Observation of the effectiveness and safety of the combination of chemotherapy and radiotherapy after the radical resection of progressive gastric cancer

X. Yu[1], R. Zhang[2], S. Cao[3*], S. Cui[1], C. Liu[1], J. Wang[1], X. Cheng[1]

[1]Department of General Surgery II Ward, Linyi Central Hospital, Linyi, Shandong276400, China
[2]Department of Radiotherapy, Linyi Central Hospital, Linyi, Shandong276400, China
[3]Department of Radiotherapy Room, Linyi Central Hospital, Linyi, Shandong276400, China

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Corresponding author:
Dr. Shuren Cao,
E-mail:
ZHANG.prof@yahoo.com

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ABSTRACT

Background: To analyze the effectiveness and safety of combination of 3-dimensional conformal radiotherapy (3D-CRT) and S-LOX chemotherapy after the radical resection of localized progressive gastric cancer, so as to provide the reference for clinical treatment. ***Materials and Methods:*** We enrolled 82 localized progressive gastric cancer patients undergoing the radical resection of gastric cancer, and divided them using the random digit table into two groups: 39 in the chemotherapy group received the S-LOX chemotherapy after operation, and 43 in the combination group received the 3D-CRT in combination with S-LOX chemotherapy. After treatment, we evaluated the clinical efficacy, adverse reaction, survival rate and recurrence rate of patients in two groups. ***Results:*** After 6 cycles of treatment, we found no statistical significance in difference of the objective remission rate of patients in two groups ($P > 0.05$), while the patients in the combination group excelled in the clinical control rate ($P < 0.05$). In the combination group, 2-year survival rate and survival time of patients were all higher and longer than those in the chemotherapy group (all $P < 0.05$), with a lower recurrence rate ($P < 0.05$). Furthermore, comparison of the incidence of adverse reactions of patients between two groups showed no significant difference ($P > 0.05$). ***Conclusion:*** After the radical resection of the localized progressive gastric cancer, 3D-CRT in combination with S-LOX chemotherapy improves the clinical control and survival of patients, while reduces the postoperative recurrence, but with no aggravation in side- or toxic-effect, thus worthy of being promoted in clinical practice.

INTRODUCTION

Gastric cancer, as the second leading factor in all malignancy-related death in the world, is severely eroding the health of human beings. In clinical practice, radical resection in combination with chemotherapy dominates in current treatment for gastric cancer, especially for the early-stage patients with promising efficacy [1]. However, localized progressive gastric cancer patients have a low survival rate even after surgery because of the high incidence rate of distant metastasis in lymph nodes, especially those in the abdomen [1]. At present, radiotherapy in combination with chemotherapy has been initiated for treatment of localized progressive gastric cancer [2]. Local recurrence in the bed of the operated tumor along with recurrence in the lymph nodes or metastasis to distant areas are almost identical causes of recurrence in patients with gastric cancer [3]. According to the US Gastrointestinal Intergroup, the standard of treatment for gastric cancer changed, and there was no evidence of distant metastasis in patients with gastric cancer passing through the stomach wall or lymph nodes involved (Stage Ib-IV) [4].

It was recommended to perform radiotherapy simultaneously with chemotherapy. In the United States, according to their study, a chemotherapy regimen containing 5FU and leucorin is used concomitantly with radiotherapy [5]. In addition, radiotherapy is recommended in those who have a positive margin of surgery during surgery (R1) or a part of the tumor remains (R2) or the tumor cannot be removed due to advanced disease [4-6]. At present, in some groups of patients with esophageal and rectal cancer, simultaneous radiotherapy and chemotherapy (neoadjuvant) are used before surgery. Therefore, neoadjuvant radiotherapy in gastric cancer has been considered in patients with gastric cancer [6].

The rapid development in computer technique and imaging technique provides the opportunity of 3D-CRT in treatment of liver cancer, esophageal cancer, pancreatic cancer and non-small cell lung cancer, with promising outcomes [7]. Zhang *et al.* [8] reported that on the basis of regular S-LOX chemotherapy,

additional application of 3D-CRT can improve the 1-year survival rate of the pancreatic cancer patients in advanced stage. In this study, we evaluated the effectiveness and safety of the combination of 3D-CRT and S-LOX after the radical resection for localized progressive gastric cancer patients, aiming to provide reference for clinical treatment, as there is not enough data available about this treatment regimen.

