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Original Article

Efficacy and safety of neoadjuvant chemoradiotherapy plus apatinib for patients with locally advanced, HER2-negative, Siewert's type II-III adenocarcinoma of esophagogastric junction: a single-arm, open-label, phase II trial

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Abstract: This study aimed to investigate the efficacy and safety of concurrent neoadjuvant chemoradiotherapy (CRT) plus apatinib in treating locally advanced, HER2-negative, Siewert's type II-III adenocarcinoma of esophagogastric junction (AEG) patients. Thirty eligible patients were analyzed in this single-arm, open-label, phase II trial. Patients received neoadjuvant regimen as follows: two cycles of apatinib (orally, 250 mg/day on day 1-28), two cycles of capecitabine (orally, 1,000 mg/m^2 twice daily on day 1-14), oxaliplatin (intravenously, 130 mg/m^2 on day 1), and concurrent radiotherapy (a total dose of 45 Gy in 25 fractions) started on day 1 of chemotherapy. Then, surgery was performed within 8-12 weeks after the completion of neoadjuvant therapy. This trial was registered on the ClinicalTrials.gov website (access number: NCT03349866). After neoadjuvant CRT plus apatinib treatment, 18 (60.0%) patients achieved objective response, 29 (96.7%) patients achieved disease control, and 20 (66.7%) patients achieved down-staging. Encouragingly, tumor regression grade (TRG) 0, TRG 1, TRG 2 and TRG 3 were observed in 33.3%, 20.0%, 30.0% and 10.0% patients, respectively; the pathological complete response rate was 33.3%, and the R0 resection rate was 93.3%. Regarding survivals, the 1-year and 2-year progression-free survival rates were 96.7% and 88.1%, respectively. Meanwhile, the 1-year and 2-year overall survival rates were 100.0% and 96.6%, respectively. As to safety, the majority of the adverse events were of mild grade, and the post-operative complications were manageable. In conclusion, neoadjuvant CRT plus apatinib exhibits high efficacy and acceptable tolerance in patients with locally advanced, HER2-negative, Siewert's type II-III AEG.

Keywords: Neoadjuvant chemoradiotherapy, apatinib, adenocarcinoma of esophagogastric junction, efficacy, safety

Introduction

Adenocarcinoma of esophagogastric junction (AEG) is a heterogenous malignancy with an alarming and increasing incidence worldwide, especially in Eastern Asia [1, 2]. Due to its special anatomical location joining esophagus and noncardia stomach as well as its lack of a unified definition or classification, AEG has not been regarded as a disease independent from esophageal cancer or gastric cancer until recently [3]. AEG is mainly classified by Japanese typing or Siewert's typing, among which Siewert's typing (including Siewert's type I, II and III) is based on the refined anatomic staging of AEG to tailor surgical approaches [4, 5]. Currently, surgical resection is the primary curative paradigm for the treatment of AEG patients, while the prognosis remains deteriorative with five-year survival rate of about 30% in AEG patients with surgery alone owning to high risk of distant/locoregional recurrence following surgery [1, 2, 6, 7]. The above-mentioned situation emphasizes the continual need for novel and more effective regimens in the management of AEG patients.

Several studies have demonstrated that neoadjuvant or perioperative multimodal treatments consisting of chemotherapy, radiation or their combination improve the R0 resection rate and survival compared to surgery alone in gastric adenocarcinoma patients or AEG patients [8-10]. Meanwhile, our previous studies have illuminated that concurrent neoadjuvant chemoradiotherapy (CRT) increases treatment response, pathological response and/or prolongs survivals in AEG patients with Siewert's type II-III compared to surgery alone or neoadjuvant chemotherapy alone [11, 12]. More recently, apatinib has been introduced as an anti-angiogenic, small-molecule VEGFR2 inhibitor in the treatment of gastric adenocarcinoma patients or AEG patients, showing good efficacy and well-tolerant safety profiles [13, 14]. Additionally, the efficacy and safety of neoadjuvant chemotherapy plus apatinib are reported by one previous study, which illuminates that the regimen displays promising treatment response, pathological complete response (pCR) and acceptable safety profiles in locally advanced gastric adenocarcinoma patients [15]. However, in locally advanced AEG patients, the application of neoadjuvant CRT plus apatinib is seldom reported.

