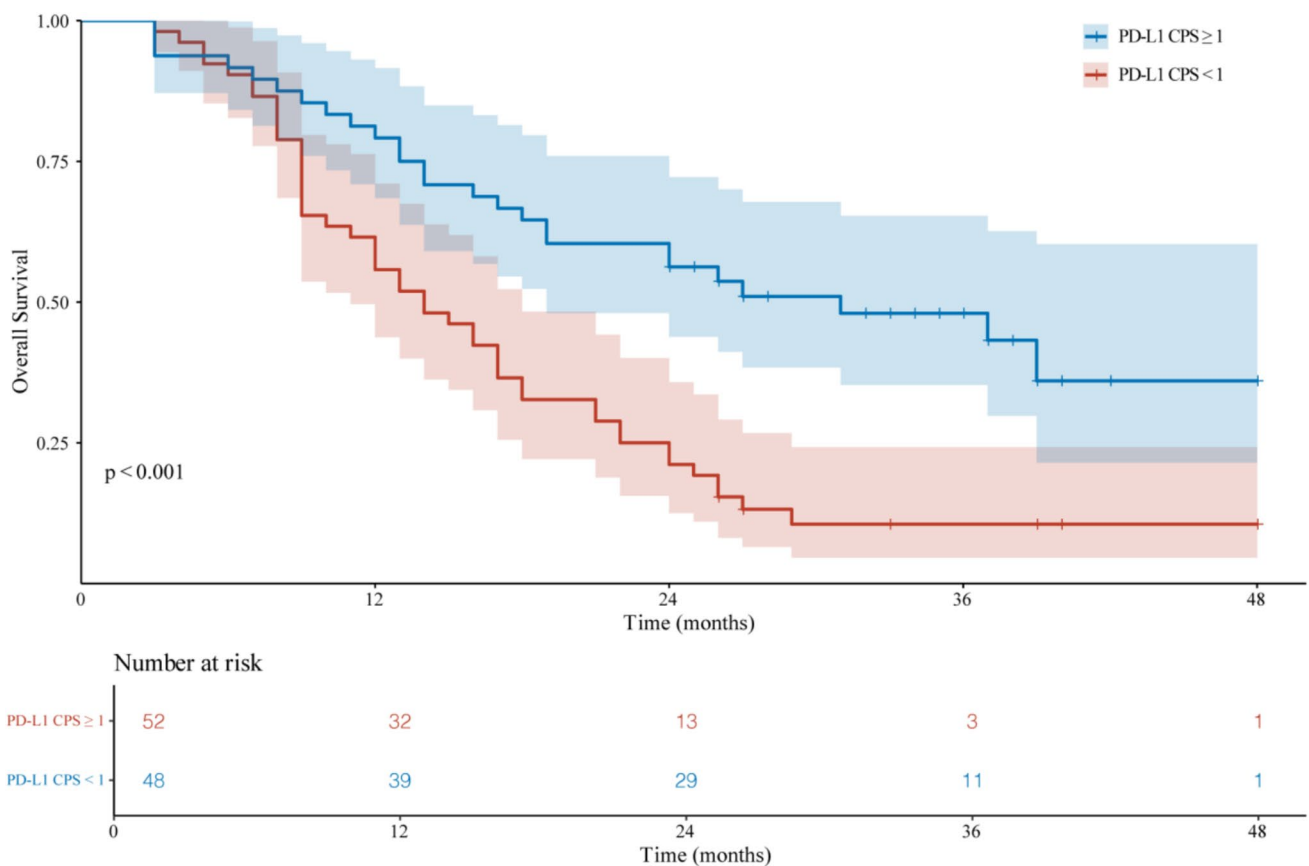


Fig. 3 Kaplan–Meier estimates of the overall survival of patients with PD-L1 CPS ≥ 1 and PD-L1 CPS < 1

independent predictors of OS. These results indicate that patients undergoing conversion therapy and responding positively to chemoimmunotherapy could derive substantial survival benefits from subsequent conversion surgery. Additionally, results from the COMPASSION-15 study showed that a significant improvement in OS and PFS was observed in patients with unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma treated with cadonilimab combined with chemotherapy compared to those receiving chemotherapy alone [30]. Therefore, whether bispecific immune checkpoint inhibitor combined with chemotherapy is a favorable factor for conversion therapy deserves further investigation.

