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Effect of *Helicobacter pylori* infection on survival outcomes of patients undergoing radical gastrectomy after neoadjuvant chemotherapy: a multicenter study in China

Qi-Chen He[1,2,3,4†], Ze-Ning Huang[1,2,3,4†], Chen-Bin Lv[7†], Yong-He Wu[9], Wen-Wu Qiu[1,2,3,4], Yu-Bin Ma[8], Ju Wu[1,2,3,4,5], Chang-Yue Zheng[1,2,3,4,6], Guo-Sheng Lin[1,2,3,4], Ping Li[1,2,3,4], Jia-Bin Wang[1,2,3,4], Jian-Xian Lin[1,2,3,4], Mi Lin[1,2,3,4], Ru-Hong Tu[1,2,3,4], Chao-Hui Zheng[1,2,3,4], Chang-Ming Huang[1,2,3,4*], Long-Long Cao[1,2,3,4*] and Jian-Wei Xie[1,2,3,4*]

Abstract

Background Neoadjuvant chemotherapy (NAC) has been confirmed to improve the prognosis of patients with advanced gastric cancer (AGC). However, no study has investigated whether *Helicobacter pylori* (HP) infection affects the postoperative survival of patients who receive NAC.

Methods This retrospective cohort study included 307 patients with AGC who underwent laparoscopic radical gastrectomy after NAC at three hospitals in China between January 1, 2016, and April 31, 2020. Cox regression was used to assess prognostic factors for survival. Kaplan–Meier was used for survival analysis.

Results The HP + and the HP- group included 141 and 166 cases. The 3-year overall survival (OS) and disease-free survival (DFS) of the HP + group were significantly better than the HP- group (3-year OS: 75.9% vs. 60.2%, 3-year DFS: 70.2% vs. 52.3%; All $P < 0.001$). For the HP + group, ypTNM Stage III (HR, 4.00; 95% CI, 1.11–14.39; $P = 0.034$), NAC ≥ 4 cycles (HR, 0.43; 95% CI, 0.20–0.90; $P = 0.026$), and adjuvant chemotherapy (AC) ≥ 4 cycles (HR, 0.20; 95% CI, 0.09–0.48; $P < 0.001$) are independent prognostic factors for OS. In the cohort of HP + patients who received ≥ 4 cycles of NAC, the prognosis of patients who received ≥ 4 cycles of AC after surgery was better than that of patients who received < 4 cycles of AC (3-year OS: 92.5% vs 71.4%; $P = 0.042$).

Conclusions Following NAC, HP + patients with AGC exhibit better prognosis than that of HP- counterparts. For potentially resectable HP + AGC patients, radical surgery following ≥ 4 cycles of NAC with ≥ 4 cycles of sequential AC might be recommended to improve survival.

Keywords Neoadjuvant chemotherapy, *Helicobacter pylori*, Gastric cancer, Gastrectomy

†Qi-Chen He, Ze-Ning Huang, and Chen-Bin Lv contributed equally to this work and should be considered co-first authors.

*Correspondence:
Chang-Ming Huang
hcmlr2002@163.com
Long-Long Cao
1291821982@qq.com
Jian-Wei Xie
xjwhw2019@163.com
Full list of author information is available at the end of the article

Introduction

Gastric cancer is the fifth most common malignant tumor and the fourth leading cause of cancer-related deaths [1]. Currently, treatment strategies dominated by surgical resection remains the cornerstone of gastric cancer treatment. Despite advancements in surgical techniques that can reduce the morbidity and mortality associated with gastric cancer surgery [2], the prognosis for patients with advanced gastric cancer (AGC) remains poor even after complete tumor resection [3]. Recently, perioperative chemotherapy has gradually become an essential component of the comprehensive treatment of AGC [4–7]. Several large-scale randomized controlled trials have shown that perioperative chemotherapy can improve the overall survival (OS) and disease-free survival (DFS) of patients with AGC [8, 9].

In 1994, *Helicobacter pylori* (HP) was classified as a type I carcinogen by the International Agency for Research on Cancer, with studies indicating that HP infection could be a risk factor for gastric cancer in an intact gastric mucosa [10]. However, some reports have suggested that gastric cancer patients with a positive HP infection have a better postoperative prognosis [11, 12], and benefit more from adjuvant chemotherapy (AC) [13–16]. Nishizuka et al. [13] postulated that HP could regulate the host immune system, enhancing the efficacy of chemotherapy and improving prognosis. Choi et al. [14] found that patients with advanced or metastatic gastric cancer and HP infection had a better chemotherapy response and OS than those without HP infection. Based on multiple previous studies indicating that HP infection may improve survival in gastric cancer patients undergoing postoperative chemotherapy, we hypothesize that HP infection could influence the response of patients with locally advanced gastric cancer to NAC, as well as their postoperative survival outcomes. We propose that HP + patients may attain better expected chemotherapy responses following NAC. However, currently, no research has explored the relationship between HP infection and the efficacy of neoadjuvant chemotherapy (NAC).

Therefore, this multicenter, retrospective cohort study investigated the effect of HP infection status on the survival of patients with AGC who received NAC.

Methods

Study population

This retrospective cohort study analyzed data from 327 patients with AGC who underwent NAC and radical gastrectomy between January 1, 2016, and April 31, 2020, at three hospitals in China (191 cases at the Affiliated Union Hospital of Fujian Medical University, 59 cases at the Affiliated Zhangzhou Hospital of Fujian Medical University, and 77 cases at the Affiliated Hospital of Qinghai University). The inclusion criteria were as follows: 1) aged 18–80; 2) primary gastric tumor pathologically confirmed as adenocarcinoma with clinical stages cT2-4N0/ + M0; 3) received NAC; and 4) complete imaging data before and after chemotherapy. The exclusion criteria included 1) history or coexistence of other organ malignancies, 2) evidence of metastasis found in preoperative and intraoperative examinations, 3) previous gastrectomy or ESD, 4) remnant gastric cancer, and 5) R1 resection. The screening process used in this study is illustrated in Fig. 1. Finally, 307 patients were included in the analysis, among which 141 cases were in the HP + group and 166 cases in the HP- group. Although this study is a retrospective analysis, all participants signed a general informed

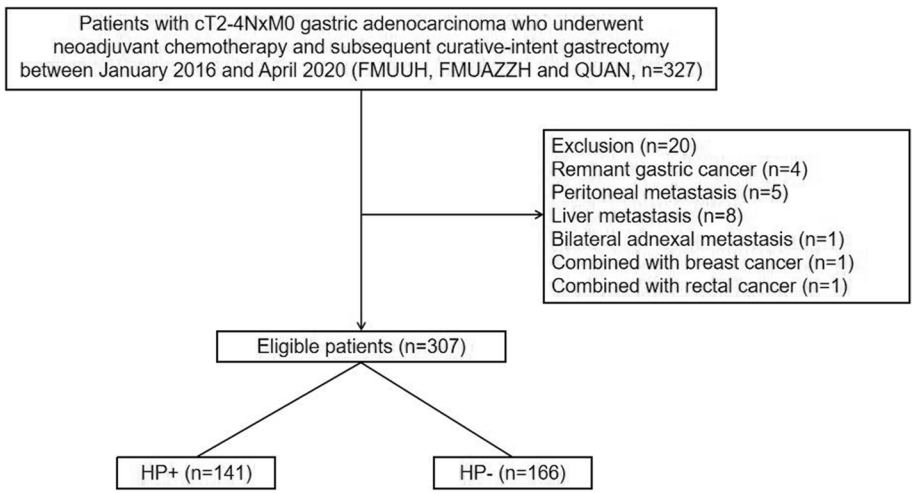


Fig. 1 Diagram of study population in all patients

consent form at the time of data collection (during hospital admission and perioperative chemotherapy), explicitly allowing the use of their anonymized data for future research. This consent process was reviewed and approved by the ethics committees of Fujian Medical University Union Hospital, Fujian Medical University and the Affiliated Zhangzhou Hospital of Fujian Medical University, and the Affiliated Hospital of Qinghai University (Number of IRB: 2024KY090), in accordance with the ethical requirements of Article 32 of the Declaration of Helsinki regarding the "Secondary use of medical record data."

