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A clinical analysis of systemic chemotherapy combined with radiotherapy for advanced gastric cancer

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Abstract

This study aims to investigate the clinical efficacy of systemic chemotherapy combined with radiotherapy for advanced gastric cancer.

A total of 194 advanced gastric cancer patients who were treated from 2006 to 2016 were included in this study. These patients were divided into 2 groups: chemotherapy group (n = 92) and combined chemoradiotherapy group (n = 102). The clinical efficacy of these 2 groups was compared and analyzed to explore the advantageous population and duration of radiotherapy.

The remission rates in the chemotherapy group and combined chemoradiotherapy group were 73.5% and 90.6%, respectively, and median survival time was 6.7 versus 10.6 months. Furthermore, the 6-month, 1-year, and 2-year survival rates were 62% versus 83.3%, 22.8% versus 38.2%, and 7.6% versus 13.7%, respectively. All the differences were statistically significant ($P < .05$). In patients with distant lymph node metastasis, local advanced cancer and organ metastasis, who underwent chemotherapy + radiotherapy, the median survival time was 12.6, 11.1, and 9.8 months, respectively; and the differences were statistically significant compared with the chemotherapy group ($P < .05$). The median survival time in patients who received concurrent chemoradiotherapy and sequential chemoradiotherapy was 11 and 9.5 months, respectively, and the difference was not statistically significant ($P > .05$).

Combined chemoradiotherapy significantly improved the clinical remission rate, median survival time, and the 6-month, 1-year, and 2-year survival rates in patients with advanced gastric cancer. Furthermore, the survival rate of patients with simple distant lymph node metastasis was better. Concurrent chemoradiotherapy did not significantly improve survival rate compared with sequential chemoradiotherapy.

Abbreviations: 3D-CRT = three-dimensional conformal radiotherapy, CTV = clinical target volume, GTV = gross tumor volume, IGRT = image-guided radiotherapy, IMRT = intensity-modulated radiation therapy, KPS = Karnofsky performance scale, MST = median survival time, PTV = planning target volume.

Keywords: clinical efficacy, local advanced gastric cancer, metastatic gastric cancer, systemic chemotherapy combined with radiotherapy

1. Introduction

China is a country that has a high incidence of gastric cancer. The 2017 Chinese Cancer Registry Annual Report revealed that the incidence of gastric cancer in China ranked second among malignant tumors in 2013, and was the third leading cause of cancer deaths.[1] At present, surgery remains the most effective treatment with the highest response rate for gastric cancer. However, the conditions of most patients are at the middle and late stages when they go to visit a doctor, missing the chance of an operation. For the treatment of advanced gastric cancer, systemic chemotherapy is the main method. In recent years, the majority of literatures reported that[2–5] systemic chemotherapy combined with radiotherapy could improve the short-term and long-term survival rates of patients with advanced gastric cancer. However, the number of cases reported in literatures is small. This study aims to compare and analyze the clinical efficacy of systemic chemotherapy and systemic chemotherapy combined with radiotherapy for advanced gastric cancer, and further performs a stratified analysis, to explore the advantageous population of systemic chemotherapy combined with radiotherapy, and duration of radiotherapy.

2. Materials and methods

2.1. General information

From October 2006 to August 2016, 228 patients with advanced metastatic gastric cancer and surgery-intolerant locally advanced gastric cancer were admitted in our hospital. Among these patients, 20 patients were not treated with radiochemotherapy

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due to economic reasons or poor general conditions, whereas 208 patients received specific treatment in the Department of Chemoradiotherapy. Among these 208 patients, 6 patients were treated with radiotherapy alone, 1 patient was treated with radiotherapy combined with molecular targeted therapy, 7 patients were treated with single-drug chemotherapy, and the remaining 194 patients were enrolled into this study. All 194 patients were treated with systemic chemotherapy or systemic chemotherapy combined with palliative radiotherapy of primary and/or metastatic lesions. These situations included the following: organ metastasis (94 patients), refers to patients with only hematogenous metastasis in organs or hematogenous metastasis complicated with lymph node metastasis, or hematogenous metastasis complicated with primary/recurrent gastric lesions; distant lymph node metastasis (41 patients), refers to patients with only distant lymph node metastasis without hematogenous metastasis in organs; local advanced gastric cancer (59 patients), refers to patients without distant metastasis who could not undergo radical resection, or patients with residual tumors or local recurrence after radical resection. All the patients included in this study were proven to have gastric cancer by pathology, and does not have a history of other malignant tumors. The median age of these patients was 57 years. Before treatment, the Karnofsky performance scale (KPS) score was within 60 to 90 points. Among these 194 patients, 92 patients received chemotherapy alone (chemotherapy group), whereas 102 patients received chemoradiotherapy (combined chemoradiotherapy group). In the chemotherapy group, 60 patients were men and 32 patients were women; and the age of these patients ranged within 20 to 74 years, with an average age of 53.95 ± 12.72 years. In the combined chemoradiotherapy group, 72 patients were men and 30 patients were women; and the age of these patients ranged within 26 to 76 years, with an average age of 55.74 ± 12.43 years (Table 1). This study was conducted with approval from the Ethics Committee of our hospital.

