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Effects of Laparosopic Hyperthermic Intraperitoneal Chemotherapy for Peritoneal Metastasis from Gastric Cancer

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Abstract

Background: The purpose of this manuscript is to report the direct effects of hyperthermic intraperitoneal chemotherapy (HIPEC) in gastric cancer-patients with peritoneal metastasis (PM).

Materials and Methods: Thirty-five patients with PM were enrolled, and were treated with neoadjuvant laparoscopic HIPEC (LHIPEC). LHIPEC was performed at 42 to 43 centigrade for 60 minutes adding 3 liter of saline plus 12.5mg/m~~2~~ of Mitomycin C with Cisplatin (50mg/m^2). Second session of LHIPEC was done one month after the first LHIPEC in all cases. At the second session of LHIPEC, ascites volume, peritoneal cytology and peritoneal cancer index (PCI) were examined again.

Results: Intraoperative complications of bowel injury were experienced in one and three at 1st and 2nd session of laparoscopy, respectively. There was no mortality after LHIPEC. Ascites was completely disappeared in 17 of 34 patients at the second session of laparoscopy. PFCCs had been detected in 28 (80.0%) patients at the 1st session, and the positive cytology changed to be negative in 16 (57.1%) of 28 patients at the second session. PCI at the 2nd session (12.5 ± 10.5) was significantly lower than that at the 1st session (16.8 ± 9.6) (P=0.023). PCI levels at the 2nd session changed to be 0 in 6 patients.

Conclusion: This new method is not only a safe and convenient method for predicting feasibility of complete cytoredution, but also an effective treatment to control malignant ascites and to eradicate PFCCs before cytoreductive surgery. Furthermore, LHIPEC can reduce PCI levels.

Keywords: gastric cancer, peritoneal metastasis, HIPEC, laparoscopic HIPEC, hyperthermia, peritoneal cancer index

1. Introduction

Peritoneal metastasis (PM) from gastric cancer has previously been considered a terminal disease. Patients have been treated with palliative chemotherapy or best supportive care. However, the systemic chemotherapy for PM is ill-conceived and is considered as limited efficacy. Recently, a more aggressive treatment strategy called cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed with curative intent (Yonemura et al., 2005). CRS and HIPEC are also widely accepted as standard of care to achieve long-term survival in patients with PM from colorectal carcinoma, appendiceal cancer and diffuse malignant peritoneal mesothelioma (Verwaal, 2009; Piso et al., 2001; Yan, Welch, Black, & Sugarbaker, 2009).

In gastric cancer, HIPEC has been considered to prevent peritoneal recurrence after curative resection in patients with advanced gastric cancer (Hamazoe, Maeta, Mutou, & Kaibara, 1994; Yonemura et al., 2001). Recently, Yang et al. (2011) reported CRS and HIPEC improved survival of patients with PM from gastric cancer by a phase III randomized clinical trial. Furthermore, Yan (2007) reported the HIPEC as an independent prognostic factor by a meta-analysis. However, HIPEC is not still as a standard care for peritoneal metastasis from gastric

cancer. The reason may be due to no evidence of the direct effect of HIPEC on the peritoneal metastasis from gastric cancer.

Laparoscopic diagnosis and treatment became a popular method for PM, because it is minimally invasive and enables the correct and detailed evaluation of distribution and volume of peritoneal metastasis than does computed tomography.

The laparoscopic HIPEC (LHIPEC) could be a good tool in treating peritoneal malignancies in the neoadjuvant setting. The purpose of this manuscript is to report the changes of the peritoneal wash cytology and quantitative volume of PM, which were evaluated by the repeat laparoscopy. The present report is the first one to prove the direct effects of HIPEC on the PM from gastric cancer.

2. Materials and Methods

2.1 Patients

Diagnostic laparoscopy was performed in thirty-five gastric cancer-patients with PM referred to Peritoneal Surface Malignancy Centre of Kishiwada Tokushukai Hospital and Kusatsu General Hospital between 2009 and 2012. Data were collected on standard data sheets for all patients.

