

Original Article

Comparison of clinical efficacy between two treatments in locally advanced gastric cancer with unresectable factors: chemotherapy and sequential chemoradiotherapy combined with radiotherapy and chemotherapy

Wei-Bin Zhang^{1*}, Xin-Sheng Zhang^{2*}, Zhen Feng², Yun-Fei Wu¹, Chun-Yu Qiu¹, Bin Zheng¹

¹The Central Hospital of Jinzhou, Jinzhou City 121000, Liaoning Province, China; ²The 2nd Affiliated Hospital of Dalian Medical University, Dalian City 116000, Liaoning Province, China. *Equal contributors.

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Abstract: Objective: Retrospective analysis the clinical data was done to compare the clinical efficacy between two treatments in locally advanced gastric cancer with unresectable factors: Chemotherapy and Sequential chemoradiotherapy were combined with radiotherapy and chemotherapy. Methods: Clinical data from 112 patients, who were diagnosed with locally advanced gastric cancer with unresectable factors, was reviewed from the Central Hospital of Jinzhou and the 2nd Affiliated Hospital of Dalian Medical University for dates ranging from Jan 2015 to Dec 2018. Patients were divided into the chemotherapy group and the chemoradiotherapy group by the two different treatments, in which the chemotherapy group including 59 patients treated with pure chemotherapy (the XELOX regimen), 30 patients got the operations after treatment; and the chemoradiotherapy group with Tegafur-Gimeracil-Oteracil Potassium Capsules Combined with Radiation sequential Chemotherapy (the XELOX regimen), and 40 patients got the operations after treatment. The gender, age, clinical efficacy and control rate, tumor differentiation degree, operation time, intraoperative bleeding volume, neurovascular invasion, lymph node metastasis rate, R0 resection rate, incidence of complications and total survival time were compared between the two groups. Results: The total effective rate and clinical control rate of the chemoradiotherapy group were better than those of the chemotherapy group, with statistical significance ($\chi^2/P=7.223/0.007$). Neurovascular invasion was lower than that of the chemotherapy group, with statistical significance ($\chi^2/P=11.689/0.001$). The lymph node metastasis rate was lower than that of the chemotherapy group ($P=0.012$). The R0 resection rate was higher than that of the chemotherapy group, with statistical significance ($\chi^2/P=9.550/0.002$). The incidence of complications after operation was slightly higher than that in chemotherapy group (11 cases: 21 cases). The total survival time was significantly prolonged ($P=0.007$). There was no significant difference in age, sex, tumor differentiation, operation time and intraoperative bleeding between the two groups ($P>0.05$). Conclusion: Sequential chemoradiotherapy combined with radiotherapy and chemotherapy can improve the transformation effect and clinical efficiency of unresectable locally advanced gastric cancer, reduce lymph node metastasis rate, and neurovascular invasion and increase R0 resection rate, but the complications, such as anastomotic fistula, pleural effusion, peritoneal effusion, pneumonia and lymphatic fistula, occurred after the operation, while the overall survival time was significantly prolonged.

Keywords: Chemotherapy, radiotherapy and chemotherapy, unresectable locally advanced gastric cancer, preoperative transformation therapy

Introduction

The incidence of gastric cancer is in the fourth place of malignant tumors and the fatality rate is in the second place. The reasons are abundant gastric blood supply, high probability of

local invasion and lymph node metastasis. In China, 70% of the cases are advanced gastric cancer, of which 10% are unresectable gastric cancer, and the median survival time is 5-12 months [1]. Surgery is still the main method to obtain radical treatment, Whether or not R0

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resection is closely related to prognosis. The choice of preoperative transformation therapy is very important for advanced gastric cancer with unresectable factors. Reducing the stage, eliminating the unresectable factors and prolonging the survival time are essential.

Unresectable factors include: 1. Difficult to perform R0 resection, advanced gastric cancer with residual tumor after operation, such as adjacent organ involvement, peri-celiac lymph node metastasis or lymph node encapsulation; 2. Distant metastasis, such as liver metastasis and distant lymph node metastasis. Locally Advanced Gastric Cancer refers to the invasion of gastric wall muscular layer, serosa or extra-serosa with or without regional lymph node metastasis [2].

Transforming therapy refers to the initial view that there are unresectable factors in surgical technology or oncology. After preoperative treatment, it can be totally or partially eliminated, and screened out cases with surgical conditions for surgery, and finally achieve the reverse transformation from late stage to radical treatment [3].

