J Med Sci 2024;44 (5):202-207
DOI: 10.4103/jmedsci.jmedsci_133_23

ORIGINAL ARTICLE

Laparoscopic Hyperthermic Intraperitoneal Chemotherapy plus Neoadjuvant Intraperitoneal and Systemic Chemotherapy for Gastric Cancer with Malignant Ascites

Hsing-Wei Yu, Guo-Shiou Liao, Ting-Ying Lee, De-Chuan Chan

Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Background: Patients with gastric cancer (GC) and malignant ascites (MA) usually have poor outcomes and a high risk of recurrence and mortality, even after curative gastrectomy or chemotherapy. Systemic chemotherapy has been prescribed for patients with GC and MA; however, most of these patients expire within 1 year. **Aim:** To evaluate the outcomes of laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC) plus neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) in the outcomes of GC patients with MA. **Methods:** We enrolled 62 patients with GC and MA between January 1, 2016, and March 1, 2021. Four patients were excluded because of extraperitoneal metastasis, and two patients were ineligible. A total of 56 patients underwent biweekly staging laparoscopy and LHIPEC with NIPS. We also performed staging laparoscopy to evaluate the effectiveness of LHIPEC + NIPS. **Results:** The mean survival time of the 56 patients was 20.8 months. The overall complication rate was 33.93%. After the LHIPEC + NIPS intervention, the peritoneal cancer index score ($P < 0.001$), ascites volume ($P = 0.003$), and cytology ($P < 0.001$) significantly improved compared to before the intervention; quality of life (Eastern Cooperative Oncology Group) was also better than before the intervention ($P = 0.002$), and no discomfort was noted postintervention. **Conclusion:** LHIPEC + NIPS is feasible for the treatment of GC with MA and may improve patients' quality of life.

Key words: Neoadjuvant intraperitoneal and systemic chemotherapy, hyperthermic intraperitoneal chemotherapy, gastric cancer with malignant ascites, peritoneal cancer index

INTRODUCTION

Gastric cancer (GC) has an incidence of 8.2% in cancer patients worldwide.[1] Although recent advances and efforts in screening have allowed earlier detection in more endemic areas, most patients are diagnosed at advanced stages. As such, GC remains the ninth leading cause of cancer-related deaths in Taiwan.

GC is traditionally considered a terminal stage of the disease because most of these patients die within 3 months without treatment.[2] The National Comprehensive Cancer Network guidelines suggest that systemic chemotherapy be prescribed for GC with malignant ascites (MA).[3,4] However, most of these patients expire within 1 year.[2,5]

Until the early 1990s, peritoneal carcinomatosis was still considered the terminal stage of GC,[6] with slow progress regarding the treatment strategy for GC with MA. Most patients present with localized GC with ascites after undergoing curative gastrectomy with extended (D2) lymphadenectomy.[7] However, some patients still present with local-regional disease recurrence or distant spread. Positive peritoneal cytology leads to a 40%–60% recurrent rate and peritoneal carcinomatosis after curative gastrectomy, even in the absence of visible PC.[8-10] Furthermore, progressive peritoneal carcinomatosis accounts for nearly 60% of deaths in stage IV GC.[11]

Received: May 10, 2023; Revised: June 01, 2023; Accepted: June 06, 2023; Published: April 22, 2024
Corresponding Author: Dr. Ting-Ying Lee, Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center, No. 325, Sec. 2, Chenggong Rd., Neihu Dist., Taipei 114, Taiwan. Tel: +886-2-8792-7191, Fax: +886-2-8792-7372. E-mail: lty242@gmail.com

How to cite this article: Yu HW, Liao GS, Lee TY, Chan DC. Laparoscopic hyperthermic intraperitoneal chemotherapy plus neoadjuvant intraperitoneal and systemic chemotherapy for gastric cancer with malignant ascites. J Med Sci 2024;44:202-7.

Because of the blood–peritoneal barrier,[12] traditional systemic chemotherapy cannot reach ideal pharmacokinetics. Therefore, one of the challenges in improving GC with MA postcytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is to convert and eliminate the positive cytology of ascites. In 2006, Yonemura *et al*. proposed a new bidirectional chemotherapeutic strategy for patients with peritoneal carcinomatosis from GC, which included neoadjuvant intraperitoneal and systemic chemotherapy (NIPS).[13] Treatment resulted in negative peritoneal cytology in 56% of patients, and those who received a complete resection had a median survival of 20.4 months compared to 14.4 months in all patients.