MATERIAL AND METHODS

General data

Between April 2015 and April 2017, we enrolled a total of 82 localized progressive gastric cancer patients as the subjects with the diagnosis confirmed by the postoperative pathological examination. Inclusion criteria: 1) Patients with an expected survival duration of longer than 6 months; 2) Patients with KPS scores ≥ 70 points; 3) Patients with normal results in the liver and kidney function test, and routine test of blood; 4) Patients with no contraindications of chemotherapy or radiotherapy; 5) Patients with TNM stage from II to IV; 6) Patients that had undergone the radical resection of gastric cancer. Exclusion criteria: 1) Patients complicated with the malignancy in other sites; 2) Patients with the distant metastasis; 3) Patients with coagulation dysfunction or active bleeding in stomach or intestine; 4) Patients with the history of chemotherapy or radiotherapy prior to surgery. This study had been approved and reviewed by the Ethical Committee of Linyi Central Hospital On August 22, 2019（Registration number: 2019 NO.7), and all patients and their family signed the written informed consents.

According to the random digit table, these patients were divided into two groups, chemotherapy group (n=39) and combination group (n=43).

Treatment methods

At one month after radical resection of gastric cancer, patients in the chemotherapy received the chemotherapy as follows: At the first day, patients underwent the intravenous infusion of oxaliplatin (85 mg/m2, Jiangsu Hengrui Pharmaceutical Co., Ltd, SFDA No.: 20111124) dissolved in 500 mL 5% normal saline for 3 h, and from the first day to the 14th day, patients were required to take the Tegafur Capsule (Jiangsu Hengrui Pharmaceutical Co., Ltd, SFDA No.: 20111006) at a dose of 40 mg/m^2 orally, twice per day. Treatment lasted for 4 to 6 cycles, constituting 3 weeks.

On the basis of the treatment for chemotherapy group, patients in the combination group received the 3D-CRT by radiotherapy machine (Hitachi, Ltd.). In brief, patients were required to keep supine position, and fixed in the vacuum negative-pressure bag. With the assistance of radiologists, enhanced CT was carried out to delineate the target organs and involved organs to clarify the range of radiotherapy. A Synergy Medical Linear Accelerator [Elekta,Sweden; Approval No.: gsyjx (Jin) Zi 2008 No. 3323162] was used for radiotherapy. Clinical target volume included the drainage of lymph nodes and anastomotic stoma, based on which planned target volume should be expanded by at least 0.5 cm. With the 95% isodose contour and 0, 90, 180 and 270 being set as the radiotherapy angles, patients underwent the radiotherapy once per day, 1.8 Gy/ time, 5 times/week. The total dose was controlled within 45 Gy for 25 divisions, and for the residual area at R1, dose should be added by 8 to 10 Gy. Radiotherapy lasted for 5 weeks.

Observation

Clinical efficacy

Clinical efficacy, as per the criteria of RECIST stipulated by World Health Organization (WHO), was divided into four grades: complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). Objective remission rate = CR rate + PR rate, clinical control rate = CR rate + PR rate + SD rate [9].

Toxic effect

CTCAE was referred in evaluating the toxic effect of the anti-tumor drugs [10]: The adverse effect of the radiotherapy on patients was evaluated according to the grading criteria of the acute radiation injury stipulated by the Collaborative Team of Radiotherapy for tumors [11].

Follow-up

As of April 2017, statistics of 1- and 2-year survival rate and recurrence rate of patients in two groups were collected, and the medians of survival duration were calculated.

Statistical methods

All data were processed and analyzed by the SPSS 19.0 software. Enumeration data were expressed in ratio (%), including clinical efficacy and adverse reactions, and were compared by chi-square test. P / 0.05 suggested that the difference had statistical significance.

