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Original Article

Apatinib combined with three-dimensional conformal radiotherapy can prolong advanced gastric cancer patients' survival times and improve their quality of life

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Abstract: This study aimed to investigate the impacts of the combination of apatinib and three-dimensional conformal radiotherapy (3D-CRT) on advanced gastric cancer patients' survival times and quality of life. Advanced gastric cancer patients admitted to our hospital from April 2017 to May 2018 were recruited as the study cohort and divided into a control group (the CG, 59 cases) and an observation group (the OG, 62 cases). The patients in the CG received 3D-CRT treatment, and the patients in the OG were treated with apatinib combined with 3D-CRT. The overall response rate (ORR), the total incidence of adverse reactions (ADR), the tumor marker levels, and the inflammatory factor levels before and after treatment were evaluated. After 30 days of treatment, the improvement rate in the quality of life and the overall quality of life in both groups were observed. The patients in both groups were followed up for one year to generate a statistical comparison of their disease-free survival times and their total survival times. The ORR was higher in the OG than it was in the CG. There was no difference in the ADR between the two groups. The improvement rate in the quality of life in the OG after 30 days of treatment was significantly higher than it was in the CG. The CEA, CA72-4, CA19-9, hs-CRP, and TNF-α expression levels in the OG after the treatment were notably lower than they were in the CG. After the treatment, the quality of life scores were notably higher in the OG than they were in the CG. The disease-free survival times and total survival times in the OG were longer than those of the CG. Apatinib combined with 3D-CRT can improve tumor markers and the quality of life, reduce the inflammatory response, and prolong the survival times of advanced gastric cancer patients.

Keywords: Apatinib, three-dimensional conformal radiotherapy, advanced gastric cancer, survival time, quality of life

Introduction

Gastric cancer, a common malignancy, is the second leading cause of cancer-related mortality and is associated with a high incidence of death [1]. Studies have shown that the pathogenesis and etiology of gastric cancer remain to be determined, and the best way to prevent it also remains to be determined. Since patients with early gastric cancer do not have obvious symptoms and the diagnosis rate is low, most patients are first diagnosed with advanced gastric cancer when receiving treatment [2]. Clinically, surgery is still the most effective treatment method. However, in most patients, the disease has already progressed to an advanced stage when they are diagnosed, so they lose the opportunity for surgery [3]. Other conventional treatments (radiotherapy and chemotherapy) have only moderate curative effects on advanced gastric cancer or metastatic gastric cancer, so a patient's prognosis is poor [4]. Therefore, it is particularly important to find new methods of improving the survival rate and prognoses of advanced gastric cancer patients.

Three-dimensional conformal radiotherapy (3D-CRT) can focus the radiation beam into the shape of a tumor and can be used to alleviate the adverse effects of traditional radiotherapy [5]. Studies have shown that 3D-CRT can reduce the incidence rate of primary tumors,

increase the resectability rate, improve surgical conditions, reduce tumor recurrence and metastasis, and prolong patients' survival times. Studies have also found that the therapeutic effect of 3D-CRT combined with drugs is effective [6]. For example, one study suggests that the combination of apatinib and radiotherapy not only has a good therapeutic effect, but it also has controllable adverse reactions (ADR) [7]. Clinical evidence shows that apatinib, a small molecule tyrosine kinase inhibitor, can block tumor angiogenesis by inhibiting VEGFR-2 and binding with a ligand of the vascular endothelial growth factor receptor VEGFR-2 [8]. There is one study reporting that the oral administration of apatinib improves the progression-free survival and the OS of advanced gastric cancer patients who have failed to receive two or more previous chemotherapy regimens [9].

At present, there are few studies on the combination of apatinib and 3D-CRT in treating gastric cancer. This study observes the effect of the combination of the two on the prognosis of advanced gastric cancer patients, aiming to find a safer and more effective treatment scheme for advanced gastric cancer patients.

