JBUON 2021; 26(1): 211-217
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of conversion surgery after neoadjuvant intraperitoneal-systemic chemotherapy in treating peritoneal metastasis of gastric cancer

Yan Li[1], Huanrong Lin[2], Kunsong Huang[3], Jiangning Zhao[2]

[1]Department of Peritoneal Cancer Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing, China. [2]Gastrointestinal Peritoneal Cancer Surgery, the Fourth Clinical Medical School of Guangzhou University of Chinese Medicine; Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, China. [3]Department of General Surgery, Guangzhou Overseas Chinese Hospital, the First Affiliated Hospital of Jinan University, Guangzhou, China.

Summary

Purpose: *To explore the effectiveness and safety of conversion surgery after neoadjuvant intraperitoneal-systemic chemotherapy (NIPS) in treating gastric cancer patients with peritoneal metastasis.*

Methods: *80 patients definitely diagnosed with peritoneal metastasis of gastric cancer treated in our hospital from March 2016 to September 2017 were evaluated. All the patients were randomly assigned into two groups and received oral administration of S-1 + intravenous and intraperitoneal chemotherapy with paclitaxel or oral administration of S-1 + intravenous chemotherapy with oxaliplatin, with 40 patients in each group. Following NIPS conversion therapy, the patients with indications for surgery underwent radical gastrectomy. The short-term efficacy of chemotherapy and incidence of chemotherapy-related adverse reactions were compared between the two groups. The surgical methods, intraoperative conditions (lymph node dissection and surgical margins) and postoperative complications were recorded in the two groups of patients, and the survival in the two groups was recorded via follow-up.*

Results: *The efficacy was evaluated for all the patients after 4 cycles of treatment. The median cycles of chemotherapy was 6.9 in NIPS group, with a response rate of 85.0% (34/40), while it was 6.4 cycles in control group, with a response rate of 70.0% (28/40). The overall response rate (ORR) after chemotherapy in NIPS group was notably higher than in control group (p=0.041). After chemotherapy, radical gastrectomy was performed in 40 patients with surgical indications, including 22 cases of R0 resection, 10 cases of R1 resection and 8 cases of R2 resection. Some patients developed postoperative complications, including 1 case of incision infection, 3 cases each of ileus and intra-abdominal hemorrhage, 2 cases each of peritonitis and pancreatic fistula, and 4 cases of anastomotic fistula. All the patients were followed up for 2-18 months, and the median follow-up time was 14.1 months in NIPS group and 13.3 months in control group. The median overall survival (mOS) was 13.4 months in NIPS group and 10.8 months in control group.*

Conclusion: *NIPS combined with radical gastrectomy has definite efficacy in treating gastric cancer patients with peritoneal metastasis and cause tolerable adverse reactions, and it can significantly raise the patient survival compared with systemic chemotherapy alone.*

Key words: *gastric cancer, peritoneal metastasis, conversion therapy, NIPS, surgery*

Introduction

Gastric cancer ranks fifth among all tumors worldwide for its incidence rate (approximately 5.7%), and third for its mortality rate (about 8.2%) [1]. In China, the number of cases of gastric cancer is about 679,100 each year, only smaller than that of lung cancer, and the number of deaths of

Corresponding author: Jiangning Zhao, MD. Gastrointestinal Peritoneal Cancer Surgery, The Fourth Clinical Medical School of Guangzhou University of Chinese Medicine; Shenzhen Traditional Chinese Medicine Hospital, No. 1 Fuhua Rd, Futian District, Shenzhen, Guangdong, 518033, China.
Tel: +86 013686490330, Email: zhaojane_7689@qq.com
Received: 19/10/2020; Accepted: 26/11/2020

gastric cancer is about 498,000 each year, only smaller than that of lung cancer and liver cancer [2-4]. Moreover, 20-25% of patients in China suffer from unresectable late-stage gastric cancer when diagnosed, with an extremely poor prognosis. The peritoneum is the most common site of the metastasis and preoperatively or intraoperatively recurrence in gastric cancer patients is diagnosed in 20% of the cases, while more than 50% of patients with stage T3 and T4 gastric cancer experience peritoneal metastasis after radical gastrectomy [5]. According to the study results of Geng et al gastric cancer patients with peritoneal metastasis who do not receive chemotherapy or surgery have a median survival time (MST) of only 7 months, with a 1-year survival rate of only 22.2% [6].