Perioperative chemotherapy

According to the NCCN guidelines, for patients with locally advanced gastric cancer staged as cT2-4N0-3, the preferred treatment approach is a combination of neoadjuvant chemotherapy followed by adjuvant therapy, with regimens including 5-FU-based SOX, XELOX, DS, or FOLFOX4 [17]. This study included patients with locally advanced gastric cancer (cT2-4N0/ + M0) and administered one of the NAC regimens, including SOX, XELOX, DS, or FOLFOX4, to all participants. After R0 resection, patients continued with the same NAC regimen for postoperative adjuvant chemotherapy, without being stratified based on pathological staging. The detail of perioperative chemotherapy regimens were as follows: SOX (S-1 40–60 mg orally twice daily on days 1–14; oxaliplatin 130 mg/m2 intravenously on day 1) [18]. XELOX (1000 mg/m2 of capecitabine orally twice daily on days 1 to 14 and 130 mg/m2 of oxaliplatin intravenously on day 1). DS (S-1 40–60 mg orally twice daily on days 1–14; docetaxel 40 mg/m2 intravenously on day 1) [19]. FOLFOX4 (oxaliplatin 85 mg/m2 intravenously on day 1, leucovorin 200 mg/m2 as a 2-h intravenous infusion followed by bolus fluorouracil 400 mg/m2, and a 22-h intravenous infusion of fluorouracil 600 mg/m2) [20]. The SOX regimen is widely used in the East Asian population, and several phase III clinical trials (such as the G-SOX study [18]) have demonstrated its efficacy and tolerability. The CSCO guidelines recommend SOX as a first-line regimen for perioperative chemotherapy in locally advanced gastric cancer, particularly in patients with good performance status (ECOG 0–1) and without serious comorbidities. The XELOX regimen is suitable for patients who cannot tolerate S-1 or have gastrointestinal absorption disorders. The oral convenience of capecitabine has been shown to enhance patient compliance, with its efficacy equivalent to that of intravenous 5-FU [17]. The DS regimen is appropriate for patients with a higher tumor burden or poor pathological differentiation; the microtubule-stabilizing effect of docetaxel can enhance tumor-killing effects, especially in patients with signet-ring cell carcinoma [19]. For patients intolerant to S-1 or capecitabine, the FOLFOX4 regimen can be considered. This regimen has been widely validated in studies from Europe and the United States (such as the MAGIC trial [8]) and is suitable for patients requiring short-cycle intensified treatment. Upon initial admission, we provided patients with detailed information regarding the dosage, oncological efficacy, and adverse effects of each of the four chemotherapy regimens, ultimately deciding on the perioperative chemotherapy plan based on the patients' preferences. The SOX, XELOX, and DS regimens are administered in 3-week cycles, while the FOLFOX4 regimen is given in 2-week cycles. All perioperative chemotherapy regimens and dosages are determined by experienced oncologists at each center and are adjusted according to tumor response and the adverse reactions of the chemotherapy agents. CT assessments were carried out following every two cycles throughout the NAC phase. We defined completing eight or more cycles of perioperative chemotherapy as the Total Cycles Compliance (TCC) [21]. For the treatment strategies following recurrence, decisions are made by a multidisciplinary team (MDT), referencing the NCCN guidelines for gastric cancer to formulate measures including chemotherapy, radiotherapy, immunotherapy, and targeted therapy [17]. The final treatment decision is made considering the patient's general condition, recurrence pattern, and molecular characteristics. All treatment plans are adjusted according to the patient's tolerance to ensure safety and effectiveness.

Surgery

Following the completion of NAC, all patients underwent surgical resection within 2–4 weeks. To rule out peritoneal and distant metastases, routine laparoscopic exploration was carried out. Lymph node dissection adhered to the latest Japanese Gastric Cancer Treatment Guidelines (5th edition) [4]. The TNM staging was conducted based on the 8th edition of the TNM Staging System for gastric cancer by the American Joint Committee on Cancer [22].

H. pylori status determination

For the diagnosis of Helicobacter pylori infection, the status was determined by pathologists examining surgical specimens obtained from endoscopic biopsy after the first regimen of neoadjuvant chemotherapy, using Giemsa staining or immunohistochemistry to confirm the presence of the infection. HP infection was ascertained through histopathological techniques, with the surgical pathological specimens being assessed according

to the Sydney System [23]. This system evaluates criteria including inflammation, activity, atrophy, metaplasia, and HP infection presence. The detection of HP infection was verified through meticulous examination of the tissue sections. Pathological specimens underwent evaluation by pathologists who were blinded to the clinical and pathological information.

Pathological response

Tumor Regression Grade (TRG) was evaluated according to the Becker criteria [24], classifying it as "Grade 1a" for complete tumor regression, indicating no residual tumor within the tumor bed; "Grade 1b" for subtotal tumor regression, with less than 10% residual tumor; "Grade 2" for partial tumor regression, with 10–50% residual tumor; and "Grade 3" for minimal or no tumor regression, where more than 50% of the tumor remains. Pathologic Complete Response (pCR) was defined as no evidence of invasive disease in the examined gross lesions and histologically negative lymph nodes as verified by central review. In this study, "Grade 1a" corresponds to "TRG 0", "Grade 1b" to "TRG 1", "Grade 2" to "TRG 2", and "Grade 3" to "TRG 3".

Follow-up

Overall survival (OS) was delineated as the time span from the date of surgery to death resulting from any cause. Disease-free survival (DFS), on the other hand, referred to the interval from surgery to either the recurrence of the disease or death from any cause. A mandatory follow-up duration of at least 36 months post-surgery was established for every patient. Postoperative follow-up was conducted quarterly for the first two years and semi-annually in the third year. Follow-up included: 1) CEA, CA12-5, and CA19-9 tests, initially quarterly then semi-annually; 2) biannual chest X-rays and abdominal CTs for three years; and 3) annual upper gastrointestinal endoscopies. PET-CT was performed upon recurrence suspicion. Local recurrences were identified as gastric masses, D2 lymph nodes, and anastomotic sites; distant metastases encompassed non-D2 lymph nodes and organs such as liver, lungs, and pancreas. Peritoneal metastasis criteria included positive ascites for tumor cells, increased peritoneal thickening, enlarged peritoneal nodes on imaging, or invasion into the uterus or ovaries [25]. Multisite recurrences were noted when two or more sites were involved simultaneously. Recurrences at the same site were not deemed new metastases. Diagnosis was established through medical history, physical examination, imaging, cytology, or biopsy (preferred).

Statistical analyses

Continuous variables were expressed as median (range), and categorical variables were expressed as numbers (percentages). Continuous variables were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the chi-square or Fisher's exact test and expressed as percentages. All tests were two-sided, and the level of significance was set at $P < 0.05$. OS and DFS rates were calculated using the Kaplan–Meier method, and differences were assessed using the log-rank test. Univariate and multivariate analyses were performed using a COX proportional hazards regression model. Variables with $P < 0.05$ were included in the multivariate Cox analysis using the backward likelihood ratio (LR) method. The cutoff values for the number of chemotherapy cycles were defined using the X-tile software. The X-tile method was used to estimate the correlation between the number of chemotherapy cycles and survival in the HP + cohort. The covariates adjusted for in the subgroup analysis were all independent factors that influenced prognosis (DFS and OS). Cox regression analysis with interaction terms was used to determine whether the differences in effect sizes among the subgroups were statistically significant. This study is a multicenter retrospective cohort study, and all included patients adhered to standardized inclusion and exclusion criteria. To minimize inter-center variability, we controlled for potential confounding factors by adjusting key covariates (such as ypTNM staging, adjuvant chemotherapy, and HP infection status) in the multivariable models. In the competitive risk analysis based on Fine and Grey's [26] method, the endpoint event was recurrence at any site, with death from any cause or other recurrence as the competing risk. The cumulative incidence function was computed in the presence of competing risks, and competitive risk survival regression was used as an alternative to COX regression using IBM SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA) and R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

In total, 327 patients with locally AGC who underwent radical gastrectomy following NAC at Fujian Medical University Union Hospital, Affiliated Hospital of Qinghai University, and Zhangzhou Hospital Affiliated to Fujian Medical University from January 2016 to April 2020 were included in this study. After applying the exclusion criteria, 307 patients were included

in the final analysis, including 141 in the HP + group and 166 in the HP- group (Fig. 1). No statistical differences were observed between the two groups in terms of age, sex, BMI, ECOG score, surgical method, reconstruction method, tumor location, tumor size, degree of differentiation, TRG grade, ypT, ypN, ypTNM staging, CEA, CA19-9, AC, or the number of NAC cycles (All $P > 0.05$; Table 1). Perioperative chemotherapy details are presented in eTable 1. No statistically significant difference was observed in TCC between the two groups ($P = 0.058$), nor in the total number of chemotherapy cycles administered ($P = 0.058$). Both the HP + and HP- groups exhibited a median of 3 cycles for NAC, while the median AC cycles were 4 and 3, respectively. Furthermore, no significant intergroup differences were identified in NAC regimens ($P = 0.764$).