2.2. Therapeutic methods

For the 92 patients in the chemotherapy group, the systemic chemotherapy regimen used included the following: fluorouracils (5-fluorouracil, capecitabine, or tegafur) combined with platinum-based drugs (cisplatin or oxaliplatin) regimen, docetaxel 3-drug combination regimen (docetaxel + cisplatin/oxaliplatin + 5-fluorouracil), and docetaxel 2-drug combination regimen (docetaxel + oxaliplatin/cisplatin). Specific regimens and medications: FOLFOX4 regimen (oxaliplatin: 85 mg/m^2, intravenously guttae (IVGTT), D1; leucovorin: 200 mg/m^2, IVGTT, D1-2; 5-fluorouracil: 2000 mg/m^2, D1-2. Among these 5-fluorouracils, 0.5 g of 5-fluorouracil was used by intravenous injection (D1), and the remaining 5-fluorouracils were continuously pumped using a micro pump within 48 hours. The procedure was repeatedly performed every 14 days, and 2 times was regarded as 1 course of treatment. XELOX regimen (oxaliplatin: 130 mg/m^2, IVGTT, D1; capecitabine: 1000 mg/m^2/day, oral use for 2 times per day, D1-14; the procedure was repeatedly performed every 21 days). DCF regimen (DOC: 75 mg/m^2, D1; 5-Fu: 500 mg/m^2/day, D1-5; which was continuously pumped through the vein within 120 hours; docetaxel (DDP): 75 mg/m^2, which was used on D1 and D2, and the procedure was repeatedly performed every 21 days). DO regimen (docetaxel: 75 mg/m^2, IVGTT, D1; oxaliplatin: 130 mg/m^2, IVGTT, D1; the procedure was repeatedly performed every 21 days). DC regimen (docetaxel: 75 mg/m^2, IVGTT, D1; cisplatin: 75 mg/m^2, IVGTT, D1, D2; the procedure was repeatedly performed every 21 days).

Among the 102 patients in the combined chemoradiotherapy group, 41 patients had organ metastasis; 30 patients had distant lymph node metastasis; and 31 patients had local advanced gastric cancer. The chemotherapy regimens were the same with those in the chemotherapy group. The radiotherapy procedure was as follows: treatment for all patients adopted a 6-MV x-ray linear accelerator using 3-dimensional conformal radiotherapy (3D-CRT)/intensity-modulated radiation therapy (IMRT)/image-guided radiotherapy (IGRT) technology, and 2 different modes of sequential chemoradiotherapy or concurrent chemoradiotherapy were adopted. Sequential chemoradiotherapy was performed in 50 patients, that is, chemotherapy was initially performed for 2 courses, followed by radiotherapy. Then, after radiotherapy was completed, a subsequent chemotherapy was performed. Concurrent chemoradiotherapy was performed in 52 patients, that is, radiotherapy and systemic chemotherapy were performed at the same time. Thirty-one patients with local advanced gastric cancer were treated with radiotherapy of gastric lesions and regional lymph node. Among the 41 patients with gastric cancer with organ metastasis, 4 patients were treated with radiotherapy of vertebral metastasis, 5 patients were treated with radiotherapy of liver metastasis, 10 patients were treated with radiotherapy of distant lymph node metastasis, 1 patient was treated with radiotherapy of ovarian metastasis, and 1 patient was treated with radiotherapy of gallbladder metastasis, Furthermore, 25 patients were treated with radiotherapy of gastric lesion and/or regional lymph node. Among the 30 patients with distant lymph node metastasis, 12 patients were treated with radiotherapy of retroperitoneal lymph nodes, 3 patients were treated with radiotherapy of mediastinal lymph nodes, 5 patients were treated with radiotherapy of left supraclavicular lymph nodes, 1 patient was treated with radiotherapy of inguinal lymph nodes, 6 patients with gastric primary and regional lymph node metastasis were treated with radiotherapy of both primary lesion and regional lymph nodes, and 9 patients with primary gastric lesions and regional lymph node metastasis were treated with only radiotherapy of primary gastric and regional lymph node metastases, and were not treated with radiotherapy of distant lymph nodes. Targeted areas and prescription doses: radiothera-

Table 1

Condition of 228 patients (case).

Item	Case	Percentage (%)
Locally advanced gastric cancer	65	28.5
Advanced metastatic gastric cancer	163	71.5
Organ metastasis	114	50
Liver metastasis	65	57
Bone metastasis	28	24.6
Ovarian metastasis	22	19.3
Lung metastasis	10	8.7
Adrenal metastasis	5	4.4
Other organ metastasis	9	7.9
Simple distant lymph node metastasis	49	21.5
Pathological type		
Signet ring cell carcinoma	15	6.6
Poorly differentiated adenocarcinoma	102	44.7
Medium and high differentiated adenocarcinoma	28	12.3
Adenocarcinoma (no typing)	83	36.4
Primary tumor site		
Gastric antrum	129	56.5
The body of the stomach	70	30.7
Gastric cardia and gastroesophageal junction	20	8.8
Full stomach	9	4