This study collected clinical data of patients with locally advanced gastric cancer with unresectable factors. After preoperative chemotherapy and sequential chemoradiotherapy, unresectable factors were evaluated again, and corresponding surgical treatment was carried out for those who qualified for surgery. The operation time, intraoperative bleeding volume, postoperative pathology (tumor differentiation, lymph node metastasis rate), R0 resection rate, postoperative complications and total survival time are summarized and analyzed, and the therapeutic effects were evaluated.

Materials and methods

Materials

From Jan 2015 to Dec 2018, 112 patients with locally advanced gastric cancer with unresectable factors were retrospectively collected from the Central Hospital of Jinzhou and the 2nd Affiliated Hospital of Dalian Medical University.

Inclusion criteria: All patients were diagnosed as advanced gastric cancer by electronic gastroscopy and pathology, combined with CT diag-

nosis of the whole abdomen and lungs, and there were no serious abnormalities of liver and kidney function before treatment, with Karl's score >70. Given the corresponding treatment program, then re-evaluation of the progress of the disease, appropriate patients that received the radical surgery with different degrees, and were discharged smoothly after surgery. No serious complications (or improvement after symptomatic treatment) occurred.

Exclusion criteria: Longer preoperative treatment cycle (>8 cycles); Combined with serious cardiovascular, lung, liver and kidney dysfunction; Combined with serious complications, such as bone marrow transplantation, cardiotoxicity, neurotoxicity, etc. With poor results after treatment; Emergency surgery due to bleeding, perforation; Peritoneal implantation and metastasis should be considered in the diagnosis; Clinical data are incomplete.

All patients completed the corresponding informed consent and signed it.

Method

The Chemotherapy group: Chemotherapy with XELOX regimen for 6-8 cycles: oxaliplatin 100-130 mg/m², intravenous drip for 3 hours, d1; Xerox 1000 mg/m² po bid, for 2 weeks, rest for one week, repeated every 3 weeks.

The Chemoradiotherapy group: Tegafur-Gimeracil-Oteracil Potassium Capsules, 60 mg/m² po bid, were given immediately after diagnosis for 2 weeks. Synchronized radiotherapy was started after a week of rest. Before radiotherapy, the chest and abdomen were scanned by enhanced CT. The target area was defined, i.e. tumor, regional lymph nodes and dangerous organs. The total dose of radiotherapy was 45 Gy, which was divided into 25 times, i.e. 2 Gy once, 5 times a week, and 2 weeks after radiotherapy. The 4-6 cycles of XELOX regimen were continued by the same as the chemotherapy group.

All operations were performed under the leadership of senior chief-physicians. D2 radical operation was successfully performed. Symptomatic treatment including acid suppression, anti-infection and nutritional support were given after operation. Complications were counted. Before discharge, the chest and abdominal

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Table 1. No significant difference in general information between the two groups ($P>0.05$)

	Gender		Total Number (n)	Age (year)
	Male	Female		
Chemotherapy group	48	11	59	64.9±6.3
Chemoradiotherapy group	45	8	53	61.8±8.8

CT enhanced scan or PET-CT was used to evaluate the operation effect (R0 resection rate). All patients were followed up by telephone, message and email.

Observation indicators

The clinical data of the patients were summarized and analyzed, including gender, age, clinical efficacy, clinical control rate, operation time, intraoperative bleeding volume, tumor differentiation, neurovascular invasion, lymph node metastasis rate, R0 resection rate, occurrence of complications and total survival time.

The evaluation criteria of clinical efficacy and control rate were based on the standard tables of solid tumors. The clinical efficacy = (number of complete remission cases + number of partial remission cases)/total number of cases * 100%; the clinical control rate = (number of complete remission cases + number of partial remission cases + number of stable remission cases)/total number of cases * 100%.

Lymph node metastasis rate = number of lymph node metastasis/total number of lymph nodes * 100%.

Statistical method

SPSS22.0 software was used for data statistics, χ^2 test was used for counting data, t test was used for measuring data, and standard level α was 0.05. When $P<0.05$, the difference was considered statistically significant.

Results

Comparison of general information

There was no significant difference in gender, age between the two groups ($P>0.05$), as shown in **Table 1**.

The total clinical effective rate and clinical control rate of the Chemoradiotherapy group were

higher than those of the chemotherapy group, with statistical significance ($P<0.05$), as shown in **Table 2**.

Comparisons of operative related information

There was no significant difference in the degree of differentiation between the two groups ($P>0.05$), as shown in **Table 3**.