Univariate and multivariate analyses

Univariate COX analysis demonstrated that vascular invasion, neural invasion, TRG grade, ypTNM stage, AC, and HP infection status were factors affecting OS and DFS in patients with gastric cancer who received NAC (Table 2, 3). Further multivariate analysis showed that HP infection (hazard ratio (HR), 0.53; 95% confidence interval (CI), 0.36–0.79; $P = 0.002$), ypTNM stage III (HR, 3.28; 95% CI, 1.73–6.23; $P < 0.001$), and AC (HR, 0.53; 95% CI, 0.33–0.84; $P = 0.008$) were independent prognostic factors for OS (Table 2). Additionally, HP infection (HR, 0.57; 95% CI, 0.39–0.82; $P = 0.003$), ypTNM stage III (HR, 3.28; 95% CI, 1.70–6.36; $P < 0.001$), and AC (HR, 0.62; 95% CI, 0.39–0.99; $P = 0.048$) were also independent prognostic factors for DFS (Table 3). In terms of survival, the 3-year OS and DFS of the HP + group were significantly higher than that of the HP- group (3-year OS: 75.9% vs. 60.2%, 3-year DFS: 70.2% vs. 52.3%; all $P < 0.001$) (Fig. 2A, B).

Recurrence pattern in HP ± Groups

In terms of recurrence, 44 patients in the HP + group (Cumulative incidence rate of 31.2%) and 84 patients in the HP- group (Cumulative incidence rate of 50.6%) experienced recurrence after surgery. The cumulative incidence of recurrence in HP + group was significantly lower than that in the HP group ($P = 0.001$). Furthermore, in terms of distant recurrence and peritoneal recurrence, the recurrence rates in the HP + group were also lower than that in the HP- group (9.2% vs. 17.5%; 1.4% vs. 10.8%; respectively, all $P < 0.05$) (Table 4). The competing risks model further confirms the aforementioned differences. The cumulative incidence of recurrence in the two patient groups was compared using a competing risk model. Considering death as a competing event, the overall cumulative incidence of recurrence in the HP + group was significantly lower than that in the HP- group (sHR, 0.54; 95% CI, 0.37–0.77; $P < 0.001$; Fig. 3A). The cumulative incidence of distant recurrence in the HP + group was significantly lower than that of the HP- group (sHR, 0.51; 95% CI, 0.27–0.97; $P = 0.038$), with all-cause death before recurrence and non-distant recurrence as competing events (Fig. 3B). Additionally, the cumulative incidence of peritoneal recurrence in the HP + group was also significantly lower than that of the HP- group (sHR, 0.19; 95% CI, 0.06–0.64; $P = 0.003$), with all-cause death before recurrence and non-peritoneal recurrence as competing events (Fig. 3C). The overall cumulative risk of recurrence was significantly lower in the HP + group than in the HP-group, and the HP-group had a peak of late recurrence at 59.4 months after surgery (Fig. 4A). Stratifying for distant recurrence, the HP-group showed a bimodal pattern (early 3.8 months and late 58.5 months), compared with only early unimodal (5.1 months) in the HP + group (Fig. 4B). Regarding peritoneal recurrence, the HP-group showed a single peak at 36 months, but no significant peak in the HP + group (Fig. 4C).

Impact of chemotherapy cycles on survival

We used the X-tile software to determine the optimal number of NAC cycles, aiming to identify the number that would positively impact the OS and DFS of HP + patients. The results showed that when the NAC was 4, there was a significant difference in the 3-year OS and DFS on the Kaplan–Meier curve (3-year OS: 85.2% vs. 66.8%; $P = 0.018$; 3-year DFS: 82.0% vs. 61.2%; $P = 0.007$) (eFigure 1, 2). The results of the multivariate adjustment (adjusted factors: ypTNM stage, AC, HP infection status) subgroup analysis showed that in HP + patients, receiving ≥ 4 cycles of NAC was an independent prognostic factor affecting OS or DFS (OS [HR, 0.17; 95% CI, 0.08–0.35; P for interaction] < 0.001; DFS [HR, 0.18; 95% CI, 0.09–0.34; P for interaction] < 0.001) (Fig. 5A, B). These results suggest that using ≥ 4 NAC cycles can effectively improve the prognosis of HP + patients with gastric cancer.

According to the stratification analysis based on AC, the results showed that for the HP + group, the OS of patients who received AC was significantly better than those who did not (3-year OS: 81.3% vs 38.9%; $P < 0.001$; HR, 0.23; 95% CI, 0.11–0.48; $P < 0.001$). However, in the HP- group, AC did not significantly improve the OS (3-year OS: 61.3% vs 54.2%; $P = 0.880$; HR, 0.95; 95% CI, 0.50–1.81; $P = 0.881$) (Fig. 6A, B and eTable 2).

We utilized X-tile software to determine the optimal number of AC cycles, aiming to identify the

Table 1 Demographic characteristics of all patients stratified into H. Pylori-negative and H. Pylori-positive cohorts

Characteristic	Median (Range)/No. (%)		*P*[1]
	H. pylori negative (*n* = 166, 54.1%)	H. pylori positive (*n* = 141, 45.9%)	
Age, years			0.976
< 70	145 (87.3%)	123 (87.2%)	
≥ 70	21 (12.7%)	18 (12.8%)	
Sex			0.479
Male	125 (75.3%)	111 (78.7%)	
Female	41 (24.7%)	30 (21.3%)	
BMI, kg/m^2			0.117
< 25	147 (88.3%)	116 (82.3%)	
≥ 25	19 (11.4%)	25 (17.7%)	
ECOG PS			0.831
0	129 (77.7%)	111 (78.7%)	
1	37 (22.3%)	30 (21.3%)	
Surgical procedure			0.690
Distal gastrectomy	30 (18.1%)	28 (19.9%)	
Total gastrectomy	136 (81.9%)	113 (80.1%)	
Reconstruction Method			0.774
B-I	13 (7.8%)	10 (7.1%)	
B-II	17 (10.2%)	18 (12.8%)	
Roux-En-Y	136 (82.0%)	113 (80.1%)	
Tumor location			0.262
Upper	70 (42.2%)	66 (46.8%)	
Middle	41 (24.6%)	25 (17.7%)	
Lower	34 (20.5%)	37 (26.2%)	
Mix	21 (12.7%)	13 (9.3%)	
Tumor size, cm			0.356
< 4	71 (42.8%)	53 (37.6%)	
≥ 4	95 (57.2%)	88 (62.4%)	
Histology			0.274
Well and middle	69 (41.6%)	50 (35.5%)	
Poor and underdifferentiated	97 (58.4%)	91 (64.5%)	
TRG			0.349
0–1	30 (18.0%)	35 (24.8%)	
2	68 (41.0%)	54 (38.3%)	
3	68 (41.0%)	52 (36.9%)	
cT			0.688
T3	46 (27.7%)	42 29.8%)	
T4	120 (72.3%)	99 (70.2%)	
cN			0.597
N0	11 (6.6%)	14 (9.9%)	
N1	43 (25.9%)	41 (29.1%)	
N2	40 (24.2%)	27 (19.2%)	
N3	11 (6.6%)	12 (8.5%)	
Nx	61 (36.7%)	47 (33.3%)	
cM			0.999
M0	166 (100.0%)	141 (100.0%)	
cTNM stage			0.529
II	11 (6.6%)	14 (9.9%)	
III	94 (56.6%)	80 (56.8%)	

Table 1 (continued)

Characteristic	Median (Range)/No. (%)		P^1
	H. pylori negative ($n=166$, 54.1%)	H. pylori positive ($n=141$, 45.9%)	
Unknown	61 (36.8%)	47 (33.3%)	
ypT			0.296
T0	10 (6.0%)	7 (5.0%)	
T1	12 (7.2%)	8 (5.7%)	
T2	21 (12.7%)	20 (14.1%)	
T3	55 (33.1%)	62 (44.0%)	
T4	68 (41.0%)	44 (31.2%)	
ypN			0.412
N0-1	90 (54.2%)	85 (60.3%)	
N2	30 (18.1%)	26 (18.4%)	
N3	46 (27.7%)	30 (24.8%)	
ypTNM stage			0.245
pCR-I	28 (16.9%)	25 (17.7%)	
II	50 (30.1%)	54 (38.3%)	
III	88 (53.0%)	62 (44.0%)	
Pre-chemo CEA			0.727
< 5	98 (59.0%)	86 (61.0%)	
≥ 5	68 (41.0%)	55 (39.0%)	
Pre-chemo CA199			0.975
< 37	118 (71.1%)	100 (70.9%)	
≥ 37	48 (28.9%)	41 (29.1%)	
Neoadjuvant chemotherapy			0.684
1–3 cycles	98 (59.0%)	80 (56.7%)	
≥ 4 cycles	68 (41.0%)	61 (43.3%)	
Adjuvant chemotherapy			0.667
No	24 (14.5%)	18 (12.8%)	
Yes	142 (85.5%)	123 (87.2%)	

BMI Body mass index, *ECOG PS* Eastern Cooperative Oncology performance status, *TRG* Tumor regression grade

number that would positively impact the OS and DFS of HP + patients. The results showed that when the number of AC cycles were 4, there were significant differences in the 3-year OS and DFS on the Kaplan–Meier curve (3-year OS: 86.8% vs. 63.1%; $P<0.001$; 3-year DFS: 80.3% vs. 58.5%; $P=0.003$) (eFigure 3, 4). Multivariate COX analysis showed that ypTNM stage III (HR, 4.00; 95% CI, 1.11–14.39; $P=0.034$), NAC ≥ 4 (HR, 0.43; 95% CI, 0.20–0.90; $P=0.026$), AC ≥ 4 (HR, 0.20; 95% CI, 0.09–0.48; $P<0.001$) were independent prognostic factors for OS in HP + patients (eTable 3). The analysis was further stratified according to the number of chemotherapy cycles. In the HP + cohort receiving 1–3 cycles of NAC, there was no significant difference in survival between patients who received ≥ 4 cycles of AC postoperatively and patients who received < 4 cycles of AC (3-year OS: 76.5% vs. 59.1%; $P=0.062$) (eFigure 5). However, in the HP + cohort receiving ≥ 4 cycles of NAC, patients who received ≥ 4 cycles of AC postoperatively had a better prognosis than patients who received < 4 cycles of AC postoperatively (3-year OS: 92.5% vs 71.4%; $P=0.042$) (eFigure 6).

