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Clinical Trials Study

Efficacy and outcome of extensive intraoperative peritoneal lavage plus surgery vs surgery alone with advanced gastric cancer patients

Song ED *et al.* EIPL plus surgery

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Abstract

BACKGROUND

Gastric cancer (GC) is one of the most common malignant tumors. After resection, one of the major problems is its peritoneal dissemination and recurrence. Some free cancer cells may still exist after resection. In addition, the surgery itself may lead to the dissemination of tumor cells, so it is necessary to remove residual tumor cells. Recently, some researchers found that extensive intraoperative peritoneal lavage (EIPL) plus intraperitoneal chemotherapy can improve the prognosis of patients, and eradicate peritoneal free cancer for GC patients. However, few studies explored the safety and long outcome of EIPL after curative gastrectomy.

AIM

To evaluate the efficacy and long-term outcome of advanced GC patients with EIPL.

METHODS

9 According to the inclusion and exclusion criteria, a total of 150 patients with advanced GC were enrolled in this study, the patients were randomly allocated to 2 groups. All patients received laparotomy. For the non-EIPL group, peritoneal lavage was washed using no more than 3 L of warm saline; In the EIPL group, patients received 10 L or more of saline (1 L at a time) before the closure of the abdomen. The surviving rate analysis was compared by the Kaplan-Meier method. The prognostic factors were carried out using the Cox appropriate hazard pattern.

RESULTS

14 The basic information in the EIPL group and the non-EIPL group had no significant difference. The median follow-up time was 30 mo (range 0-45 mo). The 1- and 3-year overall survival (OS) rates were 71.0% and 26.5%, respectively. The symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group ($P < 0.05$). For the OS of patients, the EIPL, Borrmann classification, tumor size, N stage, T stage, and vascular invasion were significant indicators. Then multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage, and T stage were independent prognostic factors. The prognosis of the EIPL group was better than the non-EIPL group ($P < 0.001$), the 3-year survival rate of the EIPL group (38.4%) was higher than the non-EIPL group (21.7%). For the recurrence-free survival (RFS) of patients, the risk factor of RFS included EIPL, N stage, vascular invasion, type of surgery, tumor location, Borrmann classification, and tumor size. EIPL and tumor size were independent risk factors. The RFS curve of the EIPL group was better than the non-EIPL group ($P = 0.004$), and the recurrence rate of the EIPL group (24.7%) was lower than the non-EIPL group (46.4%). The overall recurrence rate and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group ($P < 0.05$).

CONCLUSION

EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. Besides, ¹² the overall survival curve and recurrence-free survival curve are better in the EIPL group.

²⁶
Key Words: Extensive intraoperative peritoneal lavage; Advanced gastric cancer; Prognosis; Recurrence; Overall survival

Song ED, Xia HB, Zhang LX, Ma J, Luo PQ, Yang LZ, Xiang BH, Zhou BC, Chen L, Sheng H, Fang Y, Han WX, Wei ZJ, Xu AM. Efficacy and outcome of extensive intraoperative peritoneal lavage plus surgery ¹³ vs surgery alone with advanced gastric cancer patients. *World J Gastrointest Surg* 2023; In press

⁹
Core Tip: This randomized study aims to evaluate the efficacy and long-term outcome of advanced gastric cancer patients with extensive intraoperative peritoneal lavage.

INTRODUCTION

Gastric cancer (GC) is one of the most common malignant tumors, its morbidity, and mortality in China have been increasing in recent years^[1,2]. Despite great advances in surgery and other treatment, the 5-year survival rate of GC is low^[3,4]. After resection, one of the major problems is its peritoneal dissemination and recurrence. Peritoneal recurrence is more likely to occur in advanced GC patients. Although chemotherapy is applied, the prognosis of these patients remains poor^[5].

Some free cancer cells may still exist after resection. In addition, the surgery itself may lead to the dissemination of tumor cells^[6,7], so it is necessary to remove residual tumor cells. Recently, extensive intraoperative peritoneal lavage (EIPL) has gotten more and more attention, it is a useful treatment that can wash the abdominal cavity completely using 10 L of physiological saline (up to 10 times). Based on previous study, EIPL is a safe and simple procedure^[8]. Some researchers found that EIPL plus intraperitoneal chemotherapy can improve the prognosis of patients^[9], this technique can eradicate peritoneal free cancer which is beneficial for the recurrence-free survival (RFS) of GC patients^[7,10]. However, few studies explored the safety and long outcome of EIPL after curative gastrectomy.