There was no significant difference in operation time and intraoperative bleeding volume between the two groups ($P>0.05$), indicating that sequential chemoradiotherapy combined with radiotherapy and chemotherapy didn't increase the difficulty of operation. Neurovascular invasion, lymph node metastasis rate and R0 resection rate were significantly better in the Chemoradiotherapy group than in the chemotherapy group ($P<0.05$), the difference was statistically significant, as shown in **Table 4**.

Comparisons of postoperative complications

The incidence of postoperative complications in the Chemoradiotherapy group was slightly higher than that in the chemotherapy group (**Table 5**). The main complications were anastomotic fistula (23.8%), lymphatic fistula (14.3%), pleural effusion (23.8%), peritoneal effusion (14.3%) and pneumonia (14.3%). However, after the corresponding treatment, the complications were significantly improved, with no sequelae, as shown in **Table 5**.

Total survival

Two groups of patients were followed up by telephone, message and email after discharge, and the total survival time was counted: chemotherapy group (19.67±6.55) months, chemoradiotherapy group (26.45±7.38) months, $P=0.007$. There was significant difference between the two groups.

In conclusion, sequential chemoradiotherapy combined with radiotherapy and chemotherapy can improve the conversion rate and the clinical control rate, reduce the invasion of nerves and vessels and the probability of lymph node metastasis, and increase the possibility of R0 resection, but the incidence of complications after operation is increased, especially anastomotic fistula, pleural effusion, peritoneal effu-

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Table 2. Comparison of clinical total effective rate and control rate between the two groups (n/%)

	CR	PR	SD	PD	Total Effective Rate	Clinical Control Rate
Chemotherapy group	7/11.86	23/38.98	28/47.46	1/1.70	50.84	98.30
Chemoradiotherapy group	23/43.40	17/32.08	9/16.98	4/7.54	75.48	92.46
χ^2/P	-	-	-	-	-	7.223/0.007

Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3. Comparison of tumor differentiation degree between two groups (cases)

	Low differentiation	Medium-Low differentiation	Medium differentiation	High differentiation
Chemotherapy group	25	13	19	1
Chemoradiotherapy group	14	19	18	1
χ^2/p	-	-	-	3.939/0.268

Table 4. Comparison of operative related information between two groups

	Operation time (min)	Intraoperative bleeding volume (ml)	Neurovascular invasion	Lymph node metastasis rate	R0 resection rate
Chemotherapy group	226.73±103.79	134.73±80.16	53.3% (16/30)	16.27±20.88%	66.7%
Chemoradiotherapy group	233.45±58.73	195.53±180.79	15% (6/40)	5.21±8.76%	95%
<i>P</i>	0.086	0.127	11.689/0.001	0.012	9.550/0.002

Table 5. Comparison of postoperative complications between the two groups (cases)

	Total occurrence	Anastomotic fistula	Intestinal obstruction	Peritoneal effusion	Pneumonia	Pleural effusion	Pulmonary embolism	Lymphatic fistula
Chemotherapy group	11	1	0	6	3	0	1	0
Chemoradiotherapy group	21	5	2	3	3	5	0	3

sion and lymphatic fistula. The total survival time was significantly prolonged.

Discussion

Gastric cancer is one of the most common malignant tumors in the world, with an annual increase of nearly 1 million cases. In China, the incidence and mortality of gastric cancer are in the forefront. Unresectable gastric cancer accounts for 10% of the total number of gastric cancer cases. Palliative chemotherapy is the main treatment at present. The median survival time is 5-12 months, and the 5-year survival rate is about 9.4%. In recent years, some scholars have reported that some patients with advanced gastric cancer complicated with unresectable factors had complete or partial remission of unresectable factors after transformation therapy, and then received radical gastrectomy D2, thus obtaining a relatively long sur-

vival time after operation, forming a new strategy of transformation therapy for unresectable gastric cancer [4].

The concept of transformational therapy was firstly proposed in 1996 by Professor Bismuth, a member of the NCCN Group of Experts on Rectal Cancer, in the treatment of colorectal cancer. At present, transformational therapy has been used as a standard mode of multidisciplinary collaborative treatment for metastatic colorectal cancer, and has become one of the important factors affecting the prolongation of life in patients with advanced or recurrent colorectal cancer [5]. Transformational therapy of gastric cancer is aimed at patients with unresectable gastric cancer. By giving systemic-chemotherapy, chemoradiotherapy, targeted-drugs and other treatments, relying on abdominal CT plain or enhanced scan, endoscopic ultrasonography, laparoscopic exploration and detec-

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tion of tumor markers, evaluating grade, radical gastrectomy, R0 resection (D2/D2+ lymph node dissection), is performed for patients with partial or complete remission of unresectable factors and adjuvant chemotherapy after operation according to pathological results, then ultimately prolong the overall survival time and improve the quality of life [6]. Especially for patients with potentially resectable, the benefits are enormous.

