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Clinical effectiveness of fluorouracil and cisplatin intraperitoneal perfusion combined with intravenous chemotherapy for peritoneal metastasis in gastric cancer

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Abstract. – OBJECTIVE: Gastric cancer (GC) is one of the most common malignancies worldwide, often accompanied by peritoneal metastasis. This work aimed to investigate the clinical efficacy of intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy for the treatment of peritoneal metastasis in GC.

PATIENTS AND METHODS: A total of 286 patients with primary GC admitted to the hospital from March 2017 to December 2020 were recruited in the study. A 1:1 matched case-control study was conducted, with the normal control (NC) group and experimental (E) group being composed of patients who underwent the corresponding treatment for primary GC with surgery within 2 months and the same pathological tumor-node-metastasis (pTNM) stage. The NC group consisted of 143 patients receiving only intravenous chemotherapy, while the E group consisted of 143 patients receiving intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy. Baseline characteristics, clinical efficacy, complications, peritoneal recurrence and metastasis, disease-free survival (DFS), and overall survival (OS) of the patients, as well as their quality of life (QoL) after chemotherapy, were compared between groups.

RESULTS: After six cycles of chemotherapy, DFS was observed in both groups (70% *vs.* 59%; 48% *vs.* 29.7%; $p<0.05$), so did OS (85.7% *vs.* 85.4%; 73.1% *vs.* 69.3%; $p>0.05$). The total effective rate of treatment in the E group (46.15%) was drastically superior to that in the NC group (27.97%), and the total recurrence and metastasis rate of the E group (23.08%) was markedly inferior to that of the NC group (83.9%) ($p<0.05$). The total incidence of adverse reactions in the E group (11.89%) was considerably inferior to that in the NC group (35.66%) ($p<0.05$). In addition, the E group had markedly superior scores for physical function (PF), emotional function (EF), role function (RF), social function (SF), and cognitive function (CF) than the NC group ($p<0.05$).

CONCLUSIONS: Intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy for the treatment of peritoneal metastasis in GC had certain benefits for patients and is worth applying in clinical practice.

Key Words:
Intraperitoneal perfusion chemotherapy, Intravenous chemotherapy, Gastric cancer, Peritoneum metastasis.

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide. According to researchers' statistics, in 2020, GC accounted for 5.6% of the new cases globally[1]. In 2022, there were 500,000 new cases of GC in China (10.6%), making it the third most common cancer that year. The number of deaths due to GC was as high as 400,000 cases, accounting for 12.5% of cancer deaths in China and ranking third among cancer deaths[2]. In the literature it was noted that from 1990 to 2019, the incidence of GC in male patients showed a monotonic upward trend, with a larger increase, while the increase was relatively

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gentle in female patients. Middle-aged and elderly patients were greatly more common among GC patients, with the highest local migration value observed in the population aged 80 years and older. Although China has already promoted the improvement of dietary habits and encouraged regular gastric endoscopy for GC prevention and treatment, the incidence of new cases of GC in China demonstrated a declining trend from 1990 to 2019. Nevertheless, with the aging of the population, the overall mortality rate of GC is on the rise[3]. Postoperative peritoneal metastasis of GC is a common recurrent and metastatic lesion second only to liver metastasis. Hence, the prevention and treatment of postoperative recurrence and metastasis of GC remains a major challenge in China's cancer diseases.

Early detection and prevention of GC are particularly imperative, as the 5-year survival rate for patients who undergo surgical resection of the lesion in advanced-stage GC is only 15%, while the 5-year survival rate for early-stage GC following timely standardized treatment can approach 90%[4]. Nevertheless, early clinical manifestations of GC are almost asymptomatic or mild, and most confirmed patients have already reached the middle and late stages of the disease. Hence, early detection of GC is extremely imperative and is the key to whether patients can survive for a long time. From the primary tumor's site of growth, malignant gastrointestinal neoplastic cells have the potential to detach and disseminate within the peritoneal cavity, giving rise to metastatic foci. Peritoneal dissemination of cancer cells stands as a preeminent cause behind postoperative cancer metastasis in GC patients, accounting for more than half of postoperative cancer recurrence cases and representing a pivotal avenue for intraperitoneal metastasis in GC[5]. Surgical resection remains the primary therapy for GC; however, it only provides localized control over cancerous lesions, leaving behind dislodged, implanted, and disseminated cancer cells that cannot be eradicated[7,8]. The clinical occurrence of cancer cell implantation, detachment, and dissemination is a prevalent phenomenon, thereby significantly predisposing to intraperitoneal metastasis in GC.

Although surgical treatment is the mainstay for treating GC, most patients still face challenges of local cancer recurrence or metastasis[9]. After surgery, patients with GC may develop metastases in the peritoneum[10], liver[11], or other areas. Systemic chemotherapy is currently the main adjuvant treatment for GC after surgery, which can effectively prevent and treat recurrence and metastasis of GC and improve patients' survival rates[12]. In addition, intraperitoneal perfusion chemotherapy (IPC) is a selective treatment modality that directly injects heated chemotherapy drugs into the peritoneal cavity. Relative to intravenous chemotherapy, IPC has a longer duration of action and higher drug concentration. Hence, it has unique advantages in treating residual micrometastases after GC surgery, preventing peritoneal recurrence, and liver metastasis. It has been proven to be a safe and effective treatment modality[13]. In clinical practice, the application of IPC for the treatment of patients with metastatic colorectal, ovarian, or GC has revealed its favorable efficacy in addressing peritoneal mesothelioma, peritoneal metastasis, and pseudomyxoma peritonei conditions[14]. IPC is a methodology for treating malignant tumors in the peritoneum, which involves directly injecting chemotherapy drugs into the peritoneal cavit[15]. It has a long duration of action and strong cancer cell-killing efficacy. Through selective location and absorption by capillaries and lymphatics, the effective drug concentration can persist in the portal vein and liver for a long time, effectively preventing liver metastases of cancerous lesions. Moreover, the anticancer drugs injected by IPC can be metabolized by the liver, thereby reducing systemic toxicity in patients. Studies involving the application of IPC for patients with peritoneal metastasis from colorectal cancer have shown that it can enhance both overall survival and disease-free survival without an increase in postoperative complications[16]. However, for elderly patients, the utilization of IPC might result in more severe complications[17]. Research employing cisplatin and paclitaxel as adjuvant intravenous chemotherapy has demonstrated that patients undergoing HIPEC exhibit improved surgical outcomes and clinical prognostic capabilities compared to those not receiving HIPEC. Furthermore, controlled studies[18] involving patients with recurrent ovarian cancer indicate that individuals subjected to HIPEC experience significantly extended disease-free survival and overall survival when contrasted with their non-HIPEC counterparts.

Fluorouracil and cisplatin are commonly adopted anti-cancer drugs in IPC, but improving the water solubility, reducing the dose of use, and enhancing their accumulation in tumor cells are the key to solving the problem. In recent years, the adoption of nanotechnology[19] in the medical field has become a hot research topic. Nanoparticles can play a specific drug-loading and releasing

function in the body through surface modification and drug packaging, thereby improving the therapeutic effect. Peritoneal metastasis of GC poses a great challenge to patient treatment, and IPC is considered to be an effective therapy approach. Fluorouracil and cisplatin combined with intraperitoneal and intravenous chemotherapy have become the standard treatment for peritoneal metastasis of GC. Nevertheless, this treatment still has some deficiencies, such as drug toxicity and resistance. Hence, by specifically packaging and modifying the drugs through nanotechnology, their targeting and efficacy can be improved, while reducing toxicity and side effects.