In this research, we explore the efficacy and 3-year outcome of advanced GC patients with the technique of EIPL, and then we analyze the possible mechanism.

MATERIALS AND METHODS

Patients

The study population is advanced GC patients with clinically T3 or T4, and M0 disease according to computed tomographic scans and ultrasonographic gastroscopy. The seventh American Joint Committee was used for the tumor, node and metastasis (TNM) stage. Each patient signed the informed consent, and this study was approved by the institutional review board of The First Affiliated Hospital of Anhui Medical University, Anqing Municipal Hospital, and First Affiliated Hospital of Wenzhou Medical University.

Inclusion and exclusion criteria

According to the inclusion and exclusion criteria, patients were included in the research. The inclusion criteria included: (1) All patients were confirmed GC with T3/4NanyM0; (2) the surgery is definite and complete resection of cancer; (3) these patients didn't have heart sickness or any important organ failures; and (4) they can keep a long touch with doctors after surgery. The exclusion criteria included: (1) they had previous malignant tumors or various primary tumors; and (2) they had accepted radiation treatment or chemo treatment previously before the treatment.

Procedure

If patients were confirmed with cT3 or cT4 and M0 disease and suitable for radical gastrectomy, they will be formally included in the study and then randomized. Patients were randomized in the EIPL group or non-EIPL group in a 1:1 ratio. Allocation was performed using sealed opaque envelopes that contained computer-generated random numbers and the procedure to which patients were allocated. Research participants will be randomized to the EIPL arm or non-EIPL arm based on random permuted blocks with a varying block size of four, assuming equal allocation between treatment arms. The cytological examination was performed by introducing saline into the cavity. The cytological statuses are all negative. After the exploratory operation, the envelopes were opened to determine whether EIPL was applied. A total, proximal or distal gastrectomy was done depending on the primary tumor location. Total gastrectomy or partial resection with D2 lymphadenectomy was performed by the guidelines of the Japanese Research Society^[11]. All patients received laparotomy, which reducing the influence of difference of surgical methods. Besides, after clinical pre-operative evaluation, patient's pre-operative nutritional status was good and has no obviously difference. For the non-EIPL group, peritoneal lavage was washed using no more than 3 L of warm saline; In the EIPL group, patients received 10 L or more of saline (1 L at a time) before the closure of the abdomen. Patients were excluded if the stage was not detected as T3 or T4 and M0,

in the end, 100 patients were finally included in this study between March 2016 and March 2017. Besides, the external population includes 50 GC patients who were hospitalized at First Affiliated Hospital of Wenzhou Medical University and Anqing Municipal Hospital from March 2016 to November 2017, and the methods and procedures are consistent with our group (Supplementary Figure 1).

Data collection and follow-up

The patient's demographic and clinicopathological data were recorded, including age, gender, tumor location, tumor size, differentiation grade, pathological type, and so on. The pathological tumor stage was categorized according to the 7th edition of the American Joint Committee on Cancer TNM staging system. The routine laboratory data were listed below: neutrophil, lymphocyte, platelet, carcinoembryonic antigen (CEA), and so on.

Peripheral blood tests were obtained within 1 wk before surgery and on the second day after surgery, the cutoff value of CEA was got according to the normal level. We determine the following indexes, neutrophil-to-lymphocyte ratio (NLR), neutrophil count, lymphocyte count. These two variables were grouped into the low group and high group according to the optimal cut-off values which were calculated based on the Youden index [maximum (sensitivity + specificity-1)]^[12].

Tumor location was classified into five subgroups according to the anatomy of the stomach: gastric cardia, fundus of stomach, body of stomach, gastric antrum, pylorus. Among them, upper means cardia and fundus of stomach. Middle means body of stomach. Low means gastric antrum and pylorus. To prevent the influence of esophageal cancer on the results of this study, gastroesophageal junction tumors were not included into our research. The postoperative complications, the length of hospital stay, and other outcomes were also recorded in this research, the complications including abscess, leakage, bleeding, and so on.

After the operation, the patients received eight 3-wk cycles of oral S-1 plus intravenous oxaliplatin. Diagnosis of recurrence is made by abdominal ultrasound, computed tomography, magnetic resonance imaging, gastroscopy and pathology tests.

We got their follow-up data through telephone and outpatient visits. This behavior got carried out in normal intervals (every 90 d within three years), until the date December 2020.