Therefore, this phase II trial aimed to evaluate the efficacy and safety of a new neoadjuvant regimen containing CRT plus apatinib in the treatment of patients with locally advanced, HER2-negative, Siewert's type II-III AEG.

Methods

Study design

This was a single-arm, open-label, phase II trial, aimed at investigating the efficacy and safety of neoadjuvant CRT plus apatinib in patients with HER2-negative, Siewert's type II-III AEG. This study was approved by the Ethics Committee of Fourth Hospital of Hebei Medical University with approval number 2017083. All eligible participants voluntarily signed the informed consents in line with the institutional and federal guidelines. The clinical trial register number was NCT03349866.

Participants

The inclusion criteria comprised of: (1) newly diagnosed AEG confirmed by histological examination; (2) aged from 18 to 70 years; (3) locally advanced (T3N+ or T4N+, M0, CY0, P0) and resectable disease; (4) Siewert's type II-III disease; (5) HER2-negative confirmed by immunohistochemistry and fluorescence in situ hybridization (FISH); (6) the maximum diameter of the tumor not exceeding 8 cm by gastroscopy and CT; (7) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1; (8) sufficient hepatic, hematological, and kidney functions (aspartate transaminase and alanine transaminase level ≤2.5 upper limit of normal (ULN); hemoglobin ≥80 g/L, neutrophil count $\geq 1.5\times10^9$/L, platelet count $\geq 9\times10^9$/L, serum total bilirubin level ≤1.5 ULN and serum creatinine level ≤1.5 ULN).

The exclusion criteria were as follows: (1) allergic reactions to study drugs; (2) patients complicated with other malignancies; (3) presence of positive peritoneal cytology (CY1) and peritoneal dissemination (P1) revealed through the staging laparoscopy and peritoneal lavage; (4) pregnant or lactating female patients.

Treatment

Treatment procedures were as follows: first, patients received neoadjuvant CRT plus apatinib and XELOX (capecitabine plus oxaliplatin) regimen prior to surgery; then surgery was performed within 8 to 12 weeks after neoadjuvant therapy; after surgery, patients received adjuvant chemotherapy with capecitabine. Specifically, before surgery, patients received two 28-day cycles of apatinib, orally, 250 mg, once a day, days (d) 1 to 28, concurrent with two 21-day cycles of capecitabine orally, 1,000 mg/m^2, twice a day, d1-14 of each cycle, plus oxaliplatin intravenously, 130 mg/m^2 on day 1 of each cycle. Meanwhile, radiotherapy was started from the day 1 of the first cycle of chemotherapy, and a total dose of 45 Gy was given at a daily fraction of 1.8 Gy, 5 days per week (excluding weekends). Radiation therapy schedule was made up of a three-dimensional CT simulation (3-5 mm slice thickness) with custom immobilization devices. Patients underwent surgery within 8 to 12 weeks after completion of neoadjuvant concurrent therapy. An open gastrectomy or laparoscopic gastrectomy was selected depending on the characteristics of the patient and the expertise of the surgeon.

