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Original Article

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Neoadjuvant PD-1 Inhibitor Plus Apatinib and Chemotherapy Versus Apatinib Plus Chemotherapy in Treating Patients With Locally Advanced Gastric Cancer: A Prospective, Cohort Study

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: This study aimed to evaluate the efficacy and safety of neoadjuvant programmed cell death-1 (PD-1) inhibitors plus apatinib and chemotherapy (PAC) in patients with locally advanced gastric cancer (LAGC).
Materials and Methods: Seventy-three patients with resectable LAGC were enrolled and named the PAC group (n=39) or apatinib plus chemotherapy (AC) group (n=34) based on the treatment they chose. Neoadjuvant therapy was administered in a 21-day cycle for 3 consecutive cycles, after which surgery was performed.
Results: The PAC group exhibited a higher objective response rate than the AC group (74.4% vs. 58.8%, P=0.159). Moreover, the PAC group showed a numerically better response profile than the AC group (P=0.081). Strikingly, progression-free survival (PFS) (P=0.019) and overall survival (OS) (P=0.049) were prolonged, whereas disease-free survival (DFS) tended to be longer in the PAC group than in the AC group (P=0.056). Briefly, the 3-year PFS, DFS, and OS rates were 76.1%, 76.1%, and 86.7% in the PAC group and 46.9%, 49.9%, and 70.3% in the AC group, respectively. Furthermore, PAC (vs. AC) treatment (hazard ratio=0.286, P=0.034) was independently associated with prolonged PFS in multivariate Cox regression analyses. The incidence of adverse events did not differ between the two groups (all P>0.05), where leukopenia, anemia, hypertension, and other adverse events were commonly observed in the PAC group.
Conclusions: Neoadjuvant PAC therapy may achieve a preferable pathological response, delayed progression, and prolonged survival compared to AC therapy with a similar safety profile in patients with LAGC; however, further validation is warranted.

Keywords: Gastric cancer; PD-1 inhibitor; Therapeutics; Survival; Safety

INTRODUCTION

Gastric cancer is the fifth most common cancer worldwide, with an estimated 1,089,103 newly diagnosed cases in 2020 globally [1]. Strikingly, approximately 30%–50% of patients with gastric cancer are diagnosed at the locally advanced gastric cancer (LAGC) stage, with

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Author Contributions

Conceptualization: W.F.; Data curation: W.C., W.Z., Z.Y.; Formal analysis: W.C., W.F.; Investigation: W.Z.; Supervision: W.F.; Writing - original draft: W.C., W.Z., Z.Y.; Writing - review & editing: W.C., W.F.

the involvement of regional lymph nodes [2,3]. The mainstay of LAGC management requires multimodal therapy in high-income countries in Europe and America, which involves surgery, neoadjuvant chemotherapy, and/or radiation [4,5]. Although neoadjuvant therapy followed by surgery does not serve as standard care in Asia, several recent randomized controlled trials (RCTs) in Asia have shown the clinical benefit of neoadjuvant therapy in treating patients with LAGC, which may serve as a viable option for patients with resectable LAGC [6,7].

Programmed cell death-1 (PD-1) inhibitors, a type of novel immunotherapy, block the binding of PD-1 with its ligand in the tumor microenvironment and have been approved for treating a wide range of solid tumors owing to their encouraging efficacy and minimal toxicity [8,9]. Moreover, PD-1 inhibitor plus chemotherapy prolongs survival in treating unresectable gastric cancer compared with chemotherapy alone in several large-scale RCTs [10,11]. Apatinib, a tyrosine kinase inhibitor, is an antiangiogenic drug approved for the treatment of metastatic gastric cancer in China [12,13]. Although PD-1 inhibitors and apatinib have been used individually to treat patients with metastatic gastric cancer, the efficacy of PD-1 inhibitors plus apatinib and chemotherapy (PAC) in treating patients with resectable LAGC in the neoadjuvant setting remains poorly understood.

Hence, this prospective cohort study aimed to compare neoadjuvant PAC therapy with apatinib and chemotherapy (AC) therapy regarding clinical response, pathological response, survival, and safety profile in patients with resectable LAGC.

MATERIALS AND METHODS

Patients

From February 2019 to January 2022, 73 patients with LAGC who intended to receive PAC or AC as neoadjuvant therapy were serially enrolled in this prospective cohort study. The enrollment criteria were as follows: i) pathological diagnosis of gastric cancer or gastroesophageal junction carcinoma; ii) age >18 years; iii) clinical stage of cT3–cT4a/cN1–cN3/cM0; iv) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1; v) intended to receive PAC or AC as neoadjuvant therapy and had a high probability of benefit from the treatment; and vi) suitable for surgical resection at diagnosis or after neoadjuvant therapy. The exclusion criteria were as follows: i) other primary solid tumors or hematological malignancies, ii) allergies to the study's medications, iii) pregnancy or lactation, iv) uncontrolled blood pressure, and v) unstable angina or myocardial infarction within 6 months before recruitment. The study was approved by the Ethics Committee. All the enrolled patients signed informed consent forms.