In recent years, conversion therapy for gastric cancer has gradually become a hotspot in the research into peritoneal metastasis of this disease. In conversion therapy, systemic chemotherapy is the core, supplemented by local intraperitoneal chemotherapy, while neoadjuvant intraperitoneal-systemic chemotherapy (NIPS) integrates the advantages of these two chemotherapies, so it is considered as the most promising conversion therapy [7,8]. In this study, a retrospective analysis was conducted on the clinical data of 80 patients definitely diagnosed with peritoneal metastasis of gastric cancer, who underwent NIPS plus conversion surgery or NIPS alone, and the safety and efficacy of conversion surgery in the treatment of such patients were explored, so as to provide a reference for their treatment.

Table 1. Demographics and general clinical data of all studied patients

Parameters	*NIPS group (n=40)* *n (%)*	*Control group (n=40)* *n (%)*	*p value*
Gender (Male/Female)	21/19	25/15	0.498
Age (years), mean±SD	56.42±10.21	57.87±10.29	0.532
Pathological type			0.690
Highly /Moderately differentiated	7 (17.5)	10 (25.0)	
Poorly differentiated	23 (57.5)	19 (47.5)	
Mucinous adenocarcinoma	2 (5.0)	1 (2.5)	
Signet ring cell carcinoma	8 (20.0)	10 (25.0)	
T staging			0.669
T2	2 (5.0)	1 (2.5)	
T3	31 (77.5)	34 (85.0)	
T4	7 (17.5)	5 (12.5)	
N staging			0.401
N1	28 (70.0)	25 (62.5)	
N2	9 (22.5)	8 (20.0)	
N3	3 (7.5)	7 (17.5)	
Degree of peritoneal metastasis			0.779
P1	7 (17.5)	8 (20.0)	
P2	26 (65.0)	23 (57.5)	
P3	7 (17.5)	9 (22.5)	
Ascites			0.232
+	22 (55.0)	19 (47.5)	
++	12 (30.0)	18 (45.0)	
+++	6 (15.0)	13 (32.5)	
PCI			0.685
0-9 points	7 (17.5)	8 (20.0)	
10-19 points	17 (42.5)	16 (40.0)	
20-29 points	13 (32.5)	10 (25.0)	
30-39 points	3 (7.5)	6 (15.0)	
PS			0.605
0	31 (77.5)	27 (67.5)	
1	7 (17.5)	10 (25.0)	
2	2 (5.0)	3 (7.5)	

NIPS: neoadjuvant intraperitoneal and systemic chemotherapy; PCI: peritoneal cancer index; PS: performance status

Methods

General data

Clinicopathological data were collected from 80 patients with peritoneal metastasis of gastric cancer admitted to our department from March 2016 to September 2017, and there were 46 males and 34 females, aged 34-73 years old, with an average age of 56.86 years. All the 80 patients were randomly assigned into two groups and received oral administration of S-1 + intravenous and intraperitoneal chemotherapy with paclitaxel (PTX) (NIPS group, n=40) or oral administration of S-1 + intravenous chemotherapy with oxaliplatin (control group, n=40). Inclusion criteria: 1) patients definitely diagnosed with gastric cancer by gastroscopic biopsy or histopathological examination, and with no history of resection of primary foci or metastatic foci, 2) those with at least one measurable focus in the abdominal cavity, 3) those receiving no radiochemotherapy previously or within 3 months, and 4) those tolerant of chemotherapy as indicated by laboratory examination. Exclusion criteria: 1) patients allergic to drugs used in this study, 2) those using chemotherapy drugs or other anti-tumor drugs recently (within 3 months), 3) those with too large tumors (the maximum diameter of intraperitoneal tumors ≥10 cm, or the volume of liver metastases >50% of the total liver volume), 4) those with only body cavity effusions (pleural effusions or peritoneal effusions), but no measurable solid foci, 5) those accompanied by severe complications (such as gastrointestinal bleeding or perforation) or severe dysfunction of the heart, liver, lung, kidney or other organs, or 6) those with cerebral or leptomeningeal metastasis. There were no statistically significant differences between the two groups regarding basic conditions, such as age, gender, pathological types, T and N stages of tumors and degree of ascites ($p>0.05$), which were comparable (Table 1). All the subjects were informed of the present study and signed the informed consent in accordance with the *Declaration of Helsinki*. This study was approved by the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University.