Surgical procedures consisted of D2 lymphadenectomy and either (1) proximal subtotal gastrectomy (with jejunal interposition surgery or an esophageal gastric remnant anastomosis) or (2) total gastrectomy (with jejunal interposition surgery). Most importantly, all the patients underwent a second-look laparoscopy and peritoneal lavage before surgery to exclude CY1 and P1 that developed during neoadjuvant therapy. For patients with CY1 or P1 developed during neoadjuvant therapy, they were administered with systemic therapy per regimen for stage IV disease. After surgery, patients received six 3-week cycles of capecitabine orally, 1,000 mg/m^2, twice a day, d1-14 of each cycle. During the treatment, toxicity surveillance was performed for all patients, which was graded referring to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Assessments

The primary outcome was the pCR. The secondary outcomes comprised the objective response rate (ORR) at two weeks before the second-look staging laparoscopy, the disease control rate (DCR) at two weeks before the second-look staging laparoscopy, successful down-staging rate, the tumor regression grade (TRG), the R0 resection rate, and the adverse events from the treatment initiation within 1 month after surgery. The response to neoadjuvant CRT plus apatinib therapy was evaluated referring to the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1). The response was made up of four classifications: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Besides, in order to further assess the response outcome, the ORR (CR+PR) and DCR (CR+PR+SD) were also calculated.

Clinical TNM staging was carried out before and after neoadjuvant CRT plus apatinib therapy in terms of the criteria developed by American Joint Committee on Cancer (8th edition). The successful down-staging was defined as the clinical TNM stage of patients decreased form stage III to stage II or I after neoadjuvant CRT plus apatinib therapy.

Pathological response of the tumor to neoadjuvant CRT plus apatinib treatment was assessed as well. The resection margin status as well as tumor regression grade (TRG) were documented. R0 resection was defined as no cancer cells at resection margins. TRG included four grades, and each grade was defined as follows: Grade 0: complete remission (no cancer cells); Grade 1: partial remission (single cells or small groups of cancer cells); Grade 2: low efficiency (residual cancer outgrown by fibrosis); and Grade 3: poor efficiency (minimal or no treatment effect with extensive residual cancer cells). Achievement of TGR 0 was defined as pCR, which was calculated in total patients who completed the neoadjuvant CRT plus apatinib therapy.

After discharge from hospital, follow-up was conducted every 6 months. Based on the follow-up records, the progression-free survival (PFS) and overall survival (OS) were evaluated. PFS was calculated from the initiation of neoadjuvant CRT plus apatinib therapy to the disease progression or patients' death. The OS was calculated from the initiation of neoadjuvant CRT plus apatinib therapy to the patients' death.

Statistical analysis

Study analysis was performed in the per protocol set (PPS, n=30) which consisted of the patients who completed the neoadjuvant CRT plus apatinib therapy. The quantitative data were described by median with range, while the categorical data were described by number and percentage. Clinical stage before and after neoadjuvant CRT plus apatinib therapy was compared by McNemar test. PFS and OS were described using the Kaplan-Meier curves. Statistical significance was defined *as a P* value <0.05. All data processing and analysis were carried out with the use of SPSS 24.0 (IBM, Chicago, Illinois, USA). All diagrams were constructed with the use of GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, California, USA).

Results

Study flow

Initially, 72 patients with locally advanced, HER2-negative, Siewert's type II-III AEG were screened, among whom 41 patients were excluded (including 19 patients who withdrew consent, 11 with CY1, 8 with HER2-positive