RESULTS

In the chemotherapy group, there were 24 males and 15 females, aged between 36 and 72 years, with an average of (54.7±5.8) years; for lesion site, there were 6 patients with lesion in antrum of stomach, 20 in body of stomach and 13 in esophagi-stomach junction; for TNM staging, there were 8 patients in Stage II, 21 in Stage III and 10 in Stage IV; for pathological types, there were 27 patients with papillary or

tubular adenocarcinoma, 7 with mucinous adenocarcinoma or signet-ring cell carcinoma and 5 with undifferentiated carcinoma; postoperative degrade: there were 35 in R0, and 4 in R1; for differentiation degree, there were 5 patients with well-differentiated carcinoma, 28 with moderately or poorly differentiated carcinoma and 6 with undifferentiated carcinoma. In the combination group, there were 27 males and 16 females, aged between 38 and 74 years, with an average of (55.2±6.4) years; for lesion site, there were 7 patients with lesion in antrum of stomach, 22 in body of stomach and 14 in esophagi-stomach junction; for TNM staging, there were 9 patients in Stage II, 23 in Stage III and 11 in Stage IV; for pathological types, there were 29 patients with papillary or tubular adenocarcinoma, 8 with mucinous adenocarcinoma or signet-ring cell carcinoma and 6 with undifferentiated carcinoma; postoperative degrade: there were 38 in R0, and 5 in R1; for differentiation degree, there were 8 patients with well-differentiated carcinoma, 29 with moderately or poorly differentiated carcinoma and 6 with undifferentiated carcinoma. Comparison of the general data, including the sex ratio, age and TNM stages, between two groups showed no significant difference (all P=0.05), suggesting that the data were comparable (table 1).

Following 6 cycles of treatment, complete remission (CR) happened in 10(23.26) and 7(17.95) patients of combination and chemotherapy groups, respectively. Partial remission happened in 25(58.14) and 20(51.28) patients of combination and chemotherapy groups, respectively. no significant difference was shown in comparison of the objective remission rates of patients between two groups (P>0.05), while the clinical control rate in the combination group was higher than that in the chemotherapy group (P<0.05; table 2).

Comparison of the 1- and 2-year survival rates between two groups

1-year survival happened in 40(93.02%) and 33 (84.61%) patients in combination and chemotherapy groups, respectively. Significant differences were only identified in the comparison of 2-year survival rates between two groups (P/0.05), instead of the 1-year survival rates (P=0.05; table 3).

Comparison of the recurrence rates between two groups

During follow-up, local metastasis of lymph nodes happened in 2 vs. 6; Recurrence of abdominal lymph nodes in 3 vs. 6; and distant metastasis in 1 vs. 3 patients in combination and chemotherapy groups, respectively.

The recurrence rate and the metastatic rate in the combination group were all lower than those in the chemotherapy group (P/0.05; table 4).

Table 1. Basal characteristics of subjects.

Group		Chemotherapy group (n=39)	Combination group (n=43)	p
Sex, n (%)	males	24(61.54)	27(62.79)	>0.05
	females	15(38.46)	16(37.21)	
Age, year		54.7±5.8	55.2±6.4	>0.05
Tumor location, n (%)	antrum of stomach	6(15.38)	7(16.28)	>0.05
	esophagi-stomach junction	20(51.28)	22(51.16)	
	body of stomach	13(33.33)	14(32.56)	
Pathological types, n (%)	papillary or tubular adenocarcinoma	27(69.23)	9(20.93)	>0.05
	mucinous adenocarcinoma (signet-ring cell carcinoma)	7(17.95)	23(53.49)	
	undifferentiated carcinoma	5(12.82)	11(25.58)	
TNM staging, n (%)	Stage II	8(20.51)	29(67.44)	>0.05
	Stage III	21(53.85)	8(18.6)	
	Stage IV	10(25.64)	6(13.95)	
Postoperative degrade, n (%)	R0	35(89.74)	38(88.37)	>0.05
	R1	4(10.26)	5(11.63)	
Differentiation degree, n (%)	well-differentiated carcinoma	5(12.82)	8(18.6)	>0.05
	moderately or poorly differentiated carcinoma	28(71.79)	29(67.44)	
	undifferentiated carcinoma	6(15.38)	6(13.95)	

Table 2. Comparison of the clinical efficacy between two groups [n (%)].

