

Safety and effectiveness of endoscopic mucosal resection combined with chemotherapy for early gastric cancer

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Abstract. – OBJECTIVE: To study the safety and efficacy of endoscopic mucosal resection (EMR) combined with chemotherapy in patients with early gastric cancer.

PATIENTS AND METHODS: Continuously, 112 patients of early gastric cancer (IA-IB) were chosen to receive the treatment of EMR. The 112 patients were divided into two groups, the control group and the observation group. The control group consisted of 56 patients who were treated with only EMR while the observation group consisted of 56 patients who were treated with both EMR and adjuvant chemotherapy (5-FU+oxaliplatin). A one-year's follow-up visit on the 112 patients was made.

RESULTS: The two groups' curative resection rate and occurrence of complication are inconsistent but the difference ratio ($p > 0.05$) is of no statistical significance. However, observation group's recurrence rate declined observable and the two groups' difference ratio ($p < 0.05$) is of statistical significance. What's more, the observation group's health index, emotional sound index and mental health index are higher than those of the control group and the difference ratio ($p < 0.05$) is of statistical significance.

CONCLUSIONS: The method of combining EMR and chemotherapy can reduce recurrence rate and improve living standard while it generates no adverse reactions and keeps the immunity of organism sound at the same time.

Key Words:

Early gastric cancer, EMR, Adjuvant chemotherapy.

Introduction

Gastric cancer is the second cause of death worldwide. Each year, about 0.93 million people become new patients of gastric cancer, among which 2/3 are people from China, Japan, and Korea¹. The diagnostic rate of early gastric cancer in China is only 10% which is comparatively low. However, the fact is that the patients of early gas-

tric cancer enjoy a higher animation prognosis than the patients with advanced gastric cancer². At present, the main therapeutic method of early gastric cancer is still performing the operation. Although the standard D2 lymphadenectomy enjoys a higher possibility of removing the whole tumor, it generates more complications. Thus, the effect of standard D2 lymphadenectomy is actually similar to that of reduction surgeries such as local resection, pylorus preservation and partial resection of the vagus nerve³. As per application and development of endoscopic therapy, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) can also remove the whole tumor with advantages including less surgical trauma, faster recovery and patients' higher acceptability⁴. Recently, most of the researches paid attention to the application of EMR and ESD as well as the comparison of EMR and ESD in the treatment of early gastric cancer⁵. However, the recurrence rate after treatment still exists. Thus, some researchers held that the recurrence rate is related with the number of lymph node transferred by the tumor⁶. There are also some clinical researches and meta-analysis about if the adjuvant chemotherapy or other kinds of chemotherapy should be added to the after-surgery treatment. Till now, no unified standard has been raised to answer the question. Our center has made follow-up analysis on the result drawn from the 112 patients' performance after EMR to see if adjuvant chemotherapy is beneficial in treating early gastric cancer.

Patients and Methods

Patients

Continuously, 112 patients with early gastric cancer in our hospital from January of 2014 to June of 2015 were taken into account. After

pathologic diagnosis on endoscopic biopsy, the possibilities of celiac lymph nodes and organ metastasis were excluded. Approved by hospital's ethics committee and conformed to patients' and their relatives' right of informed consent, this research divided the 112 patients into two 56-member groups which are the control group and the observation group respectively according to patients' time of being hospitalized. The patients in the control group received only EMR treatment, while those who in the observation group were treated with both EMR and adjuvant chemotherapy. Among the patients in the control group, 30 are male and 26 are female; their age ranges from 43 to 66 and the average age is 52.2 ± 8.6 ; there are 38 type IA patients and 18 type IB ones. According to the classification of the Endoscopic Association of Japan, the patients can also be divided into 17 type I, 24 type II and 15 type III. The maximum diameter of the tumor is 0.5-4.2 cm and the average figure is 2.7 ± 1.3 cm. As for observation group, male patients are 31 and female ones are 25. Their age ranges from 42 to 68 and the average age is 53.4 ± 8.8 . The number of type IA is 39, the number type IB is 17. According to the classification of the Endoscopic Association of Japan, there are 15 type I, 25 type II and 16 type III. The maximum diameter of the tumor is 0.4-4.7 cm and the average figure is 2.9 ± 1.5 cm. The difference ratio of the comparison between the two groups' baseline information is all of no statistical significance ($p > 0.05$).