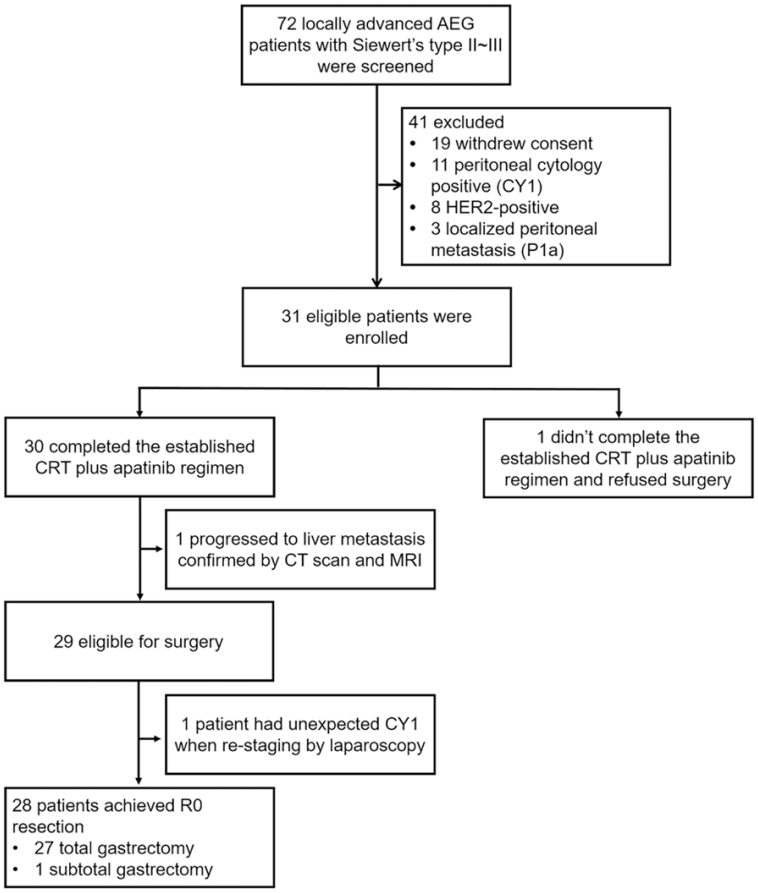

Figure 1. Study flow chart. AEG, adenocarcinoma of esophagogastric junction; CT, computerized tomography; CRT, chemoradiotherapy; MRI, magnetic resonance imaging.

AEG and 3 with localized peritoneal metastasis (P1a) (**Figure 1**). Then, out of the remaining 31 eligible patients, 30 patients completed the treatment of CRT plus apatinib regimen, while 1 patient did not complete it and refused surgery. Among 30 patients who completed the established CRT plus apatinib regimen, 1 patient progressed to liver metastasis confirmed by CT scan and MRI, leaving 29 patients who were eligible for surgery. After that, 1 patient had unexpected CY1 when re-staging by laparoscopy. Lastly, 28 patients achieved R0 resection (including 27 cases of total gastrectomy and 1 case of subtotal gastrectomy).

Clinical characteristics

The median age of patients was 61 years, with a range of 46-70 years (**Table 1**). Twenty-six (83.9%) patients were males and 5 (16.1%) were females. As for performance status, 8 (25.8%) patients had ECOG score 0, and 23 (74.2%) had ECOG score 1. Regarding Siewert's type, 21 (67.7%) patients presented with Siewert's type II and 10 (32.3%) displayed Siewert's type III. In terms of tumor stage, 2 (6.5%) and 29 (93.5%) patients exhibited cT3 and cT4 stage, respectively; 13 (41.9%), 12 (38.7%) and 6 (19.4%) patients displayed cN1, cN2 and cN3 stage, respectively; all 31 (100%) patients presented with TNM stage III. The detailed information about vertical axis diameter of the tumor, Lauren type and HER2 status in patients was shown in **Table 1**.

Treatment response and down-staging rate

Thirty patients completed neoadjuvant CRT plus apatinib treatment, and then their treatment response and down-staging rate were assessed. It was observed that no (0%) patients achieved CR, 18 (60.0%) achieved PR, 11 (36.7%) achieved SD, and 1 (3.3%) achieved PD, which results in an ORR of 60.0% and a DCR of 96.7% (**Figure 2**). Furthermore, clinical T stage (P<0.001), N stage (P<0.001) and TNM stage (P<0.001) were all reduced after neoadjuvant CRT plus apatinib treatment; 20 (66.7%) patients achieved successful down-staging (**Table 2**).

Pathological response

Among 30 patients who completed neoadjuvant CRT plus apatinib regimen, 10 (33.3%), 6 (20.0%), 9 (30.0%) and 3 (10.0%) patients achieved TRG 0, 1, 2 and 3, respectively (**Figure 3A**). Meanwhile, 10 (33.3%) patients achieved pCR, and 28 (93.3%) realized R0 resection (**Figure 3B**).