Postoperative adjuvant IPC has been increasingly emphasized in clinical practice for GC. Yu et al[20] conducted a study on 40 patients with GC peritoneal metastasis, randomly rolled them into an experimental group (treated with intraperitoneal hyperthermic chemotherapy combined with intravenous chemotherapy) and an NC group (treated with systemic intravenous chemotherapy). They found that this approach effectively improved patients' physical symptoms and increased their disease-free survival (DFS) rate. Our retrospective analysis aimed to demonstrate the clinical efficacy of intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy in the treatment of GC with peritoneal metastasis, providing effective reference for clinical treatment.

Patients and Methods

Study Samples

A retrospective sample of 286 patients with primary GC admitted to Cangshan Hospital from March 2017 to December 2020 was used. Sampling was conducted using the method of a random number table. A 1:1 matched case-control study design was employed, with the normal control (NC) group comprising 143 patients who received simple intravenous chemotherapy and the experimental (E) group comprising 143 patients receiving fluorouracil and cisplatin intraperitoneal perfusion combined with intravenous chemotherapy. Both groups underwent surgery within 2 months and had the same pathological tumor-node-metastasis (pTNM) staging.

Inclusion criteria: patients who were diagnosed with GC and met the diagnostic criteria of abdominal metastasis, no chemotherapy contraindications, completion of the prescribed chemotherapy regimen (6 cycles), use of the chemotherapy drugs 5-fluorouracil (5-Fu), calcium folinate (CF), and oxaliplatin (L-OHP); absence of a prior history of radiation or chemotherapy, comprehensive patient cases, and signed chemotherapy consent forms.

Exclusion criteria: patients with functional organ impairment such as heart or liver dysfunction, intestinal obstruction, and concurrent malignancy.

This study had obtained approval from the institutional ethics committee, and informed consent had been obtained from all enrolled patients.

Treatment Methodologies

All patients underwent adjuvant therapy within 3-4 weeks based on their response status after lesion resection surgery.

For the NC group, the regimen consisted of an intravenous infusion of oxaliplatin at 130 mg/m^2 over 4 hours on day 1, an intravenous infusion of calcium folinate at 200 mg/m^2 over 2 hours on days 1-5, and an intravenous infusion of 5-Fu at 500 mg/m^2 over 5 hours on days 1-5, with a cycle of 21 days for a total of 6 cycles.

The treatment plan for the E group was the same as that for the NC group. For IPC, one week before systemic intravenous chemotherapy, the puncture methodology was adopted to penetrate the abdominal cavity, and a transfusion tube was connected to the patient. First, 300 mL of normal saline was infused to ensure that the puncture needle was correctly placed in the abdominal cavity and the fluid path was unobstructed. Then, 2,000 mL of warm normal saline with cis-diammineplatinum dichloride (DDP) (35 mg/m^2) and 5-Fu (1,500 mg/m^2) dissolved in it was infused at a rate of 40 mL/min. Finally, the infusion tube was rinsed with normal saline before the needle was removed. Patients were instructed to rest in bed for 4 hours and to turn over every 20 minutes, which could ensure the even distribution of the chemotherapy drugs in the abdominal cavity. Ondansetron (8 mg) was administered to prevent drug-induced nausea and vomiting, and it was given intravenously for 3 days. Patients with obvious abdominal distension were given furosemide (20 mg) by intravenous injection. One cycle consisted of one intravenous plus IPC treatment. The efficacy and adverse reactions were evaluated after 2-3 cycles, and patients who responded effectively underwent an additional 3 cycles of chemotherapy.

The Fluorouracil dosage calculation equation was as follows:

(1)

$D = AUC \times CL \times (BSA + 0.25)$

D represents dosage, *AUC* represents the area under the curve, *CL* represents clearance rate, and *BSA* represents body surface area.

Cisplatin dosage calculation equation was as follows:

(2)

$D = AUC \times (GFR + 25)$

GFR represents glomerular filtration rate.

The GFR calculation equation was as follows:

(3)

$GFR = (140-A) \times W \times K / Cscr \times 72$

A represents age, *W* represents weight, *K* represents gender coefficient (1 for male and 0.85 for female for GFR), and C_{scr} represents serum creatinine concentration.

The fluorouracil blood concentration calculation equation was as follows:

(4)

$Cp = D / Vd$

C_p represents plasma concentration, and V_d represents distribution volume.

The cisplatin blood concentration calculation equation was the same as equation (4).

(5)

$DFS = |T1 - T2|$

DFS represents DFS time, T_1 represents the time when the tumor occurred, and T_2 represents the time of recurrence.

(6)

$OS = |T1 - T3|$

Overall survival (*OS*) represents OS time, and T_3 represents the time of death.

(7)

$S(t) = [N'(t) / N(t)] * k$

S(*t*) represents the probability of survival at time *t* for individuals who were alive at time 0, *N*'(*t*) represents the number of surviving cases at time *t*, *N*(*t*) represents the total number of cases followed up for *t* years, and *k* represents relative risk (RR).

(8)

$\eta = (CR + PR) / n * 100\%$

η represents total effective rate, *CR* represents complete response, *PR* represents partial response, and *n* represents the total number of cases.

(9)

$R = (n/143) \times 100\%$

R represents recurrence and metastasis rate, and *n* represents the number of cases with recurrence and metastasis in the group.

(10)

$ARR = (n/143) \times 100\%$

ARR represents adverse reaction rate, and *n* represents the number of cases with adverse reactions in the group.

Observation Indices

By observing the occurrence of postoperative complications in two groups of patients, including blood system symptoms (such as thrombocytopenia and leukopenia), digestive system symptoms (such as diarrhea and abdominal pain), and other symptoms (such as fatigue and hair loss), all patients were assessed for survival, clinical efficacy, and adverse reactions, and the relevant data were statistically analyzed. The survival rate of the two groups of patients was compared during a 2-year follow-up period. The statistical data on the clinical efficacy and lesion recurrence and metastasis of the different treatment methodologies after surgery were compared between groups. The QoL Questionnaire-Core 30 (QLQ-C30) was employed to evaluate the QoL level of the two groups of patients, including physical function (PF), emotional function (EF), role function (RF), social function (SF), and cognitive function (CF), with a score of up to 100 points, and a higher score indicating a better QoL.

Statistical Analysis

Using SPSS 22.0 (IBM Corp., Armonk, NY, USA), mean ± standard deviation was how measurement data were denoted, which were compared using *t*-tests. The count data were recorded as percentages (%) and compared using Chi-square tests. The significance level was set at 0.05.

Results

Comparison of General Clinical Data

In this work, 286 patients with primary GC who met the inclusion criteria were selected from March 2017 to December 2020. The NC group included 143 patients, with 83 males and 60 females, and a mean age of (51.37±2.48) years. The E group included 143 patients, with 83 males and 60 females, and a mean age of (50.28±2.16) years. The baseline characteristics differed inconsiderably between groups ($p>0.05$) (Figures 1 and 2).