Statistical analysis

The baseline characteristics analysis of the non-EIPL group and EIPL group patients was performed including age, gender, body mass index (BMI), smoking, tumor location, differentiated grade, T stage, N stage, tumor size, Borrmann classification, CEA, neutrophil count, lymphocyte count, NLR, and platelet. The outcome after surgery was analyzed including type of surgery, the time from surgery to first flatus, postoperative hospital stays, abdominal pain, ileus, abdominal abscess, leakage, bleeding, neutrophil count, lymphocyte count, NLR, and platelet. Continuous variables were expressed as mean \pm SD and they were analyzed by student *t*-test; Categorical values were identified by counting (percent) and they were counted by Chi-square test or Fisher exact test. The Kaplan-Meier method and Log-rank test was used to compare the prognosis of the non-EIPL group and EIPL group. In addition, variables including gender, age, EIPL/non-EIPL, tumor size, type of Surgery, tumor location, Borrmann classification, differentiated grade, T stage, N stage, and vascular invasion were enrolled into the univariate analysis using the Cox proportional hazards model to determine the factors influencing the gastric patient's OS. Subsequently, risk factors screened by univariate analysis ($P < 0.05$) were enrolled into the multivariate analysis using the Cox proportional hazards model to determine the independent risk factors influencing the gastric patient's OS. The whole data explanation got carried out by applying the SPSS app (17.0 version).

RESULTS

Baseline characteristics

The baseline characteristics analysis of the 150 patients was shown in Table 1, 109 (72.67%) were men, and 41 (27.33%) were women. The median age was 67 years (range, 35-80 years). The basic information in the EIPL group and the non-EIPL group had no

significant difference. The median follow-up time was 30 mo (range 0-45 mo). The 1- and 3-year OS rates were 71.0% and 26.5%, respectively.

Surgical outcome after gastrectomy

Table 2 presented the results of surgery, there was no significant difference in time (surgery to first flatus), postoperative hospital stays, abdominal pain, bleeding, leakage, or another blood index between the two groups ($P > 0.05$), but the symptoms of ileus and abdominal abscess appeared more frequently in the non-EIPL group ($P < 0.05$).

Overall survival of patients

Risk factors of overall survival are shown in Table 3. The result showed that the EIPL, Borrmann classification, tumor size, N stage, T stage, and vascular invasion were significant indicators. Then multivariate analysis revealed that EIPL, tumor size, vascular invasion, N stage, and T stage were independent prognostic factors (Table 4). The survival curve (Figure 1) revealed that the prognosis of the EIPL group was better than the non-EIPL group ($P < 0.001$), the 3-year survival rate of the EIPL group (38.4%) was higher than the non-EIPL group (21.7%).

RFS of patients

The risk factor of RFS included EIPL, N stage, vascular invasion, type of surgery, tumor location, Borrmann classification, and tumor size (Supplementary Table 1). EIPL and tumor size were independent risk factors (Supplementary Table 2). The RFS curve of the EIPL group was better than the non-EIPL group ($P = 0.004$) (Figure 2), and the recurrence rate of the EIPL group (24.7%) was lower than the non-EIPL group (46.4%).

Patterns of recurrence

The recurrence rate of lymph node, node, and other organs in the EIPL group and the non-EIPL group have no significant difference ($P > 0.05$), but the overall recurrence rate

and peritoneum recurrence rate in the EIPL group was lower than the non-EIPL group ($P < 0.05$) (Supplementary Table 3).

DISCUSSION

Positive peritoneal lavage cytology and peritoneal recurrence are associated with the prognosis of GC^[13,14]. Previous research has reported that EIPL combined with intraperitoneal treatment is an effective treatment for GC patients^[9], which can reduce the recurrence rate of advanced patients. However, the safety and effect of EIPL alone remain unclear, so this study explores the clinical value of EIPL.

Our results indicated that the overall survival curve and RFS curve of the EIPL group were better than the non-EIPL group, and the technique of EIPL was a significant factor in OS and RFS in advanced GC patients. So EIPL may reduce the recurrence rate of the tumor and improve the outcome for patients. Yamamoto *et al*^[6] also conducted an randomised controlled trial (RCT) of EIPL with pancreatic cancer patients and got the same conclusion. Based on these researches, the technique of EIPL needs to be applied to abdominal cancers.

