World Journal of Surgical Oncology

RESEARCH

Open Access

Efficacy and safety of neoadjuvant bevacizumab plus chemotherapy in locally advanced gastric cancer patients: a retrospective, comparative study

Bin Yin[1] and Wei Luo[2*]

Abstract

Objective The clinical benefits of neoadjuvant bevacizumab plus chemotherapy in locally advanced gastric cancer patients are controversial. This study intended to evaluate the efficacy and safety of neoadjuvant bevacizumab plus chemotherapy in these patients.

Methods In this retrospective study, 71 locally advanced gastric cancer patients receiving neoadjuvant bevacizumab plus chemotherapy or neoadjuvant chemotherapy alone were divided into bevacizumab plus chemo group ($N=23$) and chemo group ($N=48$).

Results Objective response rate (52.2% vs. 35.4%), disease control rate (91.3% vs. 81.3%), surgical resection rate (95.7% vs. 85.4%), R0 resection rate (87.0% vs. 75.0%), and the proportion of patients with tumor regression grade 0–1 (31.8% vs. 17.1%) tended to increase in bevacizumab plus chemo group versus chemo group, although there was no statistical significance. The 48-month progression-free survival (PFS) rates were 58.3% and 33.4% in bevacizumab plus chemo group and chemo group. The 48-month overall survival (OS) rates were 65.1% and 46.5% in bevacizumab plus chemo group and chemo group, respectively. PFS tended to ascend, but OS did not vary in bevacizumab plus chemo group versus chemo group. Bevacizumab plus chemo (vs. chemo) independently related to longer PFS [hazard ratio (HR) = 0.263, $P=0.015$], but not OS (HR = 0.207, $P=0.056$) in locally advanced gastric cancer patients. The incidence of grade 3–4 adverse events did not vary between groups (all $P>0.05$).

Conclusion Neoadjuvant bevacizumab plus chemotherapy achieves higher treatment response and longer survival to some extent, with tolerable adverse events versus neoadjuvant chemotherapy alone in locally advanced gastric cancer patients, but its application needs further verification.

Keywords Bevacizumab plus chemotherapy, Neoadjuvant therapy, Locally advanced gastric cancer, Efficacy, Safety

*Correspondence:
Wei Luo
luowei@hnca.org.cn
[1]Gastroduodenal Pancreas Surgery Department, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/ Hunan Cancer Hospital, Changsha 410013, China
[2] Colorectal Surgery Department, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/ Hunan Cancer Hospital, No. 283 Tongzipo Road, Yuelu District, Changsha, Hunan 410013, China

Introduction

Gastric cancer is a common malignant neoplasm of the digestive system, ranking fifth in incidence and third in mortality among all cancer types around the world [1–3]. In 2022, gastric cancer caused approximately 968,350 new cases and 659,853 new deaths [4]. Due to the insidious nature of early gastric cancer, more than 50.0% of gastric cancer patients are at least locally advanced at the time of diagnosis [5, 6]. For these patients, neoadjuvant chemotherapy based on fluorouracil, platinum, or paclitaxel is recommended due to the advantages of downstaging the tumor, increasing the R0 resection rate, and reducing the risk of recurrence and metastasis [7–9]. However, the effect of current neoadjuvant chemotherapy regimens for locally advanced gastric cancer patients is still unfavorable [10, 11]. Therefore, searching for more feasible neoadjuvant therapy regimens is important to improve the clinical management of these patients.

Bevacizumab is a humanized monoclonal antibody, which inhibits neovascularization by suppressing the vascular endothelial growth factor (VEGF) signaling pathway [12–15]. Currently, bevacizumab plus chemotherapy is considered an effective and safe neoadjuvant regimen for the treatment of several locally advanced cancers [16–18]. However, the efficacy of bevacizumab plus chemotherapy as a neoadjuvant regimen for locally advanced gastric cancer patients remains controversial in previous studies [19–23]. The inconsistent results of previous studies might be due to the differences in the included patients, timing of administration for bevacizumab, operation timing, or main outcome [19–23]. Due to the controversial results in the application of neoadjuvant bevacizumab plus chemotherapy in locally advanced gastric cancer, more clinical studies are required for further verification.

Therefore, this study retrospectively included locally advanced gastric cancer patients, aiming to compare the efficacy and safety between neoadjuvant bevacizumab plus chemotherapy and neoadjuvant chemotherapy alone in these patients.