Treatment methods

NIPS group: The patients orally took S-1 at 80 mg/m^2 twice daily for 14 consecutive days at an interval of 7 d. On d 1 and d 8, the patients received chemotherapy with PTX intravenously at 50 mg/m^2 (PTX liposome injection, 30 mg/piece, Nanjing Luye Pharmaceutical Co., Ltd.; Nanjing, China), NMPN H20030357), and intraperitoneally at 20 mg/m^2. After conventional intraperitoneal puncture and intraperitoneal infusion chemotherapy, patients were instructed to turn over at 30 min/time for 4 times in total, and routine measures were taken for the hydration of chemotherapy drugs and diuresis. A treatment course lasted for three weeks, and the treatment was terminated when patients had intolerable adverse reactions, progressive disease (PD) or surgical indications. Control group: The patients were treated according to the same regimens as those in NIPS group except for intraperitoneal chemotherapy. Blood routine review was conducted once or twice per week. Before treatment, 5-HT3 receptor antagonists were conventionally given to prevent emesis and digestive system reactions. Once bone marrow suppression occurred during treatment, colony stimulating factors were administered, and red blood cells and platelets were transfused if necessary.

Surgical indications: After NIPS conversion therapy, the patients had resectable primary gastric lesions, no or significantly lessened peritoneal metastases, and no other distant metastases besides peritoneal metastasis, and their clinical symptoms dramatically resolved. Surgical methods: Laparoscopic radical gastrectomy for gastric cancer was employed, with the scope of gastrectomy and the method of gastrointestinal reconstruction dependend on the actual intraoperative conditions. Splenectomy, distal pancreatectomy and resection of other organs were conducted in few cases. R0 radical gastrectomy and D2 lymph node dissection were conventionally performed, and palliative gastrectomy was conducted based on the intraoperative conditions.

The efficacy was evaluated after 4 cycles of treatment based on the Response Evaluation Criteria in Solid Tumors version 1.1: complete response (CR): Disappearance of all lesions, partial response (PR): a >30% decrease in the longest diameter of lesions, stable disease (SD): no sufficient shrinkage of lesions to qualify for PR, and PD: appearance of one or more new lesions or a >20% increase in the largest diameter of lesions. Total response rate (ORR) = CR + PR + SD. Toxic side reactions were assessed based on the National Cancer Institute Common Toxicity Criteria and classified as grade 0-IV, and included gastrointestinal reactions, peripheral neurotoxicity, bone marrow suppression and hypersensitivity reactions. The following intraoperative and postoperative conditions of patients were recorded: the number of cycle of NIPS before surgery, specific surgical methods, intraoperative lymph node dissection, surgical margins, and incidence of postoperative complications.

Peritoneal metastasis of gastric cancer was classified based on the 7th edition UICC classification criteria: P0: no implantation metastasis in the gastric serosa, greater omentum, lesser omentum, mesenterium, abdominal organ serosa, abdominal wall and peritoneum, P1: implantation metastasis in the peritoneum near gastric cancer (the peritoneum above the transverse colon, including the greater omentum), but no metastasis in the distant peritoneum (the peritoneum and diaphragmatic surface below the transverse colon), P2: a few countable distant peritoneal metastases (only ovarian metastases were also defined as P2), and P3: many uncountable distant peritoneal metastases [9,10]. Ascites classification was as follows: a small amount of ascites was <0.5 L, a medium amount of ascites was 0.5-2.0 L, and a large amount of ascites was >2.0 L. Sugarbaker's peritoneal cancer index (PCI) was adopted. The abdomen was first divided into 13 areas, and the lesion size (LS) was scored in each area: LS-0: no implantation lesions found, LS-1: implantation lesions <0.5 cm, and LS-2: implantation lesions of 0.5-5.0 cm, and LS-3: implantation lesions >5.0 cm. The PCI value was the sum of the LS score for each area, with a range of 0-39 points [11].

Patients' survival was recorded during postoperative follow-up, and the survival time was defined as the time from the day of surgery to the last follow-up or the time of death. The follow-up ended in December 2019.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Normally distributed measurement data were presented as mean±SD, and continuous variables were analyzed using t-test or Mann-Whitney U test. The measurement data showing skewed distribution were expressed as median and range. Categorical variables were presented as percentage and compared between groups using x^2 test or corrected x^2 test. Survival curves were plotted using the Kaplan-Meier method, and log-rank test was conducted for survival analysis. P<0.05 suggested statistically significant differences.