Materials and methods

General data

Advanced gastric cancer patients admitted to The People's Hospital of Shanxi Province from April 2017 to May 2018 were divided into a control group (the CG, 59 cases, including 27 males and 32 females, with a mean age of 44.82±5.28 years) and an observation group (the OG, 62 cases, including 29 males and 33 females, with a mean age of 45.78±5.24 years). The inclusion criteria were as follows: 1. Patients who were diagnosed with advanced gastric cancer using iconography [10] and who had an expected survival period of more than three months. 2. Patients who had not received any chemoradiotherapy or other treatment within three months. 3. Patients who tolerated treatment well. This study did not violate ethics. The study plan was submitted to the ethics committee of The People's Hospital of Shanxi Province for review and implemented after the approval was obtained, and was in accordance with the Helsinki Declaration. All the subjects and their guardians signed a fully informed consent form. The exclusion criteria were as follows: 1. Patients who quit the experiment midway. 2. Patients with complications such as severe mental diseases leading to poor treatment compliance. 3. Patients with other malignant tumors. 4. Patients who had contraindications to the drugs used in this research. 5. Patients who had communication disorders. 6. Patients lost to follow up.

Therapies

The patients in the CG received 3D-CRT treatment. The patients were required to fast for 3 hours and then take meglumine diatrizoate (Chreagen Biotechnology Co., Ltd., Beijing, China, 11500) and 200 ml warm water. After achieving the purpose of gastric development, the CT simulation positioning was performed. The patients were required to maintain a supine position, and a chest and abdomen fixing plate was placed on their backs. They were required to place their arms around their elbows on the forehead, and then they were guided to keep relaxed. The spiral scanning was enhanced, which started from each patient's umbilicus level to 5 cm above it. The scanning layer thickness was set to 5 mm, and the acquired CT scanning results were uploaded to the three-dimensional treatment planning system. Through image reconstruction and observation analysis, the target area position of the radiotherapy was located, the target organs and affected organs were delineated, and the 3-6 coplanar conformal fields were determined. The radiation therapy was performed with a 6MV-X ray or a 10MV-X ray accelerator at 2.0 Gy/time, one day/time, five times a week, for a total dose of DT45-50 Gy for 4-8 weeks. The treatment times were flexible and determined according to each patient's condition.

The patients in the OG received the apatinib combined with 3D-CRT treatment. The radiotherapy procedure was the same as the CG procedure. On this basis, 250 mg of apatinib (Jingke Chemical Technology Co., Ltd., Shanghai, China, JKRF0020) was administered orally once a day. The patients were treated with four courses (three weeks each course).

Outcome measures

(1) Efficacy: Complete response (CR): after the treatment, the focus of the patient disappear-

ed completely, and the maintenance time was observed to be longer than 4 weeks. Partial response (PR): after treatment, the focus of the patient shrunk ≥ 30%, and the maintenance time was observed to be longer than 4 weeks. Stable disease (SD): after treatment, the lesion shrunk ≤ 30%, the lesion increased ≤ 20%, and the maintenance time was observed to be longer than 4 weeks. Progressive disease (PD): after treatment, the patients' lesion increased by ≥ 25%. Disease response (CR + PR + SD)/total cases × 100%.

(2) The occurrence of any ADR during and after the treatment were observed and counted.

(3) Karnofsky (KPS) [11] was used to evaluate the patients' quality of life after 30 days of treatment. After the treatment, a KPS score that increased by more than ten points was defined as improvement. After the treatment, a KPS score that decreased or increased ≤ 10 was defined as stable. After the treatment, a KPS score that decreased by more than ten points was defined as deterioration. Quality of life improvement rate = (improvement + stability)/total cases × 100%.

(4) Detection of the tumor markers and inflammatory factors: Five mL elbow venous blood before and 24 hours after treatment was taken, centrifuged at 1500 × g at 4°C for 10 minutes, and placed in a low temperature refrigerator at -70°C for later use. The serum carcino-embryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4) and carbohydrate antigen 199 (CA-199) levels were determined using electrochemical luminescence immunoassays [12]. The operations and measurements were conducted in light of the instructions with reference to human CEA (Yaji Biological Technology Co., Ltd., Shanghai, China, CL01236), CA72-4 (Yaji Biological Technology Co., Ltd., Shanghai, China, CL02346), CA-199 (Hengfei Biotechnology Co., Ltd., Shanghai, China, SCA156Hu-1). Enzyme-linked immunosorbent assays (ELISA) [13] were applied to determine the high sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor-α (TNF-α) levels. The procedures were conducted according to the instruction manual of human hs-CRP (Yiyan Biological Technology Co., Ltd., Shanghai, China, EY-D9154), TNF-α (Huijia Biotechnology Co., Ltd., Xiamen, China, IQP-163P).

(5) After the treatment, QOL [13] was adopted. There were seven items in the scale, and the total possible score was 100 points. The higher the score, the higher the quality of life.