Materials and methods

Patients

This study retrospectively included 71 locally advanced gastric cancer patients who received bevacizumab plus chemotherapy ($n = 23$) or chemotherapy alone ($n = 48$) as neoadjuvant therapy between July 2018 and September 2021. The inclusion criteria contained: (a) newly diagnosed as gastric cancer or Siewert III gastroesophageal junction (GEJ) cancer; (b) confirmed as locally advanced stage, which was defined as T3N + M0 and T4aN + M0; (c) aged over 18 years; (d) could benefit from neoadjuvant therapy for subsequent surgery, which was evaluated before treatment; (e) received bevacizumab plus chemotherapy or chemotherapy alone as neoadjuvant therapy; (f) had the Response Evaluation Criteria for Solid Tumors (RECIST) 1.1 response information after neoadjuvant therapy (patients with unmeasured lesions were included, and patients without evaluation information were excluded); (g) had at least one available follow-up information. The exclusion criteria contained: (a) had previous history of other cancers; (b) had previous treatment history of cancers; (c) had distant metastasis. The Ethics Committee approved the study. The informed consents were obtained from patients or their family members.

Treatment

The study screened patients who had received bevacizumab plus chemotherapy or chemotherapy alone as neoadjuvant therapy. The patients who received bevacizumab plus chemotherapy were deemed as bevacizumab plus chemo group; while patients who received chemotherapy alone were deemed as chemo group. Bevacizumab was intravenously used with a dose of 7.5 mg/kg on the first day of each cycle [24]. The chemotherapy was administrated on the first day or the fifth day of each cycle according a previous study on the therapeutic window of bevacizumab [23]. A cycle lasted 21 days. The chemotherapy regimens included docetaxel + cisplatin + capecitabine, oxaliplatin + capecitabine, oxaliplatin + S-1, epirubicin + cisplatin/oxaliplatin + capecitabine, and docetaxel + cisplatin + 5-FU. The dose and duration of treatment were adjusted according to the patient's disease situation.

The routine treatment process for patients was as follows: patients received 3 consecutive cycles of neoadjuvant therapy and an interval of about 4 weeks, then operability was assessed and surgery was performed if possible. Depending on the disease situation, a small number of patients might reduce 1 neoadjuvant therapy cycle or increase several cycles to obtain better surgical conditions. If the neoadjuvant response was good, the same regimen was continued after surgery for adjuvant therapy; if the response was poor, the adjuvant therapy was applied with other regimens.

Data acquisition and assessment

The clinical characteristics of patients before neoadjuvant therapy, RECIST 1.1 response after neoadjuvant therapy, surgical resection rate, R0 resection rate, and pathological tumor regression grade (TRG) were retrospectively obtained. TRG was used to evaluate the treatment efficacy of neoadjuvant therapy according to the Chinese Society of Clinical Oncology (CSCO) guideline [25]. The TRG ranged from 0 to 3 with a higher grade indicating poorer response: 0, no viable cancer cells in the primary tumor or lymph nodes (complete regression); 1, single

cell or small groups of cancer cells (good regression); 2, residual cancer outgrown by fibrosis (partial regression); 3, extensive residual cancer (no regression). The rate of TRG 0–1 was calculated as an index to evaluate the efficacy of neoadjuvant therapy. Besides, the follow-up information of patients was retrospectively reviewed, then progression-free survival (PFS) and overall survival (OS) were evaluated. Eight patients in the study did not undergo surgery due to disease progression (1 in bevacizumab plus chemo group and 7 in chemo group), so PFS instead of disease-free survival (DFS) was adopted to reduce the deviation. Additionally, adverse event information was gathered for safety assessment. Due to retrospective settings, the adverse events were relatively poorly documented and only grade 3–4 adverse events could be obtained for analysis.

Table 1 Clinical characteristics

Items	Chemo ($N=48$)	Bevacizumab plus chemo ($N=23$)	t/X^2/Z value	*P* value
Age (years)	56.1 ± 9.8	52.5 ± 11.6	1.345	0.183
Age			0.382	0.537
<60 years	32 (66.7)	17 (73.9)		
≥60 years	16 (33.3)	6 (26.1)		
Sex			0.561	0.454
Female	19 (39.6)	7 (30.4)		
Male	29 (60.4)	16 (69.6)		
ECOG PS score			0.136	0.712
0	27 (56.3)	14 (60.9)		
1	21 (43.8)	9 (39.1)		
Tumor site			1.759	0.415
Cardia/Siewert III GEJ	13 (27.1)	3 (13.0)		
Body	16 (33.3)	9 (39.1)		
Antrum	19 (39.6)	11 (47.8)		
Histological grade			-0.989	0.323
G1 (well differentiation)	7 (14.6)	2 (8.7)		
G2 (moderate differentiation)	20 (41.7)	8 (34.8)		
G3 (poor differentiation or undifferentiation)	20 (41.7)	12 (52.2)		
Gx (unable to be assessed)	1 (2.1)	1 (4.3)		
T stage			0.905	0.341
3	18 (37.5)	6 (26.1)		
4a	30 (62.5)	17 (73.9)		
N stage			-1.320	0.187
1	24 (50.0)	7 (30.4)		
2	14 (29.2)	10 (43.5)		
3	10 (20.8)	6 (26.1)		
TNM stage			6.542	0.241
T3N1M0	9 (18.8)	4 (17.4)		
T3N2M0	7 (14.6)	2 (8.7)		
T3N3M0	2 (4.2)	0 (0.0)		
T4aN1M0	15 (31.3)	3 (13.0)		
T4aN2M0	7 (14.6)	8 (34.8)		
T4aN3M0	8 (16.7)	6 (26.1)		