To better understand the biology, indications for conversion surgery, and clinical outcomes of patients with metastatic AGC, Yoshida et al. [8] have classified patients with stage IV gastric cancer into four categories and concluded that conversion therapy might be feasible for patients in category 2, some patients in category 3, and a limited number of patients in category 4. For patients treated with chemotherapy, results from Yamaguchi et al. [25] revealed that the conversion rates of category 1, 2, 3, and 4 were 77.8%, 31.1%, 51.6% and 22.6%, respectively. And a prolong MST

was observed in patients who underwent conversion surgery following systemic chemotherapy. Similarly, our results indicated that conversion therapy based on the combination of chemotherapy and immunotherapy yields a favorable conversion rate for patients with stage IV gastric cancer, and the MST for patients in the surgery group was significantly higher than that for patients in the palliative group regardless of the category. Furthermore, for patients in categories 3 and 4, a survival benefit was observed in those who received HIPEC treatment compared to those who did not, indicating that a combination of local and systemic treatments may yield promising results for patients with peritoneal metastasis. However, this result should be interpreted with caution due to the limited sample size. Considering the complexity and heterogeneity of patients with metastatic gastric cancer across different categories, a comprehensive analysis of factors such as biological characteristics, tumor burden, organ function, and others may prove useful in more accurately predicting their clinical outcomes. However, robust evidence for establishing an optimal treatment strategy, identifying indications for conversion surgery, and predicting prognosis in these patients still needs to be gathered by conducting additional prospective clinical trials.

The toxicity of chemoimmunotherapy and complications arising from subsequent surgery presented crucial issues in evaluating the feasibility of conversion therapy. Previous studies have indicated that the combination of a PD-1 inhibitor and chemotherapy did not significantly increase the incidence of AEs compared to chemotherapy alone [13, 15, 31–33]. The most common hematological toxicities reported include anemia, leukopenia, neutropenia, and thrombocytopenia, while anorexia, nausea, diarrhea, and transaminase elevation were observed as non-hematological toxicities. Furthermore, hypothyroidism and hyperthyroidism were frequently identified as immune-related AEs in patients undergoing chemoimmunotherapy. In our study, the incidence of treatment-related AEs was comparable to that previously observed, and no new safety signals were identified. These accumulating pieces of evidence implied that the safety of chemoimmunotherapy and subsequent conversion surgery was manageable.

Judiciously selecting which patients with stage IV gastric cancer are suitable for conversion therapy may help extend the OS of the patients. Recognized as potential biomarkers, the significance of PD-L1 expression, MMR, and EBV status in both patient selection and the prediction of immunotherapy efficacy has been extensively examined in prior studies [34–37]. However, no strong evidence to support conversion therapy is yet available. Therefore, further exploratory analyses were conducted in the present study.

Previous evidence suggests that PD-1 inhibitors should be added to first-line chemotherapy for advanced gastric cancer patients, which may be associated with extended survival. However, the optimal cut-off value of PD-L1 has not been established. In the conversion therapy setting, Liang et al. [29] reported that PD-L1 CPS ≥ 5 was a favorable factor for successful conversion surgery. In contrast, a significantly improved conversion rate and ORR were observed in patients with PD-L1 CPS ≥ 1 in the present study. This result suggests that a cut-off value of 1 may be sufficient for selecting patients who could benefit from chemoimmunotherapy and subsequent conversion surgery. However, no robust evidence is yet available regarding the predictive value of PD-L1 in conversion therapy. Furthermore, variations in the cut-off value of PD-L1 reported in different studies need to be verified through prospective clinical trials with large sample sizes.