py of gastric lesions and regional lymph nodes: gross tumor volume $(GTV)_{tumor}$ was the gastric GTV, and GTV_{nodal} was the gastric regional lymph node volume. Clinical target volume (CTV) was the area expanded from the margin of GTV_{tumor} by 2 cm + GTV_{nodal} and its lymph drainage area. Planning target volume (PTV) was the area expanded from the margin of CTV by 0.5 to 1.0 cm (up and down margins was 1 cm, and other margins was 0.5 cm). Prescription doses: PTV: 45 to 50.4 Gy/25 to 28 f/5 to 6 W, 1.8 Gy/f, 1 f/d, and 5 f/w. Radiotherapy of distant lymph node metastasis: GTV_{nodal} was the metastatic lymph node volume, CTV was GTV_{nodal} and its lymphatic drainage area, and PTV is the area expanded from the margins of CTV by 0.5 cm. Prescription dose: retroperitoneal lymph node metastasis: 50 to 60 Gy/25 to 30 f/5 to 6 w, 2.0 Gy/f; other distant lymph node metastasis: 60 Gy/30 f/6 w, 2.0 Gy/f. Radiotherapy of organ metastasis: organ metastases were treated by radiotherapy of primary GTV formed by expansion of GTV, and the vertebral metastasis GTV included metastases in the vertebrae and their attachments. Prescription doses: vertebral metastasis: 30 to 45 Gy/10 to 15 f/2 to 3 w, and 3.0 Gy/f; other organ metastases: 40 to 50 Gy/20 to 25 f/4 to 5 w, and 2.0 Gy/f.

2.3. Evaluation of curative effects and toxic and side effects

Clinical efficacy was evaluated with 6-month, 1-year, and 2-year survival rates and median survival time (MST). Toxic reaction evaluation: Toxic reaction was divided into levels 0 to IV, according to the NCI-CTC 3.0 scale.

2.4. Statistics analysis

Data were statistically analyzed using statistical software SPSS 17.0. $P \leq .05$ defined as the difference was statistically significant. Measurement data were expressed in mean ± standard deviation ($\overline{x} \pm SD$), and counting data were expressed in percentage (%). The survival curve was drawn using the Kaplan-Meier method. Intergroup comparison was performed using Log-rank test. The independent prognostic risk factors were identified using Cox proportional hazard regression model.

2.5. Follow-ups

Follow-ups started at the end of the treatment. For patients died before March 6, 2017, the follow-up was ended at the death. For the surviving patients, the cut-off date of follow-up was March 6, 2017. The main follow-up methods included phone call follow-ups and outpatient review.

3. Results

3.1. General information

Among these 194 patients, 92 patients were assigned into the chemotherapy group and 102 patients were assigned into the combined chemoradiotherapy group. The differences in baseline data between the 2 groups were not statistically significant ($P > .05$), and were comparable (Table 2).

Table 2

Baseline characteristics for all patients (case).

Item	Simple chemotherapy group (case)	Percentage (%)	Combined radiotherapy group (case)	Percentage (%)	χ^2	P
Sex					0.642	.423
Male	60	65.2	72	70.6		
Female	32	34.8	30	29.4		
Age, y					0	.988
≥57	45	48.9	50	49		
<57	47	51.1	52	51		
Pathological type					5.935	.115
Signet ring cell carcinoma	8	8.7	6	5.9		
Poorly differentiated adenocarcinoma	43	46.7	43	42.2		
Medium and high differentiated adenocarcinoma	16	17.4	10	9.8		
Adenocarcinoma (no typing)	25	27.2	43	42.2		
Primary tumor site					1.603	.659
Gastric antrum	48	52.2	61	59.8		
The body of the stomach	30	32.6	30	29.4		
Gastric cardia and gastroesophageal junction	9	9.8	8	7.8		
Full stomach	5	5.4	3	2.9		
Chemotherapy regimen					2.08	.353
Fluorouracil + platinum	30	32.6	28	27.5		
Docetaxel 3-drug combination	29	31.5	27	26.5		
Docetaxel 2-drug combination	33	35.9	47	46.1		
Before treatment KPS score					0.267	.605
≥70	75	81.5	86	84.3		
<70	17	18.5	16	15.7		
Complete the number of chemotherapy cycles					0.034	.854
4–6 cycle	30	32.6	32	31.4		
2–3 cycle	62	67.4	70	68.6		
Locally advanced/metastatic gastric cancer					0	.995
Locally advanced gastric cancer	28	30.4	31	30.4		
Metastatic gastric cancer	64	69.6	71	69.6		

KPS = Karnofsky performance scale.

Table 3

Comparison of clinical symptoms improved after treatment between the 2 groups case (ratio).

Relieve symptoms	Simple chemotherapy group (%)	Combined radiotherapy group (%)	χ^2	*P*
Pain	32/42 (76.2)	51/56 (91)	4.1	.043
Nausea, vomiting, abdominal distension	29/38 (76.3)	41/45 (91.1)	2.386	.122
Hematemesis, hematochezia, melena	9/14 (64.3)	15/17 (88.2)	1.335	.248
Feeding obstruction	5/8 (62.5)	8/9 (88.9)	0.501	.479
Total	75/102 (73.5)	115/127 (90.6)	11.599	.001

3.2. Remission of clinical symptoms after treatment in these 2 groups

Before the treatment, the main clinical symptoms of all patients were digestive systemic symptoms such as pain, nausea, vomiting, and abdominal distension, and gastrointestinal bleeding symptoms, such as hematemesis, hematochezia, melena, and easting obstruction. A total of 102 clinical symptoms occurred in 92 patients in the chemotherapy group, whereas 127 clinical symptoms occurred in 102 patients in the combined chemoradiotherapy group. The remission of clinical symptoms was better in patients in the combined chemoradiotherapy group than in the chemotherapy group, and the difference was statistically significant (Table 3).