A comparison of tumor staging between groups is presented in Figure 3. In the NC group, there were 16 cases, 10 cases, 4 cases, 6 cases, 43 cases, and 64 cases of patients with pTNM pathological staging IB, IIA, IIB, IIIA, IIIB, and IIIC,

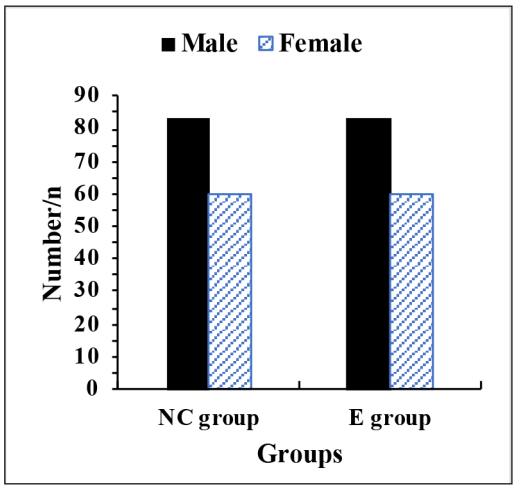

Figure 1. Gender comparison between groups.

respectively. In the E group, there were 16 cases, 10 cases, 4 cases, 6 cases, 43 cases, and 64 cases of patients with pTNM pathological staging IB, IIA, IIB, IIIA, IIIB, and IIIC, respectively, and there was a neglectable difference (p>0.05).

A comparison of the primary tumor stage between groups is presented in Figure 4. In the NC group, there were 20, 6, 1, 114, and 2 patients with primary tumors of T1, T2, T3, T4a, and T4b, respectively. In the E group, there were 20, 6, 1, 112, and 4 patients with primary tumors of T1, T2, T3, T4a, and T4b, respectively. The difference was inconsiderable (p>0.05).

A comparison of the number of regional lymph nodes between groups is presented in Figure 5. In the NC group, there were 6 cases of N0, 24 cases of N1, 45 cases of N2, and 68 cases of N3. In the E group, there were 6 cases of N0, 24 cases of N1, 43 cases of N2, and 70 cases of N3. The regional lymph node involvement demonstrated slight differences (p>0.05).

The comparison of tumor location between groups is presented in Figure 6. In the NC group, there were 100 patients with tumors located in the gastric antrum, 29 patients with tumors located in the gastric body, 7 patients with tumors located in the gastric fundus, and 7 patients with tumors located in the cardia. In the E group, there were 112 patients with tumors located in the gastric antrum, 29 patients with tumors located in the gastric body, 1 patient with a tumor located in the gastric fundus, and 1 patient with a tumor located in the cardia. There were inconsiderable differences (p>0.05).

A comparison of tumor types between groups is presented in Figure 7. There were 26 cases of early GC in each group. In the NC group, there were 2 cases of protrude type (PT), 14 cases of flat type (FT), and 10 cases of depressed type (DT). In the E group, there were 2 cases of protrude type, 6 cases of flat type, and 18 cases of depressed type. There were 117 cases of advanced GC in each group. In the NC group, there were no cases of protrude type (PT), 95 cases of localized ulcerative type (LUT), 22 cases of ulcer infiltrating type (UIT), and no cases of diffuse ulcerative type (DUT). In the E group, there were no cases of PT, 89 cases of LUT, 28 cases of UIT, and no cases of DUT. The two groups demonstrated slight differences (p>0.05).

The histological types of lesions in the two groups of patients were compared (Figure 8). In the NC group, there were 135 cases of adenocarcinoma (AC), 4 cases of undifferentiated carcinoma (UC), and 4 cases of neurosecretory carcinoma (NC). In the E group, there were 138 cases of AC, 4 cases of UC, and 1 case of NC. The difference was found to be neglectable (p>0.05).

The degree of cancer cell differentiation in the two groups of patients was compared (Figure 9). In the NC group, there were 30 cases of high differentiation (HD), 31 cases of moderate differentiation (MD), 61 cases of poor differentiation (PD), 20 cases of undifferentiation (Und.), and 1 case not evaluated. In the E group, there were 21 cases of HD, 42 cases of MD, 59 cases of PD, 20 cases of Und, and 1 case not evaluated. The difference was found to be inconsiderable (p>0.05).

The gastric resection surgical approaches of the two groups of patients were compared (Figure

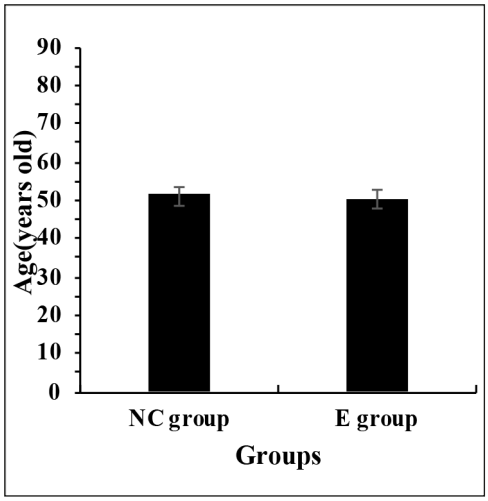

Figure 2. Comparison of age between groups.

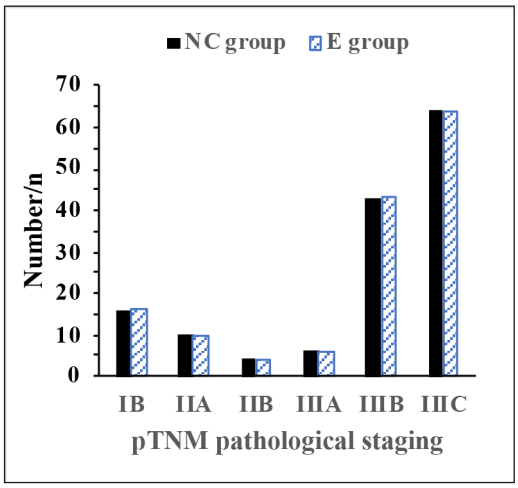

Figure 3. Comparison of pathological stages of pTNM between two groups.

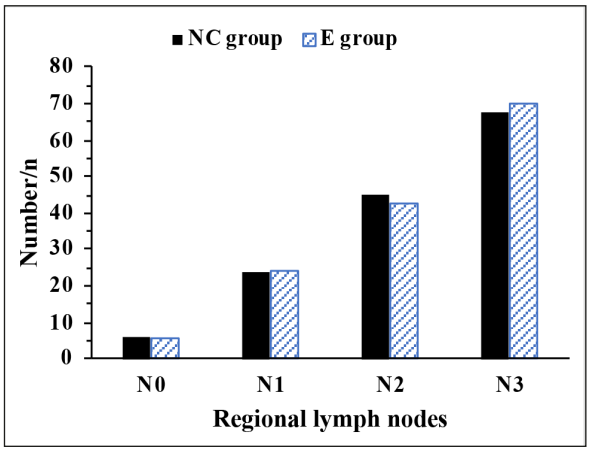

Figure 5. Comparison of the number of regional lymph nodes between groups.

10). In the NC group, there were 4 patients who underwent laparoscopy-assisted partial gastrectomy (LAPG), 86 patients who underwent laparoscopy-assisted distal gastrectomy (LADG), and 53 patients who underwent laparoscopy-assisted total gastrectomy (LATG). In the E group, there were 1 patient who underwent LAPG, 90 patients who underwent LADG, and 49 patients who underwent LATG. The difference was not considerable (p>0.05).

The lymph node dissection methods in the two groups of patients were compared (Figure 11). In the NC group, 36 cases used D1 lymph node dissection, and 107 cases used D2 or above. In the E group, 36 cases used D1 lymph node dissection, and 107 cases used D2 or above, demonstrating slight differences (p>0.05).

The intravenous chemotherapy regimens in the two groups of patients were compared (Figure 12). In the NC group, there were 90 cases using FOLFOX4, and 53 cases using mFOLFOX6. In the E group, there were 104 cases using FOLFOX4, and 39 cases using mFOLFOX6. The difference was not significant (p>0.05).

The statistical data showed that the tumor size was 21.35±6.27 in the NC group, with 27.34±4.13 malignant lymph nodes (MLNs) and 8.45±1.67 positive lymph nodes (PN). In the E group, the tumor size was 19.26±5.23, with 27.58±3.62 MLNs and 8.93±1.25 positive lymph nodes. The difference was inconsiderable (p>0.05) (Figure 13).