Moreover, we further analyzed the impact of the number of NAC cycles on the survival of the HP- cohort. Multivariate COX analysis showed that age ≥ 70 (HR, 2.15; 95%CI,1.19–3.86;$P=0.011$), ypTNM stage III (HR, 3.09; 95%CI, 1.46–6.56; $P=0.003$, NAC ≥ 4 (HR, 2.22; 95%CI, 1.40–3.54; $P=0.001$) were independent prognostic factors for OS in HP- patients (eTable 4). In HP- patients, regardless of whether they received 1–3 cycles of NAC before surgery or ≥ 4 cycles of NAC before surgery, there was no significant survival difference between patients who received ≥ 4 cycles of AC after surgery and those who received less than 4 cycles of AC (P for NAC 1–3 cycles = 0.768; P

Table 2 Univariate and multivariate analyses of prognostic factors for OS

Overall Survival								
Clinical Parameters	**Univariable**				**Multivariable**			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***
Age, years								
< 70	Ref							
≥ 70	1.501	0.906	2.489	0.115				
Sex								
Male	Ref							
Female	1.100	0.709	1.707	0.670				
BMI, kg/m^2								
< 25	Ref							
≥ 25	0.788	0.442	1.406	0.420				
Surgical procedure								
Distal gastrectomy	Ref							
Total gastrectomy	1.285	0.774	2.131	0.332				
Reconstruction Method								
B-I	Ref							
B-II	1.440	0.540	3.838	0.466				
Roux-En-Y	1.595	0.698	3.646	0.268				
Tumor location								
Upper	Ref							
Middle	1.154	0.722	1.844	0.549				
Lower	0.751	0.447	1.262	0.276				
Mix	1.192	0.659	2.156	0.562				
Tumor size, cm								
< 4	Ref							
≥ 4	1.267	0.861	1.864	0.231				
Histology								
Well and middle	Ref							
Poor and underdifferentiated	1.134	0.771	1.668	0.524				
Lymphovascular invasion								
No								
Yes	1.666	1.143	2.429	**0.008**				
Perineural infiltration								
No								
Yes	1.825	1.241	2.685	**0.002**				
TRG								
0–1	Ref							
2	1.642	0.912	2.955	0.099				
3	2.287	1.289	4.060	**0.005**				
ypTNM stage								
pCR-I	Ref				Ref			
II	1.261	0.623	2.554	0.519	1.458	0..714	2.976	0.301
III	3.036	1.609	5.728	**0.001**	3.279	1.730	6.216	**< 0.001**
Pre-chemo CEA								
< 5	Ref							
≥ 5	1.310	0.902	1.904	0.156				
Pre-chemo CA199								
< 37	Ref							
≥ 37	1.386	0.936	2.052	0.103				

Table 2 (continued)

Overall Survival								
Clinical Parameters	**Univariable**				**Multivariable**			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***
Adjuvant chemotherapy								
No	Ref				Ref			
Yes	0.530	0.332	0.846	**0.008**	0.525	0.327	0.843	**0.008**
HP status								
Negative	Ref				Ref			
Positive	0.499	0.336	0.743	**0.001**	0.529	0.355	0.788	**0.002**

BMI Body mass index, *TRG* Tumor regression grade, *HP* Helicobacter Pylori

for NAC ≥ 4 cycles = 0.071) (eFigure 7,8). To further investigate the impact of the number of chemotherapy cycles on patients without HP infection, we introduced the concept of TCC and classified HP- patients into two groups: those receiving ≥ 8 cycles of perioperative chemotherapy and those receiving < 8 cycles. The results indicated that there was no significant difference in survival between HP- patients receiving ≥ 8 cycles and those receiving less than 8 cycles (P for OS = 0.898; P for DFS = 0.350) (eFigures 9A, B).

Landmark analysis

Landmark analysis (chosen at 6 months postoperatively, with a sample size of 136 patients) was performed to investigate the association between the number of chemotherapy cycles and survival benefits in patients with HP. The results showed that in the HP + cohort that received ≥ 4 cycles of NAC, the survival rates of patients who received ≥ 4 cycles of AC were significantly better than that of patients who received < 4 cycles of AC ($P = 0.042$). However, among HP + patients who received only 1–3 cycles of NAC, there was no survival difference between those who received ≥ 4 cycles of AC and those who received < 4 cycles of AC ($P = 0.287$) (eFigure 10).

Discussion

To the best of our knowledge, this is the first study to assess the impact of HP infection status on the long-term survival of patients with AGC who underwent radical gastrectomy following NAC. Our findings indicate that in the cohort of HP + AGC patients who received NAC, postoperative AC was associated with improved OS, whereas in HP- gastric cancer patients receiving NAC, AC did not contribute to improving OS. Moreover, we found that in the HP + cohort, patients who received at least 4 cycles of NAC and more than 4 cycles of AC achieved the greatest long-term survival benefits. These conclusions suggest that HP infection status could be a pivotal factor in patients with AGC benefiting from NAC and AC.

Analyzing the dynamic changes in recurrence risk over time in different recurrence patterns in gastric cancer will help develop individualized clinical follow-up strategies. In the analysis of postoperative recurrence in gastric cancer, death (particularly non-tumor-related death) is a competing event. The traditional Kaplan–Meier method may overestimate the risk of recurrence because it assumes that competing events (such as death) are independent of recurrence. However, if patients die from other causes, subsequent recurrences cannot be observed. The Fine-Gray competing risks model incorporates competing events into the analytical framework by calculating the cumulative incidence function (CIF) and subdistribution hazard ratio (sHR), leading to a more accurate quantification of recurrence risk [26]. The dynamic relationship of recurrence risk over time after radical gastrectomy showed that the cumulative recurrence rate was always lower in the HP + group than in the HP- group, both in the overall recurrence pattern and in the distant, and peritoneal recurrence patterns. Stratified analysis revealed that the cumulative incidence of peritoneal recurrence and liver recurrence in the HP + group was significantly lower than that in the HP- group. Previous studies have shown that individuals with mutations in the PI3K/AKT pathway are more likely to experience peritoneal and hematogenous metastasis, particularly to the liver and lungs [27]. Some research suggests that HP infection plays an important role in regulating the PI3K/AKT pathway [28, 29]. From the perspective of gene mutations, the mutation frequency of PI3K/AKT pathway-related genes in patients with HP infection is significantly lower than in those without HP infection [30]. Therefore, we hypothesize that HP infection may be associated with

Table 3 Univariate and multivariate analyses of prognostic factors for DFS

Disease-free survival								
Clinical Parameters	**Univariable**				**Multivariable**			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***
Age, years								
< 70	Ref							
≥ 70	1.257	0.772	2.048	0.357				
Sex								
Male	Ref							
Female	1.127	0.752	1.690	0.564				
BMI, kg/m^2								
< 25	Ref							
≥ 25	0.879	0.528	1.465	0.622				
Surgical procedure								
Distal gastrectomy	Ref							
Total gastrectomy	1.396	0.866	2.251	0.171				
Reconstruction Method								
B-I	Ref							
B-II	1.720	0.661	4.477	0.267				
Roux-En-Y	1.949	0.856	4.438	0.112				
Tumor location								
Upper	Ref							
Middle	1.050	0.682	1.617	0.824				
Lower	0.627	0.386	1.021	0.060				
Mix	0.810	0.446	1.474	0.491				
Tumor size, cm								
< 4	Ref							
≥ 4	1.245	0.869	1.785	0.233				
Histology								
Well and middle	Ref							
Poor and underdifferentiated	1.150	0.803	1.648	0.445				
Lymphovascular invasion								
No	Ref							
Yes	1.543	1.089	2.188	**0.015**				
Perineural infiltration								
No	Ref							
Yes	1.962	1.367	2.816	**< 0.001**				
TRG								
0–1	Ref							
2	1.735	1.002	3.004	**0.049**				
3	2.379	1.388	4.078	**0.002**				
ypTNM stage								
pCR-I	Ref				Ref			
II	1.580	0.798	3.129	0.189	1.600	0.792	3.233	0.191
III	3.561	1.897	6.686	**< 0.001**	3.284	1.695	6.363	**< 0.001**
Pre-chemo CEA								
< 5	Ref							
≥ 5	1.257	0.887	1.782	0.198				
Pre-chemo CA199								
< 37	Ref							
≥ 37	1.400	0.974	2.014	0.069				