The purpose of this study was to investigate the clinical efficacy and perioperative prognosis of the chemotherapy-based or sequential chemoradiotherapy regimen for locally advanced gastric cancer with unresectable factors. The statistical results show that sequential chemoradiotherapy combined with radiotherapy and chemotherapy can effectively eliminate or control unresectable factors, such as regional lymph node metastasis, invasion of important blood vessels and nerves, and invasion of important peripheral organs. The aim of R0 resection was to reduce the clinical stage and control the progress of the disease, but for those with low differentiation, large volume and important vascular invasion, the transformation effect was not good, which may be related to the sensitivity of tumor cells and abundant blood supply of giant tumors.

After sequential chemoradiotherapy combined with radiotherapy and chemotherapy, the operation time and bleeding volume were not increased, and the difficulty of operation was not increased. Postoperative pathological results showed that the incidence of neurovascular invasion and lymph node metastasis was significantly reduced in the chemotherapy group, which indicated that sequential chemoradiotherapy combined with radiotherapy and chemotherapy could effectively control and improve regional lymph node metastasis. Re-evaluation of patients' condition after surgery showed that the rate of R0 resection was significantly increased.

There were different degrees of complications in the two groups at the recovery stage after operation. The incidence of complications was higher in the chemoradiotherapy group, especially anastomotic fistula, pleural effusion, peritoneal effusion, pneumonia and lymphatic fistula. The measures of fasting water, keeping abdominal-drainage smooth and providing nu-

tritional support were mostly effectively improved, and no obvious sequelae occurred. Fiber tissue intensification, healing ability and self-repairing ability in the lesion area were correlated. After symptomatic treatment, all patients recovered, and the overall survival time was significantly longer than that in the chemotherapy group.

However, at present, only a few single-center and small-sample reports have been reported in clinical studies related to transformational therapy. Evidence-based medical is insufficient in case-selection, scheme-formulation, efficacy-evaluation and so on. Multidisciplinary diagnostic and therapeutic teams are needed to collaborate and multi-center, large-sample randomized controlled trials provide more strategies and reliable evidence-based medical evidence for transformational therapy of unresectable locally advanced gastric cancer [7]. Appropriate transformation therapy should be chosen for patients with advanced gastric cancer, followed by selection of a reasonable transformation program, evaluation within a certain period of time, selection of the appropriate timing of surgery, and close follow-up, monitoring the overall survival period, and evaluating the feasibility of the comprehensive transformation therapy program [8]. According to the related literature, many patients with unresectable gastric cancer can receive radical gastrectomy after transformation therapy. The progression-free survival and overall survival rate can be significantly prolonged, and the quality of life has been improved.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei-Bin Zhang, The Central Hospital of Jinzhou, No. 51, Second Section of Shanghai Road, Gu-Ta District, Jinzhou City, Liaoning Province, China. Tel: +86 15754188089; E-mail: webean_zh@163.com

References

- [1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87-108.
- [2] Sano T, Ailko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer* 2011; 14: 97-100.

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- [3] Kim SW, The result of conversion surgery in gastric cancer patients with peritoneal seeding. *J Gastric Cancer* 2014; 14: 266-270.
- [4] Yoshikawa T, Oshima T, Rino Y, Masuda M. Laparoscopy-assisted gastrectomy following neoadjuvant chemotherapy for advanced gastric cancer-strategies for development. *Chinese Journal of General Surgery* 2013; 10-14.
- [5] Tanizawa Y, Terashima M. Lymph node dissection in the resection in the resection of gastric cancer: review of existing evidence. *Gastric cancer* 2010; 12: 137-148.
- [6] Yoshikawa T, Sasako M, Yamamoto S, Sano T, Imamura H, Fujitani K, Oshita H, Ito S, Kawashima Y, Fukushima N. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg* 2009; 96: 1015-1022.
- [7] Habermann CR, Weiss F, Riecken R, Honarpisheh H, Bohnacker S, Staedtler C, Dieckmann C, Schoder V, Adam G. Preoperative staging of gastric adenocarcinoma: comparison of helical CT and endoscopic US. *Radiology* 2004; 230: 465-471.
- [8] Guo RP, Zhong C, Shi M, Zhang CQ, Wei W, Zhang YQ, Li JQ. Clinical value of apoptosis and angiogenesis factors in estimating the prognosis of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2006; 132: 547-555.