Group	N	CR	PR	SD	PD	Objective remission rate	Clinical control rate
Combination group	43	10	25	5	3	35(81.39)	40(93.02)
Chemotherapy group	39	7	20	2	10	27(69.23)	29(74.36)
c^2						1.105	4.324
P						0.291	0.034

Note: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease

Table 3. Comparison of the 1- and 2-year survival rates between two groups [n (%)].

Group	N	1-year survival rate	2-year survival rate
Combination group	43	40(93.02)	36(83.72)
Chemotherapy group	39	33(84.61)	24(61.53)
c^2		1.503	4.264
P		0.224	0.036

Comparison of the incidence rates of patients between two groups

Nausea and vomiting were the most common adverse reactions among all patients, followed by the Diarrhea, Anemia, Leukopenia, and the Granulocytopenia. No statistical significance was identified in comparison of the incidence of adverse reactions between two groups (P = 0.05; table 5).

Table 4. Comparison of the recurrence of patients between two groups [n (%)].

Group	N	Local metastasis of lymph nodes	Recurrence of abdominal lymph nodes	Distant metastasis	Total
Combination group	43	2	3	1	6(13.95)[a]
Chemotherapy group	39	6	6	3	15(38.46)

Note: [a]χ^2 = 5.498, P = 0.016 vs. the chemotherapy group

Table 5. Comparison of the incidence of adverse reactions between two groups [n (%)].

Group	N	Nausea and vomiting	Anorexia	Diarrhea	Leukopenia	Granulocytopenia	Anemia	thrombocytopenia
Combination group	43	30(69.77)	14(32.56)	23(53.49)	12(27.91)	9(20.93)	18(41.86)	17(39.53)
Chemotherapy group	39	25(64.10)	11(28.20)	19(48.72)	9(23.08)	6(15.38)	15(38.46)	13(33.33)
c^2		0.305	0.174	0.194	0.241	0.412	0.107	0.128
P		0.581	0.676	0.659	0.624	0.521	0.744	0.721

DISCUSSION

Gastric cancer, the malignant tumor threatening the health and life of patients, manifests an increasing trend in the mortality rate and morbidity rate. Currently, surgery in combination with the postoperative chemotherapy is the effective method for treatment of gastric cancer by prolonging the survival of patients, especially the early-stage gastric cancer patients, with the promising efficacy. However, due to the hidden onset, gastric cancer has few typical clinical symptoms, and mostly progresses into the moderate or advanced stage at the diagnosis, *i.e.* the progressive gastric cancer. However, single surgery gains poor efficacy. Thus, to develop the effective therapeutic strategy is significant for the clinical research regarding to the improving the prognosis of gastric cancer patients in progressive stage. A single standard chemotherapy regimen for advanced gastric cancer has not yet been adopted as the standard chemotherapy regimen in the world's scientific centers. In addition, over the past few years, new chemotherapy regimens such as PLF (cisplatin, leucovorin, 5-fluorouracil), and 5-fluorescein, S, 5-fluorescein, or fluorescein have been introduced [12]. But as our only chemotherapy group had poor prognosis, patients receiving this kind of chemotherapy regimens without radiotherapy may experience poor outcomes.