Age was shown using mean ± standard deviation, and other characteristics were shown using No. (%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; T, tumor; N, node; TNM, tumor-node-metastasis

Statistics

SPSS version.26.0 (IBM., USA) was used for data processing. Comparisons were executed using Mann-Whitney U, X^2, Fisher's exact test, and t tests. PFS and OS were compared using Kaplan-Meier curves and analyzed by log-rank test. Factors related to PFS and OS were evaluated using Cox proportional hazard regression analyses. $P<0.05$ was indicated as significant.

Results

Comparison of clinical characteristics between groups

A total of 122 locally advanced gastric cancer patients were screened, of which 43 patients did not meet the inclusion criteria and 8 patients met the exclusion criteria. Thus, 71 locally advanced gastric cancer patients who received bevacizumab plus chemotherapy (bevacizumab plus chemo group, $n=23$) or chemotherapy alone (chemo group, $n=48$) were retrospectively included. In the bevacizumab plus chemo group, there were 7 (30.4%) females and 16 (69.6%) males with a mean age of 52.5 ± 11.6 years. In the chemo group, there were 19 (39.6%) females and 29 (60.4%) males with a mean age of 56.1 ± 9.8 years. No discrepancy of clinical characteristics was observed between the bevacizumab plus chemo group and the chemo group, including age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, tumor site, or histological grade (all $P>0.05$). More detailed characteristics of patients in the two groups are shown in Table 1.

Comparison of RECIST 1.1 response between groups

The RECIST 1.1 response did not vary between groups ($P=0.109$). In detail, in the bevacizumab plus chemo group, the rates of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 4.3%, 47.8%, 39.1%, and 4.3%, respectively. There was one (4.3%) patient who was not evaluable. In the chemo group, the rates of CR, PR, SD, and PD were 2.1%, 33.3%, 45.8%, and 14.6%, respectively. Two (4.2%) patients were not evaluable. There was no statistical significance in the objective response rate (ORR) (52.2% vs. 35.4%, $P=0.179$) or disease control rate (DCR) (91.3% vs. 81.3%, $P=0.484$) between the two groups; however, ORR and DCR tended to be increased numerically in the bevacizumab plus chemo group versus the chemo group (Table 2).

Table 2 RECIST 1.1 response

Items	Chemo (*N* = 48)	Bevacizumab plus chemo (*N* = 23)	X^2/Z value	*P* value
RECIST 1.1 response			-1.601	0.109
CR	1 (2.1)	1 (4.3)		
PR	16 (33.3)	11 (47.8)		
SD	22 (45.8)	9 (39.1)		
PD	7 (14.6)	1 (4.3)		
NE	2 (4.2)	1 (4.3)		
ORR	17 (35.4)	12 (52.2)	1.807	0.179
DCR	39 (81.3)	21 (91.3)	1.201	0.484

All indexes were shown using No. (%)

RECIST, Response Evaluation Criteria for Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate

Table 3 Surgery and pathological response information

Items	Chemo (*N* = 48)	Bevacizumab plus chemo (*N* = 23)	X^2/Z value	*P* value
Surgical resection rate (%)	41 (85.4)	22 (95.7)	1.629	0.261
R0 resection rate (%)	36 (75.0)	20 (87.0)	1.334	0.356
TRG			-1.836	0.066
0	2 (4.9)	3 (13.6)		
1	5 (12.2)	4 (18.2)		
2	21 (51.2)	12 (54.5)		
3	13 (31.7)	3 (13.6)		
TRG 0–1	7 (17.1)	7 (31.8)	1.801	0.213

All indexes were shown using No. (%)

TRG was assessed in patients receiving surgical resection

TRG, tumor regression grade

Comparison of surgery information and pathological response between groups

The surgical resection rate (95.7% vs. 85.4%, $P = 0.261$) and R0 resection rate (87.0% vs. 75.0%, $P = 0.356$) did not reach statistical significance between the two groups, but they showed an increased trend numerically in the bevacizumab plus chemo group versus the chemo group. Regarding pathological response, the proportions of patients with TRG 0, 1, 2, and 3 were 13.6%, 18.2%, 54.5%, and 13.6% in the bevacizumab plus chemo group, and 4.9%, 12.2%, 51.2%, and 31.7% in the chemo group ($P = 0.066$). There was no statistical significance in the proportion of patients with TRG 0–1 between the two groups, while it tended to be elevated numerically in the bevacizumab plus chemo group versus the chemo group (31.8% vs. 17.1%, $P = 0.213$) (Table 3).