The eligibility criteria included: (1) histologically or cytologically proven PM from gastric adenocarcinoma; (2) absence of hematogenous metastasis and remote lymph node metastasis; (3) age 75 years or younger; (4) Eastern Clinical Oncology Group scale of performance status 2 or less; (5) good bone marrow, liver, cardiac, and renal function; (6) absence of severe adhesion in the peritoneal cavity; and (7) absence of other severe medical conditions or synchronous malignancy.

Informed consent according to the institutional guideline was obtained from all patients.

Among 35 patients, male and female were 14 and 21, respectively. Average age was 60.6 ± 9.5 years old, ranging from 39 to 71 years old. Patients with synchronous and metachronous PM were 32 and 3, respectively.

2.2 Methods of Laparoscopic Diagnosis of Peritoneal Cancer Index and Laparoscpic HIPEC

The patients were put under general anesthesia. A 12 mm blunt port was placed from the 2cm longitudinal incision above the umbilicus. A second trocar (12 mm) was placed in the right upper quadrant, following by a third trocar (12mm) in the left lower quadrant. A 5 mm trocar was added if necessary in the left upper quadrant.

Most of the ascites was suctioned and the amount was measured with cytological examination. If there is no ascites, peritoneal wash cytology was done using aspirated saline recovered after intraperitoneal administration of 200 ml of saline.

To improve the accuracy of the cytology, an immunohistochemical examination using monoclonal antibodies for anti-human carcinoembryonic antigen (TAKARA Bio INC., Tokyo, Japan) and anti-human epithelial antigen (DAKO, Copenhagen, Denmark) was performed. A peritoneal wash cytological examination was performed at the first and second session of LHIPEC in all patients.

Biopsy specimens were routinely taken from the peritoneal nodules. Quantitative evaluation of peritoneal metastasis in the entire abdominal cavity was done using the peritoneal carcinomatosis index (PCI) based on the regions involved in the abdominal cavity and the lesion size (Sugarbaker, 2007). Following the confirmation of the diagnosis and PCI determination, a longitudinal 5cm midline incision was made on the midline of the lower abdomen for open laparotomy. Three drainage tubes were place on the bilateral subdiaphragmatic space for the inlet tubes and on the rectovesical pouch for male and Douglas' pouch for female patients for an outlet tube. One liter of saline was introduced into the partitoneal cavity, and the saline was completely washed out. The procedure was repeated for ten times to remove the peritoneal free cancer cells (PFCCs) (Kuramoto et al., 2009). Then, HIPEC was performed at 42 to 43 centigrade for 60 minutes adding 3 liter of saline plus 12.5 mg/m2 of Mitomycin C with Cisplatin (50mg/m2) (Figure 1). At the completion of HIPEC, the midline laparotomy incision was closed with 1.0 Maxon stitches (Covidien, Japan), the trocars were reinserted for controlling peritoneal cavity to be sure lack of visceral injury and/or bleeding.