Survivals

The mean PFS was 31.4 months, with a 95% CI of 28.8-34.0 months. Meanwhile, the 1-year

Table 1. Baseline characteristics of AEG patients

Characteristics	AEG patients (n=31)
Age (years)	
Median	61
Range	46-70
Gender, No. (%)	
Male	26 (83.9)
Female	5 (16.1)
ECOG score, No. (%)	
0	8 (25.8)
1	23 (74.2)
Siewert's type, No. (%)	
II	21 (67.7)
III	10 (32.3)
Vertical axis diameter of the tumor (cm)	
Median	6
Range	4-8
Lauren type, No. (%)	
Intestinal	20 (64.5)
Diffuse	11 (35.5)
HER2 status, No. (%)	
0	8 (25.8)
1+	16 (51.6)
2+ and Fish(-)	7 (22.6)
Clinical T stage, No. (%)	
cT3	2 (6.5)
cT4	29 (93.5)
Clinical N stage, No. (%)	
cN1	13 (41.9)
cN2	12 (38.7)
cN3	6 (19.4)
Clinical TNM stage III, No. (%)	31 (100.0)

AEG, adenocarcinoma of the esophagogastric junction; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

and 2-year PFS rates were 96.7% and 88.1%, respectively (**Figure 4A**). Regarding OS, the mean OS was 32.5 months, with a 95% CI of 30.4-34.5 months; the 1-year and 2-year OS rates were 100% and 96.6%, respectively (**Figure 4B**).

Adverse events

With neoadjuvant CRT plus apatinib treatment, the following hematological adverse events were observed: leukopenia (76.7%), thrombocytopenia (56.7%) and neutropenia (50.0%). At the same time, the following non-hematological adverse events occurred: nausea (66.7%), fatigue (63.3%), abnormal liver function (53.3%), vomiting (36.7%), hypertension (33.3%), radioactive esophagitis (23.3%), diarrhea (10.0%) and hand-foot syndrome (3.3%) (**Table 3**). Notably, most of adverse events were of mild grades (grade 1-2); only a small number of adverse events were of grade 3, and no grade 4-5 adverse events were found.

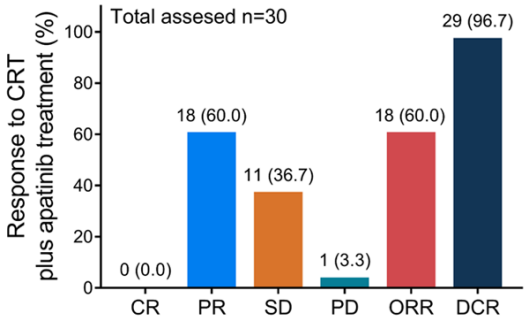

Figure 2. Treatment response to neoadjuvant CRT plus apatinib. CRT, chemoradiotherapy; AEG, adenocarcinoma of esophagogastric junction; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Complications

Among 28 patients who received surgery, 4 (14.3%), 4 (14.3%) and 3 (10.7%) patients experienced pneumonia, hydrothorax and anastomotic leakage postoperative complications, respectively (**Table 4**).

Discussion

This phase II trial evaluated the indication of neoadjuvant CRT plus apatinib in treating patients with locally advanced, HER2-negative, Siewert's type II-III AEG, which observed that: (i) The ORR was 60.0%, the DCR was 96.7%, and the successful down-staging rate was 66.7%; (ii) The pCR rate was 33.3%, and the R0 resection rate was 93.3%; (iii) The 1-year, 2-year PFS rates were 96.7% and 88.1%, respectively; the 1-year, 2-year OS rates were 100.0% and 96.6%, respectively. (iv) Adverse events and postoperative complications were acceptable and manageable.