3.3. Survival situations

3.3.1. Total survival of patients. For patients died before March 6, 2017, the follow-up was ended at the death. For the surviving patients, the cut-off date of follow-up was March 6, 2017. The follow-up rate was 98.5%. The reason patient was lost to follow-up was that the patient did not return to the hospital for reexamination at the end of the treatment, and changed the way of communication. The median follow-up duration was 8.0 months. For the 194 patients who received chemotherapy/chemoradiotherapy, the total 6-month, 1-year, and 2-year survival rates were 63.9%, 28.9%, and 10.8%, respectively; and MST was 9 months (95% confidence interval [CI] was 7.973–10.027) (Fig. 1).

3.3.2. Comparison of survival between the chemotherapy group and combined chemoradiotherapy group. The 6-month, 1-year, and 2-year survival rates in the chemotherapy group and combined chemoradiotherapy group were 62% versus 83.3%, 22.8% versus 38.2%, and 7.6% versus 13.7%, respectively, whereas MST in the chemotherapy group and combined chemoradiotherapy group was 6.7 months (95% CI 5.572–7.828) versus 10.6 months (95% CI 9.582–11.618), respectively. The 6-month, 1-year, and 2-year survival rates and MST were significantly higher in the combined chemoradiotherapy group compared with the chemotherapy group, and the differences were statistically significant (Fig. 2).

3.3.3. Comparison of survival in patients with local advanced gastric cancer between the chemotherapy group and combined chemoradiotherapy group. All the patients with local advanced gastric cancer were divided into 2 groups, the chemotherapy group (n=28), and the combined chemoradiotherapy group (n=31). In patients with local advanced gastric cancer, the 6-month, 1-year, and 2-year survival rates in the chemotherapy group and combined chemoradiotherapy group were 82.1% versus 93.5%, 21.4% versus 32.3%, and 3.6% versus 9.7%, respectively, whereas MST was 7.5 months (95% CI was 5.944–9.056) versus 11.1 months (95% CI was 10.263–11.937). The 6-month, 1-year, and 2-year survival rates and MST were significantly higher in the combined chemoradiotherapy group compared with the chemotherapy group, and the differences were statistically significant (Fig. 3).

3.3.4. Comparison of survival in patients with advanced metastatic gastric cancer between the chemotherapy group and combined chemoradiotherapy group. Among the included patients with advanced metastatic gastric cancer, 64 patients were from the chemotherapy group, and 71 patients were from the chemoradiotherapy group. In patients with advanced metastatic gastric cancer, the 6-month, 1-year, and 2-year survival rates in the chemotherapy group and combined chemoradiotherapy group were 53.1% versus 83.1%, 23.4%

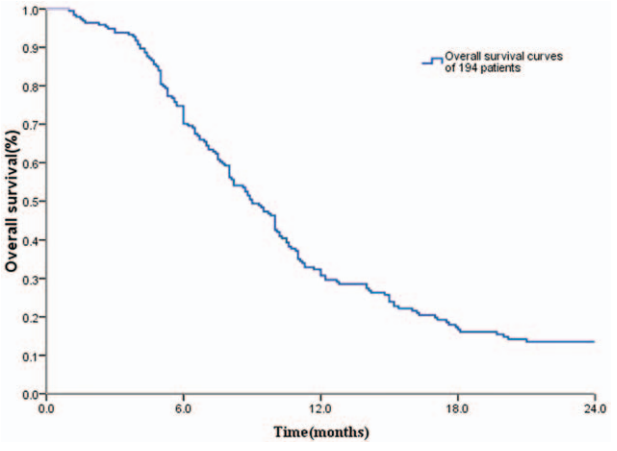

Figure 1. Overall survival curves for all patients.

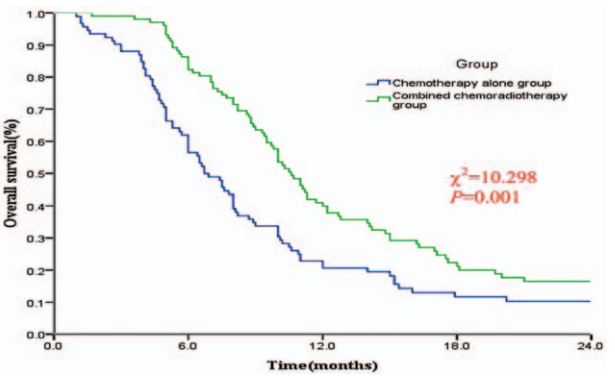

Figure 2. Overall survival curves for patients treated with or without radiotherapy.