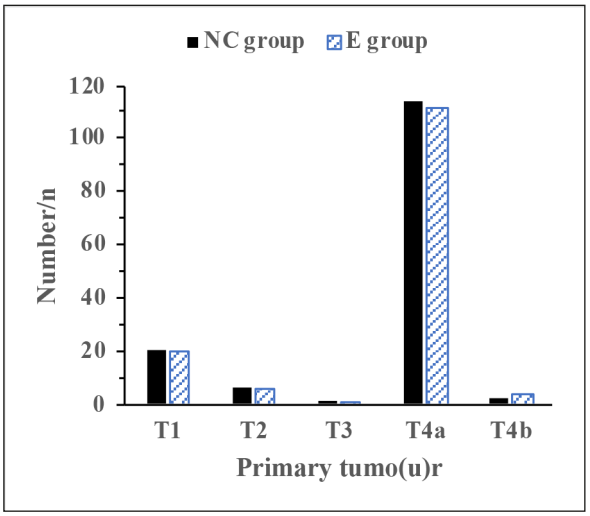

Figure 4. Comparison of primary tumor period between groups.

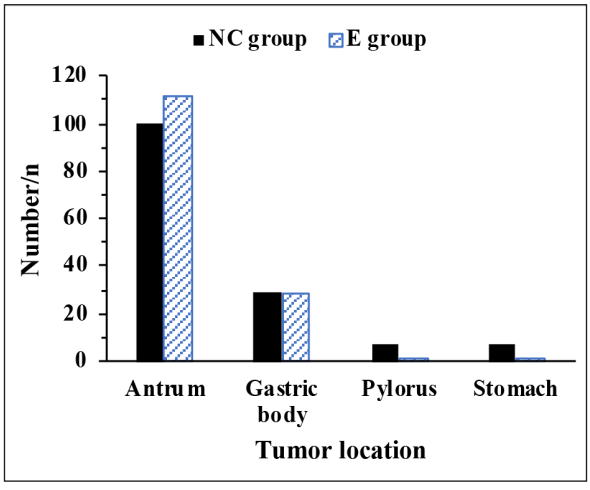

Figure 6. Comparison of the number of tumor sites in patients.

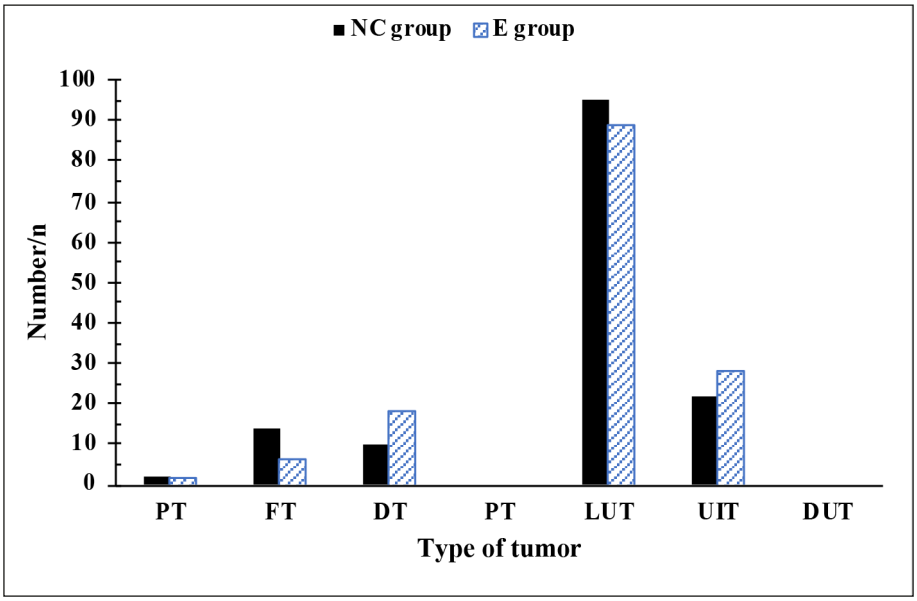

Figure 7. Comparison of tumor types between two groups.

Comparison of Complications

The incidence of postoperative complications such as infection, bleeding, fever, delayed wound healing, and anastomotic leakage was compared between groups. The overall incidence of post-chemotherapy complications in the E group (20%) was similar to that in the NC group (24%), demonstrating a slight difference ($p>0.05$) (Figure 14).

Disease-Free Survival and OS Rate

The follow-up rate of all patients was 90.2% (129/143), and the follow-up rate was 9.7% (14/143), with 8 lost to follow-up cases in the NC group and 6 in the E group. The DFS after treatment was compared between groups, with the average DFS in the E group being 2 years and the average DFS in the NC group being 18 months, showing a marked difference after a test ($p<0.05$) (Figure 15). The OS after treatment was compared between groups, with the average OS in the E group and NC group both being 41 months ($p>0.05$) (Figure 16). The patients in both groups were followed up for 1 year and 2 years, and the statistical analysis showed that the E group had DFS rates of 70.0% and 48.5%, respectively, while the NC group had DFS rates of 59.0% and 29.7%, respectively. The OS rates of the E group were 85.7% and 73.1%, respectively, while the OS rates of the NC group were 85.4% and 69.3%, respectively.

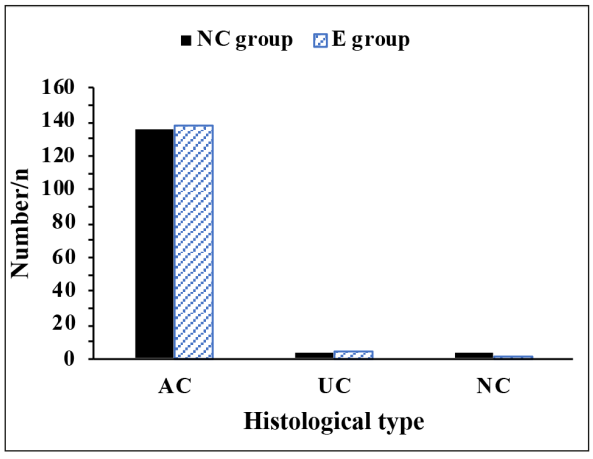

Figure 8. Comparison of histological types of lesions between two groups.

Clinical Efficacy

The study results revealed that the total effective rate of the combined treatment in the 143 patients of the E group was markedly higher (46.15%) than that of the NC group (27.97%) ($p<0.05$) (Figure 17).

Recurrence and Metastasis

Comparison of cancer recurrence and metastasis after chemotherapy in the two groups of patients revealed that E group had drastically inferior total recurrence and metastasis rate (23.08%) [intra-abdominal lymph node metastasis (24 cases), peritoneal implantation metastasis (16 cases), ovarian metastasis (1 case), hepatic metastases (1

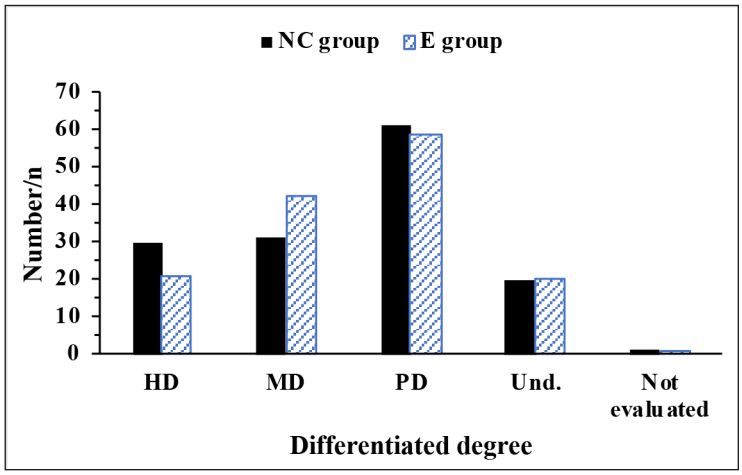

Figure 9. Comparison of differentiation degree of cancer cells between two groups.

case), lung, bone and other sites of metastasis (2 cases), and local recurrence (5 cases)] than NC group (83.9%) ($p<0.05$) (Figure 18).