In 2014, Canbay *et al*. assessed the early- and long-term outcomes of NIPS in 194 patients with positive peritoneal cytology results ($P < 0.001$). After induction treatment, 78% of patients with negative cytology underwent CRS and HIPEC.[14] We aimed to evaluate laparoscopic HIPEC (LHIPEC) combined with NIPS for GC with MA through a prospective single-arm study.

MATERIALS AND METHODS

We enrolled 62 patients with GC, peritoneal metastasis, and massive ascites at our medical center between January 1, 2016, and December 1, 2021. An extensive diagnosis was performed in all cases using gastroscopy and thoracic-abdominopelvic computed tomography with double contrast; positron emission tomography was performed in doubtful cases. We excluded patients with extraperitoneal metastases ($n = 4$) and those who were transferred to another hospital ($n = 2$) [Figure 1]. Finally, 56 cases were enrolled. Our study adhered to the principles of the Declaration of Helsinki and received *a priori* approval from our Institutional Ethics Committee and was registered with the Institutional Review Board of our hospital (TSGH-IRB No: B202305031). The patient consent was obtained.

A total of 56 patients underwent staging laparoscopy, and the peritoneal cancer index (PCI) score, amount of ascites, and ascitic cytology were measured before the intervention. The peritoneal cancer index (PCI) is a valuable tool aids in evaluating peritoneal metastasis by segmenting the abdomen into nine distinct regions and further subdividing the small bowel into four sectors. The cumulative lesion size score is then calculated for each of these sectors, ultimately yielding the total score for assessment.[15] Thereafter, we administered LHIPEC (regimen: mitomycin C 30 mg plus oxaliplatin 400 mg; 42°C for 90 min). After LHIPEC, the patient received NIPS systemic chemotherapy regimen: Xelox: Oxaliplatin 85 mg × Body surface area (BSA) biweekly + TS-1 40 mg bid; intraperitoneal chemotherapy regimen: docetaxel 40 mg biweekly. All patients underwent a staging laparoscopy 3 months after the intervention.

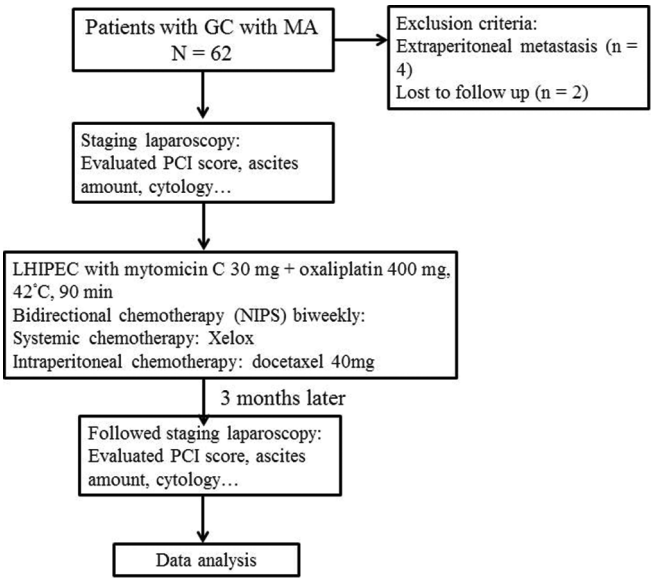

Figure 1: Flow chart of the study. GC = Gastric cancer; MA = Malignant ascites; PCI = Peritoneal cancer index; LHIPEC = Laparoscopic hyperthermic intraperitoneal chemotherapy; NIPS = Neoadjuvant intraperitoneal and systemic chemotherapy

We also collected data on complications after LHIPEC and evaluated the amount of ascites, peritoneal positive cytology conversion rate, PCI score, visual analog scale (VAS) score, and patient performance (Eastern Cooperative Oncology Group patient performance [ECOG]) between preintervention and postintervention of LHIPEC + NIPS therapy.

Preintervention and postintervention variables, including PCI score and ascites amount, were recorded. Data management and statistical analyses were conducted using the SPSS statistical software (version 22.0; IBM, Chicago, IL, USA). A statistically significant value was defined by $P < 0.05$.

