PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroentero, 2000; 6(2):284-286
World Journal of Gastroenterology
 ISSN 1007-9327

A clinical and long-term follow-up study of peri-operative sequential triple therapy for gastric cancer

Shou Chun Zou, Hua Sheng Qiu, Cheng Wu Zhang and Hou Quan Tao

Subject headings stomach neoplasms/surgery; stomach neoplasms/drug therapy; intra-arterial chemotherapy; intra-peritoneal chemotherapy; curative resection; survival rate

Zou SC, Qiu HS, Zhang CW, Tao HQ. A clinical and long-term follow-up study of perioperative sequential triple therapy for gastric cancer. *World J Gastroentero*, 2000;6(2):284-286

INTRODUCTION

Although the long-term postoperative survival rate of gastric cancer (GC) patients has been improved significantly since the local dissection of lymph node was widely used in China, yet the low curative resection rate and the high recurrence rate from peritoneal and hepatic metastases hinder it from further improvement. To alter the current unsatisfactory status of GC treatment, a sequential triple therapeutic scheme (STTS), consisting of pre-operative regional intra-arterial chemotherapy, curative resection of GC, and intra-operative or early postoperative intraperitoneal chemotherapy, was designed and adopted in this department since 1989. The follow-up data demonstrated that the therapeutic response of STTS is rather satisfactory. The results are reported as follows.

MATERIAL AND METHODS

General data

From February 1989 to October 1997, a total of 211 patients with GC were treated in this department, among them 167 were treated by surgical resection of GC, and follow-up data were obtained in 134 cases, with a rate of 80.24%, and a follow-up period of 5.144 months, averaging 34.6 months. Among the followed up patients, 112 had curative resection and 22 had palliative resection.

Sequential triple therapeutic scheme (STTS)

One or two times of selective intra-arterial chemotherapy with FAP or FMP scheme was done by DSA, and then surgical operation was performed in 2 weeks. The surgical operation was performed as follows: D1 resection for TNM staging I, D2+ or D3 resection (including combined organ resection) for TNM staging Ib to IIIb, D4 resection for only a few cases, palliative resection for TNM staging IV patients. Hyperthermic intraperitoneal chemotherapy was performed immediately after operation, MMC 40mg+ CDDP 200mg were dissolved in 4000mL NS, lasting 15 minutes at 42℃-45℃, the abdominal wall was sutured after the chemot herapy was completed. Among the 134 followed up cases, 81 received STTS treatment and 53 underwent only simple resection. Based on the new TNM staging system, the staging of two groups was essentially similar and comparable (Wilcoxon test, $P>0.05$).

Table 1 The TNM staging of STTS group and simple operation group

Stage		STTS group (*n*)	%	Simple operation group (*n*)	%
I	Ia	2	2.4	2	3.8
	Ib	6	7.4	4	7.5
II		15	18.5	11	20.7
III	IIIa	21	25.9	12	22.6
	IIIb	25	30.9	15	28.3
IV		12	14.0	9	17.0
Total		81		53	

Statistical analysis

Based on the data from the case with simple operation as a control, the treatment response of STTS was evaluated, the comparison between the two groups was anal ysed by Chi-square test, the cumulative survival rate was calculated by the life-table method. *P* value of less than 0.05 was considered as significant.

RESULTS

Effect of preoperative regional intra-arterial chemotherapy on the cur ative resection rate

Among the 211 patients, 101 were treated by preoperative regional intra-arterial chemotherapy, of whom 80 (79.2%) had curative resection. But among 110 cases treated by simple operation, only 68 (61.8%) had curative resection, hence the curative resection rate was significantly different between the two groups ($P<0.01$).

Department of Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang Province, China
Professor Shou Chun Zou, Head of Department of Surgery, Zhejiang Provinc ial People's Hospital, China, having 15 papers published.
Correspondence to: Prof. Shou Chun Zou, Department of Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310014, Zhejiang Province, China
Tel. 0086-571-5132615 Ext.3013, Fax. 0086-571-5131448
Received 1999-04-15 **Accepted** 1999-07-18

Comparison of survival rate between STTS and simple operation group

Among the 134 followed up cases, 43 died, the survival rates of 1, 3, 5 and 7 years were 87%, 64.6%, 60.9% and 55.2%, respectively. Statistical data demonstrated significant difference of survival rate between STTS and simple operative group except the 3-year survival rate. Among the 112 cases with curative resection, 71 cases received STTS treatment, and 41 received simple operation, the survival rate of the two groups was significantly different except for the 3 and 7-year survival rate (Table 2).