Results

Comparison of the efficacy of chemotherapy between the two groups of patients

After 4 cycles of treatment, the efficacy was evaluated in all the patients. In NIPS group, the median chemotherapy cycles was 6.9, and there were 7 cases of CR, 14 cases of PR, 13 cases of SD and 6 cases of PD, with a response rate of 85.0% (34/40) (CR + PR). In the control group the median chemotherapy cycles was 6.4 cycles, and there were 3 cases of CR, 11 cases of PR, 14 cases of SD and 12 cases of PD, with a response rate of 70.0% (28/40) (CR + PR). A statistically significant difference was observed between the two groups in terms of ORR after chemotherapy, and NIPS group had a considerably higher ORR than control group (p=0.041) (Table 2).

Table 2. Chemotherapy effective rates of the two studied groups

	NIPS group (n=40) n (%)	*Control group (n=40) n (%)*	*p value*
CR	7 (17.5)	3 (7.5)	
PR	14 (35.0)	11 (27.5)	
SD	13 (32.5)	14 (35.0)	
PD	6 (15.0)	12 (30.0)	
ORR	34 (85.0)	28 (70.0)	0.041

NIPS: neoadjuvant intraperitoneal and systemic chemotherapy; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate

Chemotherapy-related adverse reactions

Among the adverse reactions of patients during chemotherapy, bone marrow suppression occurred in 29 (72.5%) cases and 24 (60.0%) cases, respectively, in the two groups, including 5 (12.5%) cases and 3 (7.5%) cases of grade III-IV bone marrow suppression. Besides, there were 6 (15.0%) cases and 4 (10.0%) cases of allergic reactions, respectively, in the two groups. The incidence rate of gastrointestinal reactions such as nausea and vomiting, abdominal pain and diarrhea, was 70.0% and 62.5%, that of neurotoxicity was 57.5% and 62.5%, respectively, in the two groups, that of hepatic function impairment was 50.0% and 40.0%, and that of renal function impairment was 35.0% and 27.5%. The adverse reactions were mainly of grade I-II and relieved after symptomatic treatment. Chemotherapy was successfully administered, with no cases of severe chemotherapy-related adverse reactions or death. Of all the patients undergoing chemotherapy, only 1 had chemotherapy-related ileus, and the remaining patients did not experience chemical peritonitis or intestinal adhesion-induced ileus (Table 3).

Surgical conditions in NIPS group

After chemotherapy, 40 gastric cancer patients had surgical indications in NIPS group, and among them, 16 received 1-4 cycles of chemotherapy, 14 had 5-10 cycles, and 10 underwent more than 10 cycles. The surgical procedures and specific surgical conditions of patients are presented in Table 4. There were 2 (5.0%) cases of proximal gastrectomy, 9 (22.5%) cases of distal gastrectomy and 29 (72.5%) cases of total gastrectomy. Moreover,

Table 3. Comparison of chemotherapy adverse reactions of the studied patients in two groups

Parameters	*NIPS group (n=40)*		*Control group (n=40)*		*p value*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Bone marrow suppression	24 (60.0)	5 (12.5)	21 (52.5)	3 (7.5)	0.237
Allergic reactions	6 (15.0)	0 (0)	4 (10.0)	0 (0)	0.499
Gastrointestinal reactions	25 (62.5)	3 (7.5)	23 (57.5)	2 (5.0)	0.478
Neurotoxicity	19 (47.5)	4 (10.0)	22 (55.0)	3 (7.5)	0.648
Hepatic function damage	18 (45.0)	2 (5.0)	15 (37.5)	1 (2.5)	0.369
Renal function damage	13 (32.5)	1 (2.5)	9 (22.5)	2 (5.0)	0.469