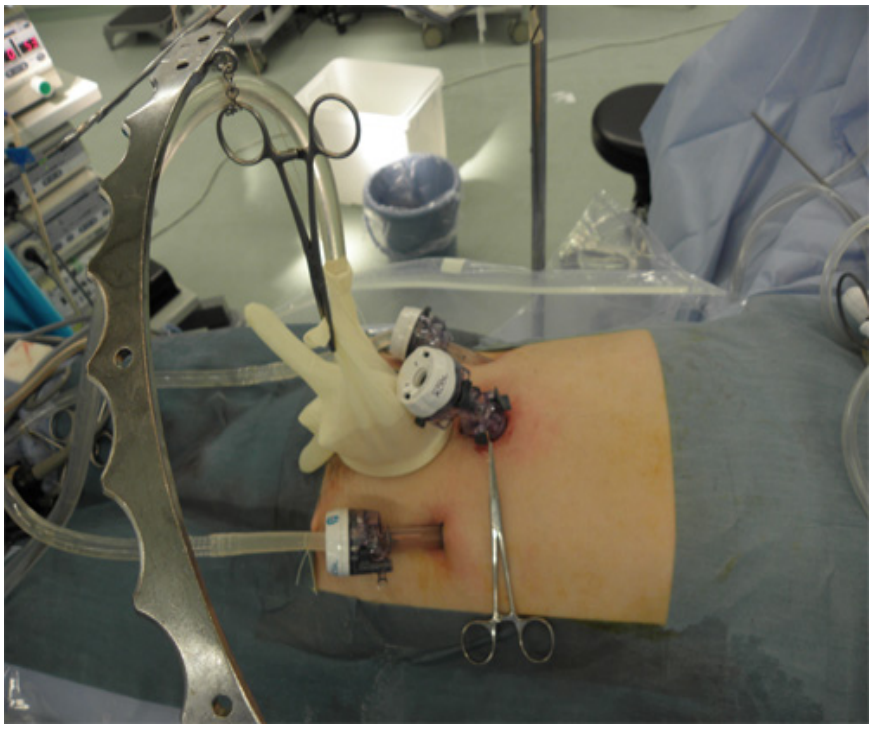


Figure 1. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) (LHIPEC) for gastric cancer patients with peritoneal metastasis

Second session of LHIPEC (SSLHIPEC) was done one month after the first session of LHIPEC in all cases. At the SSLHIPEC, ascites volume, peritoneal cytological study and PCI were examined again. Informed consent according to the institutional guideline was obtained from all patients.

2.3 Mortality and Morbidity

Complications were graded according to the classification established by Dindo and colleagues (Dindo, Dermartines, & Clavien, 2004). Grade 1 complications were defined as minor that are left untreated or requiring a simple bedside procedure without drugs (with the exception of analgesics, antipyretics, antidiarrheals or oral antibiotics), Grade 2 is requiring blood transfusion and pharmacological treatment, Grade 3 is requiring surgical, endoscopic or radiological interventions, Grade 4 is requiring intensive care unit management and Grade 5 was defined to leading to death.

2.4 Evaluation of Neoadjuvant HIPEC and Follow up

Evaluation of neoadjuvant HIPEC was made peritoneal cancer indices (PCI), cytological status and ascites volume at the first LHIPEC and SSLHIPEC.

2.5 Statistical Analyses

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patients' interview. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA).

The amount of ascites and PCI of the first and SSLHIPEC were analyzed by student T-test. Statistical significance was defined as a p-value ≤ 0.05.

3. Results

3.1 Operation Time, Morbidity and Nortality

Mean operation time was 154 ± 19 minutes, ranging from 132 to 212minutes. Intraoperative complications of bowel injury were experienced in one and three at 1st LHIPEC and SSLHIPEC (Table 1). There was no mortality after LHIPEC. In postoperative course, mild azotemia of Grade 2 was developed in four patients and was resolved in postoperative day 7 (Table 1). Mechanical ileus was developed in one patient, but was relieved by the suction through nasogastic tube. Mean hospital stay was 8.0 days (range 5–17).

Table 1. Adverse effects during and after LHIPEC

Side effects	1st session	2nd session	total
Intraoperative complications			
bowel injury	1	3	4
Postoperative adverse effects			
non-hematological adverse events			
azotemia	2 (Grade 2)	2 (Grade 2)	4
ileus	0	1	1
hemtological toxicity			
thromboocytopenia	0	1 (Grade 3)	1
neutropenia	0	0	0

3.2 Changes of the Amount of Ascites, Cytological Status and PCI

The amounts of ascites at the 1st LHIPEC and SSLHIPEC were 1354 ± 1574 and 391 ± 546 ml, respectively. There was a significant difference between the two groups. Ascites was completely disappeared in 17 of 34 patients at the SSLHIPEC.

PFCCs had been detected in 28 (80.0%) of 35 patients at the 1st LHIPEC, and the positive cytology changed to be negative in 16 (57.1%) of 28 patients at SSLHIPEC (Table 2).