(6) Prognoses: The patients were followed up for one year to record and compare their progression-free survival times and total survival times.

Statistical methods

SPSS 21.0 (EASYBIO, China) was used for the statistical analysis. The count data were expressed as the number of cases/percentage [n (%)]. Chi-square tests were utilized to compare the count data between the two groups. When the theoretical frequency in a chi-square test was less than 5, a continuity correction chi-square test was adopted. The measurement data were expressed as the mean ± standard deviation (mean ± SD). The measurement data in the two groups were compared using independent sample t-tests, and paired t-tests were applied for the intra-group comparisons before and after. GraphPad Prism 6 software was used to draw the figures. When $P < 0.05$, there was a significant difference.

Results

General data

There was no significant difference between the two groups in terms of the general clinical baseline data such as gender, average age, course of the disease, smoking history, drinking history, TNM staging, history of hypertension, tumor differentiation, metastatic site, KPS score, residence, nationality, or education background ($P > 0.05$), as shown in **Table 1**.

Comparison of the overall response rates (ORR) in the two groups

After the treatment, the ORR in the OG was 91.94%, and the ORR in the CG was 77.97%, which was significantly lower in the CG than in the OG ($P < 0.05$), as shown in **Table 2**.

Comparison of the ADR between the two groups during the treatment

The total incidence of ADR was 12.90% in the OG and 22.03% in the CG. There was no considerable difference in the total incidence of ADR between the two groups ($P > 0.05$), as shown in **Table 3**.

Table 1. A comparison of the general patient data in the two groups [n (%)] (mean ± SD)

Classification	Observation group (n=62)	Control group (n=59)	t/χ^2 value	*P* value
Gender			0.012	0.911
Male	29 (46.77)	27 (45.76)		
Female	33 (53.23)	32 (54.24)		
Average age (years)	45.78±5.24	44.82±5.28	1.004	0.317
Course of disease (months)	2.87±0.45	2.89±0.47	0.239	0.811
Smoking history			0.358	0.549
With	38 (61.29)	33 (55.93)		
Without	24 (38.71)	26 (44.07)		
Drinking history			0.335	0.563
With	43 (69.35)	38 (64.41)		
Without	19 (30.65)	21 (35.59)		
TMN staging			0.713	0.870
Grade I	14 (22.58)	16 (27.12)		
Grade II	17 (27.42)	14 (23.73)		
Grade III	16 (25.81)	17 (28.81)		
Grade IV	15 (24.19)	12 (20.34)		
History of hypertension			0.358	0.549
With	38 (61.29)	33 (55.93)		
Without	24 (38.71)	26 (44.07)		
Tumor differentiation			0.745	0.688
Poor differentiation	18 (29.03)	17 (28.81)		
Middle differentiation	24 (38.71)	19 (32.20)		
High differentiation	20 (38.71)	23 (38.98)		
Metastatic site			0.188	0.910
Liver metastasis	15 (24.19)	16 (27.12)		
Splenic metastasis	23 (37.10)	20 (33.90)		
Colonic metastasis	24 (38.71)	23 (38.98)		
KPS rating	76.39±8.37	78.08±8.09	1.128	0.261
Residence			0.381	0.536
Countryside	35 (56.45)	30 (50.85)		
City	27 (43.55)	29 (49.15)		
Nationality			0.365	0.546
Han	37 (59.68)	32 (54.24)		
Minority	25 (40.32)	27 (45.76)		
Education background			0.237	0.626
≥ high school	33 (53.23)	34 (57.63)		
< high school	29 (46.77)	25 (42.37)		

Comparison of the quality of life in the two groups

After 30 days of treatment, by comparing the quality of life in the two groups of patients, it was found that there were 29 cases (46.77%) of improvement, 26 cases (41.94%) of stability, and 7 cases (11.29%) of deterioration in the OG, for a quality of life improvement rate of 88.71%. And there were 18 cases (30.51%) of improvement, 25 cases (42.37%) of stability, and 16 cases (27.12%) of deterioration in the OG. The quality of life improvement rate in the OG was higher than it was in the CG ($P < 0.05$), as shown in **Table 4**.