NIPS: neoadjuvant intraperitoneal and systemic chemotherapy

Table 4. Comparison of parameters related to surgery

Parameters	*NIPS group (n=40) n (%)*
Surgical methods	
Proximal gastrectomy	2 (5.0)
Distal gastrectomy	9 (22.5)
Total gastrectomy	29 (72.5)
Combined resection organ	
Splenectomy	3 (7.5)
Distal pancreatectomy	2 (5.0)
Bilateral adnexectomy	2 (5.0)
Small intestine resection	1 (2.5)
Colectomy	9 (22.5)
Surgical margin	
R_0 resection	22 (55.0)
R_1 resection	10 (25.0)
R_2 resection	8 (20.0)
Lymph node dissection	
D1+a	27 (67.5)
D2	13 (32.5)
Complications	
Incision infection	1 (2.5)
Ileus	3 (7.5)
Peritonitis	2 (5.0)
Intra-abdominal hemorrhage	3 (7.5)
Pancreatic fistula	2 (5.0)
Anastomotic leakage	4 (10.0)
NIPS courses before surgery	
≤4	16 (40.0)
5-10	14 (35.0)
>10	10 (25.0)

NIPS: neoadjuvant intraperitoneal and systemic chemotherapy

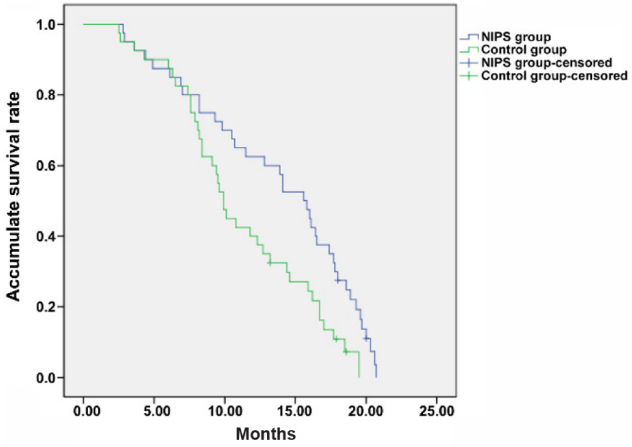

Figure 1. Kaplan-Meier survival curves of patients in NIPS group and Control group showing that the overall survival rate of patients in NIPS group was significantly higher than that of Control group (p=0.011).

total gastrectomy combined with splenectomy was performed in 3 patients with splenic hilar invasion by gastric cancer, total gastrectomy combined with splenectomy and distal pancreatectomy was performed in 2 patients with pancreatic tail invasion by gastric cancer, and 2 patients with ovarian metastasis of gastric cancer underwent total gastrectomy combined with bilateral appendectomy, with 1 case of combined small intestine resection and 9 cases of combined colectomy. Among the 40 patients, 22 had R0 resection, 10 R1 resection and 8 R2 resection. Some patients had complications postoperatively, and there was 1 case of incision infection, 3 cases each of ileus and intra-abdominal hemorrhage, 2 cases each of peritonitis and pancreatic fistula, and 4 cases of anastomotic fistula (Table 4).

Patients' survival based on follow-up results

All patients were followed up for 2-18 months, and the median follow-up time was 14.1 months and 13.3 months, respectively, in the two groups. The median overall survival (mOS) of patients was 13.4 months in NIPS group and 10.8 months in control group. According to the survival curves drawn using the Kaplan-Meier method (Figure 1) and log-rank test results, the difference in the OS rate was different between the two groups, being significantly superior in NIPS group compared to control group (p=0.011).

Discussion

In 2003, Yonemura and other Japanese scientists first proposed NIPS conversion therapy. The principle of this therapy is that micrometastases in the abdominal cavity are eliminated through NIPS before surgery, and primary tumors are downstaged to increase the R0 resection rate, thereby achieving the purpose of conversion therapy [12]. NIPS attacked extensive attention in the treatment of peritoneal metastasis of gastric cancer for its combination of the advantages of systemic chemotherapy and intraperitoneal local treatment. In NIPS, intraperitoneal chemotherapy is different from hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC involves filling the abdominal cavity with accurately thermostated perfusion solution containing chemotherapy drugs for a certain period of time by circulatory perfusion, while intraperitoneal chemotherapy is a process in which chemotherapy drugs are infused into the abdominal cavity through an intraperitoneal chemotherapy pump subcutaneously indwelled in the right iliac area of patients and a catheter placed in the

pelvic floor. For example, PTX dissolved in 1,000 mL of 0.9% normal saline solution was infused at 20 mg/m^2 for more than 1 h. Compared with HIPEC, NIPS is characterized by easy operation and drug administration, milder and more acceptable pain in patients, preservation of an intraperitoneal chemotherapy pump for 1-2 years and multiple times or courses of drug administration according to the patient's condition [13,14].