RESULTS

The clinical characteristics of the patients are shown in Table 1. The study included 29 males and 37 females, with an average age of 60.3 years. Most patients were low American Society of Anesthesiologists grade (I-II, 92.8%) and had a good level of functioning (ECOG ≤2; 89.28%). Most patients also had tumors invading the serosa (T4 lesion, 57.1%) and lymph node metastases (N1-3; 83.9%). All patients experienced massive ascites, epigastric pain, and fullness (100%). Some patients also showed symptoms of upper gastrointestinal bleeding (57.1%), gastric outlet obstruction (30.4%), and body weight loss (71.4%). Most patients showed synchronous ascites (78.6%) and there were some patients with recurrent GC with MA (metachronous; 21.4%). The mean survival time was

Table 1: Clinical characteristics of patients (n=56)

Variable	NIPS, n (%)
Age (years)	60.3±11.7
Sex (male)	29 (51.8)
Comorbidity	
HTN	10 (17.9)
CAD	3 (5.4)
Diabetes	3 (5.4)
CVA	1 (1.8)
Pulmonary	2 (3.6)
ASA grade	
I–II	52 (92.9)
III–IV	4 (7.1)
PS ECOG	
0	18 (32.1)
1~2	32 (57.1)
>3	6 (10.7)
VAS	1.5±0.97
TNM stage	
T2	8 (14.3)
T3	16 (28.6)
T4	32 (57.1)
N1	3 (5.4)
N2	27 (48.2)
N3	17 (30.4)
Symptoms	
Ascites	56 (100)
Epigastric pain	56 (100)
UGI bleeding	32 (57.1)
Gastric outlet obstruction	17 (30.4)
BW loss	40 (71.4)
Malignant ascites	
Synchronous	44 (78.6)
Metachronous (postgastrectomy)	12 (21.4)
Lab test	
WBC	7080.9±2516.6
Hgb	10.9±2.8
Na	137.1±3.6
K	3.7±0.4
AST	19.4±9.9
Cr	0.8±0.2
Albumin	3.4±0.6
Mean survival time (months)	20.8
Median survival (months)	18.8±0.7
Progression-free survival (months)	11.6±1.2

ASA=American Society of Anesthesiologists; BW=Body weight; CAD=Coronary artery disease; Cr=Creatinine; CVA=Cerebrovascular accident; Hgb=Hemoglobin; HTN=Hypertension; K=Potassium; Na=Sodium; NIPS=Neoadjuvant intraperitoneal and systemic chemotherapy; PS ECOG=Patient performance Eastern Cooperative Oncology Group; UGI=Upper gastrointestinal; VAS=Visual analog scale; WBC=White blood cells; TNM=Tumor, nodes and metastases; AST=Aspartate aminotransferase

20.8 months, and the median survival time was 18.8 months. The progression-free survival time was 11.6 months.

Regarding complications in patients who underwent LHIPEC [Table 2], one patient suffered from trocar site bleeding, two patients suffered from gastrojejunostomy bypass (for gastric outlet obstruction) leakage (common terminology criteria for adverse events [CTCAE] grade 4), and four patients had leukopenia and infection. Two patients developed acute kidney injury owing to chemotherapy (oxaliplatin, CTCAE grade 3). The most common complication observed was postoperative ileus. In summary, one patient suffered from major complications (anastomotic leakage), and 18 patients had minor complications.

We evaluated postintervention LHIPEC + NIPS after 3 months via staging laparoscopy [Table 3]. Compared to before, patient PCI scores significantly improved after the intervention (19.44 ± 8.9 vs. 7.83 ± 6.3, $P < 0.001$) [Figure 2a and b]. The amount of ascites (ml) also significantly decreased after LHIPEC + NIPS treatment (2014.12 ± 829.6 ml vs. 342.65 ± 22.6 ml, $P = 0.003$) [Figure 3a and b] and the number of patients with malignant cytology also significantly decreased (87.5% vs. 5.32%, $P < 0.001$). Patient performance (ECOG) also improved postintervention (0.982 ± 0.12 vs. 0.421 ± 0.11, $P = 0.002$). There was no significant difference between pre- and postintervention VAS scores ($P = 0.092$).

DISCUSSION

In our study, patients with GC and MA had poor outcomes, even when treated with variable regimens of systemic chemotherapy. Most of them died within 2 years, which corresponds with other studies.[5,16] We enrolled all GC patients with massive ascites, with or without positive cytology, to exclude pseudo-negative results. Most GCs with peritoneal carcinomatosis have mild ascites and may be at high risk for intra-abdominal free cancer cells.