Therapeutic Methods

The main steps of EMR: a, Inject glycerin fructose into the area below the mucous membrane to ensure that the focus is lifted; b, Cover transparent cap at the front end of the endoscope and the high-frequency endoloop should be equipped inside the transparent cap; c, Pump out the diseased mucosal membrane in the transparent cap with the help of negative pressure suction. Then, use the endoloop to remove the focus. If a large focus cannot be removed entirely at one time, several attempts are allowed; d, Wound treatment. Spraying hemostatic and electrocoagulation using hot biopsy forceps are available to stop the bleeding. If it is necessary, titanium clips could also be used. Eating is forbidden in the coming 24 hours after surgery. Patients who used titanium clips to stop bleeding and patients who have perforation caused by bleeding are not allowed to eat at a longer time. After that, liquid

and semi-liquid food is gradually available. After the surgery, proton pump inhibitor, antibiotic, hemostatic, fluid infusion and other drugs should be taken by patients normally. On the same day of the surgery, patients in observation group were treated with adjuvant chemotherapy. The plan is as follow: a, 450 mg/m² 5-FU (Shanghai Xu Dong Hai Pu Pharmaceutical co., LTD, China) and 500 ml 5% glucose are intravenously injected. The intravenous injection should be performed in 1-5 days and it lasts for 4-6h; b, 130 mg/m² oxaliplatin (Aiheng, Jiangsu Hengrui Medicine co., Ltd, China) and 500 ml 5% glucose are intravenously injected in 2 hours. The intravenous injection lasts for two periods and three weeks for one period. Adverse reactions are closely observed to see if drug withdrawal and further observation are needed.

Observation Target

The difference between the two groups in curative resection rate, adverse reaction after surgery and chemotherapy, recurrence rate, living standard rate, and the classification of T-cells are compared. The curative resection rate is defined as a total resection of the whole tumor and the specimen from the surgery must conform to Japan's guideline for staging stomach cancer, which demands the name of reducing lymph node metastasis at the most extent. Adverse reactions after surgery and chemotherapy include hemorrhage (> 100 ml, delayed hemorrhage during and after surgery), gastric mucosa perforation, nausea and vomiting and damage of the liver's and kidney's functions. The recurrence rate refers to the discovery of tumor during the follow-up visit period, which is histologically identical to the former tumor in the same location. The living standard rating used Table SF-36 for reference to measure patients' 8 aspects – physiological functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. To sum up, the 8 aspects can be generalized into three parts: health index, emotional index and psychological index. The classification of T-cells should be detected by using type XL-2 (Coulter Corp, Hialeah, FL, USA) flow cytometer (FCM).

Statistical Analysis

Typing in and analyzing with the help of statistical software SPSS19.0. The quantitative figure is shown as "mean \pm standard deviation"; the comparison between groups is tested with the

Table I. Comparison of the curative resection rate and surgery with the chemotherapy adverse reactions and recurrence rate [example (%)].

Group	Number of cases	Curative resection rate	Bleeding	Perforation	Nausea and vomiting	Liver and kidney dysfunction	Others	Adverse drug reaction	Recurrence rate
Control group	56	50 (89.3)	1	1	1	0	0	3 (5.4)	10 (17.9)
Observation group	56	51 (91.1)	1	1	1	1	1	5 (8.9)	3 (5.4)
χ^2	0.101						0.135	4.264	
p	0.751						0.714	0.039	

help of “t”; Qualitative data are shown as “case number” or is shown by using “%”. Comparison between groups is tested with the help of χ^2 and $p < 0.05$ means that the difference is statistically significant.

Results

Comparison of the Curative Resection Rate and Surgery with the Chemotherapy Adverse Reactions and Recurrence Rate

Comparison of the curative resection rate and complication rate between the two groups, the difference has no statistical significance ($p > 0.05$); the recurrence rate of the observation group is significantly reduced, and the difference is statistically significant ($p < 0.05$) (Table I).

Comparison of the Quality of Life Score

Observation group’s health index, emotional and psychological index scores are significantly higher than the control group, and the difference is statistically significant ($p < 0.05$) (Table II).

Comparison of T-Cell Sorting

Comparison of the two groups of T-cell sorting, and the difference has no statistical significance ($p < 0.05$) (Table III).

Discussion

Clinical Application of EMR

The basic procedure of EMS includes injection, precutting, and endoscopic submucosal dissection and so on. Specifically, these refer to causing false polyps by submucosal injection, capturing the false polyps by clamping device,

Table II. Comparison of the quality of life score.

Group	Health index	Sentiment index	Psychological index
Control group	33.5 ± 4.7	19.4 ± 4.3	16.3 ± 3.7
Observation group	42.6 ± 5.5	35.2 ± 4.2	31.7 ± 3.9
t	6.527	6.134	5.857
p	0.008	0.013	0.016

Table III. Comparison of T cell sorting (%).