Table 2. Changes of peritoneal cytology at 1st and 2nd session of laparoscopy

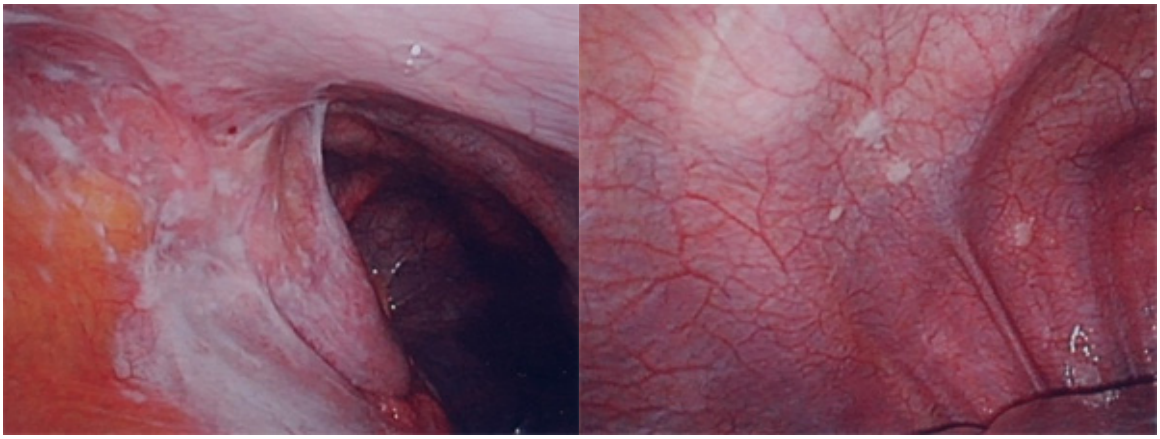
Peritoneal cytology	at 1st LHIPEC positive	at SSLHIPEC negative	total
positive	12	16	28
negative	1	6	7
total	13	22	35

3.3 Changes of PCI

PCI at the SSLHIPEC (12.5 ± 10.5) was significantly lower than that at the 1st LHIPEC (16.8 ± 9.6) (P=0.023). Figure 2 shows a photograph of peritoneal surface at the 1st LHIPEC and SSLHIPEC. PCI at the 1st HIPEC was 15, and PCI at the 2nd session changed to be 1. In 23 patients, PCI levels at the 1st LHIPEC decreased at the SSLHIPEC, and those of 2 patients did not change. PCI of the other 10 patients increased at SSLHIPEC (Figure 3). PCI levels at SSLHIPEC changed to be 0 in 6 patients (complete response).

Among 22 patients whose PCI levels at the 1st LHIPEC were higher than 11, PCI levels of 6 patients changed to those lower than 10.