Comparison of PFS and OS between groups

The 12-, 24-, 36-, and 48-month PFS rates were 85.8%, 72.8%, 58.3%, and 58.3% in the bevacizumab plus chemo group. In the chemo group, the 12-, 24-, 36-, and 48-month PFS rates were 69.4%, 47.0%, 33.4%, and 33.4%, respectively. There was no statistical difference in PFS between groups, but it tended to ascend numerically in the bevacizumab plus chemo group versus the chemo group ($P = 0.078$) (Fig. 1A).

Regarding OS, the 12-, 24-, 36-, and 48-month OS rates were 94.7%, 86.8%, 65.1%, and 65.1% in the bevacizumab plus chemo group. The 12-, 24-, 36-, and 48-month OS rates were 90.4%, 76.2%, 46.5%, and 46.5% in the chemo group. The OS was not different between the bevacizumab plus chemo group and the chemo group ($P = 0.224$) (Fig. 1B).

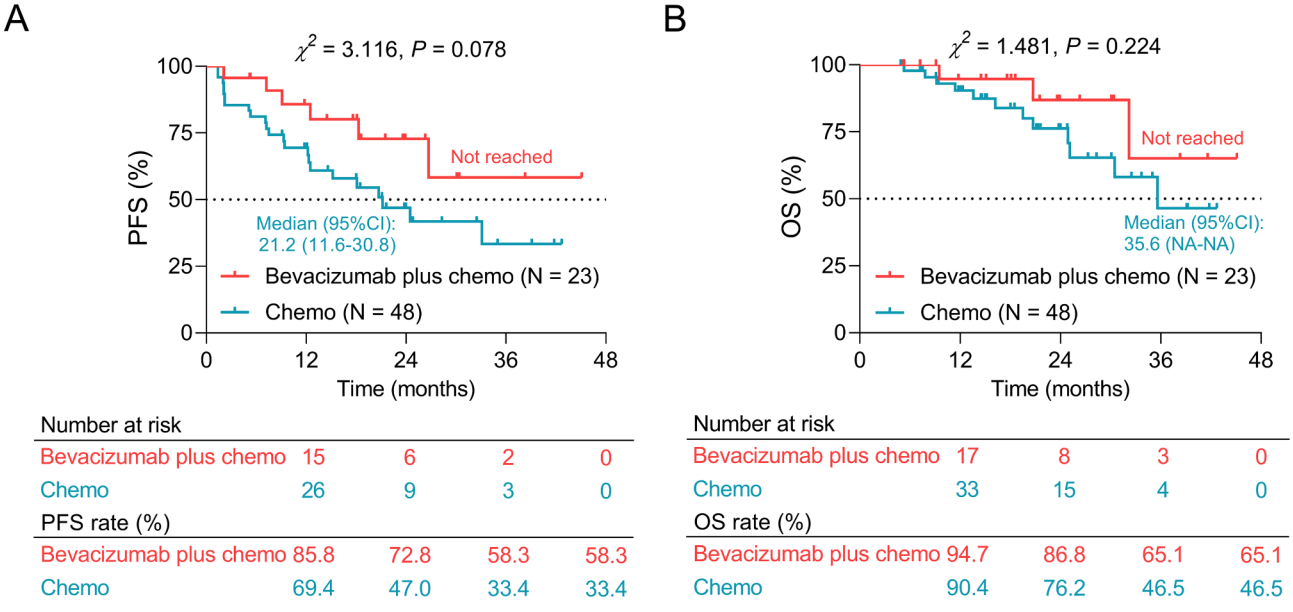


Fig. 1 PFS and OS between groups. Comparison of PFS (**A**) and OS (**B**) between bevacizumab plus chemo group and chemo group

Subgroup analyses for PFS and OS according to different clinical features

Subgroup analyses were performed based on age, sex, ECOG PS score, tumor site, histological grade, T stage, and N stage, respectively. The univariate Cox proportional hazard regression analysis revealed that bevacizumab plus chemo (vs. chemo) was not related to PFS or OS in any subgroup (all $P > 0.05$) (Table 4).

Table 4 Subgroup comparisons of prognosis between patients with different neoadjuvant regimens