Gastric cancer with the dMMR status is characterized by the elevated levels of neoantigens and infiltration of PD-L1-positive T-cells, which may potentially make it more susceptible to PD-1 blockade [34]. Results from previous studies showed that a higher response rate and a favorable prognosis were achieved in patients with dMMR who were treated with anti-PD-1-based therapies in a neoadjuvant or palliative treatment setting [22, 38, 39]. However, whether the dMMR status is a favorable factor for successful

conversion surgery remains unclear. In this study, despite confirming only five cases with dMMR, a substantial conversion rate of 60.0% was observed in these patients, suggesting that individuals with dMMR may constitute an additional population with high potential for clinical benefit in the context of conversion therapy using PD-1 inhibitors. Furthermore, the NO LIMIT study [40] demonstrated that nivolumab combined with ipilimumab, as a first-line treatment, could achieve promising ORR, DCR, and median PFS for patients with advanced gastric or esophago-gastric junction MSI-H tumors. Therefore, the potential survival benefits of a treatment strategy based on dual immunotherapy for AGC patients with dMMR/MSI-H status in the conversion therapy setting deserve further exploration.

Accumulated evidence suggests that the EBV-associated gastric cancer (EBVaGC) exhibits a robust responsiveness to immune checkpoint blockade, owing to the considerable infiltration of CD8-positive T-cells and heightened expression of PD-L1 and PD-L2 within these tumors [36, 37]. In a prospective phase-2 study, Kim et al. [41] reported a remarkably promising response rate of 100% (6/6) in patients with AGC and an EBV-positive status who underwent PD-1 inhibition treatment. Similar favorable results were also reported in neoadjuvant treatment settings [32, 42]. However, there is a lack of studies exclusively evaluating the clinical benefits of combining PD-1 inhibitors with chemotherapy as a conversion therapy in patients with EBVaGC. Therefore, an exploratory analysis was conducted in the present study. Our results revealed that, among the seven confirmed cases of EBV-positivity, three underwent conversion surgery, and all these three patients achieved an MPR, as shown by the pathological evaluation. Although these encouraging findings were obtained using a small sample size and, hence, may not carry robust clinical implications, they still offer valuable insights for future research in the field of conversion therapy for EBV-positive patients.

This study had several limitations. Firstly, it was a retrospective study with a relatively small sample size. Therefore, a selection bias was unavoidable because of the nature of the retrospective research. Secondly, the follow-up duration was relatively short, requiring further exploration to understand the potential long-term survival benefits. Thirdly, only a limited amount of sample tissue was available, which prevented the detection of potential biomarkers among the enrolled patients. Finally, the interpretation of subgroup analyses (e.g., dMMR, EBV-positive) is constrained by the small sample size, and these findings should therefore be regarded as exploratory. Despite these limitations, our findings are valuable and may provide insights for future research on the conversion therapy of patients with AGC.

In conclusion, our data indicate that the combination of PD-1 inhibitors with chemotherapy in conversion therapy is feasible for patients with AGC. Patients who exhibit

improved responses to chemoimmunotherapy may potentially experience survival benefits, particularly those with PD-L1 positivity. Nevertheless, further validation of the study findings requires additional prospective clinical studies with larger samples.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00262-025-04161-6>.

Acknowledgements We thank all the study participants and research staff who participated in this work.

Author contributions L.H., P.Y. and Y.D. designed the study. H.C., H.C., and J.F, Z.Y. collected and extracted data. X.H., J.C., X.C. and C.H. analyzed and interpreted the data. X.H. drafted the manuscript. P.Y. and L.H. critically revised the manuscript.

Funding This study was supported by the Natural Science Foundation of Zhejiang Province of China (LBZ22H160002 awarded to Pengfei Yu; LTGY24H160031 awarded to Xiangliu Chen).

Data availability The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This study was approved by the Ethics Committee of Zhejiang Cancer Hospital (approval number: IRB-2022–278) and was conducted according to the Declaration of Helsinki. Informed consent was obtained from each patient enrolled in the study.

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