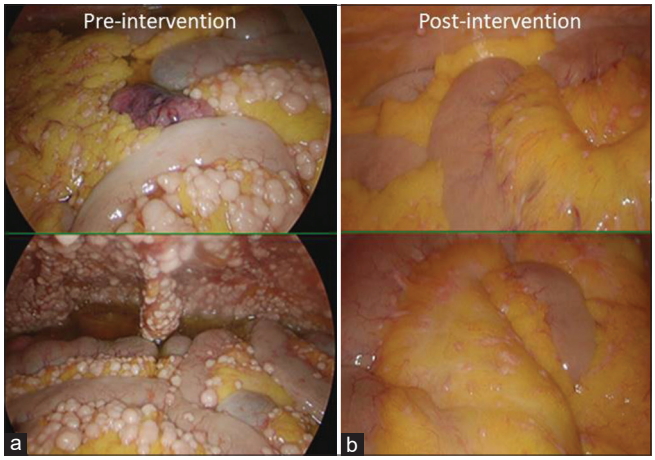

Figure 2: Peritoneal cancer index condition between pre- (a) and postintervention (b). Initial presentation of the white tumor nodule in the peritoneum and mesentery (a). After laparoscopic hyperthermic intraperitoneal chemotherapy + neoadjuvant intraperitoneal and systemic chemotherapy therapy for 3 months, the tumor nodules are significantly smaller (b)

Leake *et al*.[17] reviewed 28 articles on the accuracy and utility of perioperative peritoneal wash cytology. The recurrence rate varied widely (0%–51%), even among patients without intraperitoneal free cancer cells. The specificity of the cytological assays remains controversial, and systemic chemotherapy has a minimal advantage for PC because of the blood-peritoneal barrier.[18] Intraperitoneal chemotherapy offers potential therapeutic advantages over systemic chemotherapy by generating high local concentrations of chemotherapeutic drugs in the peritoneal cavity. This advantage can be expressed by the area under the curve ratios of intraperitoneal versus plasma exposure.[11,19] In our subsequent staging laparoscopy results, the preintervention PCI score, ascites amount, and positive cytology conversion rate were significantly better than those preintervention. This corresponds with the findings of Canbay *et al*., who first described the use of neoadjuvant intraperitoneal chemotherapy combined with systemic chemotherapy in a large single-center series with 194 patients in Japan.[14] Of these patients, 152 (78%) were classified as responders, a classification that included patients whose cytology became negative. Yonemura *et al*. also advocated that the use of neoadjuvant LHIPEC + NIPS in 52 patients could also significantly improve the PCI score compared to LHIPEC alone.[20] Complete cytoreduction was achieved in 57.6% of patients in their LHIPEC + NIPS group. Overall survival also improved because of the PCI score and ascites control.

In this study, no significant complications were observed after LHIPEC. The most common complication, postoperative ileus, subsided within 2 weeks of the procedure. Most patients tolerated this therapy and experienced minimal adverse effects. Therefore, LHIPEC may be safe and feasible for patients with GC and MA. However, one patient died of anastomotic leakage. Once anastomotic leakage occurs after HIPEC, fatal outcomes may occur. Therefore, serosal injuries to the small bowel and the colon must be avoided.

In our study, LHIPEC + NIPS showed significant improvement of the PCI score, amount of ascites, and decrease the proportion of patients with positive cytology ascites findings. A consistently high intraperitoneal chemotherapeutic concentration can eradicate peritoneal cavity micrometastases

Table 2: Overview of complications of laparoscopic hyperthermic intraperitoneal chemotherapy + neoadjuvant intraperitoneal and systemic chemotherapy (*n*=56)

Variable	NIPS, *n* (%)
Operation time (min)	212.3±23.3
Blood loss (mL)	20.4±8.8
Complications	
Bleeding	1 (1.8)
Anastomotic leakage	2 (3.6)
Infection	4 (7.1)
Acute kidney injury	2 (3.6)
Postoperative ileus	10 (14.3)
Clavien–Dindo classification	
I–II	18 (32.1)
III–IV	1 (1.78)
Total	19 (33.9)
90-days mortality	1 (1.8)
CTCAE	
1–2	10 (18.2)
3	2 (3.6)
4–5	1 (1.8)

CTCAE=Common terminology criteria for adverse events; NIPS=Neoadjuvant intraperitoneal and systemic chemotherapy