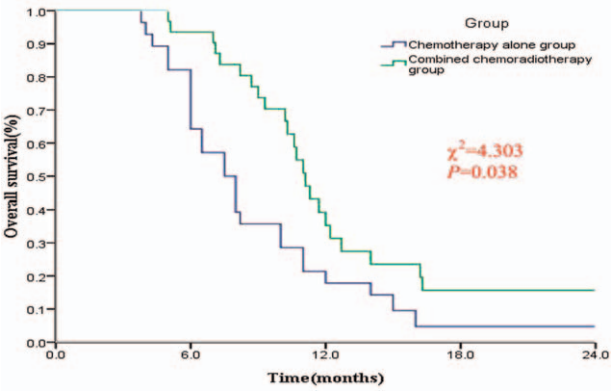

Figure 3. Overall survival curves for locally advanced gastric cancer patients treated with or without radiotherapy.

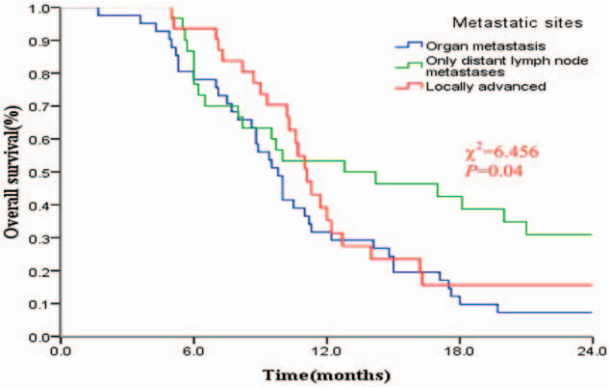

Figure 5. Overall survival curves for different metastatic sites of patients treated with radiotherapy combined with chemotherapy.

versus 40.8%, and 9.4% versus 15.5%, respectively, and MST was 6.6 months (95% CI was 4.542–8.658) versus 10 months (95% CI 8.682–11.318). The 6-month, 1-year, and 2-year survival rates and MST were significantly higher in the combined chemoradiotherapy group compared with the chemotherapy group, and the differences were statistically significant (Fig. 4).

3.3.5. Comparison of survival in patients with different metastatic conditions (including local advanced tumors) in the combined chemoradiotherapy group. Among the 102 patients who were treated with chemoradiotherapy, 41 patients had organ metastasis, 30 patients had distant lymph node metastasis, and 31 patients had local advanced gastric cancer. In the combined chemoradiotherapy group, the 6-month, 1-year, and 2-year survival rates of patients with organ metastasis, distant lymph node metastasis, and local advanced gastric cancer were 80.5% versus 86.7% versus 93.5%, 31.7% versus 53.3% versus 32.3%, and 7.3% versus 26.7% versus 9.7%, respectively, and the MST of patients with organ metastasis, distant lymph node metastasis, and local advanced gastric cancer was 9.8 months (95% CI was 8.650–10.950) versus 12.8 months (95% CI was 3.541–22.059) versus 11.1 months (95% CI was 10.263–11.937). The MST of patients with distant lymph node metastasis was the longest, followed by patients with local advanced gastric cancer, whereas the MST of patients with organ metastasis was the shortest, and the differences were statistically significant (Fig. 5).

3.3.6. Comparison of survival in patients treated with different chemotherapy regimens in the combined chemoradiotherapy group. In the chemoradiotherapy group, 28 patients were treated with fluorouracil combined with platinum-based drugs, 27 patients were treated with the 3-drug combination of docetaxel, and 47 patients were treated with the 2-drug combination of docetaxel. The 6-month, 1-year, and 2-year survival rates of patients who received fluorouracil combined with platinum-based drugs regimen, docetaxel 3-drug combination regimen and docetaxel 2-drug combination regimen were: 85.7% versus 88.9% versus 85.1%, 28.6% versus 48.1% versus 38.3%, and 3.6% versus 7.4% versus 23.4%, respectively, whereas MST of patients who received fluorouracil combined with platinum-based drugs regimen, docetaxel 3-drug combination regimen and docetaxel 2-drug combination regimen was 10.2 months (95% CI was 8.436–11.964) versus 12 months (95% CI was 8.943–15.057) versus 10.5 months (95% CI was 9.582–11.618). Differences in total survival among these 3 chemotherapies combined with radiotherapy regimens were not statistically significantly (Fig. 6).

3.3.7. Comparison of survival in patients in the combined chemoradiotherapy group between sequential chemoradiotherapy and concurrent chemoradiotherapy. In the combined chemoradiotherapy group, 50 patients were treated with sequential chemoradiotherapy and 52 patients were treated with concurrent chemoradiotherapy. The 6-month, 1-year, and 2-year

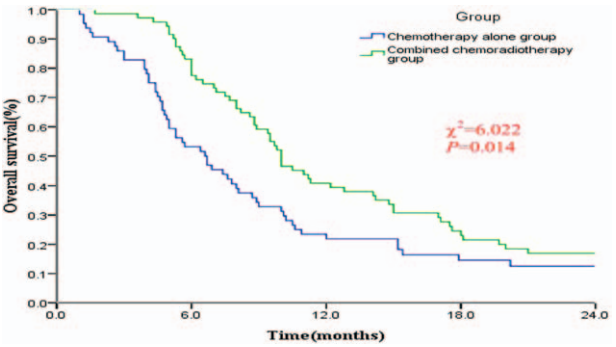

Figure 4. Overall survival curves for metastatic gastric cancer patients treated with or without radiotherapy.