Adverse Reactions

After receiving treatment, both groups of patients had varying degrees of adverse reactions, including leukopenia (LO), leukopenia decrease (LD), thrombocytopenia (TO), nausea and vomiting (NV), diarrhea, abnormal liver function (ALF), and abnormal renal function (ARF). The total incidence of adverse reactions in the E group (11.89%) was markedly inferior to the NC group (35.66%) ($p<0.05$) (Figure 19).

QoL Comparison

The results demonstrated that patients in the combined treatment group had greatly superior scores in PF, EF, RF, SF, and CF *vs.* NC group ($p<0.05$). These findings are further illustrated in Figure 20.

Discussion

In this study, a 1:1 matched case-control design was employed using a random number table method. A retrospective analysis was conducted to evaluate the clinical efficacy of combined in-

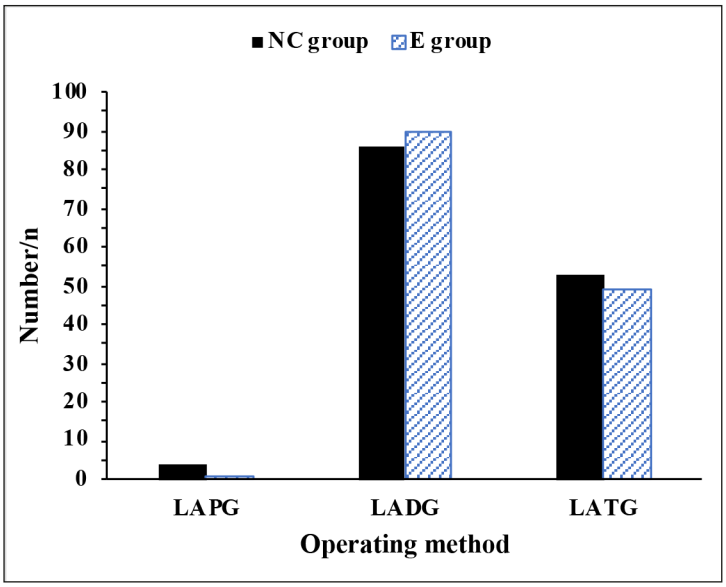

Figure 10. Comparison of surgical methodologies of gastrectomy between groups.

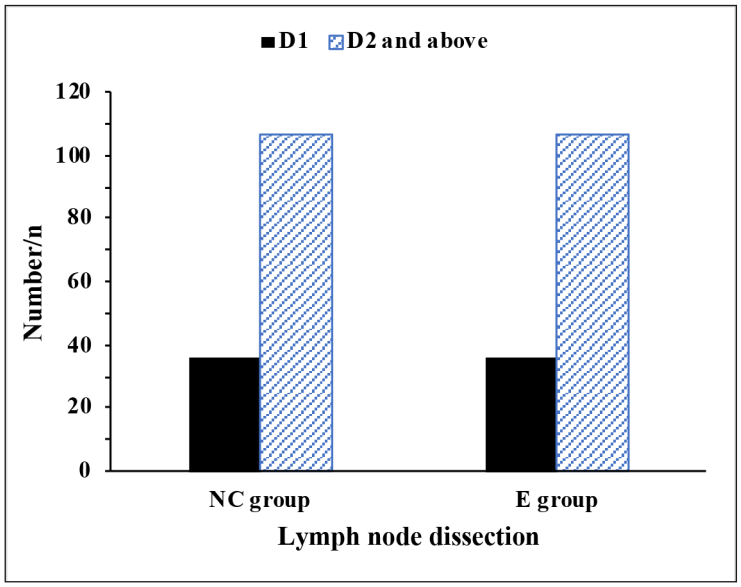

Figure 11. Comparison of lymph node dissection methods between groups.

traperitoneal fluorouracil and cisplatin perfusion with intravenous chemotherapy in treating peritoneal metastasis of GC. Compared with simple intravenous chemotherapy, the group receiving intraperitoneal perfusion of fluorouracil and cisplatin showed a drastic increase in DFS, a marked decrease in the incidence of peritoneal metastasis within 2 years of follow-up after surgery, and greatly milder adverse reactions. This methodology is worthy of widespread clinical adoption.

In recent years, prominent progress has been made in the treatment of peritoneal metastasis after gastrectomy, with the continuous development of medical technology and the improvement of therapeutic approaches. Researchers[21] have conducted extensive explorations in this field, from monotherapy with S-1 to various combination chemotherapy regimens and have continuously improved treatment outcomes. Although platinum-based and single-agent S-1 regimens have been established as standard adjuvant chemotherapy for gastrectomy in some countries, adjuvant chemotherapy after gastrectomy for GC has yet to be widely recognized worldwide. Intraperitoneal chemotherapy is a novel chemotherapy approach designed according to the anatomical principles of the peritoneal cavity, aiming to provide targeted adjuvant chemotherapy to address

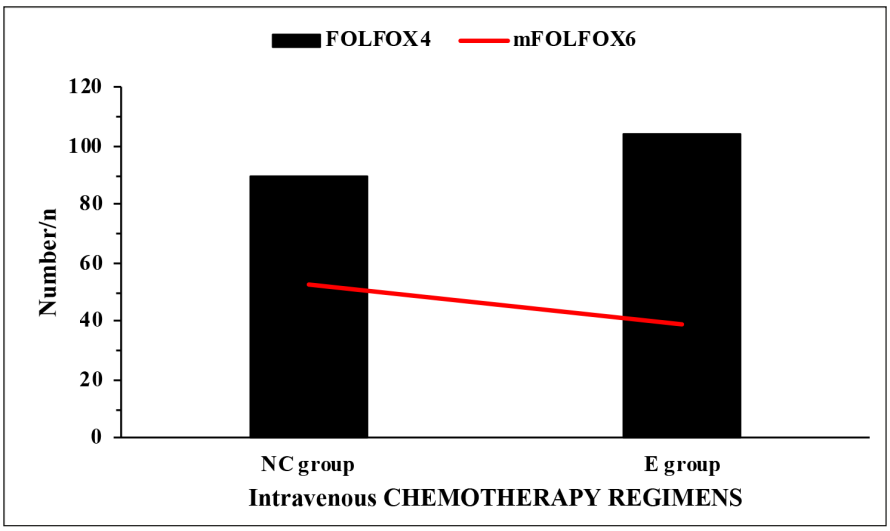

Figure 12. Comparison of intravenous chemotherapy schemes between groups.