In 2009 and 2012, Yonemura et al [15,16] reported on the safety and effectiveness of NIPS plus cytoreductive surgery, and concluded that NIPS conversion therapy is safe and effective in the treatment of peritoneal metastasis of gastric cancer. Moreover, NIPS plus tumor cytoreductive surgery can prolong the survival of patients, especially those in whom complete tumor regression was achieved, thereby notably raising the 5-year survival rate. NIPS plus tumor cytoreductive surgery lower the incidence rate of postoperative complications and mortality rate compared with HIPEC plus tumor cytoreductive surgery. Kitayama et al improved the surgical scheme after NIPS conversion therapy and advocated radical gastrectomy. They found that the surgical resection rate was 53.1%, with a R0 resection rate was 53.1%, and the mOS 16.6 months after NIPS conversion therapy for 64 gastric cancer patients with peritoneal metastasis accompanied by peritoneal effusions, including those with massive distant peritoneal metastases (82.8%). Another study revealed that the patients undergoing NIPS + radical gastrectomy have a longer mOS and higher 1-year survival rate than those receiving no surgery (26.4 *vs.* 12.1 months, 82% *vs.* 26%) [17]. According to the results of existing research, after NIPS conversion therapy, the rate of negative conversion of free cancer cells (FCCs) in the abdominal cavity is 93.2%, and these patients have a MST of 20.0 months [18]. Ishigami et al [19] reported a multicenter phase III randomized controlled trial (PHOENIX-GC) and found that there are no differences in the median survival time and 3-year survival rate between NIPS group (n=114) and systemic chemotherapy group (n=50) (17.7 months *vs.* 15.2 months, 21.9% *vs.* 6.0%). However, female patients with diffuse gastric cancer and moderate or more peritoneal effusions had a more obvious survival advantage after NIPS conversion therapy. The aim of the PHOENIX phase III clinical study released in Japan in 2016 was also to make a more significant breakthrough in further verifying the feasibility and superiority of NIPS regimen in IP group. In another clinical registration study (UMIN000002850) reported by Yamaguchi et al, 35 patients with advanced gastric cancer accompanied by peritoneal metastasis were also treated with the above-mentioned NIPS for 11 cycles on average, and the results showed that ascites disappears or declines significantly by 68%, with an intra-abdominal FCC negative conversion rate of 97%, and an MST of 17.6 months. Besides, 21 (60%) patients underwent total or subtotal gastrectomy after the effective control of tumor foci. The overall 1- and 2-year OS rates reached 77.1% and 44.8%, respectively, in all the patients, and those with a PCI <15 had a better prognosis than those with a PCI >15. This indicates again that NIPS with PTX and S-1 can effectively prolong the survival of gastric cancer patients with peritoneal metastasis [20]. In recent years, numerous research results have confirmed that gastric cancer patients with peritoneal metastasis often have no surgical indications, and they usually can obtain more suitable surgical opportunities or even undergo R0 resection after prompt NIPS conversion therapy [21,22].

In this study, 40 patients with gastric cancer and peritoneal metastasis treated with NIPS exhibited a significantly higher ORR than those receiving intravenous chemotherapy alone (85.0% *vs.* 70.0%) (p=0.041). The NIPS-related adverse reactions were tolerable. All the 40 patients in NIPS group had indications for surgery after NIPS. According to the follow-up results after radical gastrectomy, the mOS of patients was 13.4 months in NIPS group and 10.8 months in control group. Additionally, the log-rank test results revealed that the OS in NIPS group was significantly longer than that in control group (p=0.011), basically consistent with previous literature reports.

In this study, the sample size was small, the follow-up time was short, the comprehensive follow-up content was not comprehensive enough, and the possible impacts of R0 resection and the number of preoperative NIPS chemotherapy cycles on the prognosis of patients failed to be analyzed. Therefore, multi-center, large-sample randomized controlled clinical trials are needed to validate the efficacy of NIPS combined with conversion surgery in the treatment of peritoneal metastasis of gastric cancer in the future.

Conclusions

NIPS combined with radical gastrectomy for gastric cancer patients with peritoneal metastasis has exact efficacy and cause tolerable adverse reactions, and it can significantly improve the survival rate of patients compared with systemic chemotherapy alone.