Table 3: Comparison of outcomes of laparoscopic hyperthermic intraperitoneal chemotherapy + neoadjuvant intraperitoneal and systemic chemotherapy pre- and postintervention

LHIPEC + NIPS in the conversion group	Preintervention	Postintervention	*P*
PCI score	19.44±8.9	7.83±6.3	<0.001
Ascites			
Amount (mL)	2014.12±829.6	342.65±22.6	0.003
Positive cytology, *n* (%)	49 (87.5)	3 (5.32)	<0.001
PS (ECOG)	0.982±0.12	0.421±0.11	0.002
VAS	1.491±0.47	1.882±0.38	0.092

LHIPEC=Laparoscopic hyperthermic intraperitoneal chemotherapy; NIPS=Neoadjuvant intraperitoneal and systemic chemotherapy; PCI=Peritoneal cancer index; PS ECOG=Patient performance Eastern Cooperative Oncology Group; VAS=Visual analog scale

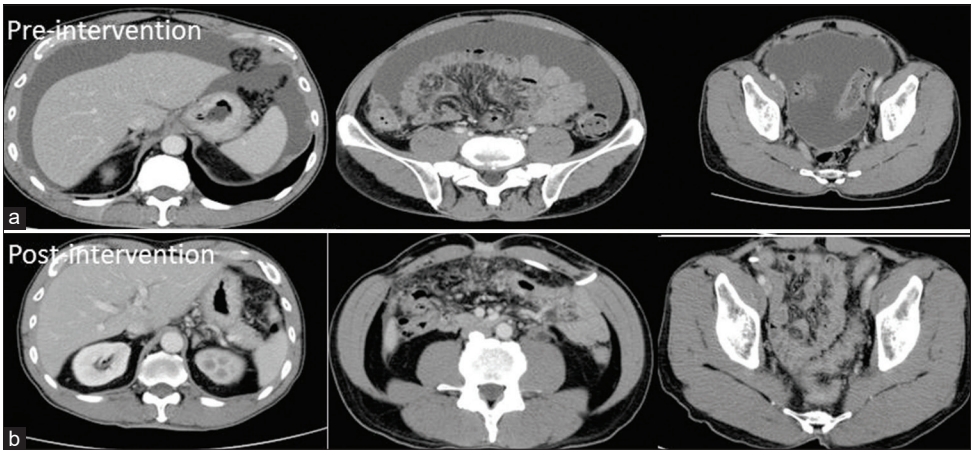

Figure 3: The abdominal computed tomography shows massive ascites in the peri-liver space, peritoneal cavity, and pelvic cavity at preintervention (a). After laparoscopic hyperthermic intraperitoneal chemotherapy + neoadjuvant intraperitoneal and systemic chemotherapy treatment for 3 months, the massive ascites is significantly decreased in the peri-liver space, peritoneal cavity, and pelvic cavity (b)

and peritoneal-free cancer cells. This may significantly improve overall survival and increase the success rate of conversion surgery.

We did not use a standard questionnaire to evaluate quality of life after the LHIPEC + NIPS intervention. However, patient performance (ECOG) also significantly improved after the LHIPEC + NIPS intervention, and there was no obvious worsening in VAS. This may be due to MA complications, including ileus, refractory peritonitis, poor appetite, and partial bowel obstruction controlled by LHIPEC + NIPS.[20,21] Therefore, LHIPEC + NIPS may also improve patients' quality of life. Some of our patients who received LHIPEC + NIPS refused further conversion surgery because of an improved quality of life. However, tumor progression was noted after 6 months of follow-up (data not shown). Therefore, the disease symptoms and PCI scores were successfully controlled within 6 months, and primary tumor resection and arrangement of CRS + HIPEC should be suggested as soon as possible.

A limitation of our study is that it was a small, prospective, single-arm, single-center study. The follow-up time should have been longer, and the overall survival benefit could not be determined. The quality of life was not objectively evaluated in this study. We also need to design standard questionnaires to evaluate the intervention effect of LHIPEC and NIPS. The effectiveness of LHIPEC and NIPS in treating GC with MA is still being debated. A larger prospective randomized clinical trial comparing LHIPEC + NIPS with NIPS and systemic chemotherapy alone is necessary to assess the clinical benefits of this treatment strategy.