A comparison of the tumor marker expression levels before and after the treatment in the two groups

There were no significant differences in the tumor markers expression levels, such as CEA,

Table 2. A comparison of the ORR in the two groups of patients [n (%)]

Group	n	Complete response	Partial response	Stable disease	Progressive disease	ORR %
Observation group	62	23 (37.10)	19 (30.65)	15 (24.19)	5 (8.06)	57 (91.94)
Control group	59	15 (25.42)	12 (20.34)	19 (32.20)	13 (22.03)	46 (77.97)
t	-	-	-	-	-	4.659
P	-	-	-	-	-	0.031

Table 3. A comparison of the adverse reactions in the two groups of patients during the treatment [n (%)]

Group	n	Myelosuppression	Gastrointestinal tract reaction	Elevation of blood pressure	Renal function injury	Liver function injury	Total incidence of adverse reactions
Observation group	62	1 (1.61)	3 (4.84)	2 (3.23)	1 (1.61)	1 (1.61)	8 (12.90)
Control group	59	3 (5.08)	4 (6.78)	2 (3.39)	2 (3.39)	2 (3.39)	13 (22.03)
t	-	1.140	0.209	0.003	0.394	0.394	1.757
P	-	0.285	0.647	0.959	0.529	0.529	0.185

Table 4. A comparison of the quality of life in the two groups of patients [n (%)]

Group	n	Improvement	Stability	Deterioration	Improvement rate (%)
Observation group	62	29 (46.77)	26 (41.94)	7 (11.29)	88.71
Control group	59	18 (30.51)	25 (42.37)	16 (27.12)	72.88
t	-	-	-	-	4.920
P	-	-	-	-	0.026

Table 5. A comparison of the tumor marker expression levels in the two groups of patients before and after the treatment (mean ± SD)

Group	n	CEA		CA72-4		CA19-9	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	62	35.48±4.32	10.26±3.21	58.32±6.32	33.57±2.89	76.24±6.09	30.23±5.09
Control group	59	34.78±4.29	16.45±3.27	57.86±6.21	39.54±3.03	75.46±6.12	42.54±5.23
t	-	0.894	10.510	0.404	11.090	0.703	13.120
P	-	0.373	0.001	0.687	0.001	0.484	0.001

CA72-4, and CA19-9, in the two groups before the treatment (P > 0.05). After the treatment, however, the tumor marker expression levels improved in both groups, and the three markers' expression levels in the OG were lower than they were in the CG (P < 0.05). As shown in **Table 5**.

The expression levels of the inflammatory factors before and after the treatment in the two groups

There was no significant difference in the hs-CRP and TNF-α expression levels in the two groups before the treatment (P > 0.05). After the treatment, the hs-CRP and TNF-α expression levels in the OG were lower than the corresponding values in the CG (P < 0.05), as shown in **Figure 1**.

A comparison of the QOL scores in the two groups after the treatment

After observing the QOL scores of the two groups of patients, we found that the QOL scores in the OG after the treatment were higher than the QOL scores in the CG (P < 0.05). As shown in **Table 6**.

Comparison of the prognoses

The progression-free survival times and total survival times of the patients in the OG were remarkably higher than they were in the CG (P < 0.05), as shown in **Figure 2**.