The intraoperative bleeding and surgery can lead to the residual tumor cell in the abdominal cavities, which may increase the risk of peritoneal metastasis. In our study, Intraoperative blood loss between two groups have no significant difference. In the non-EIPL group, intraperitoneal lavage does not exceed 3 L of saline, which may be difficult to remove free peritoneal cancer cells. The technique of EIPL can remove free cancer cells and blood in the abdominal cavity by plenty of washing (10 L or more of saline), which can prevent free cancer cells from attaching to the peritoneum^[15].

In recent years, several reports^[15-17] have shown that inflammation was linked to poor survival. Inflammation can stimulate the proliferation of malignant tumors cells, promote metastasis and destroy adaptive immunity response^[16]. In this study, we found that the preoperative inflammatory index of NLR in the non-EIPL group was lower than in the EIPL group. However, the level of postoperative NLR in the non-EIPL group was higher than in the EIPL group. As for the patients with a high level of NLR, the anti-

tumor immune response of T cells and natural killer cells in the system may be surrounded by several neutrophils, which may decrease the opportunity to contact with tumor cells^[17,18], so the free peritoneal cancer cells may survive in this course.

This study concluded that the symptoms of ileus appeared more in the non-EIPL group than in the EIPL group. Besides, EIPL can also reduce the possibility of abdominal abscess, but the complications of bleeding and leakage have no significant difference. Indeed, EIPL is similar to the so-called limiting dilution method^[19], this technique can clean up the peritoneal effusion and reduce the risk of infection. The 10 times of regular warm saline can promote intestinal motility and functional recovery, and this may also be helpful for surgeons to find the bleeding place.

All patients received laparotomy, which reducing the influence of difference of surgical methods. Besides, after clinical pre-operative evaluation, patient's pre-operative nutritional status was good and has no obviously difference. As for the factors of type of surgery, when the proximal resection margin ranged from 3 to 5 cm, there was no significant difference between distal gastrectomy and total gastrectomy for the 5-year OS of GC patients^[20], so our study concluded that EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess, so the technique of EIPL may be beneficial for perioperative complications and make patients more comfortable after the operation, and this conclusion was consistent with previous study^[21].

Although EIPL could not reduce the recurrence rate of lymph nodes, nodes, and other organs, the overall recurrence rate and peritoneum recurrence rate in the EIPL group were lower than in the non-EIPL group, besides, the overall survival curve and RFS curve are better in the EIPL group. Currently, only three RCTs are ongoing to explore the long-term efficacy of EIPL in advanced GC. Kuramoto *et al*^[9] concluded that the peritoneal recurrence rate of the EIPL group was significantly lower than that of the non-EIPL (6.7% vs 45.8%, $P = 0.013$), there is no difference in recurrence rate for liver transfer, lymph node, and other organ transfer cases between the two groups, which is similar to our study. Among 88 patients who have positive cytology, EIPL-intraperitoneal chemotherapy

(IPC) greatly improves the 5-year survival of patients (44%),⁶ compared with 0% in patients with surgery alone. The prognosis of patients is poorer than in our study because the recruited patients of their study have positive cytology. Another advantage is that IPC is not taken in our study, it may remove side effects associated with chemotherapy and confound the effect of EIPL. Misawa *et al*^[22] conducted an RCT indicating that peritoneal RFS was not significantly different¹ between the EIPL group and the non-EIPL group.³ The 3-year overall survival rate and RFS rate were better than our study, and the reason is that the proportion of T4 (49.5%) and N3 (28.1%) is smaller than our study population (T4: 96.0%, N3: 34.7%). The value of EIPL may be related to the stage of T status and N status. The patients of our study (more cases of T4 and N3) have a higher risk of recurrence, and the reduction of recurrence rate is significant in the EIPL group.⁶ One RCT is still ongoing based in Singapore^[23], eligible patients having cT3 or cT4 with M0 disease are also in their criteria, but our study collected more clinical information and explored the safety and efficacy of the EIPL group. Our study showed that the technique of EIPL can reduce the perioperative complications of patients.

Our study has several limitations. First, we analyze only advanced GC patients, they may not on behalf of all patients. Second, more cases need to verify our results.

CONCLUSION

In conclusion, EIPL can reduce the possibility of perioperative complications including ileus and abdominal abscess. Besides, the overall survival curve and RFS curve are better in the EIPL group. This technique is easy and not expensive. Therefore, EIPL can benefit advanced GC patients a lot and would be a promising therapeutic strategy in the future.

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