One prior study assessing the treatment response of neoadjuvant chemotherapy plus apatinib reported an ORR of 79.3%, a DCR of

Table 2. Clinical stage before and after CRT plus apatinib treatment

Clinical stage	Before CRT plus apatinib treatment (n=30)	After CRT plus apatinib treatment (n=30)	*P* value
Clinical T stage, No. (%)			<0.001
cT2	0 (0.0)	8 (26.7)	
cT3	2 (6.7)	7 (23.3)	
cT4	28 (93.3)	15 (50.0)	
Clinical N stage, No. (%)			<0.001
N0	0 (0.0)	22 (73.3)	
N1	13 (43.3)	8 (26.7)	
N2	12 (40.0)	0 (0.0)	
N3	5 (16.7)	0 (0.0)	
Clinical M stage, No. (%)			0.317
M0	30 (100.0)	29 (96.7)	
M1	0 (0.0)	1 (3.3)	
Clinical TNM stage, No. (%)			<0.001
Stage I	0 (0.0)	8 (26.7)	
Stage II	0 (0.0)	12 (40.0)	
Stage III	30 (100.0)	9 (30.0)	
Stage IV	0 (0.0)	1 (3.3)	
Successful down-staging	-	20 (66.7)	-

CRT, chemoradiotherapy.

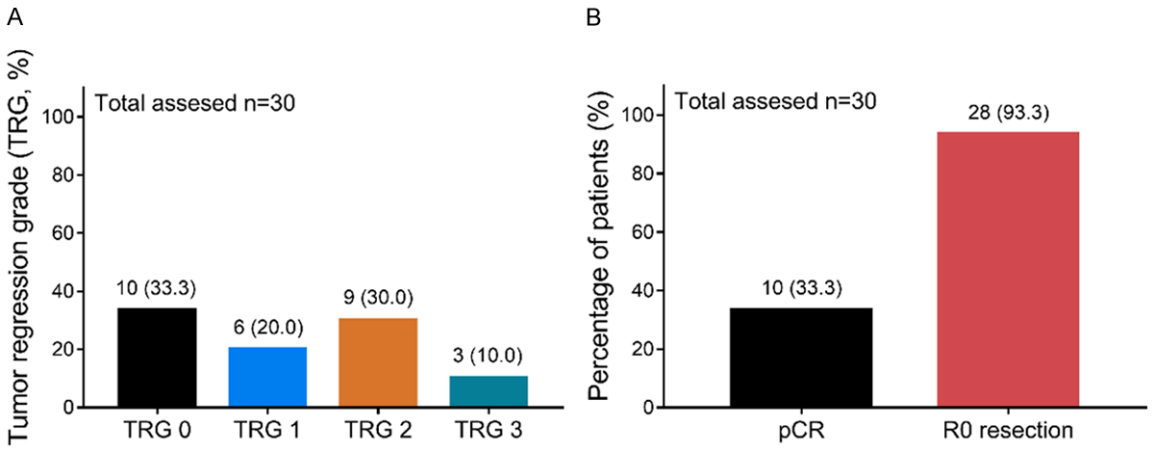

Figure 3. Pathological response. Tumor regression grade (A), pCR rate and R0 resection rate (B) in response to neoadjuvant CRT plus apatinib treatment. pCR, pathological complete response; CRT, chemoradiotherapy; AEG, adenocarcinoma of esophagogastric junction.

96.6% and a down-staging rate of 55.2% in treating locally advanced gastric adenocarcinoma patients [15]. While in AEG patients, the treatment response of neoadjuvant CRT plus apatinib is not reported yet. In the present trial, after neoadjuvant CRT plus apatinib treatment, the ORR was 60.0% and the DCR was 96.7% in patients with locally advanced, HER2-negative, Siewert's type II-III AEG. Meanwhile, the successful down-staging rate was 66.7%, which provided the higher possibility for surgery. The down-staging rate was numerically higher in the present trial than that in the prior reported study [15]. The potential explanations were as below: (i) Concurrent neoadjuvant CRT killed tumor cells via eliciting the cytotoxic effect; meanwhile, apatinib (an antiangiogenetic VEGFR2 inhibitor) induced antitumor