Table 2 Comparison of survival rate and curative survival rate betwe en STTS group and simple operation group

Group	Survival rate (%)					Curative survival rate (%)				
	n	1	3	5	7 (yrs)	*n*	1	3	5	7 (yrs)
STTS	81	92.9[c]	68.1[a]	68.1[1]	62.5[c]	71	98.0[c]	79.2[a]	79.2[c]	72.6[a]
Simple operation	53	79.7	55.5	49.1	45.6	41	90.0	72.3	64.3	60.6

[a]*P*>0.05, *vs* simple operation, [c]*P*<0.05, *vs* simple operation.

Effect of STTS on postoperative metastasis and recurrence rate

Of all 134 patients, 43 died from cancer metastasis and recurrence during follow-up period, 25 had peritoneal metastasis and 10 had hepatic metastasis. Statistical data showed that there was significant difference of the peritoneal and hepatic metastasis rate between STTS group and simple operation group (Table 3).

Table 3 Comparison of main recurrence and metastasis rate between STTS group and simple operation group

Recurrence (*n*)	Group (*n*)	*n*	Rate (%)	*P* value
Peritoneal	STTS (*n*=81)	7	8.6 (7/81)	χ^2=13.53
(*n*=25)	Simple operation (*n*=53)	18	33.9 (18/51)	*P*<0.005
Hepatic	STTS (*n*=81)	2	2.4 (2/81)	χ^2=7.39
(*n*=10)	Simple operation (*n*=41)	8	15.1 (8/53)	*P*<0.01

Relationship between free cancer cells in peritoneal cavity and TNM staging and intra-peritoneal chemotherapy

Of all 134 cases, peritoneal lavage was examined in 45 cases to detect the intra-peritoneal free cancer cells. It was positive in 11 (24.4%) cases and, 1, 1, 2, 3 and 4 cases were found at stage of I, II, IIIa and IV, respectively. In 5 followed up patients, 2 without intra-peritoneal chemotherapy died of peritoneal metastasis in 1 year and 2 years and 3 months, while in the 3 patients with intra-peritoneal chemotherapy, 1 died 5 years later and the remaining 2 were alive 5 and 8 years later respectively. Sixteen of the cases with negative free cancer cells, were followed up, only 1 of them died from peritoneal metastasis 2 year s after the operation.

Relationship between STTS and survival rate of lymph node positive cases

Among 112 cases with curative resection, lymph node metastasis was found in 66 cases, 47 of which were treated by STTS and 19 cases by simple operation. Statisical analysis showed that the survival rate of 1, 3, 5 and 7 years in STTS group were all higher than those in simple operation group, but they were not significant in log rank test.

DISCUSSION

Selection of the appropriate time for chemotherapy

The post-operative recurrence of GC arises mostly from the remnants of micro-cancerous foci. In the past, chemotherapy was done mostly post-operatively, when the vascular and lymphatic channels of the primary tumor had been cut and ligated in operation, and the cancer cells were embedded in the adhesion one week after operation. The remnant micro-cancerous foci cannot be exposed to chemotherapeutic drugs or the concentration of the drugs is insufficient, so the chemotherapy is rarely effective. Besides, during operation, free cancer cells are promoted to exfoliate and metastasis. The pre-operative chemotherapy can reduce the viability of cancer cells, reduce the tumor size, and decrease the chance of iatrogenic dissemination and hepatic metastasis so as to increase the opportunity for curative resection. Averbach *et al*[1] and Ajani *et al*[2] suggested that pre-operative, intra-operative and early post-operative period are the best time for chemotherapy.

Among the 211 cases, curative response of pre-operative regional intra-arterial chemotherapy was 79.2%, the 5-year survival rate of STTS group being 79.2%, but 61.8% and 64.3% respectively in the simple operation group (*P*<0.05). The results indicated that pre-operative regional intra-arterial chemoth erapy, intra-operative and early post-operative intra-peritoneal chemotherapy can increase significantly the curative rate and the 5-year survival rate.