Table 3 (continued)

Disease-free survival								
Clinical Parameters	**Univariable**				**Multivariable**			
	HR	**95%CI**		***P***	**HR**	**95%CI**		***P***
Adjuvant chemotherapy								
No	Ref				Ref			
Yes	0.631	0.399	0.999	**0.049**	0.624	0.391	0.996	**0.048**
HP status								
Negative	Ref				Ref			
Positive	0.524	0.364	0.755	**0.001**	0.569	0.394	0.823	**0.003**

BMI Body mass index, *TRG* Tumor regression grade, *HP* Helicobacter Pylori

a lower mutation rate in the PI3K/AKT pathway, which could partly explain the lower recurrence rates observed in HP infected patients. Additionally, studies have indicated that interferon (IFN)-γ plays a critical role in the development of chronic gastritis during HP infection [31], with IFN-γ primarily produced by CD4 + /CD8 + T cells that proliferate during HP infection and gastritis [32]. This suggests that chronic HP infection may lead to an increase in the number of these T cells, thereby enhancing the production of anti-tumor cytokines (such as IFN-γ), which is closely related to increased anti-tumor activity and reduced rates of recurrence and metastasis [33]. In terms of dynamic risk of recurrence, this study found that the overall recurrence and distant recurrence risks at various time points after surgery in the HP + group were lower than in the HP- group. We believe that this is because patients with HP- AGC have a higher risk of tumor recurrence [34]. Some studies have shown that HP + patients have significantly fewer tumor recurrences and better 5-year DFS than that of HP- patients [30]. Our study first confirmed that after NAC, compared with HP + patients, HP- patients have a higher risk of recurrence. More accurate clinical inspections and detailed clinical follow-up strategies must be developed to prolong the survival period of HP- patients.

In recent years, perioperative chemotherapy has become widely accepted in the treatment of AGC [4–7], with its benefits confirmed in large clinical trials [35]. In clinical practice, the NCCN guidelines for gastric cancer recommend that patients with good systemic conditions, potentially resectable lesions, and clinical staging of cT2-4N0-3 should preferentially receive neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy, with the preoperative adjuvant chemotherapy combined with postoperative adjuvant therapy being the preferred treatment modality for clinically staged ≥ cT2N0 gastric cancer [17]. Numerous studies have suggested that 5-Fu-based perioperative chemotherapy provides survival benefits to patients with resectable gastric or gastroesophageal junction cancers [33, 36, 37]. Previous studies have confirmed that patients infected with HP exhibit favorable responses to postoperative AC and a better prognosis [13, 14, 16]. However, the impact of HP infection on the therapeutic effect of NAC and the long-term efficacy of AC have not been confirmed. Our study found that in the HP + group, patients who received AC had significantly better OS than those who did not receive AC ($P < 0.001$). However, in the HP- group, AC did not significantly improve OS.

Previous research has indicated that in gastric cancer cell line models of postoperative patients receiving S-1 adjuvant chemotherapy, aberrant nuclear expression of the NF-κB transcription factor and polymorphism at codon 72 of TP53 (located at the NF-κB binding site) were observed, suggesting that NF-κB and p53 may serve as potential biomarkers for 5-FU sensitivity [38–40]. Additionally, studies have shown that after HP infection in gastric mucosa, the HP CagA protein is injected into gastric epithelial cells via the type IV secretion system, inducing persistent abnormal expression of NF-κB [41–44]. This suggests that HP may increase gastric cancer patients' sensitivity to 5-FU by inducing NF-κB transcription factor expression. Research regarding the mechanisms of platinum drugs in relation to HP infection is relatively sparse, but it has been found that HP infection may induce downregulation of miR-141 and upregulation of KEAP1, which could enhance sensitivity to platinum-based agents [15]. This may partially explain the impact of HP on the efficacy of platinum regimens. In terms of taxane efficacy, some reports indicate that inhibiting the PI3K/AKT pathway can reduce HIF-1α expression and enhance the therapeutic effect of taxanes in gastric cancer cells [45]. Additionally, studies have found that the AKT inhibitor capivasertib can suppress

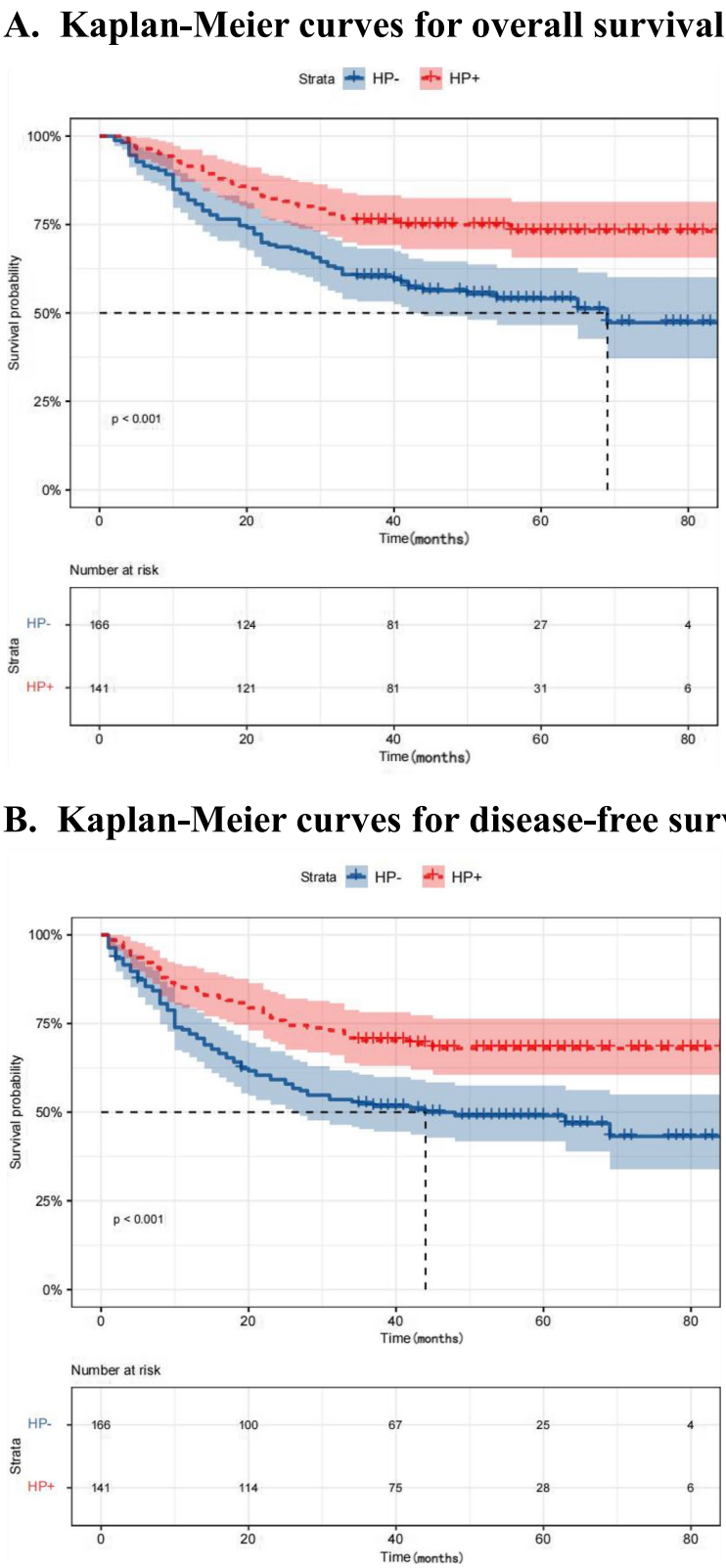


Fig. 2 Kaplan–Meier curves of overall survival and disease-free survival for H. pylori positive vs H. pylori negative after surgery. **A** Kaplan–Meier curves for overall survival; **B** Kaplan–Meier curves for disease-free survival

Table 4 Recurrences Within 3 years After Surgery of H. Pylori-negative and H. Pylori-positive groups

	H. pylori negative group (*n* = 166)	H. pylori positive group (*n* = 141)	*P*[1]
Any recurrence for all patients	84 (50.6%)	44 (31.2%)	**0.001**
Local recurrence	8 (4.8%)	7 (5.0%)	0.953
Distant recurrence	29 (17.5%)	13 (9.2%)	**0.036**
Liver	18 (10.8%)	6 (4.3%)	**0.032**
Lung	4 (2.4%)	2 (1.4%)	0.532
Pancreas	4 (2.4%)	2 (1.4%)	0.532
Distant lymph nodes	3 (1.8%)	3 (2.1%)	0.840
Peritoneum	18 (10.8%)	2 (1.4%)	**0.003**
Multiple sites	5 (3.0%)	4 (2.8%)	0.928
Unknown/ Other	24 (14.5%)	17 (12.1%)	0.538