Treatment

This study did not interfere with the treatment, and the choice of neoadjuvant therapy regimen (PAC or AC) was based on disease status and patient preference. For the PAC group (n=39), intravenous PD-1 inhibitors (sintilimab, 200 mg; camrelizumab, 200 mg; or toripalimab, 240 mg) were administered once per cycle for 3 consecutive cycles (21 days per cycle), and the choice of PD-1 inhibitor was based on patient preference and disease status [14]. Apatinib was administered orally at 375 mg/day for 3 consecutive cycles (21 days per cycle), and dose adjustment was performed according to patient tolerance. Oxaliplatin, S-1 (SOX), oxaliplatin, and capecitabine (CAPOX) were administered as chemotherapy for 3 consecutive cycles (21 days per cycle), with dose adjustment according to patient tolerance

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[15]. For the AC group (n=34), AC were administered as neoadjuvant therapy using the same administration method as the PAC group. Surgical resection was performed for suitable patients, and suitability was assessed according to tumor status after neoadjuvant therapy.

Outcome assessment

The primary outcome in the present study was defined as the pathological response of patients who underwent surgical resection (PAC group, n=39; AC group, n=32). Pathological response was assessed based on intraoperative pathological examination using the Japanese Classification of Gastric Carcinoma (JCGC) [16]. The secondary outcomes included clinical response, actual surgical rates, R0 resection rate, disease-free survival (DFS), progression-free survival (PFS), overall survival (OS), and adverse events. Clinical response according to Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) of all patients (PAC group, n=39; AC group, n=34) was assessed. Because of progressive disease (PD) of neoadjuvant therapy response by RECIST 1.1, two patients in the AC group were not suitable for surgery, and the surgical resection rate was measured according to the actual surgery rates. The R0 resection rate was measured using the American Joint Committee on Cancer criteria in patients who underwent surgery (PAC group, n=39; AC group, n=32) [17]. DFS was assessed in patients who underwent surgery (PAC group, n=39; AC group, n=32) and was calculated from surgery to disease recurrence, progression, or death. PFS and OS were measured in all enrolled patients (PAC group, n=39; AC group, n=34) and were calculated from neoadjuvant therapy to disease progression or death and from neoadjuvant therapy to death, respectively. During treatment, adverse events were closely monitored in all the patients.

Follow-up

Follow-up was carried out for all patients once at 3 months in the first year and once at 3–6 months thereafter until July 31, 2022. The median follow-up duration was 23.4 months (range 8.8–38.8 months). During follow-up, imaging examinations were performed to assess the disease status. Routine blood, urine, liver, and kidney function data were monitored at each follow-up visit. Adverse events were recorded in all patients during regular clinic visits during the follow-up period.

Statistics

SPSS v.20.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. GraphPad Prism v.7.02 (GraphPad Inc., San Diego, CA, USA) was used for graphing. Comparison analyses were performed using the Wilcoxon rank sum test, χ^2 test, Fisher's exact test, and Student's t-test. Prognosis analysis was performed using Kaplan-Meier curves and analyzed using the log-rank test. Independent prognostic factors were screened using forward stepwise multivariate Cox proportional hazard regression models. $P<0.05$ was considered significant.

RESULTS

Study flow

Initially, 123 patients with LAGC were invited, among whom 50 patients were excluded, including 30 patients who did not choose AC or PAC as neoadjuvant therapy, 12 patients who declined to participate, and 8 patients who were excluded from other criteria (**Fig. 1**). A total of 73 patients with LAGC were included in this study and named the PAC group (n=39) or AC group (n=34) based on the treatment they chose. The corresponding drug administrations and assessments are listed in **Fig. 1**. All patients with available data were included in the corresponding analysis.