Group	CD4+	CD8+	CD4+/CD8+
Control group	42.4 ± 8.2	26.3±5.5	1.3 ± 0.3
Observation group	40.3 ± 8.3	23.5±5.7	1.2 ± 0.4
t	0.632	0.967	0.427
p	0.743	0.828	0.562

precutting with a needle knife under endoscope and endoscopic mucosal resection with ligation, all these procedures are aimed to achieve complete chunk of mucosal resection. A crucial part of the technique is injecting adequate saline into the submucosa to make the mucous layer be lifted up from the submucosa, and to achieve the purpose of separating the mucosa and the muscularis propria⁷. Currently, the common methods of EMR are: (1) EMR with a cap⁸: Install a transparent cap at the top of the endoscopic, pump the lesion out into the cap, and cut it with the endoloop. For the early gastric cancer patient of typeIIc, using the transparent cap can get a higher rate of complete resection. This method's request in operation is not high, and it can cut large lesions in a narrow operating space. However, compared with others, this method can cause relatively deep wound during the removal of lesions and it has a greater potential risk of generating complications. (2) The ligation excision method⁹ is available for the patients of type I and type IIa. It generally uses variceal ligation device to pump out the lesions, and then perform the ligation and excision. This method is simple, safe and low-cost. (3) The dual pipeline endoscopic method¹⁰ is widely used in the EMR. With the help of the two-forceps endoscope, cover the lesion with endoloop, then clamp and lift up the nidus with the biopsy forceps, making that sessile lesion Arch ones, then tighten the endoloop, and then cut the tumor with the help of high-frequency electrocoagulation. (4) The peeling biopsy method¹¹ combined with endoscopic injection and electrocoagulation excision. Firstly, inject the required amount of saline into the bottom of the neoplastic foci to make part of the nidus uplift and make multiple coagulation on the surface. Secondly, use endoloop to litigate the root of the cancer focus. Finally, make eletroresection. (5) Piecemeal mucosal resection method¹². If multiple lesions cannot be removed at one time or the sunken lesions are not uplifted after injection, several attempts are available.

Study of Adjuvant Chemotherapy for Early Gastric Cancer

Liu et al¹³ summarized 23 randomized clinical trials with 4919 patients, and the results showed that compared with surgery alone, postoperative adjuvant chemotherapy reduces the occurrence rate of the liver, peritoneum and lymph node metastasis; survival (RR = 0.85, 95% CI = 0.80-0.90) and disease-free survival (RR = 0.88, 95%

CI = 0.77-0.99) were improved, recurrence rate (RR = 0.78, 95% CI = 0.71-0.86) had a downward trend.

The subgroup analysis showed that the advantage of adjuvant chemotherapy has nothing to do with the depth of invasion, lymph node metastasis, the number of lymph node dissection type, the patient's regional distribution and the route of administration. Currently efficacy and safety of adjuvant chemotherapy in a large portion of early postoperative gastric cancer clinical trial are resulting in negative, which is more common in Europe and America¹⁴. Only a part of the trials showed a positive result, which is common in Japan and other Asian countries¹⁵.

According to the literature reports¹⁶, the early gastric cancer patients with lymph node metastasis after the operation, their survival rate in 5-year was 80% to 85%, and the patients without lymph node metastasis was 97% to 100%. The number of lymph node metastasis significantly affects the prognosis, with the increase in the number of metastatic lymph nodes; five-year survival rate was significantly decreased¹⁷. Therefore, some authors have proposed that¹⁸ making adjuvant chemotherapy according to the intensity of lymph node metastasis of early gastric cancer is appropriate. Kurihara et al¹⁹ proposed that submucosal cancer of type SM3 infringes deeper, and tends to have N2 metastasis, and it needs adjuvant chemotherapy; but a small amount of lymph nodes (1 to 2) transfer, doesn't need chemotherapy, if there were five or more positive lymph nodes, chemotherapy would be needed. The chemotherapeutic agent always uses 5-FU or FT-207, warranty from 3 months to 2 years. According to the principle of individuation, intramucosal cancer, SM1, a little cancer, small gastric cancer, stomach cancer don't need adjuvant chemotherapy, while SM2, SM3, superficial spreading cancer, multiple cancer lesions larger than 5 cm², and the malignant patients who have six or more lymph node metastasis, pathological pattern of high malignant degree or low differentiation, need appropriate adjuvant chemotherapy²⁰.

It can be generalized from the research: Comparison of the curative resection rate and complication rate between the two groups, the difference has no statistical significance; the recurrence rate of the observation group is significantly reduced, and the difference has statistically significance. Observation group's health index, emotional and psychological index scores are

significantly higher than the control group, and the difference has statistical significance. Comparison of the two groups of T-cell sorting, the difference has no statistical significance.

Conclusions

Combining EMR and adjuvant chemotherapy in treating early gastric cancer can reduce the recurrence rate and improve the quality of life without generating adverse reactions, and without decreasing immunity. Therefore, it is safe and effective for the patients to accept adjuvant chemotherapy. It can get more convincing conclusions through a larger sample of clinical, randomized controlled study and extending the time of follow-up.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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