Subgroups	Univariate Cox for PFS Bevacizumab plus chemo vs. chemo		Univariate Cox for OS Bevacizumab plus chemo vs. chemo	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age				
<60 years	0.074	0.361 (0.118–1.105)	0.245	0.392 (0.081–1.898)
≥60 years	0.972	1.028 (0.213–4.958)	0.748	1.449 (0.150-13.953)
Sex				
Female	0.750	1.247 (0.321–4.845)	0.993	1.010 (0.112–9.123)
Male	0.057	0.293 (0.083–1.036)	0.212	0.367 (0.076–1.774)
ECOG PS				
0	0.082	0.264 (0.059–1.182)	0.307	0.020 (0.000-36.908)
1	0.812	0.869 (0.272–2.773)	0.793	0.833 (0.213–3.266)
Tumor site				
GEJ/cardia	0.393	0.031 (0.000-88.456)	0.619	0.031 (0.000-2.654E + 04)
Body	0.973	1.020 (0.321–3.238)	0.890	1.134 (0.189–6.815)
Antrum	0.088	0.165 (0.021–1.304)	0.205	0.258 (0.032–2.095)
Histological grade				
G1	0.460	0.024 (0.000-469.359)	0.725	0.032 (0.000-7.360E + 06)
G2	0.267	0.305 (0.037–2.480)	0.398	0.028 (0.000-112.826)
G3	0.158	0.474 (0.168–1.336)	0.450	0.582 (0.143–2.370)
T stage				
3	0.446	0.432 (0.050–3.742)	0.681	0.026 (0.000-9.399E + 05)
4a	0.064	0.391 (0.145–1.058)	0.240	0.465 (0.130–1.670)
N stage				
1	0.202	0.369 (0.080–1.706)	0.191	0.245 (0.030–2.021)
2	0.907	0.917 (0.214–3.937)	0.897	1.200 (0.075–19.185)
3	0.116	0.185 (0.023–1.512)	0.316	0.325 (0.036–2.930)

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; T, tumor; N, node

Independent factors related to PFS and OS

Enter multivariate Cox proportional hazard regression analysis showed that bevacizumab plus chemo (vs. chemo) was independently linked with longer PFS in locally advanced gastric cancer patients [hazard ratio (HR) = 0.263, $P = 0.015$]. However, higher histological grade (HR = 2.480, $P = 0.009$) and higher tumor (T) stage (HR = 2.816, $P = 0.033$) were independently related to shortened PFS in locally advanced gastric cancer patients (Fig. 2A). In terms of OS, bevacizumab plus chemo (vs. chemo) was not independently linked with OS in locally advanced gastric cancer patients (HR = 0.207, $P = 0.056$). Other factors were not independently related to OS in locally advanced gastric cancer patients, either (all $P > 0.05$) (Fig. 2B).

Comparison of grade 3–4 adverse events between groups

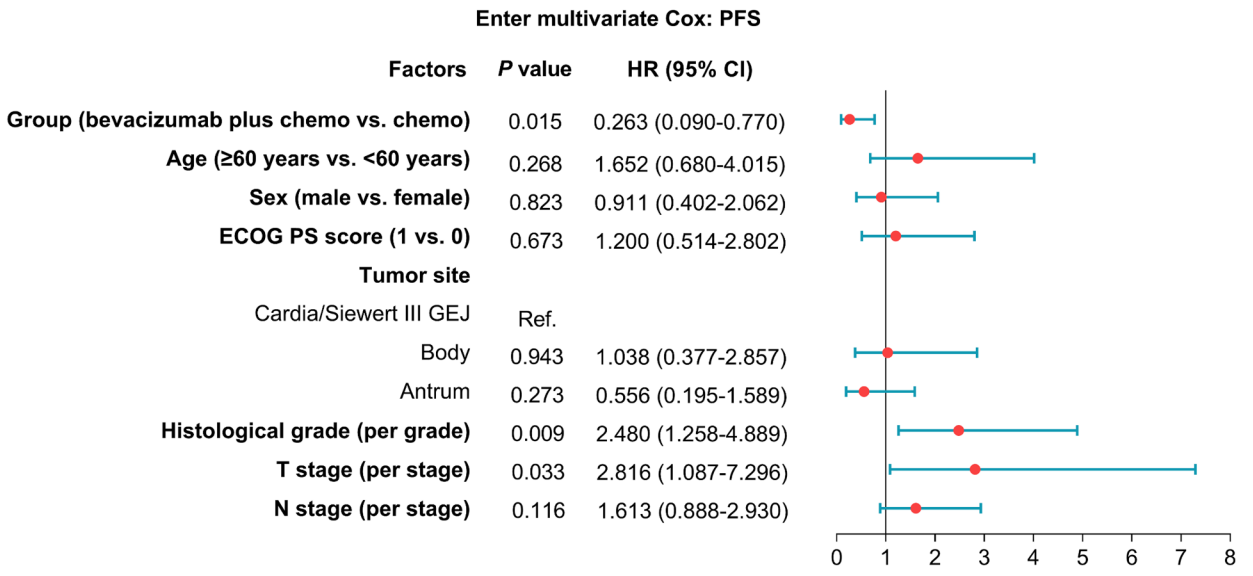
The grade 3–4 adverse events in the bevacizumab plus chemo group included nausea and vomiting (8.7%), anemia (4.3%), leukopenia (4.3%), neutropenia (4.3%), fatigue (4.3%), and diarrhea (4.3%). In the chemo group, the grade 3–4 adverse events included nausea and vomiting (6.3%), anemia (4.2%), leukopenia (4.2%), neutropenia (2.1%), fatigue (2.1%), liver dysfunction (2.1%), and lethargy (2.1%). No difference was found in the incidences of grade 3–4 adverse events between groups (all $P > 0.05$). Notably, there were no grade 3–4 hypertension or hemorrhage in either group (Table 5).