1:Pearson's Chi-squared test; Fisher's exact test

Recurrence refers only to first-time recurrence. Multiple sites indicate patients who have recurrence simultaneously in 2 or more metastatic sites. Other or uncertain sites indicate hematogenous recurrence at sites other than liver (brain, bone, et al.), and recurrence at uncertain sites

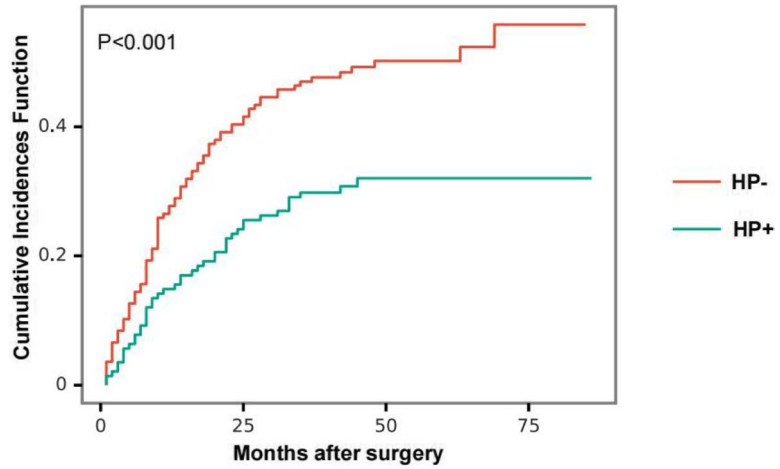
AKT expression, leading to the inhibition of the PI3K/AKT signaling pathway, which in turn enhances the cytotoxicity of taxanes against gastric cancer cells [46]. Previous research has reported that the proportion of PI3K/AKT pathway genetic mutations is lower in HP + gastric cancer compared to HP- cases [30]. Since genetic mutations are a significant cause of pathway activation, we speculate that the activation rate of the PI3K/AKT signaling pathway in HP + gastric cancer patients is lower than that in HP- patients. Thus, HP may increase gastric cancer patients' sensitivity to taxane drugs by reducing the activation of the PI3K/AKT pathway.

Existing cohort studies have also confirmed that HP infection is more common in microsatellite instability (MSI) + patients [47], and that high-level MSI gastric cancer has a better prognosis [48–50]. Therefore, the better prognosis of HP + patients compared to HP- patients might be related to the systemic response of the individual and a certain degree of anti-tumor activity. Additionally, some researchers believe that the poor prognosis of HP- patients might be attributed to an aggressive form of gastric cancer. HP- is significantly correlated with invasive tumor types (Borrmann stages III and IV), advanced tumor stages, and duodenal infiltration [51, 52]. In this scenario, the gastric mucosal cells are severely damaged, resulting in an alkaline gastric environment non-conducive to HP growth [53].

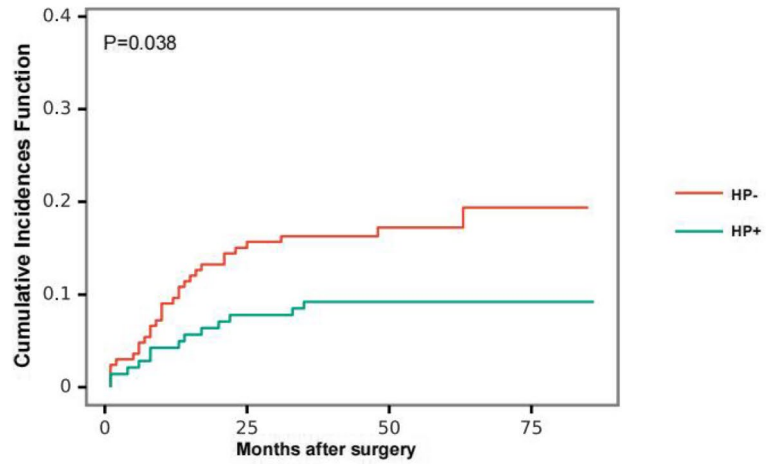
Although NAC can shrink tumors and downstage them in patients with AGC, leading to more complete removal of tumor lesions by surgeons, patients are often recommended to continue receiving AC after radical gastrectomy to improve survival [54]. However, there is currently no clear consensus on the number of cycles of AC for patients with AGC after sequential radical surgery following NAC. In accordance with the NCCN guidelines, we recommend that patients with locally advanced gastric cancer receive four cycles of neoadjuvant chemotherapy preoperatively, followed by an additional four cycles of adjuvant chemotherapy postoperatively [17]. During the entire NAC phase, we suggest performing an abdominal enhanced CT scan every two cycles, after which the treatment plan for the next steps will be determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) [55] guidelines. Our study using a detailed stratified analysis according to the number of cycles of NAC and AC chemotherapy suggests that HP + patients can achieve the greatest long-term survival benefits by continuing to receive ≥ 4 cycles of AC after receiving ≥ 4 cycles of NAC. Previous studies have demonstrated that complete perioperative chemotherapy is crucial for improving the long-term survival of gastric cancer patients [56]. This study recommends administering ≥ 4 cycles of NAC combined with ≥ 4 cycles of AC for patients with HP + AGC to maximize survival benefits. However, it is important to weigh the risks and benefits during chemotherapy. Therefore, we suggest establishing a dynamic evaluation system for clinical implementation, which would involve multidimensional assessments—including ECOG performance status, grading of toxic reactions, and evaluation of socioeconomic support systems—after every two cycles of treatment. This approach would facilitate the development of individualized treatment plans tailored to each patient's needs. This finding was further confirmed by the 6-month postoperative landmark analysis, reinforcing its significance in clinical decision-making. However, this study was retrospective, and the number of cases included was relatively small. Therefore, a multicenter, prospective study is warranted to determine the improvement in prognosis for HP + patients based on the number of cycles of sequential AC following NAC.

The present study has the following limitations: First, as a retrospective study, our results may be influenced by selection bias, and further validation with a larger population of patients from different countries and ethnic groups is necessary. Second, we used only histopathological methods to detect HP infections. Although histopathological examination is the gold standard for detecting HP [57, 58] and histological diagnosis of HP infection can better predict the

A. Competing risk model in overall recurrence.



B. Competing risk model in distant recurrence.



C. Competing risk model in peritoneum recurrence.

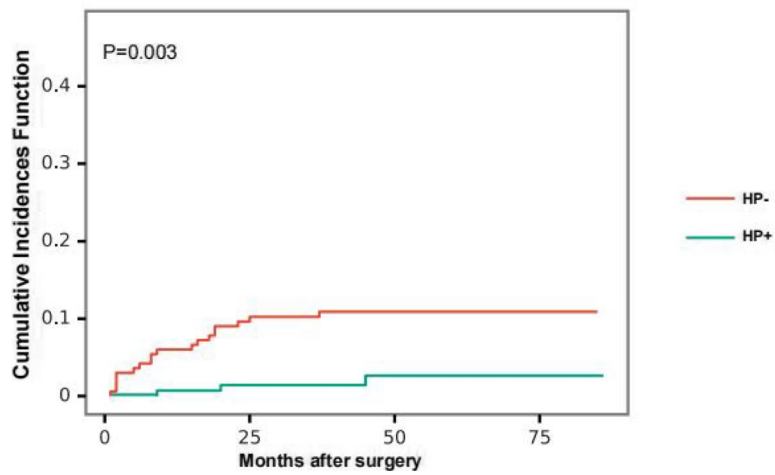
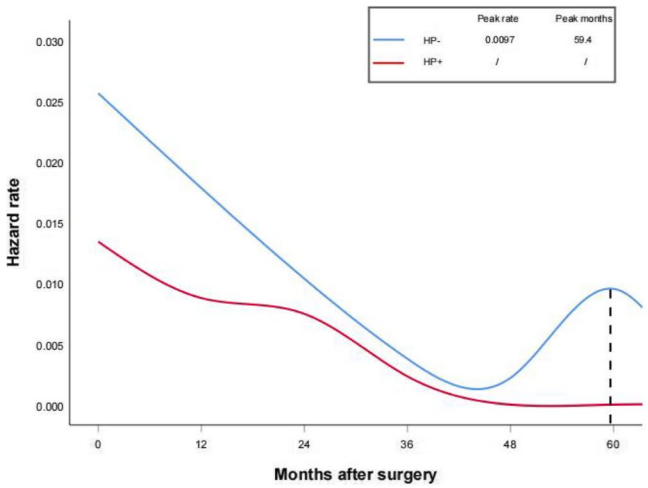
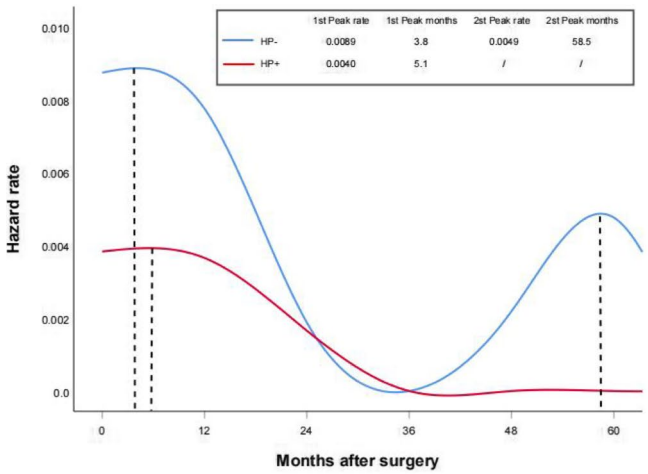