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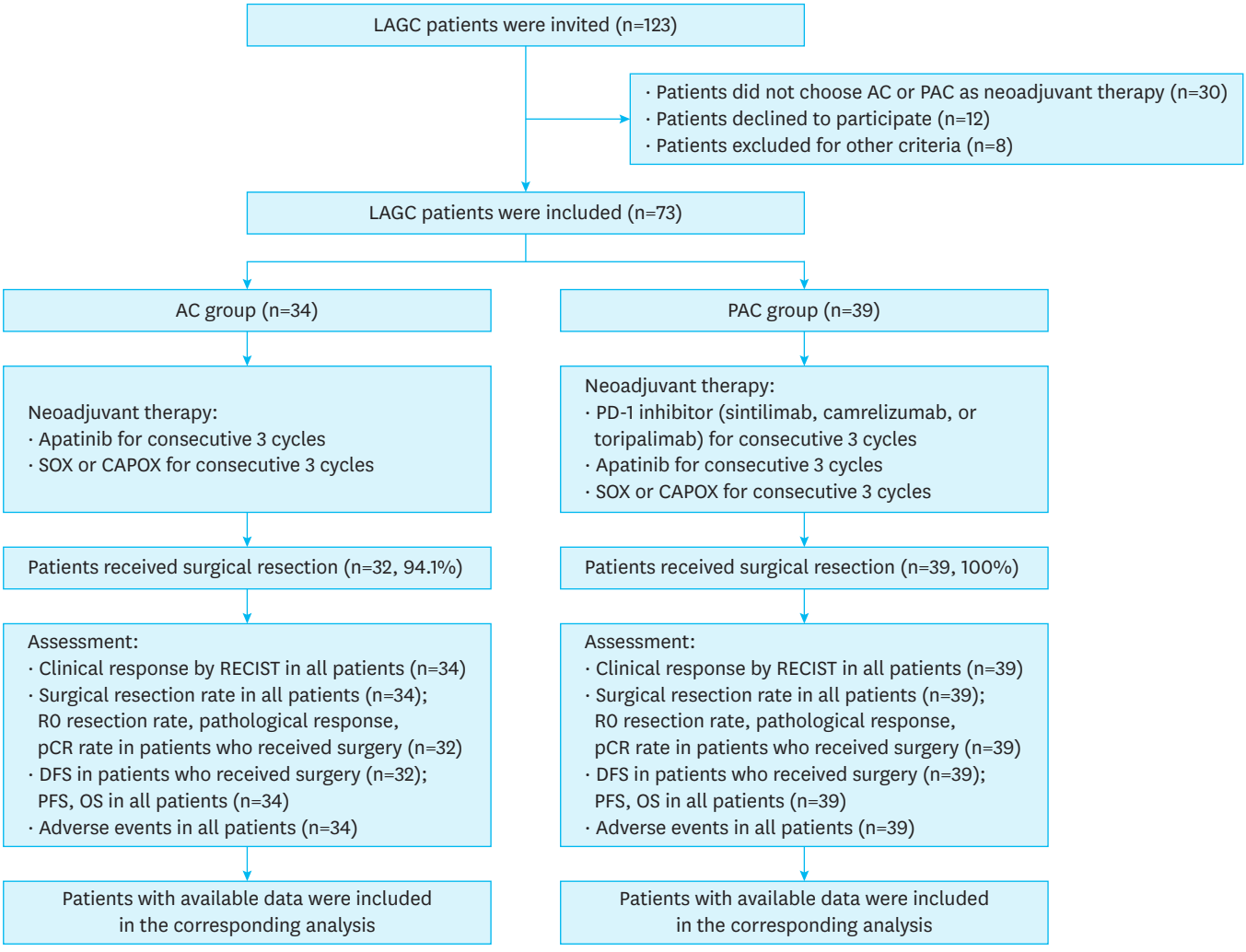


Fig. 1. Study flow.
LAGC = locally advanced gastric cancer; AC = apatinib and chemotherapy; PAC = PD-1 inhibitor plus apatinib and chemotherapy; SOX = oxaliplatin, S-1; CAPOX = oxaliplatin and capecitabine; PD-1 = programmed cell death-1; RECIST = Response Evaluation Criteria for Solid Tumors; pCR = pathological complete response; DFS = disease-free survival; PFS = progression-free survival; OS = overall survival.

Clinical characteristics

The mean age of the PAC group was 57.9±9.1 years, with 14 (35.9%) women and 25 (64.1%) men included (**Table 1**). Moreover, the AC group consisted of 9 (26.5%) women and 25 (73.5%) men with a mean age of 58.9±10.2 years. There were no differences in demographic characteristics, chronic comorbidity, *Helicobacter pylori* infection, Epstein–Barr virus positivity, ECOG PS score, tumor features, or microsatellite instability status between the PAC and AC groups (all P>0.05), except that the PAC group displayed a higher proportion of PD-L1 combined positive score (CPS) than the AC group (P<0.001). The detailed clinical features of the patients with LAGC are listed in **Table 1**.