Conflict of interests

The authors declare no conflict of interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Tekesin K, Emin GM, Tural D et al. Clinicopathological characteristics, prognosis and survival outcome of gastric cancer in young patients: A large cohort retrospective study. JBUON 2019;24:672-8.
3. Jia X, Wen Z, Sun Q et al. Apatinib suppresses the Proliferation and Apoptosis of Gastric Cancer Cells via the PI3K/Akt Signaling Pathway. JBUON 2019;24:1985-91.
4. Zhou G, Yang J. Correlations of gastrointestinal hormones with inflammation and intestinal flora in patients with gastric cancer. JBUON 2019;24:1595-600.
5. Allemani C, Matsuda T, Di Carlo V et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018;391:1023-75.
6. Geng X, Liu H, Lin T et al. Survival benefit of gastrectomy for gastric cancer with peritoneal carcinomatosis: a propensity score-matched analysis. Cancer Med 2016;5:2781-91.
7. Takeshita K, Liu Y, Ishibashi H, Yonemura Y. Laparoscopic Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Carcinomatosisfrom Gastric Cancer: Its Beneficial Effects on Reduction and Exact Evaluation of the Peritoneal Cancer Index. Am Surg 2017;83:1315-20.
8. Gong Y, Wang P, Zhu Z et al. Benefits of Surgery After Neoadjuvant Intraperitoneal and Systemic Chemotherapy for Gastric Cancer Patients With Peritoneal Metastasis: A Meta-Analysis. J Surg Res 2020;245:234-43.
9. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. Jpn J Surg 1981;11:127-39.
10. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077-9.
11. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res 1996;82:359-74.
12. Yonemura Y, Bandou E, Kinoshita K et al. Effective therapy for peritoneal dissemination in gastric cancer. Surg Oncol Clin N Am 2003;12:635-48.
13. Fujiwara Y, Takiguchi S, Nakajima K et al. Neoadjuvant intraperitoneal and systemic chemotherapy for gastric cancer patients with peritoneal dissemination. Ann Surg Oncol 2011;18:3726-31.
14. Macri A, Morabito F. The use of intraperitoneal chemotherapy for gastric malignancies. Expert Rev Anticancer Ther 2019;19:879-88.
15. Yonemura Y, Endou Y, Shinbo M et al. Safety and efficacy of bidirectional chemotherapy for treatment of patients with peritoneal dissemination from gastric cancer: Selection for cytoreductive surgery. J Surg Oncol 2009;100:311-6.
16. Yonemura Y, Elnemr A, Endou Y et al. Effects of neoadjuvant intraperitoneal/systemic chemotherapy (bidirectional chemotherapy) for the treatment of patients with peritoneal metastasis from gastric cancer. Int J Surg Oncol 2012;2012:148420.
17. Kitayama J, Ishigami H, Yamaguchi H et al. Salvage gastrectomy after intravenous and intraperitoneal paclitaxel (PTX) administration with oral S-1 for peritoneal dissemination of advanced gastric cancer with malignant ascites. Ann Surg Oncol 2014;21:539-46.
18. Emoto S, Kitayama J, Ishigami H, Yamaguchi H, Watanabe T. Clinical significance of cytological status of peritoneal lavage fluid during intraperitoneal chemotherapy for gastric cancer with overt peritoneal dissemination. Ann Surg Oncol 2015;22:780-6.
19. Ishigami H, Fujiwara Y, Fukushima R et al. Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial. J Clin Oncol 2018;36:1922-9.
20. Yamaguchi H, Kitayama J, Ishigami H, Emoto S, Yamashita H, Watanabe T. A phase 2 trial of intravenous and intraperitoneal paclitaxel combined with S-1 for treatment of gastric cancer with macroscopic peritoneal metastasis. Cancer 2013;119:3354-8.
21. Li F, Shi J, Xu Z et al. S100A4-MYH9 Axis Promote Migration and Invasion of Gastric Cancer Cells by Inducing TGF-beta-Mediated Epithelial-Mesenchymal Transition. J Cancer 2018;9:3839-49.
22. Kim DW, Park DG, Song S, Jee YS. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy as Treatment Options for Peritoneal Metastasis of Advanced Gastric Cancer. J Gastric Cancer 2018;18:296-304.