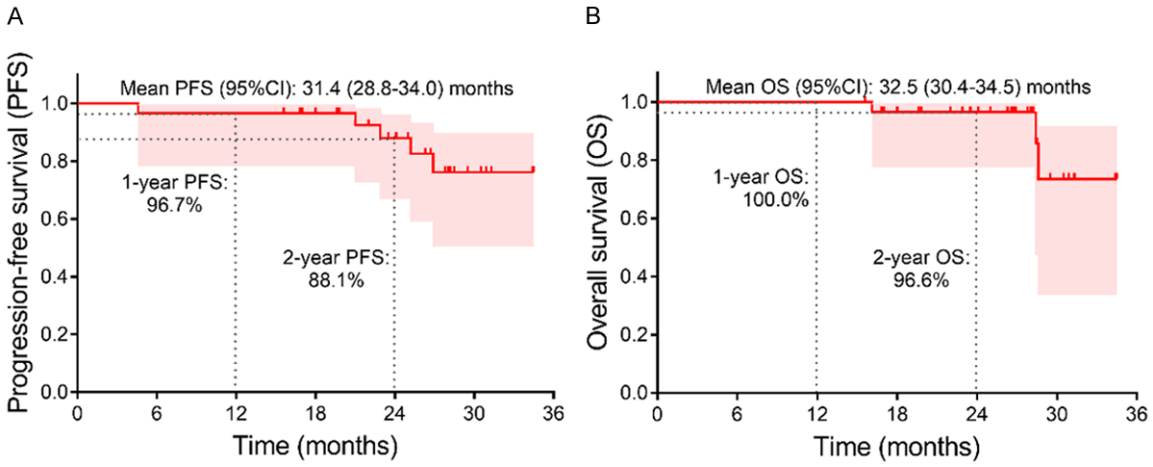

Figure 4. PFS and OS. The PFS (A) and OS (B) shown by Kaplan-Meier curve. PFS, progression-free survival; OS, overall survival.

Table 3. Adverse events prior to surgery in 30 patients during CRT plus apatinib treatment

Adverse events	Total	Grade 1	Grade 2	Grade 3	Grade 4/5
Hematologic, No. (%)					
Leukopenia	23 (76.7)	5 (16.7)	13 (43.3)	5 (16.7)	0 (0.0)
Thrombocytopenia	17 (56.7)	14 (46.7)	2 (6.7)	1 (3.3)	0 (0.0)
Neutropenia	15 (50.0)	7 (23.3)	6 (20.0)	2 (6.7)	0 (0.0)
Non-hematologic, No. (%)					
Nausea	20 (66.7)	10 (33.3)	8 (26.7)	2 (6.7)	0 (0.0)
Fatigue	19 (63.3)	14 (46.7)	5 (16.7)	0 (0.0)	0 (0.0)
Abnormal liver function	16 (53.3)	15 (50.0)	1 (3.3)	0 (0.0)	0 (0.0)
Vomiting	11 (36.7)	7 (23.3)	2 (6.7)	2 (6.7)	0 (0.0)
Hypertension	10 (33.3)	8 (26.7)	2 (6.7)	0 (0.0)	0 (0.0)
Radioactive esophagitis	7 (23.3)	5 (16.7)	2 (6.7)	0 (0.0)	0 (0.0)
Diarrhea	3 (10.0)	2 (6.7)	0 (0.0)	1 (3.3)	0 (0.0)
Hand-foot syndrome	1 (3.3)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)

CRT, chemoradiotherapy.

Table 4. Postoperative complications

Postoperative complications	Surgery patients (n=28)
Pneumonia, No. (%)	4 (14.3)
Hydrothorax, No. (%)	4 (14.3)
Anastomotic leakage, No. (%)	3 (10.7)

activities via inhibiting tumor angiogenesis. Hence, the synergic effect of concurrent neoadjuvant CRT plus apatinib probably devotes to the good treatment response and the successful down-staging in studied patients [8, 9, 15, 16]. (ii) The higher down-staging rate in the present trial than that in the prior reported study might be due to the additional antitumor effect by radiotherapy in the present trial and different studied population between the studies [15].