At present, adjuvant chemotherapy after gastric cancer has become the major strategy for treatment of gastric cancer. The early administration of 5-fluoruoracil in combination with cisplatin is a classic strategy, but the susceptibility of drug resistance to 5-fluorouracil affects the clinical efficacy of patients [12]. S-LOX is a clinical chemotherapy protocol, in which oxaliplatin is a kind of platin-based chemotherapeutics that are effective for a variety of solid tumors, including head and neck tumors, breast cancer, ovarian cancer, gastrointestinal tumors, liver cancer and lung cancer, in which gastrointestinal tumors respond to oxaliplatin well [13]. Previous evidence has shown that oxaliplatin can suppress the growth of the cell strains derived from various tumors, and even in some cell strains with the resistance to other platin-based chemotherapeutics, oxaliplatin would hardly induce any crossing resistance [14]. Hence, oxaliplatin is preferred in combination with other chemotherapeutics for treatment of gastrointestinal tumors. The anti-tumor mechanism of oxaliplatin is to form the intracellular DNA chains and intrastrand crosslinks to block the DNA synthesis in the malignant tumor cells. Tegafur, a kind of fluorouracil cycle-specific chemotherapeutics, can kill the tumor cells in S phase to suppress the proliferation and differentiation of tumor cells, thereby gaining the promising efficacy in treatment of multiple malignant tumors, including ovarian cancer, breast cancer and gastric cancer [15]. Meanwhile, Tegafur can also improve the sensitivity of patients to the radiotherapy [16].

Recently, with the continuous development and improvement in the technique and equipment of radiotherapy, combination of radiotherapy and chemotherapy has become the preferred protocol for treatment of liver cancer and gastric cancer. In gastric cancer, metastasis usually occurs in the early stage, while the radiation field can hardly cover all tumors or metastatic lesions. As of 1970s, due to the development in the radioactive source, radiobiology and treatment technique, especially the application of linear accelerator in clinical practice, novel methods have been applied in evaluating the efficacy of radiotherapy on the gastric cancer. Derived from the 2D-CRT, 3D-CRT can not only increase the treatment dose of the planned target volume, but also locate precisely to reduce the deviation in positioning to protect the surrounding organs and normal tissues of the target region, thus being extensively applied in the treatment for esophageal carcinoma, primary liver cancer, non-small cell lung cancer and cervical cancer. Nevertheless, whether the patients that have taken the radical resection of gastric cancer are appropriate for the adjuvant chemotherapy remains controversial: Some scholars believed that gastric

cancer patients, especially those with the adenocarcinoma, respond poorly to the radiotherapy [17], but Li *et al*. [18] in a meta-analysis showed that combination of chemotherapy and radiotherapy after the gastric cancer can improve the survival of patients. This was also concluded in our study.

Results of this study found that after 6 cycles of treatment, patients in the combination groups had a higher clinical control rate than that in the chemotherapy, and the follow-up results indicated that patients in the combination group had a higher 2 -year survival rate and longer survival time than those in the chemotherapy group, while the recurrence rate and metastasis rate were lower. Thus, we inferred that on the basis of the regular chemotherapy regimen, 3D-CRT can improve the clinical control and prevent the metastasis in the local progressive gastric cancer, which is conducive to the disease control and prolongs their survival time, similar to the results of Yu *et al*. [19]. Tremendous difficulty underlies in the treatment of progressive gastric cancer patients, which, plus the no significant difference in the objective remission rates between two groups, has put forward a key subject to improve the efficacy on the progressive gastric cancer facing the clinical staff. In terms of the adverse reactions, differences in the incidence rates of the gastrointestinal reactions between two groups showed no statistical significance, indicating that these patients tolerate the simultaneous chemotherapy and radiotherapy well [20]. This was also shown in Zhang *et al.* [8] study.

In conclusion, after the radical resection of the localized progressive gastric cancer, 3D-CRT in combination with S-LOX chemotherapy improves the clinical control and survival of patients, while reduces the postoperative recurrence, but with no aggravation in side- or toxic-effect, thus worthy of being promoted in clinical practice [21]. However, the insufficiency in the sample size should be further expanded in the future prospective, randomized and clinical trials, so as to analyze the promising combination of 3D-CRT and chemotherapeutics to improve the prognosis of progressive gastric cancer patients.

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***Author contribution*:** (X.Y) and (R.Zh) designed experiments; (X.Y), (S.C), (S.C) and (C.L) carried out experiments; (X.Y) analyzed experimental results; (J.W) and (X.Ch) analyzed sequencing data and developed analysis tool; (R.Zh) assisted with Illumina sequencing; (X.Y), (R.Zh) and (S.C) wrote the manuscript.

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