1st LHIPEC



2nd LHIPEC

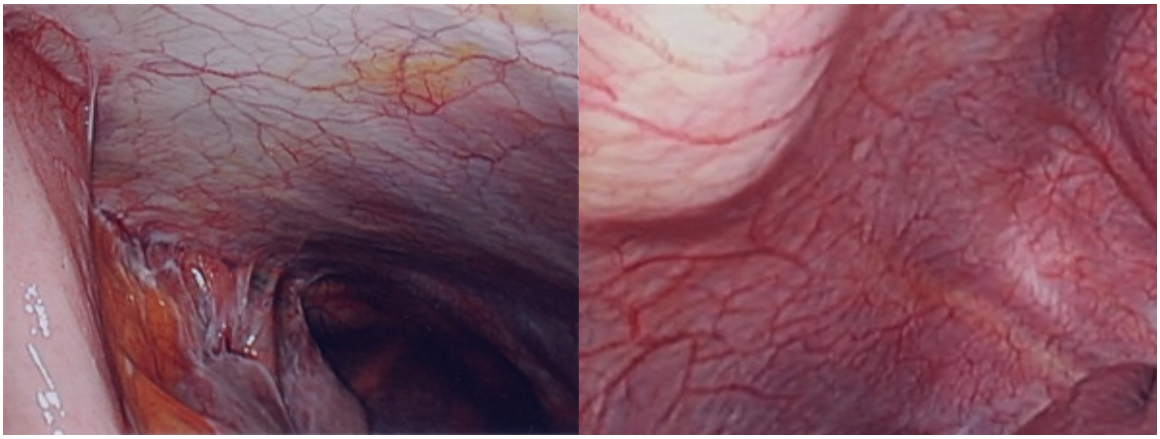


Figure 2. Laparoscopic findings before and after LHIPEC

4. Discussion

This study demonstrate a benefit of LHIPEC with number of important findings such as the correct evaluation of PCI, decreased/disappeared ascites, induction of the disappearance of PFCCs and decreased PCI levels in patients with PM from gastric cancer.

The preoperative diagnosis and estimation of PCI for PM from gastric cancer is limited because of the insensitivity of CT, US, MRI and PET. Current imaging modalities cannot consistently detect low-volume PM with sizes of 5 - 8 mm or less (Koh, Yan, Glenn, & Morris, 2009; Yan, 2008). The diameter of PC in gastric cancer tends to be smaller than that from colorectal and appendiceal cancer, and small PC ≤ 5 mm in diameter were detected using CT with a sensitivity of 11% (Koh et al., 2009; Yan et al., 2008; Yonemura, 2012). The most difficult lesions to detect using CT or MRI are PM on the mesentery of the small bowel with a low depiction rate of 8%. Recently, staging laparoscopy has been introduced for the diagnosis of PM from gastric cancer; this practice has an excellent diagnostic accuracy for small PM on the small bowel mesentery (Valle & Garofalo, 2006). The accuracy of laparoscopy for PC is reported to be 92% (Koh, 2009). Valle (2006) performed a full laparoscopic PCI assessment on 97 patients with PC, and only 2 (2.1%) cases were understaged. A good correlation between the open surgery data and the laparoscopic PCI was reported (Badgwell et al., 2008).

In gastric cancer, a threshold of PCI for good or bad prognosis is reported as PCI= 6 (Yonemura et al., 2005). In our experience, among 44 patients who had been diagnosed as having a PCI ≤ 6 using preoperative CT, the number of patients with an intraoperative PCI ≤ 6 was 29 (66%). In contrast, 12 (41.3%) of the 29 patients who had been diagnosed as having a preoperative PCI ≥ 7 using CT showed an intraoperative PCI ≤ 6 (Yonemura, 2012). Accordingly, patients with a PCI ≤ 6 and who have a significantly favorable prognosis cannot be correctly diagnosed based on preoperative CT.

In the present study, a significant decrease in the ascites was found after the 1st session of LHIPEC and ascites

was completely disappeared in 17 (50%) of 34 patients after one session of LHIPEC. Facchiano, Risio, Kianmanesh and Msika (2012) and Valle, Van del Speeten (2009) reported the results of 57 patients who had been treated using LHIPEC, and the complete clinical regression of ascites was found in all the patients. By LHIPEC, PFCCs and the cytokines which may contribute to accelerate the vessel permeability may be washed away from the peritoneal cavity, and ascites may be decreased or disappeared (Yonemura, 2012). Accordingly, LHIPEC is considered as a useful method to control ascites.

Furthermore, histological and cytological proof can be assured by performing a laparoscopy, and a laparoscopy may become a reliable tool for the evaluation of neoadjuvant induction chemotherapy. Peritoneal free cancer cells are a sign of poor prognosis even if there is no macroscopic PM (20). In contrast, the prognosis of patients with macroscopic PM and negative PFCCs had significant better survival than those with PM and positive PFCCS (Bando, 1999).