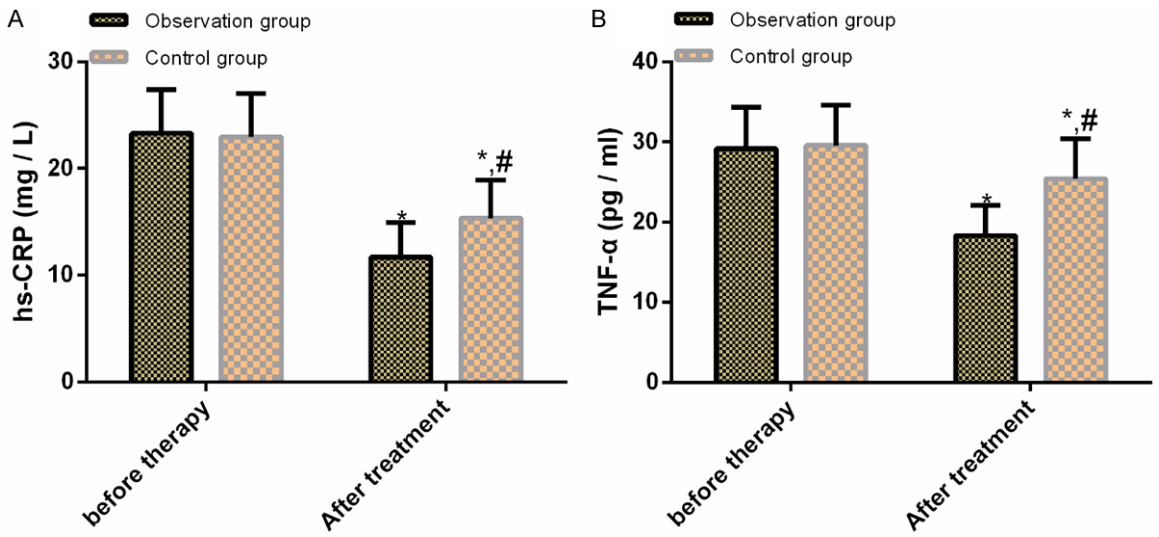

Figure 1. The inflammatory factor expression levels before and after the treatment in the two groups of patients. A. There was no difference in the hs-CRP levels in the two groups before the treatment, and the hs-CRP expression levels in the observation group were significantly lower than they were in the control group after the treatment. B. There was no difference in the TNF-α levels in the two groups before the treatment, and the expression levels of TNF-α in the observation group were significantly lower than they were in the control group after the treatment. Notes: Compared with before the treatment * < 0.05, comparison with the postoperative control group # < 0.05.

Table 6. A comparison of the QOL scores in the two groups of patients after the treatment (mean ± SD)

Group	n	Body recovery	Emotional function	Social relations	Quality of life	Cognitive function	Self-help ability
Observation group	62	58.32±4.34	62.34±5.76	68.73±5.49	70.34±6.98	56.78±5.22	63.74±5.72
Control group	59	50.23±4.28	52.65±5.01	54.72±5.03	50.34±4.32	52.67±5.18	49.65±5.19
t	-	9.278	9.853	14.610	18.840	4.345	14.170
P	-	0.001	0.001	0.001	0.001	0.001	0.001

Discussion

Gastric cancer is still a major cause of cancer-related deaths worldwide [14]. Most gastric cancer is already in an advanced stage at the time of diagnosis, with frequent metastasis and invasion [15]. The rapid aging of the global population leads to an increasing number of elderly patients with locally advanced gastric cancer. Although surgery is the basic treatment method for locally advanced gastric cancer, its risk of postoperative complications is high (as high as 18-32%), and the mortality associated with surgery is as high as 3.8-9.5% [16]. Therefore, finding effective treatment methods for advanced gastric cancer patients has become a focus of clinical research.

In this study, we used apatinib combined with 3D-CRT to treat advanced gastric cancer and found that the patient prognosis after treatment was remarkably improved. Radiotherapy can suppress or kill tumor cells via different rays, reducing the size of tumor lesions, and patients undergoing radiotherapy have a lower risk of complications than patients with tumors treated surgically [17]. In the study by Su et al., 3D-CRT was found to be effective in hepatocellular carcinoma patients, and they also found it can increase patients' survival times without increasing radiotherapy toxicity [18]. For patients with chemotherapy-refractory advanced liver cancer, apatinib improves their progression-free survival and total survival times [19]. In Wang et al.'s research, apatinib was found to improve the overall survival rate and the progression-free survival of advanced gastric cancer patients and to maintain great safety [20]. The results of this study revealed