Clinical response

The clinical response was evaluated using the RECIST 1.1 criteria in all recruited patients, and 2 (5.1%), 27 (69.3%), and 10 (25.6%) patients with LAGC in the PAC group achieved complete response (CR), partial response (PR), and stable disease (SD), respectively, whereas 0 (0.0%)

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Table 1. Clinical characteristics of patients with locally advanced gastric cancer

Items	AC group (n=34)	PAC group (n=39)	P-value
Age, yr	58.9±10.2	57.9±9.1	0.664
Sex			0.387
Female	9 (26.5)	14 (35.9)	
Male	25 (73.5)	25 (64.1)	
Nationality			0.595
Han	32 (94.1)	38 (97.4)	
Others	2 (5.9)	1 (2.6)	
History of smoke	11 (32.4)	14 (35.9)	0.750
History of drink	16 (47.1)	16 (41.0)	0.604
History of hypertension	12 (35.3)	18 (46.2)	0.347
History of hyperlipidemia	8 (23.5)	9 (23.1)	0.964
History of diabetes	4 (11.8)	5 (12.8)	1.000
Helicobacter pylori infection			0.442
Negative	17 (50.0)	16 (41.0)	
Positive	17 (50.0)	23 (59.0)	
EBV			1.000
Negative	31 (91.2)	35 (89.7)	
Positive	3 (8.8)	4 (10.3)	
ECOG PS score			0.345
0	19 (55.9)	26 (66.7)	
1	15 (44.1)	13 (33.3)	
Tumor site			0.798
Gastric	27 (79.4)	30 (76.9)	
Gastroesophageal junction	7 (20.6)	9 (23.1)	
Differentiation			0.883
Well	4 (11.8)	3 (7.7)	
Moderate	12 (35.3)	17 (43.6)	
Poor	18 (52.9)	19 (48.7)	
cT stage			0.610
cT3	7 (20.6)	10 (25.6)	
cT4a	27 (79.4)	29 (74.4)	
cN stage			0.390
cN1	8 (23.5)	7 (17.9)	
cN2	16 (47.1)	17 (43.6)	
cN3	10 (29.4)	15 (38.5)	
cM stage			-
cM0	34 (100.0)	39 (100.0)	
cTNM stage			-
cTNM III	34 (100.0)	39 (100.0)	
MSI status			0.698
MSI-L/MSS	30 (88.2)	36 (92.3)	
MSI-H	4 (11.8)	3 (7.7)	
PD-L1 CPS			<0.001
0	16 (47.1)	0 (0.0)	
1–4	8 (23.5)	9 (23.1)	
5–9	8 (23.5)	16 (41.0)	
≥10	2 (5.9)	14 (35.9)	

Values are presented as mean±standard deviation or number (%).
AC = apatinib and chemotherapy; PAC = PD-1 inhibitor plus apatinib and chemotherapy; EBV = Epstein–Barr virus; ECOG PS = Eastern Cooperative Oncology Group Performance Status; cT = clinical tumor; cN = clinical node; cM = clinical metastasis; cTNM = clinical tumor-node-metastasis; MSI = microsatellite instability; MSI-L = microsatellite instability-low; MSS = microsatellite stable; MSI-H = microsatellite instability-high; PD-L1 CPS = programmed cell death ligand 1 combined positive score.

patients had PD (**Table 2**). Moreover, 1 (2.9%), 19 (55.9%), 12 (35.3%), and 2 (5.9%) patients in the AC group achieved CR, PR, SD, and PD, respectively. Although the objective response rate (ORR) was numerically higher (74.4% vs. 58.8%) in the PAC group than in the AC group, the difference was not statistically significant (P=0.159). Moreover, the disease control rate (DCR) was similar (100.0% vs. 94.1%, P=0.213) between the PAC and AC groups.

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Table 2. Clinical response by RECIST

Items	AC group (n=34)	PAC group (n=39)	P-value
Clinical response by RECIST			0.123
CR	1 (2.9)	2 (5.1)	
PR	19 (55.9)	27 (69.3)	
SD	12 (35.3)	10 (25.6)	
PD	2 (5.9)	0 (0.0)	
ORR			0.159
No	14 (41.2)	10 (25.6)	
Yes	20 (58.8)	29 (74.4)	
DCR			0.213
No	2 (5.9)	0 (0.0)	
Yes	32 (94.1)	39 (100.0)	

RECIST = Response Evaluation Criteria for Solid Tumors; AC = apatinib and chemotherapy; PAC = PD-1 inhibitor plus apatinib and chemotherapy; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; DCR = disease control rate.