Fig. 3 Competing risk model between H. pylori positive and H. pylori negative in all patients. **A** Competing risk model in overall recurrence; **B** Competing risk model in distant recurrence; **C**, Competing risk model in peritoneum recurrence

A. **Dynamic recurrence hazard rate plot in overall recurrence patients.**



B. **Dynamic recurrence hazard rate plot in distant recurrence patients.**



C. **Dynamic recurrence hazard rate plot in peritoneum recurrence patients.**

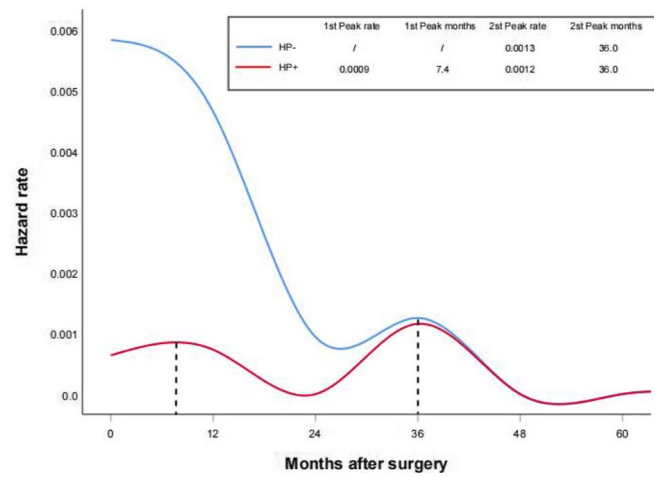


Fig. 4 Dynamic recurrence hazard rate plot. **A** Dynamic recurrence hazard rate plot in overall recurrence patients; **B** Dynamic recurrence hazard rate plot in distant recurrence patients; **C** Dynamic recurrence hazard rate plot in peritoneum recurrence patients

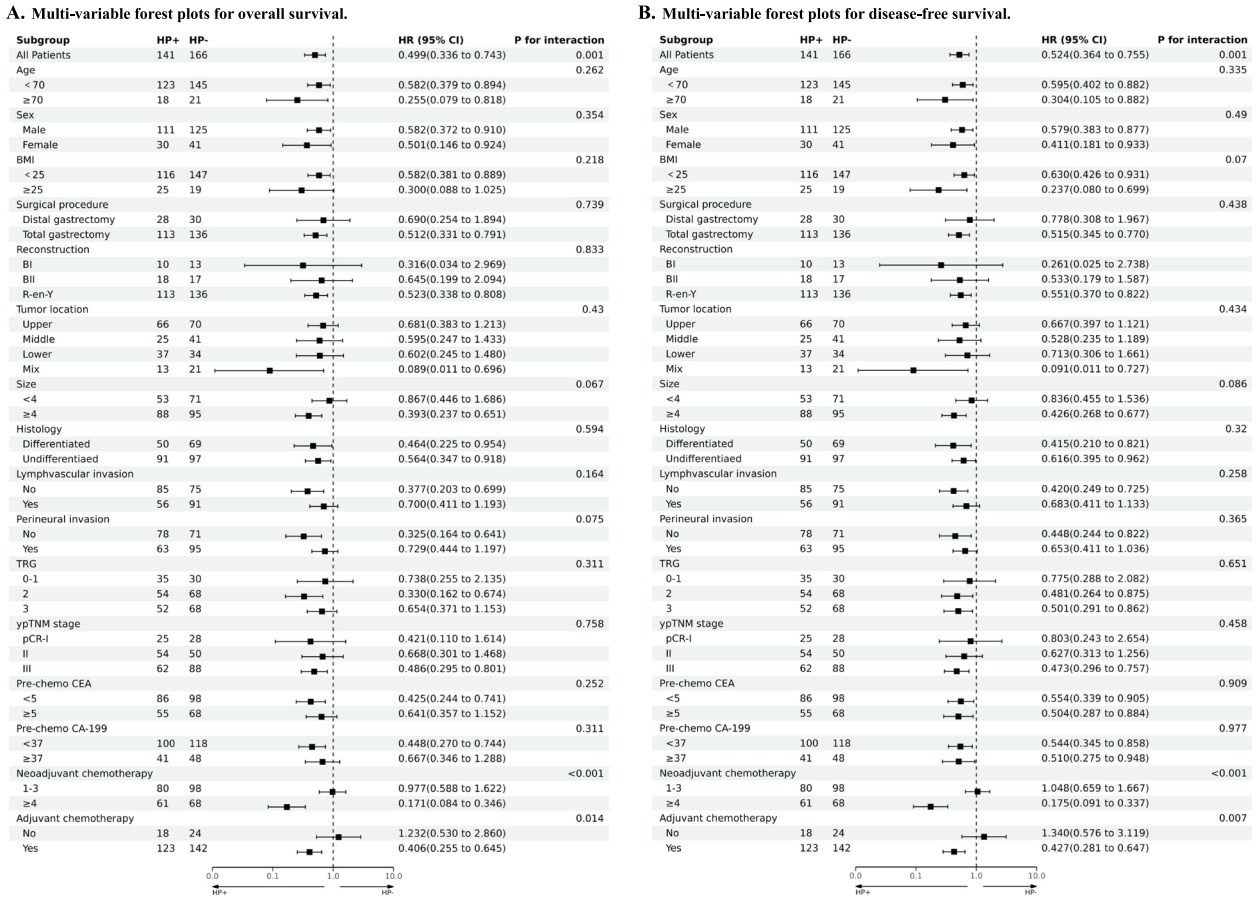
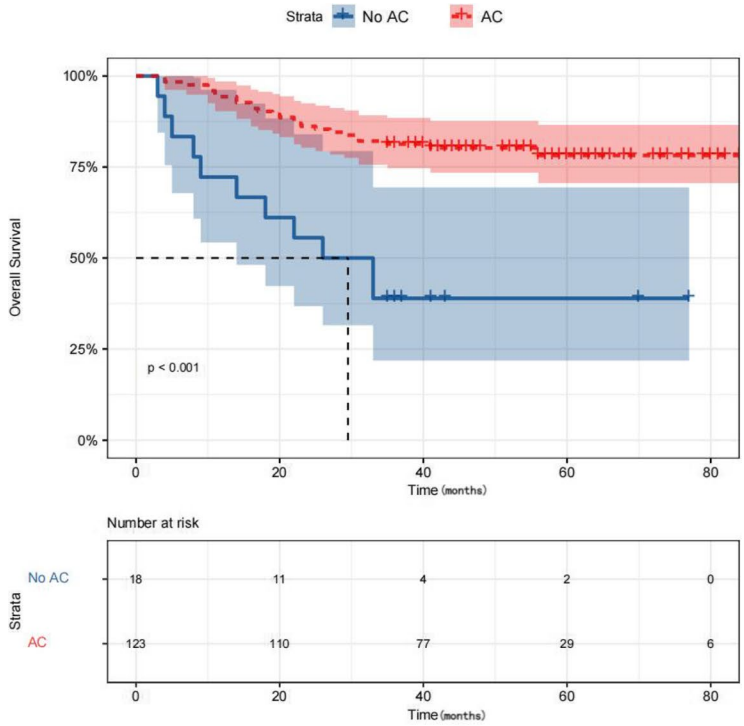


Fig. 5 Substratified analysis of multi-variable forest plots for overall survival and disease-free survival in all patients. **A** Multi-variable forest plots for overall survival; **B** Multi-variable forest plots for disease-free survival

survival of gastric cancer patients [59], other methods including urea breath test, PCR, serological tests, and bacterial culture can also be used. The sensitivity of histopathological detection for HP infection is approximately 80–90%, which may miss cases of low-grade or focal infections [60, 61]. This could lead to some HP + patients being misclassified as HP-, thereby underestimating the survival advantage in the HP + group. The urea breath test is a commonly used diagnostic tool, with a sensitivity and specificity of about 95% [62, 63]. However, the results may be affected by concurrent medications, which can lead to false-negative results. PCR methods used for diagnosing HP are highly sensitive and specific and allow for rapid and safe diagnosis; however, several factors limit their clinical application, including time consumption, low yield, and the risk of contamination. Serological testing has a sensitivity of 80–95% and specificity of 80–95%, but it cannot distinguish between recent and past infections. Bacterial culture has a lower sensitivity but is highly specific for diagnosing HP infection (100% specificity); however, the stringent culture conditions limit its clinical use [58]. A combination of multiple methods can improve the sensitivity and specificity providing additional insights. Third, the sample size was relatively small, and there may have been bias due to inconsistent chemotherapy regimens. Larger-scale and well-designed prospective cohort studies are needed to validate our findings and provide new avenues for individualized treatment of HP-infected gastric cancer.