Discussion

Bevacizumab plus chemotherapy has brought a certain degree of clinical benefits in advanced gastric cancer patients, while its efficacy as a neoadjuvant regimen remains controversial [19–22, 24, 26, 27]. Our study showed that neoadjuvant bevacizumab plus chemotherapy increased clinical and pathological response compared to neoadjuvant chemotherapy alone to some extent in locally advanced gastric cancer patients. It would be explained by: (1) Bevacizumab inhibited angiogenesis by inhibiting the VEGF signaling pathway, which might suppress the proliferation, invasion, and metastasis of gastric cancer cells [28, 29]. (2) Bevacizumab normalized the tumor vessel, which increased the delivery efficiency of chemotherapy drugs [30, 31]. (3) Bevacizumab blocked the binding of VEGF with its receptors, which elevated the sensitivity of gastric cancer cells to chemotherapy drugs [32, 33]. Thus, neoadjuvant bevacizumab plus chemotherapy elevated clinical and pathological response in locally advanced gastric cancer patients.

Previous studies showed that neoadjuvant bevacizumab plus chemotherapy increased DFS and PFS, but

A



B

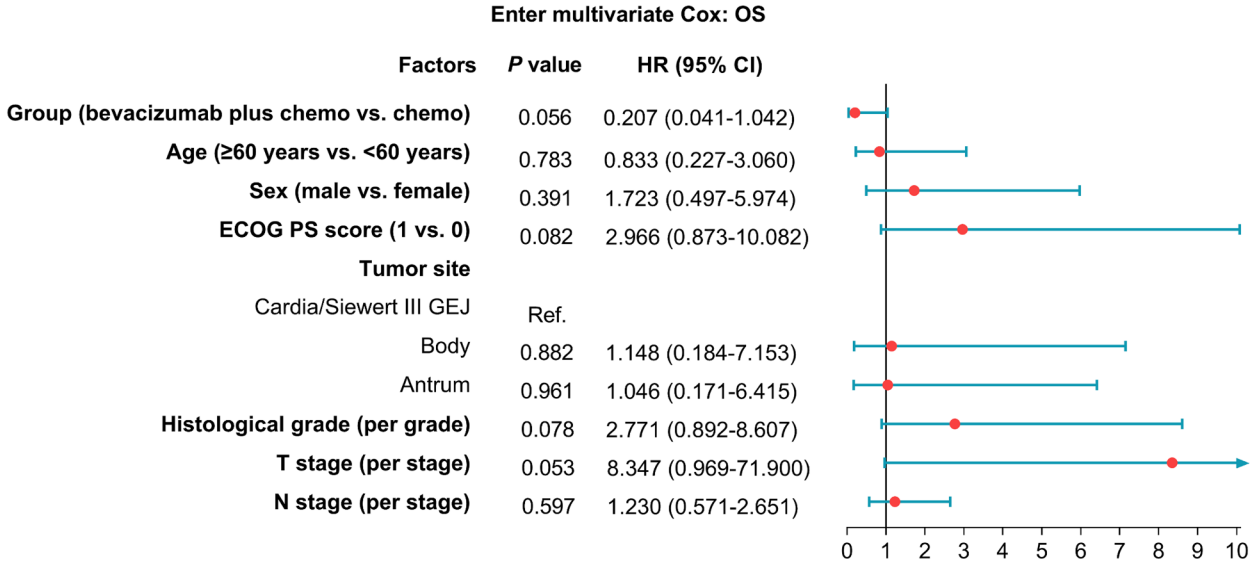


Fig. 2 Enter multivariate Cox proportional hazard regression analysis for PFS and OS. The multivariate analysis of independent factors associated with PFS (**A**) and OS (**B**) in locally advanced gastric cancer patients

did not elevate OS compared to neoadjuvant chemotherapy alone in locally advanced gastric cancer patients [19, 21, 22]. Our study also explored the survival benefits of neoadjuvant bevacizumab plus chemotherapy in locally advanced gastric cancer patients. Notably, in our study, eight patients did not undergo surgery due to disease progression, thus our study assessed PFS instead of DFS to reduce the deviation. The findings of our study were similar to the above studies [19, 21, 22], which showed that neoadjuvant bevacizumab plus chemotherapy increased PFS to a certain degree, while it did not improve OS versus neoadjuvant chemotherapy alone in locally advanced gastric cancer patients. Moreover, neoadjuvant bevacizumab plus chemotherapy independently predicted prolonged PFS, but not OS, in locally advanced gastric cancer patients. The possible explanations might be as follows: (1) As described above, bevacizumab elevated clinical and pathological response, thereby resulting in a longer PFS. (2) The OS of locally advanced gastric cancer patients might be influenced by a variety of factors, such as the differences in patient individual characteristics and different subsequent treatments [34].