CONCLUSION

LHIPEC + NIPS can improve MA and improve the findings on cytology. This also improves peritoneal metastasis and may improve the quality of life. LHIPEC + NIPS is a feasible and reasonable strategy for the treatment of GC with MA.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Hsing-Wei Yu & Ting-Ying Lee, upon reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2022;68:394-424.
2. Boku T, Nakane Y, Minoura T, Takada H, Yamamura M, Hioki K, *et al.* Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. Br J Surg 1990;77:436-9.
3. Ajani JA, Bentrem DJ, Besh S, D'Amico TA, Das P, Denlinger C, *et al.* Gastric cancer, version 2.2013: Featured updates to the NCCN guidelines. J Natl Compr Canc Netw 2013;11:531-46.
4. De Vita F, Giuliani F, Galizia G, Belli C, Aurilio G, Santabarbara G, *et al.* Neo-adjuvant and adjuvant chemotherapy of gastric cancer. Ann Oncol

2007;18 Suppl 6:i120-3.
5. Lordick F, Kang YK, Chung HC, Salman P, Oh SC, Bodoky G, *et al.* Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): A randomised, open-label phase 3 trial. Lancet Oncol 2013;14:490-9.
6. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, *et al.* Peritoneal carcinomatosis from non-gynecologic malignancies: Results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358-63.
7. SEER Cancer Stat Facts: Stomach Cancer. Available from: https://seer.cancer.gov/statfacts/html/stomach.html. [Last accessed on 2019 Oct 10].
8. Wu CW, Lo SS, Shen KH, Hsieh MC, Chen JH, Chiang JH, *et al.* Incidence and factors associated with recurrence patterns after intended curative surgery for gastric cancer. World J Surg 2003;27:153-8.
9. Glehen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, *et al.* GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: A randomized and multicenter phase III study. BMC Cancer 2014;14:183.
10. Bonenkamp JJ, Songun I, Hermans J, van de Velde CJ. Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. Br J Surg 1996;83:672-4.
11. Yonemura Y, Elnemr A, Endou Y, Ishibashi H, Mizumoto A, Miura M, *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.
12. Jacquet P, Sugarbaker PH. Peritoneal-plasma barrier. Cancer Treat Res 1996;82:53-63.
13. Yonemura Y, Bandou E, Sawa T, Yoshimitsu Y, Endou Y, Sasaki T, *et al.* Neoadjuvant treatment of gastric cancer with peritoneal dissemination. Eur J Surg Oncol 2006;32:661-5.
14. Canbay E, Mizumoto A, Ichinose M, Ishibashi H, Sako S, Hirano M, *et al.* Outcome data of patients with peritoneal carcinomatosis from gastric origin treated by a strategy of bidirectional chemotherapy prior to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a single specialized center in Japan. Ann Surg Oncol 2014;21:1147-52.
15. Tabrizian P, Shrager B, Jibara G, Yang MJ, Romanoff A, Hiotis S, *et al*. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: outcomes from a single tertiary institution. J Gastrointest Surg. 2014;18:1024-31.
16. Tamura S, Miki H, Okada K, Takeno A, Uji K, Yoshida A, *et al.* Pilot study of a combination of S-1 and paclitaxel for patients with peritoneal metastasis from gastric cancer. Gastric Cancer 2010;13:101-8.
17. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, *et al*. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer 2012;15 Suppl 1:S27-37.
18. Sugarbaker TA, Chang D, Koslowe P, Sugarbaker PH. Patterns of spread of recurrent intraabdominal sarcoma. Cancer Treat Res 1996;82:65-77.
19. Los G, Mutsaers PH, van der Vijgh WJ, Baldew GS, de Graaf PW, McVie JG. Direct diffusion of cis-diamminedichloroplatinum (II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: A comparison with systemic chemotherapy. Cancer Res 1989;49:3380-4.
20. Yonemura Y, Ishibashi H, Hirano M, Mizumoto A, Takeshita K, Noguchi K, *et al.* Effects of neoadjuvant laparoscopic hyperthermic intraperitoneal chemotherapy and neoadjuvant intraperitoneal/systemic chemotherapy on peritoneal metastases from gastric cancer. Ann Surg Oncol 2017;24:478-85.
21. Zheng LN, Wen F, Xu P, Zhang S. Prognostic significance of malignant ascites in gastric cancer patients with peritoneal metastasis: A systemic review and meta-analysis. World J Clin Cases 2019;7:3247-58.