Pathological response and adjuvant therapy

After neoadjuvant therapy, all patients (100.0%) in the PAC group and 32 (94.1%) of the 34 patients in the AC group underwent surgical resection (**Table 3**). In patients who underwent surgical resection, R0 resection rates were 97.4% and 93.8% in the PAC and AC groups, respectively. There was no difference in the surgical resection rate (P=0.213) or R0 resection rate (P=0.215) between the two groups. Regarding pathological response, 2 (5.1%), 28 (71.8%), and 9 (23.1%) patients in the PAC group achieved grades 1, 2, and 3, respectively, according to the JCGC criteria. Moreover, 7 (21.9%), 20 (62.5%), and 5 (15.6%) patients in the AC group achieved grade 1, grade 2, and grade 3 pathological responses based on the JCGC criteria, respectively. The pathological response of the JCGC criteria tended to be elevated in the PAC group compared to the AC group (which indicated a better response), while no statistical significance was observed (P=0.081). Moreover, the pathological CR (pCR) rate (P=0.432) did not differ significantly between the two groups.

Regarding adjuvant therapy, 37 (94.9%) and 31 (96.9%) patients with LAGC in the PAC and AC groups received adjuvant therapy, respectively, and their detailed regimens are listed in **Supplementary Table 1**. Regarding adjuvant systemic therapy, more patients in the PAC group received adjuvant PD-1 inhibitors than those in the AC group (P=0.002). Moreover, fewer patients with LAGC in the PAC group received adjuvant radiotherapy (P=0.004) or adjuvant concurrent chemoradiotherapy (CRT) (P=0.009) than in the AC group.

Table 3. Surgery information and pathological response

Items	AC group	PAC group	P-value
Assessed patients	34	39	0.213
Surgical resection	32 (94.1)	39 (100.0)	
Assessed patients	32	39	
R0 resection	30 (93.8)	38 (97.4)	0.585
Pathological response			0.081
Grade 0	0 (0.0)	0 (0.0)	
Grade 1	7 (21.9)	2 (5.1)	
Grade 2	20 (62.5)	28 (71.8)	
Grade 3	5 (15.6)	9 (23.1)	
pCR	5 (15.6)	9 (23.1)	0.432

AC = apatinib and chemotherapy; PAC = PD-1 inhibitor plus apatinib and chemotherapy; pCR = pathological complete response.

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Survival profile

The 1-year, 2-year, and 3-year PFS rates in the PAC group were 100.0%, 85.6%, and 76.1%, respectively (**Fig. 2A**). The 1-, 2-, and 3-year PFS rates in the AC group were 87.9%, 68.3%, and 46.9%, respectively. PFS was prolonged in the PAC group compared to that in the AC group (P=0.019) (**Fig. 2A**). Moreover, the 1-year, 2-year, and 3-year DFS rates in the PAC group were 100.0%, 85.7%, and 76.1%, respectively, and 86.1%, 72.8%, and 49.9%, respectively (**Fig. 2B**). Although DFS seemed to be longer in the PAC group than in the AC group, the difference was not statistically significant (P=0.056) (**Fig. 2B**). Regarding OS, the 1-year, 2-year, and 3-year OS rates in the PAC group were 100.0%, 96.3%, and 86.7%, respectively, while they were 96.9%, 76.7%, and 70.3%, respectively, in the AC group (**Fig. 2C**). In comparison, OS was longer in the PAC group than in the AC group (P=0.049) (**Fig. 2C**).

Forward stepwise multivariate Cox regression analyses revealed that after adjustment, treatment (PAC vs. AC) (hazard ratio [HR]: 0.286; P=0.034) was independently associated with prolonged PFS (**Fig. 3A**). In addition, worse differentiation was an independent factor for shortened PFS (HR: 8.324, P=0.003), DFS (HR: 8.122, P=0.004), and OS (HR: 8.708, P=0.033) (**Fig. 3A-C**).

Adverse events

Regarding hematological adverse events, 18 (46.2%), 17 (43.6%), 13 (33.3%), and 7 (17.9%) patients in the PAC group experienced leukopenia, anemia, neutropenia, and thrombocytopenia, respectively (**Table 4**). Furthermore, 22 (56.4%), 14 (35.9%), 12 (30.8%), 11 (28.2%), 11 (28.2%), 10 (25.6%), 9 (23.1%), 8 (20.5%), 7 (17.9%), 5 (12.8%), and 4 (10.3%) patients in the PAC group experienced fatigue, hypertension, hand-foot syndrome, pruritus, elevated transaminase levels, peripheral neuropathy, nausea and vomiting, diarrhea, fever, anorexia, and elevated bilirubin levels, respectively. In terms of grade 3–4 adverse events, 2 (5.1%), 1 (2.6%), 1 (2.6%), 1 (2.6%), 2 (5.1%), and 1 (2.6%) patients experienced grade 3–4 leukopenia, anemia, neutropenia, fatigue, nausea and vomiting, and diarrhea, respectively, in the PAC group. In comparison, no difference in the incidence of adverse events was observed between the PAC and AC groups (all P>0.05). Furthermore, 2 (5.9%) and 0 (0.0%) patients with LAGC in the AC and PAC groups, respectively, discontinued apatinib due to severe adverse events.