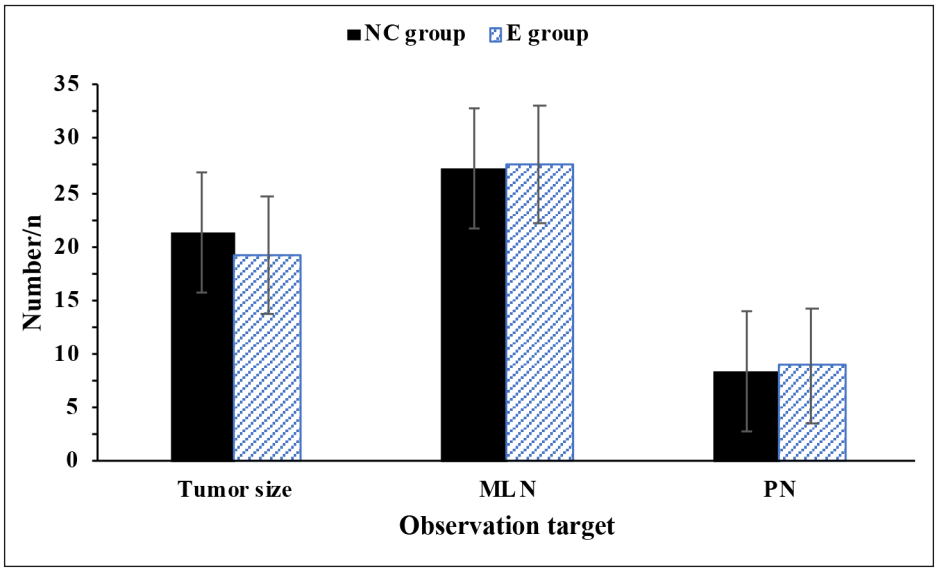

Figure 13. Comparison of tumor observation index between groups.

the common recurrence and metastasis of GC after surgery. The combination of IPC and systemic intravenous chemotherapy is a comprehensive treatment approach that treats abdominal malignant tumors from the inside out, whose feasibility has been confirmed in the study of Guchelaar et al[22]. Currently, literature on IPC combined with intravenous chemotherapy for the therapy of GC peritoneal metastasis is scarce. There is no unified conclusion on whether it can prolong the DFS and OS of patients, reduce toxic and side effects, and the safety of this method. In this retrospective study, the survival status after intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy, adverse reactions after chemotherapy, QoL, and postoperative peritoneal metastasis were mainly analyzed. This provides a reference for the clinical efficacy of IPC combined with systemic intravenous chemotherapy in the treatment of GC peritoneal metastasis.

There is currently no unified standard protocol for adjuvant chemotherapy after gastrectomy for GC. In the study by Sammartino et al[23], the combination of intraperitoneal hyperthermic per-

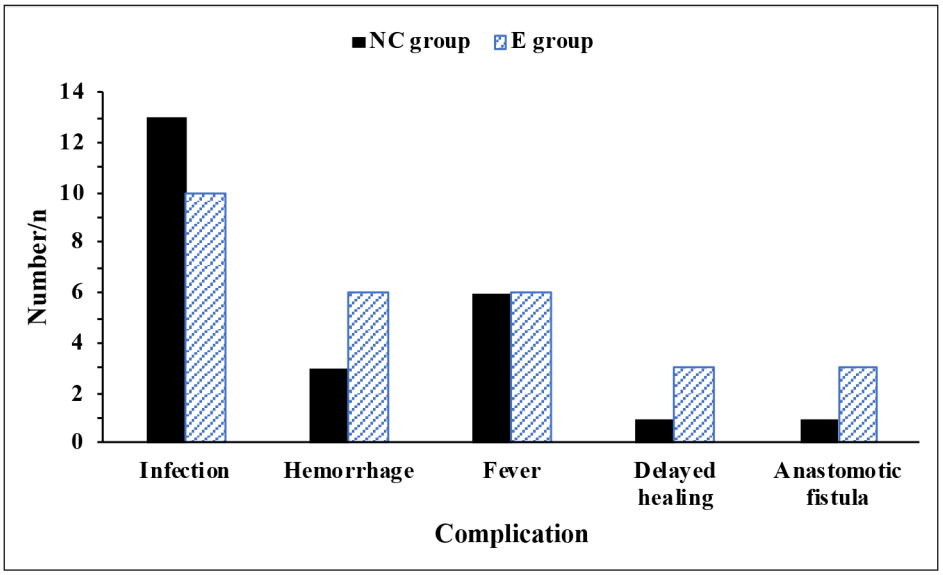

Figure 14. Comparison of complications after chemotherapy between groups.

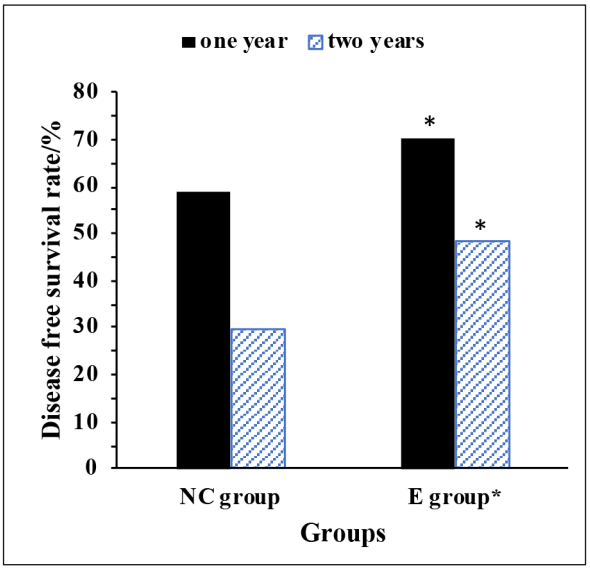

Figure 15. Comparison of 1-year and 2-year DFS between groups. * indicates $p<0.05$ *vs.* controls.

fusion chemotherapy with cisplatin and intravenous chemotherapy had a good effect in treating advanced GC, effectively relieving symptoms, and thus was applied in the adjuvant chemotherapy regimen after gastrectomy for GC. As early as 2000, a study[24] investigated the value of the 5-FU and cisplatin (FUP) regimen in the adjuvant treatment of GC after surgery. This work included 260 patients with TNM stage II-IV GC without distant metastasis, who were randomly rolled into a treatment group (postoperative adjuvant chemotherapy with 5-FU and cisplatin) and a control group (surgery alone). The study followed up for 97.8 months, and the 5-year and 7-year survival rates in the treatment group (46.6% and 44.6%, respectively) were greatly superior to those in the control group (41.9% and 34.9%, respectively). Furthermore, after multiple-factor analysis, it was found that adjuvant chemotherapy in the treatment group could reduce the recurrence rate and mortality. Some researchers[25] have proposed whether IPC can prevent peritoneal metastasis after GC surgery. Later, in a study by Lu and Zheng[26], a total of 837 patients were included (438 in the HIPEC group and 415 in the control group), with the HIPEC group showing a higher 1-year survival rate (1-os) and 2-year survival rate (2-os) than the control group. HIPEC can prolong the survival of patients with GC peritoneal metastasis without increasing the incidence of adverse reactions. Hence, in this work, intraperitoneal perfusion with 5-FU and cisplatin combined with intravenous chemotherapy was adopted to treat GC with peritoneal metastasis.

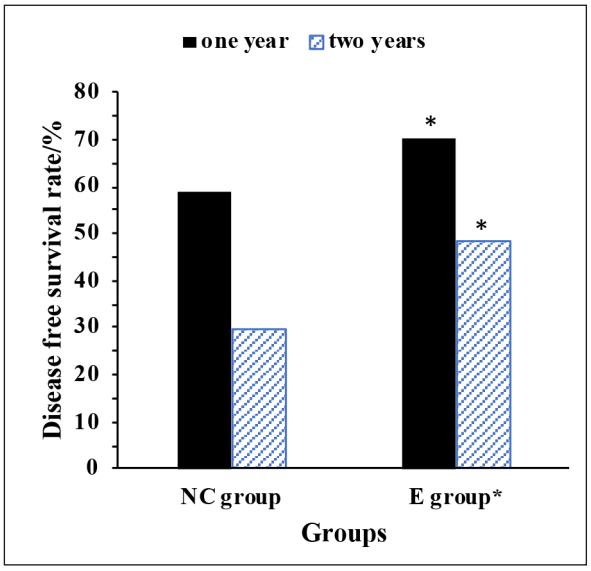

Figure 16. Comparison of OS rates between groups after 1-year and 2-year follow-up. * indicates $p<0.05$ *vs.* controls.