A. Kaplan-Meier curves for overall survival in H. pylori positive patients



B. Kaplan-Meier curves for overall survival in H. pylori negative patients

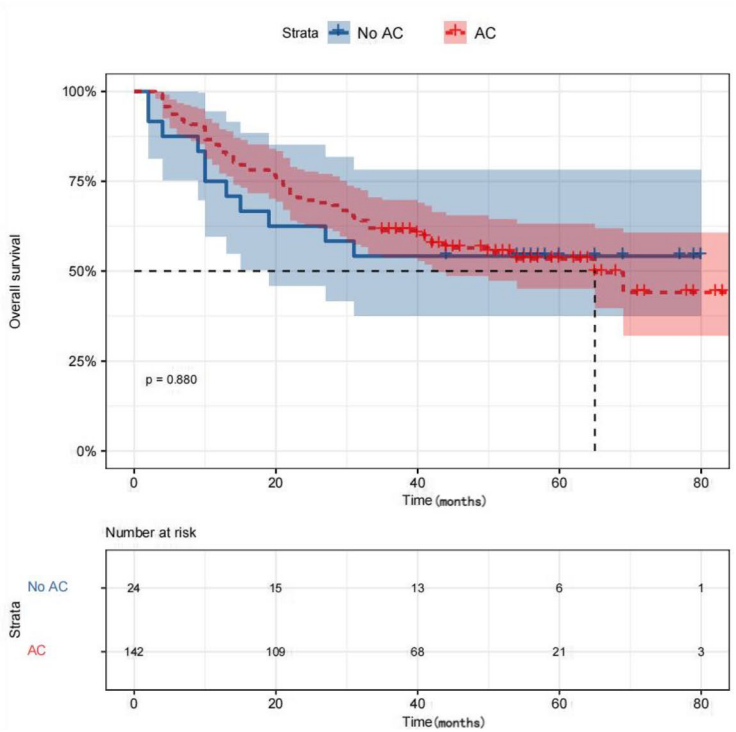


Fig. 6 Kaplan–Meier curves for overall survival stratified by AC between H. pylori positive and H. pylori negative patients. **A** Kaplan–Meier curves for overall survival in H. pylori positive patients; **B** Kaplan–Meier curves for overall survival in H. pylori negative patients

Conclusions

HP infection may influence the chemotherapy effectiveness in patients with AGC. For resectable HP + AGC patients, we recommend administering ≥ 4 cycles of NAC combined with ≥ 4 cycles of postoperative AC to improve survival rates. Future multicenter, large-sample, prospective randomized controlled trials targeting different chemotherapy regimens are needed to enhance the evidential strength of these conclusions.

Abbreviations

NAC	Neoadjuvant chemotherapy
AGC	Advanced Gastric Cancer
HP	*Helicobacter Pylori*
OS	Overall Survival
DFS	Disease-Free Survival
AC	Adjuvant Chemotherapy
MDT	Multidisciplinary Team
TRG	Tumor Regression Grade
pCR	pathologic Complete Response
LR	Likelihood Ratio
HR	Hazard Ratio
CIF	Cumulative Incidence Function
sHR	subdistribution Hazard Ratio
RECIST	Response Evaluation Criteria in Solid Tumors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13840-7.

Supplementary Material 1. X-tile cutoff NAC cycles value selection method based on overall survival analysis. A, Optimal truncation value selection; B, Survival analysis based on optimal truncation value

Supplementary Material 2. X-tile cutoff NAC cycles value selection method based on disease free survival analysis. **A**, Optimal truncation value selection; **B**, Survival analysis based on optimal truncation value.

Supplementary Material 3. X-tile cutoff AC cycles value selection method based on overall survival analysis. A, Optimal truncation value selection; B, Survival analysis based on optimal truncation value

Supplementary Material 4. X-tile cutoff AC cycles value selection method based on disease free survival analysis. A, Optimal truncation value selection; B, Survival analysis based on optimal truncation value

Supplementary Material 5. Kaplan-Meier curves for overall survival stratified by NAC 1-3 cycle(s) in HP+ patients

Supplementary Material 6. Kaplan-Meier curves for overall survival stratified by NAC ≥4 cycle(s) in HP+ patients

Supplementary Material 7. Kaplan-Meier curves for overall survival stratified by NAC 1-3 cycle(s) cycle(s) in HP- patients

Supplementary Material 8. Kaplan-Meier curves for overall survival stratified by NAC ≥4 cycle(s) in HP- patients

Supplementary Material 9. Kaplan-Meier curves for overall survival stratified by TCC in HP- patients. A, Kaplan-Meier curves for overall survival; B, Kaplan-Meier curves for disease-free survival

Supplementary Material 10. -month Landmark analysis of overall survival stratified by NAC cycles in patients with HP+ cohort. Patients who experienced death within 6 months after surgery were excluded from the 6-month landmark analysis, with sample sizes of 136 . The time zero was set as 6 months after surgery. A, Landmark analysis of overall survival stratified by NAC ≥4 cycles; B, Landmark analysis of overall survival stratified by NAC 1-3 cycle(s)

Supplementary Material 11. Perioperative Chemotherapy of Patients. DS,Docetaxel+S-1;SOX,Oxaliplatin+S-1;XELOX,Oxaliplatin+Capecitabine;FOLFOX4,Oxaliplatin+Leucovorin+Fluorouracil

Supplementary Material 12. Univariable analyses for overall survival in the cohort. BMI, Body mass index; TRG, Tumor regression grade; HP, Helicobacter Pylori

Supplementary Material 13. Muti-ivariable analyses for overall survival in the HP+ cohort

Supplementary Material 14. Muti-ivariable analyses for overall survival in the HP- cohort

Conflict of interest disclosures

None of the authors have any conflicts of interest or financial ties to disclose.

Human rights statement and informed consent

All procedures of the study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the principles of the Helsinki Declaration of 1964 and later versions. Informed consent or a substitute for it was obtained from all patients for inclusion in the study.

Authors' contributions

Conception and design: Qi-Chen He, Ze-Ning Huang, Chen-Bin Lv, and Jian-Wei Xie Provision of study materials or patients: all authors Collection and assembly of data: all authors Data analysis and interpretation: Qi-Chen He, Ze-Ning Huang, Chen-Bin Lv, Chao-Hui Zheng, Ping Li, and Chang-Ming Huang Manuscript writing: all authors Final approval of manuscript: all authors Accountable for all aspects of the work: all authors.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol has been reviewed and approved by the Ethics Committees of Fujian Medical University Union Hospital, Fujian Medical University Affiliated Zhangzhou Hospital, and Qinghai University Affiliated Hospital (Number of IRB: 2024KY090), in accordance with the ethical regulations for biomedical research in the People's Republic of China. All participants from the three hospitals signed written informed consent forms prior to their inclusion in the study. The consent forms clearly included the following elements: 1) the purpose, methods, and expected duration of the study; 2) foreseeable risks and potential benefits; 3) the voluntary nature of participation and the right to withdraw unconditionally; and 4) data anonymization and confidentiality measures. For patients unable to provide direct consent (such as those in a coma), we obtained proxy consent from legal guardians or close relatives. All patient data are stored in a de-identified coded format, with access to the original data restricted to core members of the research team. When the study results are published, no identifiable personal information will be included.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of Gastric Surgery, Fujian Medical University Union Hospital, No. 29 Xinquan Rd, Fuzhou 350001, Fujian Province, China. [2]Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China. [3]Key Laboratory of Gastrointestinal Cancer (Fujian Medical University), Ministry of Education, Fuzhou, China. [4]Fujian Key Laboratory of Tumor Microbiology, Department of Medical Microbiology, Fujian Medical University, Fuzhou, China. [5]Department of General Surgery, Affiliated Zhongshan Hospital of Dalian University, Dalian, China. [6]Department of Gastrointestinal Surgery, The Affiliated Hospital of Putian University, Putian, China. [7]Department of Gastrointestinal Surgery, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, China. [8]Department of Gastrointestinal Surgery, Qinghai University Affiliated Hospital, Xining, China. [9]Department of Pathology, Zhangzhou Affiliated Hospital of Fujian Medical University, ZhangZhou, China.

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