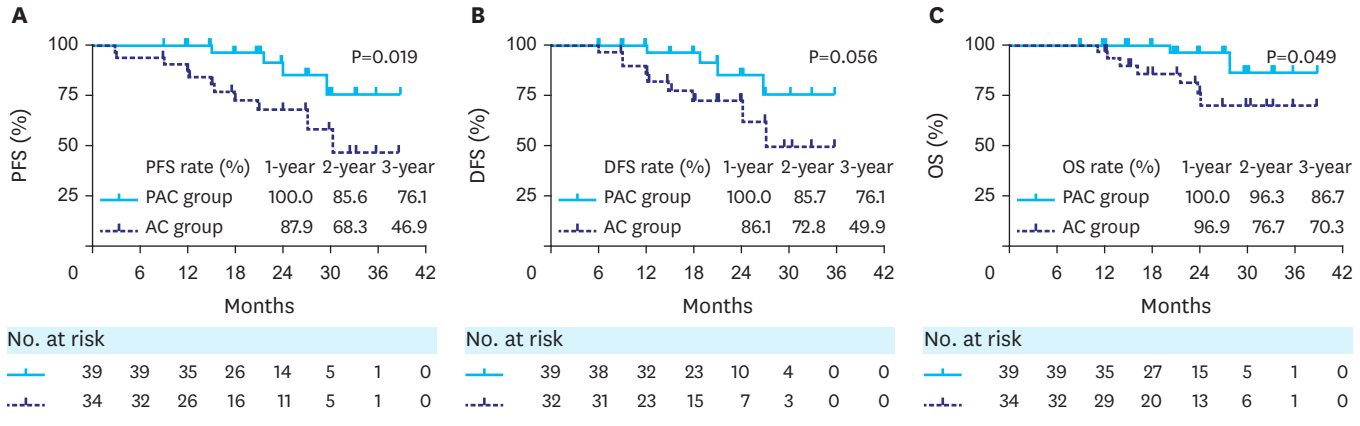


Fig. 2. Neoadjuvant PAC prolonged PFS and OS compared to AC in treating patients with locally advanced gastric cancer. Comparison of PFS (A), DFS (B), and OS (C) between the PAC and AC groups.
PFS = progression-free survival; PAC = PD-1 inhibitor plus apatinib and chemotherapy; AC = apatinib and chemotherapy; DFS = disease-free survival; OS = overall survival.

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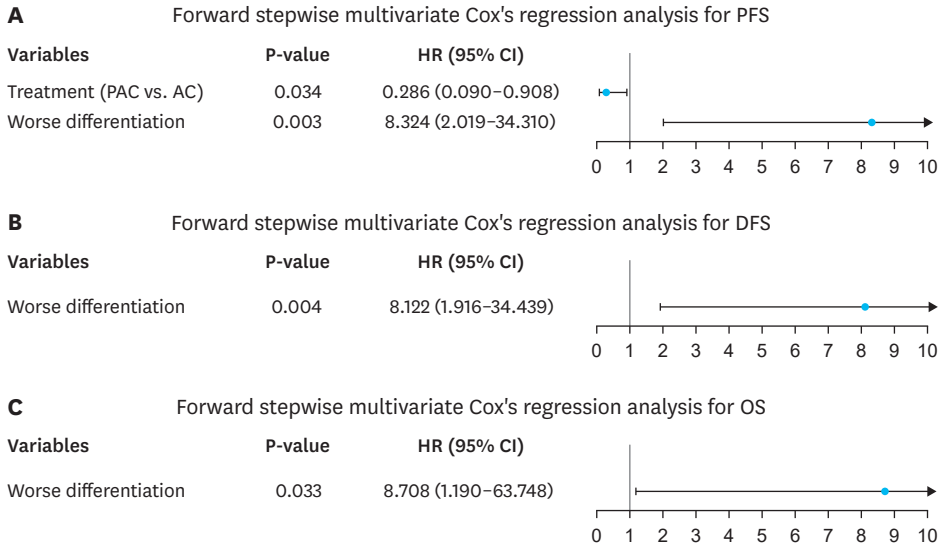


Fig. 3. Neoadjuvant PAC (vs. AC therapy) and worse differentiation independently estimated unfavorable survival in patients with locally advanced gastric cancer. Independent prognostic factors related to PFS (A), DFS (B), and OS (C) by forward stepwise multivariate Cox regression model.
PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; DFS = disease-free survival; OS = overall survival.