Table 5 Grade 3–4 AEs

Items	Chemo (*N* = 48)	Bevacizumab plus chemo (*N* = 23)	X^2value	*P* value
Nausea and vomiting	3 (6.3)	2 (8.7)	0.142	0.656
Anemia	2 (4.2)	1 (4.3)	0.001	1.000
Leukopenia	2 (4.2)	1 (4.3)	0.001	1.000
Neutropenia	1 (2.1)	1 (4.3)	0.291	0.546
Fatigue	1 (2.1)	1 (4.3)	0.291	0.546
Diarrhea	0 (0.0)	1 (4.3)	2.117	0.324
Liver dysfunction	1 (2.1)	0 (0.0)	0.486	1.000
Lethargy	1 (2.1)	0 (0.0)	0.486	1.000

All AEs were shown using No. (%)

AEs, adverse events

Therefore, neoadjuvant bevacizumab plus chemotherapy did not prolong OS in these patients.

The application of bevacizumab may lead to some adverse events, such as hypertension and hemorrhage [35–38]. In our study, there was no grade 3–4 hypertension or hemorrhage in locally advanced gastric cancer patients who received neoadjuvant bevacizumab plus chemotherapy. Moreover, no discrepancy was found in grade 3–4 adverse events between patients who received neoadjuvant bevacizumab plus chemotherapy and those who received neoadjuvant chemotherapy alone. Our results revealed a favorable safety profile of neoadjuvant bevacizumab plus chemotherapy. In addition, the grade 3–4 adverse events of our study in locally advanced gastric cancer patients who received neoadjuvant bevacizumab plus chemotherapy included nausea and vomiting, anemia, leukopenia, neutropenia, fatigue, and diarrhea. The result of our study was partly similar to the findings of previous studies [19, 20, 22].

The limitations of our study were as follows: (1) Our study had a small sample size, with a total of only 71 cases. (2) There might be some selection bias due to the retrospective study design, which could influence the results. (3) The uneven sample size between the bevacizumab plus chemo group and the chemo group might also affect the results to some extent. Overall, the small and uneven sample size, as well as retrospective study design might affect the reliability of the study results. Thus, future larger-scale prospective studies were required to validate these findings.

Conclusions

In conclusion, neoadjuvant bevacizumab plus chemotherapy shows certain clinical benefits and comparable safety profit versus neoadjuvant chemotherapy alone in locally advanced gastric cancer patients. More evidence is still required to further validate the benefits of neoadjuvant bevacizumab plus chemotherapy in these patients.

Acknowledgements
Not applicable.

Author contributions
Bin Yin contributed to the syudy conception and design. Data collection and interpretation were performed by Bin Yin and Wei Luo. Wei Luo contributed to the data analysis. The manuscript was drafted and revised by Bin Yin and Wei Luo. All the authors have read and approved the final manuscript.

Funding
No funding available for this work.

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

Declarations

Ethics approval and consent to participate
The Ethics Committee approved the study. The informed consents were obtained from patients or their family members.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 22 October 2024 / Accepted: 15 December 2024
Published online: 28 January 2025

References

1. Yang WJ, Zhao HP, Yu Y, et al. Updates on global epidemiology, risk and prognostic factors of gastric cancer. World J Gastroenterol. 2023;29(16):2452–68.
2. Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2022;20(2):167–92.
3. Lordick F, Carneiro F, Cascinu S, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(10):1005–20.
4. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
5. Yeh JH, Yeh YS, Tsai HL et al. Neoadjuvant chemoradiotherapy for locally advanced gastric cancer: where are we at? cancers (Basel). 2022;14(12).
6. Pelcovits A, Almhanna K. Locoregional gastric cancer: a narrative review of multidisciplinary management. Ann Transl Med. 2020;8(17):1108.
7. Wang FH, Zhang XT, Tang L, et al. The chinese society of clinical oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2023. Cancer Commun (Lond). 2024;44(1):127–72.
8. Koerner AS, Moy RH, Ryeom SW, Yoon SS. The present and future of neoadjuvant and adjuvant therapy for locally advanced gastric cancer. Cancers (Basel). 2023;15(16).
9. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol. 2023;16(1):57.
10. Zhu Z, Gong YB, Xu HM. Neoadjuvant therapy strategies for advanced gastric cancer: Current innovations and future challenges. Chronic Dis Transl Med. 2020;6(3):147–57.
11. Tong X, Zhi P, Lin S. Neoadjuvant chemotherapy in asian patients with locally advanced gastric cancer. J Gastric Cancer. 2023;23(1):182–93.
12. Garcia J, Hurwitz HI, Sandler AB, et al. Bevacizumab (Avastin(R)) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020;86:102017.
13. Xu D, Luo Y, Wang P, et al. Clinical progress of anti-angiogenic targeted therapy and combination therapy for gastric cancer. Front Oncol. 2023;13:1148131.
14. Cao Y, Langer R, Ferrara N. Targeting angiogenesis in oncology, ophthalmology and beyond. Nat Rev Drug Discov. 2023;22(6):476–95.