The above results revealed that concurrent neoadjuvant CRT increased R0 resection rate (96.7% vs. 82.5%) and pCR rate (16.7% vs. 3.2%) compared with neoadjuvant chemotherapy alone in patients with locally advanced, Siewert's type II-III AEG. Furthermore, concurrent neoadjuvant CRT elevates R0 resection rate (100% vs. 80%) compared with surgery alone in resectable AEG patients [11, 12]. Additionally, a more recent study evaluating the pathological response of neoadjuvant apatinib plus chemotherapy in locally advanced gastric adenocarcinoma patients demonstrated a R0

resection rate of 96.6% and a pCR rate of 13.8% [16]. While the pathological response of neoadjuvant CRT plus apatinib remains unknown in AEG patients. In the present trial, the pathological response was also evaluated in patients with locally advanced, HER2-negative, Siewert's type II-III AEG. Encouragingly, the results showed that the R0 resection rate was 93.3% and the pCR rate was 33.3%. It was noted that the pCR rate in this study was higher than that in the previous studies (3.2% and 13.8%, respectively) [12, 15]. The following were potential explanations: (i) On the one hand, apatinib probably promoted the cytotoxic effect of concurrent CRT on tumor cells. On the other hand, apatinib suppressed tumor angiogenesis and elicited antitumor activities. Taken together, concurrent neoadjuvant CRT plus apatinib probably killed tumor cells more effectively, resulting in an astonishing pCR rate in the studied patients [8, 9, 15, 16]. (ii) According to the above-mentioned findings, neoadjuvant CRT plus apatinib realizes a good treatment response and down-staging effect, which probably contributes to improved bridging effect, R0 resection and pCR in the studied patients. Besides, in the present trial, it was observed that with neoadjuvant CRT plus apatinib treatment bridging to surgery, the 1-year, 2-year PFS rates were 96.7% and 88.1%, respectively; the 1-year, 2-year OS rates were 100.0% and 96.6% in locally advanced AEG patients with HER2-negative, Siewert's type II-III, respectively. The findings might be explained by that neoadjuvant CRT plus apatinib treatment achieves good down-staging effect and astonishing pCR rate, which probably devotes to improved prognosis in the studied patients.

The common adverse events in apatinib treatment are hypertension, proteinuria and hand-foot syndrome. Meanwhile, the common side effects during neoadjuvant CRT treatment are gastrointestinal and hematological toxicities [8-14]. In the present trial, during and after neoadjuvant CRT plus apatinib treatment, the common hematologic adverse events were leukopenia, thrombocytopenia and neutropenia. Then the common non-hematologic adverse events were nausea, fatigue, abnormal liver function, vomiting, hypertension, radioactive esophagitis, diarrhea and hand-foot syndrome in patients with locally advanced, HER2-negative, Siewert's type II-III AEG. The results in the present trial were in accordance with those reported in the previous studies [8-14]. Notably, most adverse events were of grade 1-2 and manageable, indicating that neoadjuvant CRT plus apatinib treatment was well-tolerant in treating the studied patients. Besides, the following postoperative complications occurred in the studied patients: pneumonia, hydrothorax and anastomotic leakage, which were also tolerable and manageable.

Nonetheless, this study has some limitations. First, the relatively small sample size of eligible patients might potentially reduce the statistical power of the analysis. Second, as this was a single-arm trial, it lacked a control group, so further randomized, controlled trials would be desirable. Lastly, further studies assessing the synergic effect of CRT plus apatinib in treating these patients should be warranted.

In summary, neoadjuvant CRT plus apatinib regimen exhibits good efficacy and acceptable tolerance for treating patients with locally advanced, HER2-negative, Siewert's type II-III AEG, which might be a potential treatment strategy for the management of these patients.

Disclosure of conflict of interest

None.

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