Table 4. Adverse events

Adverse events	AC group (n=34)			PAC group (n=39)			P-value*
	Total	Grade 1–2	Grade 3–4	Total	Grade 1–2	Grade 3–4	
Hematological adverse events							
Leukopenia	13 (38.2)	13 (38.2)	0 (0.0)	18 (46.2)	16 (41.0)	2 (5.1)	0.495
Anemia	12 (35.3)	11 (32.4)	1 (2.9)	17 (43.6)	16 (41.0)	1 (2.6)	0.470
Neutropenia	9 (26.5)	8 (23.5)	1 (2.9)	13 (33.3)	12 (30.8)	1 (2.6)	0.524
Thrombocytopenia	6 (17.6)	6 (17.6)	0 (0.0)	7 (17.9)	7 (17.9)	0 (0.0)	0.973
Nonhematological adverse events							
Fatigue	17 (50.0)	16 (47.1)	1 (2.9)	22 (56.4)	21 (53.8)	1 (2.6)	0.584
Hypertension	14 (41.2)	13 (38.2)	1 (2.9)	14 (35.9)	14 (35.9)	0 (0.0)	0.644
Hand-foot syndrome	11 (32.4)	11 (32.4)	0 (0.0)	12 (30.8)	12 (30.8)	0 (0.0)	0.884
Pruritus	8 (23.5)	8 (23.5)	0 (0.0)	11 (28.2)	11 (28.2)	0 (0.0)	0.650
Elevated transaminase	8 (23.5)	7 (20.6)	1 (2.9)	11 (28.2)	11 (28.2)	0 (0.0)	0.650
Peripheral neuropathy	4 (11.8)	4 (11.8)	0 (0.0)	10 (25.6)	10 (25.6)	0 (0.0)	0.133
Nausea and vomiting	8 (23.5)	8 (23.5)	0 (0.0)	9 (23.1)	7 (17.9)	2 (5.1)	0.964
Diarrhea	6 (17.6)	6 (17.6)	0 (0.0)	8 (20.5)	7 (17.9)	1 (2.6)	0.756
Fever	5 (14.7)	5 (14.7)	0 (0.0)	7 (17.9)	7 (17.9)	0 (0.0)	0.709
Anorexia	3 (8.8)	3 (8.8)	0 (0.0)	5 (12.8)	5 (12.8)	0 (0.0)	0.716
Elevated bilirubin	2 (5.9)	2 (5.9)	0 (0.0)	4 (10.3)	4 (10.3)	0 (0.0)	0.679

Values are presented as number (%).
AC = apatinib and chemotherapy; PAC = PD-1 inhibitor plus apatinib and chemotherapy.
*Test for the occurrence rate of each adverse event.

DISCUSSION

PAC therapy has been administered to patients with unresectable LAGC or metastatic gastric cancer, achieving an ORR of 29.2% [18]. Moreover, PD-1 inhibitor plus apatinib yields an ORR rate from 20.5% to 26.3% for patients with unresectable LAGC or metastatic gastric cancer in a real-world setting [19,20]. Regarding the application of PAC therapy in the neoadjuvant setting, only one study reported that the ORR and DCR rates in patients with LAGC treated with neoadjuvant PAC therapy were 66.7% and 100.0%, respectively, among which 93.3% of patients achieved R0 resection [14]. However, this previous study was a

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single-arm study with a small sample size and short follow-up period. Therefore, this study increased the sample size, prolonged the observation period, and set the control group (AC group) to compare the efficacy of neoadjuvant PAC therapy and AC therapy in patients with LAGC. In the present study, PAC therapy achieved a numerically higher ORR (74.4% vs. 58.8%), DCR (100.0% vs. 94.1%), surgical resection rate (100.0% vs. 94.1%), R0 resection rate (97.4% vs. 93.8%), pathological response (grades 3, 2, 1, and 0: 23.1%, 71.8%, 5.1%, and 0.0% vs. 15.6%, 62.5%, 21.9%, and 0.0%, respectively), and pCR rate (23.1% vs. 15.6%) than AC therapy in treating patients with LAGC, while no significant difference was observed. The possible reasons for this interesting finding are as follows: i) PD-1 plus apatinib exhibited a stronger antitumor effect than monotherapy by increasing $CD4^+$ T cells and $CD8^+$ T cells in the tumor tissue, which further resulted in an enhanced immune response in the local tumor micromovement; thus, PAC therapy seemed to exhibit a greater response profile than AC therapy [21]. ii) PD-1 inhibitors could synergize with chemotherapy to prevent evasion from the immune surveillance of tumor cells and promote the proliferation, activation, and differentiation of T cells, thus leading to an elevated response profile to PAC therapy compared to AC therapy in patients with LAGC [22,23]. iii) The limited sample size might have impaired the statistical power of the current study; thus, the response profile and surgical outcome tended to be better in patients treated with PAC therapy than in those treated with AC therapy, while no statistical significance was observed.