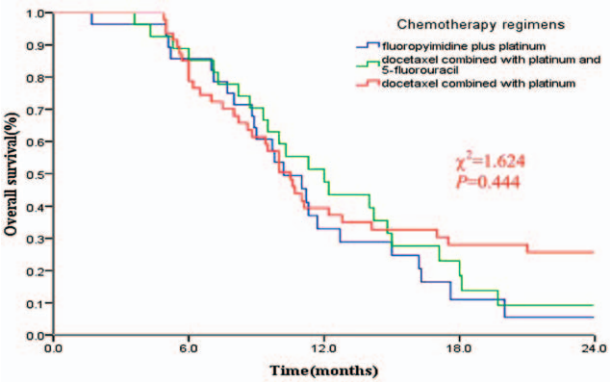

Figure 6. Overall survival curves for different chemotherapy regimens of patients treated with radiotherapy combined with chemotherapy.

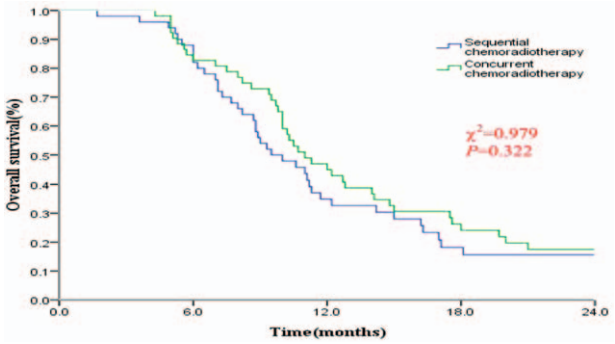

Figure 7. Overall survival curves for patients treated with sequential chemoradiotherapy or concurrent chemoradiotherapy.

survival rates of patients receiving sequential radiotherapy and concurrent chemoradiotherapy were 88% versus 84.6%, 32% versus 44.2%, and 12% versus 15.4%, respectively, whereas MST of patients who received sequential radiotherapy and concurrent chemoradiotherapy was 9.5 months (95% CI 7.160–11.840) versus 11 months (95% CI 8.703–13.297). The survival of patients treated with concurrent chemoradiotherapy was better than that of patients treated with sequential chemoradiotherapy, but the differences were not statistically significant (Fig. 7).

3.4. Prognostic factor analysis

Univariate analysis revealed that, the location of primary tumor (total gastric cancer and gastric carcinoma), organ metastasis, KPS score of <70 points before treatment, absence of radiotherapy and <2 to 3 chemotherapy cycles were the factors for poor prognosis. Multivariate analysis revealed that, the KPS score before treatment, the presence of combined radiotherapy, and the number of chemotherapy cycles were independent prognostic factors (Table 4).

3.5. Toxic and side effects

The main toxic and side effects were hematologic toxicity, gastrointestinal reaction, toxic and side effects of the skin and mucosa, fatigue, and abnormal liver function. These were mostly at levels I to II, and the incidence of levels III to IV of toxicity and side effects was low. After symptomatic treatment, most of the patients could return to normal or basic normal levels, without affecting continuous medication. No treatment-related deaths occurred during the treatment period (Table 5).

4. Discussion

4.1. Efficacy of systemic chemotherapy combined with radiotherapy on advanced gastric cancer

At present, for advanced metastatic gastric cancer or local advanced surgery-intolerant gastric cancer, systemic chemotherapy is the main treatment.[6] A literature revealed that[7] for advanced gastric cancer, both radiotherapy alone and radiotherapy combined with surgery could achieve a survival benefit. For patients with surgery-intolerant local advanced gastric cancer, radiotherapy can reduce the local symptoms, reduce its local recurrence and distal metastasis, which has important clinical significance.[8,9] The continuous development of precise radiotherapy technology, 3D-CRT/IMRT/IGRT technology not only makes the tumor target area more accurate, and also makes the positioning error of radiotherapy even lower, providing favorable conditions for the radiotherapy of gastric cancer and metastasis. The results of the present study reveal that in the treatment of local advanced and metastatic gastric cancer with radiotherapy combined with chemotherapy, the 6-month, 1-year, and 2-year survival rates and MST were significantly higher, compared with chemotherapy alone. Furthermore, these are similar to those reported in the literatures.[4,5,10] However, in overall, the MST of patients in the present study was lower than the survival time reported in literatures. We considered that the reason may be that in the present study, part of the patients had poor general conditions, many patients had metastases and multiple organ metastases, and the patients completed few courses of chemotherapy (Table 1 and Table 2). In the present study, patients with a KPS score of <70 points accounted for 17%, most patients (67.4%) completed only 2 to 3 courses of chemotherapy, and patients who completed 4 to 6 courses of chemotherapy were few (32.6%). Furthermore, in literature, the majority of patients had a KPS score of >70 points, and most of these patients completed 4 to 6 courses of chemotherapy.

Table 4

Univariate and multivariate analyses of the characteristics associated with overall survival (n = 194).