However, systemic chemotherapies have minimal effects on PM (Markman, 1991). The peritoneal cavity acts as a sanctuary against systemic chemotherapy, probably because of the existence of a blood-peritoneal barrier consisting of stromal tissue between mesothelial cells and submesothelial blood capillaries (Sugarbaker et al., 2005). This barrier acrosses for a total thickness of 90 μm (Baron, 1941). Accordingly, only a small amount of systemic drugs are capable of penetrating this barrier and passing into the peritoneal cavity, and a higher percentage of the administered drugs instead moves to the bone marrow and vital organs other than the peritoneum, resulting in the development of adverse effects. Accordingly, systemic chemotherapy can not efficiently eradicate PFCCs. In contrast, PFCCs could be efficiently treated by the intraperitoneal chemotherapy, because high loco-regional intensity can be obtained by the intraperitoneal chemotherapy. Yonemura et al. (2010) reported that the positive cytology results became negative in 69% (47/68) of patients with PM from gastric cancer after six cycles of neoadjuvant intraperitoneal/systemic chemotherapy (NIPS). The present study demonstrated that the positive cytology changed to be negative in 16 (57.1%) of 28 patients after one session of LHIPEC. Patients with negative cytology after NIPS survived significantly longer than those with positive cytology after cytoreductive surgery combined with perioperative chemotherapy (Yonemura, 2012). LHIPEC .is a useful neoadjuvant therapy for the eradication of PFCCs before cytoreductive surgery.

The remarkable effect of the present study is that LHIPEC decreased the PCI levels. Seeding cancer nodules could be treated by direct penetration of chemotherapeutic agents after intraperitoneal administration of chemotherapeutic agents. Studies of intraperitoneal delivery of cytotoxic agents have shown the direct tumor absorption of drugs occurs to a level of 2 mm beneath the tumor surface (Loss, 1989). In addition, low transperitoneal absorption due to the plasma-peritoneal barrier allows systemic drug concentrations 18- to 620-fold lower than intraperitoneal concentrations (Markman, 1991). Accordingly, intraperitoneal chemotherapy achieves a significant high locoregional concentration but low systemic exposure.

Hyperthermia higher than 41 centigrade is known to increase the drug penetration distance from the peritoneal surface (Loss, 1989). Furthermore, laparoscopic HIPEC allows for the better penetration of drugs in peritoneal tumors than HIPEC under laparotomy and the peritoneum because closed HIPEC generates a high intraperitoneal pressure than HIPEC under laparotomy (Thomas, 2008).

The present study demonstrated that PCI at the SSLHIPEC (12.5 ± 10.5) was significantly lower than that at the 1st session (16.8 ± 9.6) (P=0.023). PCI levels of 23 (65.7%) patients at the 1st LHIPEC decreased at the SSLHIPEC. Furthermore, PCI levels at the SSLHIPEC changed to be 0 in 6 patients, and the complete response rate was 17.1%. Glehen et al reported that patients with PCI level ≤10 survived significantly better than those with PCI ≥ 11 (Glehen et al., 2010). Among 22 patients whose PCI levels at the 1st LHIPEC were higher than 11, PCI levels of 6 patients changed to those lower than 10.

Accordingly, LHIPEC can decrease the PCI levels to the threshold level corresponding with good prognosis, and exploratory laparoscopy can serve as a selection criterion for an evaluation tool of optimal candidates for cytoreductive surgery.

In terms of the intraoperative complications, bowel injury was experienced in four cases, but the injured sites were repaired in all cases. The incidence of bowel injury was higher in the SSLHIPEC than in the 1st LHIPEC, but there was no postoperative complication. There was no mortality after LHIPEC. Postoperatively, four patients developed mild azotemia of Grade 2 due to the HIPEC. Mechanical ileus was developed in one patient, but was relieved by the suction through nasogastic tube. Average hospital stay was short (8.0 ± 3 days).

5. Conclusion

This new method is not only a safe and convenient method for predicting feasibility of complete cytoredution, but also an effective treatment to control malignant ascites and to eradicate PFCCs before cytoreductive surgery. Furthermore, LHIPEC can reduce PCI levels, resulting in the increase of complete cytoreduction rates and the improvement of the prognosis after cytoreductive surgery. Further large prospective studies are necessary for determination of laparoscopy as a potential standard of a diagnostic and therapeutic algorithm in patients with PM from gastric cancer.

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