One previous study reported that PAC therapy achieves a median PFS of 6.5 months (95% confidence interval: 6.0–7.0 months) in patients with unresectable LAGC and metastatic gastric cancer, while other studies observed a shorter median PFS (approximately 3.0–3.9 months) by only applying a PD-1 inhibitor plus apatinib [18-20]. Moreover, a recent study with a small sample size and short follow-up period observed that neoadjuvant PAC therapy achieved a 2-year DFS rate of 77.7% and 2-year OS rate of 90.1% in patients with LAGC [14]. Surprisingly, in the current study, PAC therapy prolonged PFS, DFS, and OS compared with AC therapy in patients with LAGC. Moreover, PAC therapy (vs. AC therapy) was independently associated with favorable PFS in patients with LAGC in multivariate Cox regression analyses in our study. The possible reasons for these interesting findings are as follows: i) PD-1 inhibitors were reported to synergize with AC, as mentioned earlier; thus, PAC therapy might decrease the risk of locoregional recurrence and exhibit a longer survival profile than AC therapy in patients with LAGC [8,24]. ii) PAC therapy achieved a numerically higher pathological response and R0 resection rate than AC therapy, where the latter two factors could estimate favorable survival in patients with LAGC; thus, PAC therapy might be indirectly related to a prolonged survival profile in these patients [25-27]. Moreover, in the current study, worse differentiation served as an independent factor for shortened PFS and OS in patients with LAGC, which was in line with several previous studies [28,29]. A possible reason for this finding is that less differentiated tumor tissue might exhibit stemness properties, which further develops resistance to chemotherapy and distant metastasis formation, thus causing shorter survival in patients with LAGC [30].

Furthermore, in this study, the PAC group had a higher PD-L1 CPS than the AC group in patients with LAGC since PD-L1 CPS score was an important factor for the decision to administer PD-1 inhibitor; therefore, the PD-L1 CPS was significantly higher in the PAC group than in the AC group. Meanwhile, tumor PD-L1 is related to tumor immune escape, leading to worse prognosis in patients with LAGC without PD-1/PD-L1 inhibitor administration; therefore, the use of PD-1 inhibitors would greatly improve the prognosis of these patients with high PD-L1 expression, which also explains the higher PD-L1 CPS in the PAC group than in the AC group.

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Regarding the safety profile, cutaneous reactions (such as hand-foot syndrome and pruritus) and hypertension are often observed in patients receiving antiangiogenic therapy; immune-related adverse events (such as colitis, hepatitis, and pneumonitis) are commonly reported in patients receiving PD-1 inhibitors [31,32]. Previous studies have reported that elevated transaminase levels, thrombocytopenia, fatigue, proteinuria, hand-foot syndrome, nausea and vomiting, and intestinal obstruction are commonly observed adverse events following PAC therapy in patients with LAGC, among which grade 3–4 adverse events are rarely reported [14,18]. However, few studies have compared the safety profiles of neoadjuvant PAC and AC therapies in patients with LAGC. In the present study, PAC therapy did not elevate the incidence of adverse events compared with AC therapy in patients with resectable LAGC. Moreover, commonly observed adverse events in patients with LAGC treated with neoadjuvant PAC therapy were leukopenia, anemia, neutropenia, fatigue, hypertension, hand-foot syndrome, pruritus, and elevated transaminase; these adverse events were mild and manageable, which indicated that neoadjuvant PAC therapy was relatively safe in patients with resectable LAGC and might be an option for these patients to improve LAGC management.

This prospective cohort study compared the efficacy and safety profiles of PAC therapy and those treated with AC therapy. However, randomization was not applied in the current study, and further RCTs are required to resolve this issue. Moreover, the limited sample size of the present study might impair the statistical power and findings (such as the comparison of ORR and pathological response); therefore, further studies with a larger sample size are warranted to validate these results. Furthermore, the follow-up period in the present study was relatively short since the PD-1 inhibitor was approved in China just a few years ago; thus, further studies with a longer follow-up period are necessary to observe the effect of neoadjuvant PAC therapy on the survival profile of patients with LAGC.

In conclusion, neoadjuvant PAC therapy may achieve a better pathological response, postpone progression, and extend survival than AC therapy without elevating the adverse event rates in patients with resectable LAGC, although further validation is needed.

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Adjuvant therapy information

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