		Univariate analysis		Multivariate analysis	
Characteristics	**mOS, mo**	**Chi-square**	***P***	**HR (95% CI)**	***P***
Sex: male/female	8.7/9.7	2.049	.152		
Age: ≥57/<57	8.7/9.5	0.037	.847		
Pathological type: signet ring cell carcinoma/poorly differentiated adenocarcinoma/medium and high differentiated adenocarcinoma/ adenocarcinoma (no typing)	5.7/8/15/9.7	7.316	.062		
Primary tumor site: gastric antrum/the body of the stomach/gastric cardia and gastroesophageal junction/Full stomach	10.1/7/10.2/6.9	8.432	.038	1.039 (0.866–1.245)	.683
Metastasis: organ metastasis/distant lymph node metastasis/local late stage	8/10.6/10.2	8.727	.013	0.952 (0.799–1.134)	.579
Before treatment KPS score: ≥70/<70	10/5	30.490	.000	0.367 (0.262–0.514)	.000
Radiotherapy: yes/no	10.6/6.7	10.406	.001	0.295 (0.202–0.429)	.000
Chemotherapy regimen: fluorouracil + platinum/docetaxel 3-drug combination/docetaxel 2-drug combination	8.1/8.7/10	3.989	.136		
Complete the number of chemotherapy cycles: 4–6 cycles/2–3 cycles	14/7	37.223	.000	3.005 (1.989–4.541)	.000

KPS = Karnofsky performance scale.

Table 5

The toxic effects in all patients treated with radiotherapy combined chemotherapy or chemotherapy alone rate (%).

Adverse reaction	I–II			III–IV		
	Combined radiotherapy group	Simple chemotherapy group	*P*	Combined radiotherapy group	Simple chemotherapy group	*P*
Hematological toxicity						
Leukopenia	54 (52.9)	46 (50)	.682	25 (24.5)	8 (8.7)	.003
Granulocytopenia	42 (41.2)	29 (31.5)	.163	32 (31.4)	14 (15.2)	.008
Anemia	37 (36.3)	26 (28.3)	.234	5 (4.9)	10 (10.9)	.120
Thrombocytopenia	21 (22.8)	8 (8.7)	.02	3 (2.9)	5 (5.4)	.610
Nonblood toxicity						
Digestive tract reaction	63 (61.8)	48 (52.2)	.178	21 (20.6)	16 (17.4)	.571
Liver damage	18 (17.1)	6 (6.3)	.017	4 (3.8)	2 (2.1)	.762
Renal impairment	2 (2)	3 (3.3)	.907	0 (0)	0 (0)	
Peripheral neurotoxicity	9 (8.8)	6 (6.5)	.549	1 (0.9)	0 (0)	1
Arrhythmia	2 (2)	1 (1.1)	1	0 (0)	0 (0)	
Weak	31 (30.4)	26 (28.3)	.745	3 (2.9)	1 (1.1)	.688
Skin reaction	32 (31.4)	0 (0)	0	1 (1.0)	0 (0)	1
Mucosal toxic side reaction	14 (13.7)	7 (7.6)	.171	0 (0)	1 (1)	.474
Hair loss	11 (10.8)	6 (6.5)	0.294	0 (0)	0 (0)	

Patients with advanced gastric cancer can develop clinical symptoms, such as pain, nausea, vomiting, abdominal distension, hematemesis, and hematochezia. However, systemic chemotherapy has a limited effect for the remission of the above symptoms. As a local treatment, radiotherapy can alleviate some of the clinical symptoms of patients with advanced gastric cancer, such as controlling bleeding, reducing pain, and relieving compression.[10–15] The results of the present study reveal that combined chemoradiotherapy could obviously alleviate the clinical symptoms of the patients, and the main effect was obvious alleviation of pain. This is similar to the results reported by Kim et al.[16]

4.2. Effects of different chemoradiotherapy orders (sequential chemoradiotherapy and concurrent chemoradiotherapy) on the clinical efficacy of advanced gastric cancer

At present, in the comprehensive treatment of advanced gastric cancer, the timing of radiotherapy is inconclusive. Sequential chemoradiotherapy has mostly been reported in literatures, whereas there are relatively few reports on concurrent chemoradiotherapy. It was reported in literatures that[2,17] the efficacy of both sequential chemoradiotherapy and concurrent chemoradiotherapy were superior to chemotherapy alone. However, no related controlled studies have been reported at present. Wang and Jin[18] proposed that for surgery-intolerant gastric cancer without distant metastasis, concurrent chemoradiotherapy is mostly recommended. The results of the present study revealed that MST and the 1 and 2-year survival rates were higher in the concurrent chemoradiotherapy group than in the sequential chemoradiotherapy group, but differences were all not statistically significant. Further studies with an expanded sample size are needed.