Indications for intra-operative and early post-operative intra-perit oneal chemotherapy

Peritoneal metastasis is the main cause of recurrence in GC, its rate was about 50%-60% in the literature[3], and was 58% in this paper. The 3-year survival rate of cases with free cancer cells in peritoneal cavity was only 15.6%[4]. Bonen Kamp reported that the median survival period was only

1.1 years[5]. Recently, the positive rate of free cancer cells was reported to be 22.2%-32.5% in China[6,7], and was 24.4% in this paper. According to Suzuki, free cancer cells were found in peritoneal lavage in 24% of stage Ib and 40% of stage II-III patients. False positive rate was less than 5%[8]. The difference between Chinese and international reports may be due to the following factors: ¢Ù the results of examination are not exactly correct; ¢Ú the exami nation of lavage is usually performed after opening the abdomen before the operation, free cancer cells may turn from 'negative' to 'positive' at the end of the operation. In our series, one patient with negative free cancer cells and without intra-peritoneal chemotherapy died from peritoneal metastasis post-operatively. Among those with positive free cancer cells and without intra peritoneal chemotherapy, 2 were of stage I and II respectively, and 3 survived more than 5 and 8 years. As a result, the stages more than Ib in GC patients are indications for intra-peritoneal chemotherapy.

About curative resection

Curative resection is the most important means to determine whether the GC patient is cured or not. The following standards should be achieved: ① No tumor invasion of the cut ends; ② the number of stations of regional lymph nodes dissected should exceed that of positive lymph nodes (D>R); ③ no remnant cancer tissue in adjacent organs and tissues. The results should be confirmed by pathological examination, but this is often too late. In other words, even the operation has achieved the requirements of curative resection, if there are some risk factors, such as sub-clinic cancer foci, invisible free cancer cells in peritoneal cavity, indistinct potential hepatic metastasis, etc., the so-called curative resection need pre-operative, intra-operative or early post-operative chemotherapy to compose a composite therapeutic approach so as to attain the real curative resection.

About lymph node metastasis

It is well-known that the prognosis of GC patients is closely related to the lymph node metastasis. It is suggested in this paper that there was no significant difference in long-term survival rate between STTS lymph node positive group and simple operation group. This may be related to the insufficient number of cases accumulated, or due to the fact that the lymph node metastasis is an independent prognostic factor, and it depends mainly on the thoroughness of the dissection. It is impossible for various chemotherapeutic approaches to replace the curative resection at all.

CONCLUSION

We suggest that the STTS is a rational therapeutic scheme for GC. Follow-up results have demonstrated that STTS treatment can significantly increase the curative resection rate and the 5-year survival rate and decrease the post-operative recurrence rate as well. But this is still a preliminary report of the feasibility of STTS, more cases should be accumulated for further studies.

REFERENCES

1 Averbach AM, Jacquet P. Strategies to decrease the incidence of intra-abdominal recurrence in resectable gastric cancer. *Br J Surg*,1996;83:726-733
2 Ajani JA, Mansfield PF, Ota DM. Potentially resectable gastric carcinoma current approaches to staging and preoperative therapy. *World J Surg*, 1995;19:216-220
3 Tanaka A, Watanabe T, Okuno K, Yasutomi M. Perineural invasion as a predictor of recurrence of gastric cancer. *Cancer*,1994;73:550-555
4 Litsuka Y. Intraperitoneal free cancer cells and their viability in gastric cancer. *Cancer*,1979;44:1476-1480
5 Bonenkamp JJ, Songun I, Hermans J, Vande Velde CJH. Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. *Br J Surg*,1996;83:672-674
6 Chen JQ, Zhang WF, Wang SB, Qi CL, Shan JX, Liu QH, Zhang YC. Some questions about the treatment of gastric cancer. *Zhonghua Waike Zazhi*, 1991;29:220-223
7 Yang QM, Zhu ZG, Yan M, Li XF, Xue JY, Yin HR, Lin YZ, Jin XL. Establishing clinical indications of intraoperative peritoneal hyperthermic chemotherapy for gastrointestinal malignancy.*Waike Lilun Yu Shijian*,1998;3:11-13
8 Wu CC, Chen JT, Chang MC, Ho WL, Chen CY, Yeh DC, Liu TJ, Peng FK. Optimal surgical strategy for potentially curable serosa-involved gastric carcinoma with intraperitoneal free cancer cells.*J Am Coll Surg*,1997;184:611-617

Edited by Ma JY