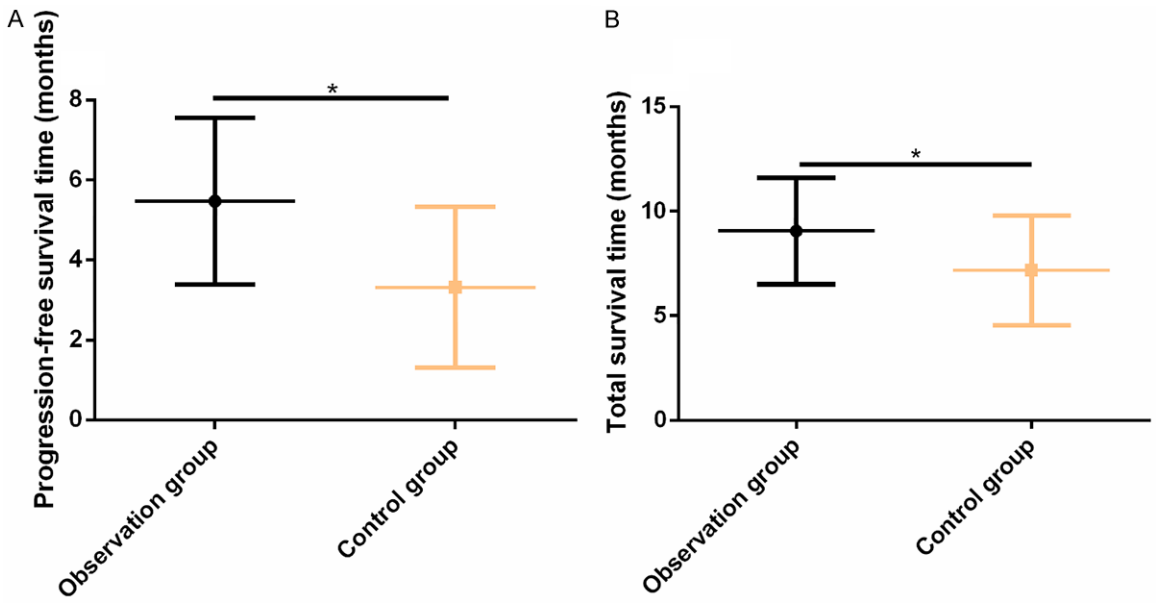

Figure 2. A comparison of the prognoses. A. After the treatment, the progression-free survival times of the patients in the observation group were notably higher than they were in the control group. B. After the treatment, the total survival times of the patients in the observation group were remarkably higher than they were in the control group. Note: Compared with the postoperative control group * < 0.05.

that the ORR of the OG after treatment was remarkably higher than it was in the CG, indicating that the combination of apatinib and 3D-CRT has a higher curative effect than radiotherapy alone. According to the research of Cheng et al. [21], the combination of apatinib and chemotherapy has a better curative effect on advanced gastric cancer patients and can also improve their quality of life. Although ADR such as hypertension and proteinuria occur during the treatment, they are all within the controllable range. This is similar to the results of this study. The results showed that patients in both groups had ADR in the treatment process, all of which were within the controllable range, and there was no significant difference in the total incidence of ADR between the two groups. After observing the improvement in the quality of life in the two groups, we found that the quality of life in the OG after 30 days of treatment was notably higher than it was in the CG, suggesting that apatinib can improve the quality of life of patients by inhibiting tumor angiogenesis, thus improving the curative effect of the radiotherapy.

Clinical research shows that measurements of the serum tumor markers in gastric cancer patients can be used to evaluate their prognosis, diagnosis, and monitoring after treatment [22]. Moreover, studies have revealed that elevated serum CA19-9 and CEA levels in gastric cancer patients are related to poor prognosis [23]. This study revealed that the CEA, CA72-4, and CA19-9 expression levels in the OG were notably lower than they were in the CG after treatment, indicating that apatinib combined with 3D-CRT can reduce the serum tumor marker expressions in advanced gastric cancer patients, thus improving their prognosis. Some studies have shown that the expression of hs-CRP is related to the progress of the cancer, and its abnormal expression is a key indicator of the recurrence of advanced gastric cancer and postoperative diseases [24]. TNF-α is an inflammatory factor, which plays a vital role in the immune response and also participates in controlling the progress of gastric cancer [25]. The results of this study also showed that the hs-CRP and TNF-α expression levels of the patients in the OG were remarkably lower than those in the CG after the treatment, indicating that apatinib reduces cell damage and the release of inflammatory factors caused by radiotherapy, thus improving patients' inflammatory responses. Quality of life is considered to be an important endpoint for cancer patients after treatment [26]. Also, this study showed that the quality of life scores, the progression-free survival times and the total survival times

of the OG after the treatment were remarkably higher than they were in the CG, suggesting that the combination of apatinib and 3D-CRT can improve the quality of life of advanced gastric cancer patients, thus prolonging their progression-free survival times and total survival times.

This study confirmed that apatinib combined with 3D-CRT can benefit patients with advanced gastric cancer, but there is still room for improvement in this study. For example, we can supplement the basic experiments of the therapeutic mechanisms of the two treatments and explore the risk factors affecting the curative effect of patients at the molecular level. We will gradually improve the study from the above perspective in the future.

To sum up, apatinib combined with 3D-CRT can improve tumor markers and quality of life, reduce the inflammatory response, and prolong the survival times of advanced gastric cancer patients.

Disclosure of conflict of interest

None.

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