4.3. Efficacy of systemic chemotherapy combined with radiotherapy on different types of advanced gastric cancer (local advanced gastric cancer, distant lymph node metastasis gastric cancer, and organ metastasis gastric cancer)

For local advanced gastric cancer, since tumors are located in the stomach, in which regional lymph nodes and distant metastasis have not yet occurred, the majority of literatures reported that systemic chemotherapy combined with radiotherapy of gastric lesions and regional lymph nodes could improve its effective rate and survival time.[2,3] For gastric cancer with lymph node metastasis, a retrospective study in South Korea revealed that[19] the survival time of patients with gastric cancer with lymph node recurrence in the abdominal cavity after an operation, who underwent radiotherapy of recurrent lymph nodes, was significantly longer than patients who did not undergo radiotherapy (36 vs 16 months, $P < .001$). Sun et al[20] retrospectively analyzed 79 patients with celiac lymph node metastasis after D2 radical resection of gastric cancer, where patients received external radiotherapy on the basis of systemic chemotherapy or supportive treatment. Compared with the nonradiotherapy group, the MST (11.4 vs 4.8 months), 1-year survival rate (43.9% vs 19%) and 2-year survival rate (27.6% vs 4.1%) significantly increased. For gastric cancer with organ metastasis, due to the occurrence of hematogenous metastasis, systemic chemotherapy is the main treatment. However, there are few reports on systemic chemotherapy combined with radiotherapy. Zhang et al[17] conducted a study on 38 patients with advanced metastatic gastric cancer, divided these patients into 2 groups (chemoradiotherapy group and chemotherapy group), and the data obtained from these patients were analyzed. Results revealed that the effect of combined chemoradiotherapy was more significant. The results of the present study revealed that the 6-month, 1-year, and 2-year survival rates and MST of patients with local advanced gastric cancer, gastric cancer with distant lymph node metastasis, and gastric cancer with organ hematogenous metastasis significantly improved in the combined chemoradiotherapy group, compared with the chemotherapy group. This suggests that for any type of advanced gastric cancer, radiotherapy based on chemotherapy is beneficial. However, few studies have determined the type of advanced gastric cancer that can achieve better efficacy by combined chemoradiotherapy. The results of the present study also revealed that the MST of patients with distant lymph node metastasis was the longest. This suggests that advanced gastric cancer patients with distant lymph node metastasis are the advantageous population for combined chemoradiotherapy.

4.4. Efficacy of different chemotherapy regimens combined with radiotherapy

There is no standard chemotherapy regimen for advanced gastric cancer. Studies[21–24] have revealed that different chemotherapy regimens have similar efficacies for advanced gastric cancer, but these efficacies were all unsatisfactory. Present literatures have revealed that combined chemoradiotherapy could improve efficacy. In the combined regimen of fluorouracil and platinum-based drugs chemotherapy with radiotherapy, the MST was 14.3 months,[4] whereas in the docetaxel 2-drug chemotherapy combined with radiotherapy regimen, the MST was 14.7 months.[17] However, no related controlled study has determined which chemotherapy regimen has better efficacy when combined with radiotherapy. In the present study, the survival of patients receiving fluorouracil combined with platinum-based drugs regimen, docetaxel 3-drug combined regimen, and docetaxel 2-drug combined regimen were compared. Results revealed that in patients with advanced gastric cancer, the clinical efficacies of these 3 different chemotherapy regimens combined with radiotherapy were similar. However, there is no definite evidence at present on whether there is a difference in efficacy among the different chemotherapy regimens combined with radiotherapy, and whether chemotherapy regimen combined with radiotherapy has the best efficacy. This remains to be confirmed through further clinical controlled studies.

4.5. Prognostic factors of advanced gastric cancer

In the present study, systemic chemotherapy combined with radiotherapy of primary and/or metastatic lesions had a significant influence on the survival of patients with advanced gastric cancer. Multivariate analysis revealed that, the KPS score before treatment, the presence of combined radiotherapy and the number of chemotherapy cycles were independent prognostic factors for patients with advanced gastric cancer. This is similar to a present reports.[25]

4.6. Toxic and side effects of systemic chemotherapy combined with radiotherapy for advanced gastric cancer

The results of the present study revealed that hematologic toxic and side effects, and gastrointestinal-related toxic and side effects such as nausea and vomiting were the main toxic and side effects of chemoradiotherapy of gastric cancer, whereas the incidence of toxic and side effects, such as liver and kidney function impairment, arrhythmia, and fatigue, were relatively low, which were mostly at levels I to II; and the incidence of levels III to IV was low. Combined chemoradiotherapy did not significantly increase toxic and side effects compared with chemotherapy alone, which was similar to those reported in literatures.[2–4]

5. Conclusion

The results of the present study revealed that combined chemoradiotherapy significantly improved MST, and 6-month, 1-year, and 2-year survival rates in patients with advanced gastric cancer. This obviously alleviated the clinical symptoms of these patients, and its toxic and side effects were tolerable. Systemic chemotherapy combined with radiotherapy for patients with distant lymph node metastasis resulted in a longer MST than that for patients with organ metastasis and local advanced gastric cancer. The survival of patients treated with concurrent chemoradiotherapy was better than sequential chemoradiotherapy, but the difference was not statistically significant. A variety of factors influenced the prognosis of the patients, and the KPS score before treatment, the presence of combined radiotherapy, and the number of chemotherapy cycles were independent prognostic factors.

6. The limitations of this study

The present study was a nonrandomized controlled study. Disuniform chemotherapy schemes may be a shortcoming of this study.

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