15. Mukherji SK. Bevacizumab (Avastin). AJNR Am J Neuroradiol. 2010;31(2):235–6.
16. Ou W, Li N, Wang SY, et al. Phase 2 trial of neoadjuvant bevacizumab plus pemetrexed and carboplatin in patients with unresectable stage III lung adenocarcinoma (GASTO 1001). Cancer. 2016;122(5):740–7.
17. Clavarezza M, Turazza M, Aitini E, et al. Phase II open-label study of bevacizumab combined with neoadjuvant anthracycline and taxane therapy for locally advanced breast cancer. Breast. 2013;22(4):470–5.
18. Song J, Wang Y, Yu H, Zheng L, Cai X, Chen Y. Neoadjuvant chemotherapy plus bevacizumab combined with total mesorectal excision in treating locally advanced rectal cancer patients with braf mutation: clinical benefit and safety. Comput Math Methods Med. 2021;2021:4227650.
19. Ma J, Yao S, Li XS, Kang HR, Yao FF, Du N. Neoadjuvant therapy of DOF regimen plus bevacizumab can increase surgical resection ratein locally advanced gastric cancer: a randomized, controlled study. Med (Baltim). 2015;94(42):e1489.
20. Yu D, Wang Z, He T, Yang L. Neoadjuvant bevacizumab plus docetaxel/cisplatin/capecitabine chemotherapy in locally advanced gastric cancer patients: a pilot study. Front Surg. 2022;9:842828.
21. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2–3 trial. Lancet Oncol. 2017;18(3):357–70.
22. Wei F. Clinical efficacy and adverse reactions of bevacizumab plus radiochemotherapy in the treatment of advanced gastric cancer. J Oncol. 2022;2022:4900037.
23. Zheng YB, Cao FY, Liu KJ, Gan HF, He XB, Tong SL. Value of normalization window of tumor vasculature in neoadjuvant chemotherapy for patients with unresectable gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi. 2012;15(1):55–8.
24. Ohtsu A, Shah MA, Van Cutsem E, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2011;29(30):3968–76.
25. Wang FH, Zhang XT, Li YF, et al. The Chinese society of clinical oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. Cancer Commun (Lond). 2021;41(8):747–95.
26. Meulendijks D, de Groot JW, Los M, et al. Bevacizumab combined with docetaxel, oxaliplatin, and capecitabine, followed by maintenance with capecitabine and bevacizumab, as first-line treatment of patients with advanced HER2-negative gastric cancer: A multicenter phase 2 study. Cancer. 2016;122(9):1434–43.
27. Wang L, Li W, Liu YG, Zhang C, Gao WN, Gao LF. Clinical efficacy and safety of bevacizumab, apatinib, and recombinant human endothelial inhibitor in the treatment of advanced gastric cancer. J Oncol. 2022;2022:6189833.
28. Nakayama I, Takahari D. The role of angiogenesis targeted therapies in metastatic advanced gastric cancer: a narrative review. J Clin Med. 2023;12(9).
29. Kang Y, Li H, Liu Y, Li Z. Regulation of VEGF-A expression and VEGF-A-targeted therapy in malignant tumors. J Cancer Res Clin Oncol. 2024;150(5):221.
30. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005;307(5706):58–62.
31. Bergsland E, Dickler MN. Maximizing the potential of bevacizumab in cancer treatment. Oncologist. 2004;9(Suppl 1):36–42.
32. Hwang JE, Lee JH, Park MR, et al. Blockade of VEGFR-1 and VEGFR-2 enhances paclitaxel sensitivity in gastric cancer cells. Yonsei Med J. 2013;54(2):374–80.
33. Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? Science. 2006;312(5777):1171–5.
34. Patil S, Agarwal V, Drupad HS. Significance of emerging clinical oncology endpoints in support of overall survival. Indian J Cancer. 2022;59(Supplement):S106–18.
35. Li M, Kroetz DL. Bevacizumab-induced hypertension: Clinical presentation and molecular understanding. Pharmacol Ther. 2018;182(152 – 60.
36. Hong S, Daniels B, van Leeuwen MT, Pearson SA, Vajdic CM. Incidence and risk factors of hypertension therapy in Australian cancer patients treated with vascular signalling pathway inhibitors. Discov Oncol. 2022;13(1):6.
37. Gressett SM, Shah SR. Intricacies of bevacizumab-induced toxicities and their management. Ann Pharmacother. 2009;43(3):490–501.
38. Shord SS, Bressler LR, Tierney LA, Cuellar S, George A. Understanding and managing the possible adverse effects associated with bevacizumab. Am J Health Syst Pharm. 2009;66(11):999–1013.

Publisher's note