Currently, in clinical practice, a combination of docetaxel, cisplatin, and 5-fluorouracil is often utilized as an adjuvant chemotherapy regimen for GC after surgery. 5-fluorouracil primarily acts during the S phase of the cell cycle and has a short half-life, making it a cell cycle-specific drug. Studies[27,28] have shown that intravenous infusion of 5-fluorouracil can greatly improve the efficacy of treatment for colon cancer. Cisplatin is a commonly utilized potent anti-cancer drug. Nevertheless, cisplatin can easily bind to DNA, resulting in damage to the entire cell. It can also easily bind to molecules such as serum proteins, glutathione, and cysteine in the body, leading to adverse reactions such as nephrotoxicity, bone marrow toxicity, neurotoxicity, vomiting, hair loss, and deafness in patients. Nano-drug delivery systems can prolong the half-life of drugs in the body and continuously target the release of drugs, thereby reducing systemic toxicity. In addition, nano-drug delivery systems can produce a synergistic effect and overcome the body's resistance to single drugs. Hence, the solution to the toxicity and resistance of cisplatin is to use nanotechnology to deliver the drug into tumor cells[29]. Cisplatin can be wrapped in a nano-carrier and delivered directly into tumor cells through the EPR effect of nano-particles or targeting molecules on the drug surface. Then, the drug can be released in response to the tumor microenvironment using nanomaterials, thereby increasing efficacy, reduc-

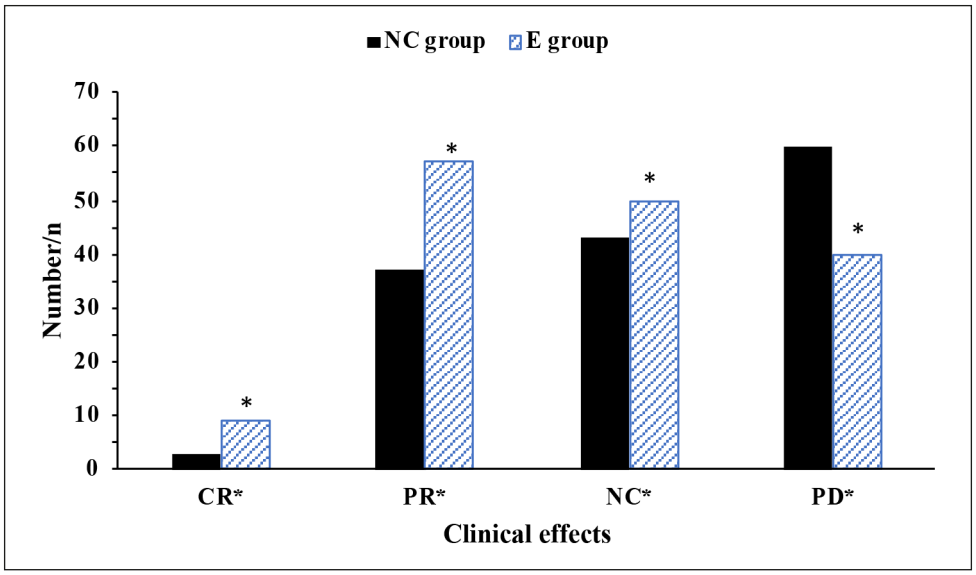

Figure 17. Comparison of clinical efficacy between groups after chemotherapy. *indicates $p<0.05$ *vs.* controls.

ing drug toxicity, and overcoming drug resistance. In addition, in the study by Hayata et al[30], the area under the concentration-time curve of cisplatin in the peritoneal fluid was five times greater with intraperitoneal administration than with intravenous administration. Since the systemic toxicity of cisplatin is time-dependent, the anti-tumor cell activity of cisplatin is positively correlated with the area under the drug concentration-time curve.

Currently, IPC and intravenous chemotherapy are mainly adopted as adjuvant therapies for GC surgery, aimed at preventing and treating peritoneal recurrence and metastasis of cancer lesions. Nevertheless, there is no conclusive evidence on the GC types that can be effectively treated using these approaches. In the study by Kang et al[31], the recurrence rate after GC surgery was as high as 50% to 70%, with peritoneal metastasis accounting for 34.9%. Once metastasis occurs, the probability of 5-year survival for patients is very low. Hence, fluorouracil and cisplatin were utilized for IPC, combined with intravenous chemotherapy in this work, and it was believed that patients with lymph node metastasis and peritoneal metasta-

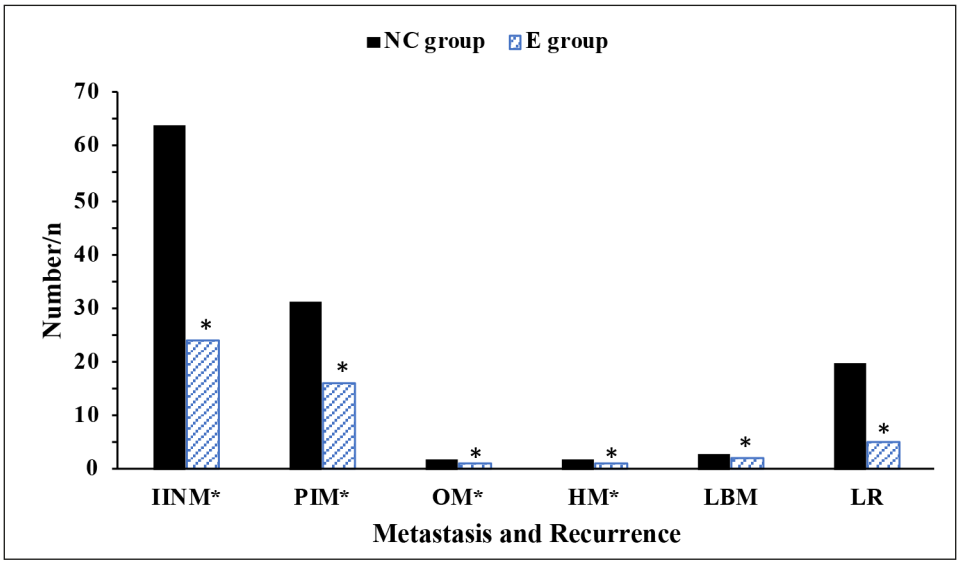

Figure 18. Comparison of recurrence and metastasis of cancer focus between two groups after chemotherapy. *indicates $p<0.05$ *vs.* controls.

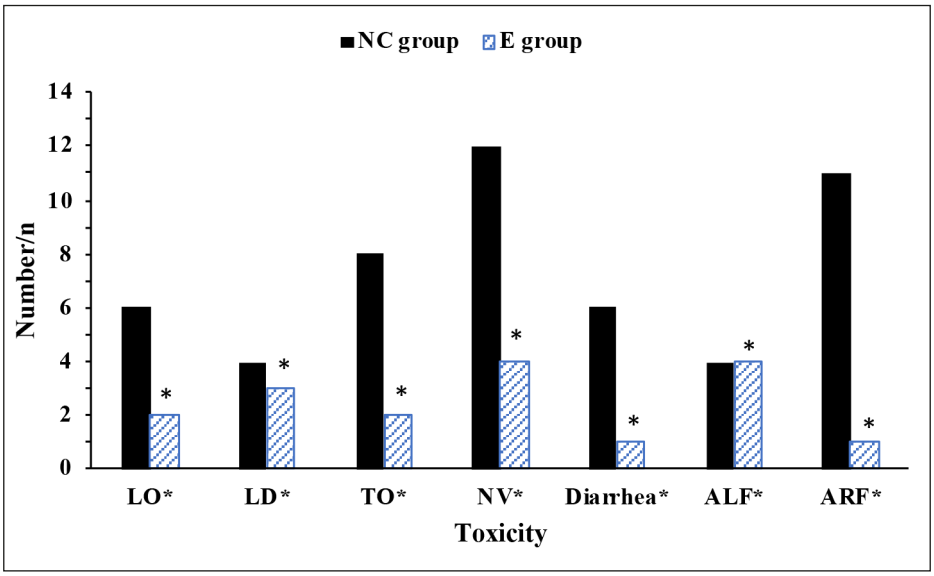

Figure 19. Comparison of adverse reactions between two groups after chemotherapy. *indicates $p<0.05$ *vs.* controls.

sis could potentially benefit from this combined treatment.

A total of 286 patients with primary GC were retrospectively analyzed in this work. The results showed that the average DFS after combined chemotherapy was 2 years, while the average DFS in the NC group was 18 months. The DFS in the E group was remarkably superior to that in the NC group, without a considerable difference in OS between groups, which was consistent with the results of a study by Cho et al[32] on the combination therapy of docetaxel and cisplatin in 39 AGC patients in phase II, which notably prolonged DFS. In the study conducted by Yu et al[33], patients receiving a comprehensive treatment regimen involving intraperitoneal hyperthermic perfusion (L-HIPEC), bidirectional intraperitoneal and systemic induction chemotherapy (BISIC), along with cytoreductive surgery combined with intraperitoneal hyperthermic perfusion (CRS-HIPEC), were compared to patients undergoing solely CRS-HIPEC treatment. The results demonstrated that patients receiving the comprehensive treatment regimen exhibited a significantly longer median survival (20 months) compared to those receiving only CRS-HIPEC treatment (8.6 months). Additionally, the comprehensive treatment regimen yielded a higher tumor clearance rate. In this work, there was also a difference in OS between the two groups, but it was inconsiderable, possibly due to insufficient follow-up time. To improve the radical resection rate of GC, IPC was adopted in this work to clear gastric tumor metastases outside the surgical field of view. Systemic intravenous chemotherapy can relieve the pain of GC patients, but for patients with peritoneal metastasis, its relief rate is low, possibly due to the duration of effective drug concentration maintenance and its toxic effects on cancer cells being affected[34]. After IPC combined with intravenous chemotherapy, anticancer drugs circulate in the patient's body and can be located and cleared from the peritoneal cavity, which can increase the clearance rate of anticancer drugs against tumor cells. Furthermore, the sub-mesothelial vasculature and interstitial tissue between the mesothelial cells in the blood-peritoneal barrier contain a rich extracellular matrix, which effectively prevents the penetration of anticancer drugs. Nevertheless, after intravenous chemotherapy, it is difficult to achieve the required drug concentration and duration for treating peritoneal metastasis. Intraperitoneal chemotherapy can deliver chemotherapy drugs directly to the peritoneal cavity through circulatory perfusion, maintaining a high concentration of chemotherapy drugs to clear tumor cells. This can solve the problem of insufficient drug concentration and duration to clear the lesions caused by systemic intravenous chemotherapy. Moreover, chemotherapy drugs metabolize more slowly in the peritoneal cavity, prolonging the duration of drug action and increasing their toxicity to tumor cells. In addition, the peritoneal administration of chemotherapy drugs undergoes hepatic metabolism, maintaining high levels of drug concentration in the liver, peritoneal cavi-

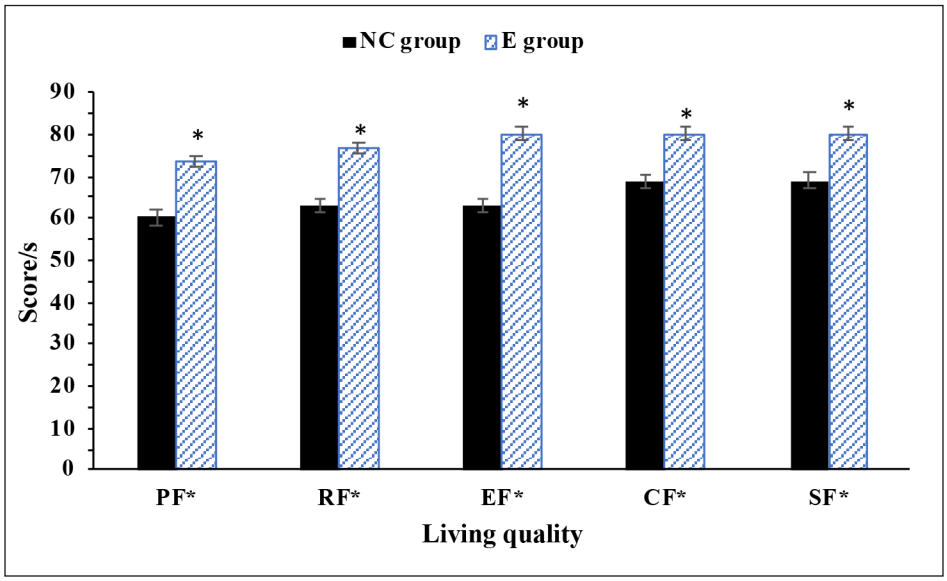

Figure 20. Comparison of QoL scores between groups after chemotherapy. *indicates $p<0.05$ *vs.* controls.

ty, and portal vein, while minimizing systemic circulation and reducing drug dosage. Hence, the adverse reactions of chemotherapy drugs are reduced, and the drug concentration in the liver is increased, which can effectively eliminate liver metastatic cancer cells. In addition, IPC can also effectively kill tumor cells. Normal human tissue cells can tolerate an environment of 47°C for 1 hour, while malignant tumor cells can only tolerate an environment of 43°C for 1 hour[35]. Intraperitoneal hyperthermic perfusion can improve the efficiency of chemotherapy drugs in clearing tumor cells and can more effectively remove deep tumor cells. The synergistic effect of intraperitoneal hyperthermic perfusion chemotherapy and systemic intravenous chemotherapy can effectively control postoperative peritoneal metastasis of GC, thereby treating patients' symptoms, and its clinical adoption is safe and reliable.

Conclusions

The combination of intraperitoneal perfusion of fluorouracil and cisplatin combined with intravenous chemotherapy is a safe and effective approach for treating postoperative peritoneal metastasis in GC. This treatment approach can improve therapeutic outcomes while reducing the incidence of adverse effects, providing a new option for clinical management.

Conflicts of Interest

All the authors declare that there is no conflict.

Ethics Approval

This study was conducted according to the Declaration of Helsinki guidelines, and all procedures involving research study participants were outlined in the study protocols approved by the Fengcheng People's Hospital and were conducted in agreement with the principles of Helsinki declarations and local ethical standards. Ethical Approval No. FC0124316.

Informed Consent

Patients of study participants provided written informed consent.

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Authors' Contributions

The authors confirm their contribution to the paper as follows: study conception and design: Xiqiong Li, Xinghui Xiong. Data collection: Qingchao Mao. Analysis and interpretation of results: Shiyao Chen. Draft manuscript preparation: Jinwu Yang. All authors reviewed the results and approved the final version of the manuscript.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

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